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OF

MICROSCOPIC ANATOMY

BY

EDWARD ALBERT SCHÄFER, LL.D., Sc.D., M.D., F.R.S.

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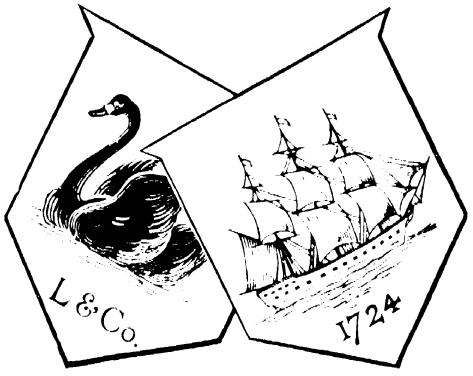

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QUAIN'S
ELEMENTS OF ANATOMY

ELEVENTH EDITION. IN FOUR VOLUMES. ROYAL 8vo.

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EDITORS

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PREFACE

THE present part of QUAIN'S ANATOMY is intended to serve as a TEXT-BOOK OF MICROSCOPIC ANATOMY. With this view, the subject-matter has been re-arranged and re-written, and a large number of new figures added. Many are original, the rest are from various sources. Acknowledgment is due to the authors and publishers who have given consent to the use of their illustrations, and especially to Professor J. SOBOTTA, who has permitted a number of his coloured figures of human tissues and organs to be reproduced for this work in the form of lithographic plates; to these have been added other coloured plates of drawings by Mr. RICHARD MUIR, from specimens furnished by the author. The wealth of illustration provided by these and by the numerous text-figures will, it is hoped, add to the interest as well as to the value of the work.

The chapter dealing with the structure of the Vascular System is by Professor G. MANN of Tulane University, New Orleans.

The Index has been prepared by Dr. JOHN TAIT of Edinburgh University, who has also assisted in reading the proofs.

E. A. SCHÄFER.

EDINBURGH: *March* 1912.

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Corrigenda

Page 10, line 4, *for* bioplasts *read* bioblasts.
,, 18, line 5, *for* cytomytome *read* cytomitome.
,, 22, footnote 2, *for* Fleming *read* Flemming.
,, 32, line 12, *for* astropheres *read* astrospheres.
,, 158, line 26, *for* p. 127 *read* p. 117.
,, 188, footnote 3, *for* Meiggs *read* Meigs.
,, 189, line 34, *for* Frohmann *read* Frommann.
,, 200, line 29, *omit* the larger.
,, 200, footnote 3, *for* Herring *read* Hering.
,, 238, *add* From a preparation by H. Pringle *after* description of fig. 374.
,, 264, line 3, *for* fig. 412 *read* fig. 415.
,, 271, line 7, *for* Solokoff *read* Sokoloff.
,, 373, footnote 3, *for* Sieman *read* Seemann.
,, 351, *add* (Mann) after description of fig. 540.
,, 414, last line but one, *for* Seeman *read* Seemann.
,, 482, footnote, *for* Advanced *read* Schäfer's.
,, 642, line 22, *for* Schlacter *read* Schlachta.
,, 644, line 10, *for* There *read* These.
,, 670, footnote 1, *for* Arch. f. Int. Med. *read* Arch. of Int. Med.
,, 670, footnote 6, *for* Halstead *read* Halsted.
,, 674, line 2, *for* Fig. 979 *read* Fig. 980.
,, 684, line 7 from bottom, *for* and *read* which.
,, 684, line 6 from bottom, *for* form *read* forms.

GENERAL ANATOMY

HISTOLOGY.

Definition and division of the subject.—The *microscopic anatomy* of the body is known as *histology*—from ἱστός, a web or tissue—since the various organs which compose the body are made up of several textures or tissues. It is necessary to preface the description of the microscopic structure of the organs by an account of the structure of these tissues.

Four principal kinds of tissue—the *four elementary tissues*—are enumerated, viz. **epithelial, connective, muscular,** and **nervous,** but varieties of each of these are met with. Most organs are formed of more than one tissue, the connective tissues

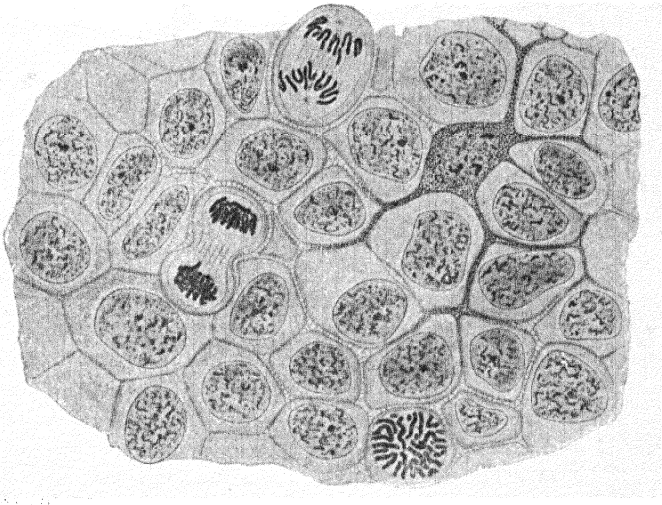


FIG. 1.—EPIDERMIS CELLS OF A LARVAL SALAMANDER.
Magnified 400 diameters. (E. B. Wilson.)

Three of the cells are undergoing division. The intercellular channels are bridged across by fine fibres. At one place a branched pigment-cell is lying between the epithelium-cells.

especially being widely distributed and entering into the composition of nearly all parts of the body. It is the preponderance of one or other tissue and the arrangement of the tissue elements which characterises the structure of the various organs. Some organs are formed so largely of a single tissue that in describing the structure of the constituent tissue one almost necessarily describes the structure of the organ itself; whereas other organs, chiefly on account of their greater complexity, require a description apart from that of the tissues composing them. The subject thus tends to arrange itself into two parts, one (*histology proper*) dealing with

the elementary tissues in general, and the other (*histological organology*) dealing with their arrangement to form the organs. Further, some organs are strictly localised, whilst others, on the contrary, are widely distributed ('general systems,' Bichat). Examples of the latter class are the blood-vessels, lymph-vessels, and nerves; which all penetrate into, and thus come to form, constituent portions of most parts of the body. Other organs, again, while less generally diffused, are not confined to one place, but occur in many situations; with local modifications, it is true, but nevertheless with sufficient uniformity of structure to warrant their being described together. Examples are met with in the lymphoid organs, in internally secreting glands, in externally secreting glands, in serous, synovial, and mucous membranes, and in the membrane which forms the general integument. It will be convenient to consider these after the elementary tissues are described.

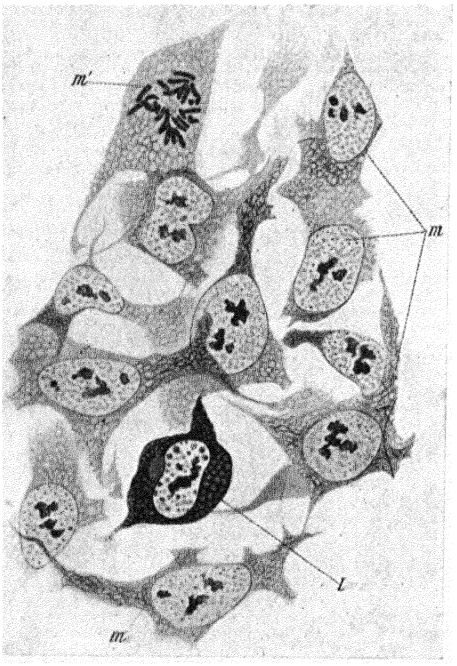


FIG. 2.—MESODERM CELLS OF RABBIT EMBRYO, UNITING TO FORM A SYNCYTIUM. (Maximow.)

m, ordinary mesoderm cells; *m'*, a cell in karyokinesis; *l*, a lymphocyte.

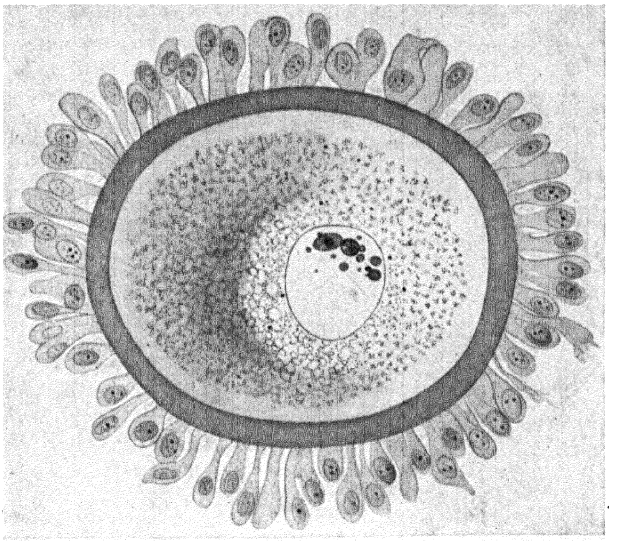
All the tissues and organs of the body are formed of cells (fig. 1), between which is found a variable amount of intercellular substance, which in some tissues may be not inconsiderable, whilst in other cases the cells may touch one another, or even come into complete continuity (fig. 2). This is not unfrequently the case with the branches of adjacent cells. When the continuity of the cell-substance is complete the congeries of cells receives the name of *syncytium*.

The life of the tissues is dependent upon that of the cells, which govern all metabolic changes within the body. These changes are the actual source of all vital phenomena, including development and growth; and since growth and chemical changes proceed in intercellular substance as well as in the cells themselves, it is believed by some authorities that intercellular substance is also formed of living matter.[1] But the cells are capable of forming fresh intercellular material, and of causing chemical changes in that which is already formed, even although it is not immediately in contact with their protoplasm, through the agency of chemical substances (metabolites, enzymes) which they produce, so that it is not necessary to assume that the changes which occur in intercellular substance are brought about by its own activity. It is at any rate certain that intercellular substance shows no such changes apart from the cells which belong to it.

The cells which constitute the body must be regarded as all exhibiting a period prior to differentiation, a period of differentiation, and a period of regressive metamorphosis which ultimately leads to the death of the cell.[2] In some cells the whole life-history is comprised within a limited time, the degenerated cells being either absorbed or cast off: the blood-cells and the cells of stratified epithelia furnish examples of these. In other cells their life-history is coterminous with the life of the individual, as in the case of nerve-cells and muscle-cells.

[1] Cf. F. Mall, Amer. Journ. Anat. i. 1901–2, and M. Heidenhain, Plasma u. Zelle, 1907.
[2] C. S. Minot, Science, xiii. 1901, p. 401.

Development of the tissues.—The whole of the animal body with all its organs and tissues is developed from a single cell, the *ovum* (fig. 3). This after conjugation (fertilisation) with the male cell (*spermatozoon*, fig. 4, II.), undergoes repeated division, and forms, in the first instance, a mass of cells which ultimately become arranged in three layers overlying or surrounding a cavity; the ovum having in the meantime grown to many times its original size. It is now known as the **blastodermic vesicle,** or **blastocyst**; and the three layers of which the wall of this vesicle is composed are termed collectively the **blastoderm,** and are named respectively from without in, **ectoderm, mesoderm,** and **entoderm.**[1] All are at first composed exclusively of undifferentiated embryonic cells, but as development and growth proceed these cells become variously modified structurally and chemically, and gradually produce or build up the several tissues of which the body is ultimately composed. A study of their development shows that, speaking generally, certain tissues are formed out of each layer of the blastoderm, and we may thus classify the tissues according to the layer from which they originate, as ectodermic, mesodermic, and entodermic.[2] The histogenetic connexion which is thus established between the blastoderm layers and the several tissues is expressed in the appended table.



PROLIGERUS. (Van der Stricht.)

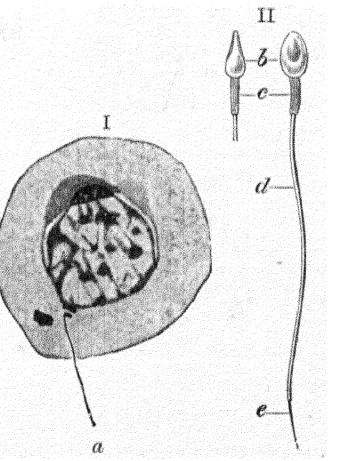


FIG. 4.—I. A CELL OF TESTICLE (SPERMATID) DEVELOPING INTO A SPERMATOZOON. (Niessing.)

a, tail-filament growing out from centriole.

II. HUMAN SPERMATOZOON IN PROFILE AND VIEWED ON THE FLAT. (Retzius.)

b, head formed of cell-nucleus; *c*, middle piece, formed from cell-protoplasm; *d*, tail; *e*, end-piece of tail.

[1] For the formation of the blastoderm, see Embryology.

[2] By this classification it is by no means implied that a tissue can only be produced by the cells of one blastodermic layer, for there are cases in which a tissue which is normally formed by cells from one layer of the blastoderm may be regenerated by cells of a different origin. Some tissues, *e.g.* stratified, ciliated, and glandular epithelia, are normally formed either from ectoderm or entoderm, and plain muscle, which is ordinarily of mesodermic origin, is developed in certain situations from ectoderm. Cf. on this subject, A. v. Szily, Anat. Hefte, xxxiii. 1907. Minot ('Address to the Association of American Anatomists,' Amer. Journ. Anat. iv. 1905) insists that 'each germ layer produces its own specific set of tissues, which are not duplicated by the tissues of any other germ layer.' It is obvious that this statement must be accepted with certain reservations.

Tissues derived from ectoderm.

The epidermis and its derivatives—viz. hairs, nails, epithelium of sebaceous, sweat, and mammary glands, including also the plain muscular tissue of the sweat-glands.

The epithelium of the mouth and its derivatives—viz. the enamel of the teeth; the taste-buds; the epithelium of the salivary and other glands which open into the mouth; the epithelium of the anterior and intermediate parts of the pituitary body.

The epithelium of the anus and of part of the anal canal.

The epithelium of the distal portion of the male urethra.

The epithelium of the nasal fossæ, and that lining all the cavities in the cranial bones which communicate with them; the epithelium of the glands of the nasal mucous membrane; the olfactory epithelium.

The epithelium covering the front of the eye, lining the eyelid and continued along the lacrymal canals to the nasal fossæ. The epithelium of the lacrymal glands.

The crystalline lens.

The epithelium lining the membranous labyrinth of the ear, including the sense-cells of the maculæ and cristæ, and those of the organ of Corti.

The epithelium lining the central canal of the spinal cord and the aqueduct of Sylvius; also lining the third, fourth, and lateral ventricles of the brain.

Neuroglia cells and fibres.

All nerve cells and fibres, whether within the central nervous system or in the ganglia or in peripheral nerves.

The retina of the eye.

The epithelium of the ciliary region, and that covering the back of the iris. The muscular tissue forming the sphincter and dilatator pupillæ.

Certain ductless glands and parts of those glands, such as the pineal, the posterior lobe of the pituitary and the medulla of the suprarenal capsules, as well as other small glands of like nature (paraganglia) derived from the sympathetic.

Tissues derived from mesoderm.

The epithelium of the capsules of Bowman, and of the convoluted, looped, and junctional tubules of the kidney. The epithelium of the ureters and renal pelves, and of the collecting tubules of the kidney.

The cortex of the suprarenal capsules.

The epithelium of the ducts of the testis, that of the ovary and Fallopian tubes, uterus and greater part of the vagina. Also that of the prostatic vesicle in the male.

The generative products in both sexes.[1]

All the connective tissues, including areolar, fibrous, elastic, reticular, adipose, cartilage, bone, and dentine.

The endothelium (mesothelium) lining the vascular and lymphatic systems.

The corpuscles of the blood and lymph.

The blood- and lymph-glands, including the spleen, the lymph-glands and lymphoid organs in general, and the hæmal lymph-glands.[2]

All muscular tissue, except the plain muscle of the iris and of the sweat-glands, the origin of which is ectodermic.

Tissues derived from entoderm.

The epithelium of the pharynx, œsophagus, stomach, small and large intestines, and all its derivatives, including the epithelium of the small glands of the mucous membrane and that of the large glands which open into the intestine—viz. the pancreas, and the liver with its gall-bladder.

The epithelium of the Eustachian tube, and that lining the cavity of the tympanum.

The epithelium of the larynx, trachea, bronchial tubes, and pulmonary alveoli.

The epithelium of the thyroid vesicles and of the parathyroids.

The reticulum and the concentric corpuscles of the thymus.

The epithelium of the female urethra, of the proximal part of the male urethra, and of the urinary bladder.

The epithelium of the prostatic glands and of the glands of Cowper in the male; of the lowest part of the vagina (vestibule) and glands of Bartholin in the female.

[1] The germ-cells from which the sexual cells are eventually formed are found in some animals to be differentiated from the remaining cells resulting from division of the ovum even before there is a distinction into blastodermic layers. In a sense, therefore, they may be regarded as *sui generis* and independent of these layers. But since in man and all the higher animals they are found in the wall of the cœlom—which unquestionably belongs to the mesoderm—these cells may, with reservation, be included amongst the mesodermic tissues.

[2] The connective tissues, the plain muscular tissue, the endothelium of the vascular and lymphatic systems (including that of the serous membranes), as well as the blood- and lymph-corpuscles, constitute a special class of mesodermic tissues, derived from loosely arranged cells which have become budded off from the layers of cells which form the mesoderm proper. To these loosely arranged and often much-branched cells the name parablast (His), or mesenchyme (R. and O. Hertwig), has been given, and the tissues which are formed from these cells are often termed the mesenchyme tissues. But it is doubtful if there is any valid reason for this segregation from the rest of the tissues formed from mesoderm. In the Embryology (vol. i.) the term mesenchyme is used to denote the blastema of the connective tissues.

General structure of the tissues.—All the tissues are, as has just been explained, originally derived from embryonic cells, and, in all, these cells become modified to form permanent constituents of the tissue. In some tissues other constituents are formed in the intercellular substance, the relation of which to the cells has been already noticed. If the intercellular substance is in considerable amount (fig. 5) it is termed *ground-substance*; as in ordinary connective tissue, in cartilage, in bone, and in dentine. When, on the other hand, it is met with only in very small amount (fig. 6), it has been termed *cement-substance*, since it serves merely to cement the cells together. Intercellular substance varies in consistency in different tissues, being in some nearly or entirely fluid in character, whilst in others it has acquired considerable rigidity, as in cartilage; or it may even become hard and calcified, as in bone and dentine. But, wherever occurring, the presence of intercellular substance can always be exhibited by the method

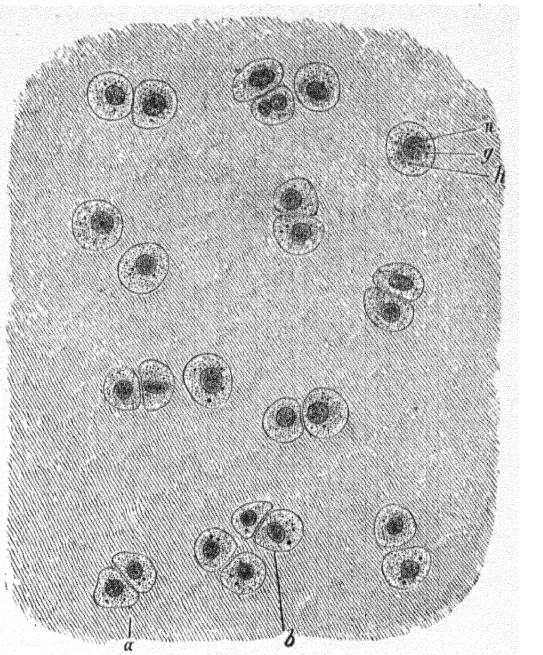


FIG. 5.—ARTICULAR CARTILAGE FROM HEAD OF METATARSAL BONE OF MAN. 340 diameters. (Schäfer.)

a, group of two cells; *b*, group of four cells; *h*, protoplasm of cell, with *g*, fatty granules; *n*, nucleus.

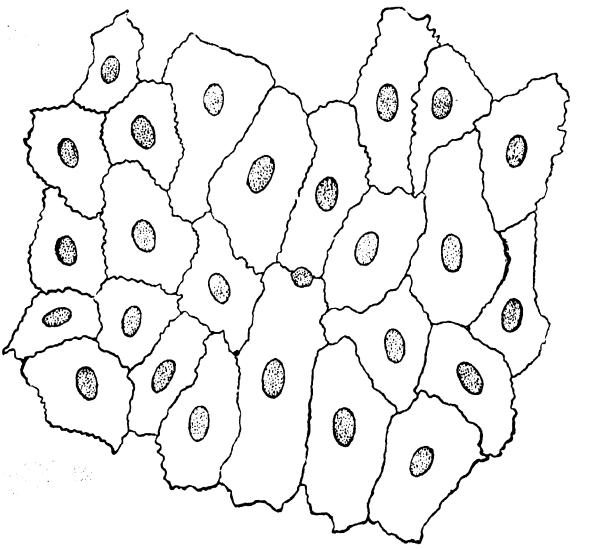


FIG. 6.—PAVEMENT-EPITHELIUM (ENDOTHELIUM) FROM THE OMENTUM OF THE RABBIT. Nitrate of silver staining. (Schäfer.)

of staining devised by v. Recklinghausen, which consists in subjecting the fresh tissue to the action of a solution of silver nitrate and subsequently exposing it to sunlight.

Under these circumstances a fine deposit of reduced silver is produced in all intercellular substance, which shows brown or even nearly black in consequence, thus contrasting with the material of which the cells themselves are composed, which

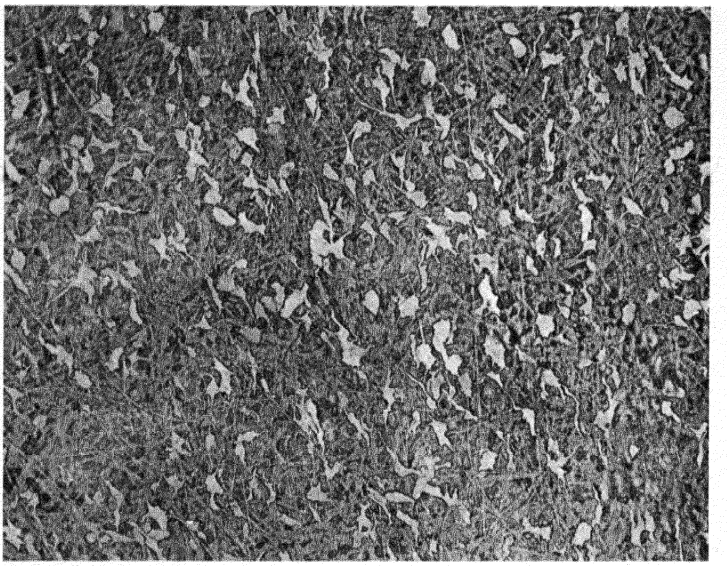


FIG. 7.—AREOLAR TISSUE PREPARED BY RECKLINGHAUSEN'S SILVER METHOD. (Schäfer.) Photograph: magnified 200 diameters.

The cells are seen as clear spaces in the (brown) stained ground-substance, through which the fibres course.

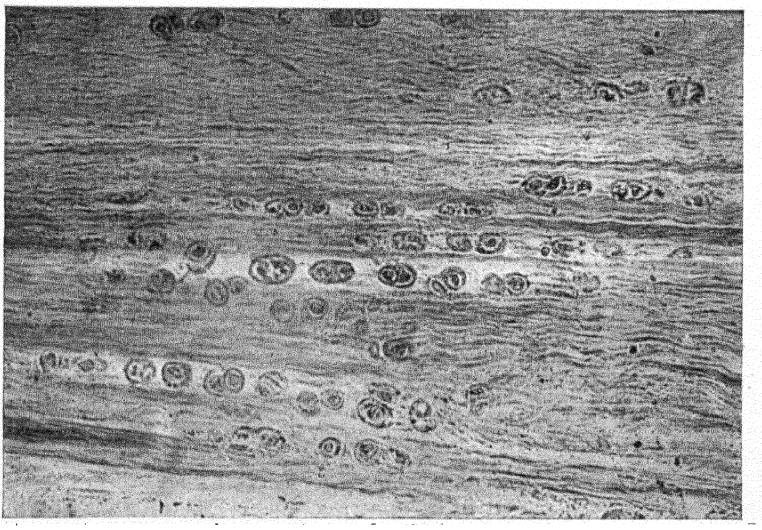


FIG. 8.—SECTION OF WHITE FIBRO-CARTILAGE. (Schäfer.) Photograph: magnified 200 diameters.

The ground-substance is pervaded by wavy connective-tissue fibres.

remains entirely colourless (fig. 7. See also the plate opposite p. 102).[1] Under the agency of the cells, fibres of various kinds may be formed within intercellular

[1] A. S. Dogiel (Arch. f. mikr. Anat. xxxiii. 1889) has shown that a similar effect—*i.e.* staining of intercellular substance alone—may be obtained by impregnating a tissue with strong solution of methylene blue and afterwards washing in diluted picrate of ammonia.

substance (fig. 8); these fibres, which form part of the elementary constituents of the tissue, may either grow out from the cells and afterwards lose connexion with them, or they may be simply deposited in the ground-substance, without being directly connected with the cells of the tissue: fibres of this kind—*i.e.* coursing through the intercellular substance without direct connexion with the cells—are, at least in the adult, characteristic of the connective tissues. In epithelium, on the other hand, such fibres as occur in the intercellular substance bridge across it, passing from cell to cell and serving the purpose of connecting the cells of the tissue together (fig. 9). In some situations where this arrangement occurs, as in the deeper layers of a stratified epithelium, the intercellular substance may be merely a sort of lymph,[1] such as bathes all the living tissues, and not of the nature of a firmer cementing material such as may be assumed to be present when these bridging fibres are absent. But, as Flemming has pointed out, it differs chemically from lymph such as occurs in lymph-vessels in the fact that it becomes darkly stained by Recklinghausen's silver-nitrate method. In epithelium,

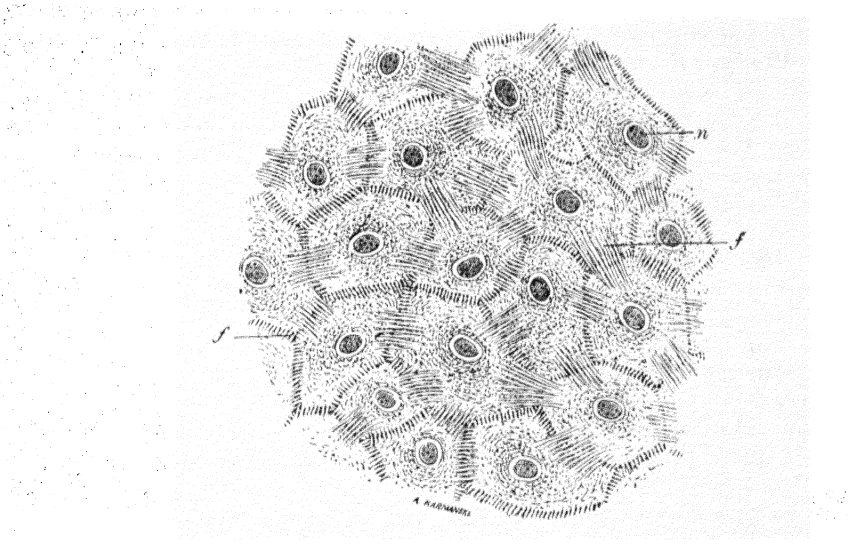


FIG. 9.—CELLS OF A STRATIFIED EPITHELIUM (EPIDERMIS) WITH FIBRILS BRIDGING ACROSS THE INTERCELLULAR SPACES. (Ranvier.)

n, a cell-nucleus; *f*, bridging fibrils.

as in connective tissue, there may be, and probably are, varying degrees of firmness of the intercellular substance, but it never, as does that of bone and dentine, undergoes calcification, with the possible exception of the cement-substance between the prisms of the enamel of the teeth, which has sometimes been looked upon as furnishing an example of calcified intercellular material.

Differentiation.—The changes which take place in and by means of embryonic cells in the production of tissues are collectively termed *histogenesis*. Great variations are found to occur in the tissues regarding the amount of differentiation which their cells undergo. Some cells, such as the lymph-corpuscles (lymphocytes), retain throughout their whole life-history most of the characters of undifferentiated cells; others, such as the cells of nervous and muscular tissues, become so greatly modified that the original structure of the constituent cells is completely obscured; while others again, such as the cells of the connective tissue and many epithelial cells, occupy an intermediate position in the scale of differentiation.

[1] Flemming, Anat. Hefte, vi. 1896; Waldeyer, Arch. f. mikr. Anat. lvii. 1901.

Differentiation of a certain sort begins to show itself very early in the development of the ovum; so that different kinds of embryonic cells are distinguishable, even before the blastoderm is fully formed, and even, with some ova, during the first stages of segmentation. By the time the blastodermic layers are laid down, there is always a clear distinction in the character of the cells which compose them: the ectoderm and entoderm appearing as layers of connected cells which have already the appearance of epithelial tissue, although without the variation in the structure of the individual cells which in many epithelia shows itself later; while a large part of the mesoderm very soon becomes loosely arranged, and its cells begin to be separated by a relatively large amount of intercellular substance—appearances which are characteristic of developing connective tissue. Somewhat later also the ectoderm in and near the middle line of the embryo undergoes the thickening and folding which presages the formation from it of the central nervous system. Further, the part of the mesoderm which is nearest to this begins to show indications of the differentiation which is preliminary to the development of the skeletal muscles; whilst that part which is placed more peripherally exhibits the splitting into somatic and splanchnic layers which is the first sign of the formation of the cœlomic cavity. *Pari passu* with these and other successive changes in the disposition of the cells of the several blastodermic layers, proceeds a gradual differentiation produced by alterations in form and eventually in structure of the constituent cells—alterations which eventually lead to the formation of the various tissues. Since every tissue in the body is at first composed wholly of cells which individually show little or no special differentiation of structure, it is clear that the undifferentiated cell is to be regarded as the type. The structure of cells in general and the various modifications which they exhibit must be studied before the structure of the tissues which have been formed from them can be considered.

THE ANIMAL CELL.

The actual discovery of the cellular constitution of animals dates from the 'Microscopic Researches into the Accordance in the Structure and Growth of Plants and Animals,' by Theodor Schwann, published in 1839; the botanist Schleiden having in the previous year shown such constitution to obtain for all the different tissues of plants. The existence of cells had, indeed, been described in certain vegetable tissues, such as cork, as long ago as the seventeenth century,[1] and the presence of a nucleus had been noticed by Fontana in the latter end of the eighteenth century. But it was not until shortly prior to the work of Schleiden that the nucleus was recognised as an integral constituent of the plant-cell by R. Brown (1831); and the generalisations of Brown and Schleiden for the plant were extended and amplified in so able a manner by Schwann that the ideas which he enunciated still remain, under the name of the 'cell-theory,' the accepted doctrine regarding the structure of all the higher animal organisms.

The term *protoplasm* was applied by Purkinje to the substance of animal cells in 1840, but first came into extensive use after its employment by v. Mohl, in 1846, who applied it to the living substance of the plant-cell. The material itself, with all its most prominent characteristics as displayed in Infusoria, was however described, in 1835, under the name of 'sarcode,' by Dujardin, the accuracy of whose description has, it will be seen, left but little for subsequent observers to add to: 'I propose to name *sarcode* that which other observers have termed a living jelly, a substance glutinous, diaphanous, homogeneous, refracting light a little more than water, but much less than oil, extensible and ropy like mucus, elastic and

[1] N. Grew, Anatomy of Plants, 1682.

contractile, susceptible of spontaneously forming within itself spherical cavities or vacuoles which become occupied by the surrounding liquid. . . . Sarcode is insoluble in water, but is eventually decomposed by it, leaving a granular residuum. Potash does not dissolve it suddenly like mucus or albumen, and seems simply to hasten its decomposition by water; nitric acid and alcohol immediately coagulate it and render it white and opaque. . . . The most simple animals, such as amœbæ and monads, are entirely composed, at least to all appearance, of this living jelly. . . . Sarcode is without visible organs and has no appearance of cellularity; but it is nevertheless organised, for it emits various prolongations along which granules pass and which are alternately extended and retracted: in one word, it possesses "life." '[1]

Gradually, both in plants as well as in the lower animals, it came to be generally recognised that the sarcode of Dujardin and the protoplasm of v. Mohl are endowed with similar attributes, and a cell was defined as composed of structureless protoplasm, endowed with irritability and contractility, containing a nucleus and enclosed by a cell-membrane. That a cell-membrane is, however, not an essential character and is often absent, especially in animal cells, was shown by Leydig (in 1856), and was especially emphasised by M. Schultze and by Brücke (in 1861). Even at the present time the definition of a cell proposed by Leydig holds good—'a mass of protoplasm furnished with a nucleus.'[2]

Taking this definition as a starting-point, we may, to begin with, study these two parts of the cell independently, although, as will presently appear, they are in the most extended sense functionally interdependent, and must ultimately be regarded as being both essential parts of the one elementary unit—the cell.

Cells show great variation in size. In the human body they vary from that of the lymphocytes of the blood and lymph and the 'granule-cells' of the cerebrum and cerebellum, which are amongst the smallest, and measure only about 4μ in diameter,[3] to the 'Betz-cells' of the motor region of the brain, and the 'giant-cells' of bone-marrow and of developing bone (figs. 54 and 64), which last measure from 40μ to 80μ, and represent the largest individual cells which are met with in man. In the animal kingdom generally, and in plants, the variation is much greater even than this. Nevertheless, although the largest are just visible to the naked eye, cells in general are of quite microscopic dimensions. In many cases a distinction has to be drawn between the part of the cell which contains the nucleus, which is usually termed the cell-body (perikaryon of Sherrington), and processes which extend from it. Such processes may be of great length, as with the axon-processes of nerve-cells; they may be either fixed, or movable and capable of being retracted, as with the processes of amœboid cells, which are known as pseudopodia; or they may be endowed with rhythmic motility, as with the processes known as cilia.

The opinion has been frequently expressed during recent years that the cell is not the ultimate living unit of the animal and plant organism, but that the living material both of cell-substance

[1] Quoted from Carnoy, 'Histoire de la Cellule,' Biologie Cellulaire, 1884. A concise account of the structure of the several parts of the cell is given by C. E. Walker, Essentials of Cytology, 1907. The following monographs on cell-structure may be especially mentioned: Flemming, Zellsubstanz, Kern u. Zelltheilung, 1882 (this has a full bibliography to that date); also a series of articles by the same author in the Arch. f. mikr. Anat. and in the Ergebn. d. Anat. (the latter commencing in 1891); Henneguy, Leçons s. l. cellule, 1896; E. Holmgren, Ergebn. d. Anat. xi. 1901; A. Gurwitsch, Morph. u. Biol. d. Zelle, 1904; Prenant, Bouin, and Maillard, Histologie, t. i. 1904; Růžička, Ergebn. d. Anat. xvi. 1906; M. Heidenhain 'Plasma u. Zelle,' in v. Bardeleben's Handb. d. Anat. 1907.

[2] This definition does not apply, however, to all living organisms, for many unicellular protozoa and phytozoa have no nucleus, its place being taken by particles of basichromatic matter which have been designated *chromidia*. Perhaps the so-called nuclei of the blood-platelets may come under this designation. See on chromidia, Dobell, Quart. Journ. Micr. Sc. liii. 1909.

[3] If, as seems probable, the blood-platelets or thrombocytes are to be considered as cells, the possible dimensions of a cell of the human body must be reduced to 2μ, or even 1μ. (The sign μ is employed to indicate the one-thousandth part of a millimeter, and is known as a *micron*.)

and nucleus is composed of an aggregate of microscopic particles, each of which is capable of multiplying and functioning independently. This independence has been ascribed to particles or granules which are often seen in protoplasm (' microsomes ' of Hanstein), and to accentuate this view they were termed by Altmann[1] ' bioplasts ' or ' elementary organisms.' Altmann attempted to establish the identity of his elementary organisms with the obvious granules which have long been recognised in cells, and which have frequently been regarded as merely adventitious in character or as products of cell-activity; not, as Altmann regards them, as the actual living material and the cause of activity. Altmann's view has not hitherto met with general acceptance by biologists, although it cannot be doubted that it is a very common character of the protoplasm of many cells to exhibit, even in the living condition, granules of protein substance, which may be so closely packed as to occupy the greater part of the cell (see pp. 22 to 24). Apart from visible ' granules,' there are strong grounds for believing that living substance is composed of ultramicroscopic particles,[2] each of which is probably constituted of a central more solid and a peripheral fluid portion. Such theoretical particles, which are themselves not molecules but groups of molecules, have been variously named micellæ (Nägeli), inotagmata (Engelmann), biophores (Weismann), biogens (Verworn)[3]; and they are assumed to fulfil all the functions of protoplasm (or rather of bioplasm), having specific characters in different cells, and being subject to metabolic processes, to growth and multiplication, and to rearrangement within the cell, so as to produce changes of form and structure of nucleus and protoplasm, and eventually cell-division. Those biophores, or groups of biophores, which constitute the nuclear chromatin of the germ-cells are assumed by Weismann to include representatives of all the specific biophores of the somatic cells, and they are regarded by him as being the transmitters of hereditary qualities; subject to variation and to increase or decrease in relation to one another according to the varying conditions to which they are exposed. The term *germinal selection* is used by Weismann to denote the result of such influences upon the biophore groups.[4]

THE PROTOPLASM OF THE CELL.

The living substance of cells, both plant and animal, is termed *bioplasm*. That part which constitutes the nucleus is known as *karyoplasm*; that which is present in the cell outside the nucleus is *protoplasm*; while a specialised portion, which is connected with the centrosome, is termed *archoplasm*. The whole substance of the cell apart from the nucleus is often alluded to as *cytoplasm*. Under this name other materials than those which constitute the living substance are included. The presence of such materials occurs, indeed, in certain cells to so great an extent that the protoplasm itself, of which the whole cell-substance in the embryonic cell was originally constituted, has become reduced to a relatively small proportion; indeed, even in cells of the same kind in different species of animals and plants, the size of the cell varies directly with the amount of non-protoplasmic material which has become accumulated within the cell. A notable example of this is met with in the ovum, which in some animals, including man, is minute and even microscopic; whereas in others, such as the bird, it attains a larger size than any other cell in the body. There may doubtless be an absolutely larger amount of protoplasm in the larger cell, but relatively to the non-protoplasmic material the actual protoplasm occurs in very much smaller amount (see vol. i. p. 9). Various names (*paraplasm, deuteroplasm*) have been proposed for the non-protoplasmic contents of cells, which may consist merely of watery fluid, as in the cell-sap of plants—or of any conceivable organic material, such as granules of starch, globules of oil, or crystals of protein matter or of hæmoglobin; but it is to be doubted whether anything is gained by including materials so diverse under a single designation.

Examined chemically, protoplasm can be resolved into (1) *water*, which constitutes from two-thirds to three-fourths of its weight; (2) *organic material* which exhibits the properties of proteins or protamines, combined usually, perhaps invariably, with a certain proportion of a phosphorus and iron containing substance known as nuclein, forming *nucleo-*

[1] Ludwig Festschrift, 1887; Die Elementarorganismen, Leipzig, 1890; 2nd edition, 1894.

[2] Not necessarily the particles which are rendered visible by the ultramicroscope. For an account of these, see W. Biedermann, Ergebn. d. Physiol. viii. 1909.

[3] Die Biogenhypothese, 1903. See also his Allgemeine Anatomie, 1908.

[4] Weismann, The Evolution Theory, transl. by A. and M. R. Thomson, 1904. See also T. H. Bryce, Embryology (vol. i. of this work), p. 20.

proteins;[1] and (3) *inorganic substances* (ions), certain of which are constantly found associated with the proteids of protoplasm and enter into loose combination with them, forming ion-proteins. Some of these appear to be essential to its functional activity. The most constant are the kat-ions, *calcium*, *potassium*, and *sodium*, and the an-ion, *chlorine* (J. Loeb[2]). Further, a supply of *oxygen*, either free or in some combination from which it can be dissociated by the living substance of the cell, is essential to the metabolic activity of protoplasm; and an invariable result of this activity is the production of *carbon dioxide*, which is never permitted to accumulate, but is speedily removed by extrusion into the surrounding medium. The interchange which thereby occurs in all living substance constitutes *respiration*.

The cell-proteins are 'colloid' substances in the sense in which this term was used by Graham,[3] and the electrolytes with which they are associated in the protoplasm are 'crystalloids.' It is upon the presence of the latter that the osmotic properties of cell-protoplasm, which are intimately connected with many of its functions, essentially depend. Enzymes (ferments) are present in all protoplasm, and are probably associated with its protein constituents or are elaborated from them by the living substance of the cell. Hence the occurrence of autolysis (auto-digestion) of cells and tissues kept under aseptic conditions.[4]

Besides proteins and nucleoproteins, certain non-proteid organic substances seem constantly to occur in small proportion as essential constituents of cell-protoplasm. The most important of these are the lipoids, such as *lecithin*, and the alcohol *cholesterin*. Lecithin is composed of *glycerophosphoric acid*, associated with fatty acid (*stearic*), and united with the ammonium base, *cholin*. Its physical properties are of a peculiar nature, since, whilst insoluble in water and watery solutions of electrolytes, it is capable of absorbing them and of permitting their passage through its substance. Thus it may play within the cell the part of a semi-permeable membrane, and whilst serving to confine the colloid constituents of the protoplasm, may permit the passage of and exchange between its crystalloid constituents and those of the surrounding medium.

In the red blood-corpuscles, or erythrocytes, it is capable of direct proof that the external film is partly of a lipoid nature, and it is probable, from the behaviour of animal cells to watery solutions of electrolytes, that a similar film is always present at the surface of protoplasm.[5] As for the main substance of the cell-protoplasm, it has been suggested (Hardy) that we may conceive this to be made up of infinitesimal particles of colloid material (protein) suspended in a watery solution of electrolytes, with which the colloid may enter into loose combination. The behaviour under various conditions of such a colloidal suspension and its relation to cell-activity have been studied of late years by many observers,[6] and especially in this country by Hardy.[7]

The main conclusions arrived at by Hardy may be summarised as follows:

1. The osmotic pressure of a mixture of colloid and crystalloid is not affected by the colloid particles, but solely by the electrolytes.

2. The colloid particles, which when finely divided and suspended in the interparticulate fluid have all the appearance of a solution, under certain conditions become fused into aggregations, and these may further become linked together either into a network (or spongework) with the fluid occupying the interstices, or into a honeycomb with the fluid occupying the cavities. When such fusion occurs the colloid substance becomes relatively solid, passing from apparent

[1] For the constitution of these substances, and the chemistry of cells generally, see A. Kossel, Arch. f. Physiol. 1891; Miescher, Arbeiten, 1897; O. Colnheim, Chemie der Eiweiss-körper, 1900; Abderhalden, Vorlesungen, 1909. M. Heidenhain, Plasma und Zelle, also deals with this subject. The discovery of nuclein is due to Miescher, who first obtained it from pus-cells (1871); it is contained in much larger amount in the nucleus than in the protoplasm (see also p. 38).

[2] American Journ. of Physiol. vol. i. and ii. 1900, 1902. On phosphorus in cells, see A. B. Macallum, Proc. Roy. Soc. lxiii. 1899; on potassium, Journ. Physiol. xxxii. 1905. For the literature of the subject the article by the same author on 'Microchemical methods and results' in Ergebn. der Physiol. 1908 may be consulted.

[3] Phil. Trans. 1861.

[4] On cell-ferments, see W. Jacoby, Ergebn. d. Physiol. 1902.

[5] Overton, Viertelj. d. Naturforschergesellsch. in Zürich, 1899; and in Nagel's Handb. der Physiol. ii. 1907. Rhumbler has shown that the external layer in amœba differs in its behaviour to alkalies from the internal part. See further on cell-lipoids, I. Bang, Ergebn. d. Physiol. 1907 and 1909; C. Ciaccio, Anat. Anz. xxxv. 1909.

[6] Picton and Linder, Journ. Chem. Soc. vol. lxvii. 1895, and vol. lxxi. 1897; Bütschli, Unters. ü. Struktur &c., 1898; A. Fischer, Bau des Protoplasmas, 1899; G. Mann, various papers, referred to in Physiological Histology, 1902; Rhumbler, Arch. f. Entwicklungsmechanik, xvi. 1903; Hamburger, Osm. Druck u. Ionenlehre, 1904. A concise account of the subject, with bibliography to date, will be found in two papers by H. Aron, 'Ueber organische Kolloide,' in Biochemisches Centralblatt, 1905, iii. pp. 461, 501, and iv. p. 505. See also Pauli, Ergebn. d. Physiol. 1906 and 1907; Botazzi, *ibid.* 1908; and Zangger, *ibid.* 1908.

[7] W. B. Hardy, Journ. Physiol. 1899, xxiv. 158, 288; Proc. Roy. Soc. 1900, lxvi. pp. 95–110; Proc Physiol. Soc. May 1903; Journ. Physiol. xxxiii. p. 251, 1905.

solution into the condition of a jelly: these are termed respectively the 'sol' and 'gel' phases of the colloid (Graham).

3. The conditions which produce a variation in the physical state (aggregation) of the colloid particles may be mechanical, thermal, chemical (addition of electrolytes) and electrical.

(a) *Mechanical.*—The mere shaking up of a colloidal solution may produce aggregation and coagulation. This is the case as shown by Ramsden [1] with the colloids of white of egg. The coagulation which occurs from contact with porous material such as animal charcoal, or by the addition to a colloid solution of a solid colloid of different chemical nature, may perhaps also be referred to a mechanical cause.

(b) *Thermal.*—A colloid substance which is fluid within a certain range of temperature may have its aggregation condition increased by either a depression or rise in temperature. Thus, a solution of gelatin is fluid at high temperatures owing to an increase in the kinetic energy and consequent disaggregation of its particles; on the other hand, it sets into a 'gel' on cooling: a solution of albumin is fluid in the cold and 'coagulates' (*i.e.* forms a 'gel') on heating, but probably this is accompanied by a change in the molecular constitution of the albumin; a solution of caseinogen coagulates when heated in the presence of calcium salts and redissolves on cooling.[2] When the conditions of temperature are reversed, some 'gels,' such as that formed by gelatin and that of caseinogen, become redissolved, others remain in the 'gel' condition: these are termed respectively by Hardy *reversible* and *irreversible*. Reversible 'gels' can be converted into irreversible by certain (fixative) reagents: thus, an ordinary gelatin jelly is so converted by fixation with formaldehyde. It then exhibits under the microscope a reticular aggregation of the colloid, and the effect of heating now is to cause a closer aggregation of the particles and a shrinking of the 'gel' with expression of interparticulate fluid. In some cases (fibrin) such shrinking may occur without artificially increasing the temperature, but even in these it is accelerated by heat. In certain solutions the gelation may occur abruptly on a particular temperature being reached, and the re-solution of the gel may also occur abruptly at a higher temperature (low and high 'critical points' of Hardy).

(c) *Chemical and Electrical.*—The particles of a colloid substance in apparent solution may be positively or negatively charged, according to the ionic combinations which they have formed. When electrolytes are added their effect depends upon the nature of the ions. Thus, an electrolyte carrying a charge of the opposite sign to that borne by the colloid particles causes them to become aggregated—*i.e.* causes jellying or coagulation. On the other hand, an electrolyte carrying a charge of the same sign as that borne by the colloid particles causes them to subdivide still further, and as a result an increase of liquefaction occurs. The passage of an electrical current produces similar effects. If the colloid particles are negatively charged they tend to undergo aggregation around the anode, disaggregation around the kathode. Hardy concluded that the behaviour of colloidal solutions to electrolytes and to the poles of a galvanic battery shows that the 'sol' phase is due to the fact of the particles carrying an electrical charge of the same sign and being thus mutually repelled and disaggregated, the 'gel' phase to the introduction of an electrical charge of the opposite sign, so that they become mutually attracted and aggregated.

Action of fixing reagents on colloids.—Hardy further finds, as had indeed been previously noticed, that many of the ordinary fixing agents, which act, it may be remarked, by causing gelation or coagulation of colloid, produce definite types of structure in the 'gel': either particulate aggregation or reticulation, or a honeycomb or froth-like structure—all similar to the types of structure which have been described, as will be seen later, in protoplasm itself. The usual result with such proteins as are present in egg-white was the formation of a reticulum or spongework; and this was obtained, although with a different-sized mesh, with reagents so various as osmium tetroxide (osmic acid), heat (momentarily applied), potassium bichromate, and corrosive sublimate. On the other hand, the thin edge of a film of albumen solution sometimes showed complete homogeneity after fixation, although the thicker parts of the film exhibited a reticulated structure.

Some of Hardy's experiments upon coagulation and fixation have been repeated by G. Mann,[3] who has pointed out that whereas most of the ordinary fixative solutions employed in histology contain electrolytes and produce coagulation of colloids by the action of their ions, there are two very important reagents acting pre-eminently as fixatives, viz. osmium tetroxide and formaldehyde, which are non-electrolytes. According to Mann, these substances, when used in a *pure* form, do not tend to produce an artificial structure in colloid solutions, but coagulate them with the formation of a transparent homogeneous mass.

[1] Arch. f. Physiol. 1894, p. 517.
[2] S. Ringer, Journ. Physiol. xi. 1890; and xii. 1891.
[3] Methods and Theory of Physiological Histology, 1902.

Effects of strain and stress in colloid solutions.—It has been observed by Bütschli,[1] Hardy,[2] and others, that if during the process of coagulation by fixatives a film of colloid solution is subjected to strain in definite directions, the effect shows itself along definite paths (lines of

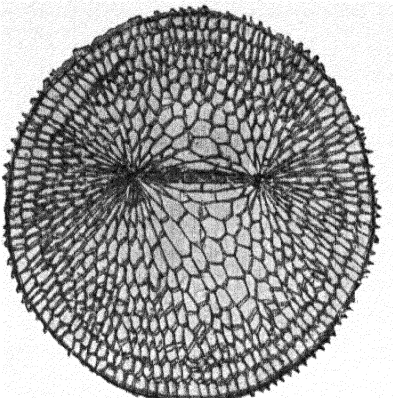


FIG 10.—LINES OF STRESS IN A NETWORK OF INDIARUBBER THREADS DRAWN TOGETHER AT TWO POINTS, SHOWING THE FORMATION OF A SPINDLE BETWEEN THE POINTS OF TRACTION. (Verworn, after Rhumbler.)

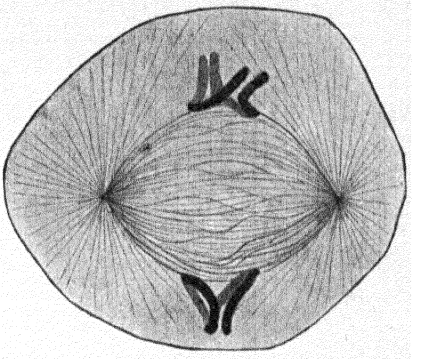


FIG. 11.—LINES OF STRESS IN A CELL IN PROCESS OF DIVISION: SPERMATOCYTE OF SALAMANDER. (Meves.)

stress) within the film, and the structure of the resulting coagulum shows the threads of the network arranged with reference to the point or points from which the strain proceeded. This observation is highly instructive with reference to the 'stress' appearances which are observable

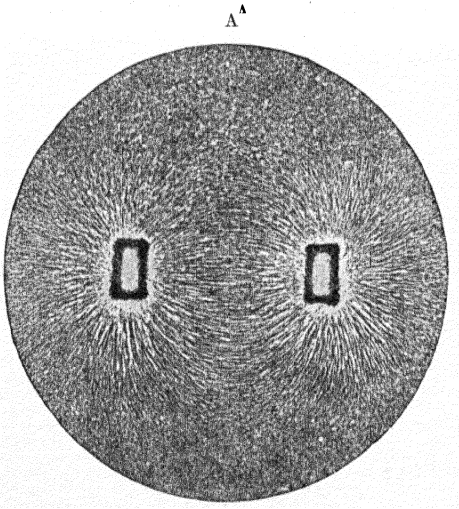


FIG. 12A.—LINES OF STRESS IN A MAGNETIC FIELD. (Verworn, after Rhumbler.)

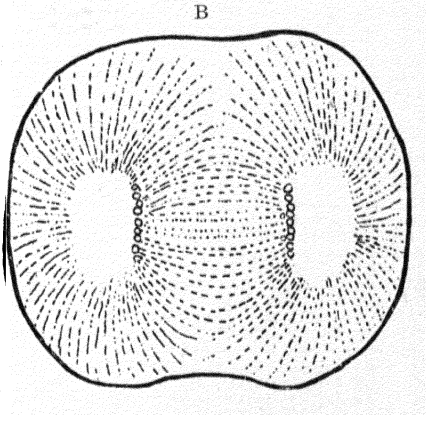


FIG. 12B.—LINES OF STRESS IN LIVING DIVIDING OVUM OF TOXOPNEUSTES. (Verworn, after E. B. Wilson.)

in cells in process of nuclear division, and in ova during fertilisation; which are singularly like those assumed by iron particles within a magnetic field[3] (compare figs. 10, 11, and 12). The appearance of a condition of strain or stress in previously homogeneous colloidal

[1] Unters. ü. Struktur &c., Leipzig, 1898. [2] *Op. cit.*

[3] See on this subject, Bütschli, Heidelberg Verhandl. v. 1892; M. Heidenhain, Arch. f. Entwicklungsmechanik, i. 1895; Rhumbler, Ergebnisse der Anatomie, Bd. viii. 1899; also various papers in Arch. f. Entwicklungsmechanik, 1896 to 1903; M. M. Hartog, Proc. Roy. Soc. B. lxxxvi. 1905; and R. S. Lillie, Amer. Journ. Physiol. vol. xv. 1905.

material is accompanied by the assumption of the property of double refraction, due to the linear arrangement of the molecules of the colloid.

Thus much being premised regarding the effects produced by reagents upon colloidal solutions, such as unquestionably exist in cell-protoplasm, we are in a better position to form a judgment respecting the structural appearances which have been described as characteristic of this substance.

THE STRUCTURE OF CELL-PROTOPLASM.

It is obvious from what has been stated regarding the action of fixative reagents upon colloid solutions, that it would be improper to infer the pre-existence of

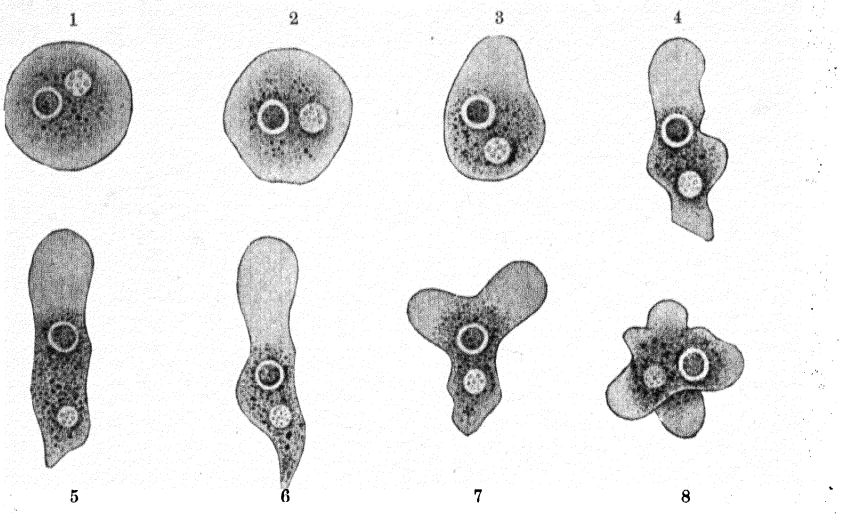


FIG. 13.—SUCCESSIVE CHANGES EXHIBITED BY AN AMŒBA. (Verworn.)

The protoplasm appears completely structureless, although containing granules near the nucleus and a contractile vacuole.

structure in protoplasm unless such structure can be shown to be present under the normal conditions of the living organism. An organism which has always been regarded as typically protoplasmic is the unicellular and uninuclear animalcule

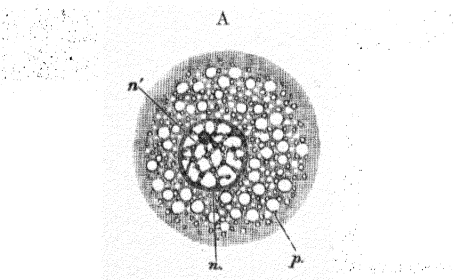


FIG. 14A. — DIAGRAM OF A CELL, THE PROTOPLASM OF WHICH IS STRUCTURELESS, ALTHOUGH OCCUPIED BY VACUOLES AND GRANULES.

p, protoplasm; *n*, nucleus; *n'*, nucleolus.

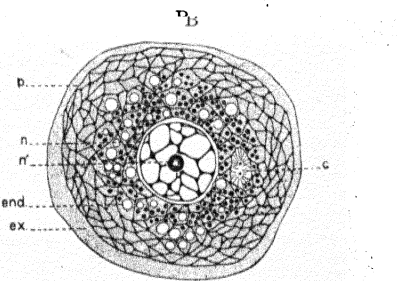


FIG. 14B.—DIAGRAM OF A CELL, THE PROTOPLASM OF WHICH IS RETICULATED.

p, protoplasm, consisting of hyaloplasm and a network of spongioplasm; *ex*, clear external layer of cytoplasm; *end*, central part of cytoplasm, with distinct granules and vacuoles; *c*, double centrosome; *n*, nucleus; *n'*, nucleolus.

known as Amœba limax. This can be easily examined in the living condition. It is capable of performing all necessary functions of the animal organism, including

multiplication by division; change of shape and place (locomotion); intake, digestion, and assimilation of food; excretion, and a localised intermittent contractility which serves to disseminate accumulated fluid material through the cell-substance, and perhaps to eject it from the organism. Nevertheless, even under the highest powers of the microscope, and with the aid of the most modern methods of investigation, its protoplasm shows no appearance of structure (fig. 13).[1] It must therefore be admitted that visible structure is not essential to living cell-protoplasm, and it may accordingly be represented diagrammatically as a homogeneous material (fig. 14A).[2]

A distinction between a granular and sometimes vacuolated part of the protoplasm in which the nucleus is embedded, and which may occupy a considerable part of the cytoplasm, and a clear external part or layer, is sometimes very

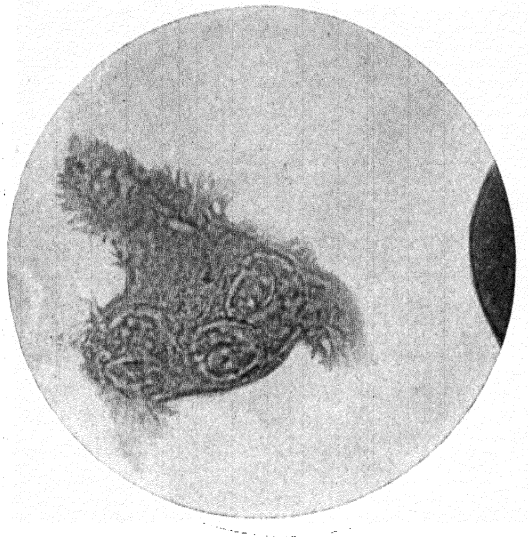


FIG. 15.—UNTOUCHED PHOTOGRAPH OF LIVING LEUCOCYTE OF TRITON, SHOWING RETICULAR STRUCTURE OF THE PROTOPLASM. (Schäfer.) Magnified 1360 diameters.

The photograph was taken in monochromatic light with Zeiss' 2 mm. apochromatic objective and projective eyepiece. The polymorph nucleus also exhibits a reticular structure.

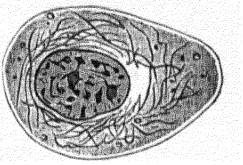


FIG. 16.—A CARTILAGE CELL IN THE LIVING STATE, FROM THE SALAMANDER. Highly magnified. (Flemming.)

FIG. 17.—COLUMNAR EPITHELIUM-CELLS SHOWING LINES OF GRANULES. (Altmann.)

apparent in unicellular organisms like the amœba (fig. 13). The terms *endoplasm* and *ectoplasm* have been employed to indicate this difference of appearance; although it is not certain that there is always a difference of actual structure in the two parts. But in many cells a differentiation indicative of a reticulated structure (fig. 14B) can be seen even in the living unaltered protoplasm (fig. 15).

Fibrils within cell-protoplasm.—In many cells—indeed, in most cells of the higher animals—structures which can be seen only with difficulty, or not at all, in the living condition of the cell appear distinctly after the cell has been fixed by reagents. The structure is generally in the form of a network of threads or as separate filaments (fibrils) of extreme tenuity (fig. 16), or their place may be taken by lines of granules (fig. 17). These appearances when present in the living cell are

[1] In the ectoplasm of Amœba terricola, Greeff has described a radiate fibrillar structure (Marburg Verhandlungen, 1890) similar to that described by Strasburger in the ectosarc of the myxomycete Œthalium septicum (Studien in Protoplasma, 1876).

[2] Cf. Lukjanow, Grundzüge einer allgem. Path. d. Zelle, 1891.

still more distinct after the protoplasm has been fixed by reagents (fig. 18). They undoubtedly indicate a differentiation of structure, for they are most frequent in specialised cells, such as those of columnar epithelium (fig. 19), cells of secreting glands (fig. 20), and cells of ciliated epithelium (fig. 21), in all of which fibrils traverse the cell-protoplasm and are permanent features of its structure. A still more complete fibrillar differentiation is found in the highly specialised cells which form the nervous and muscular tissues (figs. 22, 23, and 24), in which many of the features of ordinary cell-protoplasm have become completely masked, along with assumption of the peculiar modifications of its functions which has taken place. All these are to be regarded as instances of fixed differentiation of a fibrillar character; but in many cells—especially those in process

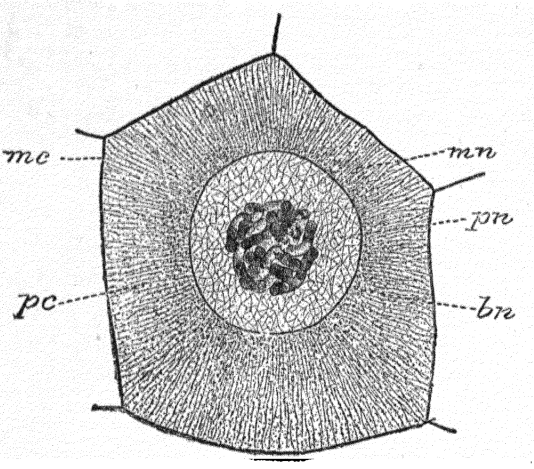


FIG. 18.—CELL WITH RADIALLY DISPOSED FIBRILS FROM THE INTESTINAL EPITHELIUM OF A WORM. (Carnoy.)

mc, membrane of the cell; *pc*, protoplasm of the cell; *mn*, membrane of the nucleus; *pn*, achromatic substance of the nucleus coagulated in the form of a network, with convoluted chromatin filaments, *bn*, contracted into the centre.

FIG. 19.—A COLUMNAR EPITHELIUM-CELL, SHOWING MASS OF FIBRILS (CYTOMITOME) WITHIN THE CYTOPLASM. (M. Heidenhain.)

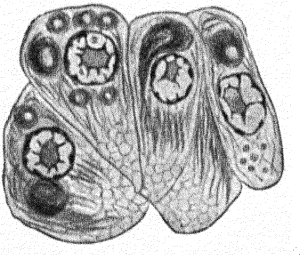


FIG. 20.—PANCREAS CELLS OF FROG, SHOWING PARANUCLEUS AND CHONDROMITOME FIBRILS FORMED FROM MITOCHONDRIA. (Gurwitsch, after Matthews.)

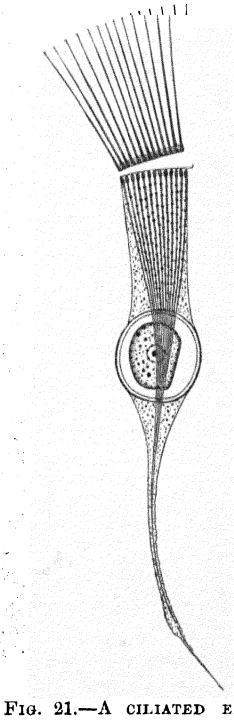


FIG. 21.—A CILIATED EPITHELIUM-CELL OF A MOLLUSC. (Engelmann.)

of division—a linear or fibrillar arrangement of the protoplasm appears which is temporary only, and which disappears again after the phase of activity which accompanies it has ceased to be exhibited (fig. 11). Yet other cells—and these are indeed so numerous in the Metazoa that the structure has been supposed by some to be constant in animal cells—exhibit an appearance within their protoplasm of lines radiating from (or converging towards) a specially differentiated particle known as the centriole (fig. 25). These lines may be

regarded as due to a fibrillation of the protoplasm, which, being present and visible in the fresh and unaltered cell, is a true structural (and functional)

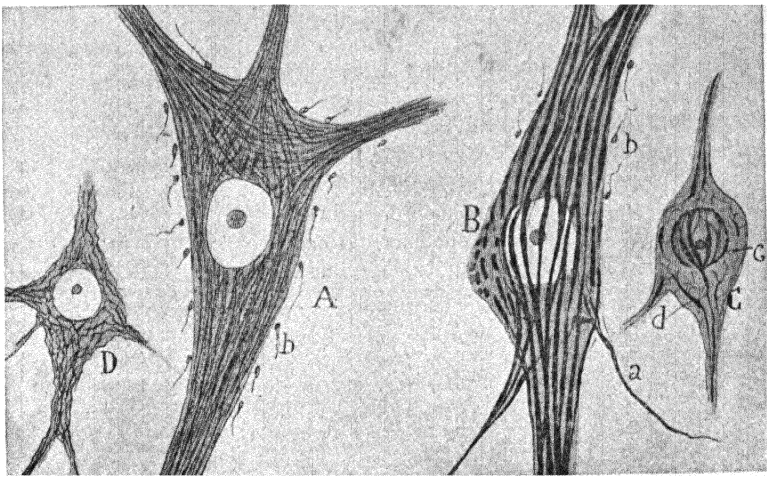


FIG. 22.—FIBRILS WITHIN NERVE-CELLS. (Cajal and Tello.)

differentiation, although it is possible that the lines do not represent fixed structures, but alterations in the protoplasm which come and go.

FIG. 23.—PORTION OF A PLAIN MUSCLE-CELL, SHOWING FIBRILS WITHIN ITS CYTOPLASM. (Schäfer.) Magnified 450 diameters. Untouched photograph.

We see from these instances that every phase of fibrillation may present itself within cell-protoplasm—from the transitory lineations which occur during the division of an otherwise undifferentiated cell to the distinct fixed fibrillations which are met with in the protoplasm of highly specialised cells. These differen-

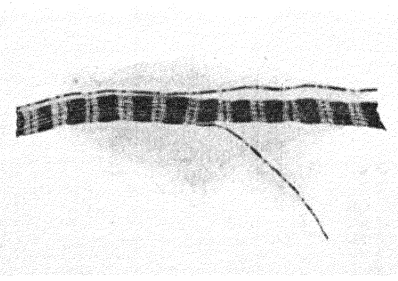


FIG. 24.—SMALL PORTION OF A MUSCLE-FIBRE OF CRAB SPLITTING UP INTO FIBRILS. (Schäfer.) From a photograph. Magnified 600 diameters.

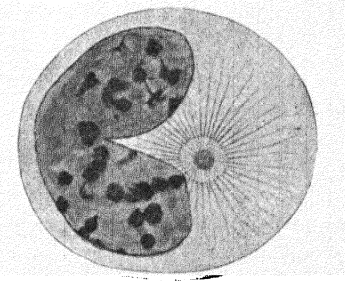


FIG. 25.—LEUCOCYTE OF LEPIDOSIREN, SHOWING LINES IN PROTOPLASM RADIATING FROM CENTRIOLE. (T. H. Bryce.)

tiations can in no sense be regarded as artifacts, even if they can be imitated by subjecting colloid material to stress or strain during the process of fixation and consequent gelation; for they can be made out quite distinctly in the

living unaltered cells, although to study all the details of such structure it may be necessary to fix and stain the cells which exhibit it.

Although the linear differentiations which have been mentioned, and which take the form of a fibrillation of the cell-protoplasm (*cytomytome*), are generally admitted to be pre-formed structures, the pre-existence of the spongy or honeycomb differentiation which is manifest in cells which have been subjected to the action of fixative reagents has been called in question. Since this differentiation is seen in cells which have been fixed and their protoplasm coagulated by a great variety of reagents, such as chromic acid, picric acid, corrosive sublimate, formalde-

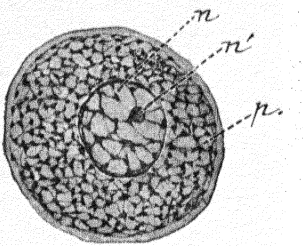


FIG 26.—DIAGRAM OF CELL, SHOWING PROTOPLASM CONSISTING OF SPONGIOPLASMIC RETICULUM WITH HYALOPLASM IN ITS MESHES; THE HYALOPLASM IS ACCUMULATED AT THE PERIPHERY. (Schäfer.)

p, protoplasm; *n*, nucleus; *n'*, nucleolus.

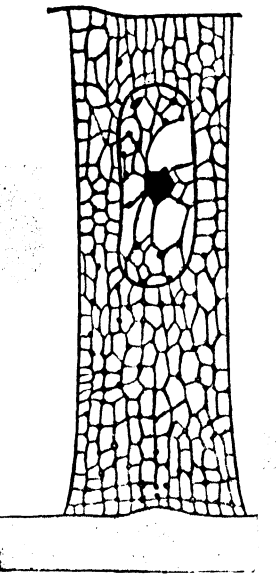


FIG. 27.—DIAGRAM OF RETICULAR APPEARANCE OF PROTOPLASM AND NUCLEUS OF A COLUMNAR CELL. (Verworn, after Bütschli.)

hyde, osmic acid, heat, and alcohol, a *reticular structure* was described as a general feature of protoplasmic structure by Frommann, whose researches were extended by Heitzmann, Klein, Carnoy, and many others. Leydig[1] pointed out that the apparent reticulum was rather of the nature of a sponge-work than a network (fig. 26), and proposed for it the name of *spongioplasm*, the clear substance (?fluid) occupying its interstices, which Carnoy had termed the *enchylema*, being designated by Leydig *hyaloplasm*: these designations have since become widely adopted.[2] Bütschli,[3] on the other hand, took the view that the appearance of a network or spongework with intercom-

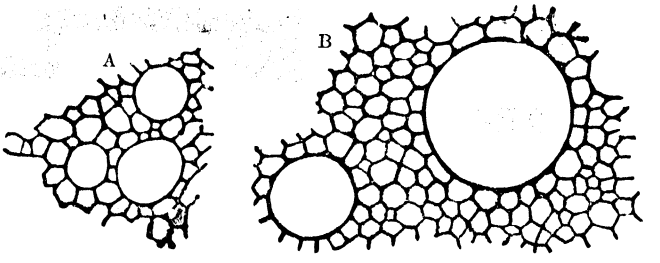


FIG. 28.—COMPARISON OF PROTOPLASM WITH OIL AND WATER EMULSION.

A. Protoplasm of Thalassicola.
B. Froth-like appearance of a mixture of oil and cane sugar. (Verworn, after Bütschli.)

[1] Zelle u. Gewebe, 1885. See also on this subject, Schäfer, Proc. Roy. Soc. xlix. 1891.

[2] Some recent writers (following Bütschli) have introduced confusion into this terminology by employing the word hyaloplasm in the sense of Leydig's spongioplasm (using the word enchylema for the hyaloplasm of Leydig). But in this work the expressions spongioplasm and hyaloplasm will be used in the sense in which they were originally employed by Leydig.

[3] Biol. Centralbl. 1890; also Mikroscopische Schäume, Leipzig, 1892; transl. by Minchin, 1894. On the supposed foam-structure of protoplasm, see Frommann, Anat. Anz. v. 1890.

municating interstices (fig. 27) is illusory, and that the actual structure of all protoplasm is that of a honeycomb, the partitions of which are formed of more solid matter than the contents of its cavities, and give in optical section the appearance of a net or sponge (fig. 28). This view is expressed by the terms *foam-* or *honeycomb-structure of protoplasm*, and has found acceptance by many cytologists.[1] But both a spongy and a honeycomb appearance may well occur in different samples of protoplasm, for in the jellying of colloidal solutions either one or the other may show itself, according to the concentration of the solution (Hardy) (see p. 11).

It is, however, clear, as already mentioned, that the results of Hardy and others regarding the action of fixative agents upon colloid solutions should render one careful in drawing conclusions from the action of the same fixatives upon protoplasm, and in every case it behoves us if possible to ascertain (1) the existence of the structure in question in the living protoplasm before it has been subjected to the action of a fixative; (2) whether, if the apparent structure is pre-existent, it is modified by the fixative; (3) whether different strengths of the same fixative, or different kinds of fixative, give rise to an apparent structure, which is identically the same under all conditions.

If (1) can be proved for any particular sample of cell-protoplasm, it follows that, at least in that kind of cell, there does exist a preformed differentiation which takes the form of a network or spongework or honeycomb of more refractive (and probably therefore less fluid) material enclosing a more fluid substance in its meshes; and similarly, if (3) be answered affirmatively, it is extremely probable that (1) is also true, and that the network seen after the action of the reagent is the accentuation under the influence of the fixative of a pre-existent

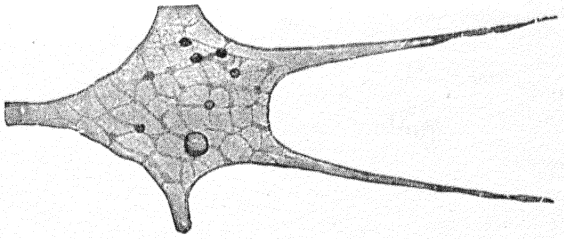


FIG. 29.—RETICULAR PROTOPLASMIC STRUCTURE IN A PSEUDOPODIUM OF A FORAMINIFER (MILIOLA). (Verworn, after Bütschli.)

network. Now, although from what has already been said as to the absence of all appearance of structure in the living protoplasm of Amœba limax it cannot be affirmed in the present state of knowledge that all protoplasm is differentiated into spongioplasmic and hyaloplasmic parts, neither can it be denied that the protoplasm of very many cells gives an affirmative answer to (3), and of others to (1) also (see figs. 15 and 29). From which it must be concluded that an apparent network *is* a common differentiation in cell-protoplasm, although such appearance of structure is not essential to the idea of protoplasm. And this is indeed what might be expected from Hardy's observations on colloid solutions, which very readily, on change in their physical or chemical surroundings (heat, galvanic currents, electrolytes), tend partially to pass out of solution in the form of an aggregation of particles, which most generally takes on the appearance of a network or spongework with more fluid interstices, but sometimes of a honeycomb with fluid droplets enclosed by more solid material. If cell-protoplasm is essentially a colloid solution, this may also, as a result of chemical and physical changes taking place *in vivo* within the cell, undergo a transformation similar to that which occurs in a colloid solution *in vitro*; and thus a structural differentiation would be produced which may either become permanent, or may go and come with changing conditions within the cells, as is the case with Hardy's irreversible and reversible 'gels.' In point of fact,

[1] *E.g.* E. B. Wilson, The Cell in Development and Inheritance, 1896; 2nd edition, 1904, and O. Hertwig, Allgemeine Biologie

the observations of Hardy, which have thrown much light upon the constitution and properties of colloidal solutions, and which have been looked upon—if not by Hardy himself, at any rate by other writers on protoplasmic structure—as indicating that the structural differentiation of the protoplasm of many cells into spongioplasm and hyaloplasm is an artifact, really cast considerable probability upon the existence of such differentiation, since they show how easily this structure can be produced in a colloidal solution (such as occurs in cell-protoplasm) by changes which may take place even during the life of the cell.

The proof that such changes do actually occur *in vivo* was furnished by Greely,[1] who showed that the protoplasm of Protozoa (Paramœcium, Stentor, Amœba) exhibits structural changes during life in response to variations in temperature and in chemical changes of the circumjacent fluid, as well as to the electrical current, which are strictly comparable to the changes described by Hardy in colloidal solutions; being coagulated (often in a reticular manner) by certain agencies, liquefied by others—and these changes are intimately associated with such vital manifestations of the organism as amœboid and ciliary movement. It has further been suggested [2] that the appearance of radiating structure which characterises the 'astrosphere' formed within the fertilised ovum as the result of the introduction of the spermatozoon (middle piece with centrosome) is due to a localised coagulation; for a similar appearance can be produced by various agencies of a chemical and mechanical nature, which act in this way upon colloid solutions. Similar localised coagula have also been shown to accompany (or precede) artificial parthenogenesis in Echinoderm ova (see p. 32). The conclusion to be drawn is, therefore, that protoplasm is essentially a colloidal solution (suspension) whose particles become aggregated or disaggregated by various agencies, electrical, chemical, or mechanical; and that such aggregation may determine both structural and functional modifications within the cytoplasm.

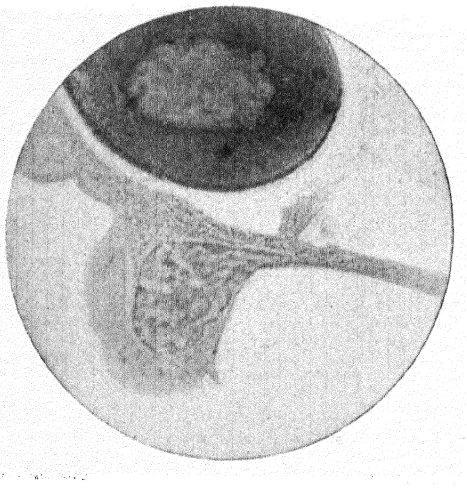


FIG. 30.—LACE-LIKE APPEARANCE OF LIVING PROTOPLASM OF A LEUCOCYTE OF SALAMANDER. (Schäfer.) Magnified 1,200 diameters. Untouched photograph.

The lacelike protoplasm is partly spread over an erythrocyte.

It has been stated (p. 15) that in the case of certain animal-cells it can be shown, without the action of any reagents, that a reticular (spongy) structure is present during life. In gland-cells, where a reticular appearance of the living cell has been remarked by many observers, the appearance may be produced by the fact that the protoplasm is filled with secretion-granules, and the protoplasm left between these necessarily has a reticular appearance in optical section. In other fixed cells with a single definite function one might expect to find that the protoplasm has undergone more or less differentiation. But such differentiation is not confined to the protoplasm of fixed cells; it shows itself also in free cells, such as Rhizopoda (fig. 29) and leucocytes (fig. 15). In many of the latter, when spread out by their amœboid activity over the cover-glass of a microscopic preparation, it is possible to detect, in spite of its high degree of translucency, a distinct spongy or reticular appearance in the protoplasm, and in thin films under a high magnifying power the effect of fine lace is produced (fig. 30).

The proof of the pre-existence of a colloidal reticulum in many cells—which is derived from the fact that a large number of different fixations produce a similar reticular appearance within the cell—is more easy of demonstration than the

[1] Biol. Bull. 1904, vol. vii. No. 1.
[2] M. H. Fischer and W. Ostwald, Pflüger's Arch. Bd. cvi. p. 229, 1905.

direct observation of a reticulum within the living cell, and it has been upon it that the doctrine of a spongy or reticular structure—*i.e.* of the differentiation of the protoplasm into spongioplasm and hyaloplasm, has been mainly based. The extreme constancy of the appearance in the same kind of cell with diverse fixatives, and also with the same fixative but in different strengths of solutions—conditions which would produce reticular structures of diverse character in a mere colloidal solution—affords strong evidence of the pre-existence of such reticula. Naturally, it does not follow that the reticula seen are fixed in the sense of being permanent. It is possible that they are constantly changing—liquefying and re-forming—in this or that part of the protoplasm. But they represent a structure which is present at the time in one part or another of the protoplasm, or even throughout the whole cell, and in this sense they constitute a structural and functional differentiation which in many cells becomes fixed permanently during life. Such structure cannot, it is true, be regarded as essential to all protoplasm, so long as in any cells (*e.g.* some Protozoa) no such differentiation can be detected. But, as we have seen, in these also an ill-defined reticular structure makes its appearance under certain conditions, even during life (Greely). And the fact that this is in all probability due to the segregation of particles from a colloidal solution seems to indicate the manner in which a similar but more permanent structure of the protoplasm of other cells may have been brought about.

FIG. 31.—UNTOUCHED PHOTOGRAPH OF LEUCOCYTE OF TRITON, FIXED WHILST IN AMŒBOID CONDITION BY A JET OF STEAM DIRECTED ON COVER-GLASS; STAINED WITH HÆMATOXYLIN. (Schäfer.) Magnified 1,360 diameters.

The internal part of the protoplasm shows an indistinctly reticular structure (spongioplasm), but the external layer and the pseudopodia are completely clear.

The fact that protoplasm, like other colloidal solutions, may at one time and at one place exhibit a reticular or honeycomb structure, which at other times and in other places is lacking, renders nugatory the discussion as to whether the reticulum (spongioplasm) or the enchylema (hyaloplasm) is the contractile part of the cytoplasm. All protoplasmic movements are of a 'flowing' nature, and imply fluidity of the moving part, which may be the whole protoplasm. If a less fluid part (spongioplasm) has become separated out from the rest, the flowing would be primarily a movement of the hyaloplasm, which, *ex hypothesi*, is the part of the protoplasm remaining fluid after the separation out of the less fluid spongioplasm. In amœboid cells this less fluid part may also be carried along with the flow, although in some cases the pseudopodia may at first be formed wholly of the more fluid substance (fig. 31).[1] The flowing itself, there is every reason to believe, is consequent upon alterations in the tension of a solid film at the surface of the cytoplasm, and in some cases also at internal surfaces within its substance (see p. 76).

It must be accepted as an axiom that 'every free cell is surrounded by a solid film. The pseudopodia of many infusorians could not exist were they entirely liquid'; they would fall apart into droplets. 'As the interior of the pseudopodia shows the phenomena of streaming, the solid part of the pseudopodia can only be at their surface.'[2] It is highly probable that this film is of a lipoid nature (see p. 11).

[1] Schäfer, Proc. Roy. Soc. vol. xlix. 1891.

[2] J. Loeb, The Dynamics of Living Matter, p. 38. Ramsden has shown that solid or extremely viscous filmy matter forms at the surface of protein solutions, even if evaporation be prevented (Zeitschr. f. physik. Chemie, xlvii. 1904). Traube long ago also showed that when certain liquid colloids, or a colloid and a crystalloid, come in contact a solid film may be formed at the contact surface (Arch. f. Anat. u. Physiol. 1867).

The granules of cell-protoplasm.—Attention has already been drawn to the fact that granules or globules (apparently composed of protein) are frequent, and in most cells constant, constituents of the protoplasm of cells. This has been long recognised in the cells of secreting glands (figs. 32, 33), where their presence was demonstrated by Langley,[1] who showed that they are here closely related to the elaboration of the secretion, and especially of the enzymes and organic materials which are produced by the gland. Granules occur, however, in cells such as leucocytes and developing ova[2] (fig. 34), which, so far as is known, are not concerned in the preparation of secretion, although, in view of recent researches which point to the fact that the occurrence of enzymes of some kind is well-nigh universal in all cells, it is less easy to draw a distinction between secretory and other cells than seemed previously possible. And while in some cells special methods of fixing and staining are required to show the granules,[3] in others they are visible in the fresh condition or may be stained and observed *intra vitam*[4] (fig. 35). The

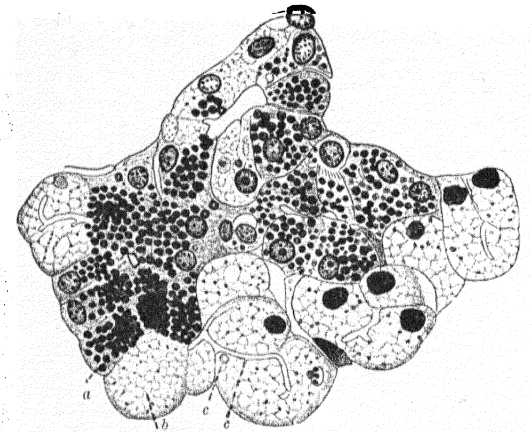


FIG. 32.—SUBMAXILLARY GLAND OF RABBIT. (E. Müller.)

The cells are in different functional states, as indicated by the condition and staining of the granules. *a*, cell filled with darkly staining granules; *b*, clear cell, the granules being swollen and having a reticulum of protoplasm between them; *c*, secretory canaliculi penetrating into the cells.

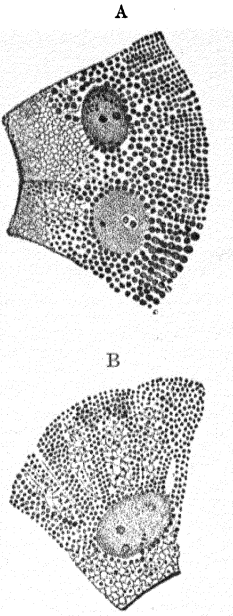


FIG. 33. — GRANULES WITHIN CELLS FROM DUCT OF PAROTID.

A, prior to secretion; B, after secretion. (Mislawski and Smirnow.)

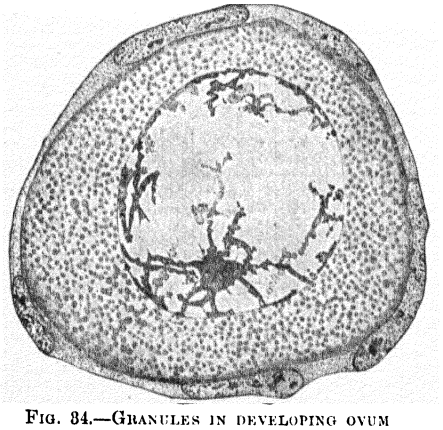


FIG. 34.—GRANULES IN DEVELOPING OVUM OF RABBIT. (Winiwarter.)

[1] Proc. Roy. Soc. xxix. 1879, xl. 1886; Journ. Physiol. ii. 1879–80, x. 1889.

[2] Schäfer, Proc. Roy. Soc. xxx. 1880; Fleming, Zellsubstanz &c., 1882, pp. 30–34.

[3] Such as Altmann's method, Die Elementarorganismen, 1890. See also L. and R. Zoja, Mem. d. r. istit. lombard. 1891; R. Metzner, Arch. f. Physiol. 1894; J. Arnold, Arch. f. mikr. Anat. lii. 1898; Schridde, Anat. Hefte, xxviii. 1905; Loewenthal, Journ. de l'Anat. 1906.

[4] O. Schultze, Anat. Anz. ii. 1887; Kuhn, Arch. f. Anat. 1890; A. Fischel, Anat. Hefte, xvi. 1901; J. Arnold, Arch. mikr. Anat. lv. 1900, and Anat. Anz. xxiv. 1903 and xxxi. 1907; Růžička, Zeitschr. f. allg. Physiol. iv. 1904; E. E. Goldmann, Beitr. z. klin. Chirurg. lxiv. 1909.

granules are not all of the same character, either in different cells or within the protoplasm of the same cell. The readiest way to exhibit them is by the employment of differential methods of staining: some—presumably of an acid nature—becoming stained more readily by basic colouring substances; others—presumably of a basic nature—by acid colouring substances; others by both basic and acid dyes; and others, again, most effectively by neutral dyes.[1] This has led to the use of the terms basi- or baso-phil, oxyphil (or eosinophil), amphophil, and

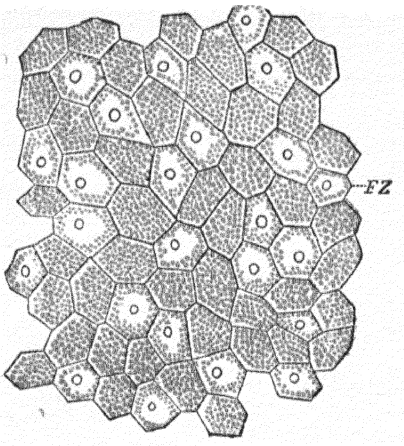


FIG. 35. —EPITHELIUM-CELLS OF SALAMANDER LARVA, STAINED *intra vitam* WITH NEUTRAL RED, SHOWING THE CELL-GRANULES. (Fischel.) Magnified 300 diameters.

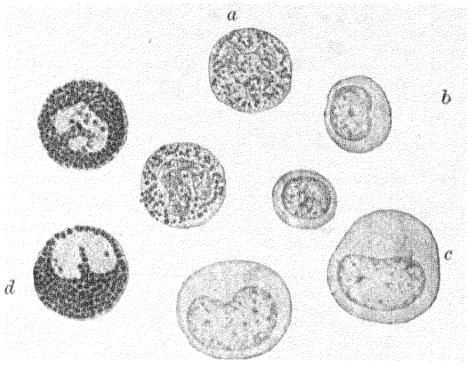


FIG. 36.—VARIOUS KINDS OF COLOURLESS CORPUSCLES, SHOWING DIFFERENT CHARACTERS OF THE GRANULES. (From a film preparation of normal human blood.) Two of each kind are represented.

neutrophil, to describe these several kinds of granules—terms originally introduced by Ehrlich[2] to designate the granules of the white blood-corpuscles (fig. 36). In size, also, there is much variation, some granules being so small as to be almost ultramicroscopic, and others large enough to be easily seen with a moderately high power of the microscope. In shape they are generally globular, although in some secreting cells crescentic granules occur; in the leucocytes of the cat they are cylindroidal. There is strong reason to believe that the granules sometimes represent material which is in process of gradual elaboration; for the granules in cells of the same kind at different times, or even in the same individual cell in different parts of its substance, exhibit gradations in size and chemical constitution, indicative of growth and chemical changes in the granules. A striking illustration of this is seen in the production of fat within cells, both in the cells which form adipose tissue, and in those of the intestinal epithelium during fat absorption (fig. 37). In both cases, according to Altmann and his fellow-workers, the cell-protoplasm shows at first fine granules which appear from their reactions to be of protein nature. These become gradually transformed into, or at any rate replaced by, granules which begin to give the reactions of fat (fig. 38); by a constant increase in number these ultimately fill the greater part of the protoplasm, and eventually run together to form large and distinct globules of fat.[3] In mucus-secreting cells

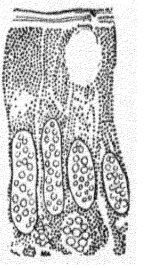


FIG. 37. — GRANULES IN INTESTINAL EPITHELIUM OF FROG. (Altmann.)

[1] On the differential staining of the granules in cells and nuclei, see G. Schlater, Arch. f. mikr. Anat. xliv. 1895.
[2] Farbenanalyt. Unters. z. Histol. u. Klin. d. Blutes, 1891
[3] Krehl, Arch. f. Anat. 1890; R. Metzner, *ibid*

the various steps of transformation of the protein granules into mucin granules can be still more readily followed.[1] Other secreting cells offer a similar illustration.

The granules of cells are not confined to the protoplasm; others may, by appropriate fixation and staining, be demonstrated also in the nucleus. In the protoplasm the granules probably lie in the hyaloplasm; the corresponding part of the karyoplasm can also be shown to contain granules (see p. 35 and fig. 68, B). The cell-granules are sometimes uniformly diffused through its substance, sometimes more accumulated at one part than at another. There is evidence to show that the granules of protoplasm are formed under the influence of the nucleus, and that the substance of which they are composed may even be extruded from the nucleus. This matter will be again alluded to when the functions of the nucleus and nucleolus are discussed.

The granules have received various names,[2] that by which they are most usually designated being *microsomes*, distinguishable into *cyto-* and *karyo-microsomes*. Certain of these granules appear to be specialised in connection with the formation of contractile fibrils and other active portions of the cell-protoplasm; these can be stained distinctively, and from their tendency to produce fibrillæ have been named *mitochondria* (fig. 39).[3] Sometimes the fibrils which they form are collected into a spherical mass, usually near the nucleus, and apparently bearing some relation to its metabolic activity. The names *paranucleus* (p. 16 and fig. 20) and *chondromitome* have been applied to this structure.[4]

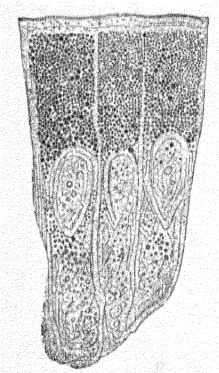


FIG. 38.—GRANULES IN FAT-ABSORBING CELLS OF FROG'S INTESTINE BEGINNING TO BE TRANSFORMED INTO FAT-PARTICLES. (Krehl.)

The fat droplets are stained black with osmic acid.

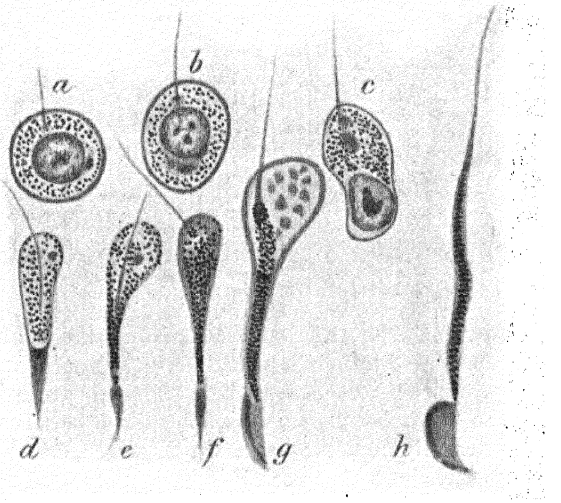


FIG. 39.—CELLS FROM THE TESTICLE OF THE MOUSE IN PROCESS OF TRANSFORMATION INTO SPERMATOZOA. (Benda.)

The 'mitochondria' are darkly stained and are seen in the successive stages (*a* to *g*) to be arranging themselves so as to constitute the spiral filament of the spermatozoon (*h*).

[1] Schäfer, Quain's Anatomy, 10th edit. 1891.

[2] Bioblasts (Altmann), plasomes (Wiesner), plasmasomes (Arnold), microsomes (Hanstein), protomeres (M. Heidenhain); these names are not, however, all strictly synonymous. Until more is known regarding the particles in question, it is questionable whether anything is gained by the employment of another term than 'granule.'

[3] From *μίτος*, thread, and *χόνδρος*, grain. Benda, Ergebn. d. Anat. xii. 1902; F. Meves, Anat. Anz. xxxi. 1907, xxxiv. 1909, and Arch. f. mikr. Anat. lxxii. 1908. Meves designates these specialised granules *chondrosomes* or *chondroconta*. He describes their occurrence in embryonic cells, and considers that they may share with the chromosomes of the nucleus the functions of hereditary transmission. See also J. Duesberg, Arch. f. mikr. Anat. lxxi. 1908, and Anat. Anz. xxxiv. 1909 (Verhandl. d. Anat. Ges.) and xxxv. 1910.

[4] The relations of the chondromitome to the metabolic activity of the nucleus have been studied in the pancreas cell by Mathews (J urn. Morph. xv. 1899, Suppl.).

Canaliculi in cell-protoplasm.—Many cells show a network of fine anastomosing canaliculi within their protoplasm (figs. 40 to 42). These were first described in certain nerve-cells,[1] later in gland-cells,[2] in columnar epithelium-cells,[3]

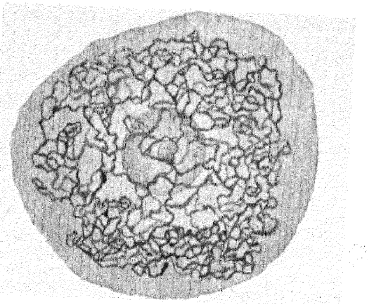


FIG. 40.—DEEP NETWORK OF CANALICULI WITHIN PROTOPLASM OF SPINAL GANGLION-CELL. (Golgi.)

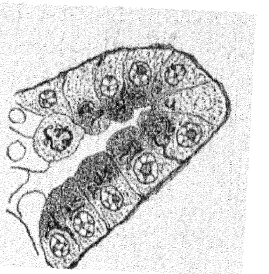


FIG. 41.—CANALICULI WITHIN PANCREAS-CELLS. (Holmgren.)

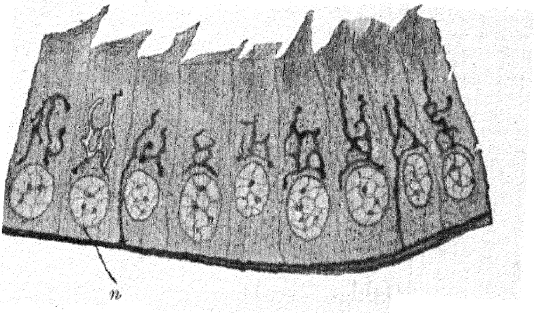


FIG. 42.—CANALICULI WITHIN COLUMNAR EPITHELIUM-CELLS OF EPIDIDYMIS. (Holmgren. *n*, nucleus.

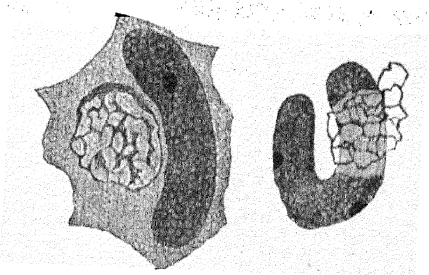


FIG. 43.—A CELL OF DESCEMET'S MEMBRANE OF THE CORNEA OF THE CAT, SHOWING A NETWORK IN THE PROTOPLASM NEAR THE NUCLEUS. (Ballowitz.)

It is uncertain whether this network is of the nature of a paranucleus or of a trophospongium.

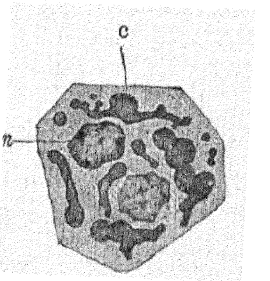


FIG. 44.—A CELL FROM THE HUMAN LIVER, SHOWING INTRACELLULAR CANALICULI. (Browicz.)

and in the cells of the decidua[4]; and a network which has been noticed by Ballowitz[5] in the epithelium of the membrane of Descemet in the eye (fig. 43) is perhaps of a similar nature, although some are inclined to regard it as of the nature

[1] Golgi, Boll. d. soc. med.-chir. di Pavia, 1898; and Verhandl. Anat. Gesell., Anat. Anz. xviii. 1901; Held, Arch. f. Anat. 1902.
[2] Négri, Boll. soc. med.-chir. di Pavia, 1900.
[3] E. Holmgren, Anat. Anzeiger, xxi. 1902; S. R. y Cajal, Trabajos, T. iii. 1903, and T. iii. 1904.
[4] Vecchi, Anat. Anz. xxxiv. 1909.
[5] Arch. mikr. Anat. lvi. 1900.

of a paranucleus (see p. 16).[1] Well-marked canaliculi also occur in the liver-cells (fig. 44), where they may occasionally contain blood-corpuscles in stages of disintegration[2]: these are capable of being injected from the portal vessels (fig. 45),[3] thus indicating that in this organ there is a very intimate relationship between the blood-vessels and the cells of the tissue. Holmgren[4] has described the canaliculi of

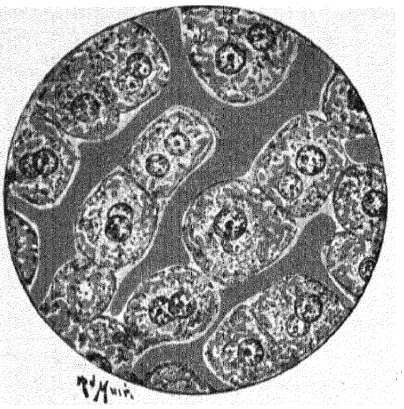


FIG. 45.—FROM A SECTION OF RABBIT'S LIVER INJECTED FROM THE PORTAL VEIN, SHOWING INTRACELLULAR CANALICULI COMMUNICATING WITH THE INTERCELLULAR BLOOD-SINUSOIDS.

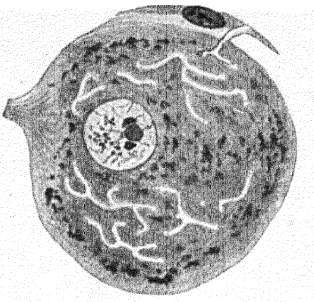


FIG. 46.—TROPHOSPONGIUM (CANALISATION) WITHIN A GANGLION-CELL. (E. Holmgren.)

protoplasm as opening on the exterior of the cells where they occur (fig. 46), thus affording means for the passage of lymph into or from the protoplasm, and con-

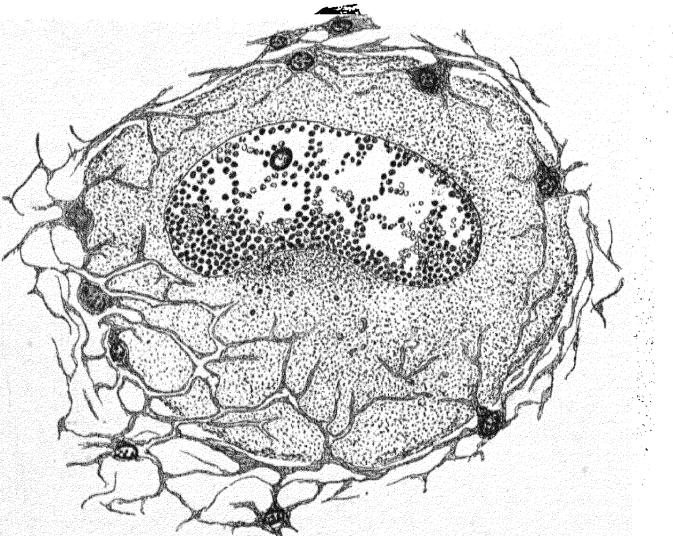


FIG. 47.—TROPHOSPONGIUM OF NERVE-CELL OF SNAIL, SHOWING ANASTOMOSING CANALICULI OCCUPIED BY PROCESSES OF CONNECTIVE-TISSUE OR NEUROGLIA CELLS. (E. Holmgren.)

siders that they are occupied in part by processes from the surrounding connective-tissue cells (fig. 47). He has termed the network which these form in the cell a

[1] This has also been suggested for the network described by Golgi within the nerve-cell (Popoff, Anat. Anz. xxix. 1906).

[2] Browicz, Bull. Acad. Sci. de Cracovie, 1899, 1900, 1906; Virch. Anat. 1902.

[3] Schäfer, Proc. Roy. Soc. Edin. xxiv. 1902, and Anat. Anz. xxi. 1902; G. L. Houser, Science, xv. 1902; Herring and Simpson, Proc. Roy. Soc. B. lxxviii. 1906.

[4] Anat. Anz. xvi. 1890, xviii. 1891, xxi. 1902, xxii. 1902, xxiv. 1904; Arch. mikr. Anat. lx. 1902; Arch. f. Anat. 1904; Anat. Hefte, xxv. 1904.

'trophospongium,' and the canals into which they are described as penetrating 'lymph-canaliculi,' regarding the arrangement as ministering directly to the nutrition of the cell. His statement that there is always a permanent communication of the canaliculi in question with the exterior is denied by v. Bergen, who has studied them in various situations (ganglion-cells, leucocytes, connective tissue, cartilage, and epithelium from different parts). v. Bergen is of opinion that the canaliculi are not permanent, but come and go; he states that they show in different cells different phases of formation.[1] It is clear that if canaliculi are present in such cells as leucocytes and cartilage-cells, they cannot be occupied by a trophospongium derived from connective-tissue cells.

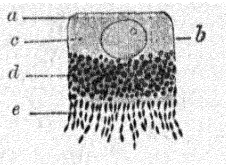


FIG. 48.—A PIGMENTED EPITHELIUM-CELL OF THE RETINA, SEEN IN PROFILE. (Greeff.)
Magnified 1,000 diameters.

a, free surface; *b*, nucleus; *c*, pigment-free cytoplasm; *d*, pigmented cytoplasm; *e*, pigment-containing processes.

Cell-contents: paraplasm, deuteroplasm.—The protoplasm of a cell usually contains a certain number of chemical substances, either in the solid or liquid form, which, while forming part of the substance of the cell, do not form any portion of the actual living material, although this material may make use of such substances, by way of oxidation or otherwise, to produce a supply of energy for carrying on the functions of the cell. Examples of such substances are the protein granules and crystals which are found in many plant-cells; particles and crystals of pigment (fig. 48) or of protein; globules of fat (fig. 49); starch-granules (in plant-cells); also substances in solution, such as hæmoglobin, glycogen, and sugar; and substances which are to be regarded as waste protoplasmic or nuclear products, such as creatin, creatinin, urea and urates. All such non-protoplasmic matter within a cell is sometimes termed collectively the *paraplasm* or *deuteroplasm*: it may be accumulated in so great an amount as almost completely to obscure the actual protoplasm. This is the case in fat-cells, in many plant-cells which are filled with starch or fat or aleuron grains, and in large animal ova, where the material which forms the greater part of the yolk is paraplasm. When the cell-contents other than protoplasm are of a fluid nature they often take the form of *vacuoles*, which appear as clear globules of varying size, less refracting than the cell-substance. In some plant-cells the vacuoles become very large, and their contents much exceed in bulk the actual protoplasm of the cell, which is then reduced to a thin external film enclosing a large cavity, which may be traversed here and there by threads of protoplasm. The fluid which occupies such a cavity is known as the cell-sap (fig. 50).

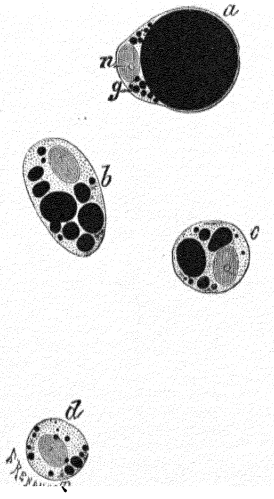


FIG. 49.—FAT-CELLS FROM YOUNG ANIMAL. (Ranvier.) Osmic acid preparation.

The drops of fat are stained of an intense black. *n*, nucleus; *g*, small globules of fat.

Sometimes a complete physical and chemical transformation of the cell-substance occurs, so that the place of the protoplasm is occupied partly or wholly by a material of an entirely different character. This is the case normally with those cells which undergo keratinisation; in these keratin is substituted for the cell-protoplasm, and the cell becomes of a hard, horny nature, losing all vital activity and assuming

[1] Arch. f. mikr. Anat. Bd. lxiv. 1904.

a passive, protective function. Abnormally, various other kinds of transformation of cell-protoplasm may occur, producing the several kinds of degeneration known under the names of amyloid, fatty, and the like.

Cell-membranes.—When the discovery of the cellular composition of plants and animals was made, it was assumed that all cells consist of a cell-membrane with fluid cell-contents. This assumption was mainly based upon the fact that the cells of plants are almost universally provided with a definite enclosing envelope of cellulose (fig. 50) which has become formed by the cell-protoplasm, and which serves to separate one cell from another except in so far as they are connected by protoplasmic fibres which pass through pores in the cellulose partitions (W. Gardiner). It was, however, shown (by Leydig, and subsequently by E. Brücke and M. Schultze) that such an envelope is not to be regarded as essential to the conception of an animal cell, although certain animal cells, such as ova and the cells which produce cartilage, are provided with a definite membrane. This, when present, is either secreted by the cell-protoplasm and produced externally to the cell, or, as many histologists hold, formed by the direct transformation of the external layer of the protoplasm.

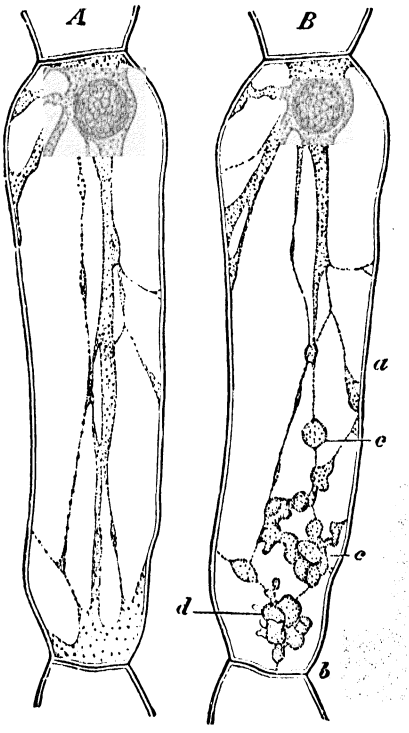


FIG. 50.—A CELL OF A TRADESCANTIA HAIR, A, IN NORMAL CONDITION; B, AFTER THE PASSAGE OF AN ELECTRIC SHOCK. (Verworn, after Kühne.)

a, cellulose wall; *b*, partition between two cells; *c*, collection of the protoplasm into clumps as the result of stimulation. The large spaces contain cell-sap.

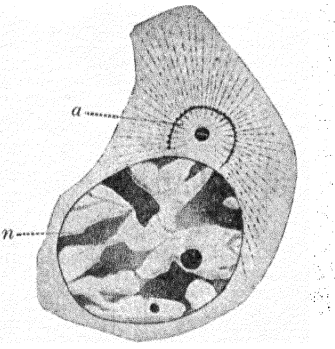


FIG. 51.—A CELL (WHITE BLOOD-CORPUSCLE), SHOWING ITS ATTRACTION-SPHERE. (Wilson, after M. Heidenhain.)

In this, as in most cases, the attraction-sphere, *a*, lies near the nucleus, *n*.

Nevertheless, although such definite membrane is absent from the majority of cells, it is none the less true that the most external layer or film which invests the protoplasm is physically and probably chemically different from the remainder, since all reactions show that a cell behaves to electrolytes exactly as if its protoplasm were enclosed by a semi-permeable solid membrane. The existence, therefore, of such a special surface film must be postulated for every protoplasmic cell, whether it be surrounded outside this by a definite envelope or not. Overton has brought together reasons for the belief that the superficial film through which osmosis occurs consists largely of the lipoids (cholesterin and lecithin) which are found along with nucleoproteid entering into the chemical composition of cell-protoplasm.

Overton's views on this subject have received a certain amount of criticism,[1] but the hypothesis appears on the whole more consistent with the known facts of cell-osmosis than others which have been suggested to explain them.

Centrosome and attraction-sphere.—Many, but not all, cells possess a small area somewhere near the centre of the cell and frequently at the side of the nucleus from which lines radiate into the neighbouring part of the protoplasm and are sometimes traceable to its extreme limits. The central part of the area is usually —but not always—occupied by a particle of protein material (fig. 51), which takes up certain special stains the employment of which is generally necessary in order to bring it distinctly into view. This particle, which is frequently double, even

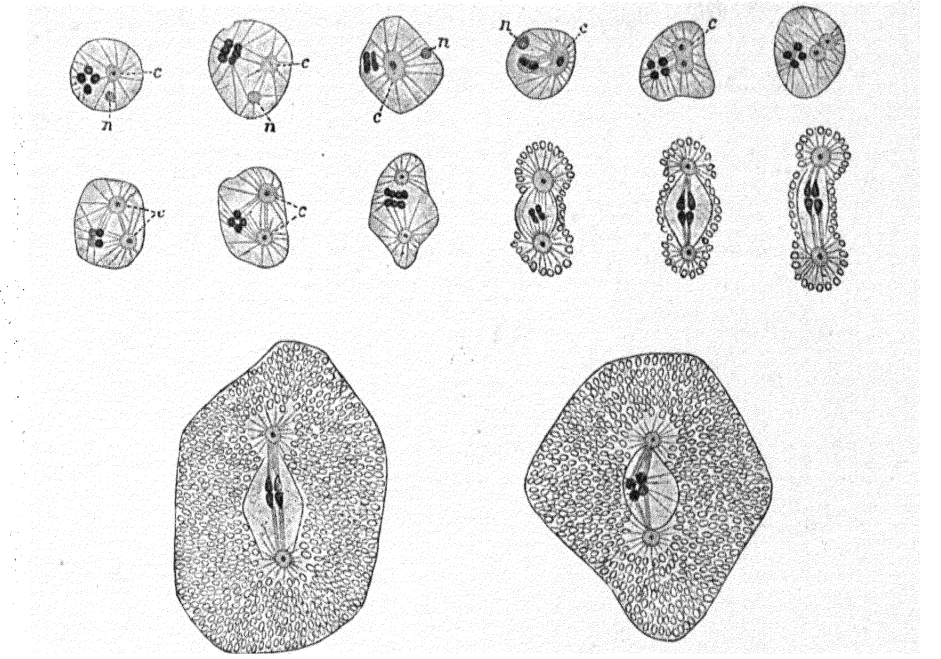


FIG. 52.—SPERMATOCYTES OF ASCARIS, SHOWING THE CENTROSOME WITHIN THE NUCLEUS, ITS DIVISION INTO TWO WITH THE FORMATION OF A DIVISION SPINDLE BETWEEN THEM, AND THE PASSAGE OF THE RESULTING CENTROSOMES FROM THE NUCLEUS INTO THE ADJACENT CYTOPLASM. (Verworn, after Brauer.)

The whole cell is represented only in the two lowest figures.

n, nucleolus; *c*, centrosome. The chromosomes are dark.

in the resting cell, is known as the *central particle*, *attraction-particle*, or *centriole* (Boveri), and it evidently occupies a point in the protoplasm which possesses stronger attractive or repulsive properties than the rest, as is indicated by the directive lines which converge to or radiate from it, which are exactly like lines of strain or stress which may be formed in colloid solutions in the process of fixation. These lines cannot, as a rule, be traced quite into the centriole,[2] but lose themselves within a spherical area of protoplasm which immediately surrounds it, and which is itself again surrounded by a clearer zone: this spherical area is termed the *attraction-sphere* or *centrosome*,[3] and the protoplasm within and immediately around the sphere, which may exhibit granules or fibrils of the nature of mitochondria (fig. 65),

[1] T. B. Robertson, Journ. Biol. Chem. iv. 1908. For the literature on cell-lipoids, see p. 11, footnote 5

[2] This may, however, be due to the presence of a refraction-halo.

[3] The name centrosome is sometimes used in a more restricted sense to denote the central particle, here called centriole.

is known as the *archoplasm* (Boveri) or *kinoplasm* (Strasburger), a name intended to indicate that it exerts a dominating influence over the rest of the protoplasm.

The attraction-sphere and centriole were first noticed in the dividing ovum by Flemming, and independently by Kupffer, in 1875, and by E. Van Beneden in 1876, but their true significance was not understood until the publication, independently, of the observations of Boveri and Van Beneden upon the developing ovum of Ascaris megalocephala in 1887, although a radiation from two points in the protoplasm on either side of the nucleus had been already described in dividing cells. Later the centrosome was recognised as a general feature of cell structure,[1] although a centriole cannot positively be affirmed to be of constant occurrence in all cells; indeed in the cells of the higher plants, and in Protozoa amongst animal organisms, a distinct central particle usually appears to be absent.[2] In some cells, as in the erythrocytes of the Lepidosiren larva, as described by Bryce,[3] and in the spermatocytes of Ascaris, as described by Brauer,[4] these structures only make their appearance in the protoplasm shortly before cell-division is about to occur: in the last-named case they emerge from the interior of the nucleus, having first undergone fission within that structure (fig. 52). In the large majority of animal cells a centrosome can be detected within the protoplasm in all phases, even in the fully resting (*i.e.* non-dividing)

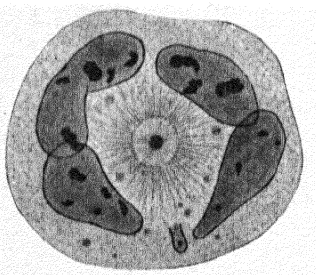


FIG. 53.—WHITE BLOOD-CORPUSCLE OF LEPIDOSIREN, WITH LOBED AND ALMOST ANNULAR NUCLEUS AND WELL-MARKED CENTROSOME. (T. H. Bryce.)

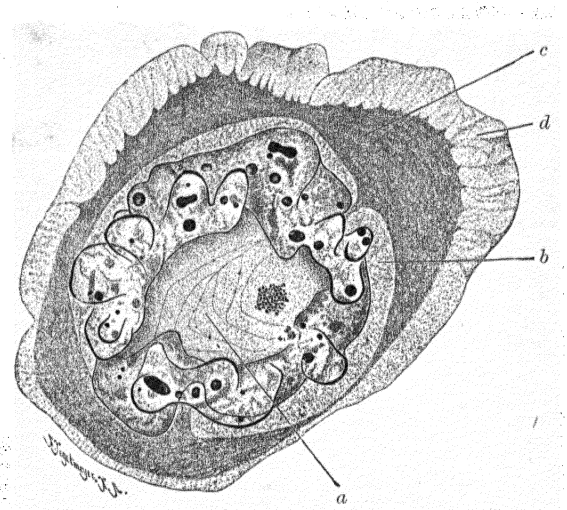


FIG. 54.—GIANT-CELL OF MARROW WITH NUMEROUS CENTRIOLES. (M. Heidenhain.)

a, *b*, *c*, *d*, various zones of the cytoplasm. The nucleus is large and annular, with irregular lobes and numerous nucleoli.

condition of the cell, although it may be close up against the nucleus, and on that account difficult of observation. Seeing, therefore, that its origin is sometimes within the nucleus, sometimes independent of the nucleus in the cell-protoplasm, the centrosome is regarded, when present, as a special cell-constituent, the function of which is intimately connected with the mechanism of nuclear division. A dumb-bell shaped or double centrosome (*diplosome*) is sometimes present in a cell not immediately about to divide, although in this condition of the cell the centrosome is more often single. If the centrosome is single in the resting cell, division of the nucleus is always preceded by that of the centrosome, the centrioles of the dividing cell (along with their attraction-spheres and radiating filaments) occupying a special relationship to the changes in the nucleus which accompany cell-division, as will be noted when the division of cells is dealt with. According to M. Heidenhain the centrosome is usually less than 1μ in diameter, the centrioles being of course considerably smaller. When the nucleus is annular or horse-shoe shaped the centrosome lies in the centre of the ring or half-ring (fig. 53).[5]

Some cells with multiple or lobed nuclei have the centrioles replaced by a group of particles (multiple centriole). This is the case, for example, with the giant-cells of bone-marrow (fig. 54).

[1] Flemming, Anat. Anz. vi. 1891; M. Heidenhain, *ibid.* For historical accounts of the centrosome, see Solger, Berl. med. Woch. 1891, and M. Heidenhain, Plasma u. Zelle, 1907.

[2] Cf. Farmer, Anat. Anz. xiii. 1897; F. Meves, Verhandl. d. Anat. Ges., Anat. Anz. 1902; R. Hertwig, Sitz. d. Ges. f. Morph. u. Physiol. Munich, 1895.

[3] Trans. Roy. Soc. Edin. 1904.

[4] Biol. Centr. 1893, vol. xiii. and Arch. f. mikr. Anat. xlii. 1893.

[5] F. Meves, Diss. Kiel, 1893.

Occasionally the centrosome assumes an irregular form and is of considerably larger size than usual.[1] The centrosome is connected, as we have seen, with fibrillar formations (asters, spindles) within the protoplasm. In columnar epithelium-cells (figs. 55, 56) the (double) centriole lies near

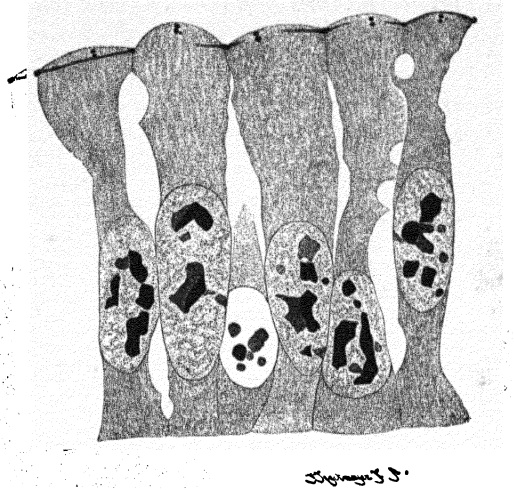


FIG. 55. — COLUMNAR EPITHELIUM-CELLS FROM DUCK-EMBRYO EACH CONTAINING A DIPLOSOME NEAR THE FREE BORDER. (M. Heidenhain.)

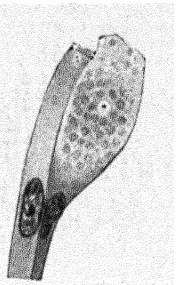


FIG. 56. — CENTROSOMES IN EPITHELIUM-CELLS OF ILEUM OF MAN. (Gurwitsch, after Zimmermann.)

Two cells are seen: one, a columnar cell, has a double centrosome near the free border; the other, a goblet-cell, shows a single centrosome amongst the mucin granules.

the free surface; in goblet-cells it is in the middle of the mucin-containing part (fig. 56), and from one side a fine filament may project towards the free surface, while from the other side another

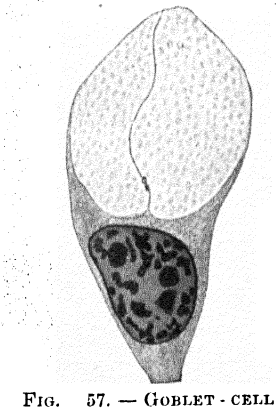


FIG. 57. — GOBLET-CELL OF SALAMANDER LARVA, SHOWING A DIPLOSOME WITH FIBRIL PROCEEDING FROM EACH OF ITS TWO PARTICLES WHICH LIE WITHIN THE MUCIN-CONTAINING PART OF THE CELL. (Gurwitsch, after Joseph.)

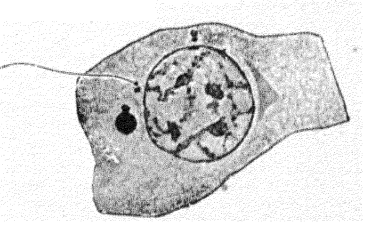


FIG. 58. — [illegible] TESTICLE (SPERMATID), SHOWING THE TAIL FILAMENT OF SPERMATOZOON GROWING OUT FROM THE DOUBLE CENTRIOLE. (Niessing.)

fine filament may extend into the protoplasm (fig. 57). The centriole is in close relationship with the development of the tail-fibril in spermatozoa (fig. 58) and with a very fine

[1] For variations in this body, cf. M. Heidenhain, Plasma u. Zelle, 1907. In the spermatogonia of the salamander the centrosomes are large and well-marked and remain connected together in adjacent cells for some time after completion of cell-division (F. Meves, Arch. f. mikr. Anat. xliv. 1895; B. Rawitz, *ibid.*).

cilium-like filament (centriole-filament) which is attached to certain secretory epithelium-cells (fig. 59).[1] Possibly the basal particles of ciliated cells (see p. 72) are produced by division and multiplication of the centrioles (Lenhossék, Henneguy) (fig. 60). Centrosomes have also been thought to be concerned with the formation of cell-membranes.

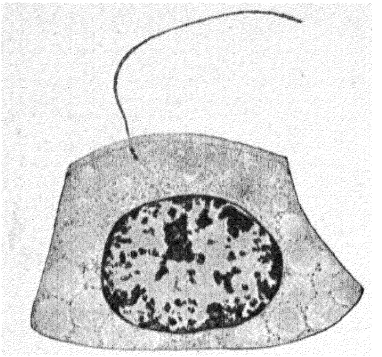


FIG. 59.—A RENAL EPITHELIUM-CELL OF SALAMANDER LARVA, WITH CENTRIOLE FILAMENT. (M. Heidenhain, after Meves.)

As has already been explained, the phenomena of radiation from certain points can be imitated by inducing localised coagulation in the gel condition of colloidal solutions (p. 13). Moreover, structures (artificial astropheres) closely resembling centrosomes, and like these having the property of initiating cell-division, can be made to appear in the ova of Echinoids by adding certain excitatory agents[2] to the sea-water in which the ova are suspended (fig. 61). Facts such as these would lead one to suppose that the centrosome is produced by a physical alteration

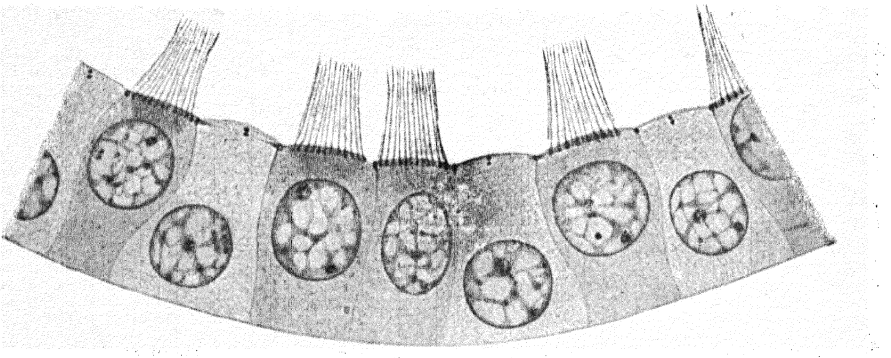


FIG. 60.—CILIATED AND NON-CILIATED CELLS FROM THE EPIDIDYMIS OF RABBIT. (v. Lenhossék.)
Each non-ciliated cell has a diplosome at its free border; these are not seen in the ciliated cells, but in the latter the free border is occupied by a row of double particles with which the cilia are connected.

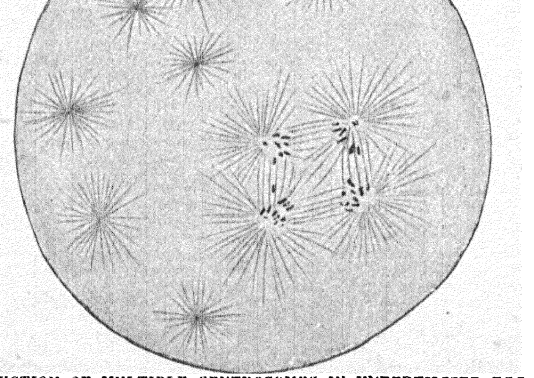


FIG. 61.—PRODUCTION OF MULTIPLE CENTROSOMES IN UNFERTILISED EGG OF SEA-URCHIN. (E. B. Wilson.)

[1] K. W. Zimmermann, Arch. f. mikr. Anat. lii. 1898 (Centralgeisselapparat).
[2] Morgan, Arch. f. Entwicklungsmechanik, iii. 1896; viii. 1899; x. 1900; J. Loeb, Amer. Journ. Physiol. iii. and iv. 1900 and 1901; A. P. Mathews, *ibid.*; E. B. Wilson and Mathews, *ibid.* xii. and xiii. 1901; J. Loeb, Dynamics of Living Matter, 1906.

in the cell-protoplasm and may be formed within this *de novo* and not necessarily by the division of an existing centrosome. Nevertheless the latter is the ordinary method of production of centrosomes, and in most cells the centrosome, if not the centriole, is to be regarded as a permanent organ.

THE STRUCTURE OF THE CELL-NUCLEUS.

The **cell-nucleus**, in the so-called 'resting' (*i.e.* non-dividing) condition, is a spherical, ellipsoidal (fig. 62), annular (fig. 54) or irregularly shaped body

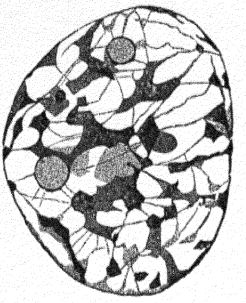


FIG. 62.—NUCLEUS FROM A CELL OF THE INTESTINAL EPITHELIUM OF A YOUNG SALAMANDER LARVA. (M. Heidenhain.)

Magnified 2300 diameters.

The membrane and network of basi-chromatin (karyomitome) with enlargements (pseudonucleoli) at the nodes of the network are stained. Two nucleoli are seen.

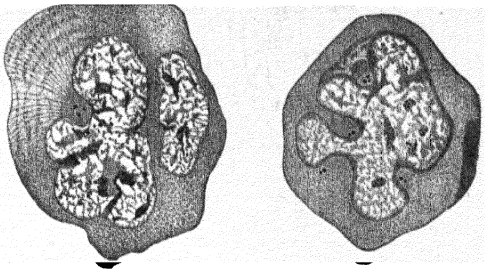


FIG. 63.—CELLS WITH IRREGULAR LOBED NUCLEI FROM BONE-MARROW OF RABBIT. (M. Heidenhain.)

(fig. 63), usually single, sometimes double (fig. 45), and rarely multiple (fig. 64), occupying a position in the cell which is generally near the centre, but may be altogether to one side; or near one end of an elongated cell.

The nucleus consists essentially of two parts, viz.: (1) of a formed material, the *karyomitome*, which usually takes the shape (*α*) of threads disposed to form a network or spongework throughout its substance and (*β*) of a membrane bounding it superficially and separating it from the cytoplasm; (2) of a formless substance, the *karyoplasm*, clear and apparently structureless in the living condition, which occupies the meshes of the network and resembles the clear material of the cytoplasm. The relation of these substances to one another is similar to that of the spongioplasm and hyaloplasm of the cell-protoplasm. That the hyaloplasm is of a similar nature in both nucleus and protoplasm is obvious from the similarity of their behaviour to staining reagents and from the fact that when, in the dividing cell, the membrane of the nucleus disappears, the karyoplasm is in full continuity with and is indistinguishable from the hyaloplasm of the cell-substance. Chemically the karyomitome is largely composed of nuclein, containing

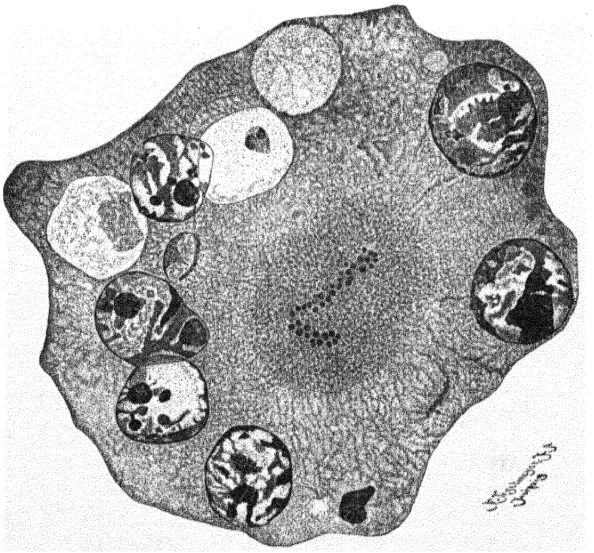


FIG. 64.—GIANT-CELL WITH MULTIPLE NUCLEUS AND MANY CENTRIOLES FROM LYMPH-GLAND OF RABBIT. (M. Heidenhain.)

both as a primary constituent and as an alteration product. It is a common alteration product of most iron-bearing minerals.

It is the principal ore of iron, and supplies more than 70 per cent of the total annual production of iron ores in the United States. The streak is one of its most distinctive megascopic properties.

Limonite

Composition. — Limonite is the hydrous sesquioxide of iron, $Fe_4O_3(OH)_6$ or $2Fe_2O_3.3H_2O$, and contains when pure oxygen = 25.7, iron = 59.8, water 14.5. Often impure and is frequently admixed with other hydrous oxides of iron.

Form. — Noncrystalline. Occurs in earthy masses in rocks, and in deposits in mammillary and stalactitic forms with frequently radiating fibrous structure; also concretionary, and in earthy deposits.

General properties. — Limonite has no cleavage. Luster submetallic to dull. Hardness 5–5.5 in the compact mineral. Specific gravity 3.6–4.0. Color is usually some shade of brown, brownish-yellow to very dark opaque. Streak yellow-brown, very characteristic and serves to distinguish it from hematite.

Chemical tests. — It is difficultly fusible before the blowpipe, becoming strongly magnetic after heating in the reducing flame. Slowly soluble in hydrochloric acid, and yields much water when heated in closed tube.

Occurrence. — Limonite is a secondary mineral formed by weathering and alteration from other iron-bearing compounds. It is frequently noted in igneous and metamorphic rocks as small yellowish earthy masses derived from other iron-bearing minerals, such as pyrite, etc., by oxidation and hydration. It forms an essential part of the gossan or "iron hat" of many sulphide veins, as accumulations in beds and irregular bodies forming residual deposits from iron-bearing rocks, especially ferruginous limestones, and in porous earthy form known as bog-iron ore deposited on the bottom of swamps, bogs, and other shallow water bodies through oxidation of iron carbonate chiefly ($FeH_2(CO_3)_2$), and also from iron sulphate. Admixed with more or less clay it forms yellow ocher, and may then be of value as a mineral pigment. It occurs as a pigment or stain in various rocks and is a common cement of many.

Limonite is an important ore of iron and ranks next to hematite in importance in the United States; Alabama, Virginia, Tennessee, and Georgia being the principal producers. Other hydrous oxides of iron are frequently admixed with limonite.

Determination. — Its color, streak, and structure usually suffice to distinguish it from other minerals.

Carbonates

The carbonates are salts of carbonic acid (H_2CO_3) and are secondary minerals, formed by weathering of other minerals or derived from deeper sources within the earth. They may be deposited either in place or else carried in solution by water containing carbon dioxide into seas and lakes and precipitated by means of organic agencies as limestone, etc. Only two species of the calcite group (*calcite* and *dolomite*) of the anhydrous carbonates are of megascopic importance as rock-forming minerals.

Calcite

Composition. — Calcite is calcium carbonate, $CaCO_3$ in which $CaO = 56.0$ and $CO_2 = 44.0$ per cent.

Form. — Calcite crystallizes in the rhombohedral division of the hexagonal system. Crystals are varied in habit, are often perfect, and

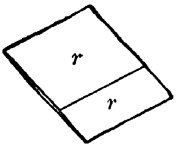


Fig. 32.

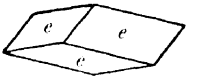


Fig. 33.

sometimes of large size. The rhombohedron is the most common crystal form (Figs. 32 to 34). Other forms represented by Figs. 35 and 36 sometimes occur. As a rock-forming mineral calcite usually occurs fine to coarse-crystalline granular in marble, compact in ordinary limestones, loose and earthy in chalk, spongy in tufa, and stalactitic in cave deposits.

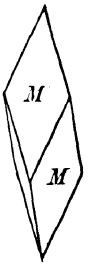


Fig. 34.

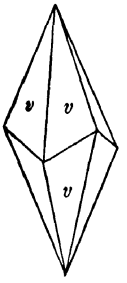


Fig. 35.

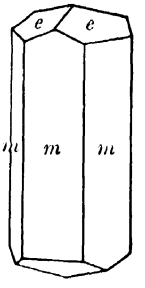


Fig. 36.

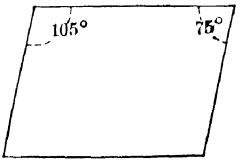


Fig. 37.

General properties. — Perfect rhombohedral cleavage in three directions intersecting at angles of 75 and 105 degrees (Fig. 37). Hardness 3. Specific gravity 2.72. Color usually white or colorless, but frequently exhibits a variety of color from impurities. Luster

number for the same species of animal in each nucleus, and capable of growth and of multiplication by division. This may also be true of their constituent chromioles.

According to a theory first propounded by Rabl,[1] the chromosomes, although joined into a reticulum or even a clump, in the resting nucleus, retain their individuality, and when the nucleus becomes active during the prophases of karyokinesis, the chromosomes, which may be spherical, rod-like, or thread-like, become merely separated from one another by a withdrawal into their substance of the strands which connected them and by an accumulation of karyoplasm between them. In point of fact, in nuclei with few chromosomes, small masses of chromatic substance (*chromoplasts*) (fig. 70), in number equal to that normal to the species, may sometimes be observed in the reticulum of the resting nucleus;[2] these serve as starting-points for the growth of the chromosomes (fig. 67).

Nuclear membrane and network.—All nuclei except those in process of division appear to be bounded by a distinct membrane formed mainly of basi-chromatin, but probably consisting also of linin. This membrane forms a sharp division between nuclear contents and cytoplasm. It was at one time thought[3] that the membrane is frequently incomplete and furnished with pores, or even in the

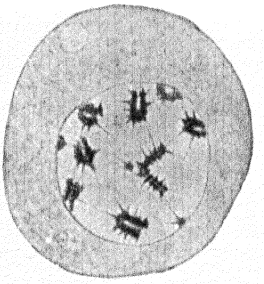


FIG. 70.—CELL SHOWING CHROMATIN OF NUCLEUS ACCUMULATED INTO EIGHT CHROMOPLASTS, WHICH ARE BEGINNING TO GROW OUT TO FORM CHROMOSOMES.

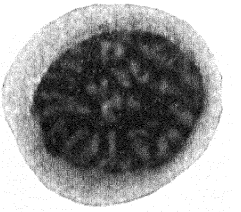


FIG. 71.—LYMPHOCYTE FROM BLOOD OF TRITON, FIXED BY A JET OF STEAM, AND STAINED WITH HÆMATOXYLIN. (Schäfer.) Magnified 1500 diameters.

The nucleus exhibits a close and even network of basi-chromatin.

condition of a basket-work. This may sometimes be the case so far as the chromatic portion is concerned, but the condition is rare: in nearly all cases of resting nuclei the membrane appears in section as a sharply bounded line (fig. 68, A). On its inner surface the membrane is connected with strands of the karyomitome reticulum, which vary greatly in number and in thickness. These form, as already stated, a network or spongework throughout the interior of the nucleus, the trabeculæ being sometimes equal and regular (fig. 71); in others, and the majority of cases, unequal in size and irregular in distribution (fig. 68, A). Sometimes the trabeculæ appear to trend towards one pole of the nucleus. The material of which these strands are composed is, in the main, like the nuclear membrane, stainable by basic dyes, and in a nucleus thus stained their nodes or junctions show out more strongly than the rest, so as to give the appearance, under a moderate magnifying power, of distinct granules. Hence the descriptive term 'granular' was constantly applied to cell-nuclei before the meaning of this appearance was understood. Occasionally the nodal thickenings

[1] Morph. Jahrb. x. 1885; Anat. Anz. vi. 1889.

[2] See further on the individuality and independence of the chromosomes, Boveri, Ergebn. ii. d. Konstitution des chromat. Subst. 1904; O. Hertwig, Allgemeine Biologie; Gerassimow, Bot. Centr. 1904

[3] Cf. Flemming, Arch. f. mikr. Anat. xiii. 1876; G. Retzius, Biol. Unters. 1881.

of the spongework are very large and the connecting strands are relatively fine, and in rare cases it is not possible to detect these strands at all, in which case the nucleus appears to contain clumps of chromatin suspended in its hyaloplasm (*pseudonucleoli*, fig. 55).

Nucleolus (plasmosome, karyosome).—Most, but not all, nuclei exhibit, generally imbedded in a part of the karyomitome, but sometimes lying free in the karyoplasm, a very distinct and generally oxyphil body, known as the *nucleolus*, usually of globular shape and composed of more highly refractive material than the rest of the nucleus. The nucleolus varies greatly in size: it is usually quite structureless, but is sometimes vacuolated, and occasionally, in doubly stained specimens, the central part appears to be differently coloured from the peripheral part.[1]

The nucleolus is usually regarded as a product of nuclear metabolism, possibly formed by a transformation of the karyoplasm. It is occasionally double (fig. 62), and in large nuclei may be multiple (fig. 54). In many cells, especially those which are in active process of growth, or in functional activity, nucleoli and parts of nucleoli are observed to be extruded into the cytoplasm, to which they appear to furnish materials which become further metabolised (*e.g.* into secretion-granules and other products of cell-activity). Numerous observations of this character have been made by Montgomery,[2] and notices on the same subject have been more recently published by Carlier[3] (in gland-cells), by Page May and C. E. Walker (in nerve-cells),[4] by Walker and Embleton (in Hydra),[5] and by Walker and Tozer[6] (in various vegetative cells). Montgomery is disposed to regard the extruded portions of nucleolus as degeneration products, and Carlier speaks of them as representing 'effete material'; but Montgomery admits that they eventually merge into cell-protoplasm, and the observations of Walker show that they undergo a gradual change in staining reaction after extrusion and gradually assimilate themselves to the protoplasm. By Walker's method of staining (combined acid and basic stain) the nucleoli were coloured by the basic stain whilst within the nucleus, and after extrusion their substance became more and more oxyphil. The extrusion of nucleolar substance may here have been accompanied by a passage from the nucleus into the cytoplasm of some of the basi-chromatin of the karyomitome; such passage has been frequently described independently of nucleolar extrusions (see p. 58).

Another view which has been expressed regarding the nucleolus is that it represents an organ of the nucleus in which basi-chromatin is elaborated or manufactured, the basi-chromatin being transferred to the chromosomes, which thus increase in size at the expense of the nucleolar substance.[7] The observations of Walker (see above) are somewhat in favour of a formation of basi-chromatin in the nucleolus, but in this case we cannot suppose that the material has to do with the growth of chromosomes, since it is extruded into the cytoplasm.

According to the old conception of cell-division the nucleolus was regarded as the organ which initiates this process—a conception which has been now transferred to the centrosome. Cases have however been recorded by modern observers in which the division of the nucleus has been preceded by that of the nucleolus. In amitotic division this is not uncommon, and it has also been observed in mitotic division.[8]

Variations in nuclei.—In some cases, as in the spermatozoa, there is no appreciable achromatic material within the nucleus, which appears as a compact mass of nuclein, staining intensely with basic dyes. In other cells the nuclein has

[1] According to Ferrata (Arch. di Fisiol. 1906) the centre only is oxyphil, the periphery basiphil, the relative proportion of the two parts being subject to variation. C. E. Walker and Tozer also figure nucleoli composed apparently of two different substances. But it is usually accepted that true nucleoli are composed mainly of oxyphil substance and stain with acid or neutral dyes; they may, however, be covered by a basiphil envelope derived from the karyomitome. Sometimes the nucleolus has attached to it a small basiphil particle, which has been termed *paranucleolus*. The meaning of this is unknown

[2] Journ. of Morph. xv. 1898 (with literature to that date).

[3] La Cellule, xvi. 1899; *ibid.* xxii. 1905; Inaugural Lecture, Birmingham, 1899; Proc. Scot. Nat. Hist. Soc. v. 1909.

[4] Quart. Journ. Exper. Physiol. i. 1907.

[5] *Ibid.*

[6] *Ibid.* ii. 1908; this paper also includes most of the literature.

[7] See, for a discussion of this view, T. H. Bryce in Quart. Journ. Micr. Sci. xlvi. 1905, where references to the literature are given.

[8] See on this subject R. Metzner, *op. cit.* and M. Heidenhain, Plasma u. Zelle, p. 194.

undergone a certain degree of vacuolation by accumulation of hyaloplasm within it, and this affords a transition to the sponge-like structure which most nuclei exhibit. In other cells again the nuclein is reduced to a very small amount and the nucleus is mainly formed of oxy-chromatic material, staining hardly at all with basic dyes.

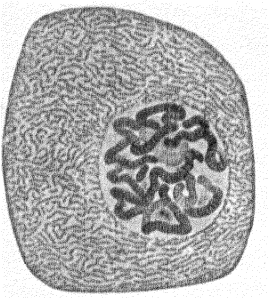


FIG. 72.—GLAND-CELL OF CHIRONOMUS LARVA. (Flemming.)

Occasionally, as in the nuclei of the cells of the salivary glands of the Chironomus larva, the chromatin is permanently in the form of a skein of interwoven threads instead of taking the shape of a network (fig. 72): this condition, which generally is characteristic of commencing nuclear division, is rarely present in resting, *i.e.* non-dividing, nuclei, although not uncommon in those of insects (Carnoy).

Although it is probable that the substance of the nucleus —at least its nuclein—is of firmer consistence than the protoplasm of the cell (which in the living condition is at most semi-fluid),[1] it must not be conceived as being solid, for it most easily alters its shape, either spontaneously or with any alterations in pressure which may be imparted to it, such as occur from movements of the protoplasm. This is strikingly exemplified in amœboid cells in which the nucleus is pulled first in one and then in another direction by the moving protoplasm, and assumes in consequence the most irregular bi-lobed, tri-lobed, or multi-lobed forms, the several parts or lobes being often nearly dragged asunder, although they are hardly ever completely separated, being joined by drawn-out threads of the nuclein material (fig. 73). The lobes are rarely angular, but usually rounded. All these circumstances indicate that the material of which the nucleus is composed is of a soft and probably slimy consistence, and as the protoplasm is still softer and more fluid than the nucleus, it follows that the whole living substance of the cell, whether protoplasmic or nuclear, is, physically speaking, more fluid than solid, and is subject to the laws which govern the behaviour of droplets of fluid material and especially the laws of surface tension.

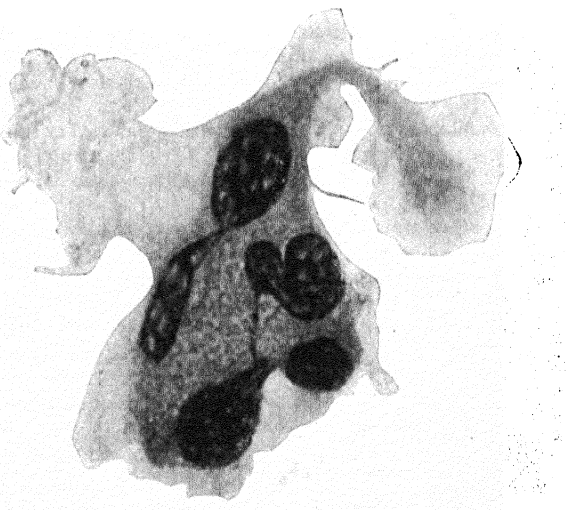


FIG. 73.—AMŒBOID LEUCOCYTE OF TRITON FIXED BY A JET OF STEAM AND STAINED WITH HÆMATOXYLIN. (Schäfer.) Magnified 1360 diameters.

The nucleus at first sight appears multiple, but on careful examination its several parts are seen to be united by threads of basi-chromatin. These are not all visible in the figure, which is an untouched photograph, and shows only one plane of the thickness of the corpuscle.

Chemically the nucleus resembles cell-protoplasm in the fact that both contain nucleic acid combined with protein. But in the nucleus the proportion of nucleic acid to protein is much larger than in the cytoplasm, and its protein tends to exhibit a simpler chemical constitution, assuming in certain nuclei, which have been specially chemically investigated, such as the nuclei of the spermatozoa of fish, the form of protamines, bodies of a far simpler composition than ordinary proteins.[2] Phosphorus is an integral constituent of nucleic acid to the extent of nearly 10 per cent.,

[1] This has of late years been especially insisted upon by Rhumbler (Zeitschr. f. allg. Physiol. 1902).

[2] Kossel, Zeitschr. f. physiol. Chem., various articles from 1886 onwards. Also Sur les protamines &c. Soc. chim. de Paris, 1903; O. Cohnheim, *op. cit.* R. Burian, Ergebn. d. Physiol. 1904 and 1906. Protamine was first obtained by Miescher (1870) from salmon-milt.

and the nucleus accordingly exhibits a much larger proportion of that element than the nucleo-proteins of cell-protoplasm, which, as just stated, are combinations of nuclein with protein, and contain much less nucleic acid. There further enters into the composition of nuclein a sufficient amount of iron to be detected in the nuclear chromatin by its micro-chemical reactions.[1] These reactions are not obtainable from the nucleo-proteid of the cell-substance, probably on account of the relatively small proportion in which iron is present in this. Iron can, however, be detected in considerable amount in the substance of certain cells, such as those of the liver and spleen, but it does not there form a part of the constitution of the protoplasm. In these places it is present in the form of an inorganic combination and not of an organic compound, as in nuclei. In the former case a direct test for ferric oxide will exhibit its presence, but in the latter case the organic compound must be broken up by the action of a mineral acid before the presence of iron can be shown.[2]

Some light is thrown upon a possible mode of formation of the appearances of resting nuclei by the experiments of W. Berg,[3] upon the behaviour of nucleic acid and protamines examined in microscopic drops under a high power of the microscope, both when mixed together in different proportions and when their compounds are treated with water and fixative reagents. Berg describes the mixing of solutions of nucleic acid and protamine as producing a precipitate at first composed of solid globules, which become hollow. These run together where they come in contact with one another, to form a sort of froth, which gradually becomes homogeneous by disappearance of their vacuoles. If nucleic acid be now allowed to pass under the cover-glass the homogeneous masses become vacuolised; if protamine solution is substituted for the nucleic acid solution, they become again homogeneous. Reagents which withdraw water cause de-vacuolisation of the vacuolised nucleate of protamine. Addition of water reverses this process. Various changes are also produced in nucleate of protamine by fixatives. But certain fixatives cause no artificial structural change in this substance. This was found by Berg to be the case with osmic acid fixation.

THE DIVIDING CELL.

Cells multiply by division of pre-existing cells. The division of the cell protoplasm is preceded by that of the nucleus, and this by that of the centriole: in this sense the last-named particle may be said to initiate the division of the cell.[4]

AMITOTIC CELL-DIVISION.

By Remak and the older histologists of the middle of the nineteenth century the division of a cell was described as produced by a simple separation of the nucleus into two parts, preceded by a similar division of the nucleolus. The separation was generally assumed to be produced by the pressure of the encircling protoplasm, this being followed by an elongation of the cell and a passage of the daughter-nuclei to opposite ends, this again by a constriction of the cell-body pinching the original cell into two, each containing one of the daughter-nuclei. There seems reason still to believe that this simple or *amitotic* method of division occurs in some cells; although it is difficult to be quite sure in all instances, unless the process can be watched from beginning to end, that karyokinetic changes, such as those immediately to be described, have not taken place rapidly and been missed. But in most cells it is impossible to follow the changes of cell-division in the living state, although in some they can be imperfectly seen. The usual method of studying the changes is to fix and stain the tissue and from the various phases of division which the cells exhibit to infer the order of change which actually occurs. And since

[1] A. B. Macallum, Quart. Journ. Micr. Science, xxxviii. 1895. Macallum found less iron in the substance of the nucleolus than in the chromatin of the nucleus. The presence of iron in nucleo-proteins had previously been shown by Bunge and others. The importance of this fact is emphasised by the observation of Spitzer (Pflüger's Arch. lxvii. 1897) that the oxidising enzyme of the cell (oxidase) is associated with those constituents of the products of cleavage of the nucleo-proteins which contain the iron-group; this points to the cell-nucleus being the oxidising organ of the cell (J. Loeb, Zeitschr. f. Entwicklungsmechanik, viii. 1899).

[2] Macallum, *op. cit.*

[3] Arch. f. mikr. Anat. lxii. 1903 and lxv. 1905.

[4] The fact that in very many plant-cells no centriole can be detected, although the formation of a division spindle and all the other phenomena characteristic of mitotic cell-division occur, shows that this body is not essential to cell-division. But an attraction-sphere (centrosome) is present in all.

certain cells, when studied in this way, show stages of constriction leading up to complete division of the nuclei without, in any of the cells observed, presenting the appearances which are characteristic of karyokinetic cell-division, the cells in

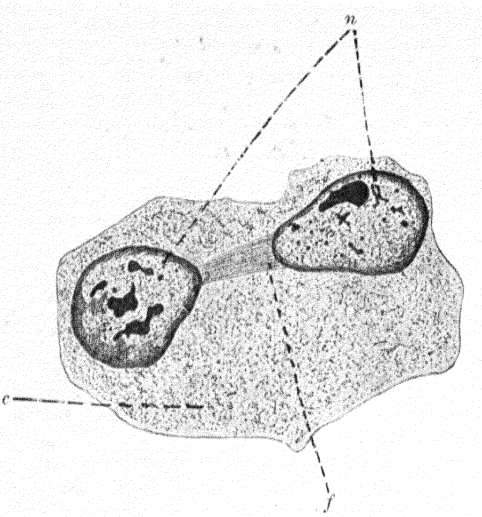


FIG. 74.—CELL OF BLADDER EPITHELIUM, SHOWING AMITOTIC DIVISION OF NUCLEUS. (Nemileff.)
c, cytoplasm; *n*, daughter-nuclei; *f*, strand of fibrils uniting daughter-nuclei.

question are regarded as undergoing division by simple fission (*amitotic division*, from *a*, privative; μίτος, a thread: a filamentous structure of the nucleus being characteristic of ordinary cell-division). Amitotic division is said to be characteristic of the superficial cells of the urinary bladder[1] (see fig. 74), and of the

FIG. 75.—A POLYMORPH LEUCOCYTE OF TRITON FIXED BY A JET OF STEAM DURING WHAT APPEARS TO BE AMITOTIC DIVISION. (Schäfer.) Magnified 1360 diameters. Untouched photograph.

cells which line the basement-membrane of the seminiferous tubules of the testicle,[2] and to be a common mode of division of the nuclei of the giant-cells of marrow.[3] The polymorph leucocytes of the blood also appear to exhibit this mode of division (fig. 75). The process has been followed in them under the microscope by E. Klein.

[1] Flemming, Arch. f. mikr. Anat. xxxiv. 1889.
[2] For instances of amitotic division, chiefly in invertebrata, see C. M. Child in Anat. Anz. xxx. 1907 in embryonic cells, Maximow, *ibid.* xxxiii. 1908.
[3] C. E. Walker, Proc. Roy. Soc. B. lxxviii. 1906.

MITOTIC CELL-DIVISION: KARYOKINESIS.

In by far the majority of cases of cell-division the nucleus undergoes a complex series of transformations preparatory to actual separation into two parts. These transformations are due to active changes in its structure and are intimately bound up with remarkable changes in the centrosome, which proceed *pari passu* with those of the nucleus. To this nuclear activity which is characteristic of cell-division the term *karyokinesis*[1] was applied by Schleicher to distinguish it from the passivity of the nucleus which was at that time supposed to be the chief feature of cell-division, this being then believed, as already explained, to be brought about by the activity of the protoplasm alone. The transformations of the nucleus during karyokinesis result in the separation of the nuclein or chromatin into a number of similar parts of equal size, constant in number for each species of animal: to these the name *chromosomes* has been applied.[2] In the majority of cases the chromosomes take the form of threads, and on this account the karyokinetic form of cell-division was termed *mitotic* by Flemming, while the nuclear appearances are known collectively as *mitoses*. As already stated, the chromosomes can in many cases be seen to be constructed of a linear series of chromatin particles (fig. 65); these eventually form a double row in each chromosome (fig. 66).

Although all the changes observable in karyokinesis are quite continuous one into the other, it is convenient for descriptive purposes to consider them as occurring in separate stages, and these again are grouped into two series—the *anaphase*, leading up to the main feature (*metaphase*) of nuclear division, viz. division of the chromosomes, and the *kataphase*, leading away from this to the complete formation of daughter-nuclei.

During the anaphase, the chromosomes are becoming distinct, being to all appearance spun out of the whole chromatic material of the nucleus, including the membrane and network (but not the nucleolus, which may persist for a time but afterwards disappears). The thread or threads of chromatin which are thereby produced have in the first instance the character of a constricted *skein* (spirem), but this is soon found to be broken up transversely into a number of chromosomes of equal length and usually V-shaped. These before long arrange themselves around the equator of the somewhat ellipsoidal nucleus. When the nuclear membrane disappears the nuclear and cell contents come into complete continuity. The nucleolus may persist for a short time, but it disappears before the equatorial stage, becoming apparently discharged into and broken up or dissolved within the protoplasm.[3]

There is occasionally seen a division of the nucleus into three (or more) parts preceded by the appearance of multiple centrosomes.[4] This is more common in pathological new formations than in normal tissues, but has been described as a normal occurrence in giant-cells of marrow.[5] It may occur in the ovum as the

[1] *κάρυον*, a kernel; *κίνησις*, movement. For the early history of this subject, with literature to that date, see Waldeyer, Arch. f. mikr. Anat. xxxvii. 1891. Since then the papers on the subject are innumerable. Amongst them may be especially mentioned those by Flemming, F. Hermann, Rabl, Meves, and other authors which have appeared in the Arch. f. mikr. Anat. and those by Carnoy and his fellow-workers which have been for the most part published in La Cellule.

[2] The number of chromosomes in the somatic cells of man is 24; in the matured germ-cells 12 (J. Duesberg, Anat. Anz. xxviii. 1905). This agrees with the earlier computations of Flemming (Arch. f. mikr. Anat. xx. 1881) and Hausmann. The following animals and plants have also been found to have 24 chromosomes in the somatic cells—viz.: Salamandra, Salmo, Helix, Lilium, Leucojum. v. Bardeleben and E. B. Wilson both give 16, and Ziegler 32, as the number in man, but 24 seems to be the true number. The number in different animals and plants varies from 2 to 64, possibly more. C. E. Walker (Proc. Roy. Soc. B. lxxviii. 1906) states that mitoses in which there are but half the usual number of chromosomes in each daughter-cell are to be seen in the cells of bone-marrow and of lymph-glands and in leucocytes, but this observation requires confirmation.

[3] See on the disappearance of the nucleolus in mitosis, E. J. Sheppard, Quart. Journ. Micr. Sc. liv. 1909.

[4] O. Hertwig, Virchow Festschr. 1891.

[5] Van Bambeke and Van der Stricht, Soc. de méd. de Gand, 1891.

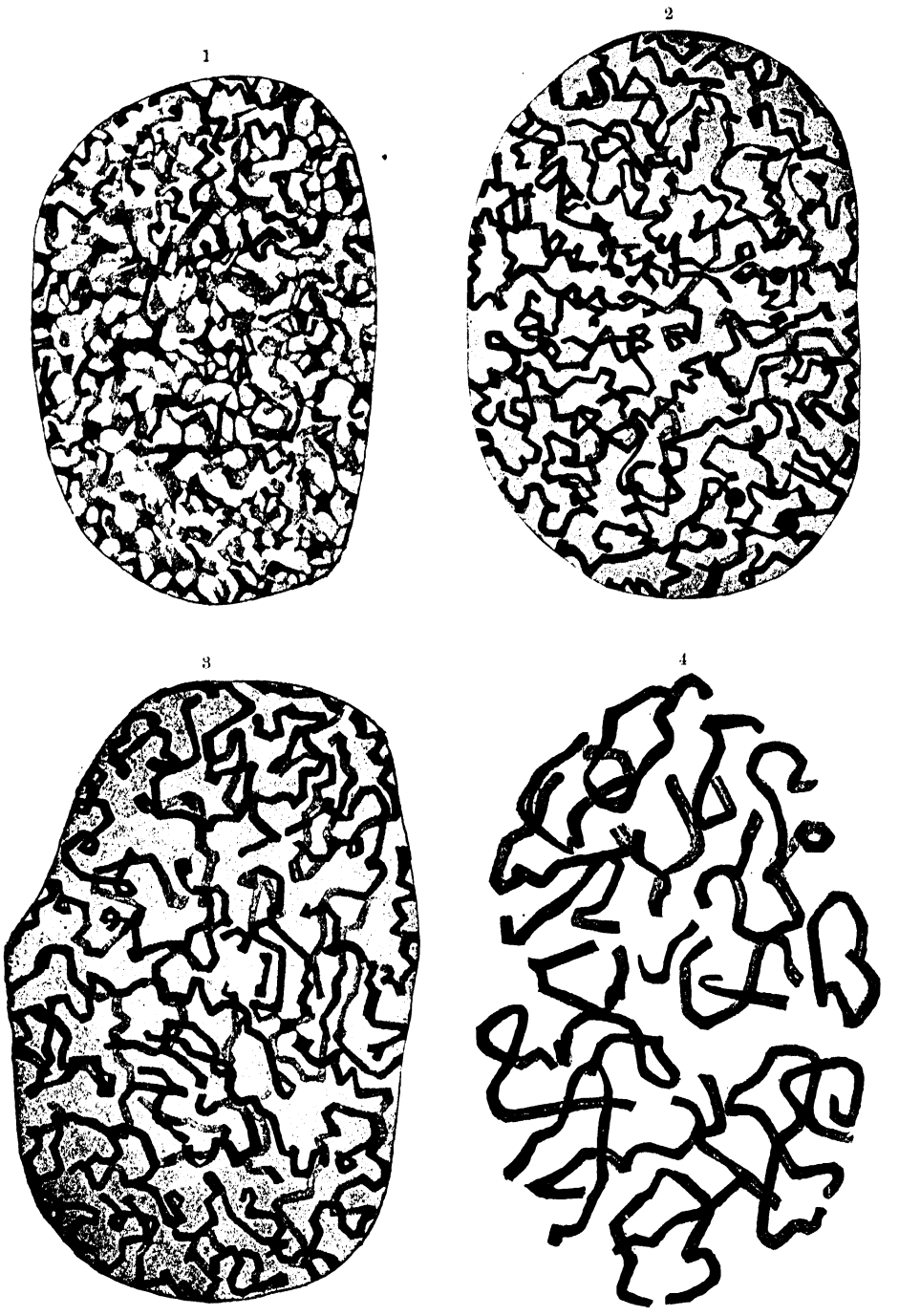


FIG. 76.—STAGES IN THE TRANSFORMATION OF THE CHROMATIN OF NUCLEI OF EPITHELIUM-CELLS OF THE SALAMANDER LARVA, LEADING TO THE FORMATION OF CHROMOSOMES. Magnified 2300 diameters. (M. Heidenhain.)

1. Chromatin still forming a network, but the fibres are becoming collected into convoluted threads. 2. Spirem condition, with distinct convoluted threads intertwined with one another. 3. The threads of the spirem are thicker and shorter, and are beginning to show their individuality. 4. The chromosomes are now distinct, and are about twenty-four in number. They already show indications of longitudinal splitting.

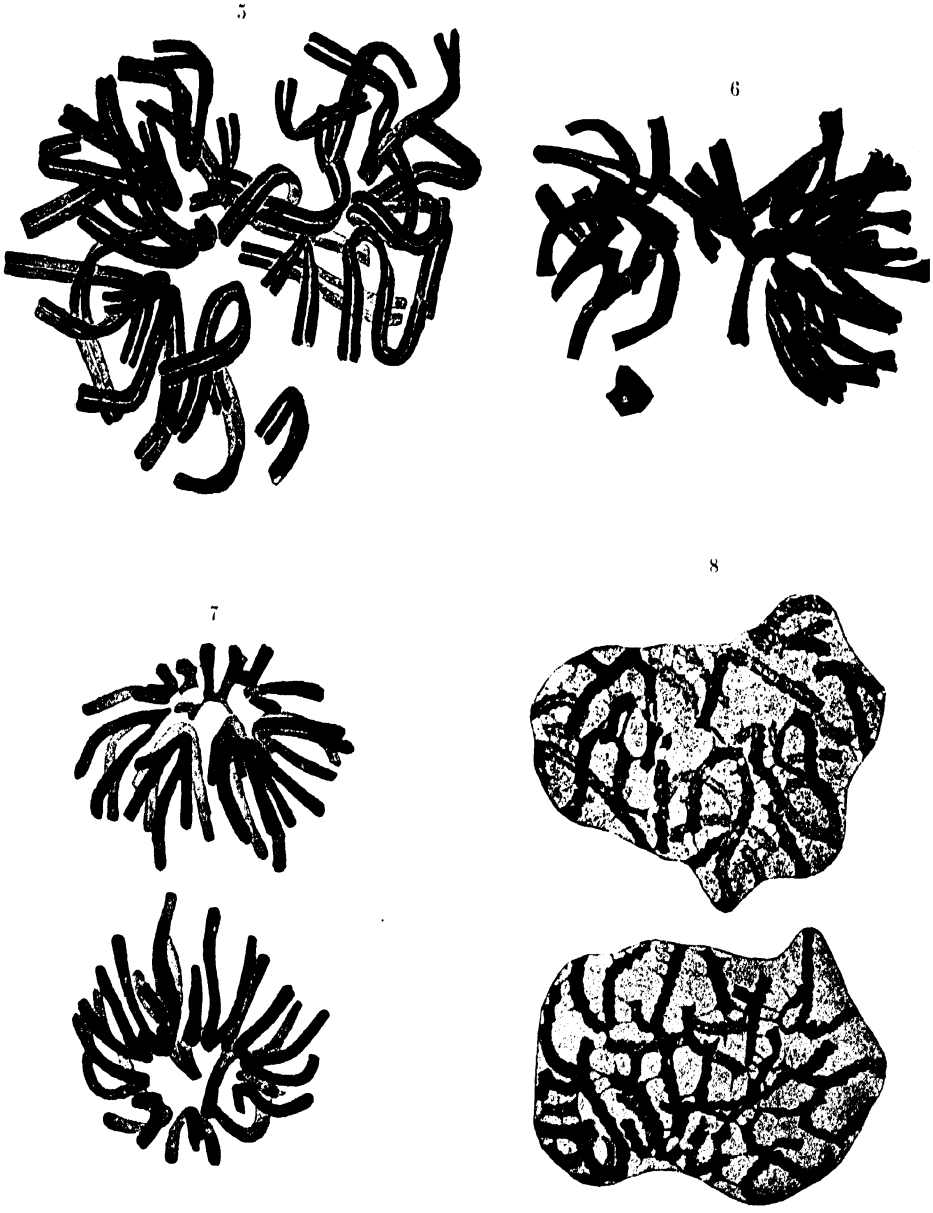


FIG. 76 (*continued*).—FURTHER STAGES IN THE TRANSFORMATION OF THE CHROMATIN OF NUCLEI OF EPITHELIUM-CELLS OF SALAMANDER LARVA, LEADING TO THE FORMATION OF DAUGHTER-NUCLEI. (M. Heidenhain.)

5. The split chromosomes are beginning to become arranged around the equator of the spindle (the spindle is not shown in any of these figures). 6. Equatorial arrangement of chromosomes; one chromosome is dislocated. 7. The split chromosomes are in two groups which have passed towards the poles of the division-spindle to form the daughter-nuclei. 8. Completion of the process; the daughter-nuclei are now distinct from one another, the cell-substance (not here shown) having also undergone division. Notice that the chromosomes within the daughter-nuclei show chromatin particles, and that a chromatin network is becoming formed by lateral outgrowths from these particles.

result of entry of more than one spermatozoon, and is common in artificial parthogenesis (fig. 61).[1]

Long before the formation of chromosomes is completed a remarkable series of alterations has occurred in connexion with the centrosome (figs. 78, 79). This, as already stated, always divides prior to cell-division and even before any alteration is perceptible in the nucleus, and from each of the two centrosomes which are thus produced achromatic fibrils radiate in all directions into the surrounding protoplasm. Those which are directed towards the other centrosome are especially well marked and serve to join the two centrosomes, constituting a spindle-shaped system which has been termed the *division-spindle*. This division-spindle lies at first lateral to and wholly outside the area occupied by the nucleus, but with the disappearance of the nuclear membrane and the formation of chromosomes it rapidly enlarges and its fibres are found to traverse the nucleus from end to end, the two centrosomes occupying the poles of the now elongated nuclear area.[2] It is around the equator of this spindle that the V-shaped chromosomes arrange themselves, with the apices of the V's directed towards the centre of the spindle, so that when regarded in optical section, from the direction of either pole, the V's radiate in a stellate fashion around the equator (*equatorial arrangement of chromosomes*) (fig. 79, 5). This appearance has given rise to the term *aster* or *monaster*, which is often applied to this stage of karyokinesis. It is usually now that the chromosomes begin to split longitudinally, each into two parts (fig. 83, B); but even before this stage and whilst the threads are still convoluted it is apparent that they are double, although they are not actually separated. The process of separation (*metakinesis*) begins at the apex of each V and extends along the limbs, and the resulting apices begin to pass towards the respective poles of the nucleus, one to each, whilst the ends of the limbs are still in contact with one another at the equator (fig. 83, C). But soon the separation becomes completed and the resulting chromosomes pass bodily towards the respective nuclear poles, where they again tend to group themselves in a stellate manner (fig. 83, E). The double figure which is thereby produced is known as the *diaster* and its formation marks the completion of the object of karyokinesis—viz. *the separation of the split chromosomes*.

The movement of the daughter or secondary chromosomes (which have resulted from the splitting of the primary chromosomes) towards the poles takes place along the fibres of the division-spindle, especially along those near its surface, which appear to guide the chromosomes, and have even, but on insufficient grounds, been supposed to contract and draw them towards the respective centrosomes. When the diaster is formed by the passage towards the centrosomes and nuclear poles of the two sets of secondary chromosomes, and by their grouping near and partly around these, they may be regarded as already forming two nuclei, the *daughter-nuclei* (fig. 77, *l*). These undergo a series of changes which result in the re-establishment of a reticular structure in the nuclear chromatin: these changes form the *telophase*. They consist either of an outgrowth from the chromosomes of lateral offsets which join them together into a network, or a clumping together of the chromosomes of each daughter-nucleus to form a chromatin mass (fig. 79), the apparent fusion beginning at the middle of the chromosomes. This mass undergoes vacuolisation and is thus eventually converted into a sort of spongework, the strands of which are connected by lateral offsets with one another. In this way there becomes formed a chromatin network, at the periphery of which a membrane

[1] It has also been described in erythroblasts (Van der Stricht), testicle-cells of Myriopods (Prenant, La Cellule, 1887), amnion of rat (Solger, Anat. Anz. 1891), cornea of Triton (Geberg), and in many embryonic cells (Kostanecki, Anat. Hefte, 1892).

[2] On the mechanism of the formation of the division-spindle, see F. Hermann, Arch. f. mikr. Anat. xxxvii. 1891; Kostanecki and Siedlecki, *ibid.* xlviii. 1897; Kostanecki, *ibid.* xlix. 1897; R. v. Erlanger, *ibid.*

makes its appearance. Later a nucleolus may become formed in each of the daughter-nuclei.[1]

In the meantime and while the daughter-nuclei are in process of formation the cell-protoplasm begins to show a separation opposite the equator of the nucleus (fig. 77 *m*), and this separation extends in from the surface to the centre until the cleavage is

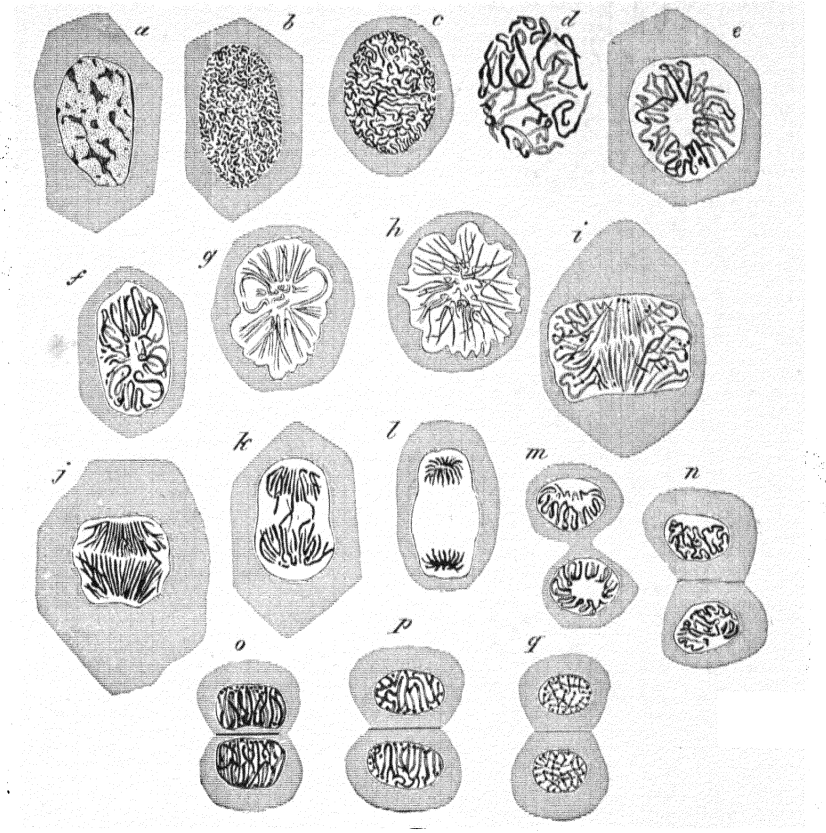


FIG. 77. — EPITHELIUM-CELLS OF SALAMANDER LARVA, SHOWING DIFFERENT CONDITIONS OF MITOSIS. THE CELLS WERE HARDENED IN PICRIC OR CHROMIC ACID, AND STAINED WITH HÆMATOXYLIN OR SAFFRANIN. (Flemming.)

a, resting cell, showing the nuclear network; *b*, first stage of division, the chromatin transformed into a skein of closely contorted filaments; *c*, second stage, filaments larger and less closely arranged: in this and all the other figures except *a* the nuclear matrix is clear; *d* (rather more magnified than the rest), filaments larger and showing an arrangement in loops: this is more evident in *e*, where they are arranged round the equator of the nucleus; *f*, filaments beginning to show signs of longitudinal division; *g*, longitudinal splitting more pronounced: star-like arrangement of chromosomes (aster); *h*, completion of longitudinal splitting of the filaments; *i*, commencing separation of filaments into two groups (metakinesis); *j*, further separation into two sets; *k*, separation more advanced; *l*, stellate phase of daughter-nuclei (diaster); *m*, commencing convolution of the filaments; *n*, filaments more contorted; *o*, *p*, gradual passage of daughter-nuclei into condition of rest (network, *q*). The division of the protoplasm is seen to begin in the stage represented by *m* and to be rapidly completed (at *n*).

complete. In most vegetable and in a few animal cells the separation of the protoplasm occurs simultaneously along a plane which exactly bisects the original cell and nucleus, and the line of separation is marked before separation actually occurs by a series of beaded enlargements of the fibres of the division-spindle, all which enlargements lie in the plane of subsequent division and seem to initiate that

[1] Grégoire et Wygaerts, La Cellule, xxi. 1903; Kowaleski, *ibid.*

division by themselves first dividing. This plane of beaded enlargements is the *division-plane* and the enlargements form collectively the *equatorial plate* (fig. 80); but this is absent in the division of most animal cells, the protoplasm of which seems as a rule to divide by a pinching-in or constriction which begins at the surface and gradually reaches the centre of the elongated cell. But the gap between these

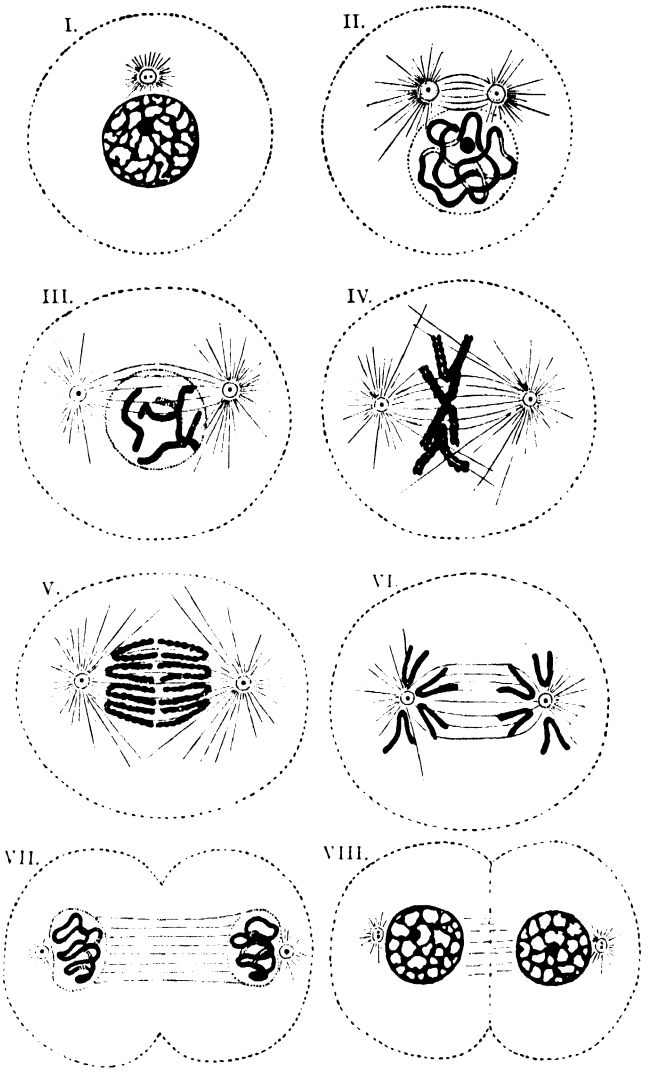


FIG. 78.—DIAGRAM SHOWING THE CHANGES WHICH OCCUR IN THE CENTROSOMES AND NUCLEUS OF A CELL IN THE PROCESS OF MITOTIC DIVISION.

The nucleus is supposed to have four chromosomes.

remains for a time bridged across by fibrils which are the remains of the equatorial part of the division-spindle, and there is often to be seen in the middle of the bridge a particle (fig. 81) which may be distinctively stained and perhaps represents the equatorial plate seen in other dividing cells.[1] This particle is the *intermediate corpuscle* of Flemming.

[1] Geberg, Anat. Anz. 1891.

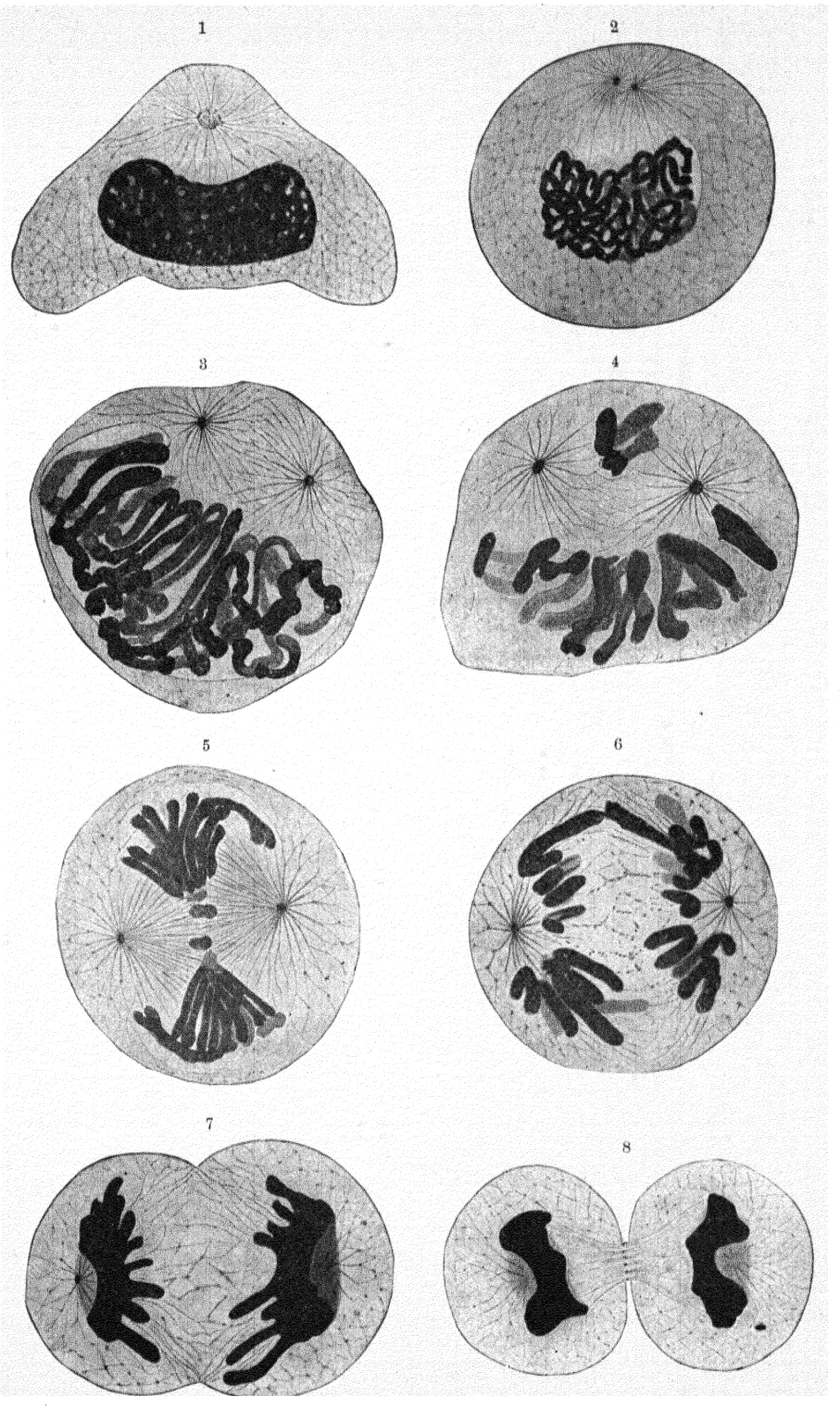


FIG. 79.—KARYOKINESIS OF ERYTHROCYTE OF LARVAL LEPIDOSIREN. (T. H. Bryce.)

The karyokinetic process has been watched in actual progress in all its stages by more than one observer. The time occupied has varied in different animals from half an hour to three hours. Observed thus in the living cell (fig. 82) it is not possible to follow out all the details of the process, which have only been elucidated in tissues the cells of which have been fixed by appropriate hardening reagents and afterwards stained.

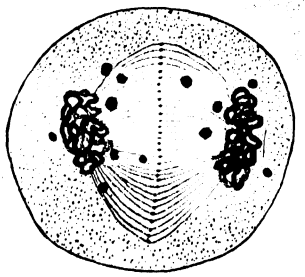


FIG. 80.—CELL-PLATE IN DIVIDING SPORE-CELL OF LILY.
(Gurwitsch, after Zimmermann.)

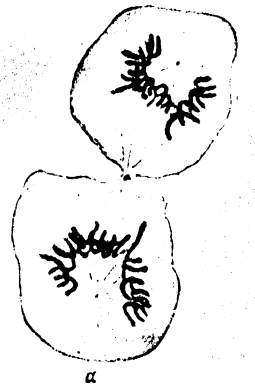


FIG. 81.—DIVIDING CELL CONSTRICTED TO FORM TWO DAUGHTER-CELLS EACH WITH CENTROSOME. (Geberg.)

The particle at the junction of the daughter-cells represents a rudimentary cell-plate.

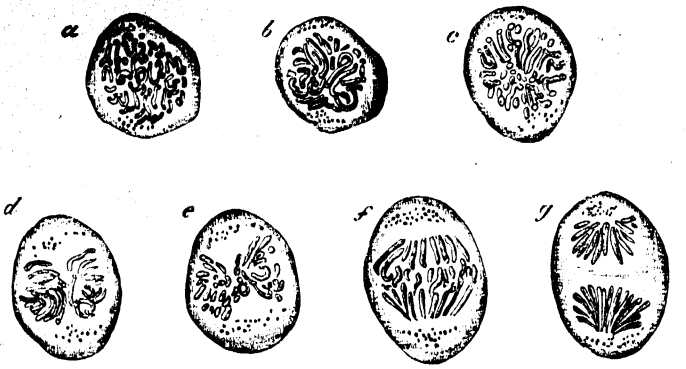


FIG. 82.—STAGES IN THE DIVISION OF THE NUCLEUS OF A LIVING EPITHELIUM-CELL IN THE EPIDERMIS OF A SALAMANDER LARVA. (Flemming.)

a, cell showing the nucleus transformed into a mass of contorted filaments; *b*, the nuclear filaments have become fewer, and begin to assume a converging arrangement; *c*, stellate form; *d*, *e*, equatorial stage, which was found to come and go more than once: eventually the filaments accumulated in a direction parallel to one another near the centre of the cell, and then gradually separated into two sets as shown in *f*. These as they retired towards the poles gradually assumed the stellate form *g* (diaster). The time occupied whilst the stages above represented were passed through was about three hours.

Leduc [1] obtains appearances closely resembling those of karyokinetic nuclei by placing in a salt solution of a certain strength, which we may term isotonic, two drops, near one another, of a stronger or hyper-isotonic solution, and in the middle of each of these a smaller drop of a weak or hypo-isotonic solution containing China ink in suspension. As seen in fig. 84 the formation of a division-spindle is singularly imitated, as well as the passage along it of chromosome-like threads which tend to become arranged at the equator of the spindle and may subsequently separate into two groups and pass towards the poles.

It has been shown by R. S. Lillie [2] that many of the positions which are successively assumed by chromosomes in the course of karyokinesis may be explained if we assume that the astral

[1] C. r. de l'assoc. franç. p. l'avancement de science, 1904.
[2] Amer. Journ. of Physiol. vol. xv. 1905.

centres are negatively charged portions of protoplasm—a condition which would be brought about if reduction processes were active at those centres. The result of this would be that the plane of the equator of the spindle joining the astral centres would become positive, and would tend to attract any negatively charged bodies floating freely in the protoplasm. This is certainly the condition of the chromosomes, which are pronouncedly acid and are to be looked

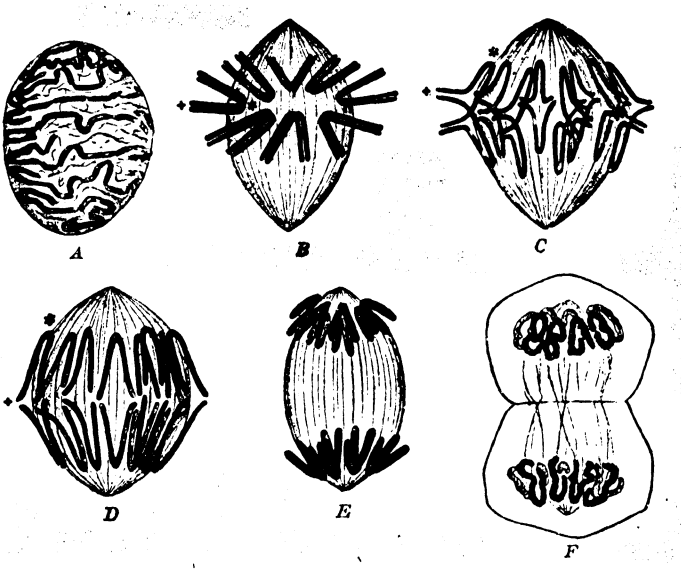


FIG. 83.—THE PRINCIPAL PHASES OF THE NUCLEAR CHROMATIN FILAMENTS IN THE PROCESS OF ORDINARY MITOSIS OF THE SOMATIC CELL. (Flemming.)

A, skein or spirem; *B*, aster with splitting of chromosomes; *C*, separation of the split chromosomes (metakinesis); *D*, continuation of this process; *E*, diaster; *F*, dispirem. The cell-protoplasm is represented in outline in *F*: it has itself undergone division at this stage. In this figure the (somatic) cells represented are supposed to have eight chromosomes.

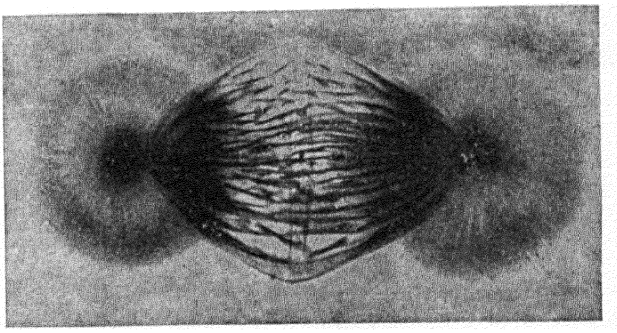


FIG. 84.—FIGURE ASSUMED BY DROPS OF A SUSPENSION OF CHINA INK IN SALT-SOLUTION WHEN PLACED IN THE MIDDLE OF LARGER DROPS OF A SALT-SOLUTION OF GREATER DENSITY. THE CIRCUMJACENT FLUID IS OF INTERMEDIATE DENSITY. (Verworn, after Leduc.)

upon as aggregates of anions; in this manner the changes in position which they assume in karyokinesis might be explained. Such changes of position can be imitated with Mayer's floating magnets, composed of magnetised needles passed through small pieces of cork and allowed to float on water with similar poles uppermost. If such magnets are conjoined by threads or wires into linear series and the repulsive poles of two fixed bar magnets are brought near the opposite

sides of a group of such 'chromosome models,' the latter tend to arrange themselves equatorially in a manner roughly similar to the equatorial arrangement of the chromosomes in karyokinesis. For explaining the further movements of the chromosomes after their splitting we should have

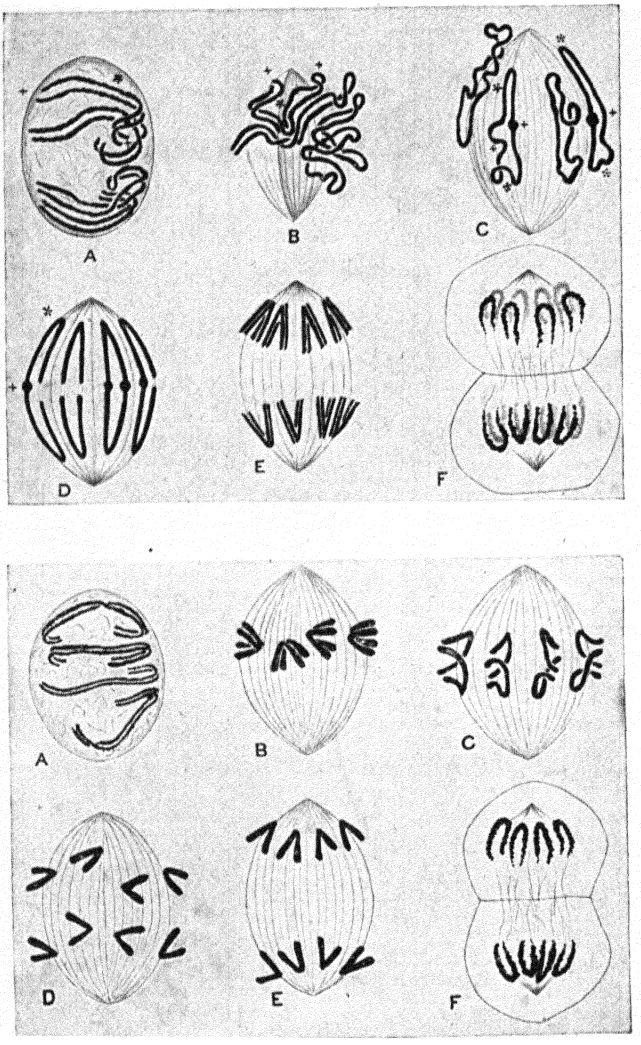


FIG. 85.—HETEROTYPICAL (I.) AND HOMOTYPICAL (II.) MITOSIS OF THE GENERATIVE CELL. (Flemming.)

The asterisk marks the middle, the cross the end of a chromosome.

The changes are to be compared with those shown in fig. 83. In the heterotypical form the chromosomes are already arranged in pairs before division commences; this condition (geminal condition, A) having been produced in the synaptic prophase. A longitudinal split is seen in the diaster stage and the daughter-nuclei have the somatic number of chromosomes (8 in this instance). In the homotypical form there is no longitudinal split of the V-shaped chromosomes (which are, however, arranged in pairs), and the separation to form the daughter-nuclei results in a reduction to one-half the somatic number.

to suppose that the electrical charge, either of the split chromosomes or of the poles of the spindle, becomes changed in character.

The phenomena shown in Leduc's experiment are also probably brought about by the electrical charges of the electrolytes in the solutions employed (Rhumbler).

Division of the generative cells.—In most instances of cell-division the two daughter-cells are exactly equal in size. But an exception to this rule occurs in the ovarian ovum or oocyte. This contains a large, well-marked nucleus and nucleolus, known respectively as the *germinal vesicle* and *germinal spot*. Just before or immediately after its extrusion from the ovary the ovum undergoes karyokinetic division twice in rapid succession, and in both instances, although the two daughter-nuclei are of equal size, the resulting cells are very unequal so much so in fact that the smaller daughter-cells were for a long time not recognised as cells at all and received the name of *polar globules* or *directive corpuscles*, because they were supposed to indicate the plane of first division of the ovum after fertilisation. It is now known, however, that the mitoses which occur in these two divisions are different from those which are seen in ordinary or somatic cells. The first of the two was termed by Flemming[1] *heterotypical mitosis* (fig. 85, I.). This form of mitosis is preceded by a *prophase* which consists of a longitudinal fusion of the chromosomes into double filaments (*synapsis*), so that each apparent

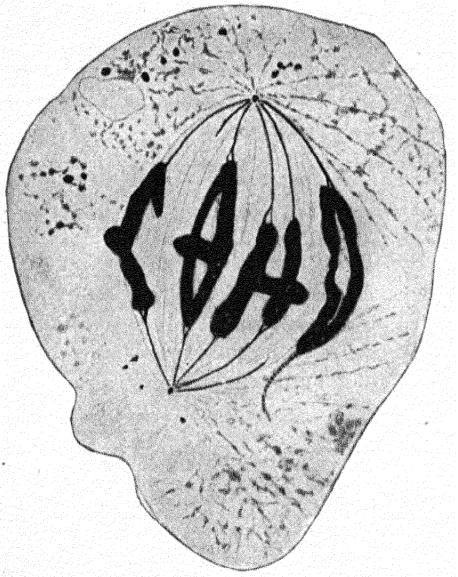


FIG. 86.—HETEROTYPICAL DIVISION OF SPERMATOCYTE OF BATRACHOCEPS, IN STAGE OF METAKINESIS. (Eisen.)

Each chromosome is attached to one of the coarser threads of the division-spindle.

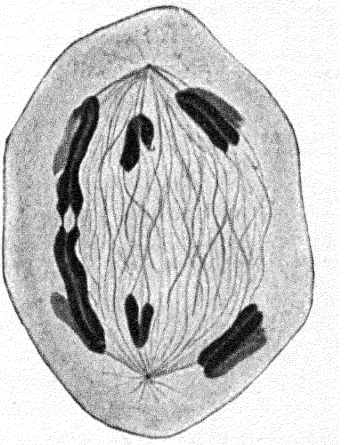


FIG. 87.—HETEROTYPICAL DIVISION OF SPERMATOCYTE OF SALAMANDRA, SHOWING COMMENCEMENT OF FORMATION OF DAUGHTER-NUCLEI. THE CHROMOSOMES SHOW THE SECONDARY LONGITUDINAL SPLITTING DESCRIBED IN THE TEXT. (F. Meves.)

chromosome represents really two (*gemini*). Presently these begin to separate again about the middle, the ends remaining connected, and they thus form elongated rings, sometimes twisted, and by a shortening of the constituent chromosomes often becoming more or less circular. Ultimately each ring breaks across and the resulting chromosomes pass towards the poles to form daughter-nuclei. As they do so they split longitudinally, so that these daughter-nuclei now have the full number of chromosomes. The formation of the second polar globule is brought about by a subsequent mitosis, which was termed by Flemming *homotypical* (fig. 85, II.). This division occurs at once without the daughter-nucleus which is left in the ovum re-assuming the resting, reticular condition. In it there is an absence of the usual longitudinal splitting of the chromosomes, the daughter-nuclei being in this case formed by the bodily transference along the division-spindle of one-half of the total number of chromosomes of the mother-nucleus towards each pole of

[1] Arch. f. mikr. Anat. xxix. 1887.

the spindle. The result is that both the second polar globule and the ovum, which represent the cells resulting from the second division, have only one-half of the number of chromosomes which is usually found within the somatic cells of the particular species of animal.[1] This phenomenon is known as the *reduction-division*, because the result is to produce a nucleus within the ovum in which the number of chromosomes is reduced to one-half the ordinary or somatic number. The nucleus remaining in the ovum, although it soon grows to a considerable size and may assume the ordinary appearance of a resting nucleus, nevertheless differs in the above important particular from the ordinary cell-nucleus. It is known as the *germ-nucleus* or the *female pronucleus*, and its formation is an essential preliminary to the completion of fertilisation. The changes which lead to the extrusion of the polar globules and the production of an ovum which is ready for fertilisation are known collectively as *maturation of the ovum*.

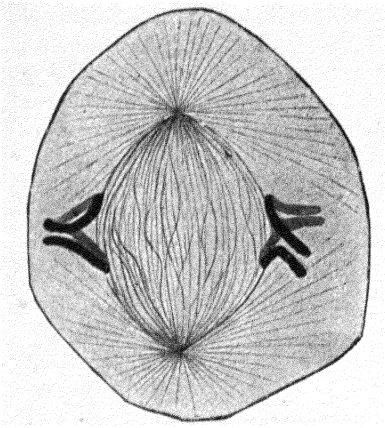


FIG. 88.—HOMOTYPICAL DIVISION OF SPERMATOCYTE (SECOND GENERATION) OF SALAMANDRA AT STAGE OF METAKINESIS. (F. Meves.)

The chromosomes (only four of which are represented) are beginning to pass towards the poles of the nucleus.

Similar heterotypical and homotypical mitoses, preceded by a synaptic phase and eventually resulting in reduction of the number of chromosomes to one-half, occur also in the division of the cells (*spermatocytes*) (figs. 87, 88) which produce the *spermatids*, which develop into spermatozoa. The latter, as a study of their development shows, are detached motile flagellated cells of exceedingly minute size, composed of head, middle piece, and tail. The head is formed almost entirely by the nucleus of the spermatid, the middle piece represents the remains of its protoplasm, and the tail or cilium contains a filament which has grown out from its centrosome (fig. 4, I.). The nuclear chromatin of the head of the spermatozoon is constituted, to more than 90 per cent., of nucleic acid. This head appears, even under the highest powers of the microscope, as a uniform mass of chromatin, but the study of its development shows it to have been formed by the blending of chromosomes which, in consequence of the reduction-division already mentioned, are just one-half the number found in the ordinary somatic cells of the same animal. It is therefore, again, not a complete but a half nucleus. This constitution of the nucleus is strikingly shown when it reaches the ovum and undergoes enlargement within that body. Having passed through the external membrane of the ovum, in some animals through a special orifice known as the micropyle, it becomes imbedded in the protoplasm, the tail disappears (although sometimes it remains visible for a time, fig. 89),

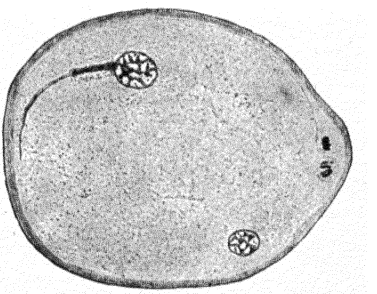


FIG. 89.—OVUM OF BAT WITH POLAR BODIES AND GERM- AND SPERM-NUCLEI. (Van der Stricht.)

The development of the sperm-nucleus from the head of the spermatozoon is very evident in this case, because the rest of the spermatozoon happens not to have been thrown off.

[1] The first polar globule may also divide into two, and each of these also has then only one-half the usual number of chromosomes. For an account of the division phenomena which characterise the maturation stages of the ovum, see vol. i. For other details, see Ries, Centralbl. f. Physiol. xxiii. 1909.

the head grows larger and exhibits the usual nuclear network. It is now known as the *sperm-nucleus* or *male pronucleus*. The centrosome which was contained in the middle piece of the spermatozoon becomes free within the protoplasm of the ovum.[1] It there divides and forms a division-spindle, whilst fine lines radiate from the poles of the spindle (centrosomes) into the surrounding protoplasm. There are now two half-nuclei in the ovum, the germ-nucleus and sperm-nucleus, or the female and male pronuclei, one derived from the nucleus of the ovum and the other from the head of the spermatozoon.[2] These (fig. 90) approach one another, the chromatin of each separates up into chromosomes, the outlines of the two nuclei blend and the chromosomes are intermingled, so that the resulting nucleus has now the number of chromosomes normal to the somatic cells

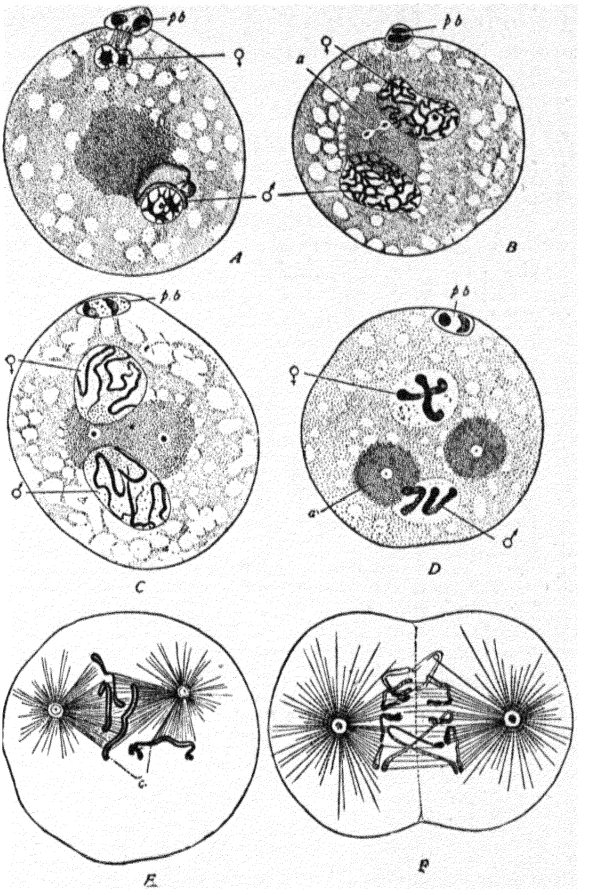


FIG. 90.—MATURATION, FERTILISATION, AND FIRST DIVISION OF OVUM OF ASCARIS MEGALOCEPHALA (BIVALENS) (slightly modified from E. B. Wilson after Boveri).

A, second polar globule just formed; the head of the spermatozoon is becoming changed into a reticular nucleus (♂), which, however, shows distinctly two chromosomes; just above it, its archoplasm is shown: the egg-nucleus (♀) also shows two chromosomes.

B, both pronuclei are now reticular and enlarged; a double centrosome (*a*) is visible in the archoplasm which lies between them.

C, the chromatin in each pronucleus is now converted into two filamentous chromosomes; the centrosomes are separating from one another.

D, the chromosomes are more distinct and shortened; the nuclear membranes have disappeared; the attraction-spheres are distinct.

E, mingling and splitting of the four chromosomes (*c*); the achromatic spindle is fully formed.

F, separation (towards the poles of the spindle) of the halves of the split chromosomes, and commencing division of the cytoplasm. Each of the daughter-cells now has four chromosomes; two of these have been derived from the ovum nucleus, two from the spermatozoon nucleus.

[1] No centrosome can be detected in the ovum after the formation of the germ-nucleus; and this is probably why the ovum does not divide again until a new centrosome is brought to it in the process of fertilisation. The centrosome of the spermatozoon is probably the essential element in initiating fertilisation (Boveri), and appears to be the parent of the centrosomes of all the cells which result from division of the fertilised ovum. In parthenogenetic ova the centrosome of the ovum does not disappear, but remains to initiate cell-division. Nor does the reduction-division above mentioned occur. For a review of the literature up to 1902, see T. H. Bryce, Quart. Journ. Micr. Soc. xlvi.

[2] This remarkable fact was discovered by O. Hertwig in 1875, Morph. Jahrb. Bd. i. Details regarding the processes of maturation and fertilisation were subsequently added by the work of E. Van Beneden, Boveri, and others, chiefly upon the threadworm known as *Ascaris megalocephala*; in one variety of which (bivalens) there are four chromosomes, in another (monovalens) only two, so that the following out of their changes in the various stages of cell-division is relatively easy.

of the species (as distinguished from the germ- and sperm-cells, which have only half that number), one half the total number having been derived from the female and the other half from the male parent. This resulting nucleus divides by ordinary karyokinesis (fig. 90, E, F); the chromosomes split; half of each passes into each daughter-nucleus, and thus each daughter-nucleus in the first and, it may be added, in every subsequent division, receives an equal portion of the chromatic material which was derived from each parent. The division of the nucleus is accompanied by changes in the division-spindle exactly similar to those which occur in the division of any other cell.

Details of the synaptic changes of the germ-cells and their reduction-divisions.—In the division of cells to form the oocytes within the ovary and in the division of the spermatocytes within the testicle, a series of changes occurs in the nucleus prior to its commencing karyokinesis, but these do not immediately lead to its division, although they are preparatory to that process. The changes are essentially the same for both sexual cells and the description in the one will apply *mutatis mutandis* to the other (figs. 91, 92).

The chromatin of the cell whose repeated division is to produce the matured sexual cell is granular: after the first division the nuclei of the daughter-cells develop chromatin filaments

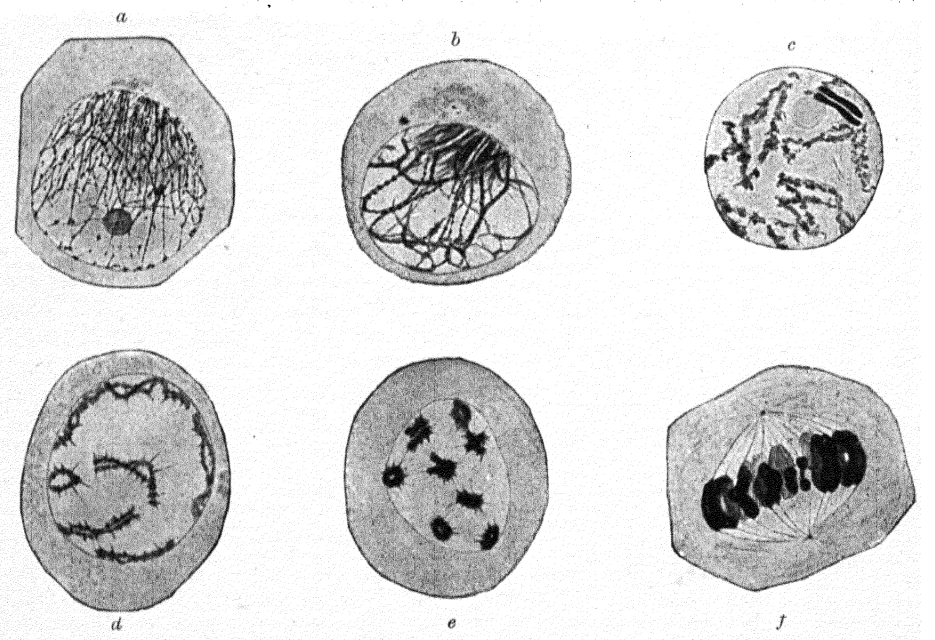


FIG. 91.—PROPHASE AND ANAPHASE IN SPERMATOCYTE OF MYXINE. (Schreiner.)

a, *b*, synaptic prophase; *c*, *d*, germinal chromosomes; *e*, tetrad formation; *f*, equatorial arrangement of chromosomes (metakinesis).

which eventually form a network. This network gives place to a tangle of chromatin threads (figs. 91, 92), which become aggregated at one place. This has been termed the *synaptic phase*. The threads, which are connected at one end with small masses of chromatin (*chromoplasts*), from which they appear to grow out, next show a tendency to assume a parallel position, lying side by side, two and two, and the pairs of chromatin threads adhere closely together, forming thicker threads of half the original number. The thicker threads thus formed presently lose their tangled arrangement and are disseminated through the nucleus. The threads show a longitudinal separation indicative of their double nature, and are termed *diads*. These subsequently shorten into small masses of chromatin, the duplicate nature of which is often obscure at this stage. This phase is followed by a marked growth of the cell, which

is then ready to undergo the divisions by which the mature ovum and polar globules, or by which the spermatids, are produced.[1]

There is another peculiarity sometimes observable in these changes of the germ-cells which may be here alluded to. This is the so-called tetrad formation. It consists in the chromosomes

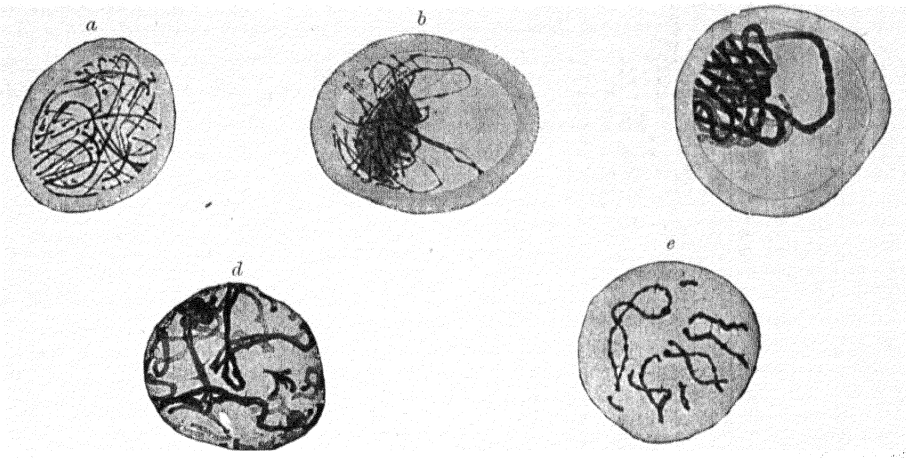


FIG. 92.—SOME STAGES IN THE MATURATION OF THE EGG OF THE RABBIT. (Winiwater.) Magnified 1700 diameters.

a, nuclear network converted into delicate looping threads; *b*, synaptic prophase (fine threads); *c*, synaptic prophase (thick threads); *d*, nucleus now occupied by double filaments; *e*, double chromosomes.

which have been produced in the manner above described becoming connected together into groups of four, which are known as *tetrads*. These take the form either of quadruple bundles of chromatin rods or of minute squares with a chromatin particle at each corner, or of chromatin rings which exhibit enlargement at four equidistant points (fig. 93). When formed, the number of tetrads is always half that of the ordinary number of chromosomes, but as each consists of four elements they contain collectively twice the ordinary number of chromatic elements, a splitting of the diads having occurred to produce the tetrad groups. When the ovum

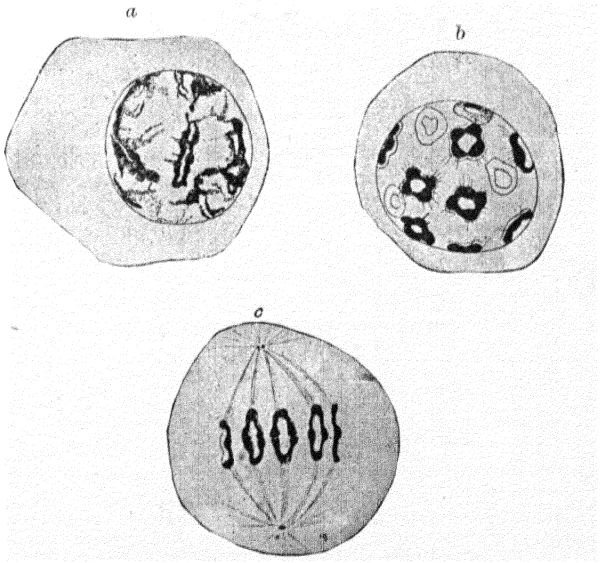


FIG. 93.—THREE STAGES OF HETEROTYPE MITOSIS IN SPERMATOCYTE OF TRITON. (Moore.)

a, geminal condition of chromosomes; *b*, gemini arranged in quadrate loops or tetrads; *c*, separation of tetrads into the duplex chromosomes of the daughter-nuclei.

[1] These changes were described in the ovary of the rabbit by v. Winiwarter (Arch. de biol. 1900), whose account has been confirmed by Miss J. Lane-Claypon (Proc. Roy. Soc. 1905); in the cat by Winiwarter and Sainmont (Arch. biol. xxiv. 1908); in the spermatocytes of Myxine by A. and K. E. Schreiner (Arch. de biol. xxii.); and in Selachians by J. Maréchal (Anat. Anz. Bd. xxv. p. 383, 1904). The synaptic stage, which has also been described in the process of spermatogenesis, is not universally met with in that, according to Duesberg (Arch. f. Zellforschung, iii. 1909). Cf. Moore and Walker, Rep. Cancer Res. Lab. Univ. Liverpool, 1906; Fick, Arch. f. Zellforschung, i. 1908; Goldschmidt, *ibid.*; F. Meves, *ibid.*

divides to form the first polar body, each tetrad separates (longitudinally, if the group is linear) into two diads; and of these one remains in the ovum and the other passes into the polar body, or, in the case of the spermatocyte, one passes into each daughter-nucleus; each resulting cell therefore contains the normal number of chromosomes peculiar to the somatic cells of the species. At the second (or reduction) division, which immediately follows the first without a resting period, each diad is halved, and of the chromosomes resulting from its division one remains in the ovum and the other passes into the second polar body, or, in the case of the spermatocytes, one passes into each spermatid, so that the ovum or spermatid, as the case may be, is left with one-fourth of each original tetrad and with a number of chromosomes which is exactly one-half the number found in the somatic cells of the species.

Object of the karyokinetic changes in the dividing cell.—Since in the process of splitting each chromosome divides into two perfectly similar portions, and this is effected by the splitting of its individual chromatin particles, it is clear that we have in the karyokinetic process a mechanism for an exact quantitative division of the chromatic substance of the nucleus between the two daughter-nuclei (Roux); whereas in the reducing division of germ-cells (ova and spermatic cells) the distribution of chromatin may be qualitative (see below). From a consideration of these facts and of many other circumstances which it is impossible here to allude to, Weismann has concluded that the chromosomes (idants) with their constituent particles (ids) contain the physical material by means of which heredity is maintained: the chromatin particles (ids) themselves being assumed to be made up of a vast number of ultra-microscopic organised particles which are distributed variously in the daughter-cells as multiplication proceeds, and are the 'determinants' of the changes in the cells which lead to the formation of the various tissues and organs of the body. The determinants again are regarded as being themselves composed of molecules of living substance to which the name of 'biophores' is applied by Weismann. The result of the reducing division of the chromosome may be supposed to effect a separation of the (probably dissimilar) ids of each chromosome, without a splitting of the individual ids, whereas in their ordinary division the resulting daughter-chromosomes are probably of exactly similar nature, since each of the ids of which the chromosomes or idants are formed has split, and takes part in the formation of each daughter-chromosome. The importance which this difference of behaviour of the ids in the reducing division may have in producing variation is insisted on by Weismann [1] and others.

The reduction-division also occurs in plants, and in them it may show itself long before the ova and spermatozoids appear. Thus in the ferns all the cells of the prothallium have the reduced number of chromosomes (Strasburger), in Hepaticæ those of the sporogonium (Farmer), and in Gymnosperms those of the endosperm (Overton, Dixon). In flowering plants the reduced number is found in the pollen grains and in the cells of the embryo-sac respectively (Guignard). A modified tetrad formation may also be observed—*e.g.* in the first division of the mother pollen-cells.

Strasburger has enunciated the interesting hypothesis that the reduced number of chromosomes is the number belonging to an ancestral type, and that the somatic number arose subsequently by conjugation of two cells. The cells which have the reduced number (germ- and sperm-cells) show therefore a return to the ancestral type, and the purpose of this reduction is to allow the mixing of chromosomes of two individuals, such as occurs in conjugation of unicellular organisms (*amphimixis* of Weismann), and as a result to assist in producing variation. The complexity of the problem relating to the chromosomes in the germ- and sperm-cells is increased by the recent observation, which has been made in certain insects (Hemiptera and Orthoptera), that in the division of the spermatogonia to produce spermatocytes one of the daughter-cells receives an extra chromosome (*heterochromosome*), usually rather smaller than the others, so that two morphologically distinct kinds of spermatozoa are produced in equal numbers. Sometimes instead of an extra chromosome one of the ordinary chromosomes is larger than the rest. Even the ordinary reduction-division, however, may produce a difference of quality in the resulting spermatozoa; and the fact that there is such a qualitative difference in the spermatozoa in particular cases seems to indicate, as McClung has pointed out, that the chromatin in the two kinds of spermatozoa represents the physical basis for the transmission of sexual characteristics.[2]

[1] Keimplasma, Jena, 1892. English translation by E. B. Poulton. Weismann's views are discussed by Bryce in the volume of this work which deals with Embryology. On the significance of the reduction-division, see also Henking, Zeit. f. wiss. Zool. liv. 1892. For a criticism of the chromosome hypothesis, see R. Fick, Arch. f. Anat. Suppl. 1905.

[2] See on the accessory chromosome, Henking, Zeitschr. f. wiss. Zool. xlix. 1890, and li. 1891; Wallace, Anat. Anz. xviii. 1900; W. S. Sutton, Bull. Univ. Kansas ix. 1900, and Biol. Bull. iv. 1902; de Sinéty, La Cellule, 1901; McClung, Biol. Bull. iii. 1902; Stevens, Publ. of Carnegie Instit. of Washington, No. 36, 1905; E. B. Wilson, Science, xxii. 1905; Journ. Exper. Zool. ii., iii. and vi. 1905, 1906, 1909; Montgomery,

Respective functions of nucleus and centrosome in cell-division. From the description of karyokinetic cell-division which has been given it might perhaps be inferred that the essential function of the nucleus is to initiate and produce the division of the cell, and this is in fact the view which until recent years was universally held. It would, however, be more correct to say that in those cells where they occur the centrosome and astrosphere initiate and govern cell-division rather than the nucleus. This is strikingly shown with the ovum, which, after the reduction-division resulting in the extrusion of the second polar globule, is found to be destitute of centrosome and astrosphere. These are supplied by the spermatozoon in fertilisation, and without a centrosome the 'matured' ovum, although possessing a nucleus, is incapable of division. That it is the centrosome or atrosphere and not the head (male pronucleus) of the spermatozoon which starts the division of the ovum is shown by the fact that the male pronucleus has occasionally been found to become atrophied (in abnormal cases); nevertheless cell-division may be commenced and completed. It is also a well-known fact that many ova in the lower animals undergo complete development without the advent of the sperm-cell (parthenogenesis). In these cases either the centrosome does not disappear from the ovum or a new one is produced in the protoplasm. That the female pronucleus may also be dispensed with is shown by the circumstance that ova and parts of ova of echinoderms, which have been deprived of their nucleus, may still be fertilised by spermatozoa and undergo division. Nor is it necessary in these ova for a spermatozoon to be introduced, for various artificial means will start the division, such as increasing the osmotic pressure of the sea-water, and the addition of minute quantities of certain salts and other substances, *e.g.* fatty acids and hydrocarbons, to the water (R. Hertwig, A. D. Mead, T. H. Morgan, J. Loeb, E. B. Wilson, and others). In every one of these cases where division of the ovum is started it is always preceded by the appearance of one or more astrospheres in the protoplasm and by the formation of a membrane on the surface of the protoplasm. Since similar appearances may be produced in colloid solutions by electrical, chemical, and mechanical agencies, and such appearances are in these cases regarded as being due to the formation of localised polar differentiation accompanied by gelation within the colloid solution, it has been conjectured that the astrospheres which appear after fertilisation—whether natural (through the spermatozoon) or artificial (from chemical reagents)—are of an analogous nature, and that the essence of fertilisation is the introduction into the ovum of some chemical substance which produces an alteration of this character in the colloid solutions which constitute its protoplasm.[1]

If this view is correct, the function of the nucleus in cell-division is, as Roux and Weismann have supposed, connected rather with the transmission of characteristic features and modes of differentiation (heredity) than with the initiation and direction of cell-division. Besides this the nucleus has important functions in connexion with the general nutrition and with the special metabolic changes of the cell; doubtless these functions are also exercised during the division of the cell.

Science, xxiii. 1906; S. Gutherz, Arch. f. mikr. Anat. lxix. 1906–7; H. E. Jordan, Anat. Anz. xxxii. 1908; P. Buchan, Arch. f. Zellforschung, iii. 1909 (the literature up to date will be found in this paper). A heterochromosome does not occur in somatic cells, nor in the female generative cells. Nevertheless in some animals (*e.g.* Aphides) the determination of sex certainly depends upon the ova, and not on spermatozoa.

[1] Cf. Fischer and Ostwald, *loc. cit.* For the literature of artificial parthenogenesis, see J. Loeb, The Dynamics of Living Matter, 1906; and Address delivered before the International Medical Congress, Buda-Pesth, 1908.

FUNCTIONS OF THE NUCLEUS OTHER THAN THOSE CONNECTED WITH CELL-DIVISION.

That the metabolic processes within the cell are dependent upon the presence of the nucleus is shown by experiments upon unicellular organisms in which various observers (Nussbaum, Hofer, Verworn, and others) have substantiated the fact, first discovered by Brandt, that if such organisms are separated into two or more parts, the nucleated fragments continue to live and become regenerated into complete organisms, whereas, although the non-nucleated fragments may survive for a time—even for hours or days—and may show movements and even take in food-particles, they have no power of digestion or assimilation and show no constructive metabolism, so that the remainder of the organism is not regenerated; eventually such non-nucleated fragments always die.[1] A well-known instance of the loss of vitality which results from the severance of a part of a cell from the nucleus is furnished by the Wallerian degeneration of a severed nerve-fibre. In this case there is a mutual reaction between cell-process and nucleated cell-body, for the severance of the fibre, while on the one hand producing the degeneration just mentioned, on the other leads to metabolic changes in the cell-body which are also of a destructive character. The influence of the nucleus upon cell-metabolism is also illustrated by the fact that the nucleus is relatively large or is more abundantly provided with chromatin in cells which are obviously undergoing chemical changes of an active character. This is notably exemplified in the actively secretory cells of the silk-glands of caterpillars [2] and in certain large cells which are found in the ovary of insects (fig. 94) which prepare nutriment for the developing ova. In these the nucleus forms a ramified structure occupying a large part of the cell. In other cells (fig. 95) it may send amœboid processes into the part of the protoplasm where the food-granules are forming.[3] And in growing cells, as in those which are dividing, the nucleus is found in the part of the cell where the metabolic activity is presumably greatest. Further, in some growing cells, *e.g.* in neuroblasts [4] (fig. 96), it has been noticed that chromatin makes its appearance in the protoplasm near the nucleus on the side where the cell-growth is proceeding most actively, and it is suggested that the chromatin has been formed within the nucleus

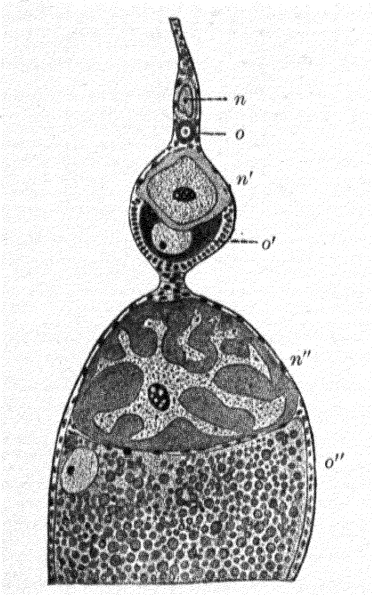


FIG. 94. — EXTREMITY OF OVARY OF FORFICULA. (Korschelt.)
n, *n'*, *n''*, nutrient cells; *o*, *o'*, *o''*, developing egg-cells.

[1] On the other hand, an absolutely bare nucleus has also apparently no recuperative power; a cytoplasmic environment seems an essential condition of its activity (Verworn; Pflüger's Arch. li. 1891). It must be added that this is not universally conceded, some authorities holding that such nuclei may exist independently, and that they may produce cytoplasm and become complete cells. There is, however, always a difficulty in deciding that the nuclei in question are absolutely bare, and unless special means are taken by the use of specific protoplasmic stains to determine this point, the fact that a thin layer of protoplasm cannot be detected is not sufficiently convincing evidence of its absence. For a discussion of this question, see Růžička, in Ergebn. d. Anat. xvi. 1906. On the question of nuclear functions, see Adami, 'The Dominance of the Nucleus,' Brit. Med. Assoc. Toronto, 1906 (reprint); Carlier, 'Nuclear Activity,' Birmingham Med. Rev. 1907.

[2] G. Gilson, La Cellule, vi.; E. Korschelt, Arch. f. mikr. Anat. xlvii. 1896; F. Meves, *ibid.* xlviii. 1897.

[3] See *inter alios* Korschelt, Zool. Jahrb. 1889.

[4] Scott, Toronto Studies, 1899.

and has been shed out from it for the nutrition of the growing and differentiating protoplasm. In gland-cells generally the nuclei become enlarged and richer in chromatin in the earlier stages of secretory activity, and in the later stages become diminished in size and poorer in chromatin, in consequence, it is suggested, of a discharge of the chromatic material into the cytoplasm for the production of the

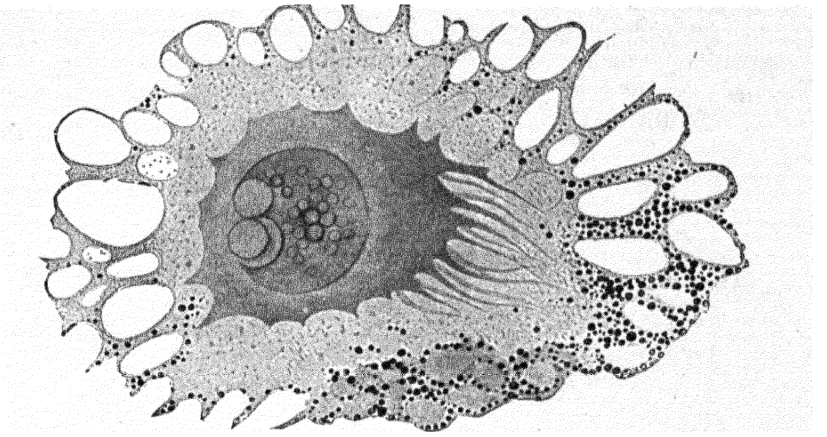


FIG. 95.—EGG-CELL OF PHOLCUS PHALANGOIDES. (Gurwitsch, after Van Bambeke.)

The germinal vesicle (nucleus) has amœboid processes extending towards the portions of the ovum where food-granules are accumulating.

special products of secretion.[1] In other cells also extrusions of material from the nucleus have been observed: in many cases these are undoubtedly derived from the nucleolus. Carlier suggests that this nucleolar extrusion is effete material, but it is generally considered to be matter elaborated within the nucleus and passed out into the cytoplasm for the formation of the metabolites of the cell (see p. 37).

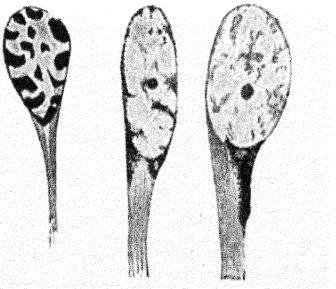


FIG. 96.—NEUROBLASTS FROM A PIG EMBRYO, SHOWING THREE STAGES OF DEVELOPMENT. (Gurwitsch, after Scott.)

In the least developed the nucleus contains abundance of basi-chromatin; the others show less within the nucleus, and an accumulation in the protoplasm near the nucleus.

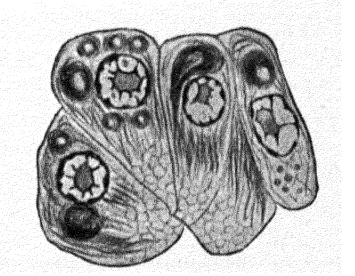


FIG. 97. — CELLS OF PANCREAS OF FROG SHOWING PARANUCLEI. (Matthews.)

In some gland-cells, *e.g.* those of the pancreas, a darkly staining spheroidal or crescentic body has been described by Ogata and others, situated in the cytoplasm, near the nucleus (fig. 97), and believed to be derived from the nucleus or nucleolus, although this is not definitely established. It has been termed *paranucleus*

[1] Cf. Carlier, La Cellule, t. xvi. 1899, and Proc. Scottish Nat. Hist. Soc. v. 1909.

(Nebenkern). A similar body was described by Balbiani in the ova of arachnids, under the name of 'yolk-nucleus,' and the presence of a yolk-nucleus has also been described in the ovarian ovum of the fowl,[1] and has since been noticed in other oocytes. Rabl finds a paranucleus in the salamander larva in the tissue-cells generally.[2] Connected with the paranucleus, and perhaps derived from it, are frequently to be seen filaments (*chondromitome*, see p. 24) which stain similarly with basic dyes and which are directed towards the part of the cell where the granules of *zymogen* are becoming formed. It has been suggested that the paranucleus and the fibrils in question are concerned in the elaboration of the secretion material, and the protoplasm which forms them has been accordingly termed the *ergastoplasm* (Garnier).

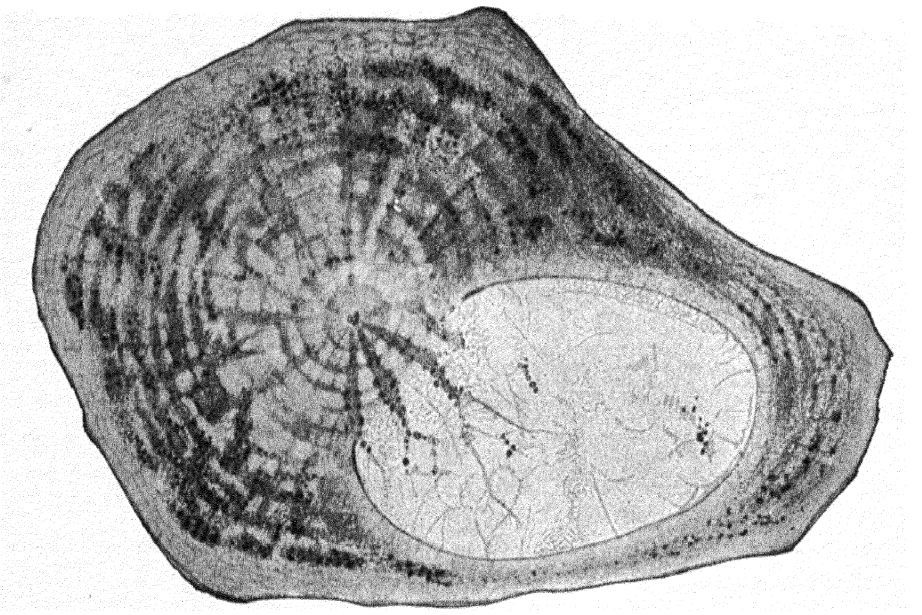


FIG. 98.—NERVE-CELL OF LOPHIUS WITH GAP IN MEMBRANE OF NUCLEUS OPPOSITE CENTROSOME. THE NISSL GRANULES APPEAR TO BE FORMING AT THIS PART. (Holmgren.)

As a further proof of the activity of the nucleus in connexion with the metabolic functions of the cell may be mentioned the fact that in the liver-cells crystals of hæmoglobin, derived, no doubt, from the breaking down of red blood-corpuscles, are occasionally to be seen not only in the cell-protoplasm but even in the interior of the nucleus, which may be distorted in shape by the presence of such a crystal.[3] Further, it has been shown by E. Holmgren[4] that in the nerve-cell the substance of the Nissl granules begins to form near the nucleus, often at one side of this, between it and the centrosome. At this place the nuclear membrane may become absorbed and nucleolar substance may be extruded (fig. 98).

[1] Schäfer, Proc. Roy. Soc. xxx. 1880.
[2] Arch. f. mikr. Anat. xlv. 1895.
[3] Browicz, Bull. Acad. Sci. d. Cracovie, 1900; P. T. Herring and Sutherland Simpson, Proc. Roy. Soc. B. lxxviii. 1906.
[4] Anat. Hefte, xii. 1899, and xv. 1900

VITAL PHENOMENA OF PROTOPLASM, CHEMICAL AND PHYSICAL CHANGES. AMŒBOID MOVEMENTS. CILIARY MOVEMENT.[1]

During the life of a cell its protoplasm is constantly undergoing chemical and physical changes. The chemical changes are in some measure determinable by comparing the products which are given off by the cells of a tissue with the nutritive material which they absorb. In all the higher animals this nutritive material is the blood or lymph, but the products which are formed are not entirely the same for all cells, since they vary in some measure with the specific activity of the cell; thus the cells of the salivary glands yield the saliva, those of the mammary gland milk, and those of the liver form the constituents of the bile and glycogen. But all protoplasm, whatever may be its specific function, has this in common—viz. that it absorbs and combines with oxygen, and yields carbon dioxide and other products of

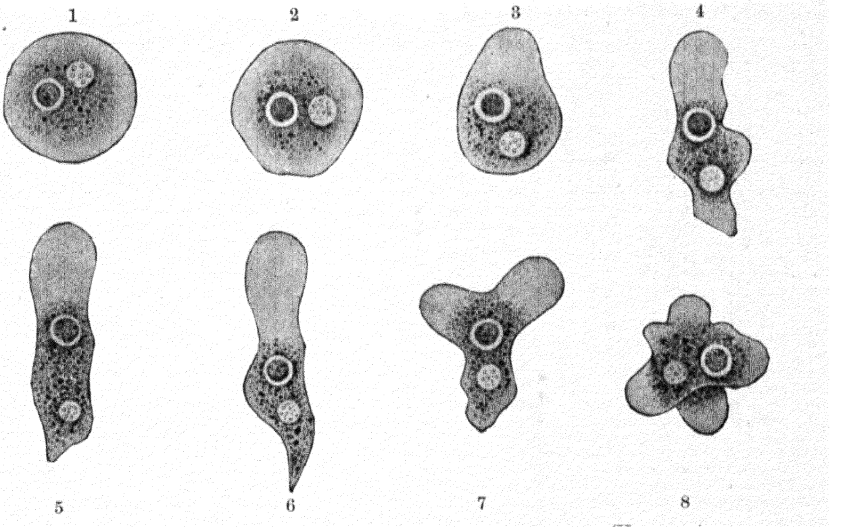


FIG. 99.—SUCCESSIVE CHANGES EXHIBITED BY AN AMŒBA. (Verworn.)

The protoplasm appears completely structureless, although containing granules near the nucleus and a contractile vacuole.

oxidation, and as a result of these processes of oxidation heat and other forms of energy are produced.[2] These chemical changes are always more marked as the functional activity of the cell becomes increased; accordingly, any circumstances which tend to promote the activity of protoplasm, such as warmth, electrical or other stimulation, the action of certain reagents, tend proportionally to increase the activity of its chemical processes. One general chemical property of living protoplasm is that by virtue of which it is able to assimilate and eventually to convert into its own substance non-living material. In this manner the protoplasm of a cell may increase in amount, or, in other words, the living substance may grow; but if the amount of protoplasm does not permanently increase, this is due to the

[1] For the vital phenomena of protoplasm, see Verworn, Allgemeine Physiologie, 1908, and J. Loeb, Dynamics of Living Matter, 1906. The literature is given by P. Jensen, Ergebn. d. Physiol. 1902, and W. Biedermann, *ibid.* 1909.

[2] According to Verworn, cell-respiration is associated rather with the protoplasm than with the nucleus (Localiz. d. Athmung in der Zelle, Haeckel Festschrift, 1907). Nevertheless, the observations of R. S. Lillie show that oxidation processes are centred round the nucleus (Amer. Journ. Physiol. vii. 1902). Cf. also footnote 1 on p. 39. The building up of oxygen into the cell and the production of carbon dioxide are probably the result of the action of different enzymes. For the literature of this question, see J. Loeb, Dynamics of Living Matter, pp. 13–23.

fact that just as much protoplasm is being broken down and removed from the cell as is added by the process of assimilation. A cell may also increase in size by the formation and accumulation of non-living material within it: in this case the accumulating material may be formed at the expense of the protoplasm, which may first grow and then break down to produce the non-living substance. Chemical processes which involve the building up of living material within a cell have received the general name of *anabolic* changes; those on the other hand which involve the breaking down of such material into other and simpler products are known as *katabolic*. By the *metabolism* of a cell is understood the sum of all the ana- and kata-bolic changes which are proceeding at any time within it.

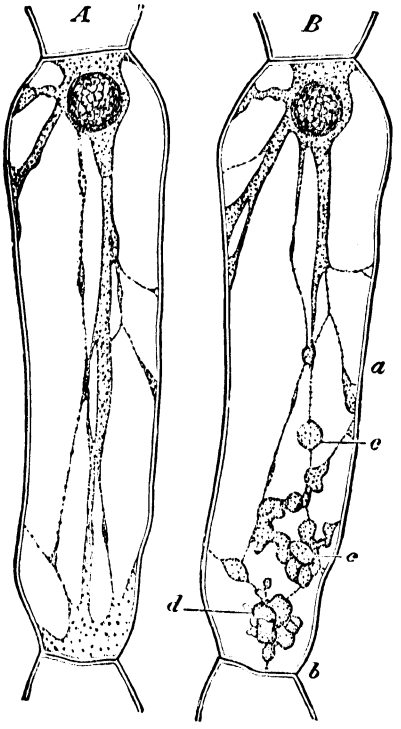


FIG. 100.—A CELL OF A TRADESCANTIA HAIR, A, IN NORMAL CONDITIONS; B, AFTER THE PASSAGE OF AN ELECTRIC SHOCK. (Verworn, after Kühne.)

a, cellulose wall; *b*, partition between two cells; *c*, collection of the protoplasm into clumps as the result of stimulations. The large spaces contain cell-sap.

Amœboid movements. — The most obvious physical changes seen in living protoplasm are those which are designated 'amœboid.' This term was derived from the freshwater amœba, the protoplasm (or sarcode) of which has long been known to exhibit spontaneous changes of form, accompanied by a flowing or streaming of its soft semifluid substance (fig. 99). The phenomenon was described by Rosenhof in the 'proteus animalcule' in 1755, but the similar movements of the cell-protoplasm of the higher animals was only recognised much later (in 1845) by Wharton Jones, who noticed the amœboid movements of the white blood-corpuscles of fish. If the protoplasm of the cell is enclosed by a membrane its movements are necessarily confined within the limits of such cell-wall, and the actual changes which are in these cases observable consist in a streaming or flowing of the soft living substance, such flowing being rendered obvious by the carrying along by the stream of any minute particles which may be imbedded in the protoplasm. The term 'rotation' has been given to a movement of this kind which is observed in many plant-cells such as those of the hairs of Tradescantia (fig. 100), and which is of a very regular character, usually in a determinate direction; but in animal cells the intrinsic streaming movements are less regular and usually less obvious in character. It is, however, on the other hand, in those animal cells which are unprovided with a cell-wall (free or naked cells) that what may be termed the amœboid movements proper present themselves, and in none more strikingly than in the white blood-corpuscles (leucocytes). If one of these be observed under a high power of the microscope it will be seen gradually to protrude a portion of its protoplasm at one part or another, and sometimes at several places simultaneously (fig. 101). The protrusions may at first consist only of the clearer portion of the protoplasm (hyaloplasm), subsequently the less clear part (spongioplasm) may extend into them

(figs. 102, 103).[1] These protrusions (*pseudopodia*) may be presently withdrawn again and others given out, or a pseudopodium which has been protruded at any one part of the corpuscle may extend itself further, and the main part or body of the

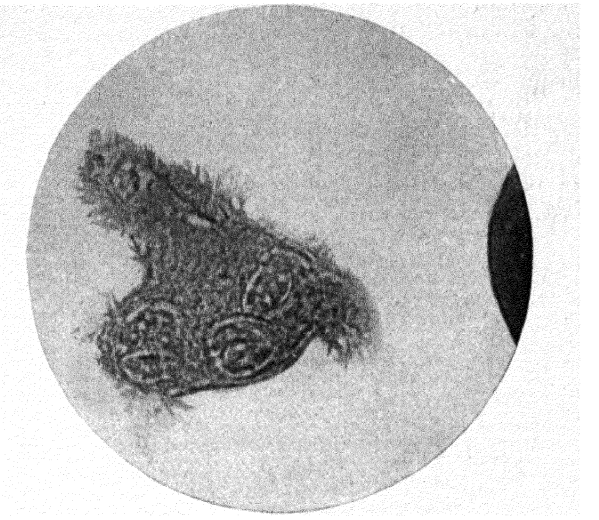


FIG. 101.—AN AMŒBOID LEUCOCYTE OF TRITON BLOOD, PHOTOGRAPHED WHILST LIVING. (Schäfer.) Magnified 1360 diameters.

The pseudopodia are fine and spine-like. The polymorphous nucleus can be detected within the cytoplasm.

corpuscle may pass gradually towards and into the extending pseudopodium. By a repetition of this process the cell may glide slowly away from its original situation, and move bodily along the field of the microscope, so that locomotion thereby

FIG. 102.—UNTOUCHED PHOTOGRAPH OF LEUCOCYTE OF TRITON, FIXED WHILST IN AMŒBOID CONDITION BY JET OF STEAM DIRECTED ON TO COVER-GLASS, STAINED WITH HEMATOXYLIN. (Schäfer.) Magnified 1360 diameters.

The inner part of the protoplasm shows an indistinctly reticular structure (spongioplasm), but the external layer and the pseudopodia are completely clear.

results. In this manner some of the white corpuscles, while the blood is circulating, pass through the walls of the capillaries and minute veins and find their way into the surrounding connective tissue, where they may further continue to exhibit amœboid movements. Corpuscles which have thus emigrated from the

[1] **Schäfer**, Proc. Roy. Soc. xlix. 1891; Griesbach, Pflüger's Arch. l. 1891.

vessels are known as 'wander cells,' and the passage through the vascular wall is known as 'diapedesis.' Although probably occurring to a certain extent normally, it is greatly increased in inflammatory conditions of the tissues.

Varieties of pseudopodia.—The pseudopodia of leucocytes, which are the characteristic amœboid cells of the blood and lymph and of certain tissues, such as the marrow, spleen, and

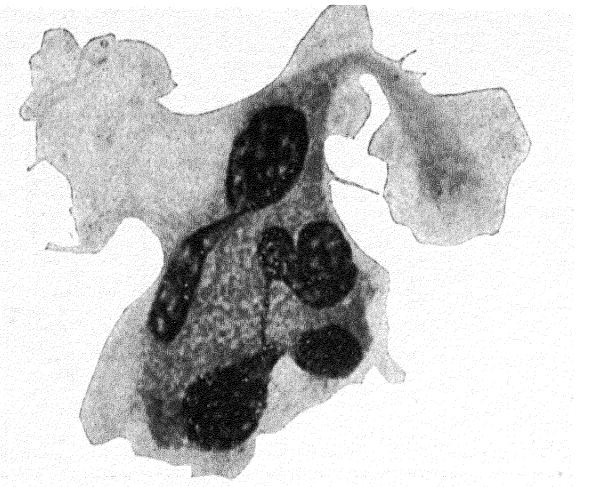


FIG. 103.—PHOTOGRAPH OF AN AMŒBOID LEUCOCYTE OF TRITON FIXED BY A JET OF STEAM AND STAINED WITH HÆMATOXYLIN. (Schäfer.) Magnified 1360 diameters.

The nucleus at first sight appears multiple, but on careful examination its several parts are united by threads of basi-chromatin. These cannot all be seen in the figure, which is a reproduction from an untouched negative, in which only one plane of the thickness of the corpuscle is photographed.

lymphatic glands, are usually broad projections from the general surface similar to those of Amœba proteus or Amœba limax (fig. 99). Such pseudopodia have been called *lobed* to distinguish them from the more pointed or even *spine-like* processes which are occasionally seen in leucocytes, characteristically in certain of those of Triton (fig. 101), and in some

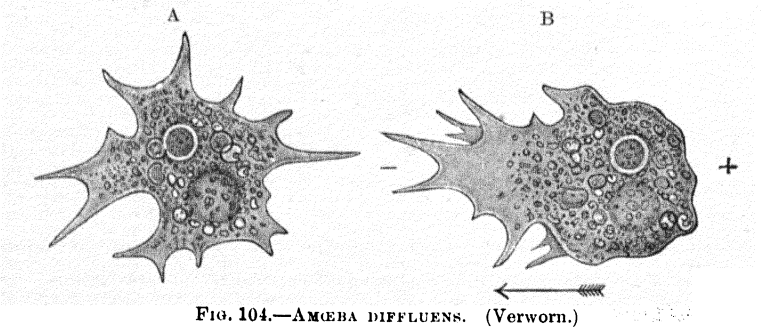


FIG. 104.—AMŒBA DIFFLUENS. (Verworn.)

A, unexcited, showing spiny pseudopodia emitted on all sides.
B, after closure of a galvanic current through the fluid. The pseudopodia are emitted only on the side nearest the kathode.

Amœbæ (A. diffluens, fig. 104), and from the *dendritically branched* amœboid processes, such as occur in the pigment-cells of Amphibia (fig. 105), as well as from the long fine *filiform* pseudopodia which are characteristic of the Heliozoa and allied Radiolarian animalcules (fig. 106). In the last-named the protrusion and retraction of the pseudopodia is very slow and the processes frequently fuse with one another. Moreover, these long filiform pseudopodia generally

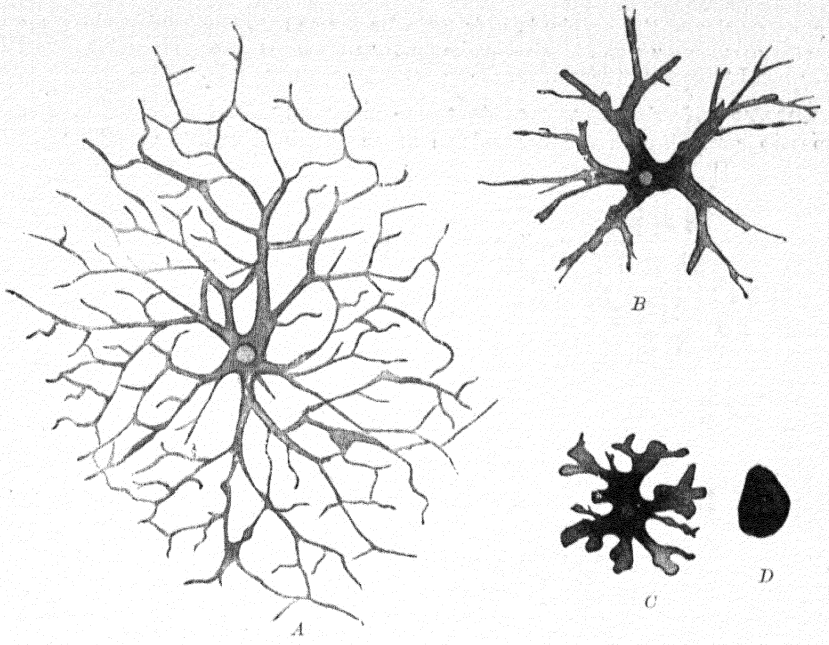


FIG. 105.—A PIGMENT-CELL FROM THE FROG'S SKIN: *A*, WITH PSEUDOPODIA FULLY EXTENDED *B*, *C*, *D*, VARIOUS DEGREES OF RETRACTION OF THE PSEUDOPODIA. (Verworn.)

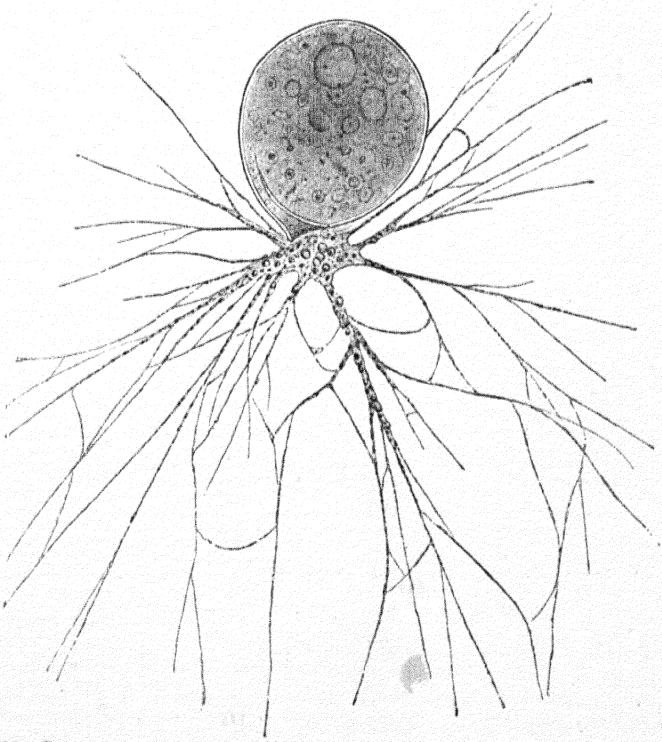


FIG. 106.—LIEBERKÜHNIA, A FRESHWATER RHIZOPOD, OUT OF WHOSE EGG-SHAPED SHELL PROTOPLASM WITH LONG PSEUDOPODIA ARE SEEN EXTENDED. (Verworn.)

show a streaming of the granules in their protoplasm in an outward direction along the one side of a pseudopodium and in the opposite direction along the other side, which is very like the so-called 'rotation' phenomenon in the protoplasm of plant-cells.

Intake of foreign particles. — When any kind of foreign particle comes in contact with the protoplasm of an amœboid cell, the particle adheres

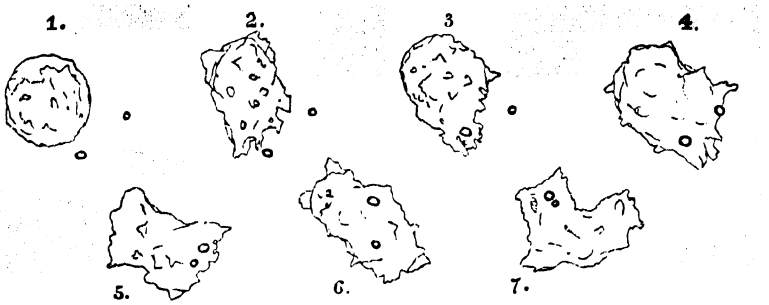


FIG. 107.—CHANGES OF FORM OF A WHITE CORPUSCLE OF NEWT'S BLOOD, SKETCHED AT INTERVALS OF A FEW MINUTES. THE FIGURES SHOW ALSO THE TAKING IN OF TWO SMALL GRANULES, AND THE CHANGES OF POSITION WHICH THESE UNDERWENT WITHIN THE CORPUSCLE. (Schäfer.)

to it, becomes enwrapped by processes of the protoplasm, and is then drawn gradually into the interior, where it may remain for some time without change, being moved about by any currents which exist in the cell, and carried along by the changes of place which the cell undergoes (see fig. 107). Eventually such foreign particles may be extruded again. If, on the other hand, the particle is of considerable size as compared with the protoplasm with which it comes in contact, the latter extends around and over it so as to envelop it more or less completely (fig. 108). This phenomenon of inception is thus dependent upon amœboid movements of the protoplasm.

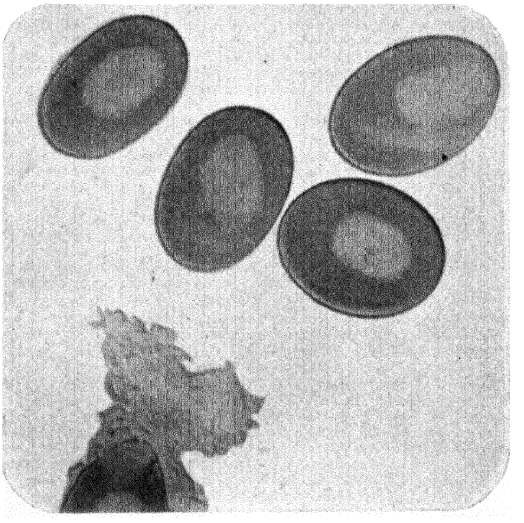


FIG. 108.—LIVING PHAGOCYTIC LEUCOCYTE OF SALAMANDRA EXTENDING AROUND AN ERYTHROCYTE OR RED BLOOD-CORPUSCLE. PHOTOGRAPHED FROM A FRESH PREPARATION OF SALAMANDER BLOOD. (Schäfer.) Magnified 600 diameters.
Four other erythrocytes are seen in the photograph.

The object of the phenomenon is clear in the case of animalcules, since their protoplasm has the power of digesting and assimilating suitable organic materials which may be taken in in this manner. Such materials are either dissolved within the body by a secretion containing digestive enzymes which accumulates around them in the form of vacuoles, or, in the case of Heliozoa, they may be digested in the pseudopodia themselves (fig. 109), and the digested products may alone be carried into the cell-body. But the digestive power of leucocytes is not of this pronounced character: indeed it has been doubted whether they can digest solid particles at all. Certainly granules of starch and globules of fat may be observed within them without undergoing any apparent change in the course even of hours. But there is abundant evidence that some leucocytes (phagocytes) attack and break down tissues of all kinds which are destined to be absorbed, and this is probably by a process of digestion. There is also strong evidence that they attack and devitalise bacteria and bacilli of disease, and thus tend to exercise a protective influence upon the body (Metchnikoff).

Intake of fluid material.—Although many amœboid cells possess the power of taking in solid material in the manner just described, it must not be forgotten that the normal method of intake of nutrient material by the cells of both plants and animals is in the fluid form. In doing this, there is no doubt that the cell-protoplasm has the property of exercising a selection; those materials of the

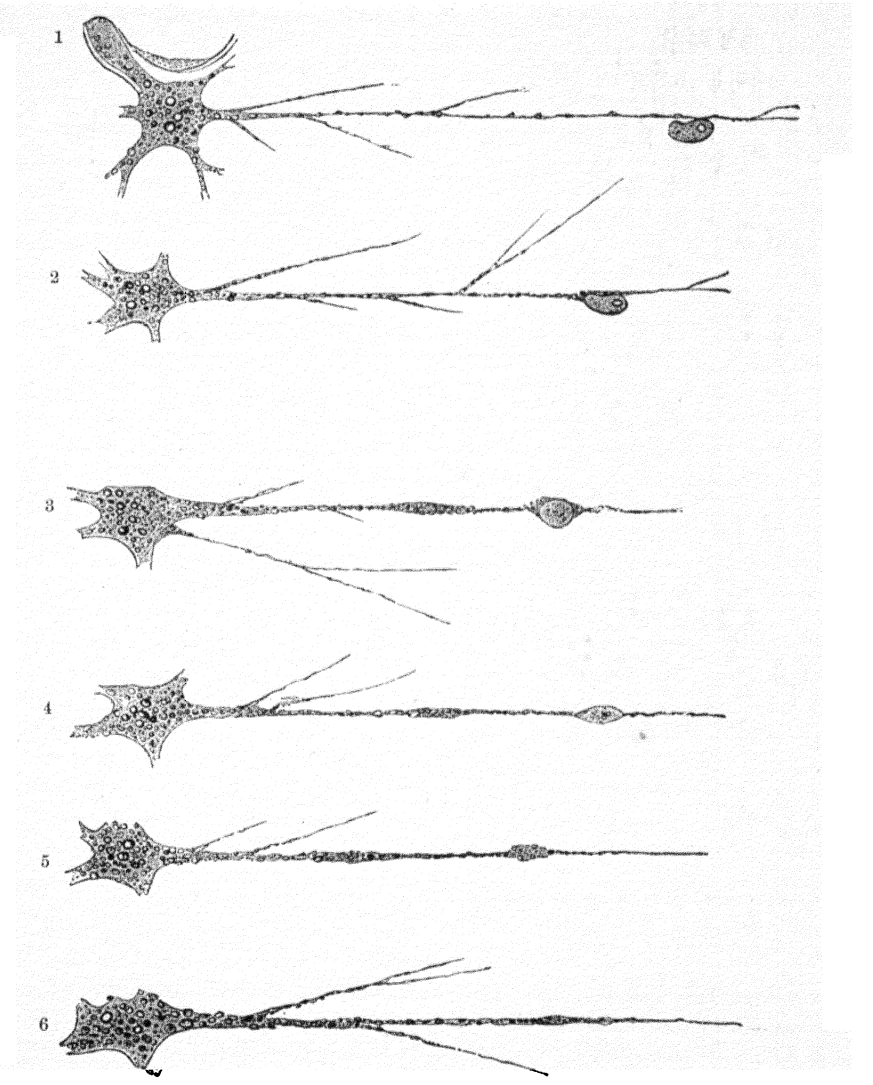


FIG. 109.—A LONG PSEUDOPODIUM OF LIEBERKÜHNIA UPON WHICH AN INFUSORIAL ANIMALCULE HAS BEEN CAUGHT. THE ANIMALCULE IS SHOWN BEING GRADUALLY ENCOMPASSED AND EVENTUALLY DIGESTED BY THE PROTOPLASM OF THE PSEUDOPODIUM. (Verworn.)

blood or lymph, or other liquid which bathes the cells, which are adapted for subserving a useful purpose in each particular case, being alone imbibed. For many animal cells this may include all the materials of the blood-plasma; for some, only certain substances. From these nutrient fluids the protoplasm builds up both its living substance and also non-protoplasmic products of its activity, and gives out again to the lymph unused or waste materials for which the cell has no further use.

PLATE IV, FIG. 1. — Banded felsite, showing flow structure.

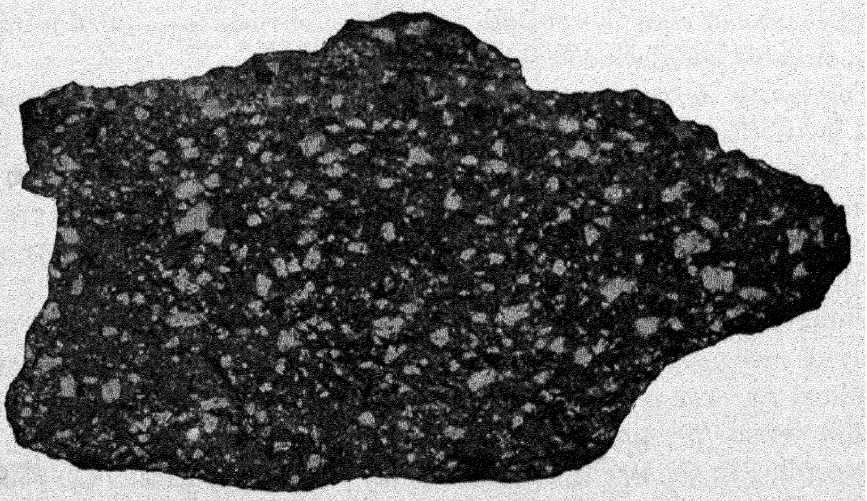


FIG. 2. — Trachyte, showing porphyritic texture.

degrees above the natural temperature of the body, although if maintained at an abnormally high temperature they are not long continued. A temperature a little above this maximum rapidly kills protoplasm, at least that of vertebrates, producing a stiffness or coagulation in it (heat-rigor), which is preceded by a general contraction; from this condition of rigor the protoplasm cannot be recovered. But the protoplasm of some organisms will stand temperatures approaching that of boiling water without passing into heat-rigor. Freezing may cause destruction of protoplasm in higher animals, but that of certain of the lower animal and plant organisms is capable of resisting extreme cold, apparently for an indefinite time. This has also been found true for seeds of plants (Dewar).

The contractility of protoplasm is dependent upon supply of oxygen. If this be withheld, the movements will, it is true, proceed for a time as usual, but this is because protoplasm, like other forms of contractile substance, such as muscle, has the power of storing away and using oxygen in some form of combination. For it is found that the active manifestations will not proceed indefinitely in the absence of oxygen, but cease after a time, to be renewed only on the accession of fresh oxygen.

Many reagents in solution influence the activity of protoplasm. Some of these act by adding to or subtracting from the water which it contains. As a general rule, and up to a certain point, the imbibition of water, varying according to the source of the protoplasm which is under observation (Thoma), accelerates the activity of the protoplasm, but beyond that point addition of water produces a destructive effect. A comparatively slight amount of desiccation is, so far at least as regards the protoplasm of the higher animals, destructive of vitality; but this statement does not hold good for the protoplasm of many of the lower animal and plant organisms. Hamburger and Hekma [1] found that phagocytosis was diminished in leucocytes on diluting the serum they are contained in with water.

Amongst reagents, acids, although very weak (even carbonic acid), stop the contractile manifestations and eventually kill the cell [2]; alkalies, on the other hand, if sufficiently dilute, increase at first their activity. The movements are stopped by chloroform and ether, but may be again resumed on the removal of those vapours. Certain drugs (*e.g.* veratria, and to a less extent quinine) rapidly arrest the movements.

Effect of electrical and other stimuli upon protoplasm.—The effect of strong electrical shocks from a Leyden jar or an induction coil upon protoplasm which is exhibiting either amœboid or streaming movements is, if sufficiently strong, to cause an immediate cessation of those movements, accompanied by a withdrawal into the main substance of any processes that may have been protruded. If the stimulation cease the movements will recommence, provided the shock has not been so severe as to injure the living substance.

Abrupt changes of temperature, and mechanical stimulation, such as is produced by sudden pressure or harsh contact, act in a similar manner.

Galvanotaxis, chemotaxis, barotaxis, phototaxis, &c.—The amœboid movements of protoplasm are also affected by the passage of a constant galvanic current through the fluid in which the organism is immersed. The result of such a current depends upon the nature of the ions which are associated with the protein particles. If, as is usually the case, these are kations, the particles are positively charged, and the effect produced takes the form of a movement in the direction of the current—*i.e.* towards the negative pole or kathode (figs. 104, 111); in other words, there is a contraction of the protoplasm on the anodal side, and a relaxation

[1] Biochem. Zeitschr. iii. 1907.

[2] This is not true of all protoplasm, for the blood-corpuscles of many insects live in a fluid which is strongly acid.

and consequent flowing out on the kathodal side (Verworn). These results are such as would be produced by the impinging of kations and anions respectively against opposite poles of the organism; the former tending to cause coagulation and contraction of colloid, the latter liquefaction and relaxation.[1] The action of the galvanic current is known by the term *galvanotaxis*, the movements thereby induced being spoken of as galvanotropism.[2] The direction of protoplasmic movements is correspondingly influenced by the (unilateral) action of chemical agents: their action is known as *chemotaxis* (*positive* if the movement is towards the source of the stimulus, *negative* if in the opposite direction). Such movements are sometimes determined merely by the addition of water to, or its withdrawal from, the protoplasm; the former tending to produce relaxation, and the latter contraction, of the side of the cell upon which the influence is exerted. But the action of most chemical agents is due to their contained electrolytes, and the effects vary according to the electrical charge which the colloid particles of the protoplasm exhibit (compare what is stated on this subject on p. 12 and on p. 79). The direction of movement is also dependent upon the concentration of the salt, and may be reversed with

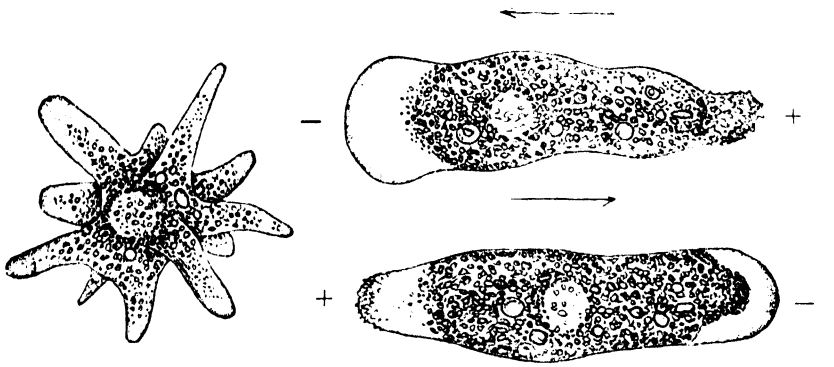


FIG. 111.—GALVANOTAXIS IN AMŒBA PROTEUS. (Verworn.)

On the left an amœba with numerous pseudopodia. On the right the same organism after closure of galvanic current passing from right to left in the upper figure; reversed in the lower. The arrows indicate the direction which the amœboid movement is taking.

increase of concentration.[3] Chemotaxis plays an important part in many physiological phenomena and is sometimes quite specific in its action. Thus the tendency which many organisms exhibit to seek oxygen (Engelmann), of leucocytes to be attracted towards the products of bacterial activity (Massart, Metschnikoff, Buchner), and the attraction which the ovum exerts upon the spermatozoon,[4] are all striking instances of positive cell-chemotaxis. The influence of unilateral variation of mechanical pressure in stimulating protoplasm, and thus producing movements of protoplasmic organisms—generally towards but sometimes away from the source of stimulation—has been studied by various observers. Such influences have been termed collectively *barotaxis* (*βάρος*, pressure) (Verworn), but it is better known under different designations according to the source of the pressure—e.g. *thigmotaxis* when this is the result of contact with a solid substance,

[1] Greeley, *op. cit.*, see p. 19.

[2] Similar terms are chemotropism, thigmotropism, geotropism, &c.

[3] See Jennings 'On reactions to stimuli in unicellular organisms (ciliate Infusoria),' Amer. Journ. Phys. xxi. 1897; also T. B. Robertson, Trans. Roy. Soc. South Australia, vol. xxix. 1905, and Quart. Journ. Exp. Physiol. ii. 1909 (see also p. 79).

[4] The susceptibility of spermatozoa to specific chemotactic influence is illustrated in the experiments of Pfeffer, who found the spermatozoids of ferns to be strongly attracted by malic acid, but indifferent to most other reagents. Loew (Sitzungsb. d. Wiener Akad. cxi. 1902) has shown that the uterine mucous membrane has a chemotactic influence upon spermatozoa.

rheotaxis when caused by moving fluid, and *geotaxis* when due to gravity or attraction towards the earth's centre. The enveloping of solid substances by amœbæ or leucocytes is an instance of thigmotaxis, the movement of the spermatozoa along the Fallopian tubes is probably an instance of rheotaxis (since it is a movement in a contrary direction to that of the current produced by the cilia lining those passages), and the tendency of various free-moving organisms to accumulate either at the top or at the bottom of a vertical column of liquid is an instance of geotaxis (negative or positive) when not due to a mere difference of specific gravity or to the chemotaxis of the oxygen of the air. It is, however, in the vegetable kingdom that most examples of thigmotaxis and geotaxis are met with.

The same is the case with the influence of light (*phototaxis*), in which numberless instances in plants of movements of their parts towards or away from this source of stimulation at once suggest themselves. Finally may be mentioned the phenomena of *thermotaxis*—*i.e.* the movement of protoplasm and of protoplasmic free-moving organisms towards or away from a source of heat. With slight raising of the temperature the movement is usually positive, but with higher temperatures it is almost invariably negative.

All influences which produce contraction (coagulation ?) of protoplasm are productive of katabolism or disassimilation; while those which produce relaxation (liquefaction ?) result in anabolism or assimilation. If assimilation and disassimilation are equally balanced throughout the condition is one of quiescence (Hering). The relation of assimilation to disassimilation during the unit of time is termed by Verworn 'biotonus,' and is expressed by the fraction $\frac{A}{D}$. 'It is the variations in this fraction which produce all change in the vital manifestations of an organism; when there is complete equilibrium $\frac{A}{D} = 1$.' A stimulus is an agency which produces disturbance in the condition of equilibrium. There is, moreover, a constant tendency in the organism to revert spontaneously from conditions in which A or D preponderate to a state of equilibrium; this property of protoplasm is termed by Hering 'spontaneous regulation' (Selbststeuerung). Such return to equilibrium is accompanied by active manifestations of a reverse character to those which previously obtained. In this way Hering explains the physiological 'rebound' which shows itself in all protoplasmic tissues which have been the subject of disturbances in their metabolic equilibrium.[1]

Ciliary movement.—Another form in which the activity of protoplasm manifests itself is that known as ciliary movement. This was discovered in the mussel by de Heide in 1683, but the movements of spermatozoa had previously been noticed by Ham and Leewenhoek. Ciliary action consists in the (apparently) spontaneous waving motion of fine processes which project freely beyond the cytoplasm: the processes are termed *cilia* (fig. 112). The movement is much more rapid in character than amœboid movement, and has usually a definite direction and a regular rhythm. It is generally, at least in the ciliated cells of the higher animals, a simple bending over of all the cilia which crown the cell, followed by their return to the vertical position; but in many of the lower organisms, and especially in those which are unicellular, the movement is less regular; in many it exhibits a spiral or corkscrew-like character.

Cilia serve very varied purposes in the animal economy. In spermatozoa and in some infusorial animalcules they are organs of locomotion; in other animals they serve to direct currents of water containing food to the alimentary canal; in others they similarly direct currents of water over the surface of the gills. In man, where they occur exclusively in connexion with epithelium-cells, their purpose seems always to be (except in the case of the spermatozoa) to produce a movement of

[1] See Hering, Zur Theorie der Vorgänge in der lebendigen Substanz, Lotos, 1888; also Verworn, Die Biogenhypothese, 1903, and Allgem. Physiol. 1908.

fluid over the surface which they cover, and, with the exception of the cilia of the cerebral ventricles and central canal of the spinal cord, this movement is always in the direction of the exterior. Thus they serve to move the mucus which moistens the interior of the air-tubes and trachea towards the orifice of the larynx, that which moistens the nasal passages towards the anterior nares, and that of the Fallopian tubes and uterus towards the os uteri.

Although very widely distributed throughout the animal kingdom, there are some exceptions, such as the arthropods, which possess no cilia and in which the spermatozoa also are not provided with a moving filament. In mammals and in vertebrates generally cilia are very fine and comparatively short, but in invertebrates, and especially in Protozoa, they are frequently larger and longer. Many unicellular organisms, both animal and vegetable, are provided with one or two relatively large cilia, which generally serve as organs of locomotion: these are often termed *flagella*. In Noctiluca miliaris (fig. 113) the flagellum has an indistinct transversely striated appearance along one border; most cilia, however, show no trace of structure, but look like direct con-

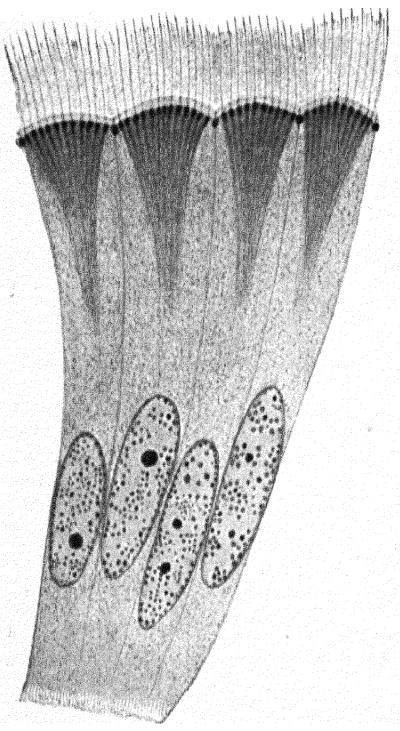


FIG. 112.—FOUR CILIATED CELLS OF MOLLUSC. (v. Lenhossék.)

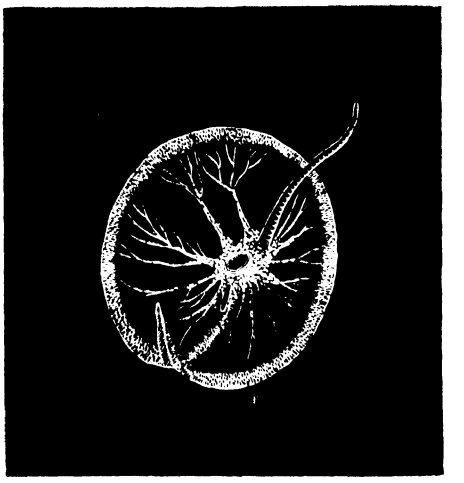


FIG. 113.—NOCTILUCA MILIARIS, A UNICELLULAR PHOSPHORESCENT MARINE ORGANISM PROVIDED WITH A SINGLE LARGE FLAGELLUM. (Verworn.)

tinuations of the cytoplasm. In the spermatozoon the tail or cilium contains a fine fibril or fibrils, continued from the centrosome which lies within the body or middle piece. In some ciliated cells, such as the large cells which line the intestine of certain molluscs, the cilia are provided near the cell with bulb-like enlargements (figs. 112, 114), which, again, are attached to or continuous with similar enlargements (*basal particles*) at the free border of the cell. Moreover, in these cells fine fibrils traverse the length of the cell from its free border to its fixed extremity (fig. 114). These fibrils are known as the *rootlets* of the cilia.[1] Although specially well developed in some ciliated cells, they appear to be similar in character to the fibrils forming the cyto-mitome in columnar epithelium-cells (fig. 19). It is doubtful if they have

[1] Engelmann, Pflüger's Arch. xxiii. 1880. See also J. Frenzel, Arch. f. mikr. Anat. xxviii. 1886; and Vignon, Arch. de zool. expér. viii. 1900.

a special relation to the cilia, since Gurwitsch found in cross-sections of such cells that there were only 30 to 40 rootlet fibrils in each cell, as against 200 to 300 basal particles.[1] The 'rootlets' are not by any means found in all ciliated cells; they may be seen, not very distinctly, in the ciliated epithelium of the air-passages of mammals.

During the life of a ciliated cell the cilia are in constant activity; bending over and recovering themselves many times a second in mammals. So rapid is the movement that the action of the individual cilia cannot be seen except when it begins to slacken, which may be caused by cooling the preparation or may accompany commencing death of the cells. But the general effect of the whole movement can be seen with a low power of the microscope, and has been aptly compared to the rhythmic wave-like motion which is produced by the wind upon a cornfield. The movement does, in fact, begin at one part of the ciliated surface, and gradually traverses the whole surface in the form of a wave, and this is succeeded by others at regular intervals (fig. 115).

The movement manifests itself in detached cells and may continue for hours or days: it is therefore independent of the rest of the tissue or of the nervous system; it may even be seen in cilia which are attached to a separated portion of cell-protoplasm.[2] It is never observed in completely detached cilia from the Metazoa, although in some Protozoa such independent action has been described.

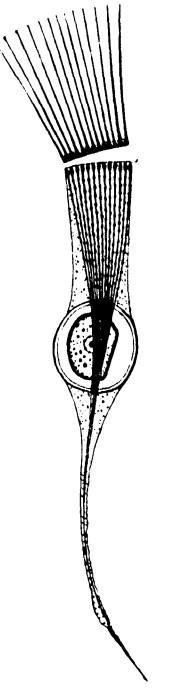


FIG. 114.—CILIATED CELL, FROM THE INTESTINE OF A MOLLUSC. (Engelmann.)

The development of cilia has been studied in Protozoa and Metazoa. The cilia first appear in Protozoa as little pseudopodium-like processes, which are not withdrawn like ordinary pseudopodia but remain permanent and tend to become gradually longer. Almost as soon as they appear they exhibit movements, but these are at first slow and irregular in character; later they become more regular, rapid and rhythmical. In some Protozoa the movements remain irregular and more or less independent of one another, as if the cilia in these cases retained to some extent the amœboid character of pseudopodia. It is probably cilia of this nature which continue to exhibit movements after complete detachment.

The analogy with the movements of pseudopodia is further shown by the fact that in certain Protozoa, *e.g.*—in Artodiscus saltans (fig. 116) as described by Pénard,[3] and Camptonema nutans (fig. 117) as described by Schaudinn,[4] the filiform pseudopodia may take on lashing

FIG. 115.—DIAGRAM TO SHOW THE MANNER IN WHICH THE CILIARY MOVEMENT PASSES IN WAVES OVER A CILIATED SURFACE. (Verworn.)

movements, even at quite a rapid rate, afterwards resuming the ordinary amœboid character of their movements. In another form (Multicilia lacustris) (fig. 118), where the processes are permanent and are therefore to be regarded as cilia, they exhibit so slow a movement that the

[1] Arch. f. mikr. Anat. 1900.
[2] Provided the basal corpuscles remain attached (K. Peter, Anat. Anz. xv. 1899).
[3] Arch. f. Protistenkunde, 1903.
[4] Sitzungsb. Preuss. Akad. 1898.

animalcule crawls over surfaces as if with pseudopodia instead of swimming about as in nearly all other free ciliated forms. Such cases seem to present transitions between cilia and pseudo-

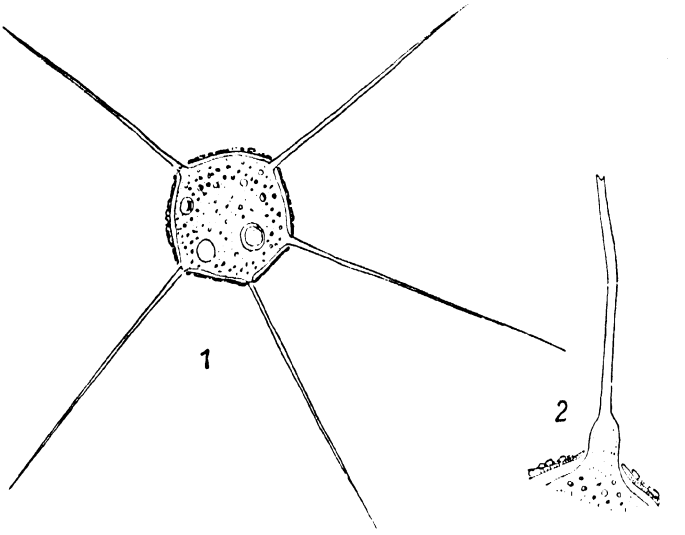


FIG. 116.—ARTODISCUS SALTANS. (Gurwitsch, after Pénard.)

1. The complete animalcule. 2. Base of a pseudopodium, highly magnified. The pseudopodium is seen to be a hollow extension of the protoplasm provided with a bulb-like enlargement at the base. These pseudopodia exhibit rhythmic pendulum-like movements.

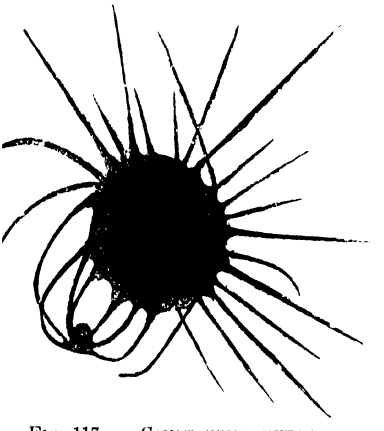


FIG. 117. — CAMPTONEMA NUTANS, AN ANIMALCULE ALLIED TO THE HELIOZOA. (Gurwitsch, after Schaudinn.)

The long tapered pseudopodia are provided each one with a hollow axial filament formed of a soft semi-fluid material, which is covered by an extension of the general protoplasm. The pseudopodia are capable of being extended and retracted, and some of them are shown in the act of seizing a minute alga. They also exhibit cilium-like movements, bending over from the base of the pseudopodium.

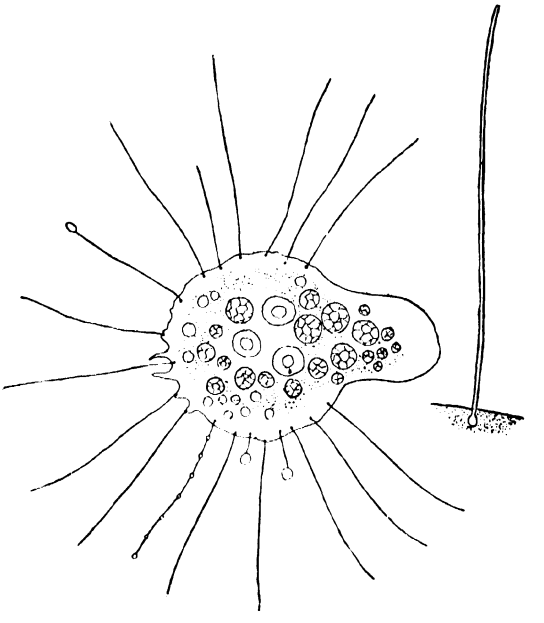


FIG. 118. — MULTICILIA LACUSTRIS, AN ORGANISM WITH PERMANENT CILIUM-LIKE PROCESSES, WHICH ARE ALSO CAPABLE OF SLOW AMŒBA-LIKE MOVEMENT. (Gurwitsch, after Pénard.)

On the right a cilium more highly magnified, showing a hollow structure springing from a bulb-like enlargement.

podia and serve to illustrate the close relationship which they bear to one another, although the character of their movements is usually so unlike.[1]

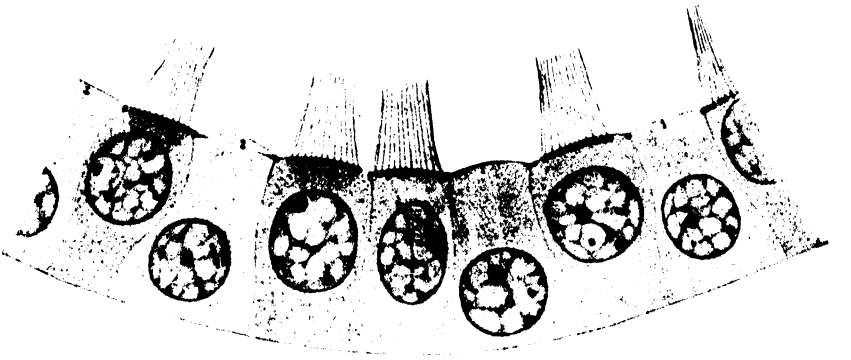


FIG. 119.—CILIATED CELLS FROM EPIDIDYMIS OF RABBIT, WITH OTHERS NOT CILIATED BETWEEN THEM. (v. Lenhossék.)

The non-ciliated cells each exhibit a diplosome (double centrosome) at the basal border; in the ciliated cells this is not seen, but the basal border is occupied by the basal particles of the cilia.

In Metazoa the cilia also grow out from the free surface of the protoplasm of the cell which is to become ciliated; but each appears as a fine filamentous projection rather than as a pseudopodium-like process. In many cases the appearance of the cilium at the surface of the cell is preceded by that of its basal particle, which closely resembles a cell-centrosome, and stains in a similar manner to that particle (fig. 119). But whether the basal particles are really derived from the original centrosome or not is still uncertain, for although Lenhossék [2] and Henneguy,[3] who described this mode of development, failed to find the ordinary centrosome, and concluded that it had passed towards the free surface to become the first basal particle (the rest being presumably formed by its division), Gurwitsch was unable to trace any connexion between the centrosome and the formation of basal corpuscles, while Seleniewsky [4] describes and figures the ordinary centrosome in developing ciliated cells along with the basal particles.[5] None the less it seems clear that the basal particle is in its nature closely allied to the centrosome of the cell. For in the development of spermatozoa the tail fibril is known to grow out from the centriole, and even in dividing spermatocytes instances are met with in which cilium-like fibrils are seen growing out from the centrosome at either end of the division-spindle (fig. 120).

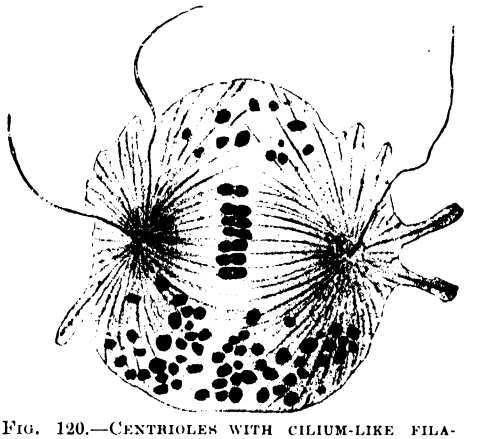


FIG. 120.—CENTRIOLES WITH CILIUM-LIKE FILAMENTS IN A SPERMATOCYTE OF PIERIS CRATEGI. (Gurwitsch, after F. Meves.)

The protoplasm of the cell from which the cilia are growing has, like all cell-protoplasm, an external film, and the cilia as they are formed must also

[1] 'The Protozoa . . . and numerous plant and animal sporoids present numberless instances of the gradual transformation of long pseudopodia into true vibratile cilia. An amœboid filiform pseudopodium may in the living object alter the character of its movement under the eye of the observer at first to a slow pendulum-like swing, which becomes more and more rapid until the vibratile action which is so characteristic of the cilium is completely developed' (Gurwitsch, Morphologie u. Biologie der Zelle, 1904, p. 59).

[2] Verhandl. d. anat. Gesellsch., Anat. Anz. 1898.

[3] Arch. d'anat. micr. i. 1898.

[4] Anat. Anz. xxiv. p. 637.

[5] According to Gurwitsch (Anat. Anz. xvii. 1900; Arch. f. mikr. Anat. lvii. 1901) the cilia sometimes make their appearance before the basal particles, being developed from a specially modified portion of the cell-protoplasm. Strasburger's observations on the cilia of plant-spores show them to be developed as processes, at first amœboid, from projections of the ectoplasm (Histol. Beitr. Heft vi. 1900).

be similarly enclosed. They may be therefore described as extensions of the cell-protoplasm covered, like that, with a delicate investment. Ordinary cilia are far too minute for the presence of a covering to be detected even with the highest powers of the microscope, but in the large flagella and cilia of Protozoa a hollow structure is sometimes distinct (figs. 113, 116, 118), and there is therefore reason for the belief that in smaller flagella and in ordinary cilia it may also exist. Cilia are either rounded or flattened in section; they are frequently broader near their attachment to the cell, from which point they taper towards the free extremity; often they are nearly uniform in size throughout, except for a bulb-like enlargement at the base which is usually present.

The action of cilia is influenced by external conditions in the same manner in all respects as amœboid movements. Thus the motion becomes more rapid, up to a certain point, with elevation of temperature, and less rapid if the external medium be cooled; it will continue, but not indefinitely, in the absence of oxygen (Sharpey); it is stopped by CO_2 and by the vapour of ether and chloroform, but is renewed if these are removed and replaced by air. Other chemical agents affect it either through the tendency they have to withdraw water from or to add it to the protoplasm of the cell, or by virtue of the electrolytes they contain. The action of galvanic currents varies with the condition of activity of the cilia and the position of the poles. Light has not been observed to have any effect on cilia in Metazoa, but effects of phototaxis are well seen and have been largely studied upon the ciliated Protozoa. There can be no reasonable doubt that the activity of cilia is closely related to the activity of amœboid protoplasm, and that both kinds of movement must be produced in a manner which is essentially similar.[1]

CONSIDERATION OF THE MODE OF PRODUCTION OF AMŒBOID AND CILIARY MOVEMENTS.

The movements of the amœba and of other protoplasmic organisms which are designated amœboid, although they appear to be spontaneous and even almost voluntary, are probably no more so than the movements of a drop of one fluid suspended in another, the two being separated by a surface film subject to local variations in tension. If the tension of the surface is uniform the drop remains spherical, but if the tension is reduced at any place the drop will tend to flow in the direction of reduced tension. This can be shown with oil-drops containing fatty acid, immersed in dilute alkaline solutions.[2] The oil-drops become coated with a solid surface film of soap, and as this becomes thinner first at one place and then at another by solution in the surrounding fluid, local variations of tension are caused and 'amœboid' movements of the oil-drop are produced. The same obtains with drops of oil-clad albumen. Further, if oil, containing fatty acid, is beaten up with an alkaline carbonate, and the mixture is placed in water, the latter penetrates between the oil-drops, and, dissolving the alkali, produces a kind of froth with a large number of internal surfaces having films of soap separating the oil from the alkaline solution, and repeating the conditions of the general surface (Bütschli).[3] A model to illustrate the production of amœboid movement by changes in surface tension may even be constructed in a much coarser manner by immersing a drop of mercury in dilute nitric acid and adding a crystal of bichromate of potash to the nitric acid. As the crystal dissolves and its solution reaches the mercury a film forms on the globule, and the latter undergoes changes of surface tension first here and then there as the film is attacked by the

[1] For the literature of cilia, see Putter, Ergebn. d. Physiol. 1904.

[2] Quincke, Pogg. Ann. 1888; Sitzungsb. d. Berliner Akad. 1888. Quincke states that the spherical form assumed by drops of cytoplasm squeezed out of a cell into water must be due to a surface film of fatty substance.

[3] Microscopic Foams, translated by Minchin, 1894.

acid now at this, now at that point; there is a corresponding tendency of the mercury to flow now in the one and now in the other direction, thus producing changes of shape and even of position which perfectly simulate those of an amœba.[1] No adequate explanation of the amœboid phenomena of protoplasm other than that of variations in surface tension has been offered, and it is now generally accepted by physiologists, although the manner in which such variations are brought about is still open to discussion. The main difference between protoplasm and the models above described lies in the fact that, whereas in them the variations in surface tension are produced by an external agency, those of protoplasm may be caused either by external agencies or by internal changes. The altered conditions of surface tension of its protoplasm are also probably responsible for the mechanical effects which are produced when the protoplasm of a cell comes in contact with another cell, as well as for the in-taking of foreign bodies by protoplasm (phagocytosis).

The view at one time held that the amœboid movements of a cell are produced by the contraction of the fibrils of a reticulum within its protoplasm is no longer tenable, since it is known that amœboid protoplasm does not necessarily contain such fibrils. Moreover, the causation of the contraction of these fibrils, if they were present, would still necessitate an explanation.

The explanation of ciliary action has been more difficult than that of amœboid protoplasm, and several hypotheses have been put forward to account for it. It has been suggested, *inter alia*, that the 'rootlets' might contract and pull upon the bases of the cilia, or that they might be rigid prolongations of the cilia, moved by movements of the cell-protoplasm and acting as levers upon the projecting filaments. But in the first place many cilia have no rootlets; and when these do occur it is in the highest degree improbable that they possess either rigidity to enable them to act as levers or contractility to enable them to pull the cilia over. Nor would the hypothesis explain the action of the detached ciliated part of the cell.

The explanation which has hitherto been received with most favour supposes that each cilium consists of two parts, one side being contractile, the other elastic. The contractile part is supposed to bend the filament over, the elastic part to produce recovery.[2] The theory is illustrated by a model which is found in most lecture theatres, consisting of a tapered steel band which is pulled over by a string attached to its apex and passing through a ring at its base. It is, however, clear that only a rigid elastic substance like steel could be bent over in this way: if the band were composed of a soft material like the substance of a cilium it would not bend over, but wrinkle up, were one side to contract. Moreover, the model will not act if the string is kept in apposition to the steel band; to produce its effect it is necessary that it should, as the steel bends over, occupy the position of the chord of the arc which the bent steel band describes—a condition impossible in the case of a cilium. It is, moreover, in the highest degree improbable that there should be so much differentiation in cilia as this hypothesis implies, seeing that they are found in the lowest and least differentiated organisms.

It may safely be asserted that no hypothesis can be satisfactory which does not bring ciliary action into line with amœboid movement; any explanation which holds good for the one ought to hold good for the other. We have seen that the hypothesis which is found best to explain amœboid activity is that of variable tension at the surface of the protoplasm. Can this hypothesis be equally applied to explain ciliary action?

The independent movement which has occasionally been observed in severed cilia of Protozoa, and the slow irregular action which has been described in developing cilia (p. 73), may certainly be caused by local changes in tension of the surface film which

[1] Bernstein, Pflüger's Arch. lxxx. 1900. The original experiment is by Paalzow, Pogg. Ann. 1885. See also M. Heidenhain, Anat. Hefte, xxvi. 1904, xxvii. 1905; J. Bernstein, Anat. Hefte, xxvii. 1905; Jansen, *ibid.*; Rhumbler, *ibid.*; H. S. Jennings, Journ. of Applied Microscopy, v. The literature of the subject up to that date is given by Heidenhain.

[2] A modification of this theory supposes the existence of an elastic skeleton in the middle of the cilium and of contractile material at its periphery. Pütter, Ergebn. der Physiol. Jahrg. 2, 1904. For a criticism of Pütter's theory, see Anat. Anz. Bd. xxiv. 1904, p. 497.

covers the protoplasmic extension of which each cilium in these instances is composed. Similarly it is conceivable that rhythmical changes of tension due to causes operating equally and alternately upon opposite sides of all the cilia of a ciliated cell might produce a movement of fluid from side to side within the protoplasm composing each cilium, and by such rhythmical transference of fluid the curving over and recovery of the cilium might be caused.[1] But the co-ordinated action of all the cilia of an ordinary ciliated cell seems to necessitate the supposition of a common cause, and if this is a variation in tension it must start at the free border of the cell from which the cilia all spring. The assumption that the cilia are direct extensions of the cell-protoplasm, with a naturally curved form, and that they are enclosed, like the cell-protoplasm, by an external film, would suffice to explain how it is that differences of tension at the free border of the cell may produce movements of such extensions. For any diminution of surface tension at the free border of the cell would tend to cause fluid to pass into such hollow extensions, and would thus cause them, if originally curved, to straighten; while an increase of surface tension would be accompanied by an inflow into the cell-body and a curving over of the cilia. In this way rhythmical variations in surface tension at the free border of the cell would be responded to by rhythmical movements of the cilia which project from that border.

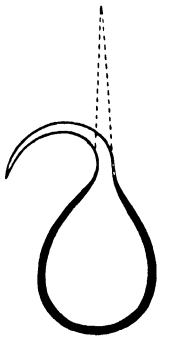


FIG. 121.—DIAGRAM OF MODEL TO SHOW HOW A CURVED TUBE WILL EITHER STRAIGHTEN OR BEND OVER IN OBEDIENCE TO FLUCTUATIONS OF PRESSURE IN ITS FLUID CONTENTS. (Schäfer.)

This hypothesis of the production of ciliary movement may be illustrated by a curved tube, preferably flattened, made of thin indiarubber. The tube is closed at one end and is attached at the other to an indiarubber ball, by gentle pressure upon which fluid can be passed into or withdrawn from the flattened tubular extension (fig. 121). With such a model the bending over and straightening of a cilium can be closely imitated, and the effect of these movements in causing currents in a body of water can be shown. If the tube has been moulded into a spiral form instead of a simple curve, the movements which are produced by variation of tension within the model are exactly similar to the corkscrew-like movements of many flagella.[2] Such a model illustrates the fact that even slight changes of pressure produce strong movements of the tube in water, the resistance of the water counting under the circumstances for comparatively little. By no other hypothesis is it possible to explain the power which cilia possess, not only to bend rapidly against the resistance of water and of mucus, but to drive these fluids vigorously over the ciliated surface, and even to move weights which are thousands of times heavier than that of the cilia upon which the weight is borne.

This hypothesis is supported by the following considerations:

(1) Cilia, whether, as with spermatozoa, they contain an axial filament derived from the centrosome or not, are developed as extensions of the cytoplasm and are therefore from the first covered with an extension of the surface film by which the cytoplasm is invested—in other words, they are extensions of the cell filled with fluid protoplasm and covered by a fine membrane.

(2) All cilia and flagella which are sufficiently large for any structure to be made out exhibit a distinct external investment enclosing a hollow interior.

[1] This explanation has been suggested by Robertson (see below, p. 80).

[2] Schäfer, Anat. Anz. 1904. See also Proc. Roy. Soc. xlix. 1901, p. 198.

(3) Certain Heliozoan animalcules which are provided with long pseudopodia, capable of being slowly extended and retracted, exhibit in the axis of each pseudopodium a structure which has been described as an axial rod or axial fibre. But its appearance indicates a tubular rather than a solid structure such as the term 'rod' or 'fibre' would imply. These 'rods' sometimes commence in the cell-protoplasm from a central globular body, which is like an enlarged centrosome. That they are actually composed of fluid or plastic material is also evidenced by their flexibility: the term 'rod' is therefore inappropriate. In *Camptonema nutans* (fig. 117), which is allied to the Heliozoa, the long pseudopodia are cilium-like, and each contains a strongly refracting axial 'fibre.' The sections of the pseudopodia have a distinctly tubular appearance (fig. 122), and the pseudopodium may bend over in any direction. The appearance of the 'rods' is consistent with their being hollow axial parts of the pseudopodia, and it is noteworthy that this hollowing out of the pseudopodia is associated with slow cilium-like movements of those processes.

(4) The Suctoria (a species of animalcule) possess hollow processes which are elongated or shortened by the flowing of fluid into them from the general substance of the cell-body. This protrusion and retraction may occur a number of times a minute, and is therefore similar in rapidity to the movement of cilia. In some forms the movement takes on a waving or bending character, reminding the observer of slow ciliary action. There can be little doubt that the movement of these processes is due to variations in surface tension of the protoplasmic cell-body.

(5) Schuberg has shown[1] that in the detached condition the cilia of some Protozoa assume a bent or, rather, a corkscrew-like form. He also describes an end-piece projecting beyond the rest of the cilium (as in the spermatozoon) and composed of an axial part enclosed by a sheath; this can be seen in stained preparations (fig. 123). Schuberg expresses the opinion that the sheath is the more fluid part of the cilium, but adduces no evidence in favour of this view, nor does he attempt to show in what manner the movements could be produced in a structure so constituted. He regards the end-piece as a projection of the *axial* part; but an examination of his figures indicates that it is rather to be regarded as a prolongation of the substance of the *sheath*. For the part of the cilium which stains dark, *like the body substance itself*, is represented by Schuberg as of less diameter than the projecting end-piece of the cilium, and if this is so it must therefore be the axial part; the real sheath or envelope of the cilium remaining colourless in these preparations and being only seen where its substance projects beyond the axis.

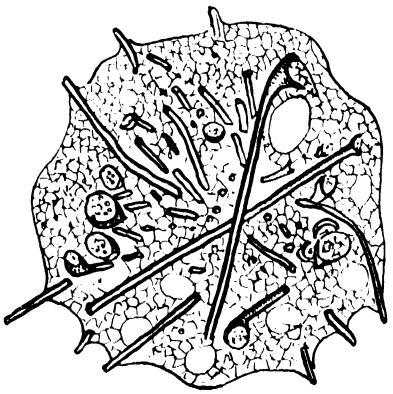


FIG. 122.—SECTION OF CAMPTONEMA NUTANS. (Gurwitsch, after Schaudinn.)

Each pseudopodium has a flexible tubular fibre projecting into it from the body of the animalcule.

Relation of amœboid and ciliary movement to ionic constitution of cell-proteins.—That the movements of amœboid cells and of cilia are the result of changes in surface tension and that these changes are brought about by changes in the ionic constitution of the proteid molecules is urged with much force by Robertson,[2] whose arguments may be given in his own words: 'We have seen that it is a characteristic of the proteid part of the ion-proteid molecule that it readily forms compounds with any ions which happen to be present in excess, while Hardy's experiments . . . show that the electrical character of the resulting ion-proteid depends upon the relative velocities of the ions in the solution in which the proteid is suspended. In the first case, consider the effect upon a unicellular (amœboid) organism of a constant current in the direction shown in the diagram (fig. 124) (A = Anode, K = Kathode), the organism being supposed to be laden with kation-proteid, by virtue of the metabolism and dissociation of which a difference of potential is maintained between the protoplasmic surface and that of the medium (indicated by the small + and − signs).

'Just as in the analogous case of the capillary electrometer, the effect of a current travelling

[1] Arch. f. Protistenkunde, vi. p. 61, 1905.

[2] T. Brailsford Robertson, 'An Outline of a Theory of the Genesis of Protoplasmic Motion and Excitation,' Trans. Roy. Soc. of South Australia, vol. xxix. 1905, and Quart. Journ. Exp. Physiol. ii. 1909.

from A to K will be to *diminish* the contact difference of potential at points such as *a*, which form the physiological anode, and to *increase* it at points such as *b*, which form the physiological kathode. Therefore . . . the effect will be to *increase* the surface tension at points such as *a*, and to *decrease* it at points such as *b*. The surface and, consequently, the volume on the kathodic side of the organism will therefore *increase*, while on the anodic side they will *decrease*. The organism will therefore move over towards the kathode as indicated by the arrow. . . . Consider now the effect of a similar current upon a "negative" amœboid organism (fig. 125); that is, one which is laden with anion-proteid. . . . In this case the contact difference of potential will be *increased* at the physiological anode and *decreased* at the physiological kathode; hence, reasoning as before, the organism will move towards the *anode*. . . .

'The effects upon ciliated organisms will be similar, for if the diagram (fig. 126) represents one of the cilia of a "positive" organism subjected to a constant current in the sense indicated, the difference of potential of the surface forming the physiological anode will be diminished and

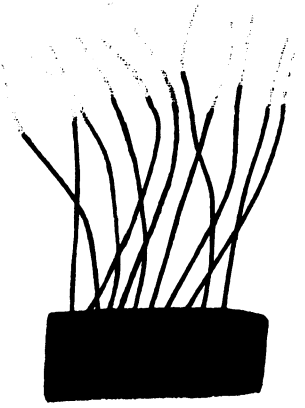


FIG. 123.—CILIA OF FRONTONIA LEUCAS. (A. Schuberg.)

The body of the organism and the cilia, as far as the end-pieces, are stained. Löffler's flagellum stain. ×2250.

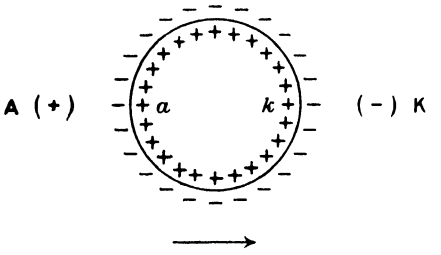


FIG. 124.—DIAGRAM OF AN AMŒBOID ORGANISM LADEN WITH KATION-PROTEIN, SUBJECTED TO A CONSTANT CURRENT IN THE DIRECTION SHOWN BY THE POLES. (T. Brailsford Robertson.)

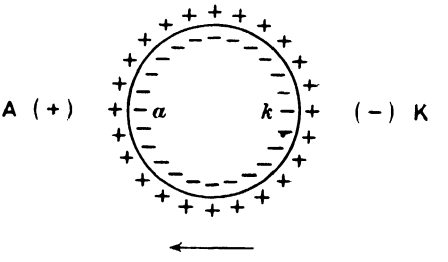


FIG. 125.—DIAGRAM OF AN AMŒBOID ORGANISM LADEN WITH ANION-PROTEIN, SUBJECTED TO A CONSTANT CURRENT IN THE DIRECTION SHOWN BY THE POLES. (T. Brailsford Robertson.)

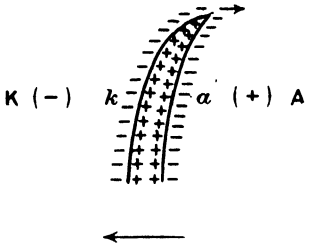


FIG. 126.—DIAGRAM OF CILIUM OF A 'POSITIVE' ORGANISM SUBJECTED TO A CONSTANT CURRENT. (T. Brailsford Robertson.)

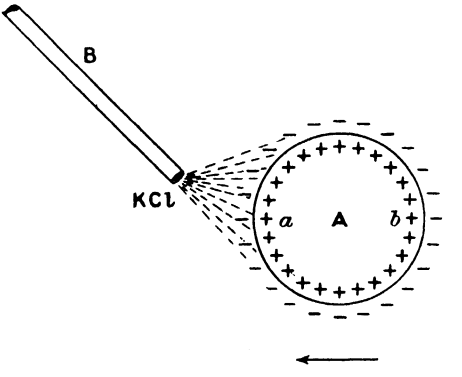


FIG. 127.—DIAGRAM INDICATING THE ACTION OF A CHEMICAL STIMULUS (KCl) UPON A 'POSITIVE' AMŒBOID ORGANISM. (T. Brailsford Robertson.)

that at the physiological kathode increased; hence the former surface will diminish owing to the increased surface tension, and the latter will increase; hence the cilium will bend towards

the anode as indicated by the small arrow. . . . The effect of the same current on a "negative" ciliated organism will, of course, be the reverse. . . .

'The phenomena of chemotaxis must be attributed to the diffusion of the ions into the protoplasm in different proportions. Consider the effect upon a "positive" amœboid cell (A, fig. 127) of a salt such as KCl, in which the kation has a greater velocity than the anion, diffusing from a capillary tube (B). Since the quicker-moving kations will diffuse faster than the anions, more kations will enter the organism in a given time than anions; that is, the contact difference of potential at such points as *a* (fig. 127) will be augmented, and at such points as *b* unaffected or much less augmented (since the concentration of the KCl is as the inverse square). Hence the surface tension at *b* will be greater than that at *a*, and the organism will move *towards* the capillary.

'With a salt like $CaCl_2$, in which many more anions would enter the organism in a given time than kations, the reverse would be the case.

'If the organism were "negative" the above effects would be reversed.

'"Isotactic" organisms—as we may call those organisms which are equally loaded with anions and kations—would, of course, be attracted by both kinds of reagents, but as the potential difference would be very small such organisms would exhibit no marked reaction.' [1]

[1] See also H. H. Dale, 'Galvanotaxis and Chemotaxis,' Journ. Physiol. 1901, p. 291; and A. P. Mathews, 'The Nature of Chemical and Electrical Stimulation,' Amer. Journ. Physiol. xi. 1904, who also considers 'that the chemical composition of the ion is of little importance compared with the importance of its electrical condition, and that electrical stimulation is due simply to the accumulation of negative or positive ions in different places in the tissue.' W. M. Strong, Journ. Physiol. xxv. 1900, applies a similar theory to the propagation of excitation in muscle and nerve. The works of J. Loeb, Studies in General Physiology, Chicago University Publications, 1905; and Dynamics of Living Matter, 1906, may especially be consulted on the question of the electrical charge of proteins (ion-protein hypothesis). Much of the general literature of the subject of the effect of variations in surface tension in producing the phenomena of protoplasmic movement will be found in Robertson's paper in the Quart. Journ. Exper. Physiol. above referred to. His application of the theory to the production of muscular contraction will be noticed when that subject is dealt with.

THE EPITHELIAL TISSUES.

A large number of tissues of varied origin and cell-structure are grouped under this head, but all agree in being composed entirely of cells, with but little or no intercellular substance ;[1] they are usually found covering or lining free surfaces, internal or external. The term which is now employed to designate these tissues was first used to signify the thin cuticle, continuous with the epidermis, which covers the red border of the lips. Ruysch found these to be beset with papillæ, and termed the covering layer *epithelia* from ἐπί and θηλή, a nipple or papilla, and the use of the term in the modified form of *epithelium* has since spread to signify any similar kind of tissue, whether covering papillary surfaces or not.[2] The epithelium lining such internal surfaces as the serous cavities and the walls of the heart, blood-vessels, and lymphatics is sometimes spoken of as *endothelium*

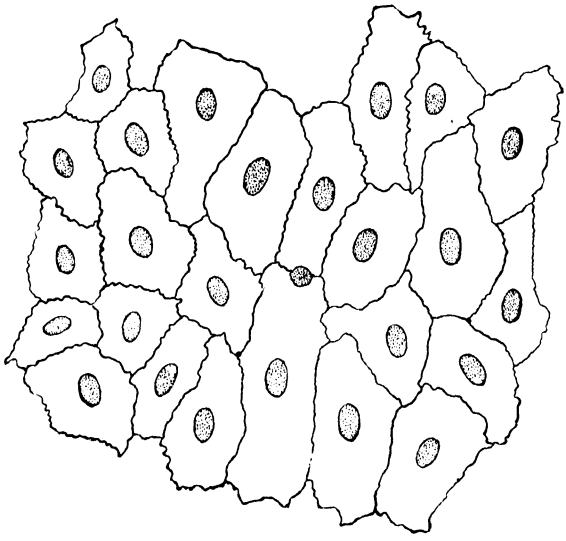


FIG. 128.—PAVEMENT-EPITHELIUM (ENDOTHELIUM) FROM THE OMENTUM OF THE RABBIT. Nitrate of silver staining. (Schäfer.)

(His), which is a contraction of the term endo-epithelium ; it is also designated *mesothelium* (Minot) to denote its origin from mesoderm.[3]

The thickness of different epithelia varies greatly. Some are composed of a single layer of very thin flattened cells set side by side to form a mosaic (*pavement-epithelium*)—the endothelia are of this nature ; in others the tissue is still only a single layer of cells deep, but the individual cells are thicker (*cubical*, *columnar*, *glandular*, and *ciliated epithelium*) ; whilst in others, again, there are several or even a great number of layers of cells, and the tissue may attain a considerable thickness (*stratified epithelium*). However great the thickness, blood-vessels do not, as a rule, penetrate between the cells of the tissue,[4] although fine channels containing lymph may exist between them. Nerve-fibrils, on the other hand, are abundantly

[1] For the nature of this intercellular material in epithelia, see p. 7.

[2] See note by Sharpey in Quain's Anatomy (8th edition), p. 43, 1876.

[3] The epithelium of the generative glands and that of the convoluted and looped tubules of the kidney are also formed from mesoderm ; these cannot be included along with the endothelia.

[4] Exceptions to this general rule are met with in the liver, in some of the internally secreting glands—including the islets of Langerhans within the pancreas—and in the stria vascularis of the cochlea. For other instances of vascularised epithelium, see F. Leydig, Zelle u. Gewebe, 1885, and Arch. f. mikr. Anat. lii. 1898; Maurer, Morph. Jahrb. 1897, and H. Joseph, Arch. f. mikr. Anat. lii. 1898.

distributed to most epithelia, ending between the cells in dendritic ramifications of their fibrils. Epithelia may be derived from any of the blastodermic layers; thus the epithelium of the skin (epidermis) and of the mouth are derived from the ectoderm, that of the gullet, stomach, and intestines from the entoderm, and that of the serous cavities and renal tubules from the mesoderm.

The functions of epithelia are very various. Some, like the epidermis, are mainly protective, others are for secretion or for absorption (glandular and intestinal epithelium), others for moving fluid over the surfaces which they cover (ciliated epithelium of air-passages, generative passages, and ventricles of brain), others for receiving impressions of sense (sense-epithelia).[1] Epithelium-cells exhibit great adaptability to variations in the surface which they cover. This is especially well seen in the epithelium lining hollow contractile viscera, such as the gall-bladder and urinary bladder. In the condition of distension of such viscera almost all the

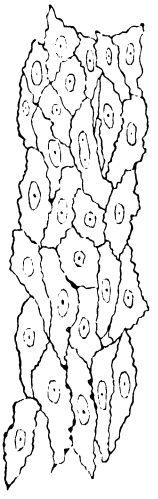


FIG. 129.—ENDOTHELIAL LAYER LINING THE POSTERIOR TIBIAL ARTERY OF MAN. (Schäfer.) 250 diameters.

Nitrate of silver preparation.

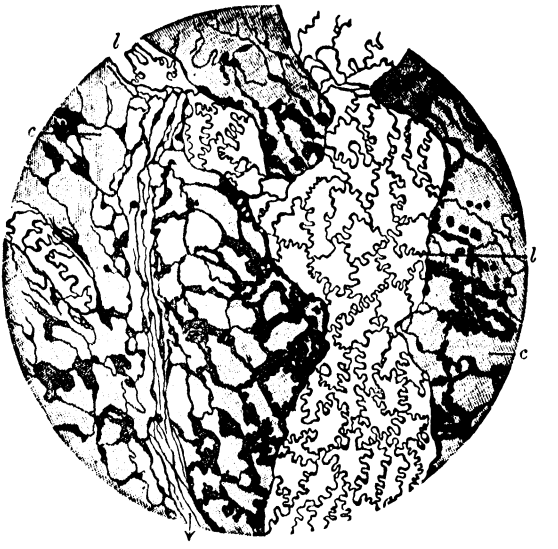


FIG. 130.—PART OF A LYMPHATIC VESSEL IN THE PLEURAL COVERING OF THE DIAPHRAGM. Nitrate of silver preparation. (Ranvier.) Magnified 116 diameters.

l, *l*, the lymphatic vessel with characteristic epithelium; *c*, cell-spaces of the connective tissue.

cells may acquire a thin flattened shape, since the surface they cover has become much extended, but in the contracted empty condition of the organ they may all become elongated perpendicularly to the corium, so as to become thicker than they are broad. This adaptability implies the possession of much extensibility and retractility, as well as very perfect elasticity.

It will be sufficient in this place to give a general description of the more common kinds of epithelium, reserving special points of structure until the organs in which they occur are treated of.

Pavement-epithelium.—This is formed of a single layer of very thin cells, often difficult to demonstrate without the silver method of staining, which blackens the intercellular material and outlines the cells. They may be polygonal in outline like a mosaic, as in serous membranes (fig. 128); or diamond-shaped, as in

[1] That the character of an epithelium may be modified by a variation in external conditions is shown by the observations of Haycraft and Carlier (Proc. Roy. Soc. Edin. 1888), who found that the ciliated epithelium of the trachea, wherever it becomes subjected to friction, tends to be transformed into stratified epithelium.

the blood-vessels (fig. 129); or with wavy borders, as in lymphatics (fig. 130); or irregular in outline (fig. 131). The edges of the cells are often serrated, the

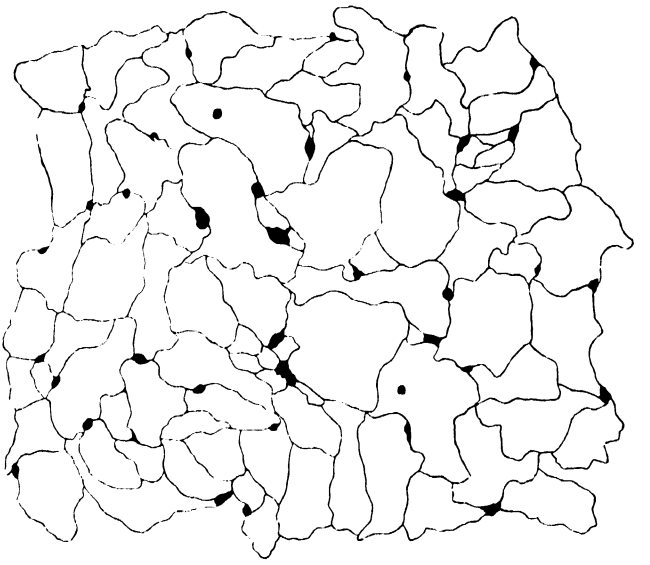


FIG. 131.—PAVEMENT-EPITHELIUM (ENDOTHELIUM) FROM THE SURFACE OF AN APONEUROSIS TREATED WITH NITRATE OF SILVER. (Schäfer.)

FIG. 132.—ENDOTHELIUM-CELLS OF SEROUS MEMBRANE SEEN IN PROFILE VIEW, SHOWING PROTOPLASMIC BRIDGES STRETCHING ACROSS THE INTERCELLULAR SPACES. (M. Heidenhain.)

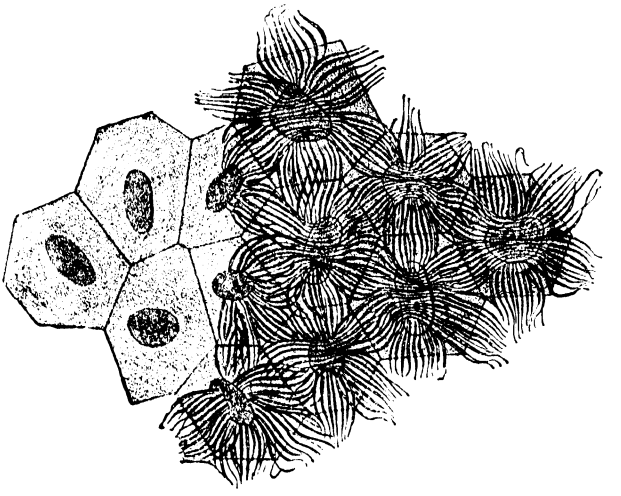


FIG. 133.—EPITHELIUM-CELLS OF DESCEMET'S MEMBRANE OF BIRD. (Smirnow.)

serrations of adjoining cells usually fitting into one another, but sometimes being point to point, the projections bridging across the intercellular substance (fig. 132).[1]

[1] M. Heidenhain, Anat. Anz. viii. 1893; A. Kolossow, Arch. f. mikr. Anat. xlii. 1893.

The cells, although usually very clear and apparently structureless, may show fibrils passing from cell to cell. This is seen in the pavement-epithelium covering the posterior surface of the cornea of some animals (fig. 133); in these cells also a reticulum of fibres, which has been regarded as a modified centrosome, may be found in the neighbourhood of the nucleus (fig. 134) (Ballowitz). A pavement-epithelium lines all serous cavities, the cavities of the heart and the interior of the blood-vessels and lymphatics, the anterior chamber of the eye, the alveoli of the lungs, the outer surface of the membrana tympani, and the ducts of the mammary glands. The epithelium which lies within the anterior part of the lens-capsule is also of this character—viz. a mosaic of flattened cells.

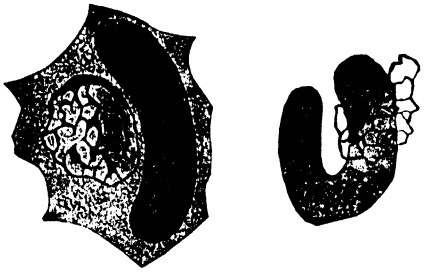


FIG. 134.—A CELL OF DESCEMET'S MEMBRANE OF THE CORNEA OF THE CAT, SHOWING A NETWORK IN THE PROTOPLASM NEAR THE NUCLEUS. (Ballowitz.)

It is uncertain whether this network is of the nature of a paranucleus or of a trophospongium.

v. Brunn[1] has described the endothelium of serous membranes as being covered on the free surface by a thin cuticular layer striated vertically. There is some reason for regarding the endothelial cells of serous membranes as flattened, superficially placed, connective-tissue cells (see p. 107).

It appears from the above that the cells which are usually grouped under the head of 'pavement-epithelia' may be not only of very different origin, but may subserve entirely different functions.

Columnar epithelium.—A second variety of simple epithelium is the *columnar* (*cylinder-epithelium* of German authors), in which the cells have a prismatic figure, and are set upright on the surface which they cover. In profile a row of these cells looks for the most part like a close palisade (fig. 135); but viewed from the surface each cell has a polygonal outline, the cells being flattened where they touch, from mutual compression, so that a mosaic pattern is produced. Columnar-epithelium cells vary much in form, in dimensions, and even in structure. Those which may be looked upon as typical are long and usually tapering, the finer extremity being set upon a surface, and the other and larger end being free. At their sides and edges they are often jagged, especially where, as is often the case, leucocytes are met with between the epithelium cells (fig. 135, *w*). Indeed the cells are not by any means so regular in shape as they are often figured, being often compressed laterally, and

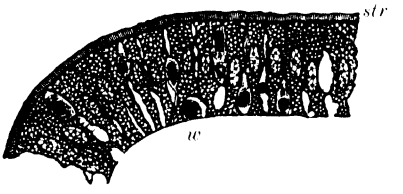


FIG. 135.—A ROW OF COLUMNAR CELLS FROM AN INTESTINAL VILLUS OF THE RABBIT. (Schäfer.)

str, striated border; *w*, wander-cells between the epithelium-cells.

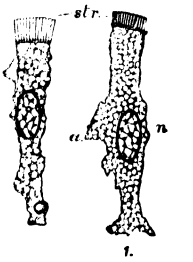


FIG. 136.—COLUMNAR EPITHELIUM CELLS OF THE RABBIT'S INTESTINE. (Schäfer.)

The cells have been isolated after maceration in dilute chromic acid. The striated border (*str*) is well seen, and the bright disc separating this from the cell-protoplasm; *n*, nucleus with intranuclear network; *a*, a thinned-out wing-like projection of the cell which probably fitted between two adjacent cells.

[1] Centralbl. f. Path. xi. 1900.

sometimes extended sideways into flattened lamellæ (fig. 136, *a*), which fit between the adjacent cells of the epithelium. Columnar epithelium-cells are described by some authors as being always joined together laterally by small protoplasmic offsets, which bridge across the intercellular spaces.[1] It may be doubted, however, whether the appearance which has been described is to be thus interpreted, for the cells after maceration in one-third alcohol or dilute bichromate solutions, readily fall apart from one another and are thus easily isolated. Leucocytes also readily push their way between them and sometimes separate the columnar cells from one another to a considerable extent (fig. 135).

In the intestine of Proteus anguineus Holmgren describes membrane-like projections from the basement-membrane projecting between the columnar epithelium-cells, and serving to separate them from one another.[2]

The nucleus may cause a bulging in the part of the cell in which it is situated, and the nuclei of adjacent cells are on this account often seated in different planes. The cell may contain fatty globules and other kinds of granules (figs. 137, 138).

In typical columnar epithelium-cells, such as those lining the mucous membrane of the small intestine, the free border differs from the rest of the cell in being more

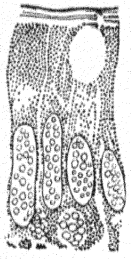


FIG. 137.—GRANULES IN INTESTINAL EPITHELIUM OF FROG. (Altmann.)

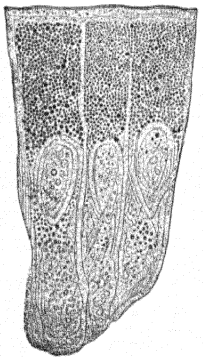


FIG. 138.—GRANULES IN FAT-ABSORBING CELLS OF FROG'S INTESTINE BEGINNING TO BE TRANSFORMED INTO FAT-PARTICLES. (Krehl.)

The fat-droplets are stained black with osmic acid.

refracting and finely striated. This *striated border* of the cell (figs. 135 and 136, *str*) after fixation by reagents may be detached from the rest of the cell, and since the striated free borders of adjacent cells often adhere together, a continuous membrane may thus be obtained, marked by a mosaic of fine lines of cement-substance indicating the division between the cells from which this 'cuticula' has become detached. The cuticula serves to close the intercellular channels so that they present no opening on the free surface. The striæ in the cuticula appear to be caused by the existence of septa extending between fine prolongations of the cell-hyaloplasm. The striated cuticula is not immediately in contact with the ordinary protoplasm of the cell, but is separated from it by a thin disc composed of a substance which refracts the light even more than the striated border. This disc (shown in fig. 136) corresponds in situation to the bright border or beaded layer of the ciliated epithelium-cells (see below); and it may be that the striated border is the morphological equivalent of the bunch of cilia upon those cells. The surface of the cytoplasm

[1] Ogneff, Biol. Centralbl. 1892; Carlier, La Cellule, xi. 1895; S. Garten, Arch. f. Physiol. 1895; Schaeppi, Arch. f. mikr. Anat. lxix. 1907.

[2] Arch. f. mikr. Anat. lxv. 1904. See also Lundahl, Anat. Hefte, xxxvii. 1908.

is in some cells covered with fine longitudinal fibrils, but whether these belong to the cell itself or to membranous septa in the intercellular substance is uncertain.

FIG. 139.—A COLUMNAR EPITHELIUM-CELL, SHOWING MASS OF FIBRILS (CYTOMITOME) WITHIN THE CYTOPLASM. (M. Heidenhain.)

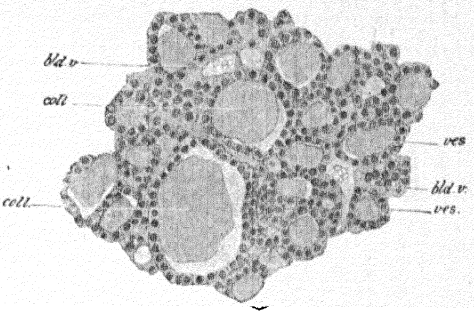


FIG 140.—SECTION OF THYROID OF CAT, SHOWING GLAND-VESICLES LINED WITH CUBICAL EPITHELIUM (Vincent and Jolly.)

The interior of the cytoplasm may also, like that of the ciliated cell, be traversed by a bundle of fine fibrils (cytomitome) (fig. 139). There is also present in these cells a reticulum lying peripheral to the nucleus, and continuous, according to Holmgren, with processes of membranous connective tissue which extends between the epithelium-cells (trophospongium, see pp. 25, 26).

Columnar epithelium-cells are met with in their most characteristic form lining the mucous membrane of the intestine, covering the villi, and extending into the ducts of all the glands which open into this part of the alimentary tract.

Columnar epithelium-cells are in some parts long, in others short, so as to look cubical when seen in profile. A typical instance of such cubical epithelium-cells is seen in the cells which line the vesicles of the thyroid (fig. 140). They vary in form, according to the shape of the surface which they cover; thus they may be larger at the fixed than at the free end, as when they line a tube or duct, and in a section of this they then appear wedge-shaped, or they may be larger at the free end than at the fixed extremity, as in many of those covering the villi.

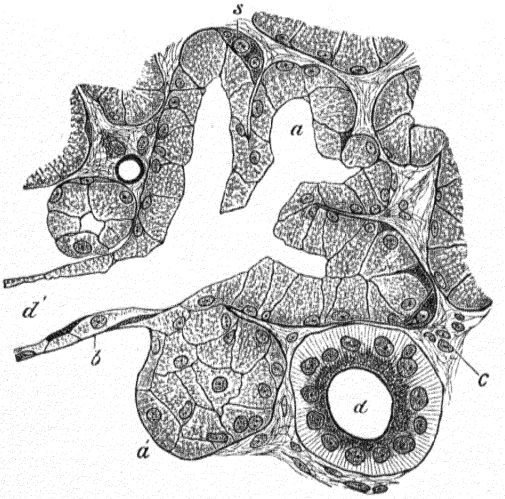


FIG. 141.—SECTION OF A RACEMOSE GLAND, SHOWING THE COMMENCEMENT OF A DUCT IN THE ALVEOLI. (Schäfer.) Magnified 425 diameters.

a, one of the alveoli, several of which are in the section shown grouped around the commencement of the duct, *d'*; *a'*, an alveolus, not opened by the section; *b*, basement-membrane in section; *c*, interstitial connective tissue of the gland; *d*, section of a duct which has passed away from its alveoli, and is now lined with characteristically striated columnar cells; *s*, semilunar group of darkly stained cells at the periphery of an alveolus.

Some epithelium-cells, which are usually reckoned in with this variety, have a peculiar striated aspect in the basal or fixed half of the cytoplasm, as if the

protoplasm were made up of fine rods. This is the case with the cells which line the smaller ducts of the salivary glands and some of the tubules of the kidney (fig. 141, *d*, and fig. 142). Under a high power of the microscope the rods resolve themselves into rows of granules.

In vertebrates, columnar epithelium is chiefly, but by no means exclusively, derived from the entoderm.

Occasionally columnar epithelium may exhibit an imperfect stratification owing to the presence of two or three layers of rounded or elongated cells between the fixed ends of the columnar cells.

Glandular epithelium.—This variety of epithelium is characteristic of the alveoli of secreting glands. In form the cells are columnar, cubical, polyhedral, or spheroidal, and are usually set round the tubular or saccular cavity of the gland, into which the secretion is poured (fig. 141, *a*). The protoplasm of the cells is generally occupied by the materials which the gland secretes or by substances which are converted into those materials in the act of secretion. These substances usually take the form of granules. They make their appearance first in the neighbourhood of the nucleus, but may ultimately fill the cytoplasm. When the cells secrete, the

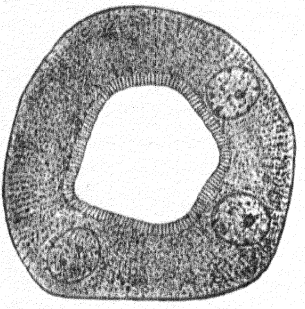


FIG. 142.—SECTION OF A CONVOLUTED TUBULE OF THE RABBIT'S KIDNEY, SHOWING THE STRUCTURE OF THE EPITHELIUM. (Szymonowicz.) Magnified 1100 diameters.

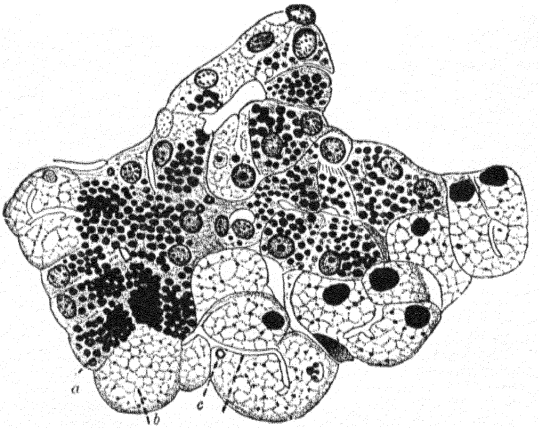


FIG. 143.—SUBMAXILLARY GLAND OF RABBIT. (E. Müller.)

The cells are in different functional states, as indicated by the condition and staining of the granules. *a*, cell filled with darkly staining granules; *b*, clear cell, the granules being swollen and having a reticulum of protoplasm between them *c*, secretory canaliculi penetrating into the cells.

granules are discharged at the free surface and the cytoplasm tends to become clear, but as the granules are continually moved towards the free surface the base of the cell tends to clear before the rest. This epithelium will be more fully described when the secreting glands are dealt with.

Goblet-cells.—A remarkable variety of glandular epithelium is furnished by the so-called *goblet* or *chalice cells*, which occur most commonly amongst the cells of columnar epithelium, as in the intestine, but are also found between the cells of ciliated epithelium, as in the air-passages. They may be looked upon as representing unicellular mucus-secreting glands, and are found in every condition of formation and discharge of the secretion. In some situations, as in the large intestine, they are nearly, if not quite, as numerous as the ordinary columnar cells (fig. 144); they are also sometimes abundant in the epithelium of the villi of the small intestine (fig. 145), and in the stomach the lining epithelium is almost entirely

formed of them,[1] and they extend also into the enlarged mouths or ducts of the gastric glands. In shape they are usually columnar, but as the mucin accumulates within them the part of the cell nearest the free surface becomes swollen out by it, whilst the fixed part of the cell tends to diminish in size, and the nucleus becomes pushed down towards the basement-membrane upon which the cells are fixed.

The secretion in these cells, as in all other secreting cells, makes its appearance in the form of granules (fig. 146), which are at first small and stain in much the same manner as the granules which are found in nearly all protoplasm. But presently the granules increase in size, and perhaps in number, and begin to take up stains which have a special affinity for mucin. The granules, however, are not stained so intensely as the fully

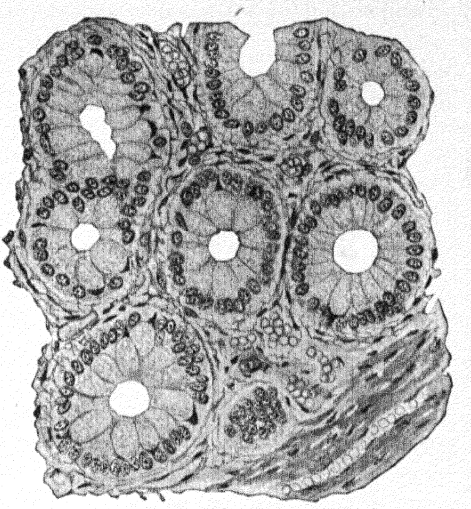


FIG. 144.—SECTION ACROSS THE TUBULAR GLANDS OF THE LARGE INTESTINE, SHOWING THE MUCUS-SECRETING OR GOBLET-CELLS LINING THE GLANDS. (Schäfer.)

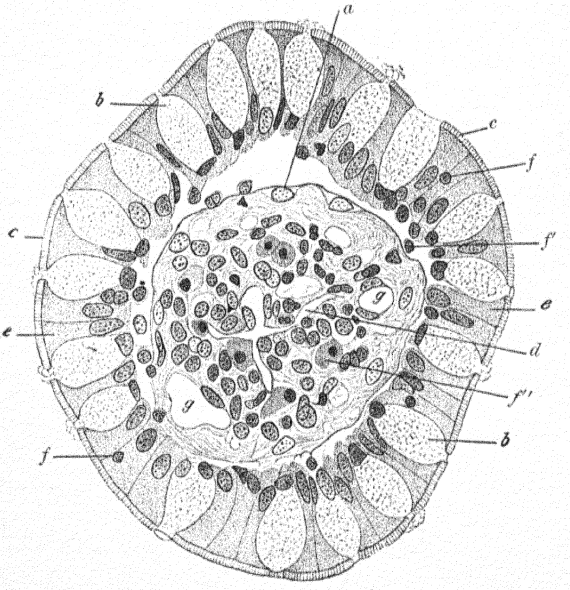


FIG. 145.—TRANSVERSE SECTION OF A VILLUS, MAN, SHOWING NUMEROUS GOBLET-CELLS BETWEEN THE ORDINARY COLUMNAR CELLS. (v. Ebner.) Magnified 530 diameters.

a, basement-membrane, here somewhat shrunken away from epithelium; *b*, goblet-cells; *c*, cuticula; *d*, lacteal; *e*, columnar epithelium; *f*, leucocytes in epithelium; *f'*, leucocytes below epithelium; *f''*, large leucocytes; *g*, blood-vessels.

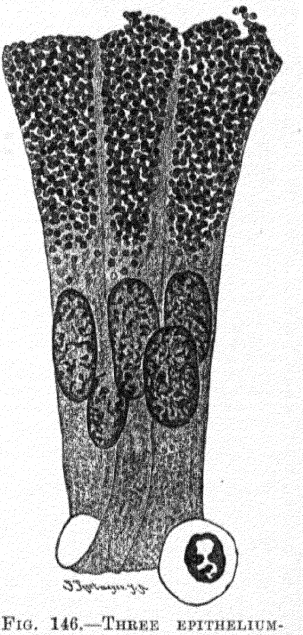


FIG. 146.—THREE EPITHELIUM-CELLS FILLED TOWARDS THE FREE END WITH MUCIN-GRANULES, FROM STOMACH; MAN. (M. Heidenhain.) Highly magnified.

formed mucin, and they probably represent a precursor of that substance: hence the term *mucigen* is sometimes used to designate them. After a time it

[1] According to Carlier (La Cellule, xi. 1895), the goblet-cells of the stomach are connected together by fine lateral bridges of cell-protoplasm.

is found that they are confined to the part of the cell which is next to the free surface; and, as already explained, this part becomes packed with them so that the cell-protoplasm is reduced to the form of a fine honeycomb-work between them.

FIG. 147.—A GOBLET OR MUCUS-SECRETING CELL IN COLUMNAR EPITHELIUM. (M. Heidenhain.) The centrosome is in the mucigen-mass. An ordinary columnar cell is also shown.

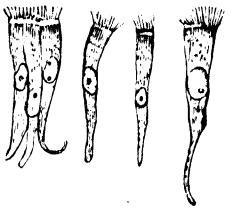


FIG. 148.—COLUMNAR CILIATED EPITHELIUM-CELLS FROM THE HUMAN NASAL MEMBRANE. (Sharpey.) Magnified 300 diameters.

When secretion occurs the granules imbibe water and become swollen into clear globules of mucus, and the part of the cell containing them is distended into a chalice-like shape, as has already been explained. Finally, as the globules swell still more, they run together and are discharged at the free end of the cell in the form of a minute drop of mucus.

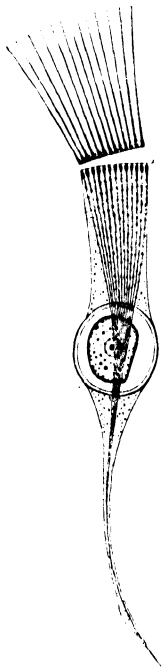


FIG. 149.—A CILIATED EPITHELIUM-CELL OF A MOLLUSC. (Engelmann.)

After the discharge of the secretion a process of regeneration begins. The remainder of the protoplasm of the cell grows so as to occupy the empty cavity left by the discharge of the mucin, and the goblet-like appearance becomes lost by a diminution in size of this cavity. The cell again, therefore, assumes a more or less columnar shape, although this form is greatly modified by the pressure of the surrounding epithelium. After a time granules again become formed in and at the expense of the newly formed protoplasm, and these granules become converted into mucin-granules as before.[1]

Each goblet-cell possesses a double centriole which lies in the middle of the peripheral half of the cell, and therefore in the part where mucin is formed (fig. 147).[2]

Ciliated epithelium.—In this form of epithelium the cells are generally columnar (fig. 148), but are sometimes cubical. In the fresh condition the cilia appear to spring from a clear border. In certain ciliated cells of molluscs—as already indicated (figs. 149, 150)—it is possible to make out that the clear border contains a number of small juxtaposed bead-like particles (*basal particles*) to each of which is connected the base of a cilium. From the ciliated

[1] M. Heidenhain, Anat. Anz. xviii. 1900. In the stomach of Triton Heidenhain finds the granules forming also in the striated border of the columnar cells.

[2] Zimmermann, Arch. f. mikr. Anat. lii. 1898; also M. Heidenhain, *loc. cit.*

border of the cell a number of varicose filaments extend down towards the fixed end of the cell; these filaments were termed by Engelmann the *rootlets* of the cilia.[1] They approach one another as they traverse the length of the cell, and may be united towards the extremity into a single thread. They are not connected with the nucleus. The cilia are attached to the basal particles, each one by a somewhat narrowed portion. It is here that the cilia are usually broken off from the cell (see fig. 149). Beyond this neck the cilium may swell out into a small bulb or knob, and from this it tapers gradually to its extremity. The rootlets, as well as the cilia themselves, are, according to the observations of Engelmann,[2] doubly refracting (anisotropous), whereas the basal particle is isotropous. A similar structure, although less distinct, is also to be made out in ciliated cells of vertebrates (frog and mammal).

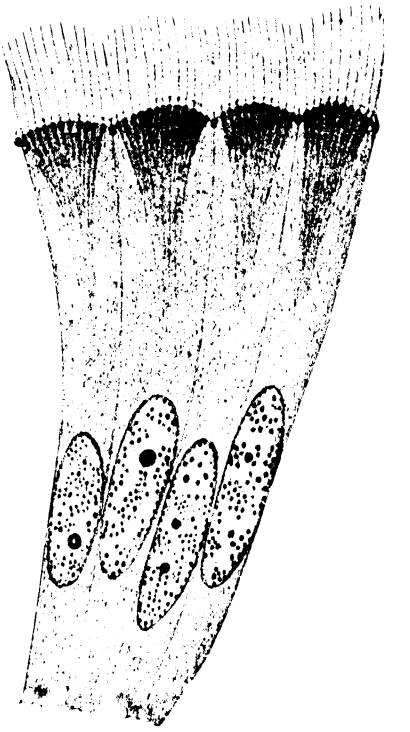


FIG. 150.—FOUR CILIATED EPITHELIUM-CELLS OF MOLLUSC, SHOWING BASAL PARTICLES, ROOTLETS, CILIA, AND NUCLEI. (v. Lenhossék.)

In the human body and in mammals generally cilia occur in the following parts—viz.: 1. On the mucous membrane of the air-passages and its prolongations. They commence at a little distance within the nostrils, cover the membrane of the nose (except the proper olfactory part) and of the adjoining bony sinuses, and extend into the nasal duct and lacrymal sac. From the posterior nares they spread backwards on the upper surface of the soft palate, and over the upper or nasal region of the pharynx; thence along the Eustachian tube and lining membrane of the middle ear, the greater part of which is ciliated. The lower part of the pharynx is covered by stratified epithelium; but ciliated epithelium begins again in the larynx a little above the glottis, and continues throughout the trachea and the bronchial tubes in the lungs almost to their smallest ramifications. Over the vocal cords, however, the epithelium is of the stratified variety. 2. On the mucous membrane and in the glands of the body of the uterus, and extending along the Fallopian tubes, even to the peritoneal surface of the latter at their fimbriated extremities. 3. Lining the vasa efferentia and coni vasculosi in the testicle. 4. Lining the true ventricles of the brain and the central canal of the spinal cord. 5. In the ducts of certain small racemose glands of various parts (tongue, pharynx, &c.). 6. In the embryo, lining the œsophagus and parts of the stomach, and extending over the whole of the pharynx.[3]

Columnar ciliated epithelium may exist as a simple layer, as in the uterus and Fallopian tubes, the finest ramifications of the bronchia, and the central

[1] Pflüger's Archiv, xxiii. 1880. The filaments were also described by M. Nussbaum (Arch. f. mikr. Anat. xiv. 1877). See on this subject also p. 73.

[2] Hermann's Handbuch der Physiologie, 1879.

[3] Cilia have also been described in some mammals at the commencement of the tubules of the kidney, a situation where in lower vertebrates they have long been known to exist; but it is doubtful if the brush-like border of the epithelium in this situation is formed of true cilia in mammals.

canal of the spinal cord and ventricles of the brain; but in various other parts—as the nose, pharynx, Eustachian tube, the trachea and its larger divisions—there is a layer of elongated and irregular cells beneath and between the superficial ciliated range, filling up the spaces amongst the pointed and forked extremities of the ciliated cells. These cells have by some been supposed to acquire cilia, and take the place of ciliated cells which are cast off; but they appear rather to be concerned with the secretion of mucus, since mucigen occurs within them in all stages of formation, and they become eventually distended by it into goblet-cells. This is illustrated in fig. 151, where the intermediate cells, m^1, m^2, and m^3 show three stages of formation of mucus.

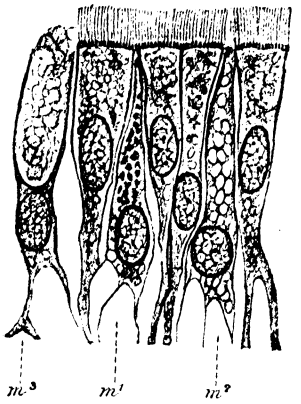


FIG. 151.—CILIATED EPITHELIUM-CELLS FROM THE TRACHEA OF THE RABBIT. (Schäfer.) Highly magnified.

m^1, m^2, m^3, mucus-secreting cells, lying between the ciliated cells, and seen in various stages of mucin-formation.

When the ciliated epithelium is artificially removed from a portion of the inner surface of the rabbit's trachea, the denuded surface speedily becomes again covered with epithelium which grows over it from the edge; the cells form at first a single layer of flattened epithelium. They next acquire cilia, and afterwards become columnar, the epithelium thus assuming the character which it has normally in that situation.

As has already been stated, the spermatozoa are to be regarded as ciliated cells, the tail of the spermatozoon representing a cilium. It must, however, be noted that the structure of the tail in the vertebrate spermatozoon is more complex than that of any other known cilium, for it contains one or more fine fibrils in its axis (axial fibrils), and in some animals a spiral fibre coiled around the enlarged part (middle piece) which is attached to the head of the spermatozoon. The axial fibrils are connected with and appear to have grown out from the centriole, which lies in the middle piece close to the head. On the other hand, the spiral fibre is developed from special granules (mitochondria) in the spermatids (fig. 39).[1]

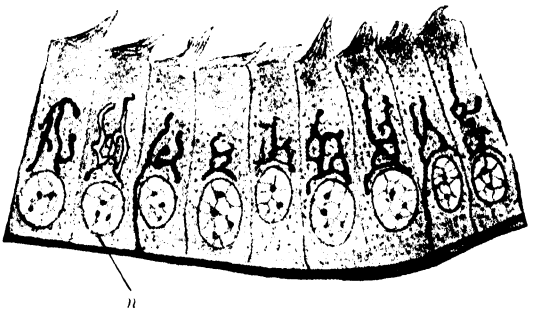


FIG. 152. —CANALICULI WITHIN COLUMNAR EPITHELIUM-CELLS OF EPIDIDYMIS. (Holmgren.)

n, nucleus.

The ciliated epithelium of the uterus has shorter cells than those of the respiratory passages,[2] and between them are more slender cells without cilia.[3] According to Barfurth there are cell-bridges crossing the intercellular substance.[4] The ciliated epithelium of the central canal of the spinal cord and that lining the ventricles of the brain is peculiar in being prolonged at the base into long fibres of neuroglia-like character (see fig. 311), which in the embryo pass

[1] Benda, Verh. d. physiol. Ges. z. Berlin, 1897, 1898, 1899; F. Meves, Arch. f. mikr. Anat. lvi. 1900.

[2] According to Björkenheim (Anat. Hefte, xxxv. 1907), they become more flattened as age advances, and tend to become keratinised.

[3] The constancy of cilia upon the cells of the epithelium of the body of the uterus seems doubtful. Keller (Anat. Hefte, xxix. 1909) was never able to convince himself of their presence in the uterus of the bitch. See also S. H. Gage, Amer. Journ. Anat. iii. 1904.

[4] Anat. Hefte, ix. 1897.

through the whole thickness of the nervous tube to abut on its outer surface. But in the adult human subject these processes cannot be traced any great distance from the cell-body, and the latter, especially in the spinal cord, is often found to have undergone dislocation from its original position and not infrequently complete degeneration.

A peculiar form of epithelium is found lining the tube of the epididymis (fig. 152). The cells resemble those of ciliated epithelium, and possess a bunch of hair-like processes. These,

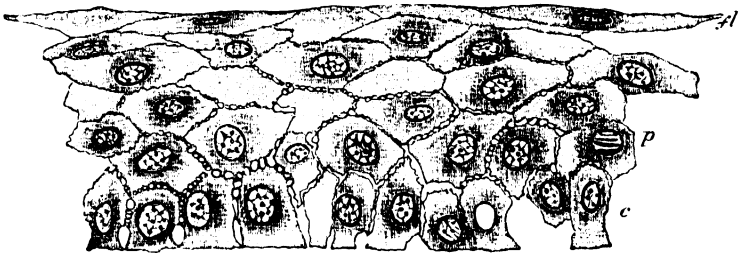


FIG. 153.—SECTION OF THE STRATIFIED EPITHELIUM COVERING THE FRONT OF THE CORNEA OF THE EYE. (Schäfer.) Highly magnified.

c, lowermost columnar cells; *p*, polygonal cells above these; *fl*, flattened cells near the surface. The intercellular channels bridged by minute processes of the cell are well seen. The lower part of the section on the right is somewhat broken.

however, are not vibratile, but seem to be adherent together; they can be traced down into the cytoplasm for a short distance.[1]

For further details regarding the structure, development, and action of cilia and the nature and causation of their movement, see pp. 71 to 81.

Protective epithelium.—The protective epithelia afford mechanical protection to the surfaces which they cover. Two varieties of protective epithelium

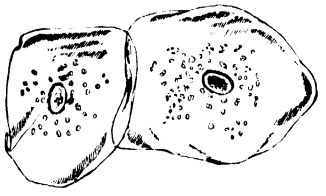


FIG. 154. EPITHELIUM-SCALES FROM THE INSIDE OF THE MOUTH. (Henle.) Magnified 260 diameters.

may be distinguished—viz. *stratified* and *transitional*.

In **stratified epithelium** the cells are disposed in a number of layers, and it is found that the constituent cells of the various strata exhibit every variety of shape. As a rule the cells of the deepest or attached layer are columnar (fig. 153, *c*), and the superficial cells are flattened scales (fig. 153, *fl*), which may be of considerable size and overlap one another (fig. 153). The cells of the layers immediately external to the columnar layer are shaped so as to enable them to fit to the columnar cells and to one another (fig. 153, *p*); but as we trace the strata towards

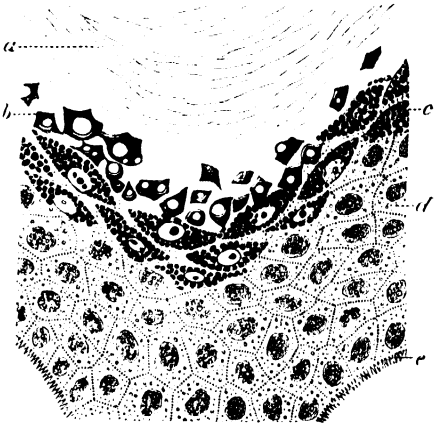


FIG. 155.—PORTION OF EPIDERMIS FROM A SECTION OF THE SKIN OF THE FINGER, COLOURED WITH PICROCARMINE. (Ranvier.)

a, horny layer; *b*, its deepest part (stratum lucidum) with flakes of eleidin; *c*, eleidin-granules in cells of stratum granulosum; *d*, deeper cells of stratum mucosum with intercellular channels; *e*, dentations by which the deepest cells are fixed to the surface of the cutis vera.

[1] Myers-Ward, Journ. Anat. and Physiol. xxxii. 1897; Gurwitsch, Arch. f. mikr. Anat. lix. 1901; H. Fuchs, Anat. Hefte, xix. 1902; xx. 1905.

the surface, we find the component cells becoming more flattened and larger, whilst at the same time in some epithelia, such as that covering the skin, they undergo a change in their chemical constitution, so that at first the external part, and afterwards the whole of the protoplasm of the cell, is converted into horny substance (*keratin*), even the nucleus being at last involved.

The conversion into horny substance is preceded by the deposit of a fluid material in droplets, which is termed *eleidin* (Ranvier). In the epidermis and some other parts the cells in which this material is first deposited form a layer of flat granular-looking cells, spindle-shaped in section, which is situated between the soft, still protoplasmic, deeper cells and the more superficial horny stratum (fig. 155). The layer is termed *stratum granulosum*, and was described by Langerhans. The eleidin forms larger drops as the cells are traced towards the surface,

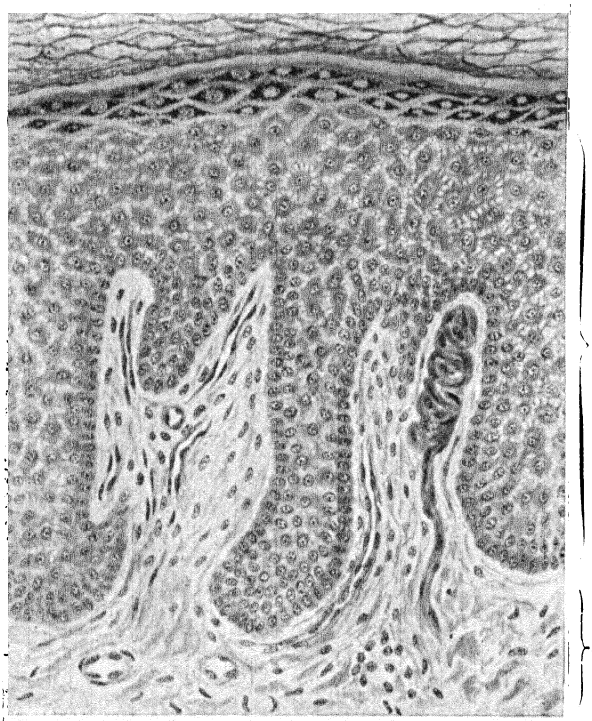


FIG. 156.—VERTICAL SECTION THROUGH THE SKIN OF THE PALMAR SIDE OF THE FINGER, SHOWING TWO PAPILLÆ (ONE OF WHICH CONTAINS A TACTILE CORPUSCLE) AND THE DEEPER LAYERS OF THE EPIDERMIS. (Schäfer.) Magnified about 200 diameters.

and loses its faculty of being stained with hæmatoxylin and basic dyes, being changed into a homogeneous-looking substance which has been termed *keratohyalin* [1] (Waldeyer). This gives the cells which it occupies a clear appearance, and they collectively form a layer, which is known as the *stratum lucidum*. Superficial to this is the true horny layer (*stratum corneum*).

The cells of stratified epithelia not infrequently show the presence of pigment-granules, not only in the coloured races of mankind, but in certain parts of the epidermis of white races. It is not certain whether this pigment is formed in the cells where it occurs or is brought there by leucocytes. The presence of wander-cells

[1] The terms 'eleidin' and 'keratohyalin' are sometimes employed as synonyms, but it is better to retain the one for the granular phase, and the other for the clear phase of the keratogenous substance.

containing pigment in the corium below such coloured parts has been noted in the normal skin by Kölliker [1] and has also been observed in connexion with the dark patches in Addison's disease, but it cannot be determined whether these are bringing pigment or taking it away.[2]

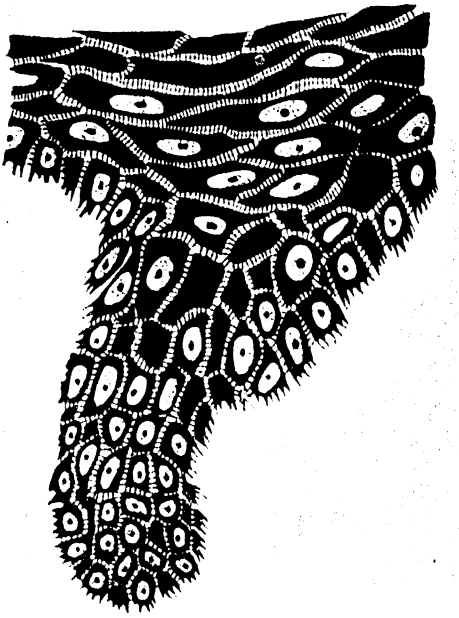


FIG. 157.—SECTION OF EPIDERMIS OF CAT'S FOOT SHOWING FIBRILS BRIDGING ACROSS THE INTERCELLULAR SPACES. (Kolossow.)

The deeper layers of a stratified epithelium are not closely applied to one another by their edges, nor are they united by cement-substance, but there exists a system of intercellular channels, which are bridged across by fibres which run from one cell to the other (see figs. 156, 157). When the cells are isolated, the fibres are broken through and appear as spikes or dentations on the surface and edges of the cells (fig. 158). Sometimes the intercellular channels become widened in consequence of an excess of fluid accumulating in them, but usually they are very narrow and but little obvious.

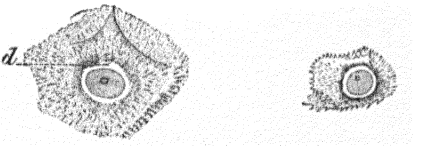


FIG. 158.—TWO 'PRICKLE-CELLS' FROM THE DEEPER PART OF THE EPIDERMIS. (Ranvier.)

d, space around the nucleus, probably caused by shrinking of the latter.

The spikes and ridges upon the deeper cells of a stratified epithelium were first noticed by Max Schultze, who was of opinion that they were for the purpose of effecting, by indenting with those on adjoining cells, a firmer connexion between the cells of the epithelium. The true relations of the structures in question, and the intercellular channels which are bridged across by them, were discovered by Bizzozero. The researches of J. Arnold and of Thoma showed that similar intercellular channels occur extensively in all varieties of epithelium.[3] The fibrils which

[1] Zeitschr. f. wiss. Zool. xlv. 1887.

[2] According to Kromayer (Arch. f. mikr. Anat. xlii. 1892), the pigment is certainly formed within the epithelium-cells. B. Rosenstadt (*ibid.* l. 1897) comes to the same conclusion.

[3] Cf. also A. Kolossow (Arch. f. mikr. Anat. lii. 1898), who, by the employment of a special method of fixation and staining, has been able to show cell-bridges in all epithelia without exception.

bridge across the intercellular spaces were described by Ranvier as passing through the protoplasm of the cells.[1] According to Cajal,[2] they are covered by a prolongation of cell-membrane. A similar view is taken by Ide, who describes the cell-membrane as reticulated.[3] A radiating system of fibrils has also been shown to occur in the pavement-epithelium cells which cover the posterior surface of the cornea (see fig. 133), and in this case also the fibrils traverse the intercellular spaces, passing from one cell into another.

Fibrillation of the cells of a stratified epithelium is not confined to the deeper layers, but extends even to the cells of the horny stratum,[4] and, according to several authors,[5] is intimately associated with the condition of keratinisation.

Stratified epithelium occurs in one of its simplest and most typical forms covering the anterior surface of the cornea of the eye, where in man there are about six layers of cells (fig. 153). A still simpler kind, containing only four layers of cells and with some mucus-secreting cells in the second layer, is described by Koch as occurring on the third eyelid of certain animals (fig. 159).[6] Stratified epithelium also lines the mouth, the chief part of the pharynx, and the œsophagus, and in the female the vagina and part of the cervix uteri; but its most extensive distribution is over the surface of the skin, where it forms the epidermis. In many parts of the epidermis the layers become very numerous and their arrangement somewhat complicated, as will be particularly noticed in the description of the skin. It may be remarked that, in most of the situations where it is found, stratified epithelium is of ectodermic origin; but this is not invariably the case, and its occurrence depends much more upon the physiological conditions of the parts which it covers. Thus, wherever a surface is liable to undergo friction or abrasion, there we find a development of this variety of epithelium.

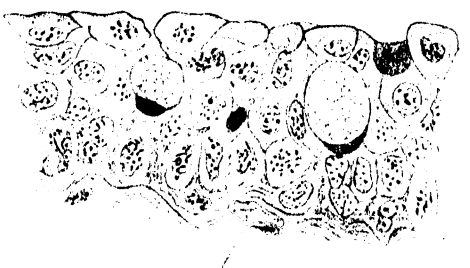


FIG. 159. SECTION OF EPITHELIUM OF THIRD EYELID OF CAT, SHOWING MUCUS-SECRETING CELLS IN A STRATIFIED EPITHELIUM. (R. Koch.)

The deeper protoplasmic cells of a stratified epithelium are continually multiplying by karyokinetic division,[7] and, as the new cells which are thus produced in the deeper parts increase in size, they compress and push outwards those previously formed. In this way cells which were at first deeply seated, become gradually shifted towards the surface, undergoing meanwhile the chemical change above spoken of. The older superficial cells are continually being removed by abrasion, while others rise up to supply their place.

Where stratified epithelium becomes continued into epithelium of the columnar kind, as at the junction of the œsophagus with the stomach, the change usually occurs abruptly, and the simple columnar epithelium seems to be a continuation of the deepest (or columnar) layer of cells of the stratified epithelium. But at the junction of the columnar epithelium of the rectum with the stratified

[1] Cf. Herscheimer, Arch. f. mikr. Anat. liv. 1899.
[2] Int. Monatschr. f. Anat. u. Histol. iii. 1886.
[3] La Cellule, iv. 1888 and v. 1889. See also on the intercellular channels and bridges in stratified epithelium, S. Garten, Arch. f. Anat. 1895.
[4] L. Merk, Arch. f. mikr. Anat. lvi. 1900.
[5] Weidenreich, Arch. f. mikr. Anat. lvi. 1901, and lvii. 1901; Apolant, *ibid.* lvii. 1901; Nussbaum, Anat. Hefte, xxxix. 1909.
[6] Arch. f. mikr. Anat. lxiii. 1903. Koch terms this 'mixed' epithelium. A similar epithelium was described in the caruncula of man by L. Stieda (Arch. f. mikr. Anat. xxxvi. 1890). Stieda regarded the 'mucus-secreting' cells of Koch as degenerated cells.
[7] Hanseman, Virchow Festschr. 1891.

epithelium of the anal canal the change is less abrupt, the number of layers of the stratified epithelium being gradually reduced until only the deepest remains.

Stratified epithelium plays an important part in connexion with the formation in the embryo of certain folds of skin and mucous membrane, as well as of tubular openings on to the surface.[1] Such folds are frequently preceded by a hypertrophy of the epithelium, which grows down into the corium in the form of a solid ridge. This subsequently splits along the middle by a dehiscence of its central cells, and one part adheres to each of the layers of corium which now bound the depression. This is the manner in which the prepuce is formed in both sexes. Similarly the vagina is developed as a solid cord of epithelium which assumes a stratified character, and by

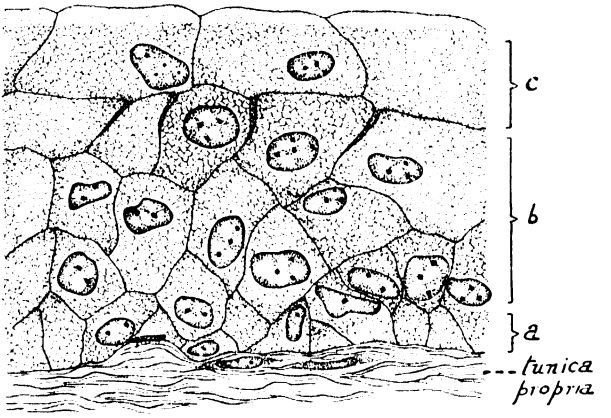


FIG. 160.—SECTION OF MUCOUS MEMBRANE OF BLADDER OF DOG, FIXED IN THE EMPTY CONDITION OF THE ORGAN. (R. W. Harvey.)

a, *b*, *c*, successive layers of the epithelium.

dehiscence of its central cells the solid cord is converted into a tube. A similar mode of formation is also said to occur in the male urethra, at least in its distal portion. In the development of the eyelids, the slit is temporarily closed by the growing together of the stratified epithelium at the edges of the lids, and it is only a little before birth that a splitting occurs in the epithelial connexion and the lids open. A familiar instance of this process of the downgrowth of stratified

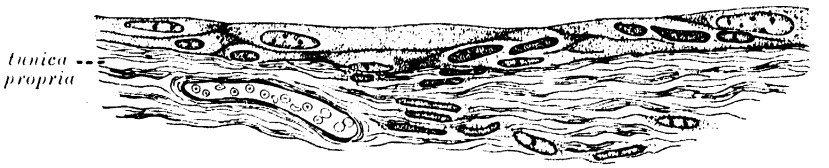


FIG. 161.—SECTION OF MUCOUS MEMBRANE OF BLADDER OF DOG, FIXED IN THE DISTENDED CONDITION OF THE ORGAN. (R. W. Harvey.)

epithelium into a connective-tissue corium, with dehiscence and consequent hollowing out of the centre of the growth, also occurs in connexion with the development of the hairs and cutaneous glands.

Transitional epithelium lines the urinary bladder and ureters. This epithelium consists of three or four layers of cells (figs. 160, 161, 162), of which the inner or most superficial are large flattened scales when examined from the

[1] Berry Hart, Journ. Anat. and Physiol. xlii. 1908.

distended bladder, but almost cubical in shape when taken from the collapsed organ; smooth over their free surface—which, according to Eggeling, is covered by a thin cuticular stratum—but pitted on the opposite side, being moulded over the rounded ends of the cells which form the next layer. These are pyriform, and the smaller end of the pear is set upon the subjacent connective tissue, whilst the larger end has the position just mentioned. Filling up the intervals between these tapering cells are the smaller irregular cells of the subjacent layers (fig. 160). In the flattened superficial cells two nuclei may often be seen in each cell: they are said to be produced amitotically (p. 39). If this is an indication that the cell is about to divide, the mode of growth of this kind of epithelium must be different from that of the stratified scaly variety, in which the multiplication of the cells takes place exclusively in the deeper layers.

This variety of protective epithelium is termed 'transitional,' as indicating a character intermediate between the simple epithelia with a single layer of cells and the more complex stratified epithelium which consists of a number of layers.

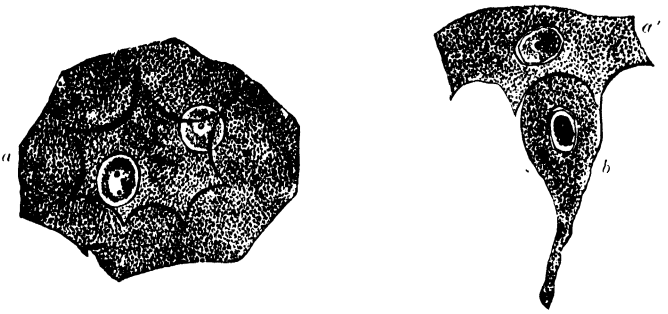


FIG. 162.—EPITHELIAL CELLS FROM THE BLADDER OF THE RABBIT. (Klein.) Highly magnified.

a, large flattened cell from the superficial layer, with two nuclei, and with strongly marked ridges and intervening depressions on its under surface; *a'*, one of the same cells shown in profile; *b*, pear-shaped cell of the second layer showing the manner in which it is adapted to a depression on the superficial cell.

The transitional epithelium of the bladder and ureters affords a striking example of the extensibility and elasticity of epithelium-cells, as shown by the manner in which it adapts itself to the variations in size of the cavity which it lines (figs. 160 and 161).[1]

SPECIAL MODIFICATIONS OF EPITHELIAL TISSUE.

Special modifications of epithelium are met with in certain situations in the body, and notably forming the enamel of the teeth and the substance of the crystalline lens of the eye. The pigment layer of the retina is also to be reckoned in this category, together with the pigmented epithelium which is prolonged in front of the retina over the choroid processes and posterior surface of the iris. Further, all the integumental appendages in vertebrates are essentially of epithelial nature, including the scales of reptiles, the feathers and beak of birds, the hairs, hoofs, claws, and nails of mammals. These integumental structures (fig. 163) are entirely composed of keratinised epithelium-cells, elongated or flattened and arranged in compact formation, and all have as a foundation from which to grow a layer or layers of protoplasmic epithelium resting upon a vascular connective-tissue corium. In many of these structures pigment of various colours is deposited within the cells before keratinisation occurs.

[1] R. W. Harvey, Anat. Record, iii. 1909.

The *enamel of the teeth* (fig. 164) is produced from the deeper cells of the stratified epithelium covering the gums. The epithelium becomes thickened and grows into the substance of the mucous membrane, a vascular papillary process of which projects into the thickening. This

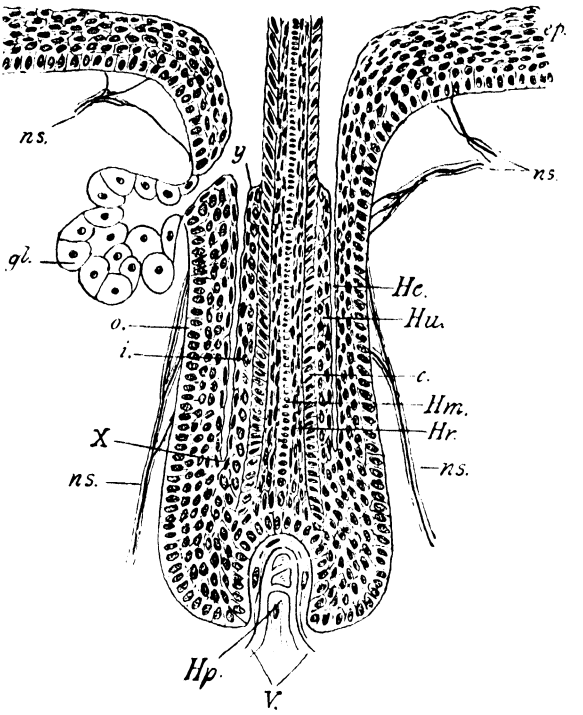


FIG. 163.—DIAGRAM TO SHOW THE DERIVATION OF A HAIR AND HAIR-FOLLICLE FROM THE EPITHELIAL LAYER OF THE SKIN. (Maurer.)

Hr., hair; *Hm.*, its medulla; *c.*, its cuticle; *o.*, outer, and *i.*, inner layers of root-sheath joining with one another at *X*; *y*, termination of inner root-sheath on hair; *Hc.*, *Hu.*, layers of Henle and of Huxley of inner root-sheath; *ep.*, epidermis; *Hp.*, hair-papilla; *V.*, blood-vessels; *ns.*, nerves; *gl.*, sebaceous gland.

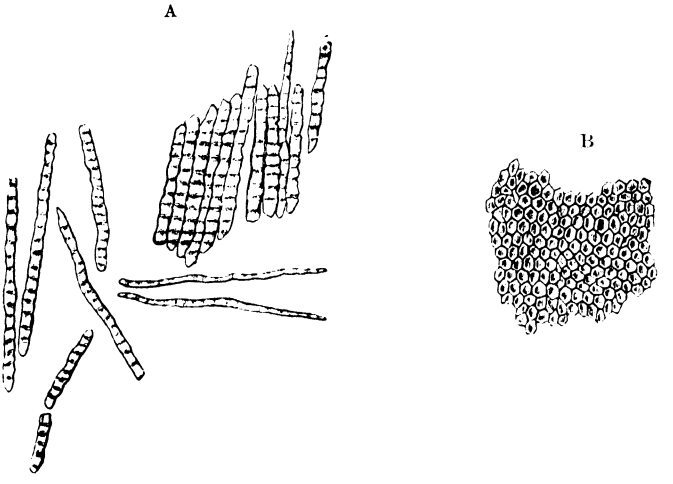


FIG. 164.—ENAMEL-PRISMS. (From Kölliker.) 350 diameters.

A, fragments and single columns of the enamel, isolated by the action of hydrochloric acid.
B, surface of a small fragment of enamel, showing the hexagonal ends of the prisms.

papilla undergoes calcification, resulting in the production of the dentine or ivory of the tooth, which is a connective-tissue structure allied to bone; and upon the surface of the dentine thus formed the cells of the epithelial thickening (which now forms what is known as the enamel organ) deposit a succession of layers of enamel in the form of closely packed prisms of calcareous substance which correspond in form to the columnar cells which produce them. After the enamel is completed, and when the tooth crown emerges from the gum owing to the growth of the roots, the cells of the enamel organ disappear entirely.[1] The enamel prisms are probably formed within the enamel-cells (ameloblasts) themselves, and not by deposition of calcareous matter external to them. When fully formed they contain scarcely any organic material.[2]

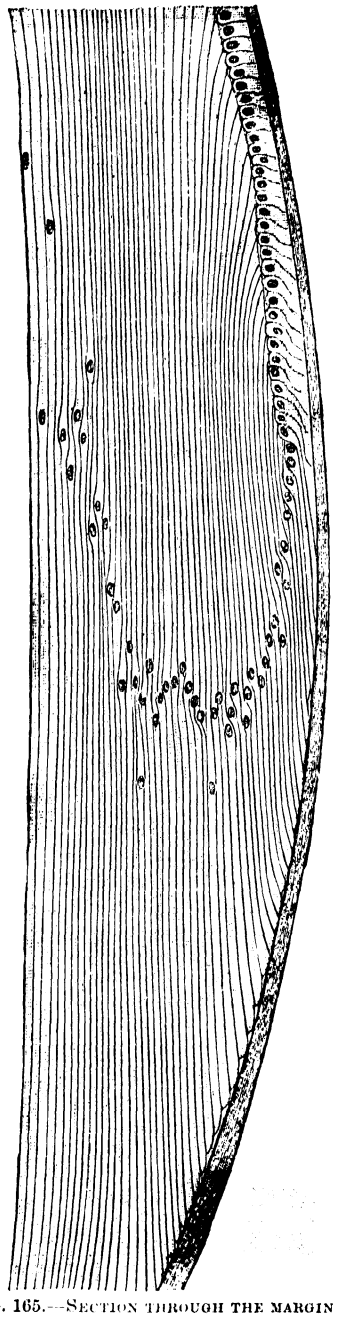


FIG. 165.—SECTION THROUGH THE MARGIN OF THE LENS, SHOWING THE TRANSITION OF THE EPITHELIUM INTO THE LENS-FIBRES. (Babuchin.)

The crystalline lens of the eye is also formed from an invagination of ectoderm, which occurs very early in embryonic development, and becoming separated from the rest of the ectoderm lies in the cup-shaped cavity which is formed by the folding of the primary optic vesicle. The globular island of epithelium thus produced consists of two layers, anterior and posterior, continuous with one another at the equator of the lens. Of these two layers the anterior remains almost unaltered except that its cells multiply with the growth of the lens; it forms the anterior or capsular epithelium of the lens. The posterior layer undergoes considerable modification. Its cells grow into long clear prismatic or flattened fibres with irregular or jagged edges interlocking with one another. They lose their protoplasmic character and become occupied by a clear fluid containing a large amount of globulin: in most of them also the nucleus atrophies so that their original cell-nature tends to be greatly obscured (fig. 165).

The pigment-cells of the retina are remarkable from the fact that they display under the alternate influence of light and darkness movements of the pigment-granules which they contain. The layer when viewed from the outer surface looks like a mosaic of hexagonal cells, but when seen in profile the cells are observed to be prolonged inwardly between the rods and cones of the retina, and it is also evident that the pigment-granules are confined to this part of the cell, while the nucleus lies in the outer part. The extent to which the pigmented part of the cell projects inwards varies with the conditions as regards light to which the eye has been exposed. If the animal had been exposed to light shortly before death, the pigment is found to extend a considerable distance from the nucleus towards the bases of the rods and cones. But if, on the other hand, the animal is kept in the dark before being killed, the pigment is withdrawn toward the nucleus. The function of this pigment is partly for the purpose of absorbing light, partly to effect a chemical change in the retinal rods, the purple colouring-matter of which becomes bleached by the action of light and reconverted into visual purple by the pigment-cells.

[1] The structure and mode of development of the enamel will be again referred to when the other tissues of the teeth come under consideration.

[2] C. S. Tomes, Proc. Odont. Soc. 1896.

At the line of cessation of the retina—known as the *ora serrata*—this membrane is prolonged over the ciliary processes as the *pars ciliaris retinæ*. This is not, however, true retina, for it has none of the nervous elements and is composed of but two layers, an inner layer of clear elongated columnar epithelium-cells and an outer layer of cubical pigmented epithelium: the latter being

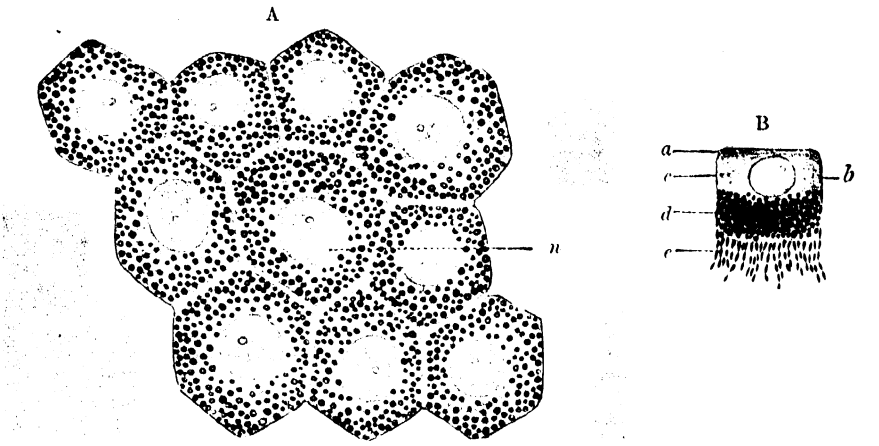


FIG. 166.—PIGMENTED EPITHELIUM OF THE RETINA. (Greeff.) Magnified 1000 diameters.
A. Surface view; *n*, nucleus.

B. A single cell in profile view.

a, free surface; *b*, nucleus; *c*, pigment-free cytoplasm; *d*, pigmented cytoplasm; *e*, pigmented processes.

continued from the retinal epithelium just described, but having none of the special charact of that epithelium with the exception of the possession of pigment, with which the cells are closely packed. These pigmented cells are continued over the back of the iris, and are here reinforced

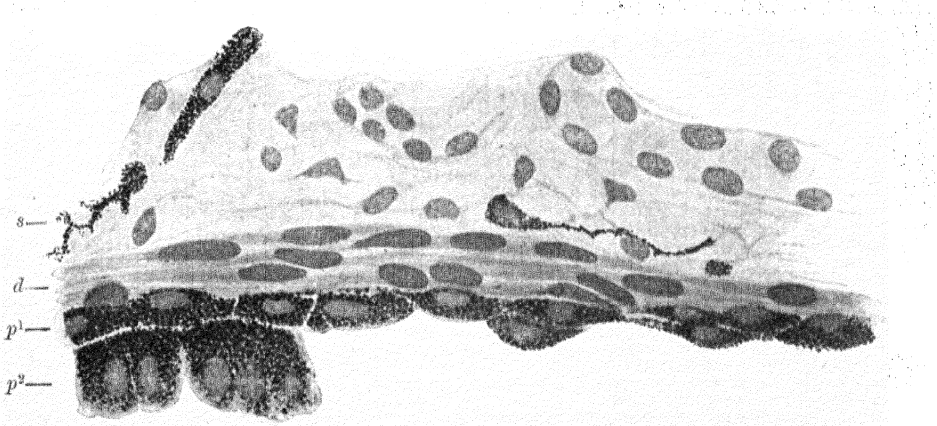


FIG. 167.—SECTION OF POSTERIOR LAYERS OF IRIS, HUMAN, NEAR ITS ATTACHMENT TO THE CHOROID. (Schäfer.) Magnified 600 diameters.

s, iris-stroma of connective tissue, showing three pigmented connective-tissue cells; *d*, plain muscle-cells of dilatator pupillæ; p^1, p^2, pigmented epithelium-cells continued from retinal layers. Most of the cells of the stratum, p^2, are broken away.

by a second pigmented layer which lies internal (posterior) to them (fig. 167). The cells of both of these layers as well as the pigment-cells of the pars ciliaris retinæ are filled with dark pigment granules, the purpose of which is to block the passage of light-rays, so that the path of these may be confined to the pupil.

CONNECTIVE TISSUES.

The connective tissues include *areolar*, *fibrous*, and *elastic* tissue, *reticular* (*retiform*) and *lymphoid* tissue, *adipose* tissue, *cartilage*, and *bone*. They agree in certain microscopic characters and also in taking origin in the looser part of the mesoderm, which has been termed mesenchyme (see p. 4), but they present many differences in the characters of their cells, which may be fibrillated or granular, or occupied by pigment or by fat; as well as in the arrangement and relative proportion of their tissue elements, and in certain special chemical characters. Their general character is the possession of a comparatively large amount of intercellular material, which constitutes a *matrix* or *ground-substance* through which fibres course; the cells lie scattered singly or in groups in this ground-substance, spaces in which they may be said to fill. The ground-substance and the fibres which it contains are stained brown by Recklinghausen's

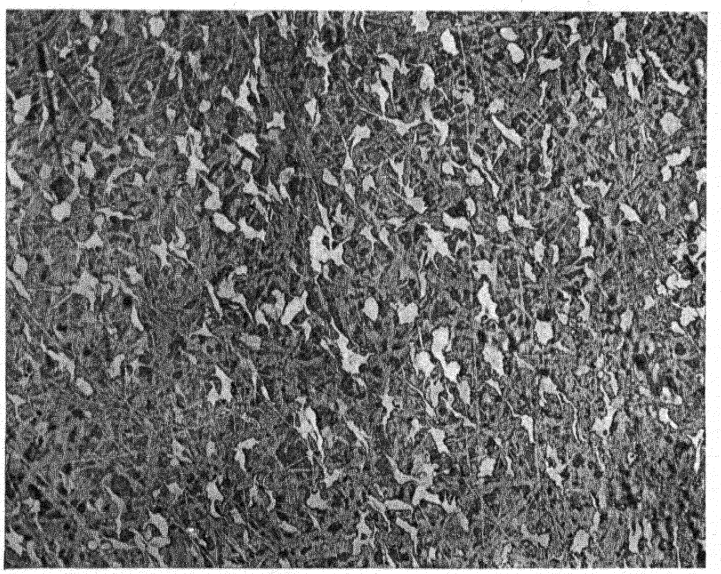


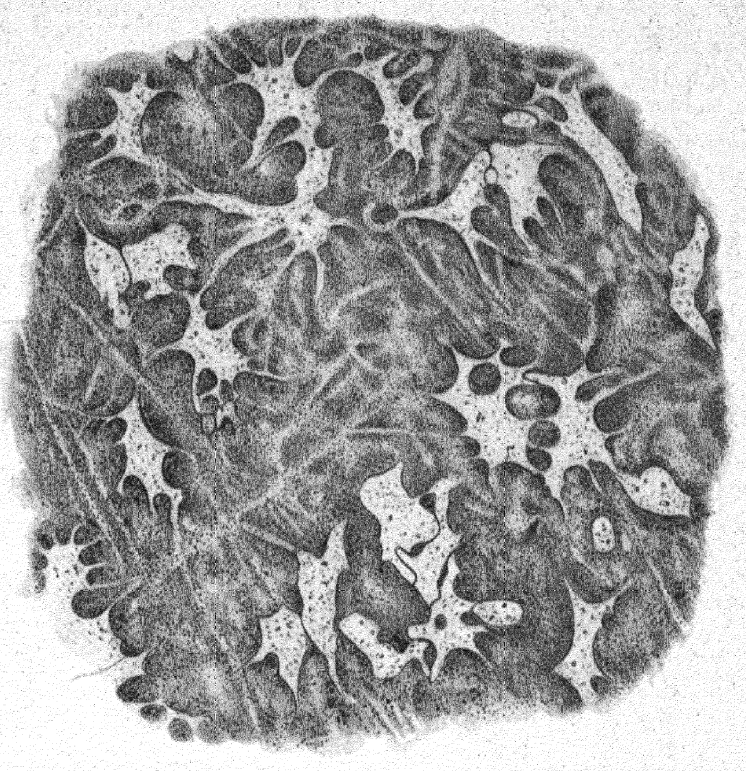
FIG. 168.—AREOLAR TISSUE PREPARED BY RECKLINGHAUSEN'S SILVER METHOD. (Schäfer.) Magnified 200 diameters.

The cells are seen as clear spaces in the (brown) stained ground-substance, through which the fibres course.

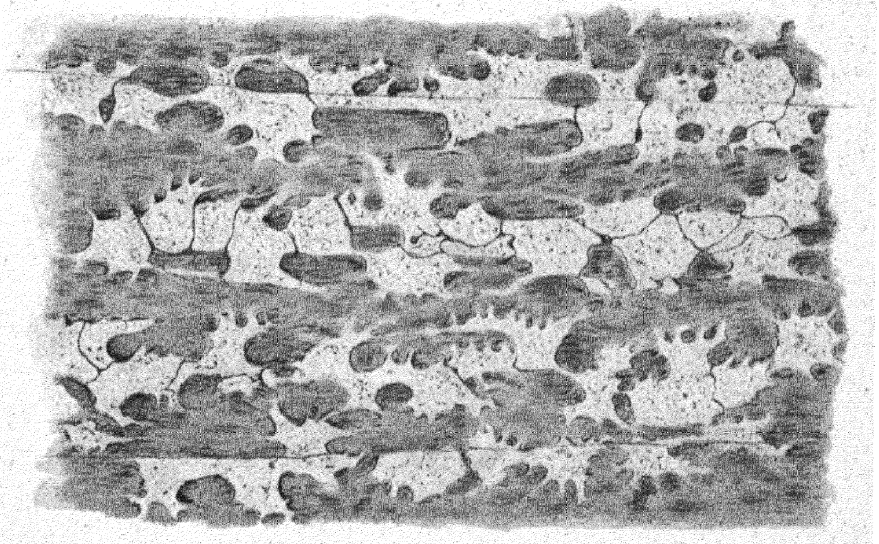
silver-nitrate method (see p. 5), which leaves the cells and therefore the cell-spaces white (see figs. 168, 169 and accompanying Plate); where the cells are in contact with one another the white spaces which appear in a silver-stained specimen give the appearance of intercommunicating channels in the ground-substance. When first seen by Recklinghausen this appearance was not fully understood, since it was not known that the spaces thus brought to view are all occupied by cells, and the term 'lymph-canaliculi' (Saft-kanälchen) was applied to the supposed channels; they are now more commonly spoken of as the *cell-spaces* of the tissue (fig. 169).[1]

The ground-substance of connective tissue is naturally soft and semi-fluid in nature. It contains a mucin-like material, which forms, in the young condition of the tissue, its chief organic constituent. But, later, as fibres become developed

[1] This term was first employed to designate Recklinghausen's 'Saft-kanälchen' in the 8th edition of this work.



Areolar tissue, stained with silver nitrate. Magnified 200 diameters. (Schäfer.)



Tendon from tail of rat; stained with silver nitrate.
Magnified 200 diameters. (Schäfer.)

in it, its physical and chemical characters become altered and the mucin becomes replaced by collagen, yielding gelatin on boiling.

Different as the several varieties of connective tissue appear in their fully developed condition, they are all, as above stated, produced from the same embryonic formation, and, in different kinds of animals, are often found to replace one another. Moreover, where they come into juxtaposition they frequently pass by a gradual transition the one into the other, so that there can be no doubt

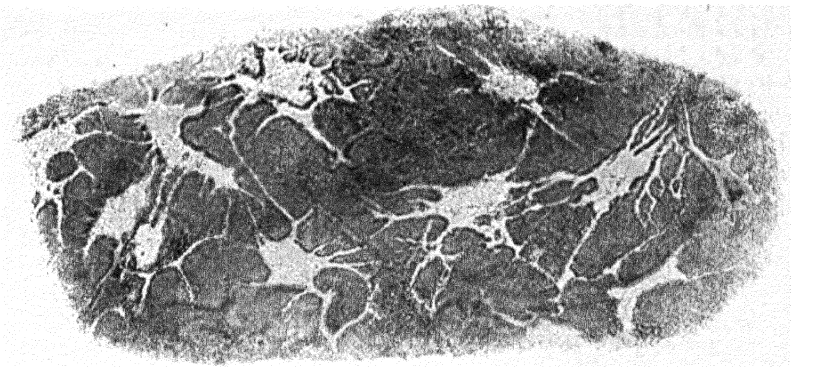


FIG. 169.—CORNEA OF RABBIT, STAINED WITH SILVER NITRATE. Magnified 800 diameters. Photographed from a preparation by H. Pringle.
The cells are unstained, and appear as white spaces on a brown ground. Compare with fig. 176, in which the corneal cells are stained.

about their close affinity. The affinity is, however, greater between the areolar, fibrous, and elastic tissues than between these and cartilage or bone. Retiform (including lymphoid tissue) and adipose may be regarded as modifications of areolar tissue, but they differ from it by the accumulation of cells which have a special function; this accumulation may occur to so great an extent as to obscure the original structure of the tissue.

AREOLAR TISSUE OR CONNECTIVE TISSUE PROPER.

Areolar tissue is the most widely diffused of all the connective tissues. It is the fleecy-looking material which is seen when the skin is reflected, and from its property of binding or connecting the several parts and organs of the body together the generic name of connective tissue (German, 'Bindegewebe') has been derived. It also enters into the composition of most organs of the body, forming a kind of framework which supports and connects the other tissues and conducts vessels and nerves to the proper elements of the organ, as in the muscles and secreting glands. Areolar tissue differs considerably in consistence in different parts, and in different animals. In some animals, including man, it is of a tough, fibrous-looking texture, composed of thin laminæ which interlace with one another, leaving interstices (areolæ) between them. These interstices intercommunicate throughout the tissue, and hence it happens that if air or liquid be forced into the tissue at any one part it may spread over a considerable space. In the young subject in man and some animals, and in other animals throughout life, the laminæ of this tissue are less tenacious, and the tissue is softer and almost jelly-like or semi-fluid in consistence: this difference is due to the fact that in the one case there is a greater development of fibres in the ground-substance than in the other. The areolæ of the tissue are moistened naturally with lymph; they are larger and the tissue is

looser in some parts; smaller, with denser tissue, in others; the denser varieties pass by gradual transition into the kind of connective tissue which is termed 'fibrous.' There are no distinct areolæ in the early stages of formation; these become developed as the ground-substance becomes fibrillated, probably by liquefaction of part of the matrix.

White fibres (*collagenous fibrils*).—Examined under the microscope a lamina or film of areolar tissue shows a number of what look at first sight like wavy fibres running in all directions in the tissue and occasionally intercommunicating. More careful observation shows that most of these apparent fibres are really bundles of fine fibres or fibrils, and that the intercommunication of the bundles is effected by the detachment of a certain number of fibres from one bundle to join another. The fibrils themselves, which run parallel with one another in the bundles (fig. 170), do not branch or join one another: they are cemented together in the bundles by an imperceptible amount of interfibrillar material, and the size of the bundles depends upon the number of fibrils in each. If the bundles are stretched they straighten out, and so do, of course, their constituent fibres, but any attempt to extend the bundle further is met by marked resistance, which shows that the material of the fibres is one of considerable strength and toughness.

FIG. 170. FILAMENTS OF AREOLAR TISSUE, IN LARGER AND SMALLER BUNDLES, AS SEEN UNDER A MAGNIFYING POWER OF 400 DIAMETERS. (Sharpey.)

These fine transparent fibrils, which always run in wavy bundles in the tissue and which never themselves branch or join one another, have a pearly-white appearance when accumulated in any quantity, and have hence been termed the *white fibres* of the connective tissue. It is to them that a connective tissue owes any toughness it possesses, and it is these fibres which, when a connective tissue is boiled, yield gelatin into solution. They have further the property of swelling up, with loss of distinctness of outline, when treated with dilute acid, and of dissolving in gastric juice. On the other hand, weak alkalies have little or no effect upon them, although serving to dissolve the cement which unites them, nor are they attacked by pancreatic juice, which dissolves almost all the elements of the tissues. Under such conditions they are brought very prominently into view, and the same is the case with the films of reticular tissue, which are of similar nature. There are also special stains which may be used to bring out the collagenous fibres, and which leave the other elements of the tissue almost unstained. The white fibres are doubly refracting, and therefore appear bright in the dark field of the polarising microscope.

Elastic fibres.—Besides the wavy bundles of white fibres which have just been described, there may be seen, under the microscope, in a thin lamina or film of areolar tissue a certain number of fibres (fig. 171), which are distinguished at once from the white fibres by the fact that they run singly, not in bundles, and, further, that they give off at frequent intervals branches which unite with adjacent fibres. They have also a more distinct outline and a measurable size, whereas the white fibres are almost too fine for measurement. In a preparation of areolar

tissue which has been stretched out upon the slide the fibres we are now considering are seen to run nearly straight and without waves ; but if in preparing the specimens

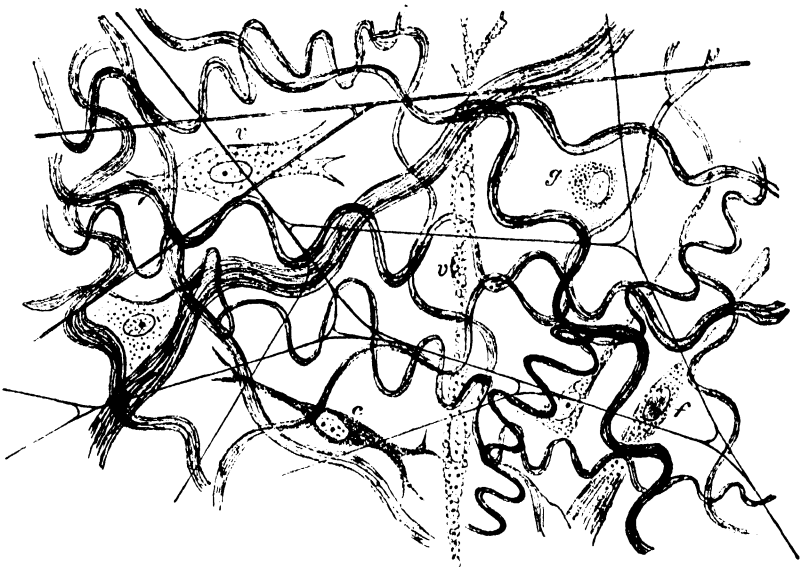


FIG. 171.—SUBCUTANEOUS AREOLAR TISSUE FROM A YOUNG RABBIT. (Schäfer.) Highly magnified.

The figure shows the appearance of the tissue examined perfectly fresh in a preparation made by the demi-desiccation method and moistened only with lymph.

The white fibres are in wavy bundles, the elastic fibres form an open network. *v*, vacuolated clasmocytes; *c*, branching finely granular clasmocyte; *g*, granular cell (mast-cell); *f*, fibrillated cell; the remainder are lamellar cells.

Drawn under Zeiss' 2 mm. apochromatic homogeneous-immersion objective, and No. 8 compensating eyepiece.

they are anywhere broken across, the broken ends tend to curl up, much in the same way that a thread of indiarubber when stretched to breaking tends to curl at the broken ends (fig. 172). These are the *elastic fibres* of connective tissue : they are also known as the *yellow fibres*, because when massed together, as occurs in an elastic ligament, they exhibit a yellowish colour. Their number as compared with the white fibres varies greatly in different parts of the areolar tissue ; in some parts they are only seen here and there crossing the field of the microscope, in other parts they occur thickly. Chemically as well as microscopically they are very different from the white fibres. They resist boiling, but eventually partly dissolve, yielding a substance known as *elastin* ; they also resist the action of dilute acids and alkalies and digestive ferments, but the latter eventually dissolve them.[1] This resistance to chemical reagents is due to a fine sheath (Schwalbe) which encloses the elastin ; the latter may be dissolved out from the sheath. They stain intensely with certain dyes (magenta, kreoso-fuchsin,[2] orcein), and may then be readily picked out wherever they occur.

FIG. 172.—ELASTIC FIBRES OF CONNECTIVE TISSUE. (From the subcutaneous tissue of the rabbit.)

[1] Cf. Pfeuffer, Arch. f. mikr. Anat. xvi 1879.

[2] Röthig, Arch. f. mikr. Anat. lvi. 1900.

The elastic fibres are angular in section (fig. 173) (sometimes with rounded angles, fig. 187), as may be seen in the elastic ligaments, where they are usually much larger than in areolar tissue. They snap straight across when stretched to breaking strain. In young animals, and sometimes also in the adult, they exhibit transverse markings here and there (fig. 186), which are best seen in the largest fibres and have been interpreted to indicate the formation of the fibres from rows of elastin particles which become subsequently fused together (Ranvier).[1]

FIG. 173. — CROSS-SECTION OF ELASTIC FIBRES FROM THE LIGAMENTUM NUCHÆ OF THE OX. (Sketched by T. P. Gostling.)

In consequence of the resistance these fibres offer to the action of acids and the readiness with which the white fibres swell and are made invisible by acids, it is sufficient to treat a fresh specimen of areolar tissue with dilute acetic acid to bring at once conspicuously into view the elastic fibres, which may previously have been concealed by the much more numerous white fibres of the tissue. It sometimes happens that the white bundles when swollen by the acid remain constricted here and there, as if encircled by a band which is unaffected by the acid (fig. 174). Sometimes the band has a spiral disposition, sometimes there are a number of separate rings. This appearance is readily seen in the areolar tissue around the arteries at the base of the brain. It has been held to be due to elastic fibres coiling round the white bundle; others have thought that the appearance may be caused by the presence of a delicate sheath to each bundle which resists acid, and which, when the bundle swells, is ruptured, except at certain places; and yet others have ascribed the bands to cell-processes extending round the bundles. Perhaps more than one of these explanations is correct for different cases.

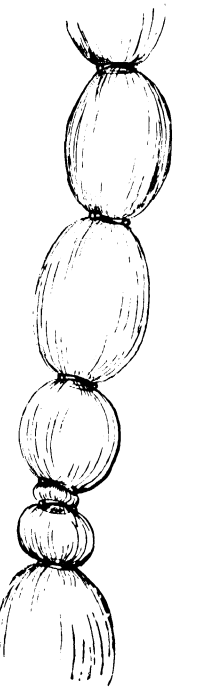


FIG. 174. — BUNDLE OF WHITE FIBRES OF CONNECTIVE TISSUE SWOLLEN BY ACETIC ACID. (Toldt.)

From the subarachnoid tissue at the base of the brain.

The cells of areolar tissue.[2]—Lying in the ground-substance, frequently in close contact with a bundle of the white fibres, or, if the tissue is dense, in the interstices between two or more bundles (but never in the interior of a bundle), are the cells of the tissue. Of these at least three different kinds occur in most areolar tissues—viz.:

1. *Lamellar cells* (fig. 175).—These are the most characteristic and widely diffused. They are usually flattened, sometimes markedly so, and where a

[1] This mode of formation is not admitted by all authorities, many contending that the elastic fibres are formed by a transformation of branching cell-processes. But the development of elastic fibres in cartilage lends support to the view taken by Ranvier.

[2] See on the cells of connective tissue, Waldeyer, Arch. f. mikr. Anat. xi. 1875; Ehrlich, *ibid.* xiii. 1877; Westphal, Diss. Berlin, 1880; Randnitz, Arch. f. mikr. Anat. xxii. 1883; O. Nordmann, Internat. Monatschr. f. Anat. u. Hist. ii. 1885; Ranvier, Arch. de Physiol. 1889, and Journ. de micrographie, 1889, 1890; Loewenthal, Arch. f. mikr. Anat. lxiii. 1903; Maximow, *ibid.* lxvii. 1906. The nomenclature is very confused. J. Schaffer (Die Plasmazellen, 1910) gives a good history of the subject.

number of them are in close contact they form an epithelium-like layer in the tissue or upon its surfaces (fig. 184). That these cells are of a similar nature to the endothelium-cells of a serous membrane is shown by the observation of Gronroos,[1] who found that if the endothelial cells are removed from the omentum of an adult cat no other cells are left either between or over the reticulating fibril-bundles. The endothelium-cells must, therefore, here be the only representatives of connective-tissue cells. When less closely arranged they tend to assume a branched irregular form, the branches themselves being often of a lamellar character. They may be connected by their branches into a network (syncytium), as is characteristically

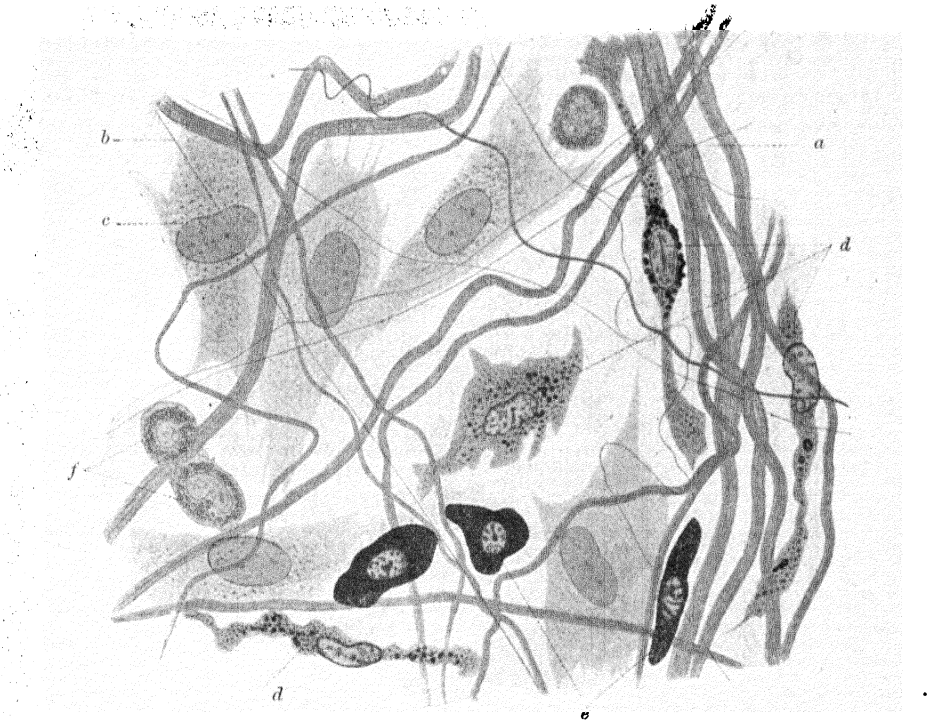


FIG. 175.—FIBRES AND CELLS OF AREOLAR TISSUE, FROM A FILM PREPARATION; GUINEA-PIG. (Maximow.) The preparation was stained, without fixation, by neutral red.

a, bundles of white fibres; *b*, elastic fibres; *c*, lamellar cells; *d*, clasmocytes; *e*, plasma-cells; *f*, oxyphil leucocytes.

seen in the cornea of the eye (fig. 176). In some connective tissues they are the only cells present.

Each cell has an oval nucleus and clear protoplasm, which may, however, contain a few granules. Occasionally a cell is seen with an appearance of fibrillation (fig. 171, *f*), but the fibrils have none of the characters of the white fibres of the tissue, although the appearance of the cells has been held to imply that these fibres are formed within the cells. The fibrillation is probably a form of cytomitome.

2. *Clasmocytes* (Ranvier).—These are elongated or irregular cells, with elliptical nuclei and granular or vacuolated protoplasm; they are common in many parts of the areolar tissue. They may represent less differentiated mesenchyme cells than the lamellar cells. Some authors derive the clasmocytes from leucocytes, terming them 'fixed wander-cells.'

[1] Anat. Hefte, xxii. 1903.

3. *Plasma-cells.*—These are characterised by their small round excentric nuclei and the basiphil granules of their protoplasm, which is often vacuolated. They may be flattened, elongated, branched or unbranched, but are usually spheroidal. They are not common in ordinary connective tissue, but are more numerous in young animals, in blood-forming organs, and in adenoid tissue.[1]

4. *Basiphil cells* (Mastzellen of Ehrlich).[2]—These are large rounded cells, the protoplasm of which is packed with basiphil granules. They are believed to be developed from lymphocytes, which have undergone enlargement, and accumulation of basiphil material. They are numerous in bone-marrow and in parts of the connective tissue where fat is becoming deposited.

Wander-cells are occasionally met with in areolar tissue. These are oxyphil or polymorph leucocytes derived from the blood.

Pigmented areolar tissue.—*Pigment-cells* resembling large branched connective-tissue cells, and containing numerous pigment-granules, occur in man normally only in the middle coat of the eye (fig. 177) and in the pia mater of the

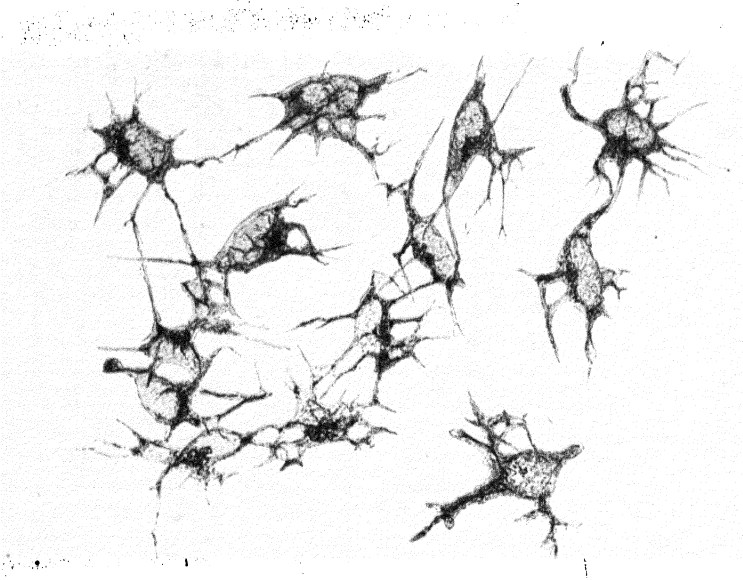


FIG. 176.—CELLS OF RABBIT'S CORNEA STAINED WITH GOLD CHLORIDE. (Schäfer.) Magnified 300 diameters.

The nuclei are unstained. The cells are connected by their branches.

upper part of the spinal cord, but in the lower vertebrates they are found in the skin, in serous membranes, and elsewhere.

The pigment (melanin) which is contained within the cells consists of black or brown granules or molecules of a round or oblong shape, and almost too small for exact measurement. These granules are densely packed together in some cells; in others they are more scattered. When they escape from the ruptured cells, they exhibit very strikingly the 'Brownian' molecular movement; and in consequence of this movement the apparent figure of the particles is subject to change. When viewed singly with a very high magnifying power they look transparent and almost colourless, and it is only when they are heaped together that their dark colour distinctly appears. The nucleus of the cell is not coloured, but is very often hidden from view by the pigment-particles.

[1] L. H. Hine, Brit. Journ. Dermat. 1907.

[2] From the German prefix Maſt, signifying 'fattened,' 'well-nourished.' But Ballowitz found Ehrlich's mast-cells just as numerous in bats after the winter sleep as before (Anat. Anz. 1891).

In the lower animals remarkable movements are often observed in the ramified pigment-cells—*e.g.* those of the frog's skin. In these the dark particles of pigment are at one time dispersed over a large ramified area, but at another time they are gathered into a heap in the central part, leaving the rest of the branched area vacant. In the former case the skin is of a dusky hue, in the latter pale. The

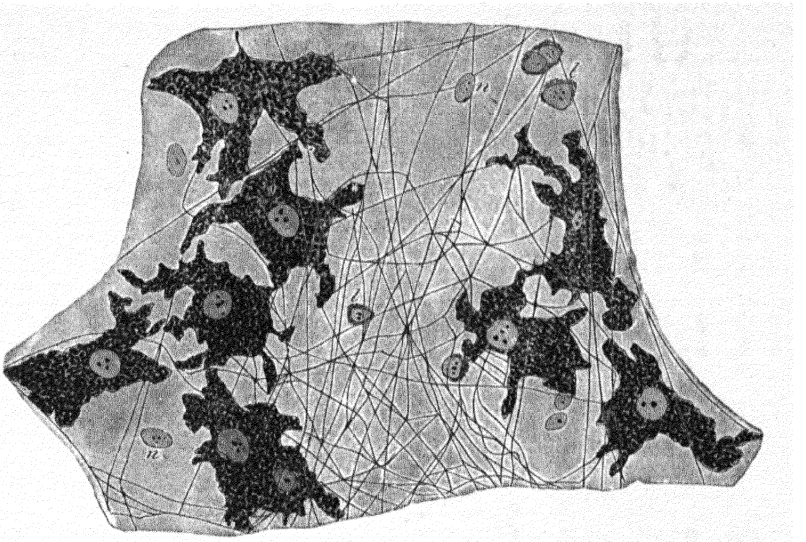


FIG. 177.—A SMALL PORTION OF THE CHOROID COAT OF THE EYE. (Schäfer.) Highly magnified. *n*, nuclei of flattened cells (the outlines of the cells are not indicated); *l*, lymphoid cells.

aggregation of the pigment-molecules can be excited through the nerves, both directly and also in a reflex manner, as by the stimulus of light upon the retina. It has usually been held that the changes in the pigment-cells above described are due to movements of the pigment-granules within the protoplasm. But Verworn states that the movement is one of the whole protoplasm of the cell, and therefore a true amœboid movement (see fig. 105, p. 65).[1]

FIBROUS TISSUE.

When the bundles of connective tissue are disposed for the most part in one or two definite directions, instead of interlacing in every direction as in areolar tissue, they confer a distinctly fibrous aspect on the parts which they compose, accompanied by the acquisition of certain properties, which are mainly due to the parallel disposition of the elements of the tissue, and to the preponderance of white fibres over elastic. This *fibrous tissue* is met with in the ligaments, connecting the bones together at the joints; it also forms the tendons of muscles, to which their fleshy fibres are attached, and which again serve to attach these fibres to the bones. In many parts it assumes the membranous form, and constitutes a class of membranes termed 'fibrous.' Examples of these are seen in the periosteum and perichondrium which cover the bones and cartilages, in the dura mater which lines the skull, in the fibrous layer of the pericardium, in the albugineous coat of the testicle, and the sclerotic coat of the eye. Fibrous membranes, named 'aponeuroses' or 'fasciæ,' are also employed to envelop and bind down the muscles of different regions, of which the great fascia enclosing the muscles of the thigh and leg is a well-known example. The tendons of muscles, too, may assume the

[1] See on the movements of pigment-cells, G. van Rynbeck, Ergebn. d. Physiol. 1906 (lit.); Babák, Pflüger's Arch. cxxxi. 1909.

expanded form of aponeuroses, as those of the broad muscles of the abdomen, which form strong fibrous layers in the walls of that cavity and add to their strength. It thus appears that fibrous tissue presents itself under two principal forms, the *fascicular* and the *membranous*.

Fibrous tissue is white, with a shining, silvery, or pearly aspect. It is exceedingly strong and tough, yet perfectly pliant; but it is almost devoid of extensibility. By these qualities it is admirably suited to the purposes to which it is applied in the animal frame. By its inextensible character it maintains in apposition the parts which it connects against any severing force short of that sufficient to cause

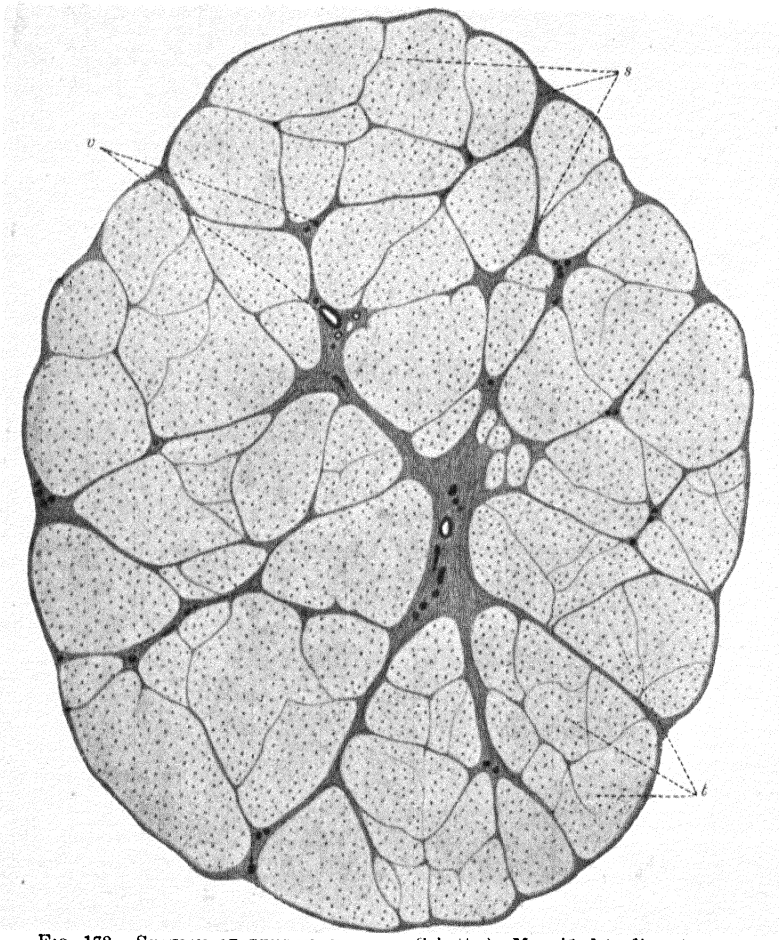


FIG. 178.--SECTION OF TENDON, HUMAN. (Sobotta.) Magnified 32 diameters.
t, tendon-bundles; *s*, septa of areolar tissue; *v*, vessels.

actual rupture, and this is resisted by its great strength, whilst its flexibility permits of easy motion. Accordingly the ligaments and tendons do not sensibly yield to extension in the strongest muscular efforts; and though they sometimes snap asunder, it is well known that bones will break more readily than tendons of equal thickness, and the fibrous membranes are proportionally strong and alike inextensible.

In fibrous tissue the bundles of white filaments run parallel, cohering very intimately. They either run all in one direction as in ordinary tendons and ligaments, or intersect each other in different planes as in some aponeuroses, or they

take various directions and decussate irregularly with each other as in the dura mater. And when they run parallel with each other, as in tendon, they do not keep separate throughout their length, but send off slips to join neighbouring bundles and receive the like in turn ; so that successive cross-sections of a tendon or ligament present different figures of the sectional areas of the bundles. A sheath of dense

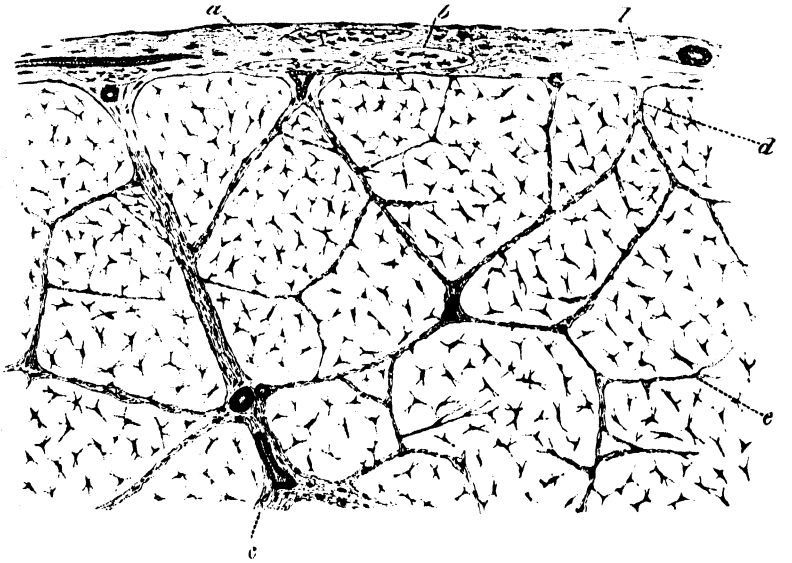


FIG. 179.—PART OF A MODERATELY LARGE TENDON IN TRANSVERSE SECTION. (Schäfer.)

a, areolar sheath of the tendon, with the fibres for the most part running transversely, but with two or three longitudinal bundles, *b*; *l*, lymphatic cleft in the sheath; immediately over it a blood-vessel is seen cut across and on the other side of the figure a small artery is shown cut longitudinally; *c*, large septum of areolar tissue; *d*, smaller septum; *e*, still smaller septum. The irregularly stellate bodies are the tendon-cells in section.

areolar tissue covers the tendons and ligaments on the outside (fig. 179, *a*), and a variable amount of the same tissue (*d*, *e*) lies between the fasciculi into which the smaller bundles are grouped, separating them from one another, and also occurring, in greater amount, between the largest fasciculi (*c*). It is in these areolar tissue septa that the blood-vessels and lymphatics of a tendon or ligament run.

The surface of a tendon or of any other part consisting of this texture, appears marked across the direction of the fasciculi with alternate light and dark streaks which give it a peculiar aspect, not unlike that of a watered ribbon. This appearance is owing to the wavy course of the filaments, for when the light falls on them their bendings naturally give rise to alternate lights and shadows.

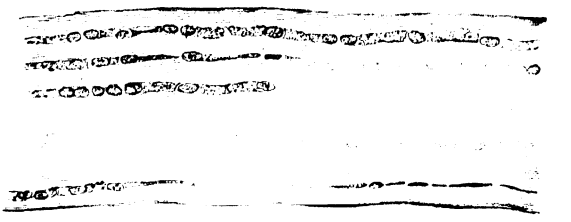


FIG. 180.—TENDON OF MOUSE'S TAIL, STAINED WITH LOGWOOD; SHOWING CHAINS OF CELLS BETWEEN THE TENDON-BUNDLES. (Schäfer.) Magnified 175 diameters.

The fibrous and areolar tissues thus agreeing in their ultimate structure, it is not to be wondered at that sometimes the limits between the two should be ill-defined, and that the one should pass by inconspicuous gradations into the other. Instances of such a transition may be seen in many of the fasciæ: these at certain parts consist of dense areolar tissue, but on being traced further are seen gradually

to become fibrous; and fasciæ which in one body are areolar in character may be decidedly fibrous in another.

In fibrous tissue the cells, which are often called 'tendon-cells,' are all of the lamellar variety. They follow the parallel arrangement of the fibre-bundles, and are disposed in rows or chains (fig. 180), which may be easily seen if a very fine tendon, such as those in the tail of the mouse or rat, or a portion only of a larger one, is examined under the microscope, and a little dilute acetic acid is cautiously added. A peculiar shape is impressed upon these cells by the close packing of the tendon-bundles, for although they may look quadrangular or oblong when the tendon is viewed longitudinally (figs. 180, 181), yet when it is cut across they have a stellate appearance (figs. 179, 182); since, like other flattened connective-tissue cells, they send lamellar extensions into the interstices between the contiguous bundles, whilst the middle of each cell, containing the nucleus, lies in the angular space between three or more bundles. When the tendon-cells are viewed longitudinally, any of the lamellar extensions, which are directed either towards or away from the observer, appear as lines on the surface of the cell (fig. 181). The same appearance is often seen upon the flattened cells of the denser forms of areolar tissue, where the cells have been squeezed in between three or more bundles.

FIG. 181.—EIGHT CELLS FROM THE SAME TENDON AS REPRESENTED IN FIG. 180. (Schäfer.) Magnified 425 diameters.

The nuclei, with their numerous nucleoli, were deeply coloured by the logwood. The dark lines on the surface of the cells are the optical sections of lamellar extensions directed towards or away from the observer.

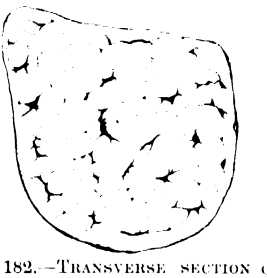


FIG. 182.—TRANSVERSE SECTION OF TENDON OF MOUSE'S TAIL STAINED WITH LOGWOOD. (Schäfer.) Magnified 175 diameters.

The flattened processes of the tendon-cells (which are stained deeply by logwood) appear in section as lines, frequently coming off at right-angles from the body of the cell. The bundles of fibres are not represented; they are very irregular, and but incompletely separated by the cell-processes.

Each tendon-cell consists of a protoplasmic body, thicker at the centre and thinning off in the extensions, and containing a flattened, round or oval, clear nucleus, with an intranuclear network and one or two nucleoli. The ends of adjacent cells are in close apposition, and form, as before noticed, chains of cells in the tendon, and the nucleus is generally so situated towards one end of the cell as to be in close proximity to the nucleus of an adjacent cell; they thus present the appearance of being arranged in pairs (figs. 180, 181). Here and there a third nucleus with a small amount of protoplasm, may be seen interpolated between two such cells.

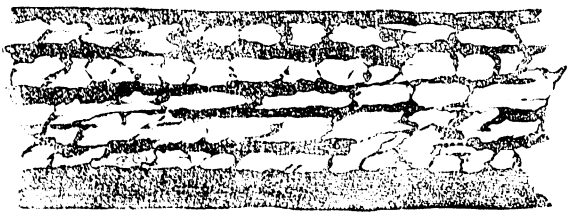


FIG. 183.—CELL-SPACES OF TENDON OF MOUSE'S TAIL, BROUGHT INTO VIEW BY TREATMENT WITH NITRATE OF SILVER. (Schäfer.) Magnified 175 diameters.

The lamellar extensions of the cells do not always end with an even line, but are themselves often prolonged into fine branches, which penetrate still farther into the ground-substance which separates the fibre-bundles of the tendon from one another.

The cells of tendon remain of course unstained when the tissue is treated with nitrate of silver, and exposed to light, and they then appear as chains of white patches on the brown ground (fig. 183). (See also Plate opposite p. 102.) Tendon contains a few elastic fibres, most of which lie between the larger bundles, but some between the smallest and in close contact with the tendon-cells.[1]

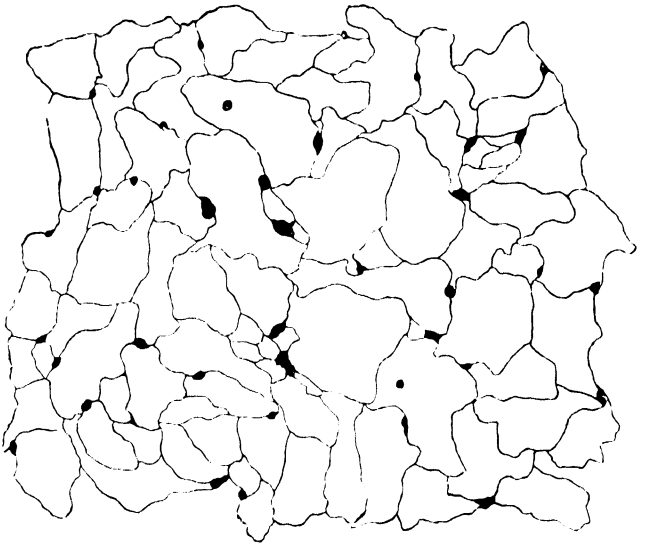


FIG. 184.—PAVEMENT-EPITHELIUM (ENDOTHELIUM) FROM THE SURFACE OF AN APONEUROSIS TREATED WITH NITRATE OF SILVER. (Schäfer.)

The cells at the surface of many tendons and aponeuroses form a continuous epithelioid layer. When treated by the silver method the outlines of the individual cells, which may be irregular in size and shape, are made manifest (fig. 184).

ELASTIC TISSUE.

In certain situations in the body a tissue is required which, while allowing a considerable amount of extension, will readily return to its original condition when the extending force is relaxed. This is provided for by the preponderance of elastic fibres in the connective tissue, and these in the most typical examples of the tissue, such as the ligamentum nuchæ of quadrupeds and the ligamenta subflava of the human spine, give it a yellowish colour. The tissue is extensible and elastic in the highest degree, but is not so strong as ordinary fibrous ligament, and it breaks across the direction of its fibres when forcibly stretched.

Examples of the texture on a large scale are seen in the horse, ox, elephant, and other large quadrupeds, in which it forms the great elastic ligament, called *ligamentum nuchæ*, that extends from the spines of the vertebræ to the occiput and aids in sustaining the head ; in the same animals it also forms an elastic subcutaneous fascia, which is spread over the muscles of the abdomen and assists in supporting the contents of that cavity. In man it occurs in the following situations, viz. :

1. Forming the *ligamenta subflava*, which extend between the arches of adjacent vertebræ ; these ligaments, while they permit the bones to be drawn apart in flexion of the body, aid in restoring and maintaining their habitual approximation in the erect posture—so far, therefore, relieving the constant effort of the erector muscles. There is, moreover, an obvious advantage in having an elastic band in

[1] J. F. Gemmill, Journ. Anat. and Physiol. xv. 1906.

this situation, instead of an ordinary ligament, which would be thrown into folds when the bones are approximated. 2. Constituting the chief part of the stylohyoid, thyrohyoid, and cricothyroid ligaments, and those named the vocal cords. Also extending, in the form of longitudinal bands, beneath the mucous membrane of the windpipe and its ramifications. 3. Entering into the formation of the coats of the blood-vessels, especially the arteries.

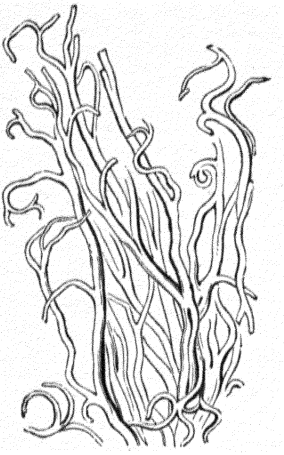


FIG. 185.—ELASTIC FIBRES FROM THE LIGAMENTA SUBFLAVA. (Sharpey.) Magnified about 200 diameters

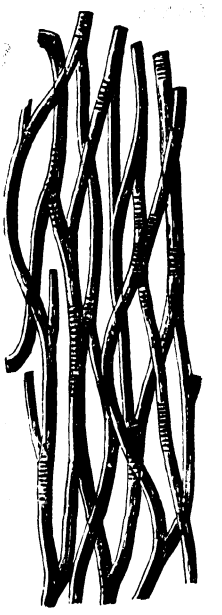


FIG. 186.—ELASTIC FIBRES FROM THE LIGAMENTUM NUCHÆ OF THE OX, SHOWING TRANSVERSE MARKINGS ON THE FIBRES. (Schäfer.) Highly magnified.

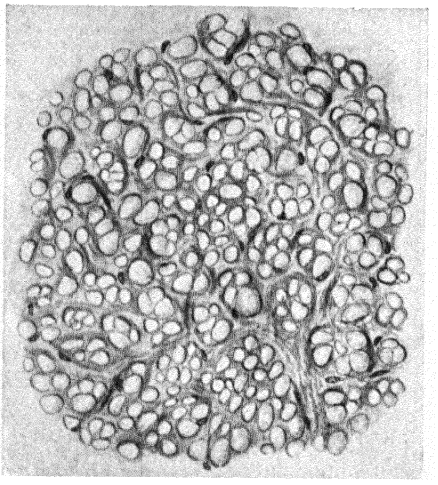


FIG. 187.—CROSS-SECTION OF THE LIGAMENTUM NUCHÆ OF THE OX.

The fibres are of various size; their angles are for the most part rounded. They are collected into small bundles, which are separated by areolar tissue. This tissue also penetrates into the bundles.

In **elastic tissue** there is a great proportionate development of the elastic fibres, the white bundles being relatively few and indistinct; but considerable variation is met with in the proportion of the two kinds of elements. The white bundles are, for the most part, disposed irregularly and course in different directions, as in areolar tissue; but, in some elastic ligaments, there are bundles of white fibres, which run as in an ordinary ligament parallel with one another, and from end to end of the structure. The elastic fibres in an elastic ligament, as is well seen in sections across their course, are collected into smaller and larger groups or bundles (fig. 187), which are separated from one another by septa of the white tissue, but the latter also penetrates between the individual elastic fibres of the group. In some situations, as in the coats of the arteries, the elastic tissue takes the form either of a close network of fibres arranged in one plane so as to form an

incomplete membrane, or of a complete membrane with holes or fenestræ in it and with elastic fibres connected with its surfaces. This is the so-called *fenestrated membrane of Henle* (figs. 188, 189).

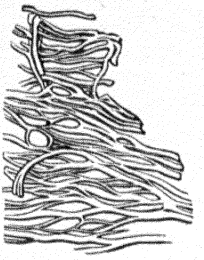


FIG. 188.—ELASTIC NETWORK OF ARTERY. (Toldt.)

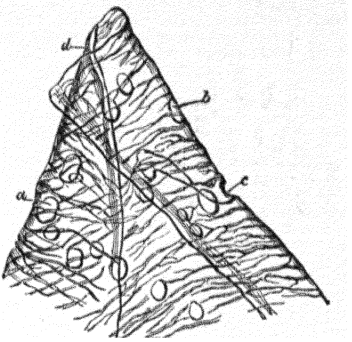


FIG. 189.—PORTION OF FENESTRATED MEMBRANE FROM THE FEMORAL ARTERY. (Henle.) Magnified 200 diameters.

a, *b*, *c*, perforations; *d*, a fold in the membrane.

The cells of elastic tissue resemble those of areolar tissue, but they are relatively fewer in number and are chiefly of the lamellar variety.

VESSELS AND NERVES OF CONNECTIVE TISSUE.

Blood-vessels, lymph-vessels, and nerves are everywhere conveyed in the areolar tissue to the places where they are to be distributed, but very few blood-capillaries are destined for the tissue itself, although abundant lymphatic networks are present in many parts; especially in the subcutaneous, subserous, and submucous tissues. In some places—*e.g.* serous membrane, subcutaneous tissue, connective tissue around joints—the areolar tissue is richly supplied with sensory nerve-endings of different kinds. These, although situated in the areolar tissue of the part, are concerned not especially with the sensibility of this tissue but with that of the organ of which the tissue forms a part. They will be described later.

Fibrous tissue receives blood-vessels, but in general they are inconsiderable both in number and size compared with the mass of tissue to which they belong. In tendons and ligaments with longitudinal fasciculi, the chief branches of the vessels run parallel with and between the larger fasciculi, and, sending communicating branches across them, eventually form a very open network with large oblong meshes.[1] Some fibrous membranes, as the periosteum and dura mater, are much more vascular; but the vessels seen in these membranes do not strictly belong to them, being destined for the bones which they cover.

Lymphatics are contained in great abundance, as Ludwig and Schweigger-Seidel showed, in the enveloping areolar-tissue sheaths of tendons and aponeuroses, where they form plexuses with polygonal meshes. In addition to these, a close network of lymphatic vessels with elongated meshes may be injected in the deeper parts of the tendons, where they run in the penetrating areolar tissue. Sometimes, as in the central tendon of the diaphragm, lymphatic spaces separate the tendon-bundles from one another. A connexion, although not an open one, exists between these lymphatics and the cell-spaces of the fibrous tissue. The lymphatic vessels of the tendons are partly concerned in the removal of lymph from the skeletal muscles, which themselves lack true lymphatic vessels.

[1] For a description of the arrangement of the blood-vessels in different tendons, see Arai, Anat. Hefte, xxxiv. 1907.

The penetrating areolar tissue of tendons, like the same tissue elsewhere, possesses areolæ, which here take the form of elongated clefts, and these may also partly serve for the passage of lymph.

All tendons and ligaments, and fibrous membranes, possess nerve-fibres, which course for the most part in a direction parallel with the fasciculi and terminate in a special manner within these tissues, as will be noticed when the peripheral distribution of nerves is described.

As to elastic tissue, the yellow ligaments, which contain this in its purest form, are but scantily supplied with blood-vessels, those that are present running in the interstitial areolar tissue between the elastic bundles. The lymphatic vessels also course for the most part longitudinally in the interstitial areolar tissue, being connected here and there by transverse branches, and in addition to these vessels the lymph may be conveyed by means of the elongated areolæ of the same tissue. Neither blood-vessels nor lymphatic vessels actually penetrate into the small bundles of elastic fibres, although the lymphatic vessels often lie close against the surface of the bundles. The mode of distribution of nerves in this tissue is unknown.

DEVELOPMENT OF CONNECTIVE TISSUE.

Those parts of the early embryo in which connective tissue is subsequently to be developed are at first composed entirely of embryonic cells, to all appearance similar to the cells which constitute the mesoderm generally (fig. 190). To the cells which form the connective tissues the name mesenchyme cells was applied by R. and O. Hertwig (see p. 4).

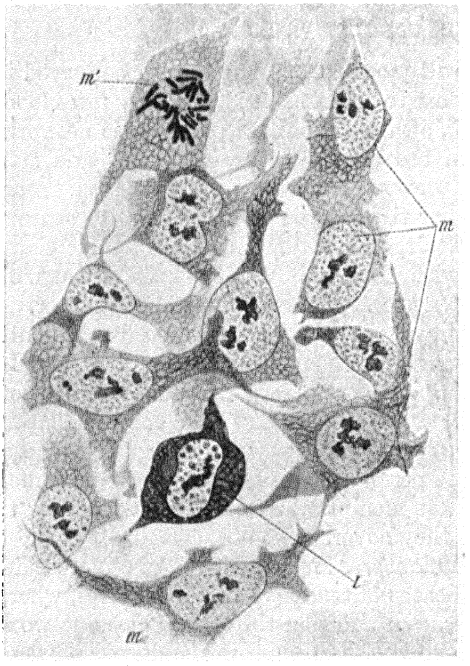


FIG. 190.—MESODERM CELLS PRIOR TO THE DEVELOPMENT OF CONNECTIVE-TISSUE FIBRES BETWEEN THEM. (Maximow.)

From an early rabbit-embryo.

m, *m*, ordinary mesenchyme cells; *m'*, a cell dividing by karyokinesis; *l*, a primitive blood-cell.

Mesenchyme cells are at first rounded in shape, and loosely packed; they may exhibit amœboid movements when examined on the warm stage. Subsequently they become irregularly ramified and tend to unite with one another to form a kind of cell-network or syncytium with open interstices (fig. 191). These interstices are at first occupied by an albuminous fluid which later acquires a mucous or muco-albuminous character, and the tissue assumes a jelly-like consistency: the interstitial substance may now be spoken of as the ground-substance or matrix.

In this ground-substance fibres of the two kinds, white and elastic, become developed, but the manner in which they are formed is by no means clear; and two distinct and opposed views are held by histologists upon the subject.[1] According to the first view, which has been maintained by

[1] These views are set forth at length and the literature and history of the subject are dealt with by Röthig, Ergebn. d. Anat. xvii. 1907. Röthig deals mainly with the elastic fibres, but it is usually held that the method of development is the same for both kinds of fibre.

Waldeyer,[1] Flemming,[2] and many others,[3] the fibres are formed within the protoplasm of the cells, the bundles of white fibrils either being produced by a direct conversion of the protoplasm of some of the cells, the others remaining

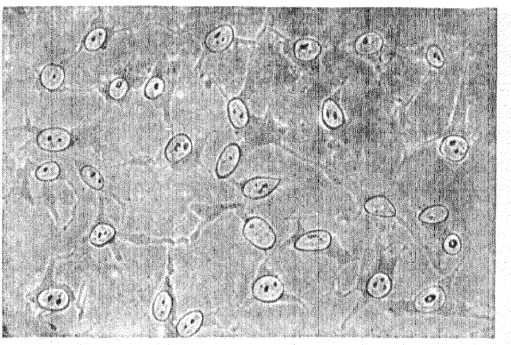


FIG. 191.—CELLS OF DEVELOPING CONNECTIVE TISSUE (MESENCHYME) UNITED TO FORM A SYNCYTIUM. (From Prenant, Bouin, and Maillard.)

No fibres are as yet developed in the intercellular substance.

as the permanent connective-tissue corpuscles; or the permanent corpuscles represent embryonic cells, layers of whose protoplasm have been successively converted directly into fibrillar tissue, the cells, meanwhile, after each such conversion, growing again to their original size, and at length remaining in contact with the bundle of fibres which they have assisted to form. Similarly the elastic fibres are supposed to be formed either by a transformation at the surface of the cells or by conversion of the cell-processes into elastic filaments, which become connected with those of neighbouring cells, and produce networks of elastic fibres.[4] According to another view, which has been adopted in successive editions of this work and is advocated by Kölliker,[5] Ranvier,[6] and Merkel,[7] the fibres, both white and elastic, are formed by a deposit in the intercellular substance, which is shed out or secreted by the cells of the tissue, and not by a direct change of the protoplasm of the cells, with which indeed they are not connected; although it is not excluded that the deposition may be influenced, or even caused by the cells.[8] A view, which may be regarded as intermediate between those above mentioned, is held by F. Mall,[9] who is of opinion that the material in which the cell-syncytium is imbedded, that

FIG. 192.—CONNECTIVE-TISSUE CELLS OF SALAMANDER LARVA, SHOWING FIBRILLATED STRUCTURE OF PROTOPLASM. (Flemming.)

Two of the cell-nuclei are dividing.

[1] Sitzungsb. d. Pr. Akad. 1895. [2] Virchow Festschrift, 1891; Arch. f. Anat. 1897.

[3] See especially, Klinke, Arch. f. mikr. Anat. xliii. 1894; Spuler, Anat. Hefte, vii. 1897; F. Meves, Arch. f. mikr. Anat. lxxv. 1910.

[4] J. F. Gemmill, Journ. Anat. and Physiol. xl. 1906. [5] Gewebelehre, 1889.

[6] Traité technique d'histologie, 1889. [7] Anat. Hefte, xxxviii. 1909.

[8] Cf. further on this question Hansen, Anat. Anz. xvi. 1899; Waldeyer, Arch. f. mikr. Anat. lvii. 1901; Laguesse, Arch. d'anat. micr. vi. 1903; Golowinski, Anat. Hefte, xxxiii. 1907.

[9] Amer. Journ. Anat. i. 1901–2.

which is here termed intercellular substance, is itself a kind of *exoplasm*, and as much a living part of the cell-syncytium as the *endoplasm*, which is the term used by Mall to designate the cytoplasm of the branched cells. Mall holds that the fibres are developed in the exoplasm; and since he regards this as living material, the opinion which he expresses of the formation of fibres exhibits a certain resemblance to that which regards them as being produced from the cell-protoplasm. A view somewhat similar to that of Mall is taken by M. Heidenhain (see p. 2).

In favour of the view of Waldeyer and Flemming is the fact that in young connective tissue there are to be seen long cells with fibrillated protoplasm which might be regarded as in process of conversion into bundles of white fibrils (fig. 192

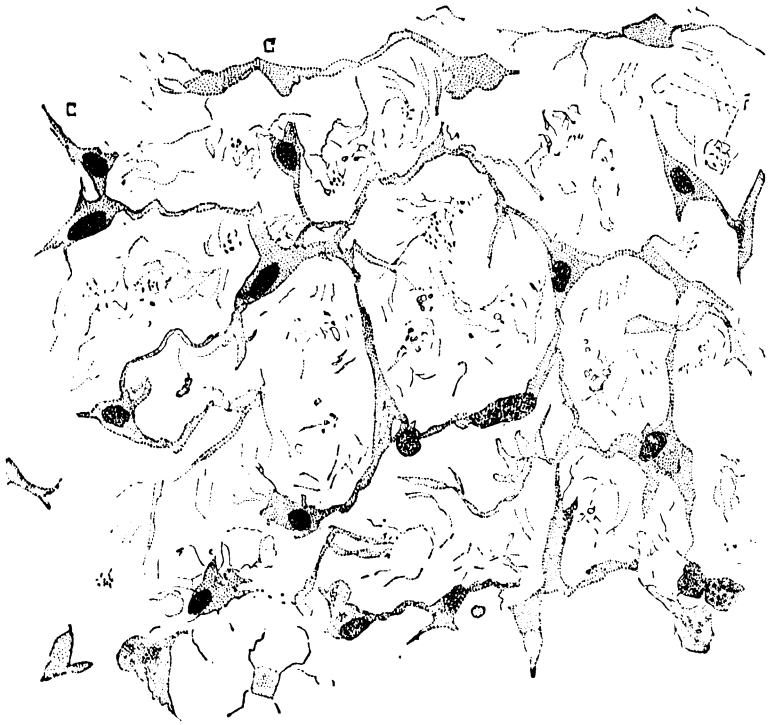


FIG. 193.—DEVELOPING CONNECTIVE TISSUE FROM THE UMBILICAL CORD OF A THREE MONTHS' HUMAN EMBRYO. (Minot.) ×511.

f, fibres developing in intercellular substance.

and fig. 171, *f*). And various authors have described an apparent continuity, both in young and in developed connective tissue, of the elastic fibres with the cells of the tissue, or even with their nuclei.

In favour of the view which was advocated by Kölliker may be instanced the appearance of the jelly-like connective tissue of the early embryo in which fibres of both kinds can be seen coursing through the intercellular substance, apart from the cells (fig. 193). In the case of the elastic fibres, these, according to Ranvier, appear in the form of rows of granules or globules, which subsequently become fused together end to end, and are not at any time continuous with cells (fig. 194). To form an elastic membrane, in place of being arranged in lines the globules are deposited in small patches, and by their fusion the membrane is formed (*p*). In elastic cartilage granules first make their appearance in the immediate neighbourhood of

the cartilage-capsules; but although this renders it probable that the deposition of the granules is influenced by the cells, there is no evidence that they are formed by a direct conversion of the cell-protoplasm. Indeed, the subsequent extension of the fibres into those parts of the matrix which were previously clear of granules (a process which can be easily followed in the arytenoid cartilage of the calf) (fig. 222), and in which no such direct conversion of cell-protoplasm is possible, is a strong argument in favour of the hypothesis that the substance of these fibres is deposited in the intercellular substance.

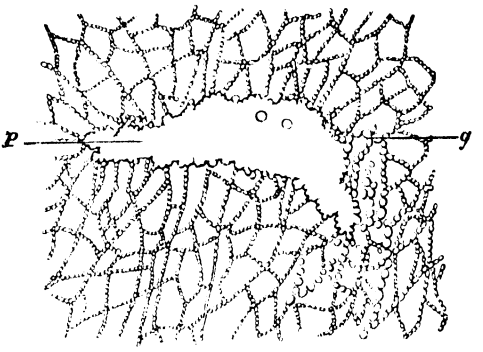


FIG. 194.—DEVELOPMENT OF ELASTIC TISSUE BY DEPOSITION OF FINE GRANULES. (Ranvier.)
g, moniliform fibres formed by rows of 'elastin' granules; *p*, flat platelike expansion of elastic substance formed by the fusion of 'elastin' granules.

The view which supposes that a direct conversion of the protoplasm of the connective-tissue cells takes place into fibres, both white and elastic, was for many years widely adopted, but it seems to rest largely upon a desire to interpret the facts in accordance with the conception (originally formulated by Lionel Beale and

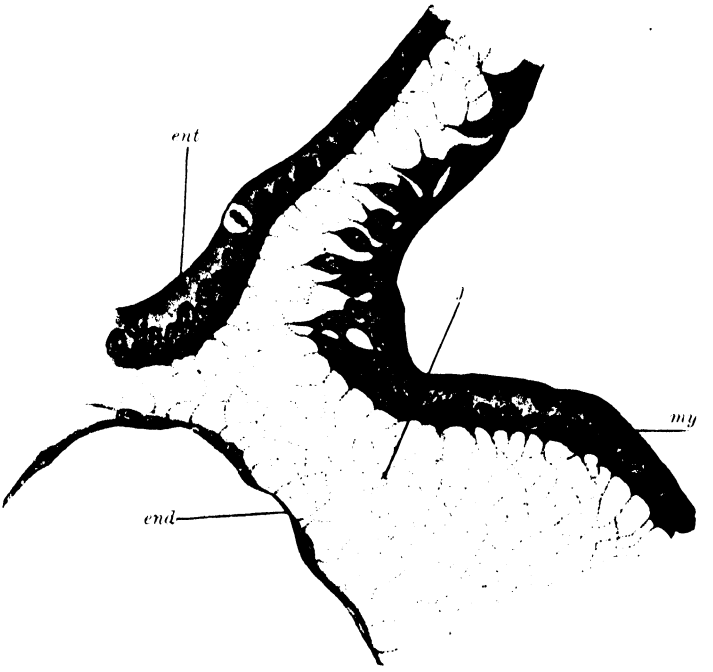


FIG. 195.—FROM A SECTION OF A TWENTY-EIGHT-HOUR CHICK-EMBRYO. (Szily.)
ent, epithelium of foregut; *end*, endothelium; *my*, myocardium; *j*, jelly-like tissue with protoplasmic fibres prolonged from the cells bounding it.

M. Schultze), according to which every part of an organised body consists either of protoplasm (formative matter of Beale) or of material which has been protoplasm (formed material of Beale), the idea of a deposition or change occurring outside

the cells in the intercellular substance being excluded. It is, however, not difficult to show that a formation of fibres may occur in the animal organism without a direct transformation of protoplasm, although the materials for such formation may be

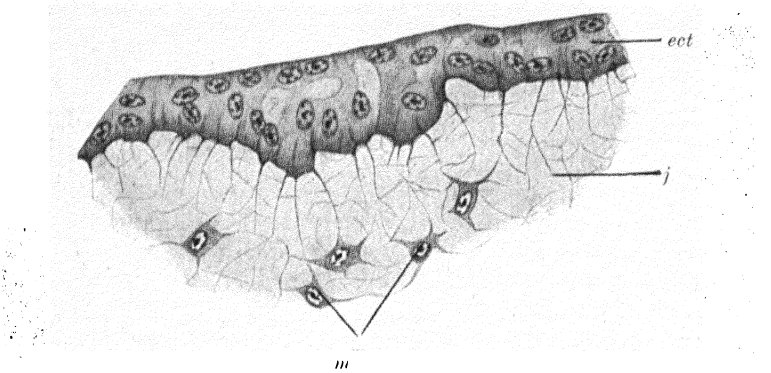


FIG. 196.—FROM A SECTION OF A FORTY-EIGHT-HOUR CHICK EMBRYO. (Szily.)
ect, ectoderm; *j*, jelly-like tissue with protoplasmic threads; *m*, mesenchyme-cells.

furnished by cells. Thus in cœlenterates, in which a low form of connective tissue first makes its appearance, this is distinguished at first by a total absence of cellular elements, a ground-substance only being developed and fibres becoming formed in it. Again, the fibres of the shell-membrane of the bird's egg are certainly not formed

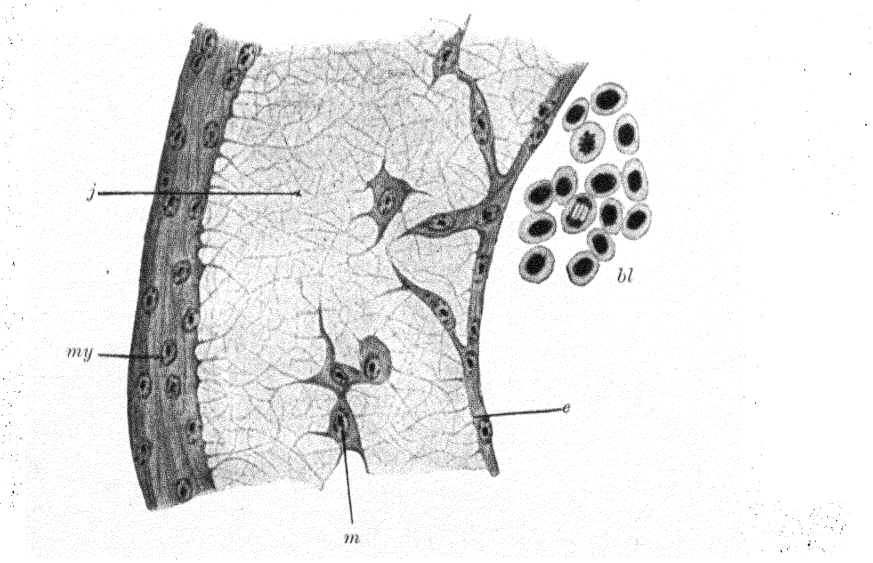


FIG. 197.—DEVELOPING CONNECTIVE TISSUE IN HEART OF EMBRYO CHICK OF FORTY-EIGHT HOURS. (Szily.)
my, myocardium; *e*, endothelium of endocardium; *bl*, blood-corpuscles in cavity of heart; *j*, jelly-like tissue formed of a network of fibrils, continuous with cells of myocardium and endothelium; *m*, mesenchyme-cells in jelly.

by the direct conversion of the protoplasm of the cells which line the oviduct, although they are formed in matter secreted by those cells, and it is through the agency of those cells that the deposit occurs in a fibrous form. And in many parts where ordinary connective tissue will subsequently be developed its place may at first be

taken, even in vertebrata, by a jelly-like tissue pervaded by a network or feltwork of fibres, amongst which mesenchyme cells only penetrate at a later stage. A jelly-

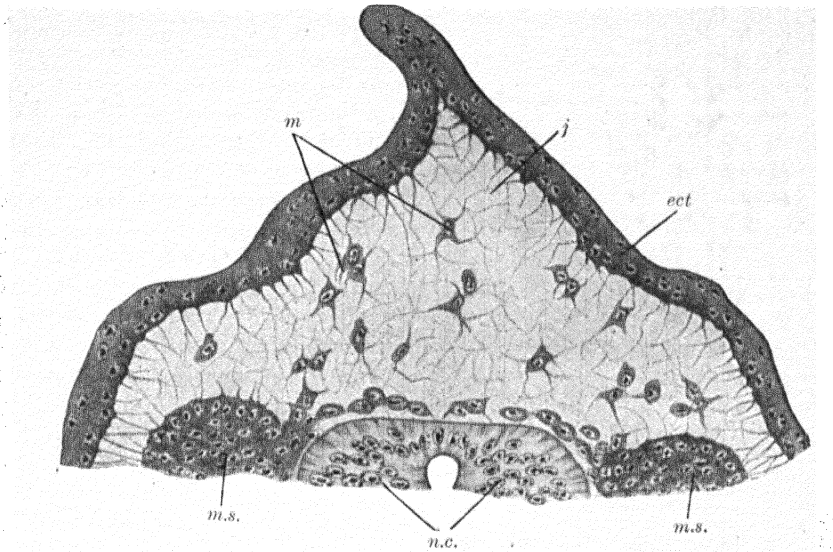


FIG. 198.—FROM A SECTION OF A NINETEEN-DAY TROUT EMBRYO. (Szily.)
ect, ectoderm; *n.c.*, neural canal; *m.s.*, mesoderm somites; *j*, jelly-like tissue; *m*, mesenchyme-cells.

like tissue of this kind has been described by Szily in various situations in the fish and bird embryo, appearing as the precursor of the permanent connective or mesenchymic tissue: it is probably derived from adjacent epithelial or endothelial formations (figs. 195 to 198).

The jelly-like connective tissue of the embryo persists in the umbilical cord until birth as the so-called jelly of Wharton (fig. 199), but the fibres in it are by this time numerous. Elsewhere it has largely lost its jelly-like character in consequence of the considerable development of fibres in the ground-substance, but the amount to which they are developed varies greatly. In the vitreous humour of the eye, which has generally been described as developing from mesoderm which has grown in between the ectoderm of the lens and that of the retina, but few fibres are developed, and such cells as there are become for the most part either atrophied or much modified, and remain relatively few

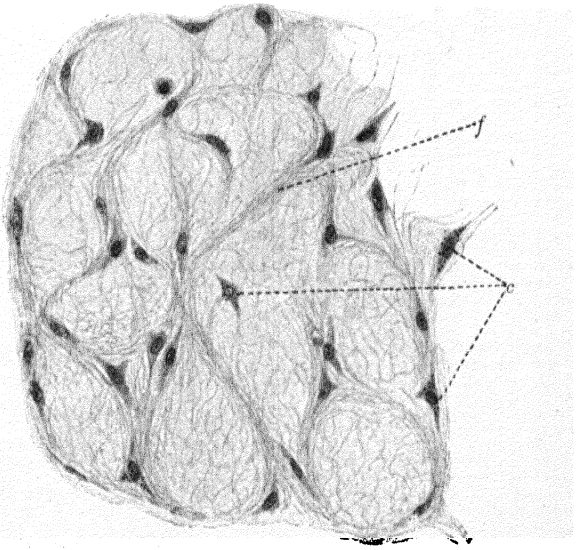


FIG. 199.—JELLY OF WHARTON FROM UMBILICAL CORD OF NEW-BORN CHILD. (Sobotta.) ×280.
f, connective-tissue fibres; *c*, cells.
The fibres are now in contact with the cells.

in number. The so-called *jelly-like connective tissue* which is thus produced consists therefore, if this view of its development is correct, mainly of ground-substance. But there appears to be some doubt whether the vitreous humour is not a product rather of ectoderm than of mesoderm. In that case it would, like the reticular tissue of the thymus, require to be removed from the list of connective tissues.

Connective tissue is readily regenerated, although the new cicatricial tissue which is formed in place of that which has been removed by the knife or by disease is not always obviously of the same character, either as regards its cells or fibres, as the tissue it replaces. It was believed by Cohnheim, whose views were supported by the experiments of Ziegler, that the new tissue was formed by the leucocytes of the granulation-tissue which first appears in the wound. On the other hand, it is affirmed by other observers that the leucocytes, although unquestionably precursors of the newly forming tissue, do not take any direct part in its formation, but are gradually supplanted by cells of the surrounding connective tissue which, after undergoing multiplication, wander into the space within which the new tissue is to become formed, and become the active agents for the production of the cicatricial tissue.[1]

SPECIAL VARIETIES OF CONNECTIVE TISSUE.

RETIFORM OR RETICULAR TISSUE.

This is a variety of connective tissue which is met with in various parts of the body, constituting the main part of the framework of many organs and entering largely into the constitution of mucous membranes and of most glands. Within

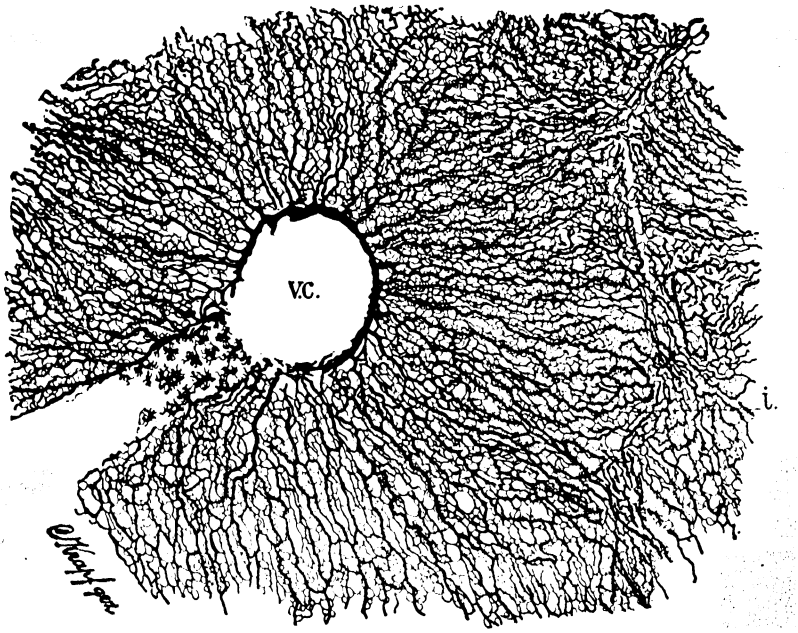


FIG. 200.—RETICULAR TISSUE OF A LIVER-LOBULE. (Oppel.)
V.C., central vein; *i*, interlobular interval.

these organs, between the larger trabeculæ of connective tissue, it forms an extremely fine and close network or feltwork of fibrils (figs. 200, 201), which serves to support

[1] Sherrington and Ballance, Journ. Physiol. x. 1889.

the epithelial elements, for which it often forms a basement-membrane, and to conduct the capillary blood- and lymph-vessels to all parts. It is composed of a very fine reticulum of connective-tissue fibrils, which in their behaviour to staining reagents and in their general microscopic appearance closely resemble the white fibres of areolar tissue, with which, in the lymph-glands, they are undoubtedly continuous. According to F. Mall,[1] they do not yield gelatin on boiling, but this is denied by Young.[2] However this may be, their anatomical continuity with the white fibrils of connective tissue is unquestionable. The tissue is formed of very fine anastomosing bundles of these fibrils, with the meshes of the network occupied by fluid ; the ground-substance has almost entirely disappeared. In some situations, such as parts of the lymph-glands, fixed cells of the tissue are applied to and are wrapped round the strands of the network, which may thus be in great measure concealed by the cells. The tissue then appears to be formed of a network of branching and anastomosing cells, and was for a long time so described ; but if the cells are brushed

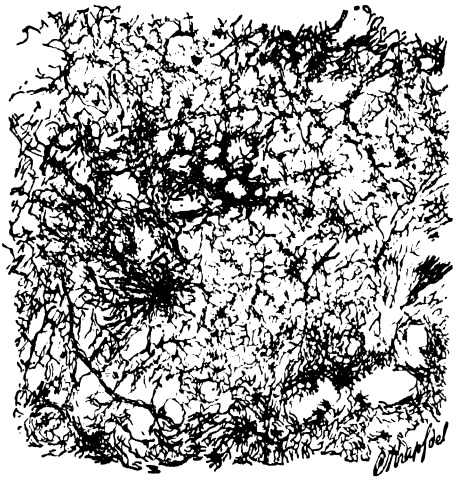


FIG. 201.—RETICULAR TISSUE OF MARROW. (Enderlen.)

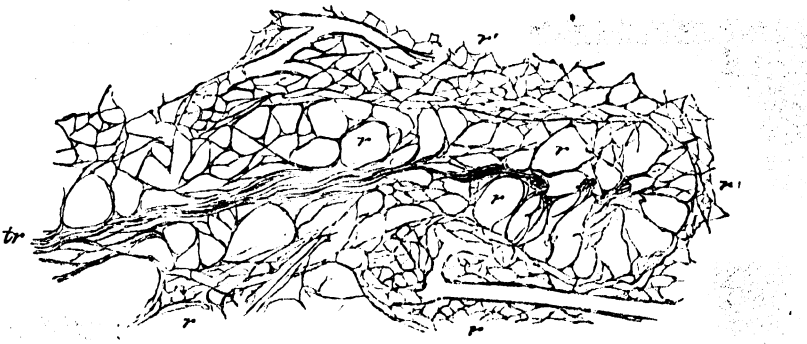


FIG. 202.—RETICULUM FROM THE MEDULLARY PART OF A LYMPH-GLAND. (Schäfer.)

tr, end of a trabecula of fibrous tissue ; *r*, *r*, open reticulum of the lymph-path, continuous with the fibrils of the trabecula ; *r'*, *r'*, denser reticulum of the medullary lymphoid cords. The cells of the tissue are not represented, the figure being taken from a preparation in which only the connective-tissue fibrils and the reticulum were shown.

away or otherwise removed, as by a short treatment with dilute alkali, the fibres of the reticulum come clearly into view (figs. 202, 203). The true structure of this tissue was first pointed out by Bizzozero.

In the thymus the reticulum is of epithelial origin (entoderm of visceral pouch), and is wholly formed of anastomosing cells. It cannot therefore rightly be classed amongst the connective

[1] Anat. Anz. iii. 1888.

[2] R. A. Young, Proc. Physiol. Soc. 1892 (Journ. Physiol. xiii.). Siegfried (Habilitationschrift, Leipzig, 1892) found gelatin in reticular tissue, but states that it also contains a special chemical substance, which he terms *reticulin*. Siegfried's conclusions have, however, been traversed by M. Christine Tebb (Journ. Physiol. xxvii. 1902), and the identity of the fibrils of reticular with those of areolar tissue must be regarded as established.

tissues, in spite of the fact that lymphocytes may occur in large numbers in the meshes of the cell-reticulum. Another epithelial (ectodermic) tissue which simulates reticular connective tissue is that of the enamel organ of the developing tooth.

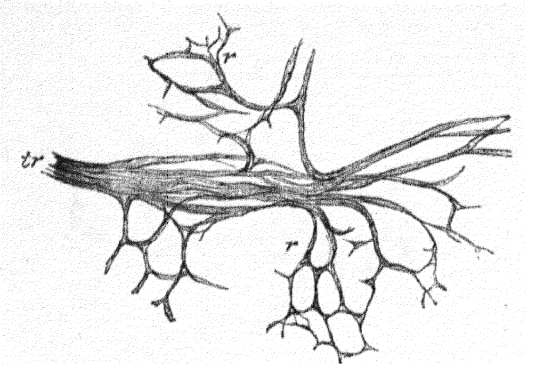


FIG. 203.—END OF A FIBROUS TRABECULA FROM THE SAME PREPARATION, SHOWING THE CONTINUITY OF THE CONNECTIVE-TISSUE FIBRILS WITH THE RETICULUM. (Schäfer.) Highly magnified.

tr, trabecula; *r*, reticulum.

In certain situations the meshes of the retiform tissue are occupied by numerous corpuscles which closely resemble the lymphocytes of the blood and lymph. They are here known as *lymph-cells*, and the tissue containing them is termed **lymphoid or adenoid tissue** (fig. 204). This tissue is found composing the greater part of the lymph-glands, and other structures allied to them, such as the solitary and agminated glands of the intestine, and the similar structures in the tonsils and elsewhere. Moreover, the alimentary mucous membrane is in some parts permeated by the same tissue, and it occurs also in other mucous membranes and, in the form either of elongated tracts or of isolated nodules, in many parts of the

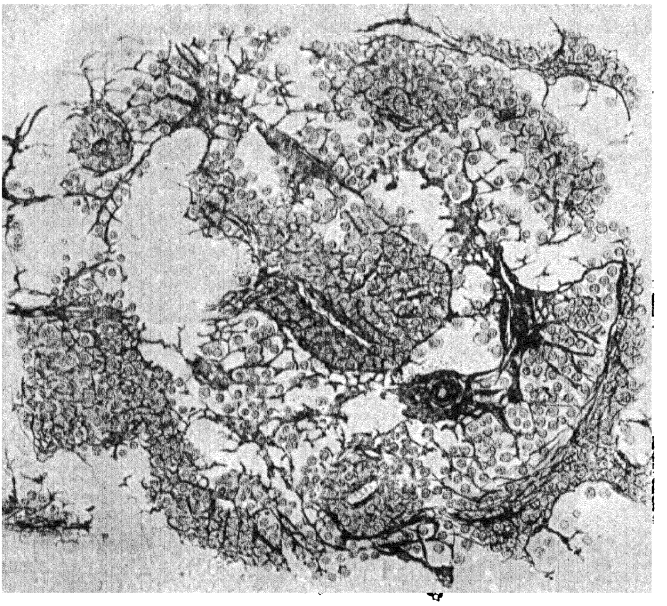


FIG. 204.—LYMPHOID TISSUE FROM MEDULLA OF LYMPH-GLAND OF DOG. (Schäfer.)

The trabeculæ and the fibres of the reticular tissue are stained dark, the lymphocytes are only faintly stained.

serous membranes. In parts of the spleen and in certain other organs known as hæmal lymph-glands the interstices of the retiform tissue are occupied by blood, instead of by lymph. Like the white fibres of connective tissue, the fibres of

reticular tissue resist the action of trypsin, and can be well shown in portions of tissue which have been subjected to tryptic digestion.[1]

Development. — In the formation of *retiform tissue* the ground-substance appears to become entirely liquefied except where it enters into the composition of the reticulum. The cells of the tissue become applied to the anastomosing fibril-bundles, and by their union constitute a network of branched cells enveloping

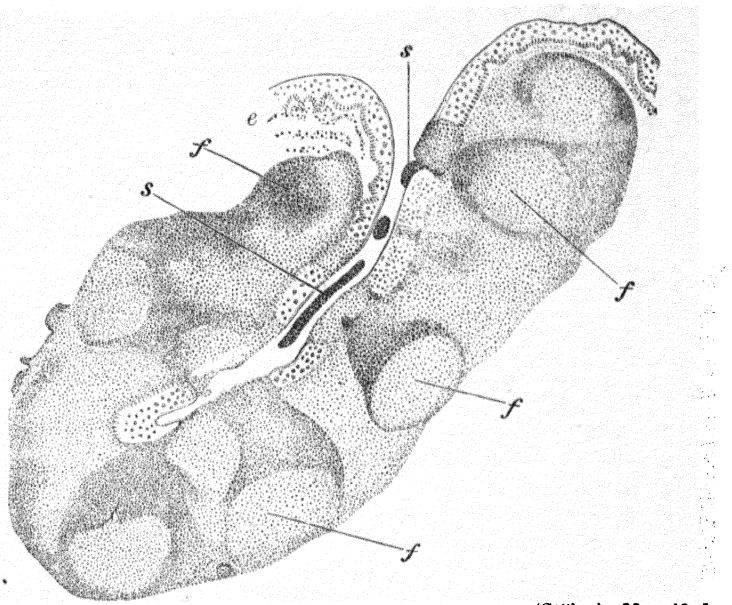


FIG. 205.—SECTION THROUGH ONE OF THE CRYPTS OF THE TONSIL. (Stöhr.) Magnified.

e, stratified epithelium of general surface, continued into crypt; *f*, *f*, follicles or nodules of lymphoid tissue; opposite each nodule or germ-centre numbers of lymph-cells are passing into and through the epithelium; *s*, *s*, masses of cells which have thus escaped from the tonsil to mix with the saliva as salivary corpuscles.

the network of fibrils. In lymphoid tissue the meshes become occupied by lymph-corpuscles which may originally have come from the blood- or lymph-vessels, but afterwards multiply by cell-division in the tissue itself. This multiplication can be seen (by observing the karyokinetic figures) to be occurring actively at certain points in the tissue, and around these points (germ-centres of Flemming) the lymph-corpuscles tend to accumulate in spheroidal nodules (lymphoid nodules, fig. 205, *f*) which are highly characteristic of lymphoid tissue.

ADIPOSE TISSUE.

Distribution. — This tissue is not confined to any one region or organ, but exists very generally throughout the body, accompanying the still more widely distributed areolar tissue in most, though not in all parts in which the latter is found. But its distribution is not uniform, and there are certain situations in which it is collected more abundantly. Thus, it forms a considerable layer underneath the skin, and, together with the subcutaneous areolar tissue in which it is lodged, constitutes in this situation what has been called the *panniculus adiposus*. It is collected in large quantity round certain internal parts; around the kidneys especially it forms a compact mass, which from a comparatively early period of

[1] C. Spalteholtz, Arch. f. Anat. 1897; Hoehl, *ibid.* On the reticular tissue of various organs, see Oppel, Anat. Anz. vi. 1891; C. Ciaccio, Anat. Anz. xxxi. 1907; Balabin, Anat. Anz. xxxiii. 1908.

embryonic development, and even before fat is deposited in its cells, appears as a distinct gland-like clump, which is sometimes termed the renal fat-organ. In amphibians this organ forms a free lobulated projection into the peritoneal cavity, being united to the tissue at the back of the abdomen by a narrow pedicle. Adipose tissue is seen filling up the furrows on the surface of the heart, and imbedding the vessels of that organ which run beneath its serous covering; and in various other situations it is deposited beneath the serous membranes, or is collected between their folds, as in the mesentery and omentum, generally at first gathering along the course of the blood-vessels and at length accumulating very copiously. Collections of fat are also common round the joints, lying on the outer surface of the synovial membrane, and filling up inequalities; in many cases lodged in folds of the membrane, which project into the articular cavity. Lastly, the fat exists in large quantity in the marrow of bones. On the other hand, there are some parts in which fat is never found in the healthy condition of the body. Thus it does not exist in the eyelids and penis, nor in the lungs except near their roots, nor within the cavity of the cranium.

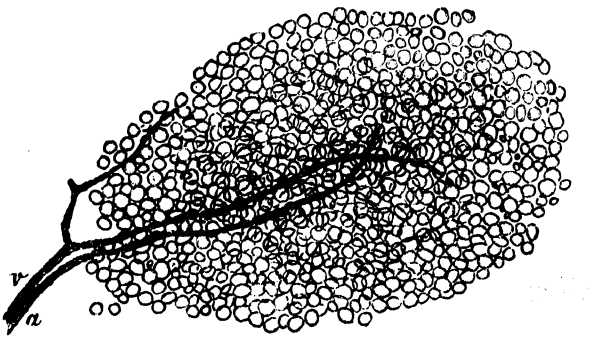


FIG. 206.—A SMALL FAT-LOBULE FROM THE SUBCUTANEOUS TISSUE OF THE GUINEA-PIG. (Schäfer.) Magnified about 20 diameters.

a, small artery distributed to the lobule; *v*, small vein; the capillaries within the lobule are not visible.

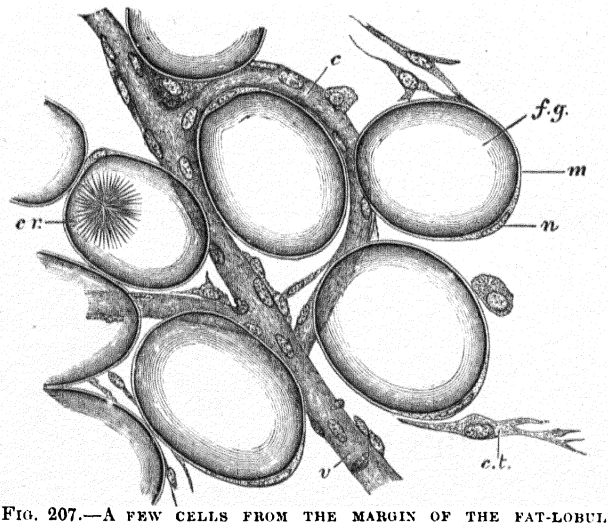
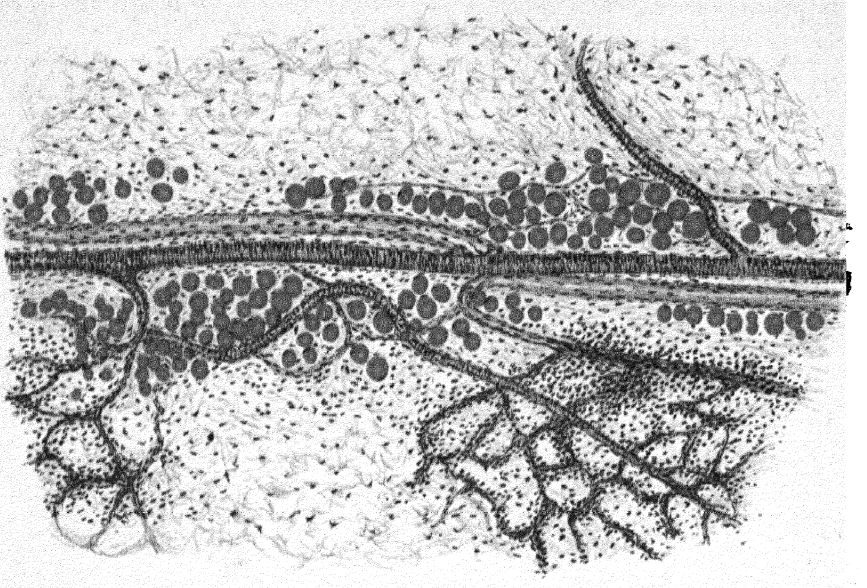


FIG. 207.—A FEW CELLS FROM THE MARGIN OF THE FAT-LOBULE REPRESENTED IN THE PRECEDING FIGURE. (Schäfer.) Highly magnified.

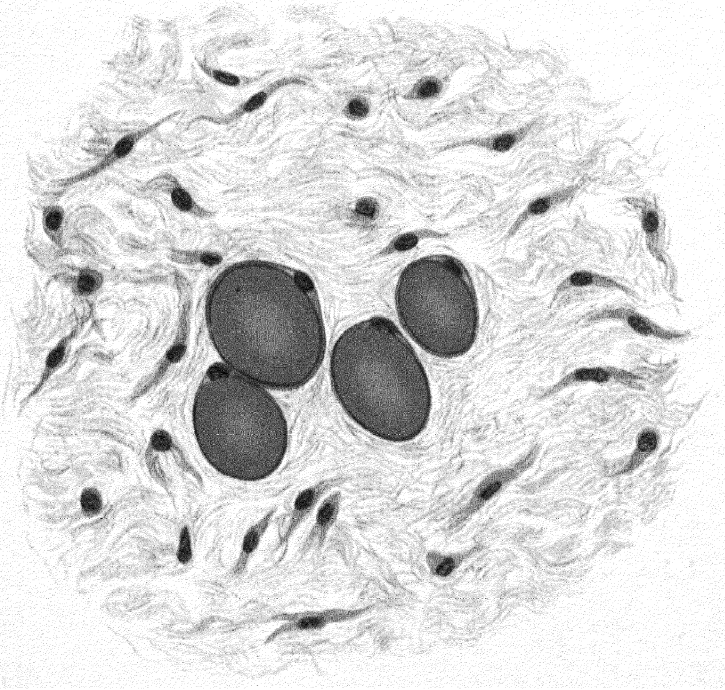
f.g., fat-globule distending a fat-cell; *n*, nucleus; *m*, membranous envelope of the fat-cell; *c r*, bunch of crystals within a fat-cell; *c*, capillary vessel; *v*, venule; *c.t.*, connective-tissue cell; the fibres of the connective tissue are not represented.

Structure.—When subjected to the microscope, adipose tissue is seen to consist of small vesicles, filled with an oily matter, and for the most part lodged in the meshes of areolar tissue. The vesicles are most commonly collected into lobular clusters (fig. 206), and these again into the little lumps of fat which we see with the naked eye, and which in some parts are aggregated into round or irregular masses of considerable magnitude. Sometimes the vesicles, though grouped together, have less of a clustered arrangement; as when they collect



Fat-cells in omentum of rabbit. Formol; Sudan III; haematoxylin. Magnified 60 diameters. (Schäfer.)

The fat-cells are distributed along the course of a small artery and vein.



Four fat-cells from the same preparation, with surrounding connective tissue. Magnified 400 diameters. (Schäfer.)

alongside of the minute blood-vessels of thin membranous parts (see upper figure of accompanying Plate).

In well-nourished bodies the fat-cells are round or oval (fig. 207 and Plate) unless where packed closely together, in which case they acquire an angular figure, and bear a striking resemblance to the parenchymatous tissue of plants. The greater number of fat-cells are from ·04 mm. to ·08 mm. in diameter, but many exceed or fall short of this measurement. Each one consists of a delicate covering (fig. 207, *m*), enclosing the oily matter (*f.g.*). It often happens that a part of the fatty contents solidifies in the cell after death, forming a bunch of delicate needle-shaped crystals (*c r*).

The covering of the oil-drop is the remains of the original protoplasm of the cell: it is generally quite transparent and of great tenuity, except in the immediate neighbourhood of the nucleus. The latter (*n*) is always present, but is often so flattened out by the pressure of the enclosed oil-drop as to be visible only with difficulty.[1] The oil-drops are stained black with osmic acid (fig. 208).

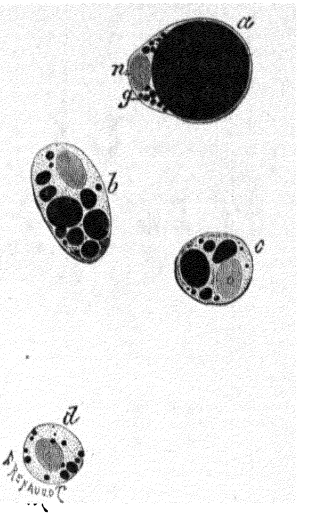


FIG. 208. — FAT-CELLS FROM YOUNG ANIMAL. Osmic-acid preparation. (Ranvier.)

The drops of fat are stained of an intense black. *n*, nucleus; *g*, small globules of fat.

Areolar tissue connects and surrounds the larger lumps of fat, but forms no special envelope to the smaller clusters; and although fine fasciculi and filaments of that tissue pass irregularly over and through the clusters, yet it is probable that the vesicles are held together in these groups largely by the fine

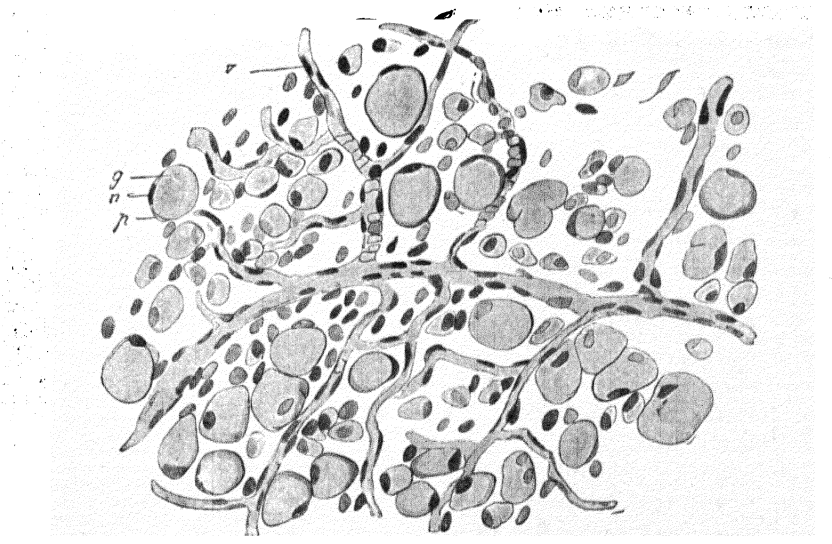


FIG. 209.—FAT IN MESENTERY OF RABBIT. (From Prenant, Bouin, and Maillard.)
v, network of capillary vessels; *g*, fat-globule; *n*, nucleus of fat-cell; *p*, protoplasmic envelope to fat-globule.
Numerous mast-cells are seen: in some of these there appears to be occurring a deposition of fat.

network of capillary vessels distributed to them. In the marrow the connective-tissue fibres are very fine and take the form of a reticular tissue (fig. 201).

[1] Rabl (Arch. f. mikr. Anat. xlvii. 1896) and de Almeida (Anat. Hefte, xii. 1899) have observed fat-globules within the nucleus of the fully developed fat-cell.

Adipose tissue is copiously supplied with **blood-vessels** (fig. 209). The larger branches of these pass into the fat-lumps, where they run between the lobules and subdivide, till at length a little artery and vein are sent to each small lobule (fig. 206, *a*, *v*), dividing into a network of capillary vessels, which pass between the vesicles in all directions, supporting and connecting them. The **lymphatics** of the fat are in close relation to the blood-vessels, accompanying and occasionally completely enclosing them as they enter the lobule. No sensory nerves seem to terminate in this tissue, although its blood-vessels receive nerve-fibres, and nerves destined for other textures may pass through it. Accordingly, it has been observed that, unless when such traversing nervous twigs happen to be encountered, a puncturing instrument may be carried through the adipose tissue without occasioning pain.

FIG. 210.—DEPOSITION OF FAT IN CONNECTIVE-TISSUE CELLS OF THE NEWBORN RAT. (Schäfer.)

f, *f'*, fat-cells; *h*, cell containing hæmoglobin.

Development.—The fat first appears in the human embryo about the fourteenth week of intra-uterine life. It is deposited in the form of minute granules or droplets in certain cells of the connective tissue (figs. 210, 211, *f*, *f'*); these droplets increase in size, and eventually run together, so as to form one large drop in each cell. By further deposition the cell becomes swollen out to a size far beyond that which it possessed originally, and its protoplasm remains as a delicate envelope surrounding the fat-drop. By the end of the fifth month the fat-cells have largely increased in number, and have become collected into small groups.

The deposit of fat within the cells is preceded and accompanied by the formation of a rich network of capillary blood-vessels (fig. 211). According to E. T. Bell,[1] the formation of fat is always preceded by the appearance of a peculiar open-meshed fibrillar connective tissue, with branched cells, which he terms the 'pre-adipose tissue.' Fat may be deposited in the cells either whilst still in the branched condition or after the branches have disappeared and the cells have become rounded.

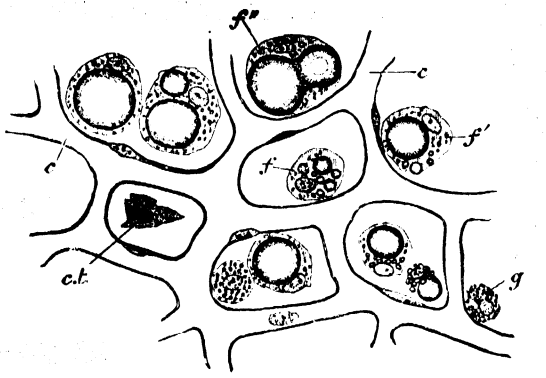


FIG. 211.—DEPOSITION OF FAT IN CONNECTIVE-TISSUE CELLS. (Schäfer.)

f, a cell with a few isolated fat-droplets in its protoplasm; *f'*, a cell with a single large and several minute drops; *f''*, fusion of two large drops; *g*, granular cell, not yet exhibiting any fat-deposition; *c.t.*, flat connective-tissue corpuscle; *c*, *c*, network of capillaries.

From the large number of basiphil 'mast-cells' (see p. 108) which accumulate at places where fat is in process of formation, it has been thought that these cells are especially concerned in the development of this tissue. The appearance of granules, probably of proteid nature, in connective-tissue cells prior to the deposition of fat within them was described by Löwe,[2] and was also noticed in the ninth edition of this work (1882). Poljakoff, in the white rat,[3] has also described the presence of a large number of granular cells in

[1] Amer. Journ. Anat. ix. 1909. [2] Arch. f. Anat. 1878. [3] Arch. f. mikr. Anat xxxii. 1888.

the situation where fat is being deposited. An actual transformation of the protein cell-granules into fat has been more particularly insisted on by Altmann[1] and by R. Metzner.[2]

According to Flemming and Hammar, the deposition of fat does not take place in the basiphil 'mast-cells,' but in ordinary cells of the connective tissue.[3] It probably occurs both in plasma-cells and in the lamellar cells. G. and

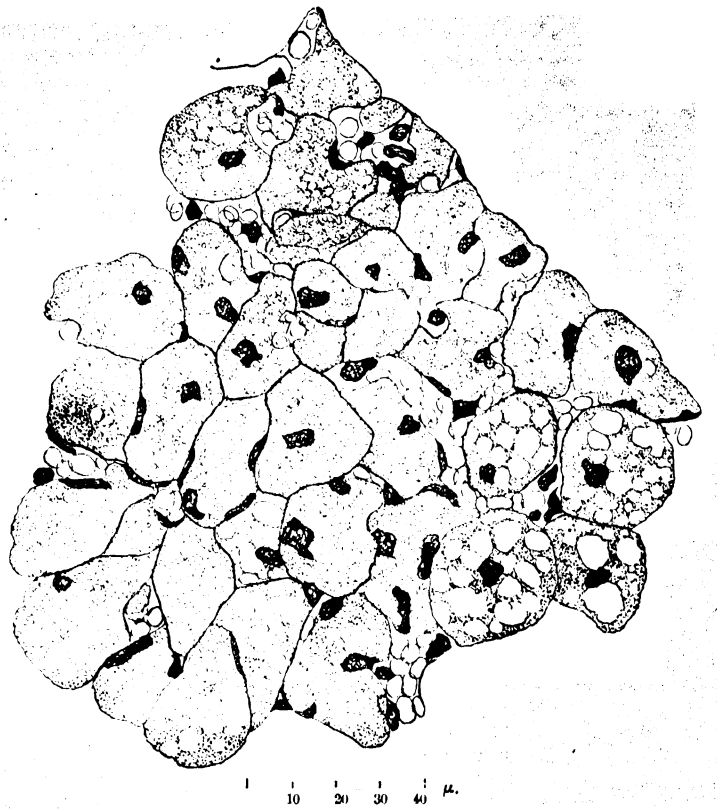


FIG. 212.—FROM A SECTION OF THE INTRATHORACIC ADIPOSE TISSUE OF A CHILD AGED THREE WEEKS. (H. Batty Shaw.)

The cells are large, spheroidal and granular, and in many of them the fat is beginning to be formed, and assumes in the prepared section the appearance of clear droplets. Numerous blood-vessels containing blood-corpuscles are seen between the developing fat-cells.

F. E. Hoggan[4] stated that it may be deposited in wander-cells: this, however, is denied by Hammar.

In some parts—especially in serous membranes such as the mesentery and omentum[5]—adipose tissue is preceded by an accumulation of lymphocytes forming masses of lymphoid tissue which accompany the blood-vessels. Whether these become actually converted into fixed cells and the latter into fat-cells, or whether they gradually disappear and are replaced by fat-forming connective-tissue cells, has not been clearly determined, but this last is the conclusion arrived at by Klein. Similarly the thymus gland, an organ mainly formed of lymphocytes supported by

[1] Arch. f. Anat. 1889. [2] *Ibid.* 1890.

[3] Flemming, Arch. f. mikr. Anat. vii. 1871; xii. 1876; Arch. f. Anat. 1879; Hammar, Arch. f. mikr. Anat. xlv. 1895.

[4] Trans. Roy. Micr. Soc. 1879. The cells which are figured in this paper seem, however, to correspond with the mast-cells of Ehrlich.

[5] E. Klein, The Lymphatic System, vol. i. 1873

a reticulum of branched cells, is known to undergo conversion into or, at least, replacement by adipose tissue. But here the fat is formed mainly in the interlobular connective tissue, while the thymus lobules themselves undergo atrophy.

The hypothesis that adipose tissue is a tissue *sui generis*, and not merely a vascular connective tissue in the cells of which fat has become deposited, was suggested by Kölliker (in 1856), but was especially urged by Toldt,[1] who pointed out the apparently specific character of the tissue in those situations where, in the embryo, fat first becomes visible to the naked eye, as in the region between the kidneys, in the groin, and in the axilla. In these and some other places the adipose tissue appears as a gland-like vascular mass, which has been termed a 'primitive fat-organ' or 'fat-gland' (see p. 126).[2] Its cells, although not yet filled

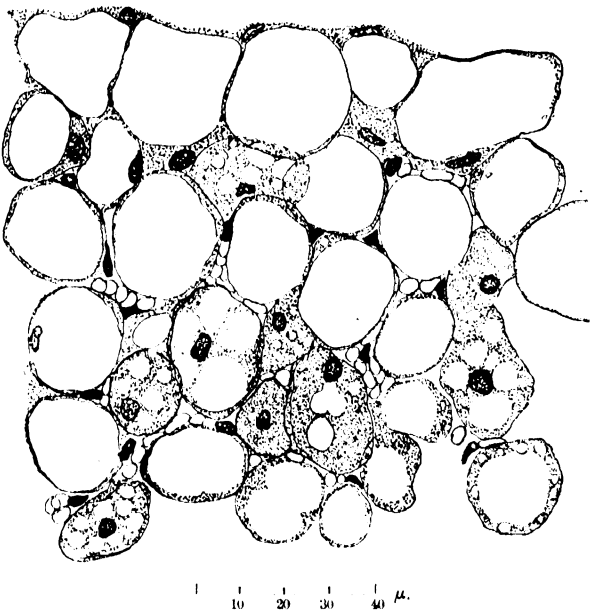


FIG. 213.—A LATER STAGE IN THE DEVELOPMENT OF ADIPOSE TISSUE, FROM A SECTION OF THE INTRATHORACIC TISSUE OF A CHILD AGED ELEVEN MONTHS. (H. Batty Shaw.)

The fat-drops now fill most of the cells, but some still contain a number of separate droplets and are chiefly composed of granular protoplasm.

with fat, may contain some fat-droplets; they are large and spherical or polyhedral, with numerous sinus-like blood-vessels between them (fig. 212); they may be nearly as large as the fully formed fat-cell. Some have a mulberry-like appearance due to the fat-drops they contain. As more fat is deposited within them the successive drops run together; a single fat-drop is eventually thereby produced in each cell (fig. 213).

But in most places where adipose tissue is found the fat is deposited in the ordinary branched cells of the connective tissue, and blood-vessels are produced *pari passu* with the deposition of fat. This form of adipose tissue never assumes

[1] Wiener Sitzungsb. lxvi. 1870.

[2] In hibernating animals adipose tissue accumulates towards autumn to form a considerable mass between the kidneys, which gradually undergoes absorption as the winter months run on, and which doubtless serves as a store of fuel for the animal during its winter sleep. This mass is known as the 'hibernating gland.' For an account of its changes in the hedgehog, see E. W. Carlier, Journ. Anat. and Physiol. xxvii. 1895.

the gland-like appearance above described, and when the fat is removed by inanition the tissue returns to the appearance of ordinary connective tissue. Under like circumstances the tissue of the so-called primitive fat-organs merely at first shows a loss of the fat within the cells, which become somewhat smaller and protoplasmic, but the glandular aspect of the mass of tissue is retained. This form of adipose tissue has been studied in its structure, development, and retrogression by Hammar in the white rat, in which animal it has a brownish-yellow colour, as compared with the white appearance of ordinary fat. Hammar comes to the conclusion that, although different in structure and to some extent in development and retrogression, it is nevertheless originally formed, like the white fat, from branched mesenchyme connective-tissue cells.[1]

Borden[2] finds that the gland-like fat-bodies are the sole source of the fat of lower vertebrata, but that in mammals this source of formation is superseded in later embryonic life by the deposition of fat in ordinary connective-tissue cells.

It is well known that fat may be deposited in many cells besides those of adipose tissue. Thus it is frequently seen in cartilage-cells—sometimes in considerable amount—in liver-cells, especially during fat-absorption from the intestine, in epithelium in many situations, and in muscle-fibres.[3] In epithelium, cartilage, and muscle, the fat-deposits appear to be independent of the condition of nutrition of the animal,[4] whereas in adipose tissue, especially in the ordinary variety such as is met with most abundantly under the skin, the amount of the tissue fluctuates, as is well known, with the nutritional conditions of the body generally.

Other special varieties of connective tissue.—Certain other kinds of connective tissue were formerly described under the heads of *basement-membranes* and *jelly-like connective tissue*. The latter is, however, only represented in the adult by the vitreous humour of the eye, and it is by no means certain that this is a true connective tissue (see p. 121). The name has also been given to the embryonic tissue which is found in the umbilical cord, where it forms what is known as *Wharton's jelly*. All forms of connective tissue, however, pass through this jelly-like stage, with their cells connected by branches and with the intercellular substance of a fluid or semi-fluid consistence, and containing relatively few fibres. If the vitreous humour is a connective tissue it is one which contains no fixed connective-tissue cells and few, if any, collagenous fibres.

Basement-membranes, which are found at the surfaces of connective tissue and are often covered by epithelium, cannot be said to form a definite tissue. They are of different nature in different situations, being sometimes merely a layer of endothelial connective-tissue cells; sometimes a stratum of ground-substance which is imperfectly fibrillated (*e.g.* the membrane of Bowman of the cornea), sometimes of the nature of modified elastic substance (*e.g.* the membrane of Descemet of the cornea[5]), and sometimes a condensation of the reticular tissue of a mucous membrane or glandular organ.

[1] Hammar, Arch. f. mikr. Anat. xlv. 1895. See also on this subject, H. Batty Shaw, Journ. Anat. and Physiol. xxxvi. 1901. In both these papers an account of the literature will be found.

[2] New York Med. Journ. 1894.

[3] Sometimes the fat-like drops which occur in these situations are of lipoid character and not true fats.

[4] E. T. Bell, *op. cit.*

[5] It is possible, however, that this is a cuticular formation produced by the adjacent cells (W. Fritz, Wien. Akad. Anz. 1906).

CARTILAGE.

This is the well-known substance commonly called 'gristle.' When in mass, it is opaque and of a pearly or bluish-white colour, in some varieties yellow; in thin slices it is translucent. Although it can be easily cut with a sharp knife, it is nevertheless of very firm consistence, but at the same time highly elastic, so that it readily yields to pressure or torsion, and immediately recovers its original shape when the constraining force is withdrawn. By reason of these mechanical properties, it serves important purposes in the construction of some parts of the body.

In the early embryo the skeleton is, in great part, cartilaginous; but the cartilage forming its different pieces, which have the outward form of the future bones, in due time undergoes ossification or gives place to bone, in the greater part of its extent at least, hence this variety of cartilage is named 'temporary' or 'fœtal.'

Of the permanent cartilages a great many are in immediate connexion with bone, and may be still said to form part of the skeleton. The chief of these are the articular and the costal cartilages; the former cover the ends or surfaces of bones in the joints, and afford these harder parts a thick springy coating, which breaks the force of concussion and gives ease to their motions; the costal or rib cartilages form a considerable part of the solid framework of the thorax, and impart elasticity to its walls. Other permanent cartilages enter into the formation of the external ear, the nose, the Eustachian tube, the larynx, and the windpipe. They strengthen the substance of these parts without undue rigidity; maintaining their shape, keeping open the passages through them where such exist, and giving attachment to moving muscles and connecting ligaments.

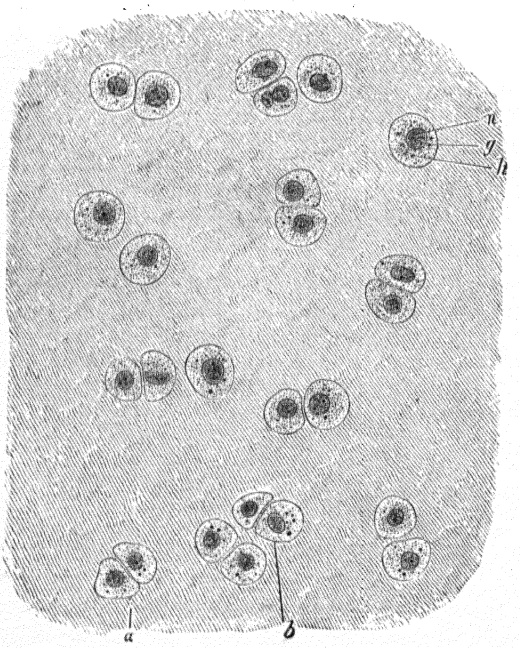


FIG. 214.—ARTICULAR CARTILAGE FROM HEAD OF METATARSAL BONE OF MAN. (Osmic acid preparation.) THE CELL-BODIES ENTIRELY FILL THE SPACES IN THE MATRIX (Schäfer.) 340 diameters.

a, group of two cells; *b*, group of four cells; *h*, protoplasm of cell, with *g*, fatty granules; *n*, nucleus.

Cartilages, except those of the joints, are covered externally with a moderately vascular fibrous membrane named the *perichondrium*.

When a very thin slice of cartilage is examined with the microscope, it is seen to consist of *cells*, disseminated in a solid *ground-substance* or *matrix* (fig. 214). The matrix is transparent, and to all appearance homogeneous; sometimes dim and either indistinctly fibrous or faintly granular, like ground glass: both these conditions occur in *hyaline cartilage*, which may be regarded as the typical form of the tissue. Two other varieties exist in which the matrix is pervaded to a greater or less extent by distinct fibres. In the one, named *elastic* or *yellow fibro-cartilage*, the fibres are similar to those of elastic tissue; in the other, named *white fibro-cartilage*, they are of the white kind as in ordinary ligament.

Hyaline cartilage : structure.—In hyaline cartilage the matrix, as just stated, is uniform, and, when examined fresh, usually appears free from fibres. Like the ground-substance of connective tissue, it becomes stained brown by nitrate of silver and subsequent exposure to the light. The cells consist of a rounded, oval, or bluntly angular *cell-body* of translucent protoplasm, imbedded in which may

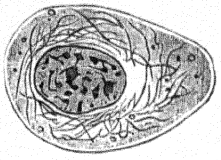


FIG. 215.—A CARTILAGE-CELL IN THE LIVING STATE, FROM THE SALAMANDER. (Flemming.) Highly magnified.

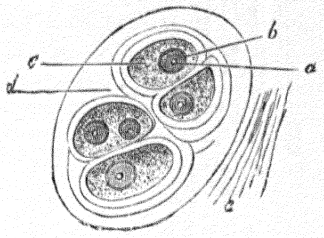


FIG. 216.—A GROUP OF CARTILAGE-CELLS SHOWING THE CAPSULAR OUTLINES IN THE MATRIX SURROUNDING THE GROUP. (Ranvier.)

a, nucleolus ; *b*, nucleus ; *c*, cytoplasm of a cell ; *d*, capsular lines in pericellular matrix ; *e*, fibrils in cartilage matrix.

sometimes be seen fine curvilinear interlacing filaments and minute granules[1] (fig. 215), sometimes fat-droplets. Each cell has a spheroidal *nucleus*, with one or more *nucleoli* ; the nucleus is occupied by a network of chromatin, which produces under a low power of the microscope a granular effect. The cell-body lies in a cavity of the matrix, which, in its natural condition, it entirely fills. This cavity is bounded and enclosed by a transparent *capsule*, which is seldom obvious to the eye, for it coheres intimately with the surrounding matrix, with which it agrees in nature, and cannot usually be distinguished without the aid of reagents. But sometimes the *capsule* which is the most newly formed part of the matrix is quite distinct, and there may further be seen surrounding the cells and cell-groups a series of outlines which mark successive stages in the formation of cartilage-matrix (fig. 216). It is also found that the part of the matrix which more immediately surrounds the cells and cell-groups is apt to become coloured by basiphil stains much more deeply than the rest of the matrix. The groups then appear imbedded in globular masses of darkly stained matrix (fig. 217). These form the so-called ' chondrin-balls ' of Mörner.[2]

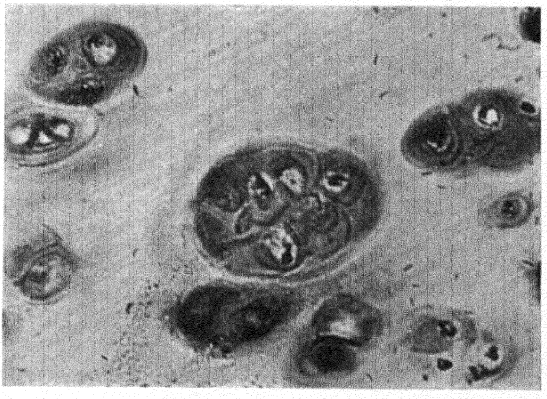


FIG. 217.—SECTION OF RIB CARTILAGE STAINED WITH HÆMATOXYLIN, SHOWING THE MATRIX AROUND THE CELLS AND THE CELL-GROUPS MORE DEEPLY COLOURED THAN THE REMAINDER. (Schäfer.) Magnified 200 diameters. Photograph.

[1] Flemming, Arch. f. mikr. Anat. xvi. 1878, and Zellbildung, Kern, u. Zelltheilung, 1882 ; N. Loewenthal, Anat. Anz. xxx. 1907.

[2] Zeitschr. f. physiol. Chemie, xii. 1888.

By exposure to water and some other liquids, as well as to the action of electric shocks, the cell-body shrinks away from the inside of the capsule, and assumes a jagged or otherwise irregular figure, and then may hide the nucleus.

The cells of cartilage often contain glycogen, and are coloured reddish-brown by iodine (Neumann).[1]

They are rarely dispersed singly in the matrix, most commonly occurring in groups of two or more. When disposed in pairs (as at *a*, fig. 214) the cells are generally triangular or pyramidal in form with rounded angles, and with their bases opposite one another; in the larger groups (*b*) the cells have a straight outline where they adjoin or approach one another, but at the circumference of the group their outline is rounded. Towards the surface of the cartilage the groups are

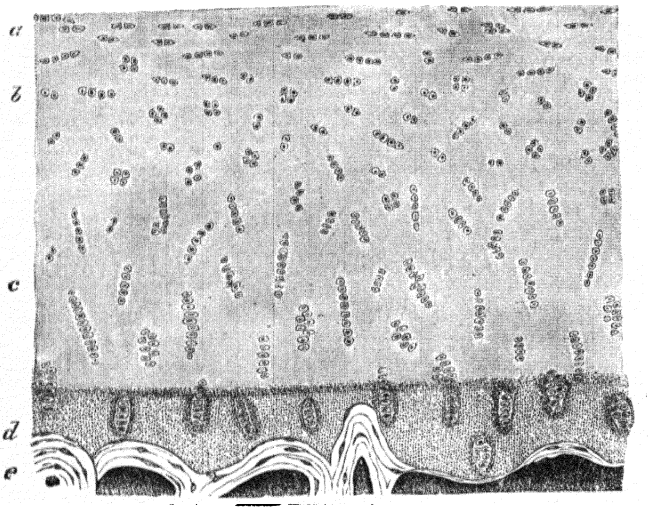


FIG. 218.—VERTICAL SECTION OF ARTICULAR CARTILAGE COVERING THE LOWER END OF THE TIBIA (HUMAN). (Schäfer.) Magnified about 30 diameters.

a, cells and cell-groups flattened conformably with the surface; *b*, cell-groups irregularly arranged; *c*, cell-groups disposed perpendicularly to the surface; *d*, layer of calcified cartilage; *e*, bone.

generally flattened conformably with the surface, appearing narrow and almost linear when seen edgeways, as in a perpendicular section (fig. 218, *a*).

Various observers have shown that the matrix of hyaline cartilage can be broken up after long maceration, and with the aid of pressure, into fine fibrils. These fibres are vertical to the surface in articular cartilage, and parallel with the long axis in rib cartilage (Cresswell Baber).[2] They are more easily seen in the cartilage of birds than of mammals. Their chemical nature is not very clear, nor is it certain how far the appearances correspond with any structure naturally present; but since gelatin and mucin can be obtained from the matrix of cartilage, the fibres in question may be chemically of the same nature as the white fibres of connective tissue, the mucin belonging to the ground-substance in which they are imbedded.

Other histologists have described a network of fine ramified canals penetrating the cartilage-matrix, and effecting a communication between the cell-spaces. Up to the present time, however, the existence of such anastomosing channels has not been conclusively proved, although often

[1] Arch. f. mikr. Anat. xiv. 1877 and xvi. 1878.
[2] Journ. Anat. and Physiol. x. 1895.

assumed in order to explain the manner in which nutritive plasma penetrates the matrix of cartilage to reach the cells. Budge[1] endeavoured to demonstrate the existence of canaliculi by forcing coloured injecting fluid into the substance of cartilage, but the result of the experiment was not conclusive. It has also been attempted to show them by the so-called natural method of injection, that is by allowing indigo-carmine (which has an intensely blue colour) to mix with the circulating blood of animals, which after a time are killed and the cartilages examined. Proceeding in this way, L. Gerlach[2] was unable to see any blue channels in the cartilage-matrix, while J. Arnold[3] obtained results from which he was led to infer the existence of minute cleft-like spaces throughout the matrix, connected by fine radiating canaliculi on the one hand with the lymphatics in the perichondrium, and on the other hand with the cell-spaces of the cartilage.

In the cartilage of Cephalopods the cells are branched, and intercommunicate by their branches.

Such is the structure of hyaline cartilage in general, but it is somewhat modified in different situations.

In **articular cartilage** the matrix in a thin section appears dim, like ground glass, having sometimes an almost granular aspect. The cells and cell-groups are smaller and more evenly dispersed, as a rule, than in rib cartilage. As already mentioned, the groups are flattened at and near to the surface, and lie parallel with it (fig. 218, *a*); deeper and nearer the bone, on the other hand, they are narrow and oblong, like short irregular strings of beads, and are mostly directed vertically (fig. 218, *c*). It is well known that articular cartilages readily break in a direction perpendicular to their surface, and the surface of the fracture appears to the naked eye to be striated in the same direction, as if they had a columnar structure; this may either be due to the vertical arrangement of the rows of cells, or to the substance of the matrix being disposed in a fibrous or columnar manner (Leidy).

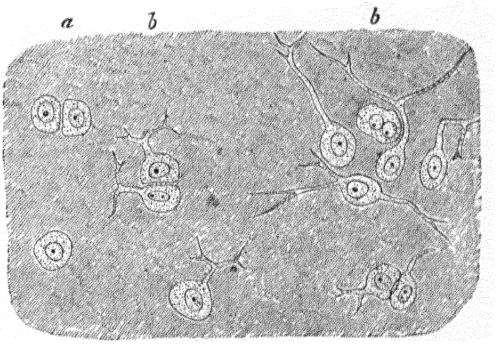


FIG. 219.—BORDER OF ARTICULAR CARTILAGE SHOWING TRANSITION OF CARTILAGE-CELLS INTO CONNECTIVE-TISSUE CORPUSCLES. FROM HEAD OF METATARSAL BONE (HUMAN). (Schäfer.) About 340 diameters.

a, ordinary cartilage-cells; *b*, *b*, with branching processes.

Near the margin of the articular cartilages connective tissue is prolonged a certain way into them from the periosteum and synovial membrane, and the cartilage-cells acquire processes and present transitions to the connective-tissue corpuscles of that membrane (fig. 219). There is no sharp demarcation between the two tissues, which here pass continuously into one another. Except at this transitional zone the matrix of articular cartilage rarely becomes converted into fibro-cartilage, nor is it prone to ossify like rib-cartilage. But a deposit of calcareous granules may occur in the deeper parts of the articular cartilage near the bone, the deposit first showing itself around the groups of cartilage-cells (fig. 218, *d*). This change may also happen at the symphyses. When the earthy matter is extracted by means of an acid, the tissue which remains has all the characters of cartilage.[4]

In the **costal cartilages**, the cells, which are of considerable size, are also collected in groups, larger for the most part than those found in articular cartilage (figs. 217, 220). Near the exterior of the cartilage they are flattened, and lie parallel

[1] Arch. f. mikr. Anat. xiv. and xvi. [2] Verhalten d. Indigschwefelnatrons, &c. Erlangen, 1876.
[3] Virch. Arch. lxviii. 1876 and lxxiii. 1878.
[4] See on the structure of articular cartilage, J. A. Hammar, Arch. f. mikr. Anat. xliii. 1894.

with the surface. As to those situated more inwardly, we can sometimes observe, in a transverse slice, that they form oblong groups disposed in lines radiating to the circumference; but this arrangement is not constant, and they often appear quite irregular. The cells, with the exception of those lying upon the surface, frequently contain drops of oil, the nucleus being often altogether concealed by the fat. The matrix is clear, except where the fibres have been developed in it, in which parts it is opaque and yellowish. Such fibrous patches are very frequent in rib cartilages; the fibres are fine, straight, and parallel, appearing transparent when few together. Besides these fibrous patches in the interior of the rib cartilages, the subperichondral layer is also pervaded by bundles of fibres which are directly prolonged from the fibre-bundles of the perichondrium and gradually lose themselves in the cartilage matrix. There is in fact no sharp line of demarcation between the perichondrium and the subjacent cartilage, the one tissue passing by imperceptible gradation into the other. There is indeed reason to believe that the superficial layers of the cartilage are formed by a transformation of the fibrous

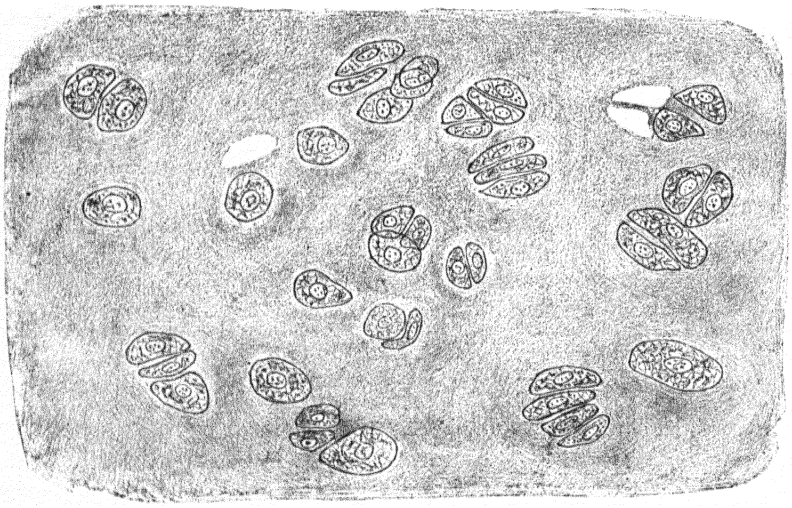


FIG. 220.—FROM A SECTION OF COSTAL CARTILAGE FROM THE CALF. Chromic acid preparation. (Schäfer.)

The matrix is indistinctly fibrous. Two or three empty cell-spaces are seen in the section, the cells having dropped out. The cell-protoplasm has a reticular appearance.

tissue of the perichondrium during the growth of cartilage. It is not uncommon to find the rib cartilages extensively ossified.

The description given of the microscopic characters of the costal cartilages will apply with little variation to the ensiform cartilage of the sternum, to the cartilages of the larynx and windpipe, except the epiglottis and cornicula laryngis, and to the cartilages of the nose. With the exception of the last, these resemble the rib-cartilages also in their tendency to ossify.

The characters of the temporary cartilages, which are hyaline, will be noticed in the account of the formation of bone.

Elastic or **yellow cartilage.**—The epiglottis and cornicula of the larynx, the cartilages of the ear and of the Eustachian tube, are formed of 'elastic' or 'yellow' cartilage. This is opaque and yellowish, more flexible and tough than ordinary cartilage, and having little or no tendency to ossify. It is made up of cells and a matrix, but the latter is everywhere pervaded with fibres (fig. 221), except in a small area or narrow zone left round each of the cells. The fibres

resist the action of acetic acid ; they are in many parts short, fine, and confusedly intersecting each other in all directions ; in such parts the matrix has a rough indistinctly granular look, but sometimes this appearance is due to the fact that the elastic fibres are incompletely developed, the granules which are to form them having not yet run together into fibres. Sometimes the fibres are longer and larger (fig. 222), but they still intercommunicate at short distances.

In large animals such as the ox, where the fibres of ordinary elastic tissue attain a considerable size, those of elastic cartilage are also very large with comparatively wide meshes, occupied of course by the ground-substance and cartilage-cells.

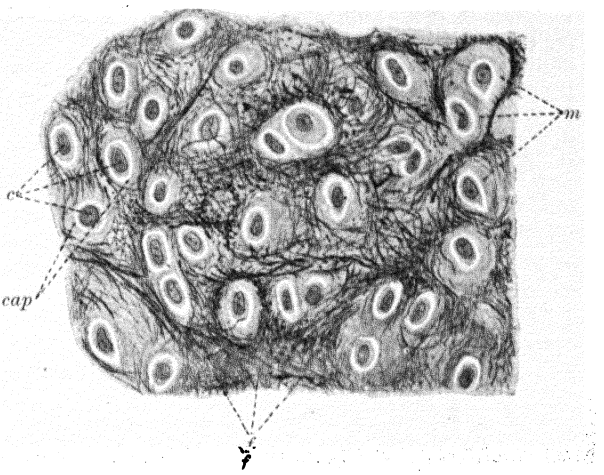


FIG. 221.—SECTION OF ELASTIC CARTILAGE OF EAR (MAN). (Sobotta.) Magnified 280 diameters.

c, cartilage-cells; *cap*, capsules; *m*, clear matrix around cells; *f*, elastic fibres, stained.

White fibro-cartilage. — This is a substance consisting of a mixture of fibrous and cartilaginous tissues, and so far partaking of the qualities of both.

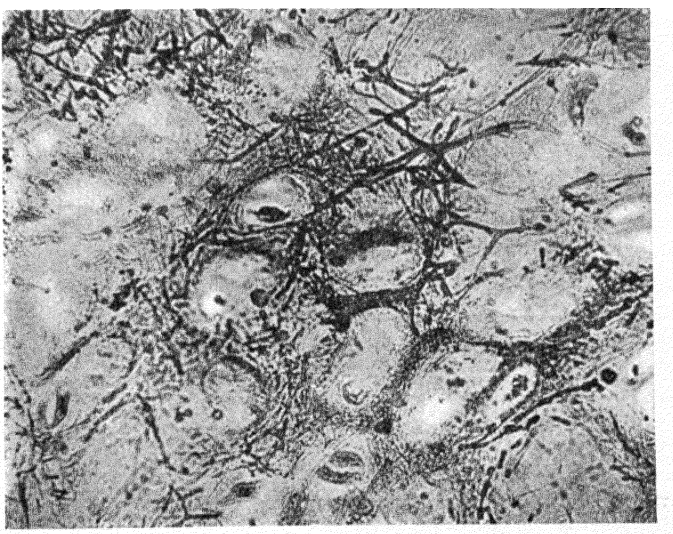


FIG. 222.—SECTION OF ELASTIC CARTILAGE (UPPER PART OF ARYTENOID OF CALF) STAINED WITH MAGENTA. Photograph. (Schäfer.) Magnified 200 diameters.

The elastin is seen partly in the form of a feltwork of fine fibrils, partly as distinct fine and coarse intercommunicating fibres. These are nowhere in contact with the cartilage-cells, which are surrounded by clear cartilage-matrix. At most parts of the section the cells have dropped out, but two or three are seen near the bottom of the figure, still *in situ*.

Like hyaline cartilage, it possesses firmness and elasticity, but these properties are united with a much greater degree of flexibility and toughness.

White fibro-cartilage occurs in various situations as follows:

1. *Forming interarticular discs.* These are interposed between the moving surfaces of bones, or rather of articular cartilages, in several of the joints. In the joint of the lower jaw and in that of the clavicle they have the form of round or oval plates, growing thinner towards the centre; in the knee-joint they are curved in form of a sickle, and thinned away towards their concave free edge. In all cases their surfaces are free; while they are fixed by synovial or fibrous membrane at their circumference or extremities. The synovial membrane of the joint is prolonged for a short distance upon these fibro-cartilages, from their attached margin.[1]

2. *As marginal fibro-cartilages.* The articular cavities of bones are sometimes deepened and extended by means of a rim or border of fibro-cartilage. Good examples of these are seen in the shoulder and hip-joints, attached round the lip of the articular sockets. In the joint of the lower jaw, the cartilage lining the glenoid cavity is also largely fibrous.

3. *As symphysial fibro-cartilages.* These connect the adjacent surfaces of bones in joints which do not admit of gliding motion, as at the symphysis of the pubis and between the bodies of the vertebræ. They have the general form of discs, and between the vertebræ are composed of concentric rings of fibrous tissue with cartilage-cells and matrix interposed; the fibrous tissue predominating at the circumference, the cartilaginous tissue increasing towards the centre.

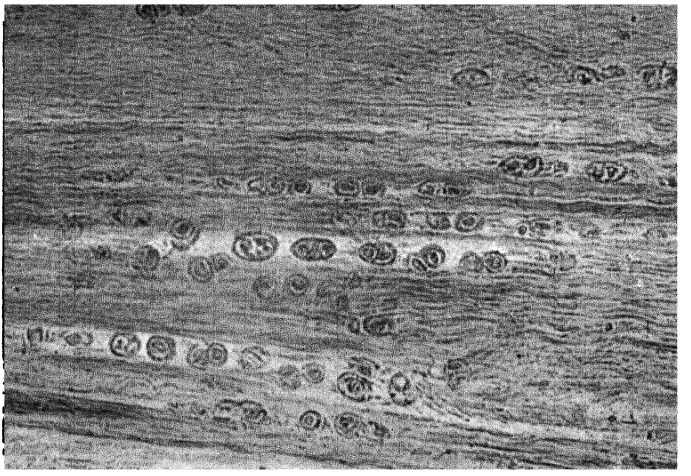


FIG. 223.—SECTION OF FIBRO-CARTILAGE FROM INTERVERTEBRAL DISC. Photograph. (Schäfer.) Magnified 200 diameters.

4. *As vaginal fibro-cartilages* lining the bony grooves in which tendons of muscles glide.

5. Forming small nodules (*sesamoid fibro-cartilages*) in the substance of tendons, of which there is an example in the tendon of the peroneus longus, and another in that of the tibialis posticus, where it passes beneath the head of the astragalus.

White fibro-cartilage appears under the microscope to be made up of wavy fibres, like those of ordinary ligament, with cartilage-cells occupying the place, and often simulating the arrangement, of the tendon-cells. As in elastic fibro-cartilage, the cells are immediately surrounded by a part of the matrix which is free from fibres (fig. 223). As a general rule they resemble the cells of ordinary cartilage, having a rounded shape, although somewhat flattened where the bundles of fibres are closely packed.

In the intervertebral fibro-cartilages, some of the cartilage-cells are provided with ramified processes extending some distance beyond the cell-body (fig. 224).

[1] It has been stated by several authors that the interarticular discs are formed of fibrous tissue only, without any intermixture with cartilage. This statement is, however, incorrect. In all cases (jaw, clavicle, and knee) there are unmistakable rows and groups of cartilage-cells enclosed in capsules between the bundles of white fibres

The proportion which the fibrous bundles bear to the true cartilage differs much in different examples of this tissue. In general the fibrous tissue very greatly predominates, and in some cases, as in the interarticular laminæ of the knee-joint, it constitutes almost the entire structure, but cartilaginous tissue with characteristic cells predominates near the surfaces. In the intervertebral discs the cartilage-corpuscles are, as already stated, more abundant towards the central pulp than near the periphery. The centre of the pulp itself does not, however, contain cartilage-cells, but a reticulated cell-structure imbedded in soft matrix, derived from the cells of the chorda dorsalis of the embryo. In all the symphyses the cartilage which is in immediate contiguity with the bony surfaces is hyaline.

Vessels and nerves of cartilage.—In the healthy state, no blood-vessels penetrate the articular cartilages. Whatever nutrient fluid they require seems to be derived from the vessels of adjoining textures, especially the bone, and to be conveyed through the tissue by imbibition. Towards the circumference of the

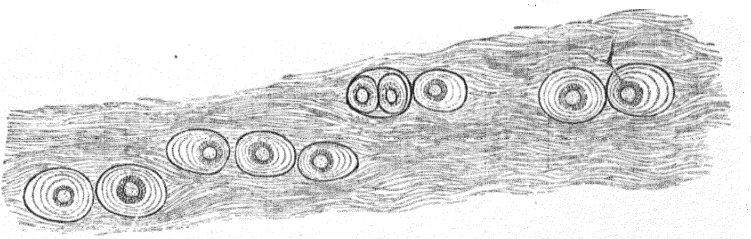


FIG. 224.—WHITE FIBRO-CARTILAGE FROM AN INTERVERTEBRAL DISC (HUMAN.) (Schäfer.) Highly magnified.

The concentric lines around the cells indicate the limits of deposit of successive capsules. One of the cells has a forked process which extends beyond the hyaline area surrounding the cell, amongst the fibres of the general matrix.

cartilage, however, underneath the synovial membrane, the synovial vessels form a narrow vascular border round it, which has been named the *circulus articuli vasculosus*.

When the tissue exists in thicker masses, as in the cartilages of the ribs, canals are here and there excavated in its substance, along which vessels are conducted for the nourishment of the parts too distant to receive it from the vessels of the perichondrium. But these canals are few and wide apart, and the vessels do not pass beyond them to ramify in the intermediate mass, which is accordingly quite extravascular. Besides blood-vessels these canals usually contain a number of cells resembling leucocytes, a few connective-tissue corpuscles, and in places some connective-tissue fibres. The contents of the canals are sometimes spoken of as 'cartilage-marrow.' The cartilage-cells in the immediate neighbourhood of the canals are disposed as at the surface of the cartilage—*i.e.* they are flattened conformably to the wall of the canal.

No nerves have been traced into any of the cartilages, and they are known to be destitute of sensibility.

DEVELOPMENT OF CARTILAGE.

The parts of the embryo which are to become cartilages are made up at first of the common mesenchyme-cells from which the connective tissues generally originate. After a time the cell-contents become clearer, the nucleus more distinct, and the cells, mostly of polygonal outline, appear surrounded by clear lines of pellucid substance, forming as it were a network of bright meshes enclosing them, but in reality consisting of the cohering capsules of the contiguous cells, and

constituting all that exists of the matrix at this time.[1] Glycogen appears at an early period in the protoplasm of cartilage-cells. Rouget found it in the sheep's embryo of two months, both in ossifying cartilage and in the cartilages of the trachea.

The subsequent changes consist in enlargement and multiplication of the cells and development of the intermediate matrix from a substance which is formed around and between them. The process appears to be as follows (fig. 225): The cartilage-cells first divide, a species of capsule being formed round each of the young cells (B), whilst the old one enclosing them becomes blended with the intercellular matrix, and, after a time, is no longer traceable (C). The new cells, in turn, divide in the same way, so as to make a group of four, each of which is surrounded by its own capsule (D), whilst the capsules of the first descent (secondary) blend with the matrix (E) like their predecessor.

The four cells may each form a succession of capsules and thus become more separated from one another, or they may divide again and form a group of eight or more. It is by reason of the cells remaining in contiguity with one another after the division is complete that the groups of corpuscles which are so characteristic of cartilage are produced.

How the capsule is produced has been a subject of much discussion: whether excreted by the cell which it afterwards encloses, as held by Kölliker; or formed

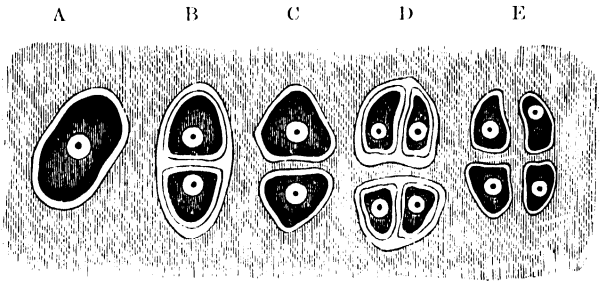


FIG. 225.—PLAN OF THE MULTIPLICATION OF CELLS OF CARTILAGE. (Sharpey.)

A, cell in its capsule; B, divided into two, each with a capsule; C, primary capsule disappeared, secondary capsules coherent with matrix; D, tertiary division; E, secondary capsules disappeared, tertiary coherent with matrix.

by conversion of a superficial layer of the protoplasm of the cell-body, as was taught by Max Schultze. The problem is of the same nature as that involved in the formation of the intercellular substance of connective tissue (p. 117) and of bone (p. 158). The probability is that the capsule is formed external to the cartilage-cell by a process of secretion. If it were produced by an immediate transformation of the protoplasm, we should find cells in which this transformation has only proceeded a certain way, but this is not the case. However formed, there is at first no matrix but what is made up of the simple capsules.

In further growth there is a difference, according as the cells do or do not undergo frequent division. In the latter case a cell (or, it may be, a small cell-group) becomes surrounded by many concentric capsules formed in succession; that is, the first capsule is expanded, and the others formed each within its expanding predecessor, so that the cartilage comes to consist of scattered cells, each with a concentric system of capsules, which by means of reagents may be rendered visible in the neighbourhood of the cells, but farther off are inseparably blended into a uniform substance. When, on the other hand, the cells have a tendency to frequent subdivision, the new capsules are produced by the daughter-cells, and

[1] Cartilages which retain this condition throughout life have been termed 'parenchymatous.' An example of this is found in the cartilage of the mouse's ear.

are included in and finally blend with those which had belonged to the mother-cells.

The matrix, although thus formed of the capsules, usually becomes to all appearance homogeneous; but in sections of cartilage that have been exposed to certain reagents, the contour lines of the capsules round cells and cell-groups may, as already stated, be more or less distinctly brought into view.

Division of the cartilage-cell takes place by karyokinesis. Schleicher[1] has succeeded in following the stages of the process in the living tissue (fig. 226).

The mode of division of the cytoplasm is different from that which obtains in most animal cells, for in place of a constriction appearing and gradually separating the protoplasm into two halves from without in, a partition is formed (*e*), in the middle of the now elongated cell, as is commonly the case in the division of plant-cells. The septum, as soon as it is broad enough, is seen to consist of two layers, which are continuous with the capsules of the two daughter-cells (*f*).

In the case of elastic cartilage the matrix is at first hyaline, and the elastic fibres are subsequently produced in it. They appear in the form of fine granules (termed by Hansen 'albumoid') in parts of the matrix which are in contiguity

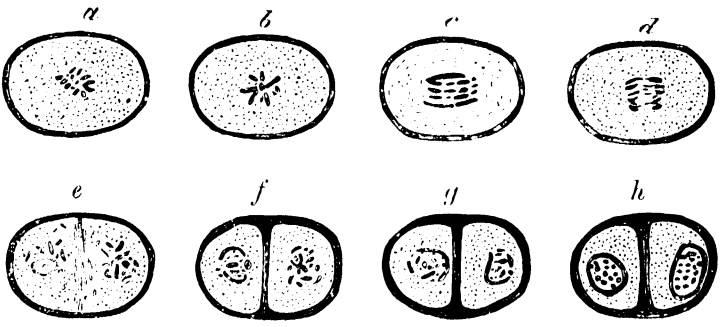


FIG. 226.—DIVISION OF A CARTILAGE-CELL. (Schleicher.)

a-h, stages of division of a cell, as seen in the living cartilage of the salamander (the chromosomes are only indistinctly seen in the fresh condition). *a*, *b*, stellate phase; *c*, *d*, commencing separation of the chromosomes; the further stages of separation are not represented; *e*, filaments fully separated into two groups, and a septum beginning to be formed between them; *f*, septum completed, seen to be double and continuous with capsules of daughter-cells; *g*, *h*, further stages in the formation of the daughter-nuclei.

with the cartilage-cells, but extend into other parts which are quite remote from the cells, around which clear matrix becomes subsequently formed. In the cartilage of the external ear in man this change occurs about the fifth month of intra-uterine life, commencing in the more central parts, and gradually extending outwards towards the perichondrium. The elastic fibres have been stated to be formed directly from the protoplasm of the cartilage-cells,[2] but their formation apart from the cells can be easily verified in the arytenoid cartilage of the calf.

The mode of development of white fibro-cartilage has not been fully ascertained, but it is stated that the fibres are formed at the same time as the matrix, instead of subsequently as in the case of elastic cartilage.

The vital changes which occur in cartilage appear to be sluggish, and when a portion is absorbed in disease or removed by the knife, it is regenerated very slowly. A wound in cartilage is usually at first healed by connective tissue, which becomes gradually transformed into hyaline

[1] Arch. f. mikr. Anat. xvi. 1878.
[2] O. Hertwig, Arch. f. mikr. Anat. ix. 1872; L. Gerlach. Morph. Jahrb. iv. Suppl. 1877.

cartilage. The reappearance of the latter seems, however, to depend upon the presence of the perichondrium, this membrane fulfilling similar functions in the regeneration of cartilage to those of the periosteum in the regeneration of bone. Schwalbe found that the cartilage of the rabbit's ear grows only by apposition at its margins and surfaces, and not interstitially; but it is certain that the temporary cartilages grow in the manner last mentioned.

Probably the rib cartilages grow in two ways—viz.: (1) by interstitial expansion accompanied by multiplication of the cells and increase of the matrix; (2) by apposition, fresh cartilage being formed under the perichondrium by transformation of its fibrous tissue into cartilage (metaplastic formation).

When a cartilage is fractured, as sometimes happens with the rib-cartilages, the broken surfaces become connected by fibrous or areolar tissue, especially dense at their circumference, and often later by a bony clasp.[1]

BONE OR OSSEOUS TISSUE.

The bones are the principal organs of support, and the passive instruments of locomotion. Connected together in the skeleton, they form a framework of hard material, which affords attachment to the soft parts, maintains them in their due position, and shelters such as are of delicate structure, giving stability to the whole fabric, and preserving its shape; and the different pieces of the skeleton being joined moveably together, serve also as levers for executing the movements of the body.

While substantially consisting of hard matter, bones in the living body are covered with periosteum and filled with marrow; they are also pervaded by blood-vessels for their nutrition.

Bone has a white colour, with a pink and slightly bluish tint in the living body. Its hardness is well known; it also possesses a certain degree of toughness and elasticity; the last property is peculiarly well marked in the ribs. Its specific gravity is from 1·87 to 1·97.

Chemical composition.—Bone consists of an earthy and an animal part, intimately commingled; the former gives hardness and rigidity, the latter tenacity and elasticity to the osseous tissue.

The earthy part may be obtained separate by calcination. When a bone is burned in an open fire, it first becomes quite black, like a piece of burnt wood, from the charring of its animal matter; but if the fire be continued with free access of air, this matter is entirely consumed, and the bone is reduced to a white, brittle, chalk-like substance, still preserving its original shape, but with the loss of about a third of its weight.[2] The earthy constituent, therefore, amounts to about two-thirds of the weight of the bone. It consists principally of phosphate of lime, with about a fifth part of carbonate of lime, and much smaller proportions of fluoride of calcium, chloride of sodium, and magnesium salts. The fluoride of calcium occurs in larger quantity in fossil than in recent bones.

The animal constituent may be freed from the earthy by steeping a bone in dilute mineral acid. By this process the salts of lime are dissolved out, and a tough flexible substance remains, which, like the earthy part, retains the perfect figure of the original bone in its minutest details; so that the two are evidently combined in the most intimate manner. The animal part has been termed the

[1] The following, besides the papers already referred to, deal with the structure and development of cartilage: G. Retzius, Nord. med. Ark. 1872; Ogston, Journ. Anat. and Physiol. x. 1875; C. Reyher, Journ. Anat. and Physiol. viii. 1874; A. Vogel, Die Saftbahnen des Hyalinknorpels, Diss., Bern, 1883; E. Zuckerkandl, Sitzungsb. der Wiener Akad. xci. 1885; A. Spina, Wiener med. Jahrb. 1886; R. Kolster, Arch. f. mikr. Anat. xxix. 1887; C. H. H. Spronck, 'Zur Kenntniss der Structur des Hyalinknorpels,' Anat. Anz. 1887; B. Solger, Arch. f. mikr. Anat. xxxi. 1888, and xxxiv. 1889; Ranvier, Traité technique d'histologie, 1889; H. Apolant, Ueber Faserknorpel, Diss., Berlin, 1890; O. Van der Stricht, Archives de biologie, vii. 1887 and ix. 1890; Hansen, Anat. Hefte, xxvii. 1905.

[2] In the compact substance of a femur that had been long buried, Aeby found only 16·5 per cent. of animal matter; but even fossil bones may contain a very appreciable amount of organic substance.

cartilage of bone, but improperly, for it differs entirely from cartilage in structure, as well as in physical properties and chemical nature. It is much softer and much more flexible, and, by boiling, it is almost wholly resolved into gelatin, which may be extracted from bones, in form of a jelly, by boiling them for a considerable time; the animal matter of bone is therefore composed, like fibrous and areolar tissue, of *collagen*.

The lining membranes of the Haversian canals and the walls of the lacunæ are formed of a material which resists the action of strong hydrochloric acid, which dissolves the remainder of the animal matter.

Minute structure of bone.—On sawing up a bone, it will be seen that it is in some parts dense and close in texture, appearing like ivory; in others,

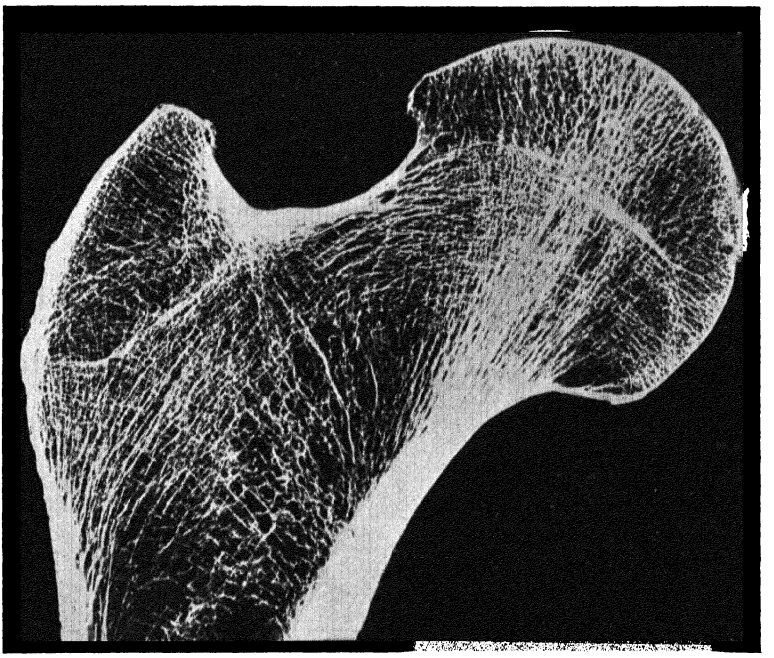


FIG. 227.—LONGITUDINAL SECTION THROUGH THE UPPER END OF THE FEMUR, SHOWING THE CANCELLOUS STRUCTURE OF THE HEAD AND THE COMPACT SUBSTANCE OF THE SHAFT. (From a photograph by Professor Robinson.)

The lines taken by the trabeculæ of the spongy substance—which are those best calculated to resist pressure on the articular surface—are well shown in this photograph.

open and reticular (fig. 227); and anatomists accordingly distinguish two forms of osseous tissue—viz. the *compact*, and the *spongy* or *cancellated*. On closer examination, however, especially with the aid of a magnifying-glass, it will be found that the bony matter is everywhere porous in a greater or less degree, and that the difference between the two varieties of tissue depends on the different amount of solid matter compared with the size and number of the open spaces in each; the cavities being very small in the compact parts of the bone, with much dense matter between them; whilst in the cancellated texture the spaces are large, and the intervening bony partitions thin and slender. There is, accordingly, no abrupt limit between the two—they pass into one another by degrees, the cavities of the compact tissue widening out, and the reticulations

of the cancellated becoming closer as they approach the parts where the transition between the two takes place.

In all bones, the part next the surface consists of compact substance, which forms an outer shell or crust, whilst the spongy texture is contained within. In a long bone, the large round ends are made up of spongy tissue, with only a thin coating of compact substance (fig. 227); in the hollow shaft, on the other hand, the spongy texture is scanty, and the sides are chiefly formed of compact bone, which increases in thickness from the extremities towards the middle, at which point the girth of the bone is least, and the strain on it greatest. In tabular bones, such as those of the skull, the compact tissue forms two plates, or tables, as they are called, enclosing between them the spongy texture, which in such bones is usually named *diploë*. The short bones, like the ends of the long, are spongy throughout, save at their surface, where there is a thin crust of compact substance. In the complex or mixed bones, such as the vertebræ, the

FIG. 228.—A. TRANSVERSE SECTION OF A BONE (ULNA) DEPRIVED OF ITS EARTH BY ACID. (Sharpey.)

The openings of the Haversian canals are seen. Natural size. A small portion is shaded to indicate the part magnified in B.

B. PART OF THE SECTION A, MAGNIFIED 20 DIAMETERS.

The lines indicating the concentric lamellæ are seen, and among them the lacunæ appear as little dark specks.

two substances have the same general relation to each other; but the relative amount of each in different parts, as well as their special arrangement in particular instances, is very various.

On close inspection the cancellated texture of bone is seen to be formed of slender bars or spicules and thin lamellæ, which meet together and join in a reticular manner, producing an open structure which has been compared to lattice-work (*cancelli*); hence the name usually applied to it. In this way considerable strength is attained without undue weight, and it may usually be observed that the strongest laminæ run through the structure in those directions in which the bone has naturally to sustain the greatest pressure (fig. 227).[1] The open spaces or areolæ of the bony network communicate freely together; in the fresh state they contain marrow and blood-vessels.

[1] On the architecture of spongy bone, see Friedländer, Anat. Hefte, xxiii. 1904.

Haversian canals.—The compact tissue is also full of holes; these, which are very small, may be seen by breaking across the shaft of a long bone near its middle and examining it with a common magnifying-glass. Numerous little round apertures (fig. 228, A) are then visible on the broken surface, which are the openings of short longitudinal passages running in the compact substance, and named the *Haversian canals*, after Clopton Havers, an English physician and writer of the seventeenth century, who more especially called attention to them. Blood-vessels run in these canals, and the widest of them also contain marrow. They are from ·025 mm. ($\frac{1}{1000}$th inch) to ·125 mm. ($\frac{1}{200}$th inch) or more in diameter; there are some no more than ·0125 mm., but these are rare; the average are about ·05 mm. ($\frac{1}{500}$th inch). The wider are met with nearest the medullary cavity, and the narrower towards the circumference of the bone. They are short, as may be seen in a longitudinal section, oblique communications connecting them freely both longitudinally and laterally. Those which are next the circumference of the bone open by minute apertures on its external surface, and the innermost ones open widely into the medullary cavity; so that these short channels collectively form a sort of irregular network of tubes running through the compact tissue, in which the vessels of that tissue are lodged, and through the medium of which these vessels communicate together, not only along the length of the bone, but from its surface to the interior through the thickness of the shaft. The canals of the compact tissue in the other classes of bones have the same general characters, and for the most part run parallel to the surface.

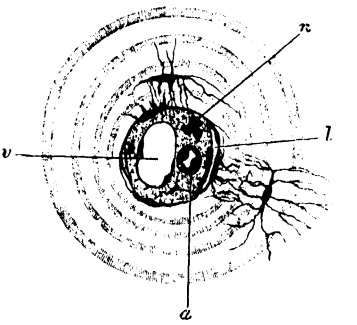


FIG. 229.—SECTION OF A HAVERSIAN CANAL, SHOWING ITS CONTENTS. (Schäfer.) Highly magnified.

a, small arterial capillary vessel; *v*, large venous capillary; *n*, pale nerve-fibres cut across; *l*, cleft-like lymphatic vessel: one of the cells forming its wall communicates by fine branches with the branches of a bone-corpuscle. The substance in which the vessels run is connective tissue with ramified cells; its finely granular appearance is probably due to the cross-section of fine fibrils.

The Haversian canals contain small blood-vessels, often two in number, arterial and venous (fig. 229), together with a small amount of delicate connective tissue containing branched cells, which are flattened close to the bone, and communicate by their branches with the ramifications of corpuscles in the substance of the bone.

Lamellar structure.—On viewing a thin transverse section of a long bone with a microscope of moderate power, especially after the earthy part has been removed by acid (fig. 228 B; fig. 230), the opening of each Haversian canal appears to be surrounded by a series of concentric rings. This appearance is occasioned by the transverse sections of concentric *lamellæ* which surround the canals (*Haversian lamellæ*). The rings are not all complete, for here and there one may be seen ending between two others. In some of the sets, the rings are nearly circular, in others oval—differences which depend on the direction in which the canal happens to be cut: the aperture, too, may be in the centre or more or less to one side, and in the latter case the rings are narrower and closer together on the side towards which the aperture deviates. Again, some of the apertures are much lengthened, and the lamellæ surrounding them have a corresponding disposition. Besides the lamellæ surrounding the Haversian canals, there are others disposed conformably with the circumference of the bone (fig. 228 B; fig. 230, *pl*); most of these are near the surface, but others run between the Haversian sets, by which they are

interrupted in many places (fig. 230, *p'l'*). Lastly, in various parts of the section, lines are seen which indicate lamellæ running in indeterminate directions. The lamellæ which do not belong to the Haversian systems are distinguished from the Haversian lamellæ under the general term of *ground-lamellæ*.

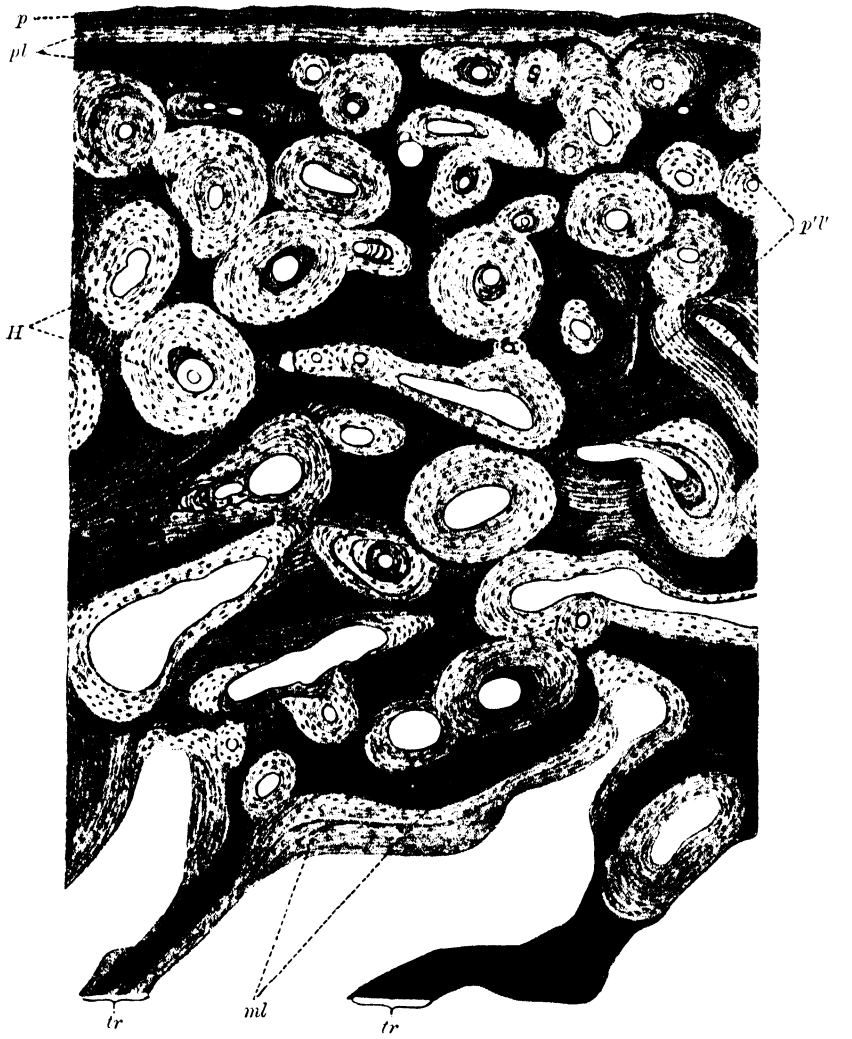


FIG. 230.—SECTION OF A DECALCIFIED HUMAN RADIUS. (Sobotta.) Magnified 48 diameters.

p, periosteum; *pl*, periosteal bony lamellæ; *p'l'*, deeply seated lamellæ parallel with periosteal surface; *H*, Haversian systems; *tr*, *tr*, trabeculæ of spongy substance; *ml*, lamellæ bounding medullary spaces.

The appearance of a longitudinal section of the bone is in harmony with the account above given: the sections of the lamellæ are seen as straight and parallel lines, running in the longitudinal direction of the bone, except when the section happens to have passed directly or slantingly across a canal: for wherever this occurs there is seen, as in a transverse section, a series of rings, generally oval and much lengthened on account of the obliquity of the section.

Many of the Haversian canals which pass through the circumferential or periosteal lamellæ carrying blood-vessels from the periosteum into the bone, are not surrounded by concentric lamellæ, but are mere channels piercing the periosteal lamellæ. They are often spoken of as *Volkmann's canals.*

The cancellated texture has also a lamellar structure. The slender bony walls of its little cavities or areolæ are made up of superimposed layers, like those of the Haversian canals, but they have fewer lamellæ in proportion to the width of the cavities which they surround (fig. 230, *ml*).

Lacunæ and canaliculi.—All over the section numerous little dark specks are seen among the lamellæ with a low power of the microscope. These were at one time known as the 'osseous corpuscles'; but, although they contain cells (fig. 232), they are in reality minute cavities in the bony substance, and the name of *lacunæ* has been applied to them. To see them properly, sections of unsoftened bones are prepared and ground very thin. Such a section, cut transversely and viewed with

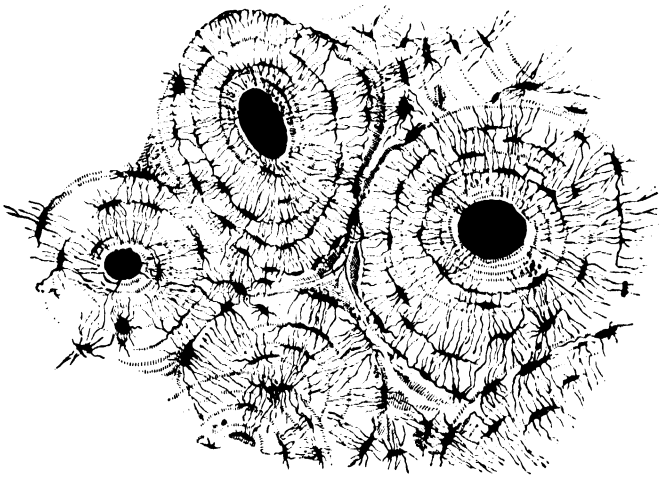


FIG. 231.—TRANSVERSE SECTION OF COMPACT TISSUE (OF HUMERUS). (Sharpey.) Magnified about 150 diameters.

Three of the Haversian canals are seen, with their concentric rings; also the lacunæ, with the canaliculi extending from them across the direction of the lamellæ. The Haversian apertures had become filled with air and débris (from the grinding), and therefore appear black in the figure, which represents the object as viewed with transmitted light.

transmitted light by a magnifying power of from 200 to 300, has the appearance represented in figs. 231 and 233. The openings of the Haversian canals are seen with their encircling lamellæ; and among these the lacunæ, which are mostly ranged in a corresponding order, appear as black, opaque or nearly opaque, oblong spots, with fine dark lines extending from them and causing them to look not unlike little black insects. The dark appearance is due to the fact that the little cavities have become filled with air in the dry bone, and when the same section is seen against a dark ground, with the light falling on it (as we usually view an opaque object), the little bodies and lines appear quite white, like figures drawn with chalk on a slate, and the intermediate substance, being transparent, now appears dark.

The lacunæ, as already stated, are minute recesses in the bone, and the lines extending from them are fine pores or tubes named *canaliculi*, which issue from their cavity. The lacunæ present some variety of figure, but in such a section as that represented they for the most part appear irregularly fusiform, and lie nearly in the same direction as the lamellæ between which they are situated; or, to speak

more correctly, they are flattened and extended conformably with the lamellæ ; for when the bone is cut longitudinally (fig. 234), their sections still appear fusiform and are still more lengthened out in the direction of the lamellæ. The canaliculi, on the other hand, pass across the lamellæ, and they communicate with those proceeding from the next range of lacunæ, so as to connect the little cavities with each other ; and thus, since the canaliculi of the most central range open into the Haversian canal, a system of continuous passages is established by these minute tubes and their lacunæ, along which fluid may be conducted from the Haversian canal through its series of surrounding lamellæ. In like manner the canaliculi open into the great medullary canal, and into the cavities of the cancellated texture ; for in the thin bony parietes of these cavities lacunæ are also contained ; they exist, indeed, in all parts of the bony tissue. The canaliculi which radiate outwards from the lacunæ near the periphery of the concentric Haversian systems do not as a rule communicate with those of the neighbouring Haversian system, but bend round and are joined to one another ; there are, however, exceptions to this rule.

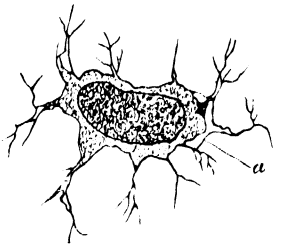


FIG. 232.—A BONE-CELL ISOLATED AND HIGHLY MAGNIFIED. (After Joseph.)

a, proper wall of the lacuna, shown at a part where the corpuscle has shrunk away from it.

Cells of bone.—As first shown by Virchow, each lacuna is occupied by a flattened nucleated cell, which sends branches along the canaliculi. Later observers have been able to detach the proper wall of the lacuna and its appertaining canaliculi after decalcification, and to obtain it separate with its included corpuscle (fig. 232). It can scarcely be doubted that the protoplasm of the nucleated corpuscle takes an important share in the nutritive process in bone, and very probably serves both to modify the nutritive fluid supplied from the blood and to further its distribution through the lacunar and canalicular system of the bony tissue. Virchow showed that the corpuscles of bone are homologous with those of ordinary connective tissue ; they represent the lamellar variety of connective-tissue cell : to this it may be added that the enclosing lacunæ and canaliculi are to be looked upon as corresponding to the cell-spaces of that tissue.

Apertures in the lamellæ.—With a little pains thin films may be peeled off in a longitudinal direction from a piece of bone that has been decalcified. These for the most part consist of several lamellæ, as may be seen at the edge, where the different layers are usually torn unequally, and some extend farther than others. Examined in this way, under the microscope, the lamellæ are seen to be perforated with fine apertures placed at very short distances apart. These apertures were described by Deutsch ; [1] they appear to be the transverse sections of the canaliculi already described, and their relative distance and position accord sufficiently with this explanation. According to this view, therefore, the canaliculi might (in a certain sense) be conceived to result from the apposition of a series of perforated plates, the apertures of each plate corresponding to those of the plates contiguous with it ; or they might be compared to holes bored to some depth in a straight or crooked direction through the leaves of a book, in which case it is plain that the perforations of the adjoining leaves would correspond ; it being understood, however, that the passages thus formed are most likely bounded by proper parietes. The apertures now referred to must be distinguished from larger holes seen in some lamellæ, which give passage to the perforating fibres to be mentioned farther on.

[1] De Penitiori Ossium Structurâ, 1834, p. 17, fig. 6.

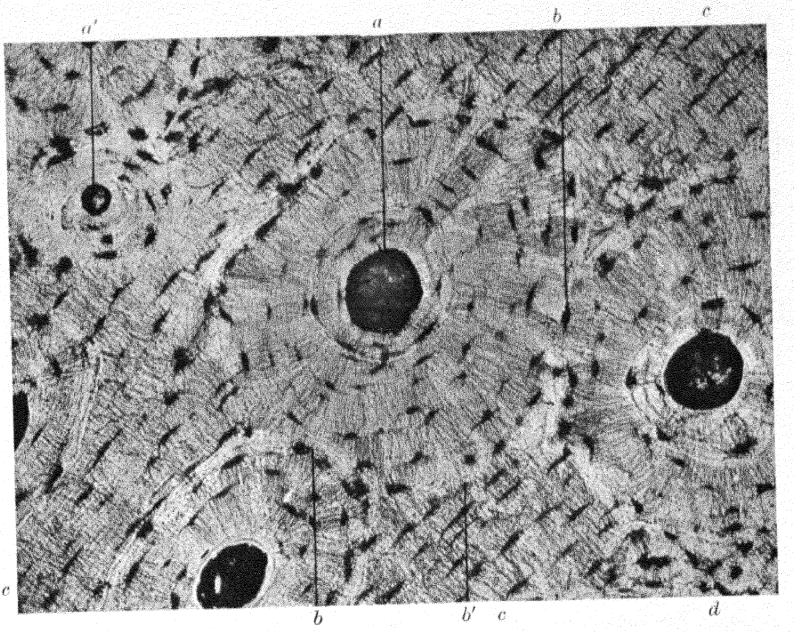


FIG. 233.—PHOTOGRAPH OF TRANSVERSE SECTION OF COMPACT BONE, MADE BY GRINDING, SHOWING THREE HAVERSIAN CANALS WITH THEIR CONCENTRIC LAMELLÆ, AND ALSO INTER-HAVERSIAN BONY SUBSTANCE. (Schäfer.) Magnified 200 diameters.

a, Haversian canal, filled with air and débris; *a'*, a very small canal; *b*, *b*, junctions of Haversian systems; *b'*, margin of Haversian system abutting on lamellæ parallel to periosteum; *c*, *c*, *c*, lamellæ parallel to periosteum; *d*, inter-Haversian bone with irregular lacunæ.

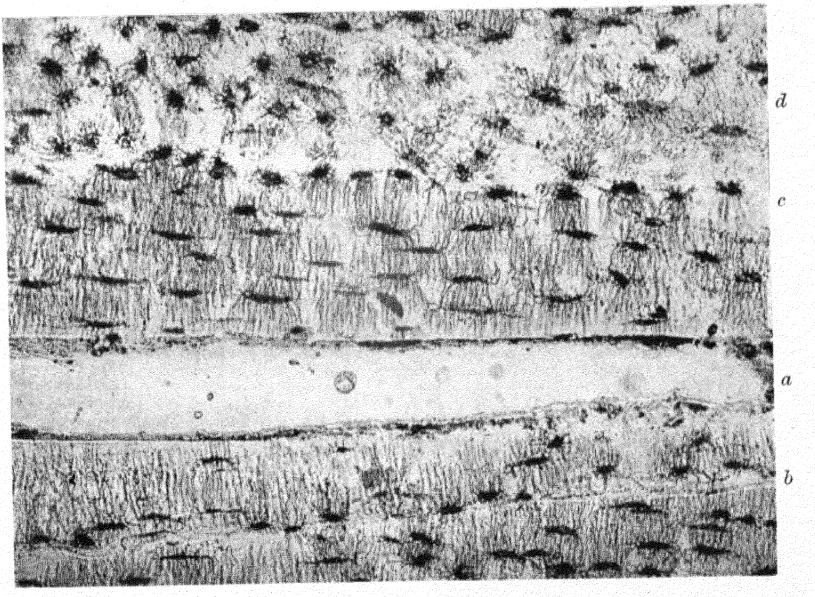


FIG. 234.—LONGITUDINAL SECTION OF COMPACT BONE, SHOWING HAVERSIAN SYSTEMS OF LAMELLÆ, AND INTER-HAVERSIAN BONE. (Schäfer.) Magnified 200 diameters.

a, Haversian canal cut longitudinally; *b*, junction of two Haversian systems of lamellæ; *c*, margin of Haversian system abutting upon inter-Haversian bone *d*, which has irregular lacunæ

Lamella-fibres (decussating fibres) of Sharpey.—If the thinnest part of a detached shred or film be examined, as shown in figs. 235 and 237, it will then appear plainly that the lamellæ are largely made up of transparent fibres, often decussating with each other in adjacent lamellæ. In the Haversian systems these fibres cross one another in different lamellæ at right angles (v. Ebner), but in most other situations at more or less acute angles, and they are united here and there by obliquely passing fibres, so that they cannot be teased out from one another; at the torn edge of the lamella they may often be seen separate for a little way, standing out like the threads of a fringe. Most generally they are straight, as represented in fig. 235; but they are not always so; for in some parts they are wavy (fig. 237). Dilute acetic or hydrochloric acid causes these fibres to swell up and become indistinct, like the white fibres of connective tissue; care must therefore be taken in their examination that the remains of such decalcifying acid be removed from the tissue, by maceration in water or in solutions of neutral salts. Moreover, the fibrous structure is not equally distinct in all parts; in some places it is less decidedly marked, as if the fibrillation were incompletely developed.

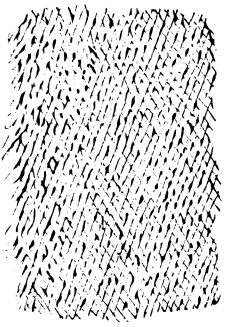


FIG. 235.—THIN LAYER PEELED OFF FROM A SOFTENED BONE, AS IT APPEARS UNDER A MAGNIFYING POWER OF 400 DIAMETERS. (Sharpey.)

This figure, which is intended to represent the fibrous appearance of the lamellæ, gives a better idea of the object when held rather farther off than usual from the eye.

These fibres, which constitute the lamellæ, were discovered by Sharpey,[1] and their constant presence was taught by him for many years before they were acknowledged by other histologists. It has since been shown by v. Ebner that the lamella-fibres of Sharpey are themselves composed of fine fibrils, so that they correspond with small bundles of white connective-tissue fibres rather than with single fibres. Like the connective-tissue fibrils, these of the bone are doubly refracting, and they are said by v. Ebner not to be calcified, the calcareous matter being confined to the matrix in which they are imbedded, so that in calcined bone they are destroyed and their place is occupied by fine tubules.[2] As already stated, they sometimes take different directions in successive lamellæ, so as to produce a granular or a striated appearance according as they happen to be cut transversely or longitudinally (fig. 236).

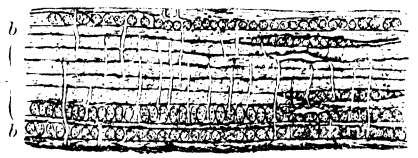


FIG. 236.—SMALL PART OF A LONGITUDINAL SECTION OF DECALCIFIED TIBIA. (v. Ebner.) Highly magnified.

a, series of six lamellæ which are cut for the most part in the direction of the fibrils, so that they appear longitudinally striated; *b*, *b*, lamellæ, the fibrils of which are cut across; the arrangement of the fibrils into bundles is indicated. Two lacunæ are seen lying between the lamellæ, also canaliculi piercing the lamellæ.

In thin sections of bone, the lines or rather bands which represent the cut edges of the lamellæ show the section of the lamella-fibres as round or angular dots, themselves punctated, which lie imbedded in the ground-substance

[1] Quain's Anat., 5th edition, 1845. The discovery of these fibres is often attributed to v. Ebner (Wiener Sitzungsb. lxxii. 1876), to whose descriptions we owe many facts regarding their arrangement and structure. Sharpey did not fully distinguish between the finest fibrils and the small bundles into which they are collected, but in all other points his account of the fibrous structure of the lamellæ was very complete.

[2] Arch. f. mikr. Anat. xxix. 1887.

(fig. 236, *b*). The lamellæ are partly separated from one another by the lacunæ which lie between them. Where these are absent they are joined together by the ground-substance ; they are also united by bundles of fibres passing obliquely from one lamella to the other.

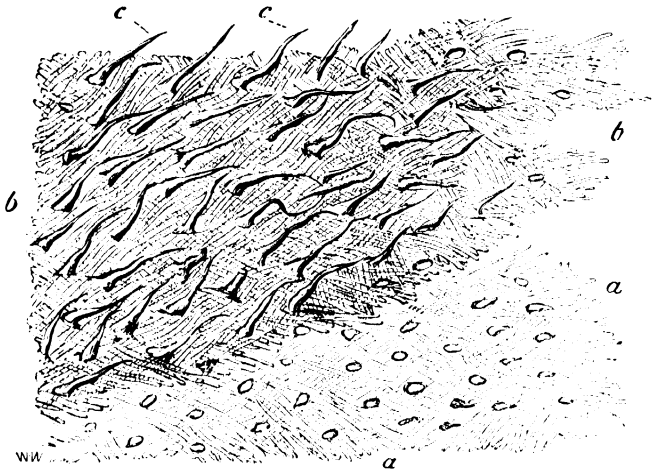


FIG. 237.—LAMELLÆ TORN OFF FROM A DECALCIFIED HUMAN PARIETAL BONE AT SOME DEPTH FROM THE SURFACE. (Sharpey.)

a, lamellæ, showing decussating fibres ; *b*, *b*, thicker part, where several lamellæ are superposed ; *c*, *c*, perforating fibres. These are actually bundles of fibres, but this is not shown in the drawing. Apertures through which perforating fibres had passed are seen especially in the lower part, *a*, *a*, of the figure. Magnitude as seen under a power of 200, but not drawn to a scale (from a drawing by Allen Thomson).

de Burgh Birch[1] describes some of the lacunæ as lying in the substance of the lamellæ. Birch, however, defines a lamella as a layer of osseous substance in which the fibres course in the same direction. But this definition would in some cases comprise several lamellæ as ordinarily understood (see fig. 236).

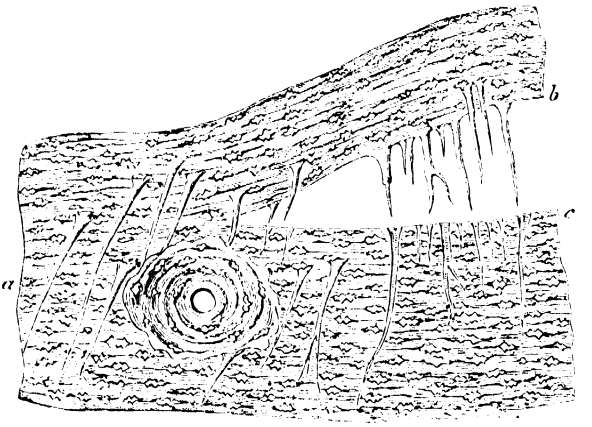


FIG. 238.—MAGNIFIED VIEW OF A PERPENDICULAR SECTION THROUGH THE EXTERNAL TABLE OF A HUMAN PARIETAL BONE, DECALCIFIED. (H. Müller.)

At *a*, perforating fibres in their natural situation ; at *b*, others drawn out by separation of the lamellæ ; at *c*, the holes or sockets out of which they have been drawn. (H. Müller.)

Perforating fibres of Sharpey.—It was further shown by Sharpey that in many instances the lamellæ are perforated by fibres, which pass through them

[1] Journ. Physiol. ii. 1879.

in a perpendicular or oblique direction, and seem to bolt them together. These perforating fibres may be seen, with the aid of the microscope, in a thin transverse slice of a decalcified cylindrical or cranial bone, on pulling asunder the sections of the lamellæ (as in fig. 238). In this way some lamellæ will generally be observed with fibrous processes attached to them (fig. 238, *b*) of various lengths, and usually tapering and pointed at their free extremities, but sometimes truncated—probably from having been divided by the knife. These fibres have obviously been drawn out from the adjacent lamellæ, through several of which they must have penetrated. Sometimes, indeed, indications of perforations may be recognised in the part of the section of bone from which the fibres have been pulled out (fig. 238, *c*). The processes in question are thus, so to speak, viewed in profile; but they may frequently also be seen on the flat surface of detached lamellæ (fig. 237), projecting like nails driven perpendicularly or obliquely.[1]

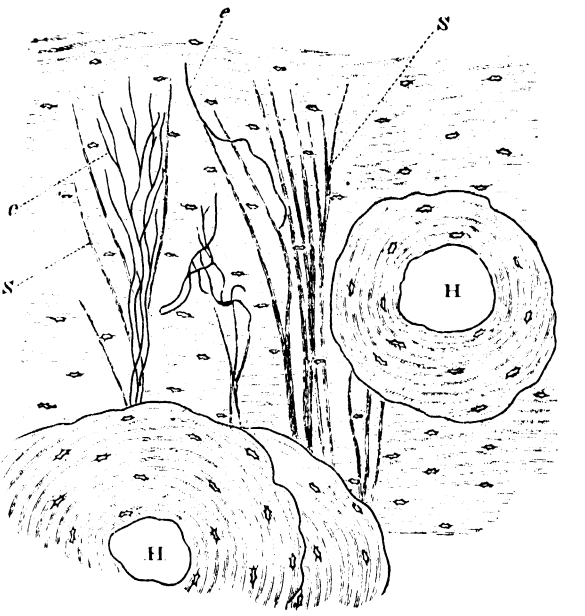


FIG. 239.—TRANSVERSE SECTION OF DECALCIFIED HUMAN TIBIA, FROM NEAR THE SURFACE OF THE SHAFT. (Schäfer.)

H, H, Haversian canals, with their systems of concentric lamellæ; in all the rest of the figure the lamellæ are circumferential.

S, S, ordinary perforating fibres of Sharpey; *e*, *e*, elastic perforating fibres. Drawn under a power of about 150 diameters.

The perforating fibres are, like the decussating fibres, bundles of fibrils which agree in character with those of the white fibrous tissue; but some perforating fibres, as shown by H. Müller, are of the nature of elastic tissue (fig. 239, *e*). These always remain uncalcified; sometimes the white fibrous bundles escape calcification. The result is that, as they shrink in drying, they leave tubes or channels in the dry bone, generally leading from the surface inwardly; but these uncalcified bundles are by no means frequent (Sharpey). The perforating fibres are usually connected with the periosteum, as is the case with most of those which penetrate the external table of the cranial bones; but in cross-sections of cylindrical bones they often appear to spring with their broad ends from the deeper lamellæ (with the fibres of which they may be directly continuous), and especially from those near the circumference of a Haversian system, and taper outwards into fine points, which do not reach the periosteum (fig. 239),[2] although without doubt they must, like the bony layers in which they occur, have been formed by subperiosteal ossification. They are never found in the concentric systems of Haversian lamellæ.

Where tendons or ligaments are inserted into bone, the fibre-bundles of the tendon are continued into the bone as perforating fibres, so that the attachment of tendon to bone is thus rendered very intimate. Some of the bundles of white fibres of the periosteum may also, as above mentioned, be traced into the bone as perforating fibres, and the same is the case with the elastic fibres.

When tendons become ossified, as is often the case, especially in birds, a calcification of the

[1] On the history of the discovery of the perforating fibres, see Sharpey, Quart. Journ. Micr. Sci. xviii. 1877, p. 142.

[2] Schäfer, Quart. Journ. Micr. Sci. xviii. 1877

ground-substance of the tendon occurs, so that, after decalcifying, the tendinous structure again becomes manifest. These so-called ossified tendons are therefore not composed of true osseous substance.

Appearances indicative of absorption and re-deposition of bone.—The animal basis of bone is made up essentially, as we have seen, of regularly arranged lamellæ; but interposed among these, layers are here and there met with of a different character, having a granular or irregularly fibrous aspect, with the lacunæ very conspicuous and regularly arranged, and sometimes appearing as if surrounded by faintly defined areas. These layers are often bounded by a scalloped border, as if made up of confluent round or oval bodies (fig. 240). The layers described appear principally to occur in the irregular interstices of the systems of concentric Haversian lamellæ: they perhaps represent remains of the bony matter which was first formed in the fœtus and most of which has become absorbed and replaced by the fibrous lamellar tissue. Irregular layers of rounded nodules, apparently solid, are also sometimes seen, and are of a similar nature. These are met with chiefly near the surface, lying among the circumferential laminæ.

Haversian spaces.—Spaces are occasionally seen which are characterised by an eroded outline, in some cases partially filled up by concentric lamellæ. These were named 'Haversian spaces' by Tomes and de Morgan[1]; they are interpolated or intruded amongst the regular Haversian systems, some of which may have been cut in upon in the excavation of the space. It was further noticed by Tomes and de Morgan that the spaces in question may sometimes be seen being filled up at one part by the deposition of lamellæ, whilst they are extending themselves by absorption at another. Haversian spaces are most numerous in young and growing bones, but they occur also after growth is completed.

FIG. 240. — SMALL PART OF A SECTION THROUGH THE SHAFT OF A FEMUR (HUMAN SIXTEEN YEARS) TAKEN A SHORT DISTANCE FROM THE EPIPHYSIS. (Kölliker.) 230 diameters.

a, remains of calcified cartilage; *b*, bony deposit in Howship's foveolæ (absorption spaces); *c*, subsequent deposit of lamellar bone.

The appearances above mentioned are due to the peculiar manner in which the absorption of bone occurs; for it is effected, as will presently be described, by the agency of large multinucleated cells, which excavate little hemispherical pits (*foveolæ of Howship*) and ultimately cavities (*Haversian spaces*) in the osseous tissue. If the process of absorption should cease and should be succeeded by a re-disposition of osseous substance, the new osseous matter filling up the hollows of the absorbed surface exhibits, when it is detached, a raised impression corresponding with the hollows into which it fitted.

In young bones the lamellar character is not evident, the tissue being constituted at first of bundles of fibres which interlace in every direction in the ground-substance; in this reticular form of osseous tissue the lacunæ are both more numerous and irregular in form than in lamellated bone. Portions of such reticulated bone may persist in the adult between the Haversian systems (figs. 233, 234).

The exact knowledge we possess of the minute structure of osseous tissue is largely the result of the investigations of William Sharpey, whose account, written in 1845, has needed no erasure, and but little addition of importance, even to the present day. His labours in this field have been to a certain extent recognised in the adoption of the name 'fibres of Sharpey' for the perforating fibres; but it must not be forgotten that the fibres which constitute the lamellæ and which he

[1] Phil. Trans. 1853.

termed the 'decussating fibres' were also first described by him, although their existence was long denied by other histologists.[1]

The **periosteum**, as already stated, is a fibrous membrane which covers the bones externally. It adheres to them very firmly, and invests every part of their surface, except where they are covered with cartilage.

It is composed of two layers; the outer, consisting chiefly of white fibres, and containing occasional fat-cells, is the means of supporting numerous blood-vessels destined for the bone, which ramify in the membrane, and at length send their minute branches into the Haversian canals of the compact substance, accompanied by processes of filamentous tissue derived from, or at least continuous with, the periosteum. The inner layer is largely made up of elastic fibres, frequently in several distinct strata.[2] Between it and the proper osseous tissue there is a fibrous stratum containing in the young bone a number of angular or cubical cells (osteoblasts), while in the adult bone these have become flattened out into an epithelium-like layer covering the osseous substance, and are in many places separated by a cleft-like space (serving probably for the passage of lymph) from the rest of the periosteum.[3]

By treating the membrane with nitrate of silver, lymphatics are discovered in it accompanying the blood-vessels in the outer layer; and, as in other aponeurotic structures, extensive epithelioid cell-markings, covering a great part of the surface, are brought into view.

Fine nerves spread out in the periosteum; they are partly associated with the arteries, and along these enter the subjacent bone; but others are for the membrane itself. Some of these end in Pacinian corpuscles, others in arborescent terminations.

The chief use of the periosteum is to support the vessels going to the bone, and afford them a bed in which they may subdivide into fine branches, and so enter the dense tissue at numerous points. Hence, when the periosteum is stripped off at any part, there is risk that the denuded portion of the bone will die and exfoliate. The periosteum also serves to give purchase to the tendons and ligaments where they are fixed to bones. Its relation to the growth and renewal of bone will be referred to later on.

The **marrow** (*medulla ossium*) is lodged in the interior of the bones; it fills up the hollow shaft in the long bones, where it is of a yellow colour and largely formed of fat, and it occupies the cavities of the cancellated structure, where it is usually of a red colour and contains but little fat; it extends also into the Haversian canals —at least into the larger ones—along with the vessels. A fine layer of a highly vascular areolar tissue lines the medullary canal, as well as the smaller cavities which contain marrow; this has been named the medullary membrane, internal periosteum, or *endosteum*, but it cannot be detached as a continuous membrane. Its vessels join on the one side those of the osseous substance, and on the other side are continuous with the capillaries of the marrow.

The marrow—at least the red variety—is the chief blood-forming organ in the adult, and the account of its structure will be deferred until the mode of development of blood-corpuscles is dealt with.

Blood-vessels of bone.—The bones are well supplied with blood-vessels. A network of periosteal vessels covers their outer surface; fine vessels run from this through all parts of the compact tissue in the Haversian canals; others

[1] See on bone-structure, Kölliker, Handbuch der Gewebelehre, 6th edition, and in Zeitschr. f. wiss. Zool. xliv. and xlv. 1886–7; v. Ebner, Wiener Sitzungsb. lxxii. 1876; O. Van der Stricht, Arch. de biol. ix. 1889; Ranvier, Traité technique d'histologie, 1889; Meyburg, Arch. f. mikr. Anat. lxiv. 1904 Novikoff, Zeitschr. f. wiss. Zool. xcii. 1909. On the structure of fossil bone, J. Schaffer, Sitzungsb. d. Wiener Akad. xcviii. 1889.

[2] On the elastic tissue of periosteum and bone, see K. Schultz, Anat. Hefte, vi. 1896.

[3] On the lymphatics of bone and periosteum, see Schwalbe, Zeitschr. f. Anat. ii. 1897.

penetrate to the cavities of the spongy part, in which they ramify; and a considerable artery goes to the marrow in the central part of the bone. In the long bones this *medullary artery*, often, but improperly, called 'the nutritious artery,' passes into the medullary canal, near the middle of the shaft, by a canal[1] running obliquely through the compact substance. The vessel, which is accompanied by one or two veins, then sends branches upwards and downwards in the middle of the marrow; from these branches arterial capillaries pass radially towards the periphery. The comparatively narrow arterial capillaries pass suddenly at the periphery of the marrow into wide venous capillaries, which form a close network of large channels throughout the medullary tissue, so that the current of blood must be considerably retarded both in these and in the large thin-walled veins.

The ramifications of the medullary artery anastomose with the arteries of the compact and cancellated structure; indeed, there is free communication between the finest branches of all the vessels which proceed to the bone, and no strictly defined limit between the parts supplied by each. In the thigh-bone there are frequently two medullary arteries entering at different points.

The veins of the cancellated texture are peculiar and deserve special notice. Their arrangement is best known in the bones of the skull, where, being lodged in the diploë or spongy texture between the outer and inner compact tables, they have received the name of the diploïc veins. They are large and numerous, and run separately from the arteries in canals formed in the cancellated structure, the sides of which are constructed of a thin lamella of bone, perforated here and there for the admission of branches from the adjoining cancelli. Being thus inclosed and supported by the hard structure, the veins have exceedingly thin coats. They issue from the bone by special apertures of large size. A similar arrangement is seen in the bodies of the vertebræ, whence the veins come out by large openings on the posterior surface. In the long bones numerous apertures may be seen at the ends, near the articular surfaces; some of these give passage to arteries, but the greater number, as well as the larger of them, are for the veins of the cancellated texture, which run separately from the arteries.

According to Hoyer[2] and Rindfleisch[3] the venous capillaries and veins of the red marrow have incomplete walls, or rather are channels bounded only by the medullary parenchyma, so that the blood-corpuscles which are being formed from marrow-cells can readily get into the circulation. Langer,[4] on the other hand, found the vascular system of the marrow to be a closed one. In birds this is certainly the case according to the testimony of Bizzozero and of Denys, but in mammals it is doubtful if the vascular walls are everywhere complete.

The blood coming from the marrow contains a larger number of leucocytes than ordinary blood, and sometimes nucleated coloured corpuscles (erythroblasts) occur in it.

Lymphatics.—In addition to the lymphatics in the periosteum (which have already been mentioned), there are others in the Haversian canals accompanying the vessels (fig. 229, *l*), and often partially or wholly enclosing them (perivascular).[5] The lymph or plasma of the blood is enabled to penetrate the hard bony substance by means of the lacunæ and communicating canaliculi.

The fine **nerves** which may be seen entering the bones along with the arteries are probably chiefly destined for those vessels; it is not known whether any end in connexion with the cells of the bony tissue itself.

As far as can be judged from observations on man and experiments on the lower animals, the bones, as well as their investing periosteum, are scarcely if at all sensible in the healthy condition, although they are painfully so when inflamed.

[1] On the nutritive canals of bones, see Schwalbe, Zeitschr. f. Anat. i. 1870.
[2] Centralbl. f. d. med. Wiss. 1869.
[3] Wiener Denkschr. 1876 and 1877.
[4] Arch. f. mikr. Anat. xvii. 1879.
[5] Budge, Arch. f. mikr. Anat. xiii. 1877

FORMATION AND GROWTH OF BONE.

The foundation of the skeleton is laid at a very early period. But it is by their outward form and situation only that the parts representing the future bones are then to be recognised. At first they do not differ materially in substance from the other structures of the embryo, being composed of undifferentiated mesoderm-cells. Very soon, however, they become cartilaginous, and ossification in due time beginning in the cartilage and continuing to spread from one or from several points, the bony tissue becomes gradually formed.

But, while it is true with respect to the bones generally that their ossification commences in cartilage, it is not so in every instance. The tabular bones forming the roof of the skull may be adduced as a decided example to the contrary; in these the ossification goes on in embryonic connective tissue altogether unconnected with any cartilage; and even in the long bones, in which ossification undoubtedly commences and to a certain extent proceeds in cartilage, it will be afterwards shown that there is much less of the increment of the bone really owing to that mode of ossification than was at one time generally believed. Two species or modes of ossification are thus distinguished, which for the sake of brevity may be called the *intramembranous* and the *intracartilaginous*, the resulting bones being termed *membrane bones* and *cartilage bones* respectively.

INTRAMEMBRANOUS OSSIFICATION: OSSIFICATION IN CONNECTIVE TISSUE.

The tabular bones of the cranium, as already said, afford an example of this mode of ossification. The base of the skull in the embryo is cartilaginous; but in the roof, that is to say, the part comprehending the parietal and frontal bones, and a certain portion of the occipital bone, we find (except where there happen to be commencing muscular fibres) only the integuments, the developing dura mater, and an intermediate connective-tissue layer, in which the ossification proceeds.

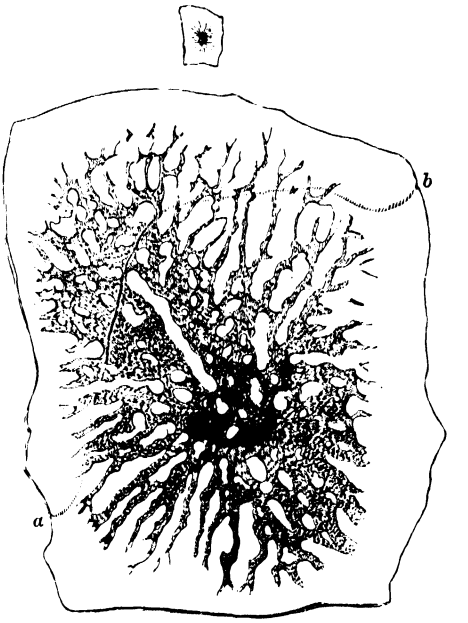


FIG. 241.—PARIETAL BONE OF AN EMBRYO SHEEP. SIZE OF THE EMBRYO 2½ INCHES. (Sharpey.)

The small upper figure represents the bone of the natural size, the larger figure is magnified about 12 diameters. The curved line *a*, *b*, marks the height to which the subjacent cartilaginous lamella extended. A few isolated particles of bone are seen near the circumference, an appearance which is quite common at this stage.

The commencing ossification of the parietal bone, which may be selected as an example, appears to the naked eye in the form of a network in which little bars or spicules of bone run in various directions, and meet each other at short distances. By-and-by the ossified part becomes extended, also gets thicker and closer in texture towards the centre, and the larger bony spicules which now appear, run out in radiating but interconnected lines to the

circumference. The ossification continues thus to spread and consolidate until the parietal meets the neighbouring bones, with which it is at length united by sutures.

Fig. 241 represents the parietal bone of an embryo sheep about two inches and a half long, and shows the character of the ossification as it appears when the object is magnified about twelve diameters. When further examined with a higher magnifying power, the tissue or membrane in which the ossification is proceeding appears to be made up of fibres and corpuscles, with a ground-substance between, and may be looked upon as connective tissue in a certain stage of development. The corpuscles are large and angular, and they are densely packed all over the area of ossification, covering the bony spicula, and filling up their interstices.

On observing more closely the points of the growing osseous rays at the circumference of the bone, where they shoot out into the soft tissue, it will be seen that the portion of them already calcified is granular and rather dark in appearance (fig. 242), but that this character is gradually lost as they are traced farther outwards in the membrane, in which they are prolonged for a little way in form of soft and pliant bundles of transparent fibres (fig. 243, *of*).

These were termed by Sharpey *osteogenic fibres*, the soft transparent matter of which they are composed being designated osteogenic substance, or simply *osteogen*. It appears, however, to be identical with the *collagen* of which white connective-tissue fibres are formed, and the so-called osteogenic fibres are in fact small bundles of collagenous fibres, and are continuous with similar bundles in the surrounding connective tissue (fig. 244). But although similar in chemical composition, they are somewhat different from these in appearance, having a stiffer aspect and straighter course. The fibre-bundles become calcified by the deposition within them of earthy salts in the form of minute globules, which produce a darkish

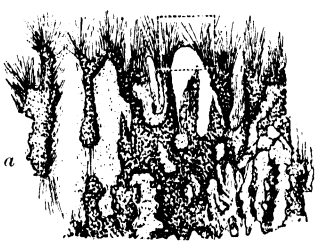


FIG. 242.—PART OF THE DEVELOPING PARIETAL BONE OF A FŒTAL CAT (1½ INCH LONG). (Schäfer.)

The figure represents a piece of the growing edge slightly magnified, showing the bony spicules terminated by bunches of osteogenic fibres; *a*, an isolated bony spicule united to the main part of the ossification by a bundle of osteogenic fibres.

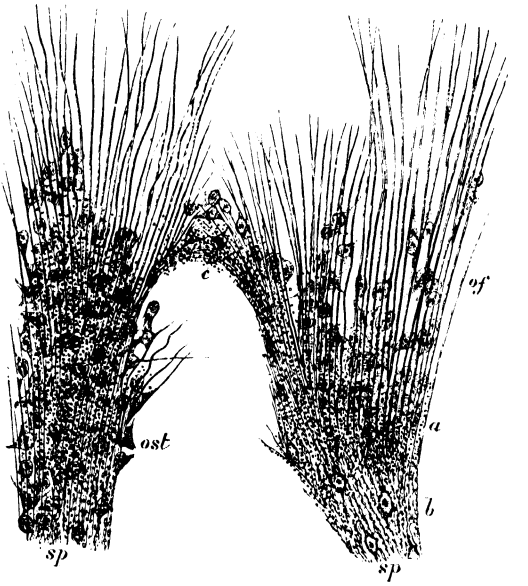


FIG. 243.[1]—THE PART MARKED *b* OF FIG. 242, HIGHLY MAGNIFIED. (Schäfer.)

sp, bony spicules, with some of the osteoblasts imbedded in them, producing the lacunæ; *ost*, osteoblasts partly imbedded in the newly formed bone; *of*, osteogenic fibres prolonging the spicules, with osteoblasts between them and applied to them; *a*, granules of calcareous deposit between the osteogenic fibres; at *b* the granules have become blended, and the matrix is clearer; at *c* a continuity is established between the two adjacent spicules.

[1] These two figures, as well as figs. 248, 253, and 254, are from the author's paper on the structure and development of bone, in the Quart. Journ. Micr. Sci. xviii. 1877. They were drawn by Mr. J. Lawrence.

granular opacity, until the interstices between the globules also become calcified, and the minute globules becoming thus fused together, the new bone again looks comparatively clear (fig. 243, *b*).[1]

As already stated, the fibrils which compose the osteogenic fibres themselves are, according to v. Ebner, not calcified; the calcification affects only the matrix which unites them.

The bundles of osteogenic fibres which prolong the bony spicules, generally spread out from the end of each spicule so as to come in contact with those from adjacent spicules. When this happens, the innermost or proximal parts of the bundles frequently grow together (fig. 243, *c*), whilst the other fibres partially intercross as they grow farther into the membrane. The ossific process extends along the osteogenic fibres *pari passu* with their growth, and thus new bony spicules become continually formed by calcification of the bundles of osteogenic fibres.

The earthy deposit occasionally appears in an isolated patch here and there on some of the osteogenic fibres in advance of the main area of ossification (see fig. 242, *a*).

The osteogenic fibres become comparatively indistinct as the interfibrillar and ground-substance calcifies; but they persist in the form of the fibres which are seen in the formed bone, although in embryonic bone their disposition is not lamellated, the bony matter having a somewhat coarsely and irregularly fibrous structure.

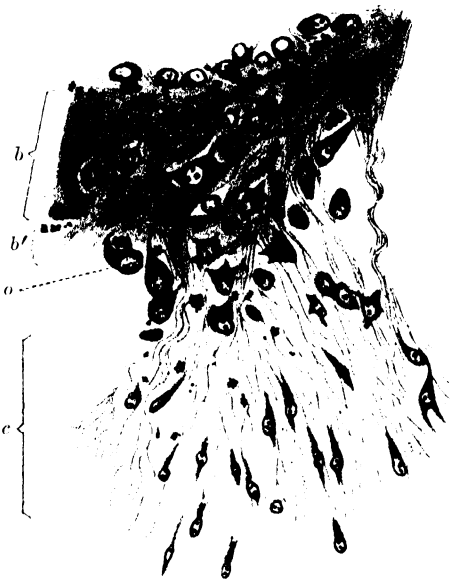


FIG. 244.—SECTION OF OSSIFYING MAXILLARY BONE OF NEW-BORN RAT. (v. Korff.)

o, osteoblasts; *b*, bony substance with osteoblasts and fibres; *b'*, growing border of bone; *c*, embryonic connective tissue, showing its fibres continuous with the osteogenic fibres of the growing border.

In this way the first bony matter becomes formed as a perforated plate or network of osseous spicules, which, whilst extending peripherally in the way above described, gradually becomes thicker nearer the centre, partly by the deposit of bony matter upon its surfaces, partly by the projection from them of bony spicules which are prolonged like those at the periphery by similar systems of osteogenic fibres. The perforations in these first-formed bony plates correspond to the bays which were seen between the advancing spicules, and to the meshes of the bony network formed afterwards by the junction of the spicules, and as the bone thickens they become enclosed and converted into reticulating interstices (like the canals of a sponge), which are occupied by blood-vessels, and by the corpuscles above mentioned. These corpuscles also everywhere cover the bundles of osteogenic fibres, to which their flattened sides are applied (fig. 243, *ost*). Where the osteogenic fibres diverge from one another, the intervals are occupied by the same cells. It is probable that the osteogenic fibres are formed by the agency of the cells in question, and that the calcification takes place under their influence, hence the name

[1] See on the fibrils in developing bone and dentine, v. Korff, Arch. f. mikr. Anat. lxix. 1909.

'osteoblasts' was assigned to them by Gegenbaur.[1] Some of the osteoblasts are involved in the ossifying matrix, and remain as the corpuscles of the future bone, the spaces enclosing them being the lacunæ. The canaliculi, which are at first short, are afterwards extended by absorption, so as to anastomose with those of neighbouring lacunæ.

Osteoblasts are probably specially modified connective-tissue corpuscles, perhaps of the nature of plasma-cells. But after becoming included within the lacunæ they may undoubtedly be regarded as homologous with the lamellar cells of connective tissue. It is improbable that they are produced from leucocytes as suggested by Kassander.[2]

The ground-substance of the bone, together with the collagenous fibres it contains, is doubtless produced by the osteoblasts. By Gegenbaur, Kölliker, and others, it has been assumed to be a kind of secretion from the cells, and this is the view which has been taken in this work.[3] It is believed by other histologists[4] that the ground-substance of bone is formed not outside the cells in an intercellular substance as here described, but by a direct conversion of the protoplasm of some of the osteoblasts into bony tissue. If this were the case, there ought to be some indication in the formed osseous substance of the cell-areas of which it was made up, but nothing of the kind has been shown to exist. There should, moreover, often be observed osteoblasts which are only partly converted into bony substance, but this also has never been described. And if, as some suppose, the peripheral part of each osteoblast becomes converted into osseous substance, while the central part and nucleus remain as the corpuscle within a lacuna, the osteoblasts would have to be originally far larger than the permanent lacunæ, which is certainly not the case. The view in question is similar to that which supposes ordinary connective tissue to have a like origin (see p. 127). A similar difference of opinion is held regarding the development of dentine.

Meanwhile, the meshes of the bony network, which were occupied as we have seen by one or more blood-vessels, and by numerous osteoblasts, become diminished in extent, and the bone at the same time increased in thickness by the deposit upon the original trabeculæ of irregular bony laminæ and trabeculæ, some of the osteoblasts remaining, and forming the corpuscles and lacunæ as before. The interstices of the bony spongework thus become gradually narrowed, each containing one or more blood-vessels surrounded by osteoblasts.

At a later stage increase in thickness takes place by successive depositions of bony lamellæ under the periosteum, a concentric deposition occurring at the same time on the walls of the vascular channels. But since the growth in thickness of a membrane bone takes place in exactly the same manner as that of one of the long bones, which will be fully described in a subsequent page, the reader is referred to the account of the process there given.

It may be observed that the appearance of the ossifying membrane-bone in the shape of a network of trabeculæ seems to be determined by the pre-existence of a vascular network in the embryonic tissue. The new bone everywhere makes its appearance in the spots which are farthest from the vessels, and the bony network everywhere alternates with the vascular network. At the edges of the advancing bone the spicules which prolong it pass between and avoid the capillary blood-vessels, which are thus left in the bays between the spicules; the divergent bunches of osteogenic fibres which prolong the adjacent spicules complete the enclosure of the blood-vessel.

After a time the membrane-bone extends so as almost to come into contact with the neighbouring bones. But as long as growth continues, there always remains in

[1] Jena Zeitschr. i. 1864 and iii. 1867.
[2] Anat. Anz. xviii. 1900.
[3] See also v. Korff. Arch. f. mikr. Anat. lxix.
[4] *E.g.* Waldeyer, Arch. f. mikr. Anat. i. 1865. For a recent account in which a similar view is taken, see Disse, Arch. f. mikr. Anat. lxxiii. 1909, and Anat. Anz. xxxv. 1909.

the situation occupied afterwards by the sutures a vascular, growing connective tissue with numerous osteoblasts. This is continually on the increase, but as fast as it grows, the osteogenic fibres and the osseous spicules extend into it from the young bones on either side. At length, however, when these have attained their full dimensions, the growth of the intermediate tissue ceases, and it becomes completely invaded by bone, with the exception of the narrow and irregular line of suture, which may eventually itself become more or less obliterated.

From a morphological point of view, such membrane-bones as those of the skull are probably to be regarded as evolved from an integumental skeleton which is extensively developed in some of the lower vertebrata, and which had in all probability as its phylogenetic precursor a formation of dentinous cutaneous spines. The membrane-formation in connexion with cartilage-bones may also have originated in a similar manner.

OSSIFICATION IN CARTILAGE.

It has already been stated that, in by far the greater number of bones, the mesodermic tissue with closely packed cells, of which they originally consist, is very quickly succeeded by cartilage, in which the ossification begins. One of the long bones taken from a very small embryo, just before ossification has commenced in it, is observed to be distinctly cartilaginous. In the tibia of a sheep, for example, at a time when the whole embryo is not more than an inch and a quarter in length, we can plainly see that the substance consists of cartilage-cells imbedded in a pellucid matrix. These cells can scarcely be said to be collected into groups, and are very irregular in size and shape. They become enlarged in the middle part of the shaft when ossification is about to commence. As it grows, the cartilage acquires firmer consistence; it represents in figure the future bone, though of course much smaller in size, and it is surrounded with a fibrous membrane, the future periosteum. Vessels ramify in this membrane, but none are seen in the cartilage until ossification is about to begin. In a long bone the ossification commences in the middle and proceeds towards the ends, which remain long cartilaginous, as represented in fig. 248. Much later, separate points of ossification appear in them, and form epiphyses, and in some also apophyses, which at last are joined to the body of the bone.

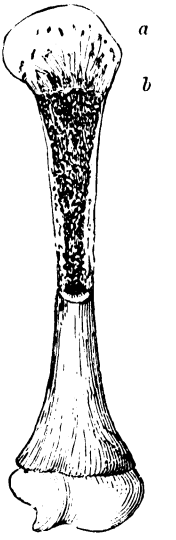


FIG. 245.—HUMERUS OF A FŒTUS. (Sharpey.) Natural size.

The upper part is divided longitudinally. *a*, cartilage, *b*, line of junction of bone and cartilage. The periosteal bone looks lighter than the endochondral bone proper.

The manner in which the process of ossification of a cartilage bone takes place is as follows:

In the middle of the cartilage the cells are enlarged, and are separated from one another by a relatively larger amount of matrix than elsewhere (fig. 246). This matrix becomes hardened by calcareous deposit, assumes a granular opaque appearance, and has a gritty feel to the knife. Meanwhile the cartilage-cells above and below the centre of ossification become enlarged and flattened, and piled up in elongated groups or columns which radiate from the centre for a certain distance towards either end. The columns taper towards their ends, where the cartilage-cells

which compose them are smaller. Near these ends the cartilage-cells multiply by mitosis,[1] and with the new cells new matrix is produced so that the cartilage in this situation is both becoming elongated and expanded laterally. Near the place where bone is forming there is no sign of division and multiplication of the cartilage-cells; here indeed there is evidence of atrophy. Into the matrix between the columns the calcareous deposit extends between and around the groups of cells, so that the calcified substance encloses the columns. The cell-spaces in the calcified matrix which are still occupied by the cartilage-cells, either singly or in elongated groups, were termed by Sharpey *primary areolæ*. Simultaneously with this deposit in the cartilage-matrix, a layer of osseous substance (fig. 246, *im*) is becoming formed on the outside of the cartilage underneath the periosteum. This last is a vascular membrane, containing numerous osteoblasts (*o*), which are chiefly collected on the inner surface next to the cartilage, and it is by their agency that the bony layer on the surface of the cartilage is formed and becomes increased both in thickness and length. The bony layer, when viewed on the surface, shows the usual component fibres of osseous substance, and as other layers are deposited upon it lacunæ become formed between them by the inclusion of some of the osteoblasts. In this first stage of ossification we see therefore two processes going on, a deposit of earthy matter in the matrix of the cartilage, the cells of which assume a highly characteristic arrangement, and a deposition of true membrane-bone, underneath the perichondrium, and closely investing the surface of the cartilage.

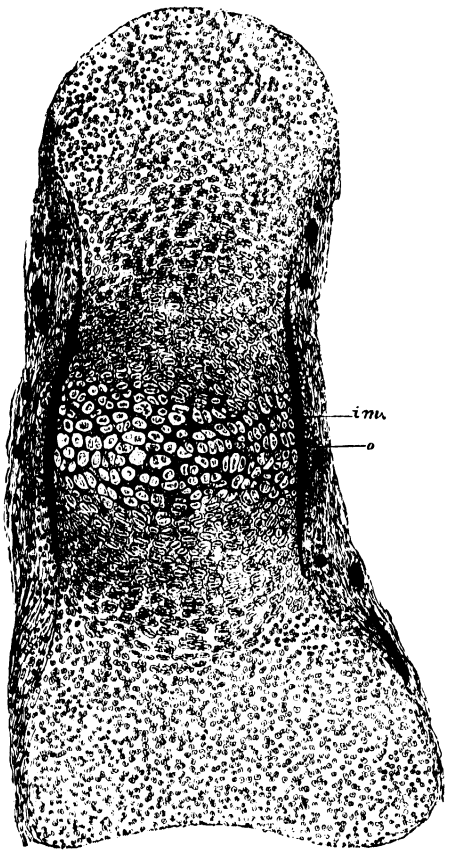


FIG. 246.—SECTION OF PHALANGEAL BONE OF HUMAN FŒTUS, AT THE TIME OF COMMENCING OSSIFICATION. From a preparation by F. A. Dixey. (Schäfer.) Magnified about 75 diameters. The drawing was made from a photograph.

The cartilage-cells in the centre are enlarged and separated from one another by dark-looking calcified matrix; *im*, layer of bone deposited underneath the periosteum; *o*, layer of osteoblasts by which this layer has been formed. Some of the osteoblasts are already imbedded in the new bone as lacunæ. The cartilage-cells are becoming enlarged and flattened and arranged in rows above and below the calcified centre. At the ends of the cartilage the cells are small and the groups are irregularly arranged; the fibrous periosteum is not sharply marked off from the cartilage.

What next happens is an irruption of the subperiosteal vascular and osteoblastic tissue into the middle of the cartilage, one or more apertures being excavated by absorption in the newly deposited osseous lamella, and the tissue in question passing through these and burrowing into the cartilage (fig. 247, *ir*). Here it absorbs a great part of the calcified matrix, and by demolishing it in this way forms larger spaces (the *secondary areolæ* of Sharpey,

[1] Leser, Arch. f. mikr. Anat. xxxii. 1888; G. Retzius, Biol. Fören. Förhandl. i. 1888.

the *marrow spaces* of H. Müller), which are filled by jelly-like embryonic marrow, with ramified cells and osteoblasts, the cartilage-cells which occupied the primary areolæ disappearing before it. All the middle of the calcified temporary cartilage becomes thus excavated with large spaces (fig. 248), sometimes with a single large space (fig. 249), and replaced by the vascular osteoblastic tissue. As the calcification of the cartilage-matrix extends towards the ends of the shaft, proceeding always in the same manner, the osteoblastic tissue closely follows, and after supplanting the cartilage-cells in the primary areolæ, absorbs parts of their walls so as to throw two or more together to form secondary areolæ; in this way a great part of the calcified cartilage-matrix is at once removed.

At a short distance below the advancing ossification, the marrow spaces become at first somewhat more enlarged by further absorption, but at the same time their walls (which were at first formed only by the remains of the walls of the primary areolæ and therefore only by calcified cartilage matrix) begin to be thickened by the deposition of layers of new bone, and this deposition increases gradually towards the middle of the shaft (compare fig. 252, *c* and *d*). The lacunæ first appear in this deposit; there are of course none in the calcified cartilage. Moreover, as layer after layer is deposited upon the walls of the marrow spaces these become gradually narrowed into intercommunicating channels, which contain little more than a blood-vessel and some jelly-like embryonic connective tissue (fœtal marrow), with a certain number of osteoblasts applied to the bone.

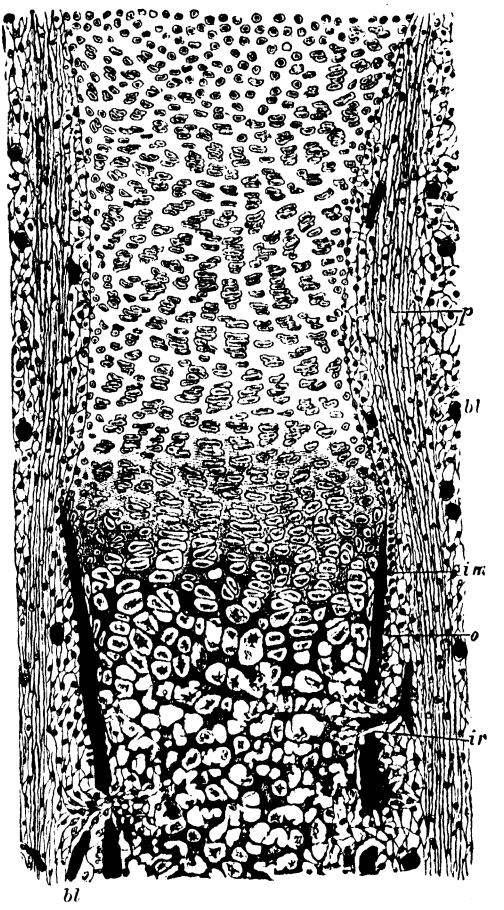


FIG. 247.—SECTION OF PART OF ONE OF THE LIMB-BONES OF A FŒTAL CAT, AT A MORE ADVANCED STAGE OF OSSIFICATION THAN IS REPRESENTED IN FIG. 246, AND SOMEWHAT MORE HIGHLY MAGNIFIED. (Schäfer.)

The calcification of the cartilage-matrix has advanced from the centre, and is extending between the groups of cartilage-cells, which are now arranged in characteristic rows. The subperiosteal bony deposit (*im*) has extended *pari passu* with the calcification of the cartilage-matrix. The cartilage-cells in the primary areolæ are mostly shrunken and stellate; in some cases they have dropped out of the space. At *ir* and in two other places an irruption of the subperiosteal tissue, composed of ramified cells with osteoblasts and growing blood-vessels, has penetrated the subperiosteal bony crust, and has begun to excavate the secondary areolæ or marrow spaces; *p*, fibrous layer of the periosteum; *o*, layer of osteoblasts: some of them are imbedded in the osseous layer as bone-corpuscles in lacunæ; *bl*, blood-vessels occupied by blood-corpuscles. Beyond the line of ossific advance the periosteum may be noticed to be distinctly incurved. This incurvation is gradually moved on, the cartilage expanding behind and in front of it until the head of the bone is reached, when it forms the periosteal notch or groove represented in fig. 248.

At the ends, some of the embryonic bone which is thus laid down remains to form the cancellated tissue, but in the shaft most of this structure is afterwards removed by absorption, to give place to the medullary canal. In the walls of many of the secondary cavities the calcified cartilage which bounded the coalesced primary areolæ may long be distinguished as arched lines forming by their union a sort of festooned outline, upon which the new bony laminæ have been deposited (see figs. 252 and 253, *c*).

In some of the smaller bones it may happen that the calcified cartilage is completely absorbed

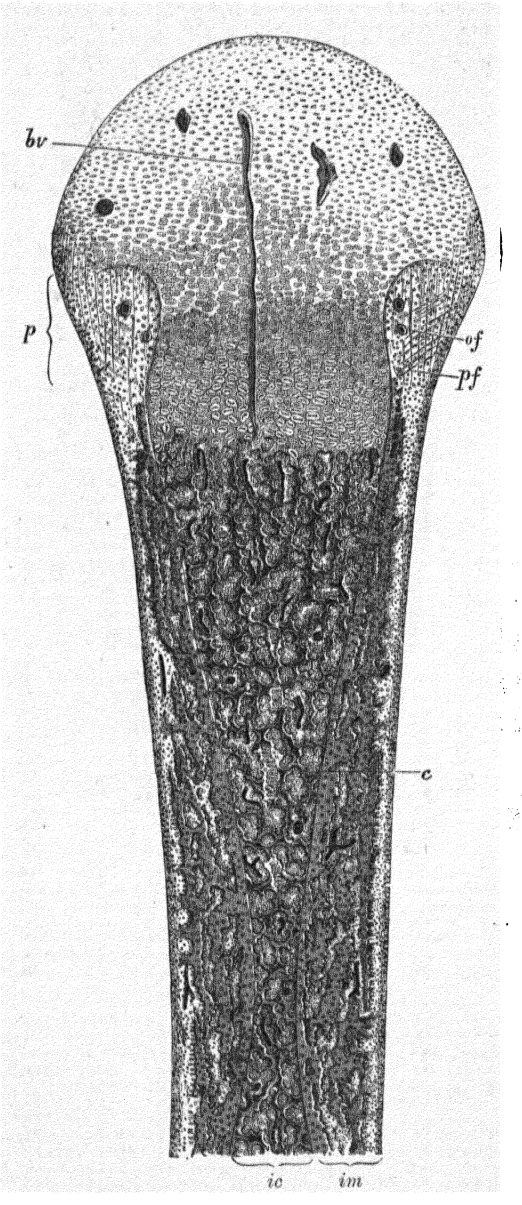
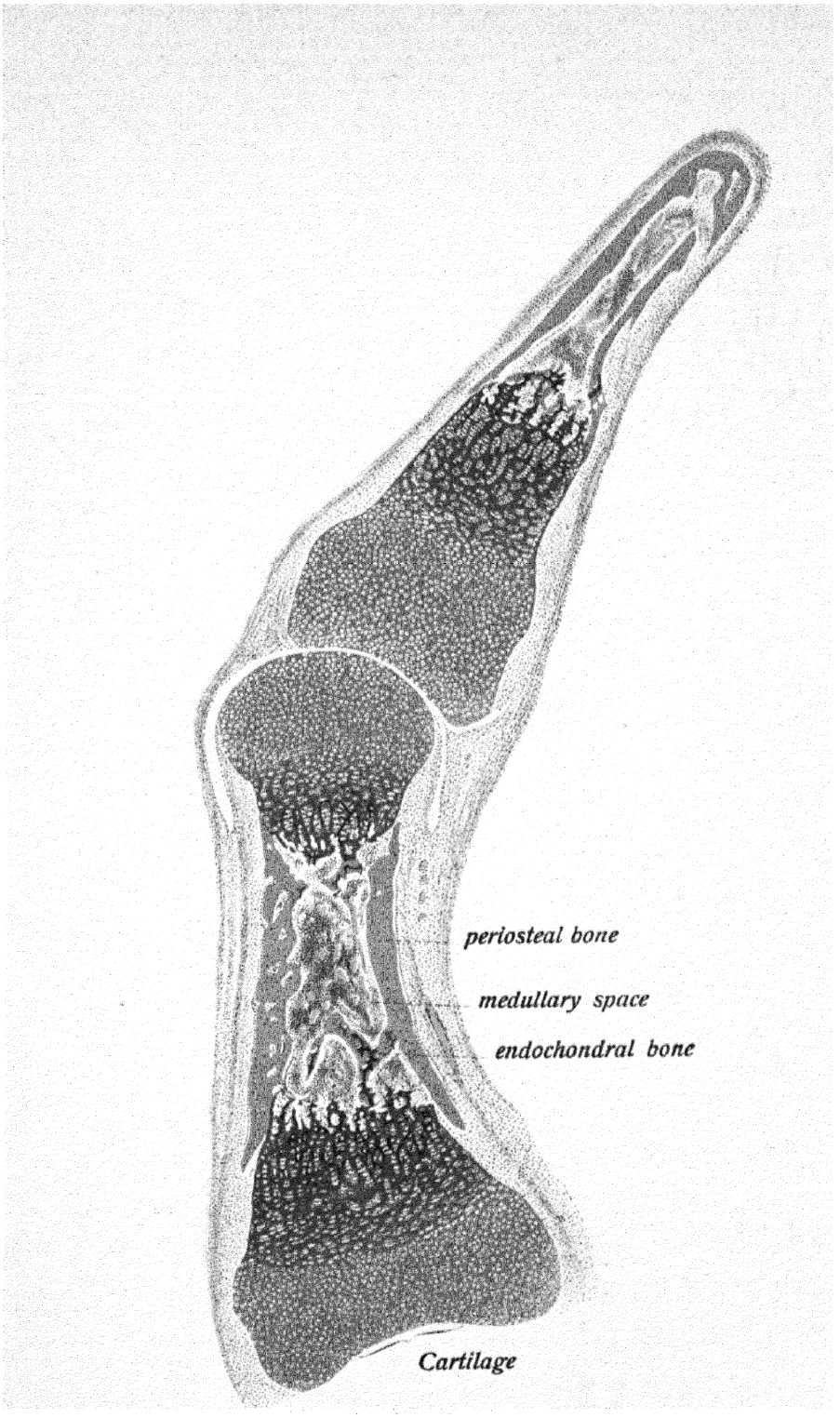


FIG. 248.—LONGITUDINAL SECTION THROUGH THE UPPER HALF OF THE DECALCIFIED HUMERUS OF A FŒTAL SHEEP, AS SEEN UNDER A MAGNIFYING POWER OF ABOUT 80 DIAMETERS. (Schäfer.)

ic, the part of the shaft which was primarily ossified in cartilage; what remains of the primary bone is represented as dark, enveloped by the clear secondary deposit. The areolæ of the bone are occupied by embryonic marrow with osteoblasts, and blood-vessels variously cut, represented as dark lines. One long straight vessel (*bv*) passes in advance of the line of ossification far into the cartilaginous head, most of the others loop round close to the cartilage. At one or two places in the older parts of the bone elongated groups of cartilage-cells (*c*) may still be seen which have as yet escaped absorption. *im*, the part of the bone that has been ossified in membrane, that is to say in the osteoblastic tissue under the periosteum. It is well marked off from the central portion, and is bounded, peripherally, by a jagged edge, the projections of which are indistinctly seen to be prolonged by bunches of osteogenic fibres. A row of osteoblasts covers the superficial layer of the bone. The subperiosteal layer is prolonged above into the thickening (*p*), which encroaches upon the cartilage of the head of the bone, and in which are seen, amongst numerous osteoblasts and a few blood-vessels, the straight, longitudinal osteogenic fibres (*of*), and some other fibres (*pf*) crossing them, and perhaps representing perforating fibres. The calcareous salts having been removed by an acid, the granular ossific deposit passing up between the rows of cartilage-cells is not seen in this specimen. Observe the general tendency of the osseous trabeculæ and the vascular channels between them to radiate from the original centre of ossification. This is found to prevail more or less in all bones when they are first formed, although the direction of the trabeculæ may afterwards become modified in relation with varying physiological conditions, and especially as the result of pressure in different directions.

from the centre of the shaft before any new deposition of bone takes place. This is the case in the phalanges (see Plate, and fig. 249).

The substance forming the original calcareous walls of the areolæ, and produced by calcification of the cartilaginous matrix, is decidedly granular, has a dark appearance, and is stained (after decalcification) by hæmatoxylin; the subsequent or ***secondary deposit*** on the other hand is transparent, and of a uniform, homogeneous



Section of terminal and subterminal phalanges of finger of 5-months foetus (Sobotta). Magnified 15 diameters. Haematoxylin-eosin.

aspect, staining with carmine. This secondary deposit begins to cover the granular bone a very short distance below the surface of ossification (see fig. 252), and, as already stated, increases in thickness farther down.

Close to the limit of advancing ossification, the blood-vessels terminate in capillary loops (see figs. 248, 252), which are often somewhat dilated. It was supposed by Ranvier that these vascular loops by their growth directly produce absorption of the cartilage, but it is more probable that this is caused by the agency of some of the cells which accompany the blood-vessels. The absorption of the walls of the primary areolæ (calcified cartilage-matrix) seems, in fact, to be effected by certain large multinucleated cells (fig. 252, *f*, *f*) which from their function are termed *osteoclasts*,[1] and which are found wherever bone is being eaten away: we shall return to them later. The secondary bone which thickens the walls of the marrow-spaces is no doubt formed by osteoblasts.

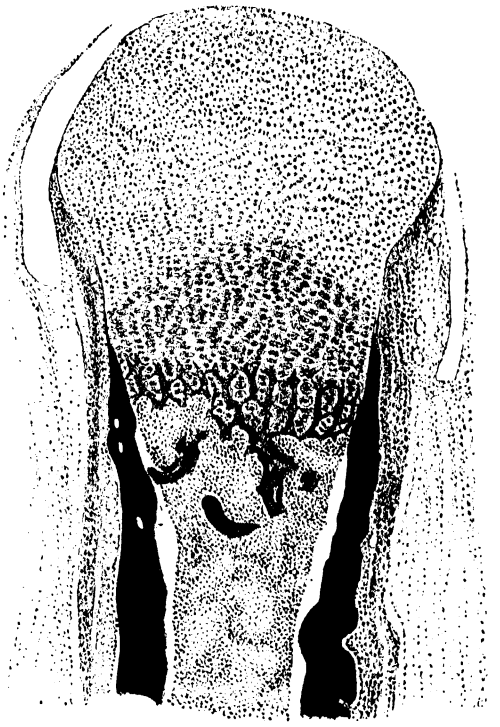


FIG. 249.—LONGITUDINAL SECTION THROUGH PART OF A PHALANX OF A SIX MONTHS' HUMAN EMBRYO. (Kölliker.)

The calcified cartilage is completely absorbed almost to the limit of advancing ossification. The darker substance on either side is the periosteal bone. The embryonic marrow has shrunk somewhat away from it.

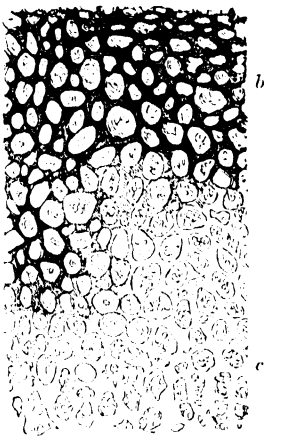


FIG. 250.—TRANSVERSE SECTION OF OSSIFYING CARTILAGE, INCLUDING A PORTION OF THE ADVANCING CALCIFICATION. FROM THE HUMERUS OF A FŒTAL SHEEP. (Sharpey.) Magnified 70 diameters.

c, cartilage, the cells of which are enlarged, but the matrix not yet calcified; *b*, primary osseous deposit in the cartilage-matrix, extending between the cartilage-cells and enclosing them in primary areolæ.

With regard to the destination of the cartilage-cells, two opposite views have been taken by histologists. According to one, which was that adopted by H. Müller, the capsules are opened by absorption, and the cells are converted, after undergoing division, into osteoblasts. According to the other, the cartilage-cells themselves become removed by absorption, and take no part, directly or indirectly, in the production of the secondary bone. The latter view of the matter was taken by Lovén, and it was also regarded by Sharpey as in all probability the more correct; it is now most generally adopted. For the line of demarcation between the cartilage-cells and the osteoblastic tissue is exceedingly abrupt (fig. 248), and the latter often, if not always, terminates either by a dilated vascular loop, or it may be by a developing capillary filled with blood-

[1] *Ostoclasts*, Kölliker.

corpuscles. The cartilage-cells close to the line of demarcation are generally much shrunken and irregular in form and show no evidence of division. It may be remarked that this is also the case when, as sometimes happens, they have not disappeared before the irruption of subperiosteal tissue, but persist untouched within the remains of the calcified cartilage-matrix (see fig. 248, *c*).

According to Dantschakoff,[1] some of the cartilage-cells disappear, whilst others divide mitotically, and the daughter-cells remain in the marrow as stroma-cells. But Retzius[2] was only able to find mitoses amongst the cartilage-cells at the ends of the cell-columns farthest from the advancing ossification—*i.e.* in the place where growth of cartilage is taking place.

As ossification advances towards the ends of the bone, the portion as yet

FIG. 251.—SMALL PORTION OF A SECTION OF DEVELOPING BONE, TAKEN AT THE JUNCTION OF THE BONE AND CARTILAGE, AND EXAMINED IN THE FRESH CONDITION. (Sharpey.) Magnified about 140 diameters.

a, *b*, two of the new-formed osseous tubes or areolæ, with a few shrunken cartilage-cells lying in them; *c*, cartilage-cells near the ossifying surface, large and clear and filling the cavities in the matrix; on the left of the figure some of them are shrunken.

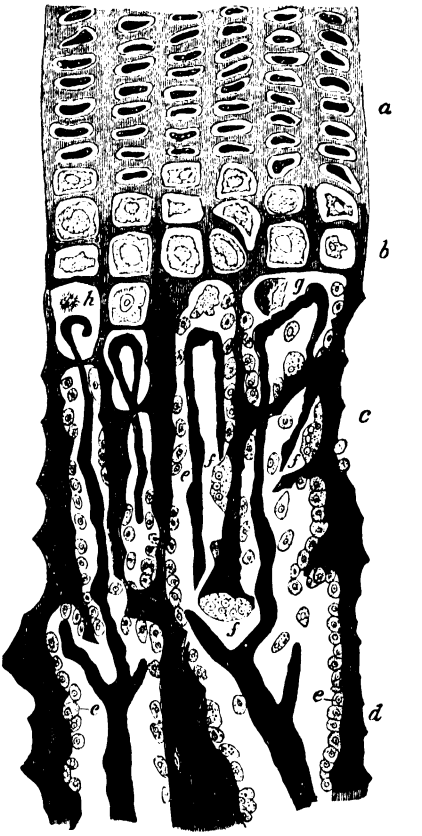


FIG. 252.—PART OF A LONGITUDINAL SECTION OF THE DEVELOPING FEMUR OF THE RABBIT. (From Klein and Noble Smith.) Drawn under a magnifying power of 350 diameters.

a, rows of flattened cartilage-cells; *b*, degenerating cartilage-cells close to the advancing bone: the matrix between them is already calcified; *c*, *d*, formed bone, the osseous trabeculæ being covered with osteoblasts (*e*), except here and there, where a giant-cell or osteoclast (*f*), is seen, eroding parts of the trabeculæ; *g*, *h*, cartilage-cells which have become shrunken and irregular in shape. From the middle of the figure downwards the dark trabeculæ, which are formed of calcified cartilage-matrix, are becoming covered with secondary osseous substance deposited by the osteoblasts. The vascular loops at the extreme limit of the bone are well shown, as well as the abrupt disappearance of the cartilage-cells.

cartilaginous continues to grow at the same time, expanding in every dimension. The part already osseous increases also in circumference; fresh bone being continually deposited in the subperiosteal membranous tissue outside that which is first formed on the surface of the cartilage (figs. 248, 253). The subperiosteal

[1] Arch. f. mikr. Anat. lxxiv. 1909.

[2] Biol. For. Forh. i. 1888.

deposit takes place in the same way as in the formation of a membrane bone. Bony spicules prolonged by osteogenic fibre-bundles (fig. 253) project out from the previously formed layer into the intervals between the blood-vessels. By the union of the spicules the vessels become in like manner enclosed in channels whose walls are gradually thickened by deposits of osseous substance, between which some of the osteoblasts are left behind as bone-corpuscles in lacunæ, whilst others remain within the meshes.

The question whether bone can be directly formed from cartilage by a transformation of the cartilage-matrix into osseous tissue, whilst the cartilage-cells become bone-corpuscles (metaplastic ossification), is one which has been much discussed ; it is probable that it should be decided in the negative. There is no evidence to show that true bone is formed in any other way than through the agency of osteoblasts.

The first formed bony tissue is different in its general appearance from the bony tissue of the adult, being reticular and not regularly lamellar, and, for a long while, even the shafts of the long bones are rather cancellated than compact in their texture. The more obviously lamellated condition does not begin to appear until about the sixth month after birth, when the periosteum deposits a succession of entire lamellæ around the embryonic bone. The blood-vessels which pass from the periosteum into the bone pierce these circumferential lamellæ, and spaces become absorbed around the vessels, the appearance known as *Haversian spaces* being produced (see p. 152). The Haversian canals of compact bone become formed later, after such absorption has taken place around the blood-vessels, the absorption being succeeded by a re-deposition of concentric lamellæ within the Haversian spaces thus formed.

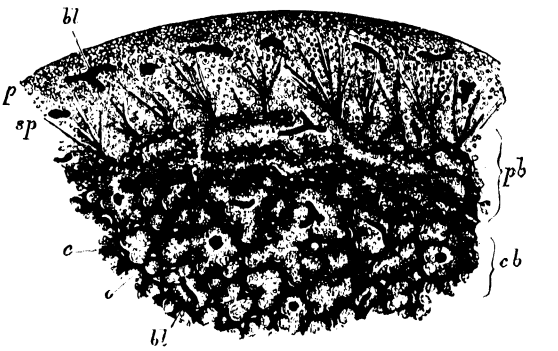


FIG. 253.—PART OF A TRANSVERSE SECTION OF A DEVELOPING LONG BONE, RATHER MORE ADVANCED THAN THAT REPRESENTED IN FIG. 248, AND UNDER A HIGHER MAGNIFYING POWER. (Schäfer.)

cb, endochondral bone which began as a calcification of the cartilage-matrix, parts of which still remain (*c*) covered over by secondary osseous deposit; *o*, secondary areolæ, occupied by vessels, fœtal marrow, and osteoblasts; *pb*, periosteal bone deposited in the form of irregular trabeculæ, prolonged externally by bony spicules passing into bunches of osteogenic fibres. These, which are everywhere covered with osteoblasts, become lost in the external fibrous layer of the periosteum, *p*; *bl*, *bl*, blood-vessels variously cut.

Immediately before the occurrence of the lamellar deposition under the periosteum just referred to, the young bone undergoes a process of absorption from the inside. The marrow canal becomes thereby enlarged, and the marrow spaces, particularly those near the marrow canal, partaking of this absorption and enlargement, the result is that at about this period there is less bony matter in a section of the shaft than there was immediately before. To the change in question Schwalbe has given the name 'osteoporosis.' It is followed by a re-deposition of osseous lamellæ both on the wall of the medullary canal and on the walls of the marrow spaces of the embryonic osseous tissue.

Since the cartilage grows in every dimension by interstitial expansion, the bone which is invading it (*endochondral bone*) extends over a gradually enlarging area as the ossification advances. It is narrowest near the centre of the shaft where the process began, and widens gradually towards the ends ; it has thereforesomewhat of an hour-glass shape (fig. 248, *i.c.*). The

cylindrical form of the shaft is maintained, however, by the thickness of the periosteal bone being greater at the centre (where the deposition of bone first began, and has been longest proceeding) than at the ends. From this part it gradually diminishes to a thin layer immediately investing that part of the cartilage into which the calcification is extending, so that the intramembranous subperiosteal ossification on the outside may be said closely to accompany, even to precede, the calcification of the cartilage in the interior. Either this investment of periosteal bone, or the calcification of the cartilage, seems to hinder the lateral expansion of that part of the cartilage in which the calcification is proceeding; but immediately beyond, the interstitial expansion mentioned takes place. By the time that the ossification has advanced to the extremities of the shaft, the enlarged and expanded end of the cartilage has extended itself over the subperiosteal layer, so that this, with the accompanying osteoblastic tissue, now seems to lie

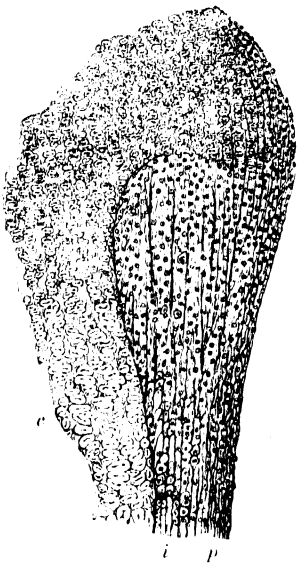


FIG. 254. LONGITUDINAL SECTION THROUGH THE PERIOSTEAL THICKENING OF A BONE AT ABOUT THE SAME STAGE OF DEVELOPMENT AS THAT REPRESENTED IN FIG. 248. (Schäfer.)

c, cartilage with the cells in rows; the tissue of the periosteal thickening is sharply marked off from it except near the surface; *p*, outer layer of the periosteum; *i*, inner layer of the periosteum or subperiosteal tissue, with osteogenic fibres and osteoblasts. One or two blood-vessels are observed cut across.

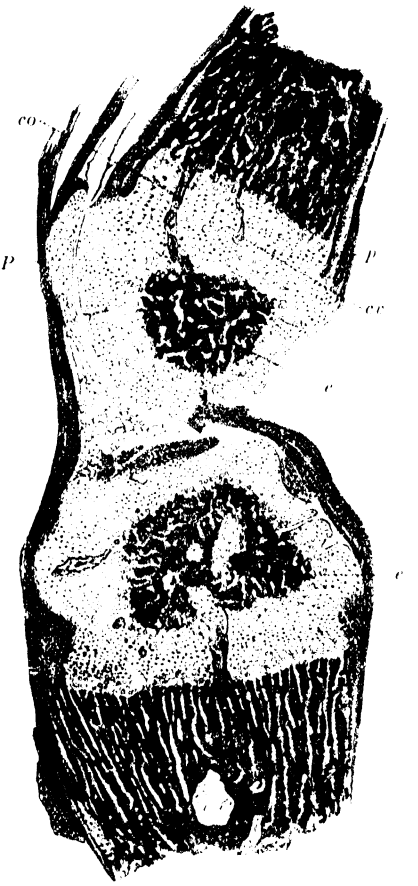


FIG. 255.—SECTION THROUGH KNEE-JOINT OF EIGHT-DAY RABBIT. (A. Bidder.)

co, canal carrying osteoblastic tissue from the diaphysis of the femur to its epiphysis; *cv*, vascular canal in cartilage; *p*, periosteal bone; *c*, epiphysis in end of femur; *c'*, epiphysis in head of tibia, containing an island of unossified cartilage; *P*, cartilaginous patella.

in a groove or notch (fig. 248, *p*) in the cartilaginous head of the bone (Ranvier). This groove is filled with the same tissue as that which underlies the rest of the periosteum—namely, a vascular tissue with branched cells and osteoblasts and osteogenic fibres. The latter are prolonged from the periosteal bone, and have for the most part a longitudinal direction (fig. 254). The tissue which fills this periosteal notch appears to become gradually converted by a metaplastic process into cartilage in the same way as the superficial part of a rib cartilage is formed by conversion of the deeper layers of the perichondrium (see p. 136). Thus, besides the interstitial growth and expansion of the cartilaginous end, there is a constant new formation of cartilage going on at its surface.

Formation of epiphyses.—Blood-vessels extend from the newly formed osseous tissue of the shaft beyond it into the cartilage where the epiphysis is to appear. The vessels are lodged in excavations or branching canals in the cartilage (fig. 248, *bv*; fig. 255, *co*), which also contain osteoblasts. Other nutrient canals enter the cartilage, and conduct vessels into it either directly from the perichondrium or from the ossifying shaft, but these are not concerned with its ossification.[1] The formation of osseous tissue begins in the extremities of the bone from one or more independent centres, and extends from those points through the epiphysial

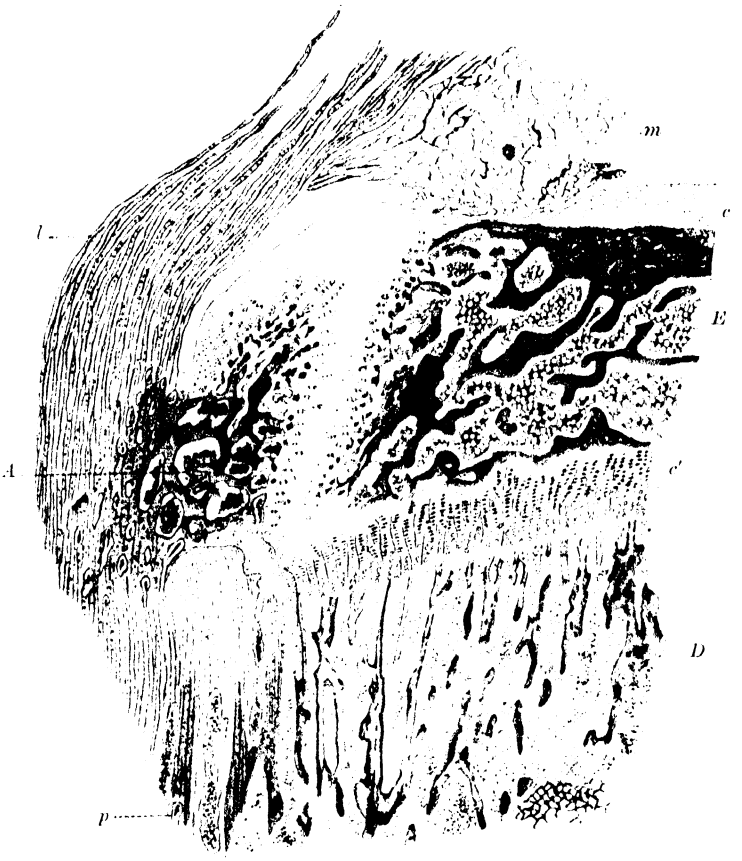


FIG. 256.—SECTION OF UPPER END OF TIBIA OF A HALF-GROWN RABBIT. (A. Bidder.) Drawn under a magnifying power of 30 diameters, but represented less magnified.

E, epiphysis; *A*, apophysis; *D*, diaphysis; *l*, ligamentum patellæ; *c*, articular cartilage; *c'*, intermediate cartilage; *p*, periosteal bone of diaphysis; *m*, ligamentum mucosum.

cartilage, leaving, however, a superficial layer of it unossified, which permanently covers the articular ends of the bone (fig. 256, *c*). Except on the side which is turned towards the advancing ossification of the shaft, the cartilage-cells do not become arranged in long columns in the manner described for the ossification of the shaft. The developing bone of the epiphysis, which is purely endochondral and owes none of its substance directly to subperiosteal ossification, is marked off fairly sharply from the adjacent cartilage (figs. 255, 256). Apophyses are formed from distinct osseous centres similar to those which form the epiphyses (fig. 256, *A*);

[1] A. Bidder, Arch. f. mikr. Anat. lxviii. 1906.

they also receive their osteoblasts by vascular canals which penetrate into them from the marrow spaces of the diaphysis. The *epiphyses* formed in the above manner are separated, as long as growth continues, from the shaft or *diaphysis* by an intervening portion of cartilage, which is constantly growing; but this is at last ossified, and the bone is then consolidated. Should the intervening cartilage become prematurely calcified or materially injured by disease, or if it is removed by the knife, the growth of the bone in length at the injured end ceases.[1]

The ossification of the short bones is also chiefly endochondral, but in the vertebræ the first ossification of the arches is periosteal, and there is also periosteal bone formed at the posterior surface of the vertebral body. Other short bones, such as those of the wrist and ankle, are almost purely endochondral. The osteoblasts which are to form the bone are carried in along vascular canals at one or more points from the perichondrium.[2]

A remarkable exception to the ordinary mode of ossification of the cartilage-bones occurs in the terminal phalanges of the digits. In these the calcification of the cartilage begins at the distal extremity or tip, and the subperiosteal deposit appears simultaneously at the same point, and forms a cap-like expansion over the end of the phalanx. The irruption of the osteoblastic tissue also first occurs at this place. The expanded portion of the phalanx which bears the nail is formed independently of cartilage.[3]

Growth and absorption of bone.—The time of final junction of the epiphyses is different in different bones; in many it does not arrive until the body has reached its full stature. Meanwhile, as above described, the bone increases in length by the ossification continuing to extend into the intervening cartilage, which goes on growing at the same time; and it appears that in the part of the shaft already ossified little or no elongation takes place by interstitial growth. This is shown by an experiment first made by Hales and afterwards by Duhamel and by John Hunter, in which, two or more holes being bored in the growing bone of a young animal at a certain measured distance from each other, they are found after a time not to be farther asunder, although the bone has in the meanwhile considerably increased in length. On the other hand, if one hole be bored in the epiphysis and another in the shaft, they become distinctly removed from one another with the growth of the bone.

Both Hales and Duhamel in experimenting on the growing tibia of a chicken, observed that the elongation was much greater at the upper end. Humphry showed that in the arm-bones the elongation is greater at the end farthest from the elbow-joint, and in the leg-bones at the end which is next the knee-joint.

In the human subject, between the first and the fourth or fifth years, the long bones grow chiefly in length, scarcely at all in thickness.

The shaft of a long bone increases in circumference by deposition of new bone on its external surface, while at the same time its medullary canal is enlarged by absorption from within. This can be determined by two methods of experimenting. Thus, in the first place, a ring of silver or platinum put round the wing-bone of a growing pigeon, becomes covered with new bone from without, and the original bone included within it gets thinner, or, according to Duhamel, who first made the experiment, is entirely removed, so that the ring comes to lie within the enlarged medullary canal. Secondly, madder given to an animal along with its food tinges those parts in which deposition of new bone is taking place. The earth of bone appears to act as a sort of mordant, uniting with and fixing the colouring matter; and, as in this way the new osseous growth can be readily distinguished from the old, advantage was taken of the fact by Duhamel, and afterwards by Hunter, in their inquiries as to the manner in which bones increase in size.

[1] For an account of the structural changes which accompany such injury, see Jahn, Morph. Arbeiten, i.

[2] For many details regarding the ossification of different bones, see Bidder, *op. cit.*

[3] F. A. Dixey, Proc. Roy. Soc. 1880.

By their experiments it was shown that when madder is given to a young pig for some weeks, the external part of its bones is reddened, proving that the new osseous matter is laid on at the surface of that previously formed. Again, it was found that, when the madder is discontinued for some time before the animal is killed, an exterior white stratum (the last formed) appears above the red one, whilst the internal white part, which was situated within the red, and had been formed before any madder was given, has become much thinner, showing that absorption takes place from within. In this last modification of the experiment also, as noted by Hunter, a transverse red mark is observed near the ends of the bone, beyond which they are white; the red part indicating the growth in length during the use of the madder, and the white beyond, that which has taken place subsequently—thus showing that the increase in length is caused by the addition of new matter to the extremities. Madder administered while the process of formation of the concentric lamellæ of the Haversian systems is going on, colours the interior and recently formed laminæ, so that in a cross-section the Haversian apertures appear surrounded with a red ring.

Flourens and Kölliker repeated and varied these madder experiments. Kölliker, in addition, carefully investigated the microscopic appearances observed in the process of absorption. From the results of his researches (which were in part anticipated by those of Lovén), it would seem, as already indicated, that the process is essentially dependent on the presence of large multinucleated cells, by him termed 'ostoclasts,' similar in general appearance to the 'myeloplaxes' of marrow, which excavate, in the part which is undergoing absorption, small shallow pits (*foveolæ of Howship*), in which also they lie. These pits occur wherever absorption is proceeding, and it is to them that the festooned appearance of the Haversian spaces (p. 152) is due. The ostoclasts or *osteoclasts* (figs. 257, 258) vary in size, but are always many times larger than

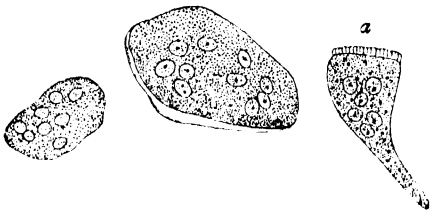


FIG. 257.—THREE OSTEOCLASTS FROM ABSORPTION-SURFACES OF GROWING BONE. (Kölliker.) 400 diameters.

a, with thickened striated border.

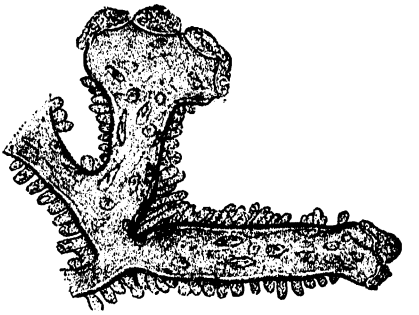


FIG. 258.—BONY TRABECULA FROM THE LOWER JAW OF A CALF-EMBRYO WITH HOWSHIP'S FOVEOLÆ AND OSTEOCLASTS AT THE ENDS WHERE ABSORPTION IS PROCEEDING AND OSTEOBLASTS COVERING THE SIDES WHERE BONE IS BEING DEPOSITED. (Kölliker.)

the osteoblasts: in shape they are spheroidal or flattened, usually with an even outline. Their substance is granular in appearance, and they each contain from two to ten clear round nuclei, but this number may be considerably exceeded. The osteoclasts have frequently on the side by which they are in contact with the bone a clear striated border (fig. 257, *a*), somewhat similar to the striated base of the columnar epithelium-cells of the intestine. The osteoclasts were regarded by Kölliker both as in the first instance derived from and as eventually breaking up into osteoblasts. Osteoclasts are found in connexion with the roots of the milk-teeth where these are undergoing absorption to make way for the permanent set. They were also noticed by Billroth to produce absorption in ivory pegs which had been driven into bone. What genetic relation, if any, they bear to the megakaryocytes or giant-cells of marrow is uncertain. Multinucleated giant-cells are not associated with bone-absorption alone, but occur in lymph-glands, in the spleen and elsewhere. The osteoclasts probably represent a specific form of such cells.

Growth and moulding of bones.—The changes of shape which the bones undergo in the process of growth, as well as any changes which may occur in them in adult life, are all produced in the same manner as the increase of size—that is to say, not by interstitial growth and expansion of the substance of the bone in one direction more than in another, but by a deposition of new bone by osteoblasts at some parts and a simultaneous absorption by osteoclasts at others; whilst in other places again neither absorption nor deposition is occurring—just as a modeller corrects his work by laying clay on at one part whilst removing it at another.

Since during the growth of bones their shape is becoming continually altered, it follows that in nearly all bones during growth there are parts of the bone which are in process of absorption, and others which are in process of more active deposition than the rest. In most of the long bones, towards their ends, absorption is generally taking place at one side and deposition on the opposite side. The former process may, and probably does, proceed to such an extent that the endochondral bone may be laid bare or even partially absorbed, but after a while, when the absorption has ceased at any part, re-deposition may take place, the osteoclasts being replaced by osteoblasts, and successive circumferential lamellæ being deposited by these.[1]

A large amount of variation is met with in the different bones of the skeleton in the relative extent to which they are formed in cartilage and in the subperiosteal tissue respectively. Whereas in some, such as the shafts of the long bones of the limbs, the endochondral bone is almost entirely removed, as we have seen, and periosteal bone substituted for it; in others, such as the bodies of the vertebræ, and the epiphyses of the long bones, a much larger proportion of the adult bone has had an endochondral formation. In one or two bones or parts of bones again, which may be said to have typically an intramembranous origin, cartilage may, according to Kassowitz,[2] become developed under the periosteum at certain places, and the continuation of the ossification may occur in this secondarily developed cartilage. This is said to be the case with the clavicle, the foundation of which is laid in membrane, but which is found at a later period to have cartilaginous ends; and also with the halves of the lower jaw-bone, which develops cartilaginous ends both towards the symphysis and towards the articular and coronoid processes, these cartilaginous ends being altogether distinct from the cartilage of Meckel, which at those parts is unconnected with the jaw-bone, although at another place (in front) it is involved in the ossification of the mandible.[3] Kassowitz has described similar cartilaginous developments in connexion with the subperiosteal tissue at the tuberosity of the radius and the spine of the scapula. They are merely an extension of the process which normally goes on at the ossification groove (p. 166).

Regeneration of bone.—In the reunion of fractured bones, osseous matter (*callus*) (often preceded by a new formation of cartilage) is formed between and around the broken ends, connecting them firmly together; and when a portion of bone dies, a growth of new bone very generally takes place to a greater or less extent, and the dead part is thrown off. The importance of the periosteum in the process of repair is shown by the fact that if a portion of periosteum be stripped off, the subjacent bone will be liable to die and exfoliate; conversely, if a large part or the whole of a bone be removed and the periosteum at the same time be left intact, the bone will, in a great measure, be regenerated. Osseous formation will even occur in connexion with portions of periosteum which have been stripped away from the bone itself and intertwined amongst the muscles of the part, or even with portions that have been entirely removed from a bone and transplanted to a soft tissue (Ollier).

The marrow-tissue assists in the regeneration of bone, especially in young bone, where the osteoblasts still retain a very active osteogenic function, and largely assist in the production of the first-formed new bone or 'callus.' In the adult such participation of the marrow in the regeneration of bone is less easy to prove, and, although it seems undoubtedly to occur, the bone-forming activity is much less than that of the young subject, in which small pieces of the bone itself can be transplanted. W. McEwen succeeded in renewing the greater part

[1] For special details of this modelling process as it is met with in the different bones of the skeleton, the reader is referred to Kölliker's memoir: Die normale Resorption des Knochengewebes, Leipzig, 1873; also Heuberger, Diss. Würzburg, 1874.

[2] Medic. Jahrb. 1879–80.

[3] Cf. J. Schaffer, Arch. f. mikr. Anat. xxxii. 1888.

of the excised humerus of a child by the introduction, at successive periods, of portions of fresh bone removed from another patient.[1]

Historical.—It was long supposed that all the bones of the skeleton were preceded by and deposited in cartilage. Nesbitt, however, showed in 1736 that some of the flat bones were formed independently of cartilage, and he further maintained that the cartilage is 'entirely destroyed'; he therefore considered it to be a mere temporary substitute; but the steps of the process of intracartilaginous ossification as now traced with the aid of the microscope were unknown to him, and it was not until the year 1845 that the manner of formation of bone and the extensive replacement of the primarily ossified cartilage by new bone formed in membrane was made clear by the researches of Sharpey, who published the results of his work in the fifth edition of Quain's Anatomy.

[1] Proc. Roy. Soc. xxxii. 1881. The previous history of the subject will be found in this paper.

MUSCULAR TISSUE.

Muscular tissue is that by means of which the active movements of the body are produced. It consists of fibres collected into muscles, generally of a red colour, and in this form it is familiarly known as the flesh of animals. The fibres, from the characteristic appearance which they exhibit under the microscope, are usually known as 'cross-striped' or 'striated'; they are many of them under the control of the will, and are hence often spoken of as 'voluntary' muscles. Those which are attached to and serve to move parts of the skeleton are also known as 'skeletal' muscles. Another kind of muscular tissue is disposed around the blood-vessels and most of the hollow viscera, often forming a distinct coat or coats to these. In this kind the fibres do not exhibit the same cross-striated appearance, and they have therefore been termed in contradistinction 'smooth,' 'plain,' or 'non-striated' muscular fibres. Most of these are entirely withdrawn from the control of the will, and they are therefore also termed 'involuntary.' The muscular tissue of the heart, although having a cross-striated appearance, differs in many respects from that of the skeletal muscles: it is therefore described separately under the term 'cardiac' muscular tissue. Muscular fibres are endowed with contractility, by virtue of which they shrink or contract more or less rapidly under the influence of certain causes which are capable of exciting or calling into play the property in question, and which are therefore named stimuli.

STRUCTURE OF CROSS-STRIATED OR SKELETAL MUSCLES.

The skeletal muscular fibres are for the most part gathered into distinct muscles of various sizes and shapes, but generally elongated, and furnished with tendons at each extremity, by which they are fixed to the bones.

The fibres are in the first place collected into bundles, of greater or less thickness, named *fasciculi* (*lacerti*) (fig. 259). The fibres are parallel in the fasciculi; and the fasciculi extend continuously from one terminal tendon to the other, except in a few instances, like the rectus muscle of the abdomen and the digastric of the

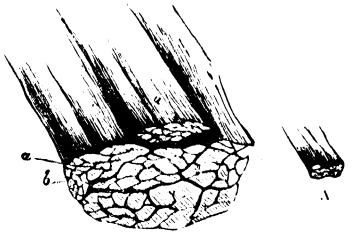


FIG. 259.—A, SMALL PORTION OF MUSCLE, CONSISTING OF LARGER AND SMALLER FASCICULI, NATURAL SIZE; B, THE SAME MAGNIFIED 5 DIAMETERS, SHOWING A TRANSVERSE SECTION. (Sharpey.)

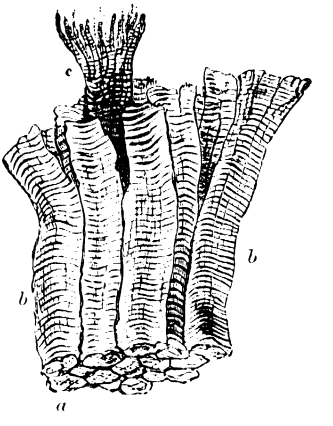


FIG. 260.—A FEW MUSCULAR FIBRES, BEING PART OF A SMALL FASCICULUS, MORE HIGHLY MAGNIFIED. (Sharpey.)

b, *b*, fibres: *a*, end view; *c*, a fibre splitting up into longitudinal elements.

inferior maxilla, in which the fleshy part is interrupted by interposed tendinous tissue. The fasciculi also very generally run parallel, and, although in many instances they converge towards their tendinous attachment with various degrees

of inclination, yet in the voluntary muscles they do not interlace with one another.

An outward investment or sheath of areolar tissue (*epimysium*) surrounds the entire muscle, and sends partitions inwards between the fasciculi, furnishing to each of them a special sheath (*perimysium*). The areolar tissue extends also between the fibres (*endomysium*), but does not afford to each a continuous investment, and therefore cannot be said to form sheaths for them. Every fibre, it is true, has a proper sheath; but this, as will be afterwards explained, is not composed of areolar tissue. The perimysium contains elastic as well as white fibres; but the elastic element is found principally in its investing, as distinguished from its penetrating, portion. In the endomysium numerous plasma-cells are found. The chief uses of the areolar tissue are to connect the fibres and fasciculi together, and to conduct and support the blood-vessels and nerves in their ramifications

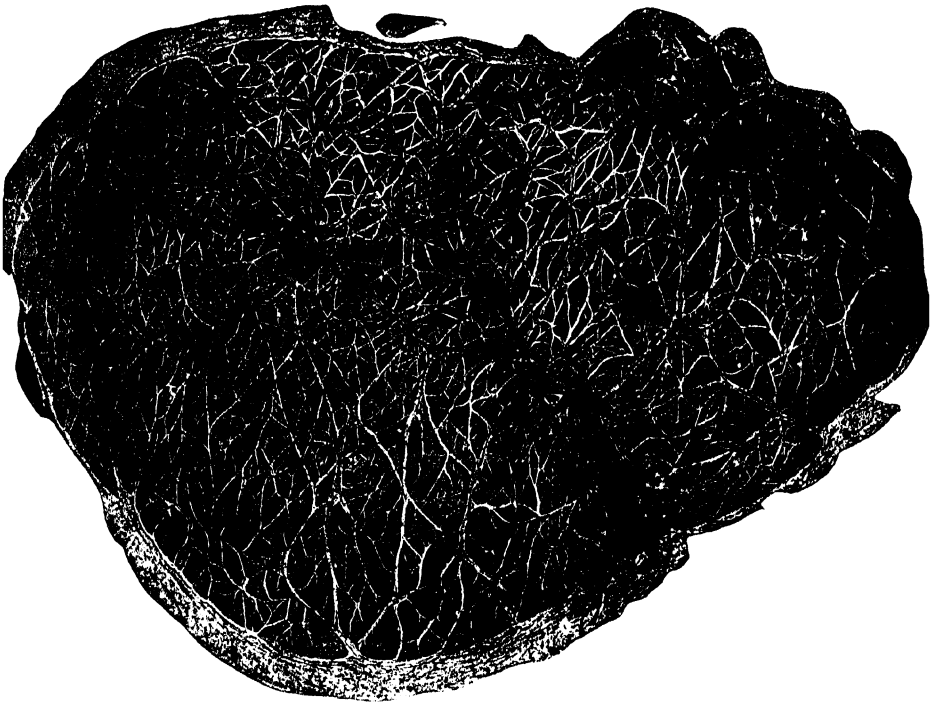


FIG. 261.—SECTION OF SARTORIUS MUSCLE (HUMAN). (M. Heidenhain.) Magnified 4 diameters. The epimysium is well seen and the division of the muscle into larger and smaller fasciculi.

between the parts. The relation of these different subdivisions of a muscle to each other, as well as the shape of the fasciculi and fibres, is well shown in transverse section (fig. 261).

The fasciculi are of a prismatic figure, and their sections have therefore an angular outline. The number of fibres of which they consist varies, so that they differ in thickness, and a large fasciculus may be divisible into two or three orders of successively smaller bundles, but of no regularly diminishing magnitude. Some muscles have large, others only small fasciculi; and the coarse or fine texture of a muscle, as recognised by the dissector, depends on this circumstance. The length of the fasciculi is not always proportioned to the length of the muscle, but depends on the arrangement of the tendons to which their extremities are attached. When the tendons are limited to the ends of a long muscle, as in the sartorius, the fasciculi, having to pass from one extremity to the other, are of great length; but a long muscle may be made up of a series of short fasciculi attached obliquely to one or both sides of a tendon, which advances

some way upon the surface or into the midst of the fleshy part, as in the instances of the rectus muscle of the thigh, and the tibialis posticus. Many short fasciculi connected thus to a long tendon produce by their combined operation a more powerful effect than a few fasciculi running nearly the whole length of the muscle; but by the latter arrangement the extent of motion is greater, for the points of attachment are moved through a longer space.

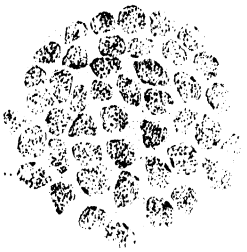


FIG. 262.—FIBRES OF RECTUS SUPERIOR OF EYE OF A MUSCULAR SUBJECT, SEEN IN SECTION. (Halban.) Magnified about 170 diameters.

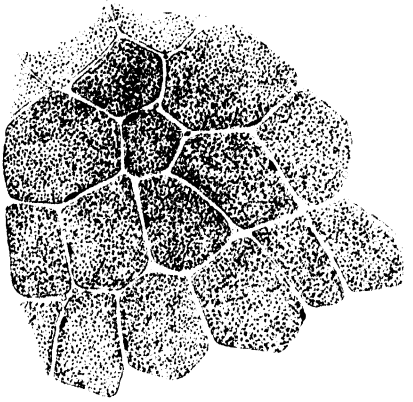


FIG. 263.—FIBRES OF GLUTEUS MAXIMUS OF A MUSCULAR SUBJECT, SEEN IN SECTION. (Halban.) Magnified about 170 diameters.

Fibres: their figure and measurement.—In shape the fibres are cylindrical, or prismatic with rounded angles. Their diameter varies greatly even in each muscle, although for the most part a prevailing standard is found to exist in every muscle. The largest fibres in human muscles are nearly 0·1 mm. ($\frac{1}{250}$ inch) in diameter; the smallest are only about one-tenth that width.

FIG. 264.—A BRANCHED MUSCULAR FIBRE FROM THE FROG'S TONGUE. (Kölliker.) Magnified 350 diameters.

Such muscles as those of the eye are mainly composed of small fibres (fig. 262), and the muscles of the limbs mainly of large ones (fig. 263), but there is no constant relation between the size of a muscle and that of its fibres. The fibres tend to be thicker in the male than in the female and are thicker in muscular subjects than in others (for the same muscles). The differences between different muscles are not evident in infancy, but manifest themselves in the process of growth.[1]

The fibres composing a muscle are of limited length, generally not exceeding 36 mm. (1·5 inch); and accordingly in a long fasciculus a fibre does not reach from one tendinous attachment to the other, but ends with a rounded or tapering extremity, invested with its sarcolemma, and cohering with neighbouring fibres. Unless when either is fixed to a tendon, both extremities of the fibre terminate in the way described, so that it has a long cylindrical shape. In some muscles—*e.g.* the sartorius—

[1] G. Schwalbe, Deutsche med. Wochenschr. 1890; Mayeda, Zeitschr. f. Biol. 1890; also Schwalbe and Mayeda, *ibid.* 1891. For statistics regarding the diameter of the fibres of different muscles, see Halban, Anat. Hefte, iii. 1894.

fibres have been measured which are much longer than the dimensions above given.

Generally speaking, the fibres neither divide nor anastomose; but this rule is not without exception. In the tongue of the frog the muscular fibres (fig. 264) as they approach the surface divide into numerous branches, by which they are attached to the under-surface of the mucous membrane (Kölliker). The same has been seen in the tongue of man and various animals; and the fibres of the facial muscles of mammals divide in a similar manner where they fix themselves to the skin (Busk and Huxley).[1]

Structure of the fibres; sarcolemma.—A muscular fibre may be said to consist of a soft substance enclosed in a tubular sheath. The latter is named the *sarcolemma*. It consists of transparent and apparently homogeneous membrane, and, being comparatively tough, will sometimes remain entire when the included muscular substance is ruptured, as represented in figs. 265, 266. It is closely applied to the substance of the fibre and follows all its changes of shape. It is especially well seen in fish and amphibia, for

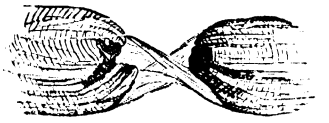


FIG. 265.—MUSCULAR FIBRE OF FISH. SUBSTANCE OF FIBRE RUPTURED SO AS TO EXHIBIT SARCOLEMMA. (Bowman.)

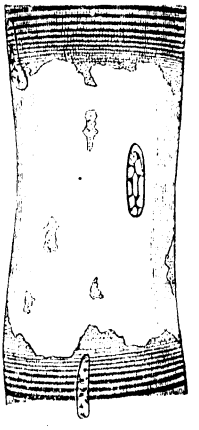


FIG. 266.—SARCOLEMMA OF MAMMALIAN MUSCLE. (Schäfer.) Highly magnified.

The fibre is represented at a place where the muscular substance has become ruptured and has shrunk away, leaving the sarcolemma (with a nucleus adhering to it) clear. The fibre had been treated with serum acidulated with acetic acid.

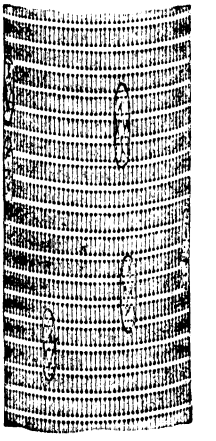


FIG. 267.—MUSCULAR FIBRE OF A MAMMAL EXAMINED FRESH IN SERUM. (Schäfer.) Highly magnified.

This figure was drawn with the surface layer of muscular substance accurately focussed, the lateral portions having been added by gradually sinking the focus.

The nuclei are seen on the flat at the surface of the fibre, and in profile at the edges.

in these it is thicker and stronger than in mammalian muscle, in which it is more difficult to render evident but nevertheless always exists (fig. 266). Nuclei are found on the inner surface of the sarcolemma, but these belong rather to the contractile substance than to the enclosing membrane, and will be afterwards more fully described.

Cross-striated substance.—When viewed by transmitted light even with a comparatively low power of the microscope, the fibres, which are clear and pellucid in aspect, appear marked with parallel stripes or bands alternately light and dark passing across them with great regularity (fig. 267), and this not only at the surface

[1] Transl. of Kölliker's Gewebelehre.

but, as may be seen by altering the focus of the microscope, throughout its substance also. In a moderately extended fibre about eight or nine dark and as many light bands may be counted in the length of 0·025 mm. ($_{1}{}^{1}{}_{0}{}^{1}{}_{0}{}^{1}{}_{0}$ inch), which would make each complete stripe about 3 μ. But whilst this may be assigned as their usual measurement in human muscle, they are in different parts found to be much narrower, so that not infrequently there are twice as many in the space mentioned. This closer approximation always characterises contracted parts of the fibre. The cross-striped appearance is found in all the skeletal muscles; but it is not confined to them, for it is seen in cardiac muscle, and striped fibres are also found in other viscera, such as the pharynx and upper part of the gullet.

When the muscular fibres are deeply focussed, the appearance of the striæ becomes somewhat altered, and a fine line, often dotted, is seen passing across the middle of each light band (see fig. 268). This is termed *Dobie's line* (*disque mince, Zwischenscheibe, Z*), and it has been supposed to represent a membrane

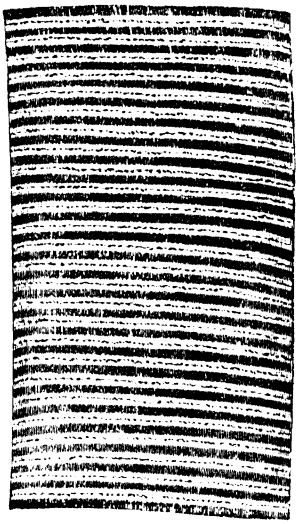


FIG. 268.—PORTION OF A HUMAN MUSCULAR FIBRE SHOWING DOBIE'S LINE IN THE MIDDLE OF THE CLEAR BAND. (Sharpey.)

FIG. 269. — SMALL PORTION OF A HUMAN MUSCULAR FIBRE TEASED INTO LONGITUDINAL FRAGMENTS. (Sharpey.) Magnified about 800 diameters.

a, *b*, *c*, larger and smaller groups of fibrils; *d*, ultimate fibrils.

stretching across the fibre and attached at the surface to the sarcolemma. The line is, however, not visible in the most superficial planes of the fibre, and although there certainly are membranes crossing the fibrils at about this situation (membranes of Krause), they are not seen in the intact fibres, but only when these are dissociated into fibrils or after they have been treated with certain reagents. There is reason to believe that the appearance of a dotted line in this situation in the fresh intact fibre is due to the peculiar optical conditions of the tissue.

A fine clear line is sometimes to be seen in the middle of each dark band. This was first noticed by Hensen, and is named the *line* or *disc of Hensen* (*Mittelscheibe, M*). In certain foci it is dark instead of light.

The proper substance of the fibre presents, besides the transverse bands, an appearance of longitudinal striation. On separating the fibres with needles, especially after hardening in alcohol, they may be broken up into fine longitudinal elements, single or in bundles, which run from end to end of the fibres (figs. 269, 270). These are the *fibrils*: the groups of fibrils have been termed *muscle-columns*

(Kölliker) or *sarcostyles*[1]; but these terms have also been applied to the individual fibrils. Each fibril appears to consist of a row of elongated rod-like cylindrical or prismatic darker particles, joined together end to end by a clearer substance and separated from one another laterally by a material termed *sarcoplasm*. The sarcoplasm in longitudinal view produces the appearance of fine lines, sometimes with varicosities or dots upon them (figs. 267, 271), running with great regularity along the fibre. It lies in larger amount between the groups of fibrils, and in transverse section takes on the appearance of a network. The rod-like darker parts of the fibrils form by their lateral juxtaposition the dark stripes, and the clearer substance which unites them longitudinally forms the light stripe; the darker parts of the fibril were termed *sarcous elements* by Bowman.[2]

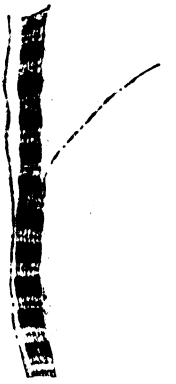


FIG. 270.—FRAGMENT OF CRAB'S MUSCLE, SPLITTING INTO FIBRILS. (Schäfer.) Magnified 600 diameters.

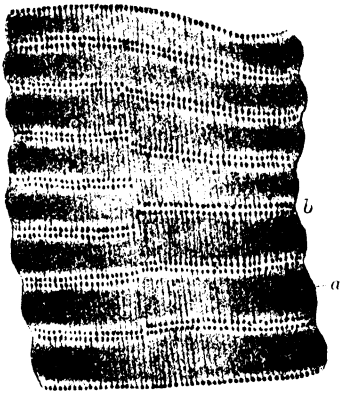


FIG. 271.—LIVING LEG-MUSCLE OF WATER-BEETLE (DYTISCUS MARGINALIS). (Schäfer.) Highly magnified.

a, dim stripe; *b*, bright stripe with rows of dots, which are enlargements or thickenings on the longitudinal septa of sarcoplasm. These septa are represented by the longitudinal lines. The continuity of these lines through the bright stripe is difficult to see in the fresh fibre, but after treatment with acid it becomes quite distinct (see fig. 272).

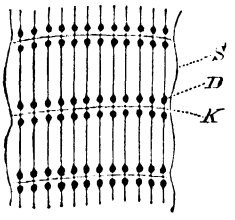


FIG. 272.—MUSCULAR FIBRE OF LEG OF VESPA VULGARIS AFTER SHORT TREATMENT WITH DILUTE FORMIC ACID. (Schäfer.)

S, sarcolemma; *D*, dot-like enlargement of sarcoplasm; *K*, Krause's membrane.

Under certain circumstances the fibres show a tendency to cleave across in a direction parallel to the bands, and even to break up into transverse plates or discs, which are formed by the lateral cohesion of the sarcous elements of adjacent fibrils. To make up such a disc, therefore, every fibril contributes a particle, which coheres with its neighbours on each side, and this with perfect regularity.

From a consideration of this fact Bowman was led to conclude the subdivision of a fibre into fibrils to be merely a phenomenon of the same kind as the separation into discs, only of more common occurrence, the cleavage in the latter case taking place longitudinally instead of transversely; accordingly, he came to the conclusion that the 'fibrillæ' have no existence as such in the fibre, any more than the discs; but that both the one and the other owe their origin to the regular arrangement of the particles of the fibre (sarcous elements)

[1] σάρξ, muscle; στῦλος, a column. Schäfer, Proc. Roy. Soc. xlix. 1891; Int. Monthly Journ. of Anat. and Physiol. viii. 1891.

[2] Phil. Trans. 1840.

longitudinally and transversely, whereby, on the application of a severing force, it cleaves in the one or in the other direction. That this conclusion was erroneous, however, is shown by the fact that a fibre can be easily dissociated into longitudinal elements after death even without the action of any reagents, but not into discs; and also by the fact that in certain muscular fibres (those which move the wings of many insects) a separation into fibrils can be obtained even in the living and contractile condition of the fibre. In these muscles, in consequence of the large amount of interstitial substance (sarcoplasm) between the fibrils, the fibre never under any circumstances cleaves across into discs.

According to J. Arnold, the glycogen of muscle is confined to the sarcoplasm. Holmgren has described a trophospongium [1] within the sarcoplasm of voluntary muscle, but its existence is denied by Arnold.[2]

If a transverse section of a muscular fibre (figs. 273, 274), or the surface of a separated disc, is examined with a high power, it appears to be marked out into small polygonal areas separated by fine lines which, in acid preparations, have the appearance of a network (fig. 275). The smallest of these areas, known as *Cohnheim's areas*, represent sections of muscle-columns, and the lines between them represent the intercolumnar substance or sarcoplasm. The lines of the network are usually coarser near the surfaces of such a disc, because, as will immediately

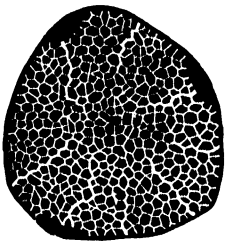


FIG. 273.

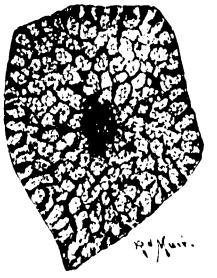


FIG. 274.

FIG. 275.

FIG. 273.—TRANSVERSE SECTION OF A MAMMALIAN MUSCULAR FIBRE SHOWING COHNHEIM'S AREAS. (Schäfer.)

Alcohol preparation. Three nuclei are visible under the sarcolemma.

FIG. 274.—TRANSVERSE SECTION OF LEG-MUSCLE FIBRE OF AN INSECT, STAINED WITH GOLD CHLORIDE. (Schäfer.)

The sarcoplasm is here stained, and appears in the form of a network, in the meshes of which lie the sections of the fibrils. Notice the mottled appearance of the sections of the sarcostyles or fibrils, indicating a porous structure, as in the wing-fibrils (see fig. 283). The central protoplasm (with a nucleus) is also evident. (From a photograph.)

FIG. 275.—A SEPARATE DISC FROM A PREPARATION LIKE THAT SHOWN IN FIG. 277, SEEN PARTLY FROM THE SURFACE AND EXHIBITING THE SARCOPLASM WITH WHAT APPEARS TO BE A RETICULAR ARRANGEMENT. FROM LEG-MUSCLE OF PTEROSTICHUS NIGER. (Schäfer.)

be explained, the sarcoplasm is increased in amount at regular intervals, corresponding with constrictions in the fibrils; by alteration of the focus, however, the appearance of a network can be made out through the whole thickness of the disc.

Although such a network as the one which is shown in fig. 275, with polygonal meshes, is characteristic of the transverse section of the muscular fibres of vertebrates and of those of some insects, the fibres of many insects have the appearance in transverse section which is shown in fig. 276, in which the lines of the apparent network—*i.e.* of the sarcoplasm—are disposed radially, and the muscle-columns also therefore have a radial disposition and a flattened shape. They are, however, subdivided by secondary septa of sarcoplasm (fig. 276A). Different muscles show considerable variety as to the conformation of the sarcostyles and the amount

[1] Arch. f. mikr. Anat. lxxi. 1907. [2] *Ibid.* lxxiii. 1909.

of sarcoplasm between them, some having a very large amount of sarcoplasm, others very little, so that in these the interfibrillar substance is almost invisible.

When a muscular fibre is examined in the fresh condition in serum, fine longitudinal lines are seen, as before mentioned, running through the cross striæ (see fig. 271). Under favourable conditions, and especially after the action of weak acid, which swells the muscular substance and renders it clearer and more transparent, these lines become more distinct and can be traced from end to end of

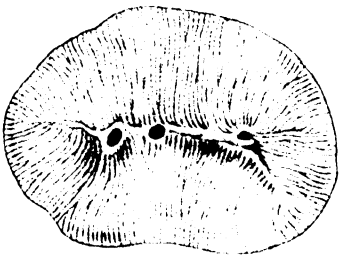


FIG. 276.—TRANSVERSE SECTION OF A LEG-MUSCLE FIBRE OF DYTISCUS, SHOWING RADIAL ARRANGEMENT OF SARCOPLASM AND SARCOSTYLES. (Schäfer.)

The nuclei of insect-muscle lie in a protoplasmic mass in the middle of the fibre. The lines represent the sarcoplasm, the clear intervals between, the radial columns of fibrils.

FIG. 276A.—PORTION OF TRANSVERSE SECTION SIMILAR TO THAT SHOWN IN FIG. 276, MORE HIGHLY MAGNIFIED TO SHOW THE RADIAL COLUMNS OF FIBRILS WITH THE MORE DARKLY STAINED SARCOPLASM BETWEEN THEM. (Schäfer.)

the fibre (figs. 272, 277, 278, 279). By careful focussing it can be made out that the lines are the optical section of the planes of separation between the sarcostyles; that is to say, they are the optical effect of the interfibrillar substance or sarcoplasm. The sarcoplasm, then, has, in transverse section of the fibre, the

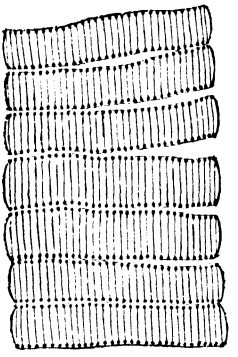


FIG. 277.—LEG-MUSCLE FIBRE OF HARPALUS RUFICORNIS TREATED WITH DILUTE ACID, SHOWING A TENDENCY TO BREAK ACROSS INTO DISCS. (Schäfer.)

The sarcoplasm is in the form of fine lines. The ordinary dark stripes of the fibre have disappeared in the acid.

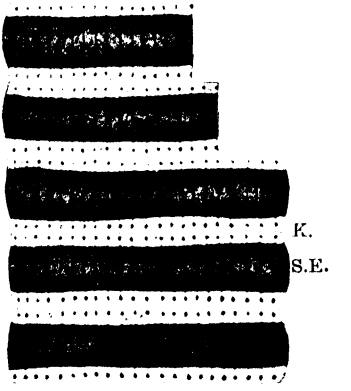


FIG. 278.—PART OF A LEG-MUSCLE FIBRE OF VESPA FIXED WITH ALCOHOL AND AFTERWARDS STAINED. (Schäfer.)

The rows of sarcous elements which form the dark stripes are stained (S.E.); the sarcoplasm has the usual appearance of longitudinal lines and dots. The lines produced by the juxtaposed membranes of Krause are just visible (K.).

appearance of a network; in longitudinal optical section the appearance of fine parallel lines; both these appearances are exhibited in the disc shown in fig. 275. It may easily be understood how these two effects would be produced by the presence of a small amount of interstitial substance lying between closely packed prismatic columns.

In most muscular fibres the sarcoplasm further exhibits a peculiarity of arrangement which has a very characteristic influence upon the optical appearance of the fibre. As is shown in the longitudinal view of the fresh muscle (fig. 271) and still more strikingly in the longitudinal view of the muscle which has been treated with acid (fig. 272), the lines which represent the intercolumnar sarcoplasm exhibit enlargements at regular intervals upon their course. These enlargements lie in the bright cross striæ, either near its junction with the dim cross striæ as shown in fig. 271, or in its middle opposite the constricted part: in the former case the enlargements form a double row in each bright stria, in the latter case they may be blended into a single row (fig. 280). In the longitudinal optical section these enlargements of sarcoplasm have the appearance of dots upon the fine longitudinal lines which run through the muscle; in the more extended fibres or parts of a fibre, these dots are in double rows, in less extended parts they are thicker and blend together in the middle of the bright stria; this difference is well exhibited in fig. 285 at the parts marked E and I respectively. Of course, wherever there is an increase in the sarcoplasm, as represented by the enlargements, the fibrils between which the sarcoplasm is situated must have corresponding constrictions, or, in other words, the lateral juxtaposition of varicose or moniliform fibrils causes an accumulation of sarcoplasm opposite to the indentations of the fibrils: this may be readily understood by reference to fig. 280.

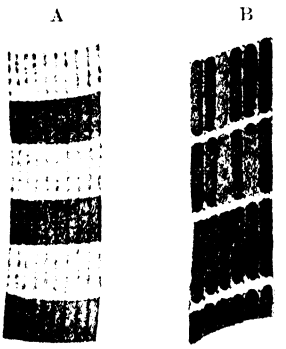


FIG. 279. — PART OF LEG-MUSCLE FIBRE OF INSECT IN EXTENDED (A) AND CONTRACTED (B) CONDITION RESPECTIVELY. Stained with gold by Rollett's method. (Schäfer.)

In A nine fibrils are represented; in B only six. The membranes of Krause are not shown. In A the sarcoplasm is represented as dark lines, in B as light lines.

The dots of the longitudinal view correspond, therefore, to the coarser transverse networks which are seen near the surface of the separated discs (fig. 275), while the fine lines of the longitudinal view correspond to the more delicate network seen in other and deeper planes of the discs. It is also clear from what has been said that these rectilinear appearances do not denote the presence of a network of filaments, but are the optical effect of septa separating the varicose fibrils or sarcostyles, which septa, at the level of the apparent dots, are thickened by the accumulation of a larger amount of sarcoplasm.

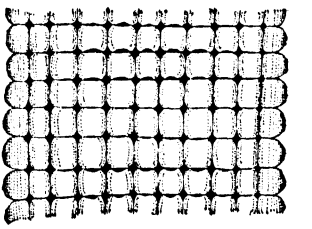


FIG. 280.—PART OF A CONTRACTED FIBRE OF INSECT-MUSCLE (LEG) TREATED WITH VINEGAR. (Schäfer.)

The moniliform appearance of the sarcostyles and the accumulations of the sarcoplasm opposite their constrictions are well seen. The ordinary cross-striation is not visible.

In muscular fibres which have been treated first with acid and afterwards with chloride of gold, and which have been placed in formic acid for twenty-four hours, or until the gold has become reduced in the tissue, the sarcoplasm becomes stained of a dark violet colour, while all the rest of the muscular substance remains unstained (Cohnheim's method). The reticular appearances are thereby rendered very distinct, and at one time led to the belief that the muscle-substance consists of a contractile *reticulum* composed of longitudinal filaments and transverse networks, and enclosing in its meshes a non-contractile fluid substance (*enchylema*, Carnoy), which is continuous in every direction in the fibre. But it can be proved, as will be seen immediately when the structure of the wing-muscles of insects is considered, that the inter-reticular substance (*i.e.* the substance forming the sarcostyles and fibrils) is undoubtedly actively contractile, whereas it is by no means clear that the

apparent reticulum or sarcoplasm possesses contractility at all. Since, however, it is in all probability of protoplasmic nature it may possess a slow contractility. Careful observation with the highest powers distinctly shows that the filaments of the reticulum are actually septa which subdivide the fibre into longitudinal elements, and are not fibres of a reticulum, as was thought by Carnoy, Cajal, and others.

Structure of the wing-muscles of insects.—The wing-muscles of insects may be looked upon as furnishing the key to the proper understanding of the structure of muscle. Although often regarded as a contractile tissue *sui generis*, they in fact agree in all essential particulars of structure with the ordinary muscles. Moreover, in some insects they are replaced by muscles of the ordinary type, and in others muscular fibres occur which may be regarded as transitional forms between the wing-fibres and ordinary fibres. The wing-fibres are bundles of large fibrils (often termed sarcostyles) which are imbedded in a considerable amount of sarcoplasm containing peculiar granules, the whole being enclosed within a sarcolemma. The nuclei of the fibre are scattered here and there in a central mass of sarcoplasm. The sarcoplasm has many of the characters of cell-protoplasm. Amongst these characters is that of staining with chloride of gold, by Cohnheim's method, in which respect the sarcoplasm of the wing-muscles resembles that which forms the apparent reticulum of ordinary muscles. The main difference between them is one of amount, the quantity of sarcoplasm in the wing-muscles being relatively far greater than in the ordinary muscles.

Rollett[1] introduced a modification of the gold method, by which, under favourable circumstances, it is possible to obtain the fibrils (at least their sarcous elements) deeply stained and the sarcoplasm colourless. This method, although precarious, affords when successful a valuable means of elucidating the minute structure of the muscle-fibril.[2]

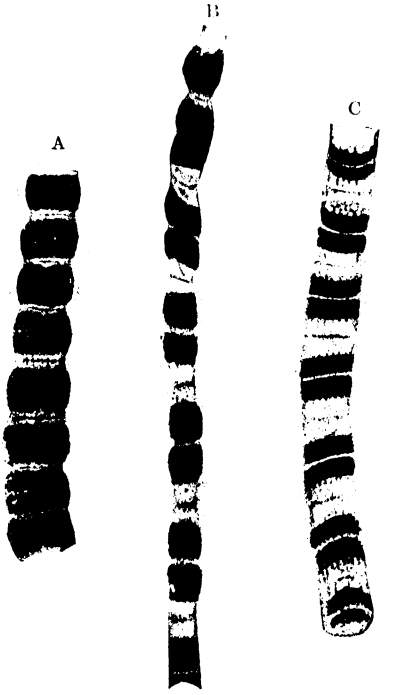


FIG. 281.—FIBRILS OF THE WING-MUSCLES OF A WASP, PREPARED BY ROLLETT'S METHOD. (Schäfer.) (From photographs.) Magnified about 2000 diameters.

A, a contracted fibril. B, a stretched fibril, with its sarcous elements separated at the line of Hensen. C, an uncontracted fibril, showing a porous structure of the sarcous elements.

When a living wing-fibre is broken up with needles in a small drop of white of egg, the sarcostyles become easily separated from the sarcoplasm which surrounds them, and they can then be studied independently of that substance. And, as has already been intimated, they can, under these circumstances, be seen to contract, whereas the sarcoplasm gives no sign of contractility: they therefore form the active portion of the fibre. The intimate structure of the sarcostyles can be advantageously investigated in such isolated elements, and this both in the living condition and after treatment of these muscles with reagents, especially by Rollett's gold chloride method (fig. 281).

[1] A. Rollett, Denkschr. d. Wiener Akad. 1885.
[2] For a description of Rollett's method, see Essentials of Histology, 8th edition.

In the living condition they show, as in the ordinary muscles, alternations of bright and dim striæ (fig. 282, C, D). Each bright stria is bisected by a line which is the optical section of a transverse septum (*membrane of Krause*). These septa thus divide the fibre into a series of segments, known as *sarcomeres* (Schäfer).

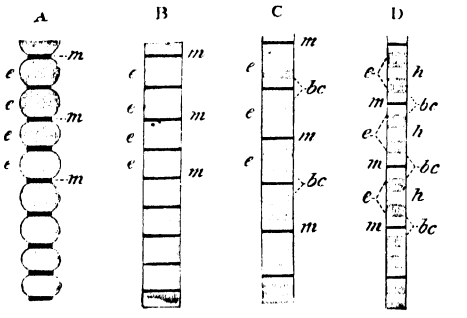


FIG. 282.—FIBRILS OF WING-MUSCLES OF HYDROPHILUS PICEUS. (Ranvier.) Highly magnified.

The fibres are in different conditions of contraction and extension from A, most contracted, to D, most extended.

m, membranes of Krause; *h*, line of Hensen; *e*, sarcous substance; *bc*, hyaline substance.

Each sarcomere can be seen to contain (1) in the middle a more strongly refracting broad disc, the *sarcous element* (Bowman); (2) at either end (next the membrane of Krause) a clear interval occupied by less refracting *hyaline substance*. With high powers, and after staining by Rollett's method, the sarcous element may be made out to be composed of a *sarcous substance*, which stains deeply, and is pierced by short tubular canals which extend from the clear interval as far as the middle of the disc (figs. 281, C, 283 and 284); these canals give it a longitudinally striated appearance. Fine longitudinal striæ, which appear to be due to delicate extensions of the sarcous substance, may also, under favourable circumstances, be seen traversing the hyaline substance and reaching the membrane of Krause (fig. 281, C). If the sarcostyle is extended, the sarcous elements separate into two parts, with an interval between them (fig. 281, B); this median clear interval corresponds with the line of Hensen (p. 176). Conversely, if the muscle is contracted the sarcous elements tend to encroach on the clear intervals and approach the membranes of Krause; and at the same time they are swollen up by the passage of the hyaline substance into their pores (fig. 284); the result of this is that the sarcomeres are bulged out at their middle and contracted at their ends (figs. 281, 282, A, and 284, B). This bulging condition of the contracted sarcomere is, however, not always observed; frequently it retains a cylindrical form in the

FIG. 283.—ISOLATED GOLD-STAINED SARCOUS ELEMENTS OF THE WING-MUSCLES OF WASP SHOWN ON THE FLAT AND IN PROFILE. Untouched photograph. Magnified 870 diameters.

Opposite *a* two sarcous elements are seen on the flat; one is complete, the other one is broken. Opposite *b* several sarcous elements are seen in profile. The pores in the sarcous elements which are seen as clear circles in *a* appear in *b* as minute tubercles which extend only to the middle of the thickness of each sarcous element.

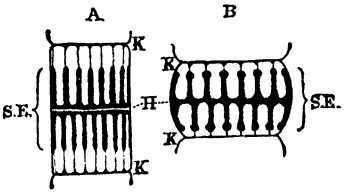


FIG. 284.—DIAGRAM OF A SARCOMERE IN A MODERATELY EXTENDED CONDITION A, AND IN A CONTRACTED CONDITION B. (Schäfer.)

K, K, membranes of Krause; H, plane of Hensen; S.E., poriferous sarcous element.

condition of contraction (fig. 279, B). This appears to be due to the fact that in such cases the membranes of Krause become stretched in place of maintaining a constriction of the fibril. Nevertheless the mixing of the hyaline substance with the sarcous substance takes place as before, and the sarcomere assumes a nearly uniform appearance, so that the cross-striations are only faintly manifested[1] (fig. 282, B). When the sarcostyles are moniliform, in fresh and unstained specimens the effect of this form upon the light transmitted through the muscle may be such that the swollen part looks comparatively clear, while the constricted part has a much darker appearance (fig. 282, A); and since this constricted part corresponds with the middle of the bright stria of the extended muscle, the striæ appear to have become reversed during contraction; a supposed phenomenon which was originally described by Merkel, in which description he has been followed by many authors. In a gold-stained fibre, however, it is easy to see that no such reversal takes place in contraction (fig. 281), and the same fact is obvious when contracted muscle is viewed by polarised light (see p. 185).

Comparison of wing-fibres of insects with ordinary muscle-fibres.—The differences of structure between the ordinary muscles of insects and the muscular fibres which move the wings are differences of degree only. Thus the sarcoplasm is in relatively small amount in the ordinary muscles, as it is in those of vertebrates, and shows regular enlargements corresponding with the lessened diameter of the sarcomeres opposite the clear substance. These enlargements appear as dots or transverse networks according to the point from which they are viewed. They are absent in the wing-fibres. Moreover, the fibrils, probably on account of the smaller amount of sarcoplasm, are difficult or impossible of isolation in the living condition in the leg-fibres, easy in the wing-fibres. But, like the fibrils (sarcostyles) of the wing-muscles, they are divided into segments or sarcomeres, at regular intervals corresponding with the middle of the bright striæ, by transverse membranes (membranes of Krause), which can be brought distinctly into view on the addition of dilute acid to the fresh or alcohol-fixed muscle (fig. 272, K). Each sarcomere contains a sarcous element, usually rod-like in form with hyaline substance between the sarcous element and the membrane of Krause at either end of the segment; this membrane may be merely represented by a dot (figs. 269, 270); the middle of the sarcous element when the muscular fibre is extended shows a clear line or interruption, as in the wing-element—the line of Hensen.

As in the wing-sarcostyles, the proportionate amounts of the sarcomere occupied respectively by the sarcous element and the clear intervals vary greatly, according to the condition of extension or contraction of the muscle. In contracted fibres the sarcous elements enlarge and approach the transverse membranes, and the clear intervals diminish proportionately, their fluid being imbibed by the sarcous element; while in extended fibres the sarcous elements become removed from the transverse membranes and narrowed, and the clear intervals become *pari passu* longer.

The ends of the sarcous element in some fibres appear detached, forming a row of dot-like portions of sarcous substance in the line of the fibril, and collectively producing the so-called 'accessory discs,' lying in the clear substance on either side of Dobie's line. But some structures which have been described as accessory discs in these muscles are merely the sarcoplasmic enlargements, which, as already stated, frequently appear as dots in longitudinal view; this is the case with the fibre represented in fig. 278.

An important influence upon the optical appearances of the ordinary muscular fibres is exerted by these sarcoplasmic accumulations (transverse networks), which lie, as we have seen, in the region of the bright stripe (clear interval of the

[1] Ranvier, Leçons sur le système musculaire, 1880, and Traité technique, 1889; Holmgren, Arch. f. mikr. Anat. lxxi. 1907.

sarcomere), and have in optical section the appearance of rows of dark-looking dots. When these dots are carefully regarded they seem each to be surrounded by a bright halo (figs. 271, 285, E), which is apparently due to the manner in which they refract the light which is transmitted through the muscle, much in the same way as an oil-globule or an albuminous granule, when viewed in water under a high power of the microscope, appears, when it is exactly focussed, to be surrounded by a bright area. Since each dot is encircled by a bright halo, and the dots are arranged in regular rows, the haloes become blended into a stripe, which is much brighter than the rest of the muscle-substance. This seems to be in part the cause of the very bright appearance of the clear bands of fresh muscle, although the effect is increased by reflection from the surfaces of the more highly refracting dark discs.[1]

When these (ordinary) muscles of insects contract, the sarcous elements, as in the wing-muscles, become wider and may be bulged out and shortened, while the fluid of the clear intervals is simultaneously diminished in amount. The ends of the sarcomeres opposite the membranes of Krause may remain smaller than their middle part, in which case the fibrils become moniliform.

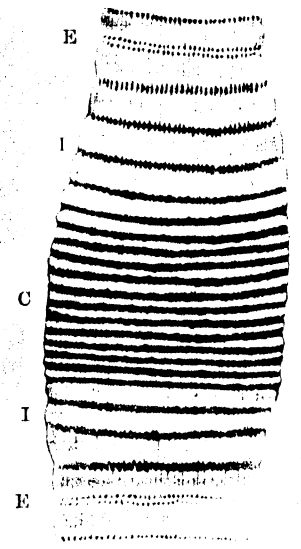


FIG. 285.—WAVE OF CONTRACTION PASSING OVER A MUSCULAR FIBRE OF DYTISCUS. (Schäfer.) Very highly magnified.

E, E, portions of fibre extended; C, contracted part; I, intermediate condition.

This alteration in shape of the fibrils necessarily affects the sarcoplasm which lies in their interstices, which must become squeezed out of the parts which are opposite the bulgings of the fibrils and into the parts which are opposite their constrictions. In other words, the sarcoplasm must accumulate in greater quantity opposite the clear bands and the membranes of Krause, and must diminish in amount opposite the sarcous elements. This is, in fact, what can be seen to take place. In fig. 280 a contracted portion of muscle in which the sarcoplasm has been rendered evident by acid is represented, and it is seen that the sarcoplasm is accumulated opposite the transverse membranes where the sarcostyles are relatively narrow.[2]

In the living muscle also this change in the position of the sarcoplasm during contraction can, with care, be observed to take place (fig. 285). In this case, also, as in the wing-fibrils, the deeply moniliform shape of the fibrils tends to cause the constricted parts to appear dark, the bulged parts light in comparison, so that the effect of reversal of the striæ is obtained. But in the ordinary or leg muscles this effect is materially increased, and the contrast between the dark and light striæ of the contracted muscle is greatly enhanced by the effect of the sarcoplasmic accumulations opposite the constrictions. For in the first place these themselves tend to produce the appearance of dark lines or planes passing across the fibre, and, secondly, the reflected light from their surfaces causes the muscular substance between these planes to appear brighter than would otherwise be the case.

Holmgren has shown that the sarcoplasm of muscle contains specific granules, which in many muscles assume a very regular arrangement. Where the sarcoplasm

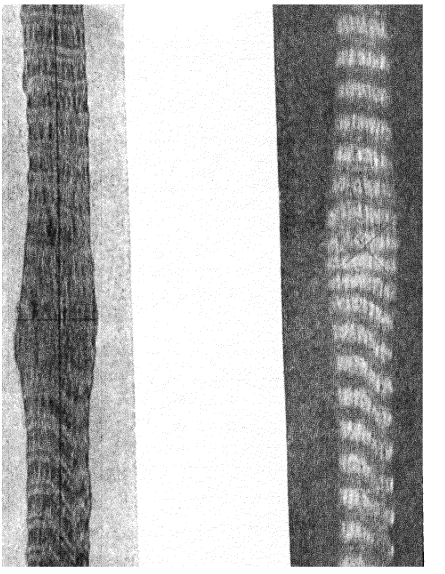
[1] Schäfer, Phil. Trans. 1877.

[2] Cf. G. Retzius, Biol. Unters. 1890, and E. Holmgren, *op. cit.* and Anat. Anz. xxxi. 1907.

is abundant the main granules lie opposite the sarcous element, others lying opposite the isotropous substance. He considers that there may occur an exchange of material between the sarcoplasm granules and the contents of the sarcostyle. In insect-muscle the tracheæ not only encircle the fibres but pierce the sarcolemma and ramify in the sarcoplasm. The cells which are concerned with the formation of these intramuscular tracheæ are regarded by Holmgren as the equivalent of the trophospongial cells which he has described as penetrating into other tissue elements.

In alcohol-preparations (both of the wing-muscles and of the ordinary or leg muscles) in which the sarcous elements have been stained, there is no appearance of reversal of striation; the darkly coloured sarcous element always occupies the central or bulged part of the sarcomere, and the unstained hyaline substance occupies the constricted parts of the sarcostyles; but if the whole of the hyaline substance is absorbed into the sarcous element the contracted sarcomere has a nearly uniform appearance.

Appearances of muscle under polarised light.—It was noticed by Boeck that, like some of the other tissues, muscle is doubly refracting (anisotropous). Brücke, however, was the first to point out that the fibre is not composed entirely of anisotropous substance, but that there is in addition a singly refracting or isotropous material. In extended fibres or parts of fibres, especially those which have been fixed by alcohol and mounted in Canada balsam, the fibre appears when examined between crossed nicol prisms to be marked by alternating broad bars of light (anisotropous) and dark (isotropous) substance, the former corresponding in position to the sarcous elements, the latter to the clear intervals of the fibrils. (In the wing-muscles also, the sarcous elements of the extended fibril appear bright, and the clear intervals, including Krause's membrane, are dark when viewed with crossed nicols. The effect of single wing-fibrils is, however, faint owing to their relatively small diameter.) In less extended parts of the fibre, the dark or isotropous bands become relatively narrower until in the contracted parts they are reduced to comparatively narrow bands, with relatively broad bright (anisotropous) intervals (fig. 286). As Engelmann has clearly shown, there is no reversal of the anisotropous and isotropous bands in polarised light, a fact of some significance as indicating that the reversal which *appears* to occur when the fibre is examined by ordinary light is really, as has been already explained, an optical effect, and is not caused by a reversal in the relative position within the sarcomere of the substance of the sarcous elements and the clear intervals (see below, Theory of Merkel). The result, therefore, of the examination of muscle under polarised light is confirmatory of the deductions which may be drawn regarding its structure



A B

FIG. 286.—LEG-MUSCLE FIBRE OF CHRYSOMELA COERULEA WITH (FIXED) CONTRACTION WAVE, PHOTOGRAPHED UNDER POLARISING MICROSCOPE.[1]

A, with uncrossed nicols; B, with crossed nicols.

[1] I am indebted to the late Professor Engelmann for these two photographs.

and the changes which occur in contraction, from the appearance of stained preparations, and tends to show that the gold-staining substance of the fibrils—the substance which forms the sarcous elements—is anisotropous, while the substance or fluid of the clear substance as well as the sarcoplasm is isotropous. In muscles which have been treated with acid, by which the sarcous elements are destroyed, all appearance of double refraction is found to have disappeared.

Living or fresh muscular fibres of the ordinary variety usually appear bright throughout when examined under crossed nicols (fig. 287). This is due to the fact that owing to their thickness and to compression to which they are subject in examination the planes of the striæ generally lie somewhat obliquely, and the polarised light which traverses the fibre must necessarily pass at some level through anisotropous substance. Under these circumstances there is no dark portion of the field visible over the fibre.

It has been shown by Ranvier that the appearance of a tissue under polarised light affords, when taken by itself, no sure guide to its structure. The same tissue or part of a tissue may appear either light or dark between crossed nicols, according to the direction and character of the 'stress' to which it may have been exposed, in the same way that a film of indiarubber, which is normally isotropous, becomes anisotropous when stretched. Looked at, however, in conjunction with other facts, and especially with the results of differential methods of staining, the appearance under polarised light affords important confirmation of the deductions which can be drawn regarding structure by the employment of these methods; this is exhibited by the observations upon muscle which have just been alluded to.

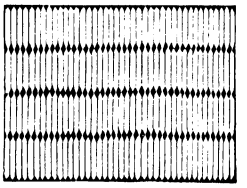


FIG. 287.—LIVING MUSCLE OF A WATER-BEETLE EXAMINED IN POLARISED LIGHT WITH CROSSED NICOL PRISMS. (Brücke.)

Brücke applied the theory of Bartholin—invented to explain the phenomena of double refraction in crystals of Iceland spar, and which supposes that those crystals are compounded of minute doubly refracting particles (disdiaclasts)—to the doubly refracting substance of muscle, and gave the same name (*disdiaclasts*) to the particles of which he supposed that substance to be composed, and which act upon the light like positive, uniaxial, doubly refracting crystals. Under certain circumstances, as after the action of water or salt solution, part of the muscular substance breaks down into a cloud of fine doubly refracting particles which are either themselves the disdiaclasts or represent groups of them.

Historical.—Until Bowman published, in the Philosophical Transactions for 1840, his important work on the structure of muscle, the subject was extremely obscure. The view which Bowman took of the constitution of muscular substance—namely, that it is composed of a series of particles joined together closely side by side into 'discs,' and less intimately united end to end into 'fibrils'—for some years occupied a dominant position in this branch of histology. Kölliker, however (1851), laying stress upon the fact that the muscular substance is much more apt to break up into 'fibrils' than into 'discs,' looked upon the appearance of the latter as altogether secondary, and regarded the 'fibrils' as the actual elements of the muscle, the alternate dark and light portions in the course of each fibril being of essentially the same nature, although differing somewhat in their optical properties. Afterwards (1867), recognising that the so-called fibrils might be composed of finer elements, or ultimate fibrils, Kölliker was led to term the structures formerly known as fibrils 'muscle-columns,' the areas of Cohnheim representing the transverse sections of those columns.

W. Krause (1868) introduced a new idea into the conception of the structure of the muscle-fibril, by looking upon the intermediate line in the light stripe as a membrane dividing the fibril up into small compartments or cases (*Muskel-kästchen*) (fig. 288, A). Each such case contains, according to Krause, a portion of the dark disc (muscle-prism) in its middle part, and portions

of the light discs (fluid) at either end, and Krause supposed that in contraction this fluid changes its situation, becoming shifted to the periphery of the dark substance, and that in this way the muscle is diminished in length, and proportionately increased in breadth (fig. 288, B). Subsequently, however, recognising the existence of longitudinal striæ, which he regarded as due to rod-like structures, within the muscle-prism, Krause described the fluid as passing between these and separating them more from one another during contraction (fig. 288 C). About the same time (1868) Hensen described the stripe which bears his name.

The next prominent writer upon the subject was Merkel (1872), who believed the transverse membranes of Krause to be double, and corroborated Hensen's description of the existence of a line or disc in the middle of the dark stria. But the most prominent feature in Merkel's account occurs in his description of the process of contraction. According to Merkel, the anisotropous substance of the dark stria first becomes diffused over the whole muscle-compartment, so that the fibre acquires a homogeneous appearance, and at a later stage becomes accumulated against the transverse membranes, while the isotropous substance on the other hand is accumulated on either side of Hensen's disc: the position of the two substances being thus reversed.

Merkel was followed by Engelmann (1873), according to whose terminology, which has been adopted by most subsequent German writers, a muscular fibre consists of a succession of superimposed parts or compartments, which are partitioned off from one another by thin discs or membranes—*intermediate discs* (Zwischenscheiben, Z). Within each compartment thus marked off is a series of layers, varying in their refractive power and in their action upon polarised light, as follows: Next to the *intermediate disc* or *membrane of Krause* comes a layer of *isotropous clear substance* (J), within which may sometimes be distinguished a thin disc of darker substance, having the appearance of a line of dots: this is the *accessory disc* (Nebenscheibe, N) or granule-layer of Flögel; then comes the broad disc of anisotropous substance (Querscheibe, Q) or *principal disc*, occupying the greater portion of the muscle-compartment, and bisected by a narrow pale disc, which lies exactly in the middle of the compartment, and is distinguished as the *middle disc* (Mittelscheibe, M) or *band of Hensen*. Beyond the principal disc come in inverse succession isotropous substance with accessory disc, and intermediate disc, and so on in the next compartment.

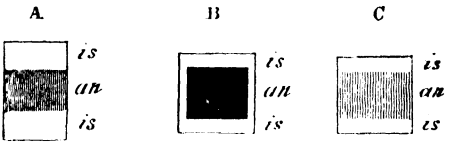


FIG. 288.—DIAGRAMMATIC REPRESENTATION OF A MUSCLE-CASE. (W. Krause.)

A, at rest; B, condition in contraction, first view; C, condition in contraction, second view. *an*, muscle-prism, consisting of a bundle of muscle-rods; *is*, fluid isotropous substance.

When contraction is about to supervene in any part of a muscular fibre, the changes which (according to Engelmann) may be observed are the following: The intermediate discs approach one another and the successive discs within each muscle-compartment become less distinct, so that the fibre loses in great measure at the part in question (that namely in which the contraction is beginning) its striated appearance, this being due to the passage of the isotropous substance into the anisotropous substance. The stage in question is termed the homogeneous stage. As the contraction progresses, transverse striæ again make their appearance, in consequence of the gradual darkening of the accessory discs and concomitant clearing up of the principal disc, so that now each intermediate disc with its juxtaposed accessory disc forms a dark isotropous band, these alternating with the narrowed and now bright-looking principal discs of anisotropous substance. The reversal of the striæ in contracting muscle was ascribed by Engelmann to changes in refrangibility in the several substances which compose the discs of the muscle-compartment, accompanied by an increase in the volume of the principal disc at the expense of the isotropous substance, and not, as Merkel had supposed to be the case, to an exchange of position between isotropous and anisotropous substance.

Both Merkel and Engelmann attached considerable importance to the occurrence of the intermediate stage, in which the striæ become indistinct. It may be caused in part by the absorption of the isotropous by anisotropous substance, but it is probable that the homogeneous appearance of that part of the ordinary fibres which is passing into or out of full contraction is often produced by a longitudinal shifting of the fibrils, owing to their being unequally pulled upon by the more contracted part. A similar mechanical shifting of the fibrils, accompanied by indistinctness of transverse striation of the fibre, is frequently produced in teasing the tissue. Moreover, the so-called homogeneous stage is not always observed either in the contraction of the ordinary muscles or in the isolated fibrils of the wing-muscles.

Heitzmann (in 1873) noticed the reticular appearances of muscle which had been treated with gold and acid, but these appearances were first fully described by G. Retzius in 1881.

The theory of the constitution of cell-protoplasm of a contractile reticulum and enchylema (see p. 18), which was about this time prevalent, had a marked influence upon the views which now came to be held regarding the structure of muscle. Various observers (Melland, C. T. Marshall, Van Gehuchten, and Ramón y Cajal), who during the next five or six years investigated the structure of muscle, mainly with the aid of acid and gold preparations, regarded the appearances of these preparations as proving the existence of a contractile reticulum in muscle, and concluded that the material in the meshes of the supposed reticulum—that is to say, the whole of the muscle-fibrils—must represent the enchylema of protoplasm. The breaking-up of the so-called inter-reticular substance into muscle-fibrils they regarded as purely artificial.

But the researches of Rollett, which were published in 1885 and 1886,[1] showed any such view to be untenable, and brought the matter back to the former standpoint. The results of these researches tended to demonstrate that the filaments of the so-called 'reticulum' of the above-mentioned authors are neither more nor less than the septa of sarcoplasm which intervenes between columns of the muscle-substance; that these columns (fibrils) pre-exist in muscle, and are the actual contractile elements of the muscle; and that the sarcoplasm between them may represent the undifferentiated remains of the protoplasm of the original cell from which the muscular fibre has been developed.

Haycraft (1891) regarded the various cross-markings upon muscle as due entirely to the optical effect caused by varicosities in the fibrils upon the light which is traversing them. As showing that this view is tenable, Haycraft found that perfectly similar appearances of cross-striation can be obtained from collodion in which impressions of alcohol-hardened muscle have been made, and in which there are certainly no structural differences. But the undoubted fact that the sarcous elements stain distinctively with certain reagents which leave the clear part of the fibril quite colourless, and that, moreover, a special structure can be demonstrated in them, proves that the experiment upon which Haycraft relied, interesting as it undoubtedly is, does not justify the conclusion he drew from it—viz. that the fibril is homogeneous throughout.[2]

McDougall (1897)[3] also assumes a homogeneity of the fibrils, except that he believes in the existence of transverse membranes, not only in the situation of Dobie's line, but also at that of Hensen and at the planes of junction of the singly and doubly refracting materials. He supposes that there is a longitudinally creased inextensible membrane of a semi-permeable character enclosing the more or less fluid contents of the fibril, and that through this by osmosis or otherwise water passes into the fibril from the surrounding sarcoplasm. Each sarcomere is thereby swollen, the swelling occurring to the greatest extent in the region of the doubly refracting substance (owing to the supposed inextensibility of Krause's membrane being greater than that of the other transverse membranes), thus producing a shortening of the sarcomeres. Later McDougall supposed that the transference of water is caused by the development of lactic acid either within or outside the sarcomere. McDougall's hypothesis has been criticised by Bernstein,[4] by Macdonald,[5] and by the author,[6] who have shown that, apart from the undoubted fact that histological differentiation can be shown to be present in the sarcomere, the passage of fluid from the sarcoplasm into the sarcomere is for various reasons not tenable as a possible explanation of the energy produced in contraction. Nor was McDougall himself able to show that the sarcomere enlarges in volume during contraction, as it must do if it imbibes water from the sarcoplasm; moreover, he admits that it is not possible to cause a model of such a fibre as he has supposed to exist, to contract to less than two-thirds of its original length, whereas it is known that muscle may contract to one-third or one-quarter of its length. Further may be mentioned the fact that the isolated fibrils of the wing-muscles of insects undergo contraction when surrounded with other fluids than sarcoplasm, such as salt-solution (even hyper-isotonic), or white of egg.

Contraction cannot therefore be explained by movement of fluid from outside to within the fibrils: the movement must be movement of fluid from one part of the sarcomere to the other. It is universally admitted by those who hold this view that this movement is from the more fluid part of the sarcomere near the membrane of Krause to the less fluid part which forms the sarcous element.[7] Granting this transfer, the question has yet to be answered, what is the

[1] Wiener Denkschriften, Bde. 49 and 51.
[2] J. B. Haycraft, Proc. Roy. Soc. xlix. 1891.
[3] Journ. Anat. and Physiol. xxxi. 1897 and xxxii. 1898; Quart. Journ. Exp. Physiol. iii. 1900. McDougall's theory has been lately adopted by Meiggs (Amer. Journ. Physiol. 1905, and Zeitschr. f. allg. Physiol. 1908).
[4] Pflüger's Archiv, cx. 1905.
[5] Quart. Journ. Exp. Physiol. 1909, ii.
[6] *Ibid.* iii. 1910. See also S. Gutherz, Arch. f. mikr. Anat. lxxv. 1910.
[7] Hürthle (Pflüger's Archiv, cxxvi. 1908) has endeavoured to investigate this question in instantaneous photographs of living muscle of insect leg, and the measurements which he gives of the dark and light stripes in rest and contraction respectively appear not to bear out the generally received view

moving cause of the transference of fluid? As to this, several hypotheses have been put forward. An ingenious one is that of Engelmann,[1] who supposes that, in the development of heat in the doubly refracting material in the central part of the sarcomere, its doubly refracting particles are able to undergo association with a greater quantity of water, which accordingly passes to them from the terminal parts of the sarcomere. This theory was subjected to criticism by A. Fick,[2] who urged that the amount of heat developed during muscle-contraction, even if it is confined to the doubly refracting material, which Fick doubts, is altogether inadequate to produce the effect ascribed to it.

Another hypothesis supposes the cause of the movement of fluid to be an electrical change occurring at the contiguous surfaces of the singly and doubly refracting elements of the sarcomere. Such an electrical change would be accompanied by alterations in surface tension at the junction of these materials, which would lead to the passage of the isotropous fluid into or out of the anisotropous material of the sarcous element;[3] and with the porous structure which this is known in some muscles to possess, the extent of surface over which this change will occur must be relatively large.[4]

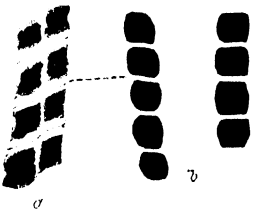


FIG. 289. — DISTRIBUTION OF POTASSIUM SALTS IN WING-FIBRILS OF DYTISCUS. (Macallum.)

a, fibrils in condition of extension; *b*, fibrils in condition of contraction.

Lastly may be mentioned a hypothesis which has been brought forward by Macdonald, founded on the alterations which, as he believes, occur in the muscle in the relationship between protein molecules and electrolytes. This hypothesis rests upon what Macdonald believes to be the fact that 'the onset of contraction is marked by a new appearance of potassium salts in the central portion of each sarcomere, sufficient to account for a considerable difference in osmotic pressure.'[5] A. B. Macallum had previously described the presence of potassium salts in considerable concentration in the anisotropous substance of the sarcomere (fig. 289). Macdonald believes that they only become separated out as the result of excitation. The electrical changes would then be the consequence of the transference of electrolytes, and the thermal change the result of a *subsequent* combustion process. Macdonald has used this hypothesis not only to explain the phenomena of muscular contraction, but also in explication of the appearance of striated structure generally, and brings forward evidence in favour of this view derived from the striations in the axis-cylinders of nerves which were originally described by Frohmann (see p. 230).[6]

that the sarcous element increases *pari passu* with the diminution of the isotropous fluid. But his results are not conclusive, for the magnification which he employed was insufficient for exact measurements, and the investigation of the question is much more difficult in the massed fibrils of the leg-muscles than in the easily isolable fibrils of the wing-muscles. It is also more than doubtful, for reasons which have been already given (p. 184), if the distinction between sarcous element and isotropous fluid can be made out with sufficient sharpness in living muscle.

[1] Ueber den Ursprung der Muskelkraft, 1893.

[2] Pflüger's Archiv, liii. 1893.

[3] By a modification of Engelmann's hypothesis it may be possible to connect such change of surface tension with a development of heat at the junction of the two materials. Another consideration in connexion with this subject is the precipitation and agglomeration of particles which is liable to occur in colloidal solutions. The occurrence of these changes in protoplasm and their association with its movements has already been referred to (p. 20). Such physico-chemical changes are regarded by J. Loeb (Pflüger's Archiv, lxix. 1898; lxxi. 1898; lxxv. 1899; see also The Dynamics of Living Matter, 1906) as a possible cause of contraction. Halliburton and Brodie found that the contraction which is produced on gradually heating a muscle occurs in stages which correspond with the temperatures of coagulation of its principal protein constituents.

[4] Theories of muscular contraction depending upon rapid changes in surface tension at the junctions of dissimilar parts of the fibrils have been suggested by several authors. Amongst these may be mentioned d'Arsonval, Arch. de Physiol. 1889; J. Gad, Arch. f. Physiol. 1893 (Verhandl. d. Berl. physiol. Gesellsch.); Verworn, Allgemeine Physiologie, 1895; Imbert, Arch. de Physiol. 1897; and J. Bernstein, Pflüger's Archiv, lxxxv. 1901 and cx. 1905. For a consideration of a surface-tension theory which assumes the existence of a contact-difference between sarcous element and isotropous fluid (corresponding with spongioplasm and hyaloplasm of cell-protoplasm) and a discussion of the effect which would be produced by the dissociation of ion-proteids at the contact-surfaces within the sarcomere, the reader may consult the paper by T. B. Robertson in the Quart. Journ. Exper. Physiol. ii. 1909, which has been already referred to in connexion with amœboid movement and ciliary action, and in which it is shown that a similar principle probably underlies all muscular and protoplasmic movement. Cf. also on this question Schäfer, Proc. Roy. Soc. xlix. p. 193, 1891, 'On the structure of amœboid protoplasm with a comparison between the nature of the contractile process in amœboid cells and in muscular tissue.'

[5] Journ. of Physiol. 1905, xxxii. p. 1.

[6] For a detailed discussion of the subject, the reader is referred to the paper by Macdonald in the Quarterly Journal of Experimental Physiology, 1909, vol. ii. pp. 5–89. See also Proc. Roy. Soc. 1905, Vol. B. 76, p. 343.

The account given in the text of muscle-structure and of the changes which it undergoes in contraction is founded upon a re-investigation by the author [1] of the structure of muscle, and especially of the muscles of insects, prepared by various methods, but chiefly that of Rollett.

Muscle-nuclei.—In connexion with the cross-striated substance a number of clear oval nuclei are found in the fibres. In mammalian muscles they lie mostly upon the inner surface of the sarcolemma (figs. 266, 273), but in frogs they are distributed through the substance of the fibre, and in many insects they form a longitudinal series situated in the middle of the fibre. Associated with and surrounding them there is a certain amount of protoplasm, not always clearly distinguishable. In the unaltered condition the nuclei are not easily seen, but they are made conspicuous by the addition of acid. They contain a network of chromatin, in which one or two nucleoli are generally visible; frequently the chromatin of the nucleus is in the form of a spiral filament, and the nuclei themselves may be spirally contorted. It has been suggested that this is caused by a spiral contraction of the fibrils. The nuclei are found in considerable numbers at the tendinous attachments of the muscle-fibres, and are also found in a granular protoplasmic layer at the place where the motor nerve ends in the fibre (see p. 256).[2]

Variations of structure in different muscles, correlated with differences of function.—In the rabbit, as pointed out by Ranvier [3] and Krause, certain of the voluntary muscles present differences in appearance and mode of action from the rest. Thus while most of the voluntary muscles have a pale aspect and contract energetically when stimulated, some, such as the semi-tendinosus and the soleus in the lower limb, are at once distinguished by their deep red colour as well as by their slow and prolonged contraction when stimulated. When subjected to microscopical examination it is found that in the red muscles the fibres are more distinctly striated longitudinally and the transverse striæ are more irregular than usual. The muscular fibres are generally finer (thinner) than those of the ordinary muscles, and have a larger amount of sarcoplasm. The nuclei are more numerous and are not confined to the inner surface of the sarcolemma, but occur scattered in the thickness of the fibre as well. There is also a difference in the blood-supply of the two kinds of muscle, to be afterwards alluded to.

A similar difference between red and pale muscles may be also seen in the rays amongst fishes. In other animals the distinction is not found as regards whole muscles, although it may affect individual fibres of a muscle. This is the case, as shown by Klein, in the diaphragm, in which in many of the fibres there are numerous nuclei, and these are imbedded in protoplasm (sarcoplasm), which forms an almost continuous layer underneath the sarcolemma. The distribution of the two kinds of fibres in different muscles has been especially investigated by Grützner.[4]

In the fin-muscles of Hippocampus the quantity of sarcoplasm is very considerable in proportion to the muscle-fibrils, which are collected into lamellar bundles (sarcostyles) separated from the sarcolemma and from one another by a large amount of sarcoplasm. Certain muscles of the bat also contain a relatively large quantity of sarcoplasm, which may perhaps bear some relationship to prolonged activity on the part of the muscles in question.[5]

Mode of attachment of muscular fibres: ending of muscle in tendon. When a muscle ends in a tendon it is found that the muscular fibres either run in the same direction as the tendon-bundles or join with the tendon at an acute angle.

[1] Int. Monthly Journ. Anat. and Physiol. viii. 1891; and Proc. Roy. Soc. xlix. 1891, p. 280. For details regarding the extensive literature of the subject, up to 1898, see M. Heidenhain, Ergebn. d. Anat. viii.

[2] On the nuclei of striated muscle, see A. B. Macallum, Quart. Journ. Micr. Sc. 1887.

[3] Compt. rend. civ. and cvii. 1887 and 1889.

[4] Recueil Zool. Suisse, 1884.

[5] Rollett, Arch. f. mikr. Anat. xxxii. 1888; Sitzungsb. d. Wiener Akad. xcviii. 1889.

In the former case the tendon becomes subdivided, either gradually or suddenly, into as many small bundles as there are fibres in the end of the muscle, and it often seems at first sight as if the tendon-fibres were directly continued into the muscular substance. In reality, however, the fibres of each tendon-bundle end abruptly on reaching the rounded or obliquely truncated extremity of a muscular fibre (fig. 290), and are so intimately united to the prolongation of sarcolemma which covers the extremity, as to render the separation between the two difficult if not impossible (Ranvier). The muscular substance, on the other hand, may readily be caused to retract from the sarcolemma at this point. The areolar tissue which lies between the tendon-bundles passes between the ends of the muscular fibres and is gradually lost in the interstitial connective tissue of the muscle.

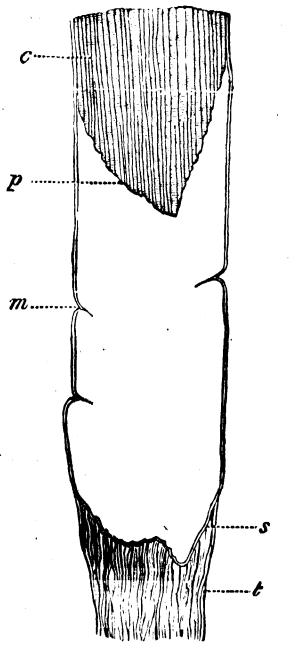


FIG. 290.—TERMINATION OF A MUSCULAR FIBRE IN TENDON. (Ranvier.)

m, sarcolemma; *s*, the same membrane passing over the end of the fibre; *p*, extremity of muscular substance; *c*, retracted from the lower end of the sarcolemma-tube; *t*, tendon-bundle passing to be fixed to the sarcolemma.

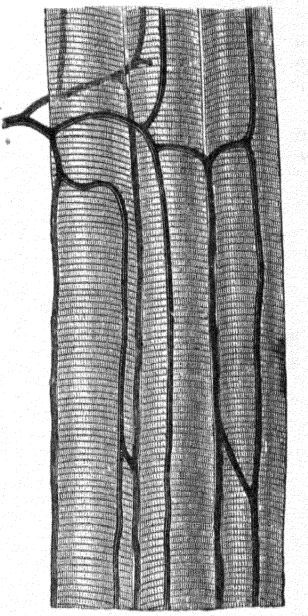


FIG. 291.—CAPILLARY VESSELS OF MUSCLE, MODERATELY MAGNIFIED. (Schäfer.)

When the direction of the muscular fibres is oblique to that of the tendon, the connexion takes place in a similar way to that above described, but the small tendon-bundles are given off laterally along the course of the tendon, which in these cases is generally prolonged into the substance or over the surface of the muscle.

When the muscular fibres divide, each branch of the fibre is directly continuous with a tendon-bundle, or connective-tissue bundle.

Blood-vessels.—The blood-vessels of the muscular tissue are very abundant, so that, when they are successfully filled with coloured injection, the fleshy part of the muscle contrasts strongly with its tendons. The arteries, accompanied by their associate veins, enter the muscle at various points, and divide into branches: these pass along the fasciculi, crossing over them, and dividing more and more as they get between the finer divisions of the muscle; at length, penetrating the smallest fasciculi, they end in capillary vessels, which run between the fibres. The vessels

are supported in their progress by the subdivisions of the sheath of the muscle, to which also they supply capillaries. The capillaries destined for the proper tissue of the muscle are extremely small; they form among the fibres a fine network, with narrow oblong meshes (fig. 291), which are stretched out in the direction of the fibres; in other words, they consist of longitudinal and transverse vessels—the former running parallel with the muscular fibres, and lying in the angular intervals between them; the latter, which are much shorter, crossing between the longitudinal ones, and passing over or under the intervening fibres.

In the deeper coloured muscular fibres of those animals which, like the rabbit, possess two kinds of voluntary muscles, some of the transverse loops of the capillary network are dilated far beyond the size of the ordinary capillaries (fig. 292).

The number of capillaries in a given space of a muscle, or their degree of closeness, is partly regulated by the size of the fibres; and accordingly in the muscles of different animals it is found that when the fibres are small the vessels are numerous and form a close network, and *vice versâ*; in other words, the smaller the fibres, the greater is the quantity of blood supplied to the same bulk of muscle. In conformity with this, we see that in birds and mammalia, in which the process of nutrition is active, and where the rapid changes require a copious supply of material, the muscular fibres are smaller and the vessels more numerous than in cold-blooded animals, in which the opposite conditions prevail.

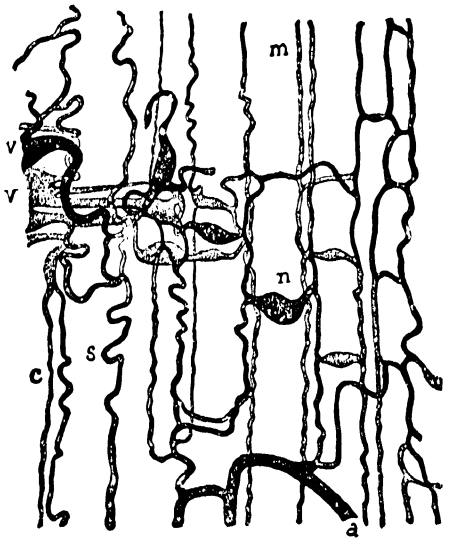


Fig. 292.—Blood-vessels of a red muscle of the rabbit, injected. (Ranvier.)

a, arteriole; *v*, *v*, venules; *n*, dilatation on transverse capillaries.

Lymphatics. — So far as is known, there are no lymphatic vessels within the voluntary muscles, although there is an abundant supply in their connective-tissue sheaths and tendons. The lymphatic vessels here would seem, as pointed out by Ludwig and Schweigger-Seidel, to serve the purpose of collecting and conveying away the lymph which is present in the areolæ of the intramuscular connective tissue.

Nerves.—The nerves of a voluntary muscle are of considerable size. Their branches pass between the fasciculi, and repeatedly unite with each other in form of a plexus, which is for the most part confined to a small part of the length of the muscle, or muscular division, in which it lies. From one or more of such primary plexuses nervous twigs proceed, and form finer plexuses composed of slender bundles, each containing not more than two or three dark-bordered nerve-fibres, whence single fibres pass off between the muscular fibres and divide into branches which are finally distributed to the tissue. Most of the nerve-fibres are motor, and pass to the structures known as 'end-plates,' but a few are sensory, and end in the so-called 'muscle-spindles.' These structures will be described later, along with nerve-endings generally.

HISTOGENESIS.

Most of the voluntary muscles of the body are developed from a series of portions of mesoderm which are early set aside for this purpose in the embryo and are termed the muscle-plates. Each muscle-plate is found after a time to consist of two layers, an *inner* and *outer*. According to Maurer, it is the

cells of the inner layer which are concerned with the development of the muscles of the trunk and limbs, but Balfour, Kästner, Graham Kerr, Kollman, Bardeen, and Lewis concur in stating that both lamellæ may form muscular tissue. The muscles of the eyes, jaw, hyoid apparatus, and some others of the head and neck are developed from cells in the parietes of the so-called head cavities, which represent in the cephalic region the muscle-plates of the trunk. When the muscular fibres are about to be formed the cells (*myoblasts*) become elongated, and their nuclei multiplied, so that each cell is converted into a long multi-nucleated protoplasmic fibre. At first the substance of the fibre is not striated but is granular in appearance. The granules seem to be of the nature of mitochondria,[1] which presently arrange themselves in longitudinal striæ along one side (second month) (fig. 293, A), and about the same time a delicate membrane may be discovered bounding the fibre. The longitudinal striation, which is the first indication of the proper muscular substance, extends along the whole length of the fibre, but at first, as just intimated, affects only a small part of its breadth, the rest being formed by a highly glycogenic protoplasm containing nuclei. In due time, however, this conversion into the proper muscular substance, further shown by the appearance of cross-striæ (fig. 293, B and C), extends round the greater part of the circumference of the fibre, and finally, about the sixth month, involves its whole thickness, except along the axis, which for some time remains occupied by undifferentiated protoplasm with nuclei imbedded in it. Eventually the nuclei take up their permanent position either between the fibrils or underneath the sarcolemma.

Schwann considered each fibre to be formed by the linear coalescence of several cells; Kölliker, Wilson Fox, and most others have maintained the contrary view, originally promulgated by Remak, that the fibres are produced as above described by the elongation of single cells, with differentiation of their contents and multiplication of their nuclei.

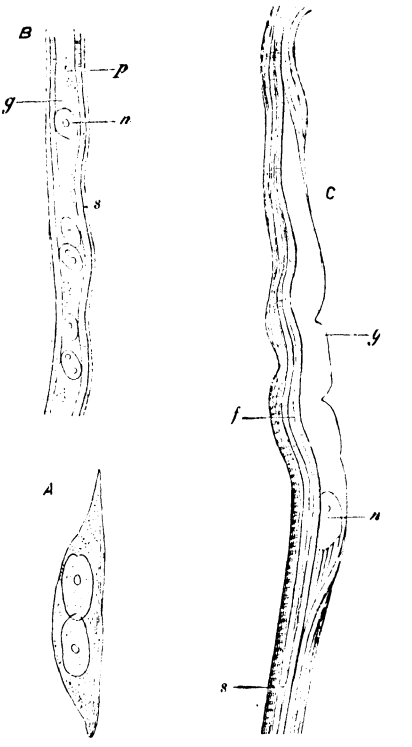


FIG. 293.—DEVELOPING MUSCULAR FIBRE. Highly magnified.

A, elongated cell with two nuclei and a striation beginning down one side of the cell (from fœtal sheep, Wilson Fox).

B, from fœtus of two months; *p*, granular protoplasm; *g*, glycogenous substance; *n*, nucleus; *s*, commencing sarcolemma, with striated muscular substance developing immediately beneath it.

C, from fœtus of three months, displayed so as to show the contractile substance collected at one side of the fibre, and partially enclosing the unaltered substance of the fibre, *g*; *f*, fibrils. B and C from Ranvier.

Growth.—The muscular fibres, after having acquired their characteristic form and structure, continue to increase in size till the time of birth, and thenceforward up to adult age. In a full-grown fœtus most of them measure twice, and some of them three or four times, their size at the middle of fœtal life; and in the adult they are about five times as large as at birth. This increase in bulk of the individual fibres would, in a measure, account for the enlargement of the entire muscles. It is uncertain how far there may be a multiplication or new formation of muscular fibres during the growth of a muscle, but it is probable that, during growth at least,

[1] F. Meves, Anat. Anz. xxxiv. 1909; J. Duesberg, *ibid.* (Verhandl. d. Anat. Gesellch. 1909).

a new formation of fibres within the muscles does occur. A mode of new formation which has been described is by the transformation of cells (myoblasts) which lie between the muscle-fibres, and which are presumably undifferentiated cells derived from the original muscle-plate. Fibres in various stages of development have been described in muscles at all stages of growth, and also in the adult condition, so that it has been conjectured that new muscular fibres may be formed in this way even after the development of the muscle is completed. But the increase in the adult which results from exercise of the muscles is mainly due to an increase in bulk of the fibres which are already developed.[1]

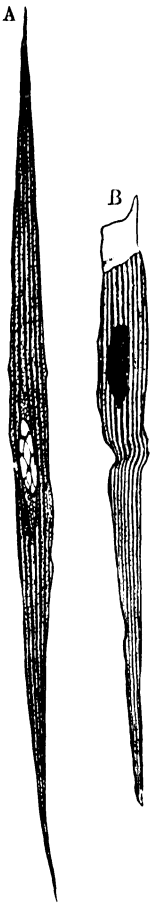


FIG. 294. MUSCULAR FIBRE-CELLS FROM THE MUSCULAR COAT OF THE SMALL INTESTINE. Highly magnified.

A, a complete cell showing the nucleus with intranuclear network and a longitudinal fibrillation of the cell-substance, with finely vacuolated protoplasm between the fibrils. B, a cell broken in the process of isolation; a delicate external layer projects at the broken end a little beyond the striated substance of the cell.

It was formerly thought that after removal by the knife or by disease striated muscular tissue is not regenerated, but that any breach of continuity which may occur in a muscle is filled up by a growth of connective tissue. It would appear, however, that the breach is, after a certain lapse of time, bridged across by muscular substance. How the new muscular tissue is formed is not fully understood, but it is usually considered that it occurs by the transformation of myoblasts into muscle-fibres, as in the original formation of muscle. Schmincke, however, states that regeneration is brought about by a budding from the ends of the existing fibres.[2]

PLAIN OR UNSTRIPED MUSCULAR TISSUE.

This is made up of cells, *contractile fibre-cells*, which were first distinguished as the true elements of the tissue by Kölliker. The cells may form fibrous bundles and strata, or may be less regularly arranged, and the tissue occurs either almost pure or mixed with other tissues in varying proportion. The cells are of an elongated fusiform shape (figs. 294 and 299), usually pointed at the ends. They are generally prismatic in transverse section, but are sometimes more flattened. In arteries which contain much elastic tissue in their middle coat the plain muscular fibres may be very irregular in shape (fig. 296). The cells vary greatly in length according to the part or organ in which they are found. Some occur which are cleft or forked at one or both ends. Their substance exhibits a longitudinal fibrillation, but no transverse striation. As shown by M. Heidenhain, the fibrils can be distinguished into superficial coarse and deep finer (fig. 295). They are doubly refracting. Each cell has a single nucleus, rarely more than one, which is always elongated and either elliptical or rod-shaped. Rod-shaped nuclei are specially characteristic of the muscle-fibres of the blood-vessels. At the ends of the nucleus the substance of the cell usually contains a few distinct granules arranged in linear series.

The nucleus shows the usual structure, having a distinct chromatin network and usually one or two nucleoli. Spiral nuclei have been described by E. Forster[3]

[1] Cf. Halban, Anat. Hefte, iii. 1894. [2] Ziegler's Beitr. xlv. 1909.
[3] Anat. Anz. xxv. 1904.

in both plain and cardiac muscular tissue. The involuntary fibre-cells possess a delicate homogeneous external layer (fig. 294, B), which may, however, be only the external layer of the cytoplasm, and is by no means comparable to the sarcolemma of voluntary muscular fibres, although, like that, it is liable to be wrinkled when the fibre is contracted, so that an indistinct appearance of transverse

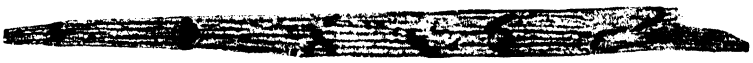


FIG. 295.—UNTOUCHED PHOTOGRAPH OF A PLAIN MUSCULAR FIBRE-CELL FROM THE CAT'S INTESTINE. (Schäfer.) Magnified 450 diameters.

The cell is broken across near the nucleus, which is indistinctly seen. At the broken part the finer internal fibrils are visible; over the rest of the cell the superficial coarser fibres are shown. Two or three incomplete knotted condensations are seen crossing the longitudinal axis of the cell.

striation may thus be sometimes produced. The cells are united by a small amount of intercellular cementing substance which becomes stained by nitrate of silver. In some parts intercellular spaces appear, but they are bridged across, as in epithelia, by fine denticulations which connect the contractile substance

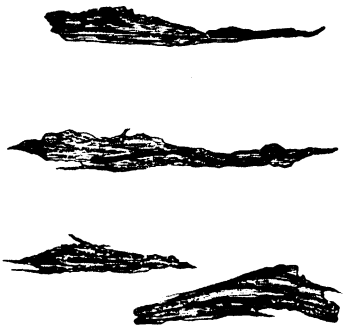


FIG. 296.—MUSCULAR FIBRE-CELLS FROM SUPERIOR THYROID ARTERY (MAN). (Schäfer.) Magnified 340 diameters.

into continuity from cell to cell so that the tissue forms a syncytium (fig. 297).[1] Each cell possesses a centriole close to its nucleus (fig. 298).

FIG. 297.—MUSCLE-CELLS OF INTESTINE. (Szymonowicz.) Magnified 530 diameters.

The fibres are represented in longitudinal section; and the interstices between them are seen to be bridged across by fine fibrils. *i*, interstice; *n*, nucleus.

FIG. 298.—PLAIN MUSCLE-FIBRE, SHOWING NUCLEUS, CENTRIOLE, AND CYTOPLASM WITH FIBRILS. (v. Lenhossék.)

The fibres are generally collected into larger and smaller fasciculi, which in many cases cross one another and interlace. The fasciculi are attached at their ends by connective tissue to the membranous and firmer parts where they occur. In some cases the attachment of the plain muscular cells takes place by means of elastic fibres which bifurcate at the end of the muscular cell. The two branches extend along each side of this and are firmly attached to it. Between the fasciculi and even penetrating between the fibres in a fasciculus is fine connective tissue with numerous elastic fibres. Involuntary fibres, especially those of the intestines, often exhibit after fixation knotted condensations of their cytoplasm

[1] For a description of these cell-bridges, see D. Barfurth, Arch. f. mikr. Anat. xxxviii. 1891.

(fig. 299), which has been interpreted by some authors to represent a condition of localised contraction. It is, however, by no means clear that this is the true interpretation of the appearance in question, for fully contracted fibres may show no such structure. A similar appearance is sometimes seen in striated muscle. The condensations stain more deeply with iron-hæmatoxylin than the rest of the fibres, and in the fresh condition they are more highly refracting. McGill describes the fibrillæ as being thickened at these knots.[1]

Plain muscular tissue is found in the coats of the membranous viscera. It is met with in the lower half of the gullet, the stomach, and the whole intestinal canal; that is, both in the muscular coat of the alimentary canal, and also as a layer in the tissue of the mucous membrane, and in the villi; in the trachea and bronchial tubes, in the bladder and ureters, and the ducts of the larger glands generally, in the uterus and its appendages, in the corpora cavernosa of both sexes, in the prostate gland, in the spleen, in the muscle of Müller at the back of the orbit, and in the ciliary muscle

Fig. 299.—A smooth muscle-fibre from the intestine showing knot-like condensations of the cytoplasm. (Grützner.)

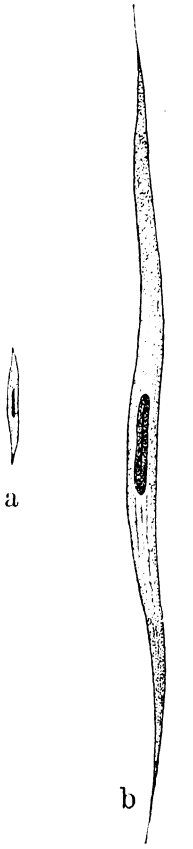


Fig. 300. Muscular fibres (*a*) from non-pregnant, (*b*) from pregnant uterus, drawn to the same scale. (Sellheim.)

and iris. The middle coat of the arteries, the coats of many veins and those of the larger lymphatics contain plain muscular tissue. In the skin it is present in the tubules of the sweat-glands lying between the secreting epithelium and the basement-membrane, in the form of minute muscles attached to the hair-follicles, and in the dartos or subcutaneous tissue of the scrotum.

Numerous nerves, chiefly of the pale variety, are supplied to this tissue; before their ultimate distribution they frequently come into connexion with microscopic ganglia. In the stomach and intestines there is a richly gangliated plexus—the *plexus myentericus* of Auerbach—between the longitudinal and circular layers of the muscular coat, and from the nerve-cells of this plexus fine non-medullated fibres pass to be distributed in ramifications

[1] For an account of the literature regarding these appearances and of plain muscle generally, see Grützner, Ergebn. d. Physiol. iii. 1904. See also on the subject of plain muscle, M. Heidenhain, Ergebn. d. Anat. x. 1900; Henneberg, Anat. Hefte, xv. 1901; Heidêrich, *ibid.* xix. 1902; Caroline McGill, Anat. Anz. 1907; also in Amer. Journ. Anat. ix. 1909. The variations in the nuclei of smooth muscle are also dealt with in this paper.

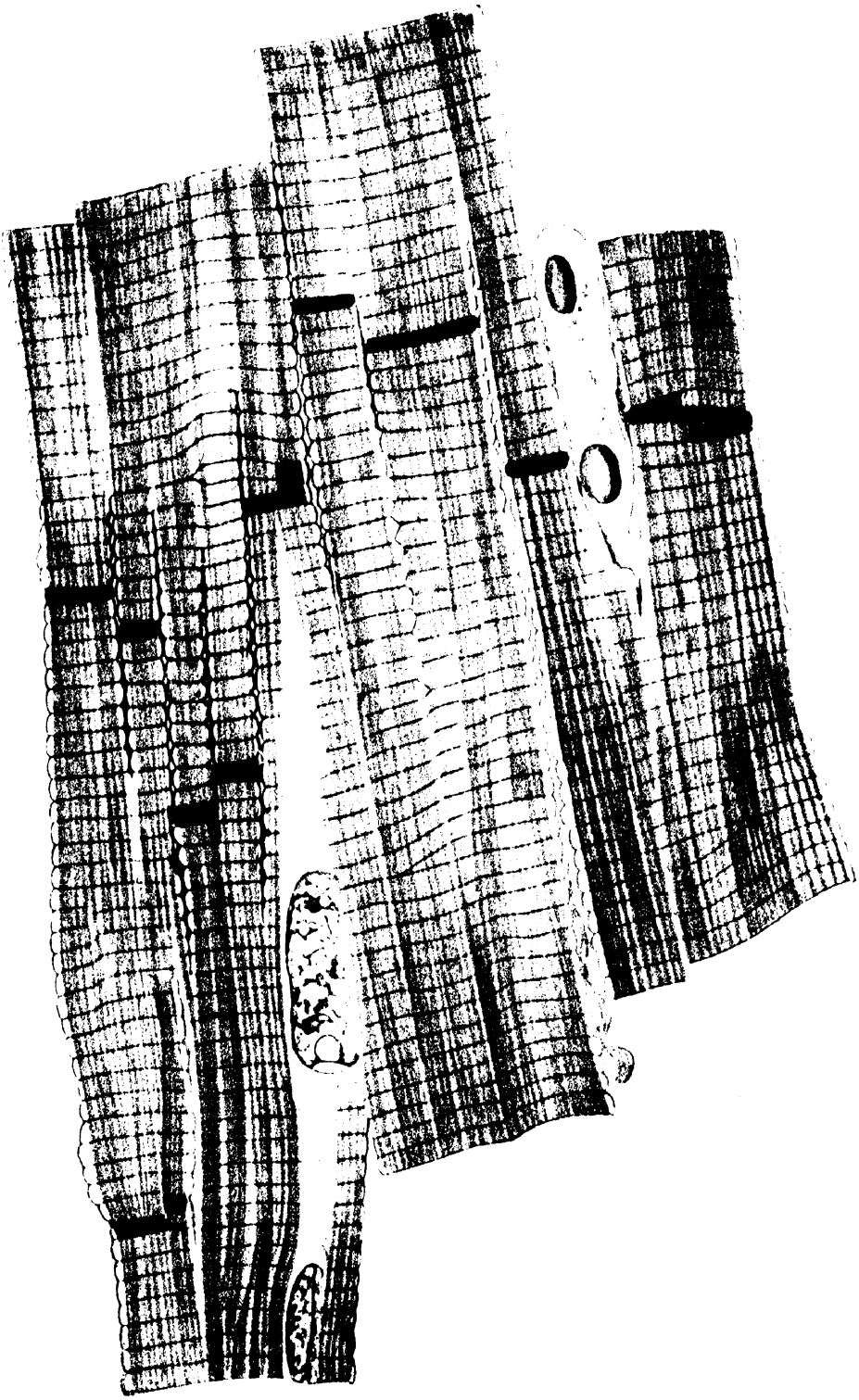


Fig. 301. Cardiac muscular fibres (human). (M. Heidenhain.)
The preparation was stained with vanadium-hæmatoxylin.

between and in contact with the muscular fibres. There is another rather finer gangliated plexus in the submucous coat from which nerve-fibres proceed to the muscular tissue of the mucous membrane.

The tissue receives blood-vessels, but these are far fewer in proportion than those of voluntary muscle. In some situations, as in the wall of the stomach and intestine, abundant lymphatic plexuses are found between the layers of the muscular coat.

Histogenesis.—The elements of the plain or unstriped muscular tissue are derived from embryonic nucleated cells, the origin of which has been traced in many cases to the myoblasts of the muscle-plates. But in other situations plain muscular fibres may take origin from other sources. Thus the plain muscle-cells of the sweat-glands are developed from ectoderm-cells, and the fibres of the sphincter and dilatator pupillæ at the back of the iris are formed from the ectoderm of the anterior part of the optic cup, which also gives origin to the pigmented epithelium of the back of the iris. The cells, whether mesodermic or ectodermic, which are to develop smooth muscle, become lengthened out and pointed at the ends, with elongation of the nucleus, whilst their substance becomes longitudinally fibrillated and anisotropous, and gradually acquires its permanent condition and characteristic properties. According to McGill,[1] the tissue is from the first a syncytium, and retains this character throughout life. Miss McGill describes a much more complete union of the cells than it is easy to admit, in view of the readiness with which they can be dissociated after death. On the other hand, some authors have denied the existence of connexions between the cells, and believe that the apparent bridges are not muscular, but an appearance due to delicate connective tissue between the fibre-cells. This, however, is difficult to reconcile with the fact that a contraction started at any part of the tissue during life is slowly propagated far beyond the limits of the point of stimulation.

The great increase in the muscular tissue of the uterus during gestation (fig. 300) takes place both by elongation and thickening of the pre-existing fibre-cells of which that non-striated tissue consists, and it is said also by the development of new muscular fibre-cells from small cells lying in the tissue. In the shrinking of the uterus after parturition the fibre-cells diminish to their previous size; many of them become filled with fat-granules, and are supposed eventually to be removed by absorption.

Regeneration of plain muscle after artificially produced lesions has been seen to be accompanied by karyokinetic multiplication of the muscle-cells adjacent to the lesion (in the newt by Stilling and Pfitzner).

CARDIAC MUSCULAR TISSUE.

The fibres of the heart (figs. 301, 302, 303) differ remarkably from those of involuntary muscular organs in general, inasmuch as they present transverse striæ. The striæ, however, are less strongly marked, and less regular, and the fibres are smaller in diameter, than in the voluntary muscles. They differ also from these in being apparently made up of cylindrical cells (fig. 302) joined end to end and often presenting a branched or forked appearance near one extremity (*c*). Each cell has a single clear oval nucleus situate near the centre; occasionally two nuclei are seen. In some animals (pig, ox, sheep) the cells are multi-nucleated, the nuclei occurring in rows; in others (cat, rabbit) they are uni- or bi-nucleated as in man.[2] The cell-substance is striated longitudinally as well as transversely, the striated substance appearing to be composed of a number of fibrils or sarcostyles, which on transverse section are seen as small polygonal areas. An investing membrane or sarcolemma

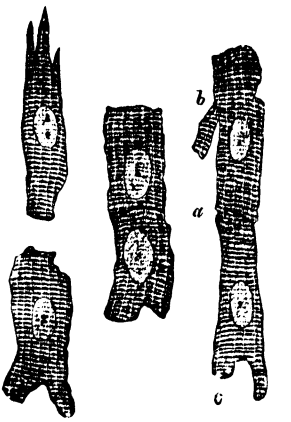


FIG. 302.—SIX MUSCULAR FIBRE-CELLS FROM THE HEART. (Schäfer.) Magnified 425 diameters.

a, line of junction between two cells; *b*, *c*, branching of cells. (From a drawing by Mr. J. E. Neale.)

[1] Int. Monthly Journ. of Anat. and Physiol. xxiv. 1907; Amer. Jour. Anat. ix. 1909.
[2] Marie Werner, Arch. f. mikr. Anat. lxxv. 1910.

has not hitherto been proved to exist on these fibres, although there is a fine homogeneous peripheral layer which bounds the fibres and is probably the most superficial layer of the original undifferentiated protoplasm. This superficial layer is regarded by v. Palczewska,[1] who has studied the cardiac muscular tissue in the human heart, and by M. Werner,[2] who has employed the hearts of various species of animals, as a true sarcolemma (see fig. 304).

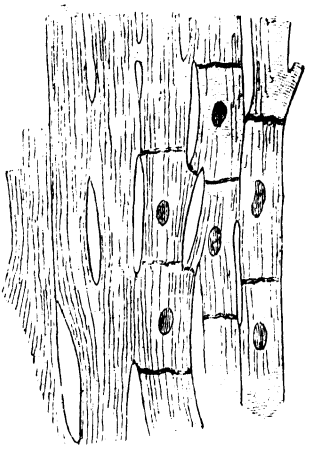


FIG. 303.—MUSCULAR FIBRES FROM THE HEART, MAGNIFIED, SHOWING NUCLEI, CROSS-STRIÆ, DIVISIONS, AND JUNCTIONS. (Schweigger-Seidel.)

The nuclei and cell-junctions are only represented on the right-hand side of the figure, which is diagrammatic.

The muscular fibres of the heart freely divide and anastomose (figs. 303, 305), so that there is continuity throughout the whole of the myocardium of both auricles and ventricles.[3]

There has been much discussion as to whether the muscular tissue of the mammalian heart is to be regarded as constituted of a number of uninucleated cells connected by bridges or whether it is a complete syncytium—*i.e.* formed of a continuous protoplasmic mass containing nuclei at intervals, with the muscle-fibrils in complete continuity throughout.

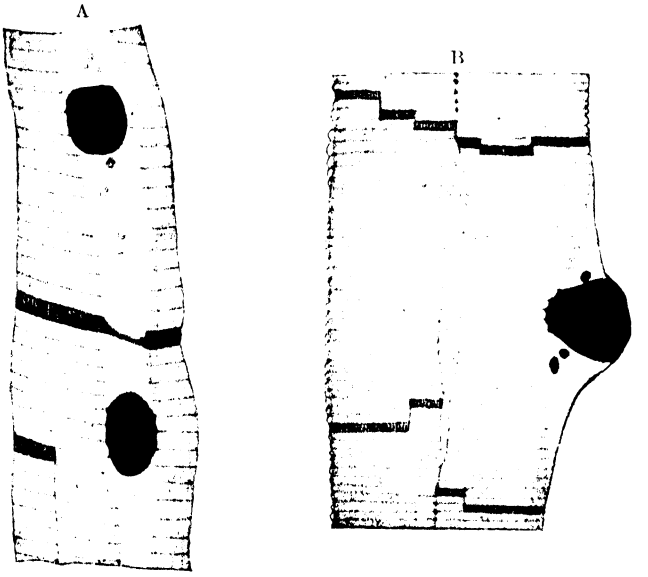


FIG. 304.—LONGITUDINAL SECTIONS OF PORTIONS OF MUSCULAR FIBRES FROM THE ADULT HUMAN HEART, SHOWING THE INTERSEGMENTAL OR INTERCELLULAR SEPTA AND THE NUCLEI, WITH UNDIFFERENTIATED PROTOPLASM (SARCOPLASM). (v. Palczewska.)

In A, a septum is seen to pass not only across the contractile fibrils but also across the cell-protoplasm. In B the protoplasm is accumulated at the side of one of the cells represented, and the nucleus is also placed laterally: this is unusual. The investing membrane (sarcolemma?) is here shown.

[1] Arch. f. mikr. Anat. lxxv. 1910. [2] *Op. cit.*

[3] Cf. Przewoski, Arch. d. sci. biol. St. Petersburg, ii. 1893; M. Heidenhain, Anat. Anz. xx. 1902, and Ergebn. d. Anat. viii. 1898; J. B. MacAllum, Anat. Anz. xiii. 1897; Godlewski, Bull. d. Krak. Akad. 1901; v. Ebner, in Kölliker's Handb. d. Gewebelehre, iii. 1902.

The former view is that which was taken by Schweigger-Seidel,[1] and is founded upon the fact that by various methods of staining, and especially by nitrate of silver, there are distinct indications of transverse septa across the fibres, each interseptal space having as a rule a nucleus somewhere near its centre (fig. 303). Moreover, by treatment with certain reagents (*e.g.* 33 per cent. caustic potash solution) the fibres tend to break up into uninucleated portions which correspond with the heart muscle-cells of Schweigger-Seidel (fig. 302). On the other hand there is evidence that the muscle-fibrils are continued across the septa and therefore pass from cell to cell (figs. 305, 306). Continuity of fibrils is also strikingly shown in the fibres of Purkinje which occur in the heart of the sheep and ox in certain parts of the myocardium near the endocardium (fig. 307). These fibres are visible even to the naked eye as clear beaded filaments; and when examined with the microscope are seen to be formed by the juxtaposition of uni- or bi-nucleated masses of protoplasm which at first glance look like large clear separate cells. But on observing more carefully it is obvious that they are not separate from one another, but are intimately united by cross-striated fibrils which occupy their periphery, and

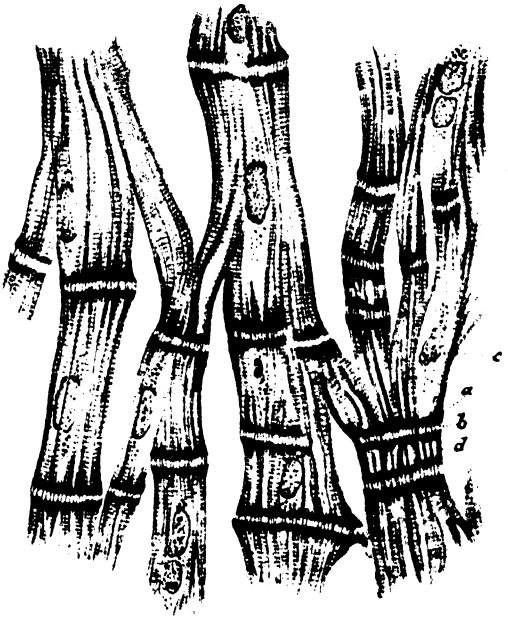


FIG. 305.—HEART MUSCLE-FIBRES SHOWING TRANSVERSE SEGMENTATION. (Przewoski.)

a, septum; *b*, bridging fibrils; *c*, nucleus; *d*, a short segment without nucleus.

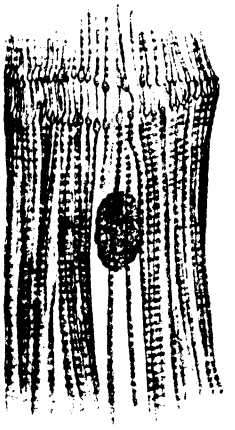


FIG. 306. — PORTION OF CARDIAC MUSCLE EXHIBITING CONTINUITY OF FIBRILS ACROSS JUNCTIONAL LINE. (Przewoski.) Highly magnified.

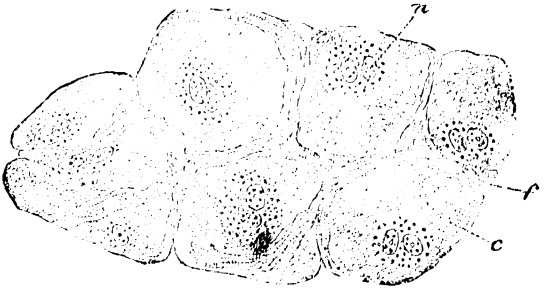


FIG. 307. — FRAGMENT OF THE NETWORK OF PURKINJE FROM THE VENTRICULAR ENDOCARDIUM OF THE SHEEP. (Ranvier.) Magnified 300 diameters.

c, cell; *f*, striated substance; *n*, nuclei.

[1] Stricker's Handb. d. Gewebelehre, 1869.

passing beyond the apparent cell-outlines are traceable over two or more of the apparent cells. The fibrils have evidently been formed in a syncytium, being developed at parts equidistant or nearly so from its nuclei, and in this way mark off what look like cell-outlines and produce a simulation of independent cell-structure. Now there is every reason to believe that the fibres of Purkinje represent an incomplete development of cardiac muscular structure, the striated substance being confined to what would be, were the cells separate from one another, the surface layer of each cell. With further development, such as obtains in ordinary cardiac muscle, the whole or nearly the whole of the protoplasm becomes converted into muscle-substance, only a small area being left around each nucleus. Purkinje's fibres therefore probably represent a less developed portion of the original syncytium, although so far as mere growth is concerned they have surpassed in size the ordinary cardiac fibres. And in fact transitions can be traced between the Purkinje fibres and ordinary cardiac muscle. In man and most animals distinct Purkinje fibres do not exist, but the cardiac fibres are rather larger near the ventricular endocardium than elsewhere. In tracing their development it is found that the fibres which are nearest the endocardium develop last.[1]

Auriculo-ventricular bundle.—It was until recently believed that in mammals the auricular and ventricular musculatures were entirely distinct, the connexion between auricles and ventricles being maintained by connective tissue, as well as in part by nerves. But muscular continuity was observed in the rat by Stanley Kent, and it has been definitely shown in mammals generally, including man, by W. His, jun., that a comparatively narrow band or bundle of somewhat modified cardiac muscular tissue connects the auricular and ventricular musculature. The band originates in the musculature of the interauricular septum and passes through the uniting connective tissue opposite the situation of the septum to reach the base of the ventricles. Here, in most animals, it forks, one branch passing to the left and the other, the larger, to the right ventricle. This *auriculo-ventricular bundle* loses itself in the less completely developed cardiac muscle which underlies the endocardium, and which it resembles in structure. In animals which have fibres of Purkinje, the ventricular end of the bundle resembles these in structure.

Most physiologists are of opinion that the function of the bundle is to conduct the contractions of the auricular muscle to the ventricles. This opinion is founded upon the statement—which is, however, contested by Kronecker and others[2]—that if the bundle be severed artificially or destroyed by disease the auricular rhythm is not communicated to the ventricle, which then beats with a slow and somewhat irregular autonomous rhythm (brachycardia, heart-block). The bundle is accompanied by nerves which have microscopic ganglia in their course (Wilson).[3]

Blood-vessels, lymphatics, and nerves of cardiac muscle.—The musculature of the heart is even more richly supplied with *blood-vessels* than ordinary muscular tissue; and, as in that, the capillaries follow the general

[1] J. B. MacCallum, Anat. Anz. xiii. 1897.

[2] Pankul, Zeitschr. f. Biol. li. 1908; M. Imchanitzki, Arch. f. Anat. 1909.

[3] The literature of the His bundle is extensive. The following are some of the principal papers relating to it: W. His, jun., Abhandl. a. d. med. Klinik z. Leipzig, 1893, and Deutsch. Arch. f. klin. Med. lxiv. 1899; A. F. Stanley Kent, Journ. Physiol. xiv. 1893; Braueng, Arch. f. Anat. 1904 (Suppl.); H. E. Herring, Pflüger's Arch. cviii. 1905, and cxvi. 1907; Keith and Flack, Lancet, 1906, and Journ. Anat. and Physiol. 1907; Einthoven, Arch. intern. de Physiol. iv. 1906; S. Tawara, Das Reizleitungssystem d. Säugethierherzens, 1906; G. A. Gibson, Brit. Med. Journ. 1906; J. Erlanger, Journ. Exper. Med. 1906, and Pflüger's Archiv. cxxvii. 1909; also (with co-workers) in Amer. Journ. Physiol. 1906, 1907, 1908; Fahr, Virchow's Arch. 1907; Wenckebach, Arch. f. Physiol. 1907; T. Lewis, Brit. Med. Journ. 1908; Briggs, Brit. Med. Journ. 1908; Trendelenburg and Cohn, Centralbl. f. Physiol. xxiii. 1909, and Pflüger's Arch. cxxxi. 1909; L. F. Barker and A. D. Hirschfelder, Arch. of Internal Medicine, iv. 1909; E. J. Curran, Anat. Anz. xxxv. 1909; J. G. Wilson, Proc. Roy. Soc. B. lxxxi. 1909.

arrangement of the muscular fibres. It differs from ordinary muscle in the fact that it has an abundant supply of *lymph-vessels*, which can be easily demonstrated by the method of interstitial injection. The lymph-capillaries form a network throughout the intermuscular connective tissue and unite to form efferent vessels which run over the surface of the organ underneath its serous covering (epicardium). These eventually pass towards lymphatics at the base of the heart and here enter lymph-glands. Small lymph-glands have also been described as occasionally occurring under the epicardium.[1]

The **nerves** which pass to the muscular tissue of the heart are derived from two sources—viz. fine medullated fibres from the vagus, and non-medullated fibres from the cervical sympathetic, chiefly from its inferior ganglion. After forming the cardiac plexuses at the base, they pass to the auricles and are distributed to minute ganglia which are found there, chiefly under the epicardium, especially near the entrance of the great veins; ganglia have also been described in the interauricular septum.[2] Other nerve-fibres proceed to the base of the ventricles, where microscopic ganglia also occur under the epicardium: from these, nerve-fibres extend into all parts of the muscular substance; they end in fine ramifications over the individual muscle-fibres.[3] The afferent nerves mostly course under the ventricular epicardium, but others are distributed to the endocardium: these end in ramified expansions in those membranes.[4]

Histogenesis.—Further evidence of the syncytial nature of the cardiac muscle is obtainable from the study of its development. For although as with other varieties of muscular tissue it is at first composed of what appear to be separate cells, derived from the mesoderm, M. Heidenhain has described a stage of development in the duck embryo in which the heart-muscle has the appearance of a complete syncytium with fibrils developed in its protoplasm passing far beyond the bounds of anything that could be thought to be the individual cells, and there is reason to believe that the same condition obtains in other avine and mammalian embryos at a similar stage. A similar condition of continuity of fibrils from one cell to another also occurs, according to G. Mann, in the frog's auricle (fig. 308), and, although the ventricle is formed

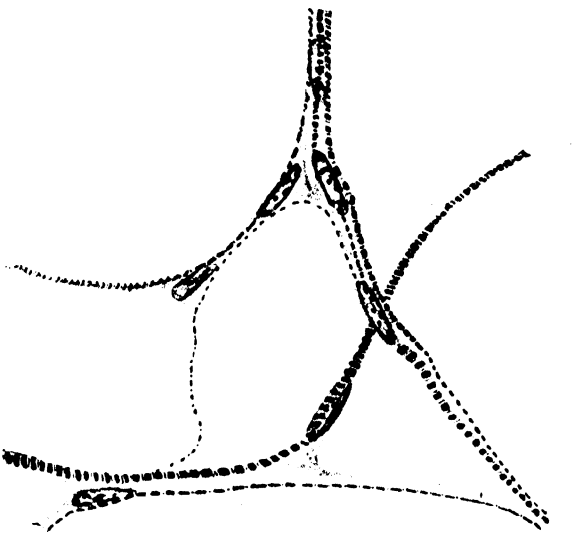


FIG. 308.—BRANCHING SYNCYTIUM OF HEART-MUSCLE OF AURICLE OF FROG WITH MUSCLE-FIBRILS PASSING THROUGH THE CELLS. (G. Mann.)

[1] On the lymphatics of cardiac muscle, see H. Bock, Anat. Anz. xxxvii. 1905; Mouché, Journ. de l'anat. 1909.

[2] M. Lissauer (Arch. f. mikr. Anat. lxxiv. 1909) could find ganglion-cells only under the epicardium of the auricles, and of the auricular septum and auriculo-ventricular groove on both sides. He states that they follow the course of the epicardial nerves, and are not to be found either in the substance of the myocardium or under the endocardium.

[3] Huber and de Witt, Journ. Comp. Morph. vii. 1898; Heymans and Demoor, Mém. de l'acad. roy. de méd. de Belgique, xiii. 1894; H. J. Berkeley, Anat. Anz. ix. 1898.

[4] Dogiel, Arch. f. mikr. Anat. lii. 1898, and liii. 1899; Smirnow, Anat. Anz. x. 1895, and xxxii 1908; Michailow, Int. Monthly Journ. Anat. and Physiol. xxv. 1908.

to all appearance of separate striated cells as already mentioned, it would seem that here also muscle-fibrils pass from cell to cell across the junctions.

If this is so, we must assume that, as was held previous to the work of Schweigger-Seidel, the fibrils and fibres of cardiac muscle are continuous throughout the myocardium both longitudinally and laterally. In this case the question naturally arises, How are we to account for the apparent cell-outlines, in the form of the transverse septa which mark the muscle-fibres off into uninuclear areas simulating and doubtless representing individual cells? Some observers have held that the septa are purely accidental, produced by bands of contraction traversing the fibres, which have been fixed by the hardening reagent.[1] M. Heidenhain has put forward the view that they are portions of the fibres in which, as in the sutures between the cranial bones, growth may proceed. But if this were so we should expect them to be more distinct in young and growing heart-muscle, whereas the contrary is the case; indeed they are not seen in developing muscle, and are said to be absent in most of the lower vertebrata and even in some mammals.[2] These septa may, when they occur, afford a certain block to the passage of the contraction wave from cell to cell. Thus it has been shown by M. Imchanitzki[3] in the heart fixed in a condition of fibrillar contraction that the individual cardiac muscle-cells may show different stages of contraction, or one may be at rest and the succeeding cell in contraction. Kronecker, in whose laboratory these observations were made, regards this as strong evidence that the passage of the contraction of the fibres from cell to cell is effected through nerves and not by muscular continuity. The opinion that the septa in question represent cell-outlines which have formed by differentiation in the original syncytium, as happens with many originally syncytial structures, is supported by the fact that they exhibit reactions which are similar to those yielded by cement-substance between cells, and that there is a tendency for the fibres to break across at these points. That the differentiation is imperfect is seen from the circumstance that the muscle-fibrils are continued across the cement lines,[4] and that it is not a necessary feature of heart-muscle structure is evidenced by its absence in some animals. It is possible that the interpolated segments in which no nuclei are visible are continuous with nucleated portions of fibres in other planes than that of the section in which they are seen. This view is that taken by K. W. Zimmermann, and upheld by his pupils, v. Palczewska and Werner, whose work has already been referred to.

[1] Cf. Hoffmann, Dissert. Leipzig, 1909. A similar view has been held by Wagener, v. Ebner, and Aschoff.

[2] Moriya, Anat. Anz. xxiv. 1903.

[3] Arch. internat. de physiol. iv. 1906.

[4] Przewosky, Arch. d. sc. biol. St. Petersburg, 1893; M. Heidenhain, *loc. cit.*

THE TISSUES OF THE NERVOUS SYSTEM.

The elements which compose the tissues special to the nervous system are (1) *nerve-cells*; (2) *nerve-fibres* (which are in every case prolongations or processes of nerve-cells); (3) *neuroglia-cells and neuroglia-fibres*, which play the part of a sustentacular tissue in the central nervous system, in which, except in the immediate neighbourhood of the blood-vessels, there is little ordinary connective tissue; (4) a peculiar ciliated epithelium (*ependyma*) which lines the ventricles of the brain and the central canal of the spinal cord. The ependyma represents a residue of the invaginated ectoderm in connexion with which the whole nervous system has become developed.

Of the above elements the *nerve-cells*, or, strictly speaking, the nucleated bodies of the nerve-cells, occur exclusively in the grey matter of the brain and spinal cord, and in those small collections, known as *ganglia*, which are found on certain of the peripheral nerves—*e.g.* on the posterior roots of the spinal nerves and of some cranial nerves, and in connexion with many of the sympathetic nerves; the main sympathetic nerves which run on either side of the vertebral column being beset with a succession of paired ganglia forming the sympathetic chain (Germ. *Grenzstrang*; Fr. *grand sympathétique*).

Nerve-fibres form the bulk of the white matter of the brain and cord, and are also found passing through the grey matter. Leaving (or entering) the cord and brain in the nerve-roots, they become ensheathed by connective tissue, and outside the vertebral canal and skull form the peripheral nerve-trunks and nerve-plexuses from which the nerves of the body generally are derived. A large amount of connective tissue enters into the structure of the peripheral nerves, giving them toughness and serving to bind together and protect the soft and otherwise easily injured nerve-fibres. Finally the fibres terminate in *nerve-endings*, which are either formed simply by the breaking up of the individual nerve-fibres into a terminal arborescence; or the nerve termination is incorporated within a special growth of the connective tissue which envelops the fibres, 'end-organs' of various kinds being thereby produced.

Neuroglia-cells or *glia-cells* are found only in the central nervous system, where they occur as irregular stellate cells with processes in the form of fibres extending from the cell-body in all directions between the proper nervous elements. The *ependyma* is also found only in the nerve-centres.

The structure and arrangement of these elements of the nervous system may now be severally described, beginning with the central epithelium of the nerve-centres which has formed the scaffolding upon and around which all the nervous elements of the spinal cord and brain are built up.

Central epithelium (ependyma) of the spinal cord and brain.—To explain the relationship of this structure to the rest of the central nervous system it is necessary briefly to consider the mode in which the nervous system is laid down in the embryo.

The first appearance of the nervous system takes the form of a thickening of the ectoderm along the middle line of the blastoderm. This thickening as soon as it becomes apparent is found to occupy the bottom and sides of a widely open groove which extends from near the front of the blastoderm to the anterior end of the primitive streak where this divaricates and becomes lost. The groove is the *neural groove* and the thickened ectoderm lining it is the *neural ectoderm*. As development proceeds the groove deepens by the folding up of its sides; presently the lateral folds bend over towards one another, and eventually grow together so as to close in the previously open groove, which is thus converted into a canal,

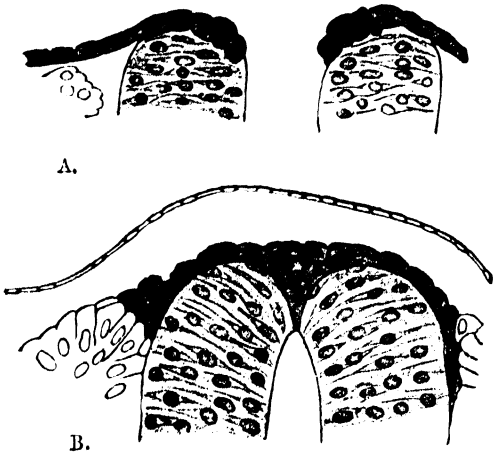


FIG. 309.—CLOSURE OF NEURAL GROOVE TO FORM NEURAL CANAL (HUMAN EMBRYO). (v. Lenhossék.)

A, canal open; B, canal just closed.

The cells at the roof of the closing canal are seen growing out on either side to form thickened masses which form the germs of the root-ganglia.

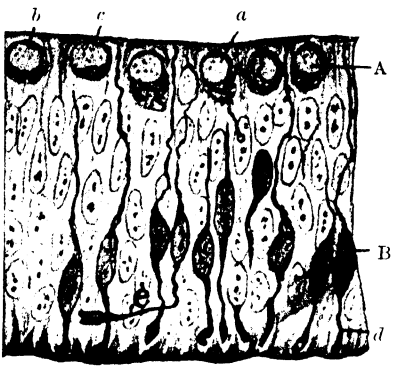


FIG. 310. SECTION OF WALL OF NEURAL TUBE OF CHICK OF THREE AND A-HALF DAYS. (Cajal.)

a, germinal layer containing, A, neuroblasts, of which *b* and *c* are spheroidal, but already possess neuro-fibrils: from *a* the axon has begun to sprout; B, neuroblasts in a bipolar stage; *d*, enlarged end of axon of one of these neuroblasts; *e*, another axon growing tangentially.

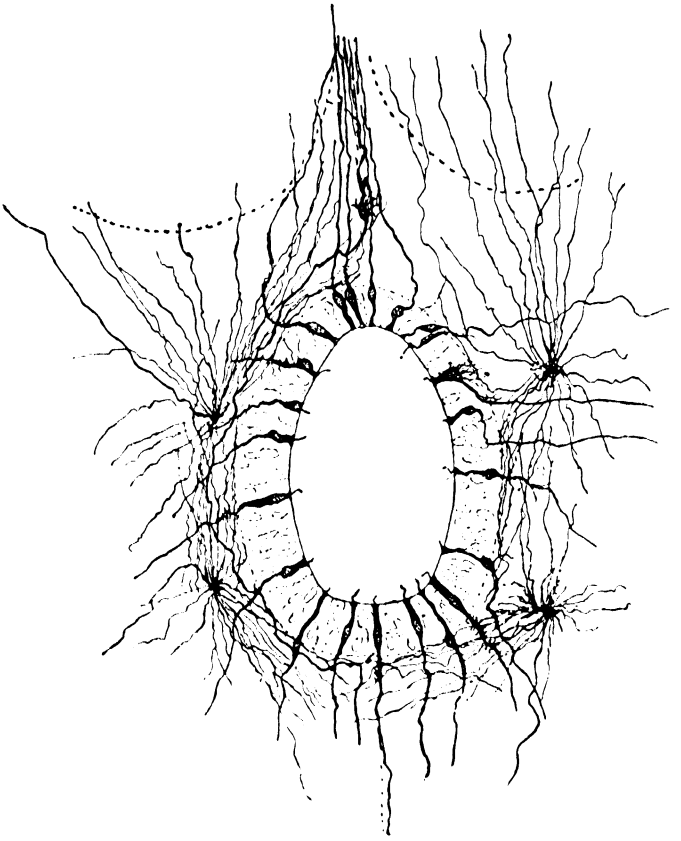


FIG. 311.—EPENDYMAL EPITHELIUM OF SPINAL CORD OF EMBRYO. (v. Lenhossék.) Stained by Golgi method.

Only a few of the ependymal cells are stained. In the grey matter four neuroglia-cells are represented.

the *neural canal.* As it thus closes up, a part of the neural ectoderm near the dorsal surface of the groove remains unenclosed, and buds out at regular intervals along each side ; these buds form the germ or blastema for the root-ganglia of the nerves (fig. 309).

Up to the present the neural epithelium is composed of columnar cells which extend from the internal surface of the groove or canal to its external surface (fig. 310) ; later some of the cells acquire cilia on the surface which is turned towards the interior of the canal, to which they continue to furnish a lining. Amongst these columnar cells—and formed as the result of the division and transformation of some of them—the proper nervous elements begin to appear in the form of scattered *neuroblasts* which become modified to form nerve-cells; nerve-fibres eventually growing out from them. Other cells of the epithelium which forms the wall of the neural canal (*spongioblasts*) are transformed into neuroglia-cells, and ultimately the nerve-cells and -fibres and neuroglia-cells and -fibres form the great bulk of the substance of the brain and spinal cord, while the fixed ends of the ciliated epithelium-cells of the neural canal become reduced to attenuated threads which extend to the peripheral part of the canal between the other elements (figs. 311, 312). This elongated condition of the ependyma-cells remains in lower vertebrates (amphibia and fishes) throughout life, but

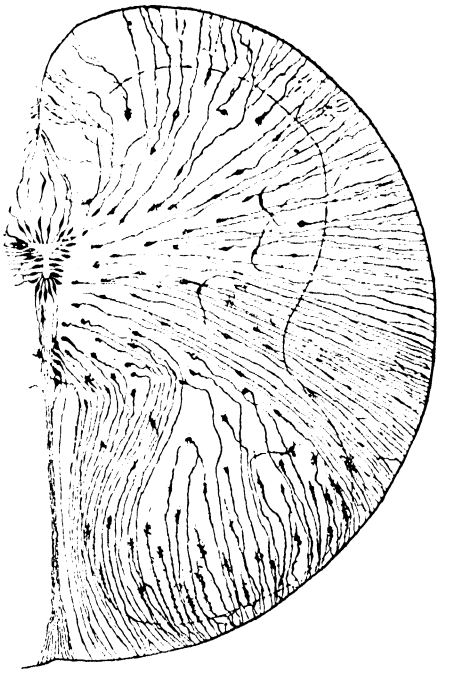


FIG. 312.—SECTION OF SPINAL CORD OF EMBRYO, SHOWING THE FORMATION OF NEUROGLIA-CELLS FROM DETACHED EPENDYMA-CELLS. (v. Lenhossék.)

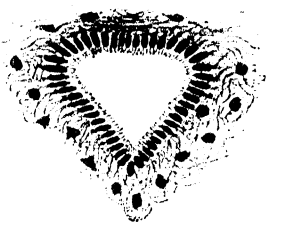


FIG. 313.—CENTRAL CANAL OF SPINAL CORD OF A CHILD SIX YEARS OLD, SHOWING ITS CILIATED EPENDYMA-CELLS. (Schäfer.) Magnified 150 diameters.

in higher vertebrates, especially in mammals, it becomes impossible to detect in post-embryonic life, and is greatly obscured or is no longer seen even in the later stages of embryonic development, many of the cells becoming detached and converted into neuroglia-cells. Some of the cell-bodies remain, however, distinct throughout life as the epithelium-cells of the central canal of the cord (fig. 313) and of the ventricles of the brain; these cells are provided with cilia on their free border, while their fixed ends, which appear to branch, are gradually lost as they are traced into the grey matter surrounding the canal.

Neuroglia.—This is the tissue which in the central nervous system occupies the interstices between the proper nervous elements (fig. 314), and serves to separate and support them.[1]

[1] The neuroglia-cells have been supposed to play a part in connexion with the nutrition of the nerve-cells, by acting as intermediaries between them and the blood-vessels. This is suggested by the observations of Andriezen (Brit. Med. Journ. 1893), and of Ford Robertson (Rev. of Neurol. 1905), who

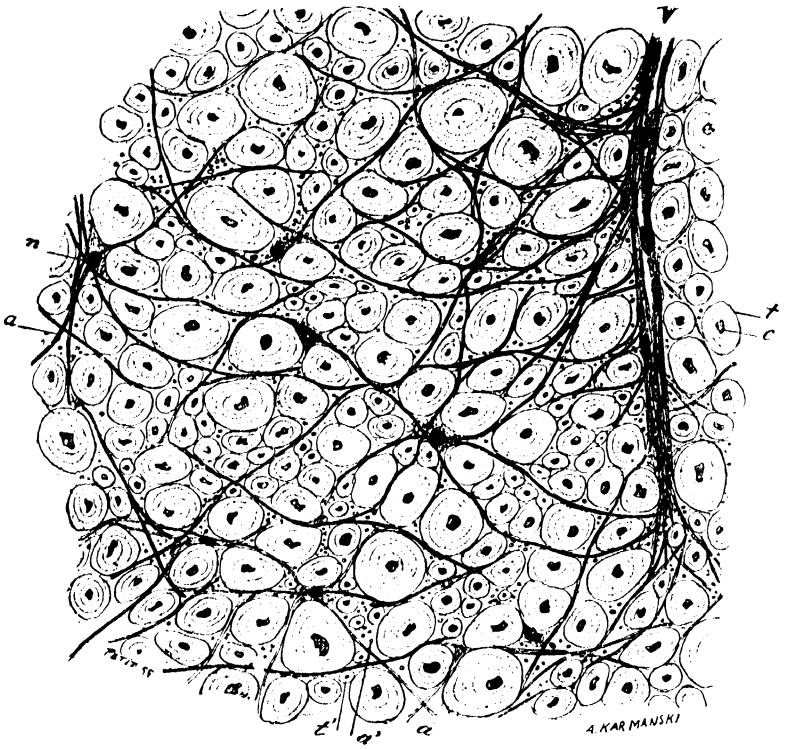


FIG. 314.—TRANSVERSE SECTION OF WHITE MATTER OF SPINAL CORD, SHOWING NERVE-FIBRES CUT ACROSS AND NEUROGLIA-FIBRES AMONGST THEM. (Ranvier.)

t, a medullary nerve-fibre; *c*, its axis-cylinder; *t'*, a small fibre; *n*, neuroglia cell-body; *a*, *a*, neuroglia-fibres; *a'*, others cut across.

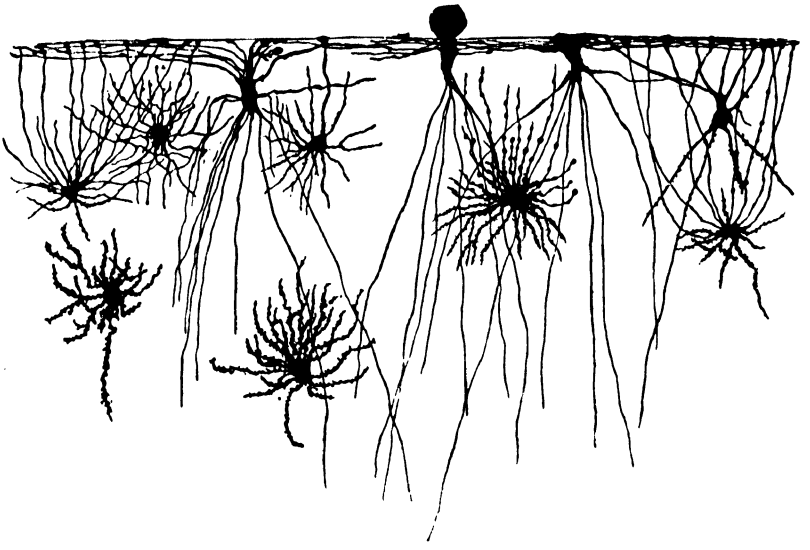


FIG. 315.—NEUROGLIA-CELLS OF CEREBRAL CORTEX. Golgi preparation. (G. Retzius.) Spider-cells, arborescent cells, and elongated cells are represented.

It is composed of cells and fibres. The latter are usually regarded as either forming or at least as being included within the processes of the cells. Some authors, however, regard it as probable that the fibres are not actually connected with the cells in the fully formed condition, but run in a ground-substance independently of the cells,[1] much as is the case with the fibres of connective tissue. This opinion is mainly based upon the fact that the fibrils can be stained distinctively,[2] but the argument would equally apply to the fibrils of nerve-cells, which are certainly parts of the cells. Like nerve-cells, neuroglia-cells are stained black by the Golgi chromate of silver method, and they then appear as stellate bodies with long fibre-like processes radiating out from the cell-body and passing between the proper nervous elements. The great majority of neuroglia-cells possess only these long, fine, and unbranched processes, which may extend a long way from the cell-body (fibrillar or spider-cells) (fig. 317). But there are a certain number in which the processes are dendritic; in this case they usually terminate at no great distance from the body of the cell (arborescent or protoplasmic cells, fig. 318).[3] In cells which are unstained (fig. 316) or in which only the fibres are stained, the cell-substance being left clear, the fibres

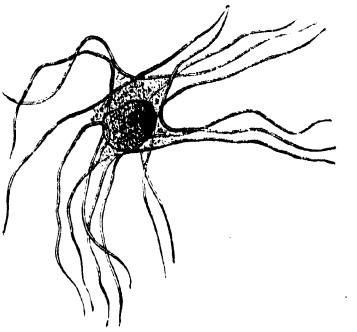


FIG. 316. — A NEUROGLIA-CELL ISOLATED IN 33 P. C. ALCOHOL (Ranvier.)

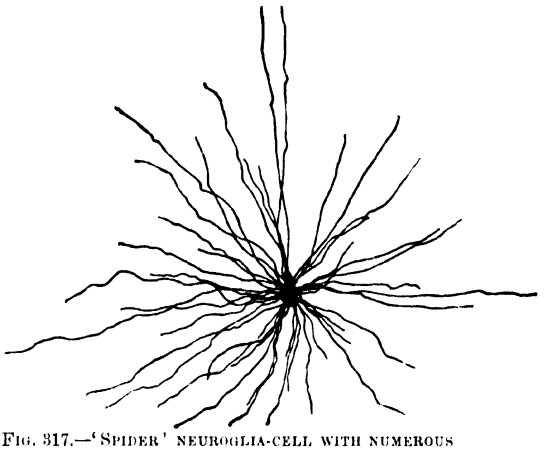


FIG. 317.—'SPIDER' NEUROGLIA-CELL WITH NUMEROUS UNBRANCHED FIBRES EXTENDING IN ALL DIRECTIONS FROM THE CELL-BODY. Golgi preparation. (Andriezen.)

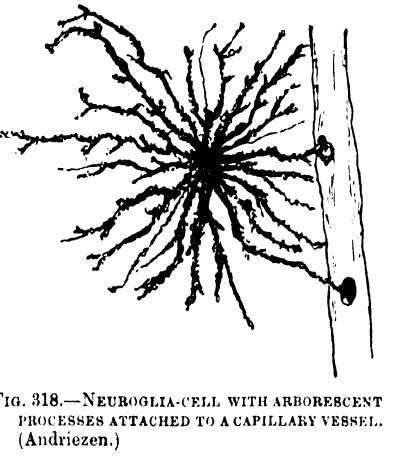


FIG. 318.—NEUROGLIA-CELL WITH ARBORESCENT PROCESSES ATTACHED TO A CAPILLARY VESSEL. (Andriezen.)

describe a special relationship between certain neuroglia-cells and blood-capillaries, as well as by those of E. Holmgren, who has described a trophospongium within nerve-cells which is penetrated by branches of neuroglia-cells. Aguerre also suggests an active function for neuroglia-cells (Arch. f. mikr. Anat. lvi. 1900).

[1] Huber, Amer. Journ. of Anat. i. 1901; Yamagiwa, Virch. Arch. clx.; Reinke, Arch. f. mikr. Anat. l. 1897; Whitwell, Brit. Med. Journ. 1898.

[2] Weigert, Anat. Anz. 1890, and Beitr. z. Kenntn. d. norm. menschl. Neuroglia, 1895. On the structure of neuroglia, see also E. Müller, Arch. f. mikr. Anat. lv. 1900 (fishes); Rubaschin, Arch. f. mikr. Anat. lxiv. 1904; and Hardesty, Amer. Journ. Anat. ii. 1902. Hardesty regards the neuroglia elements as forming a permanent syncytium, but the evidence of Golgi preparations is in favour of their being distinct from one another.

[3] Andriezen, *op. cit.*

may be observed to pass entirely through the cell-body from one process into another.[1] In this respect they resemble the neuro-fibrils of nerve-cells and the fibrils which can be seen in certain varieties of epithelium.

Although usually of a stellate shape owing to the fact that their processes extend more or less from all parts of the cell-body, in certain parts the neuroglia-cells take on an elongated shape (fig. 315), as is seen in the superficial layer of both the cerebral and cerebellar cortex.[2] The long fibre-like nucleated cells of the retina which are known as the fibres of Müller are also to be looked upon as of a neuroglial nature.

According to the observations of Hardesty[3] in the pig-embryo, the neuroglia-fibres become developed within a syncytium of neural ectoderm-cells which is known as the neuro-spongium (His). They appear relatively late, long after connective-tissue fibres have made their appearance and after medullation of the nerve-fibres has commenced.

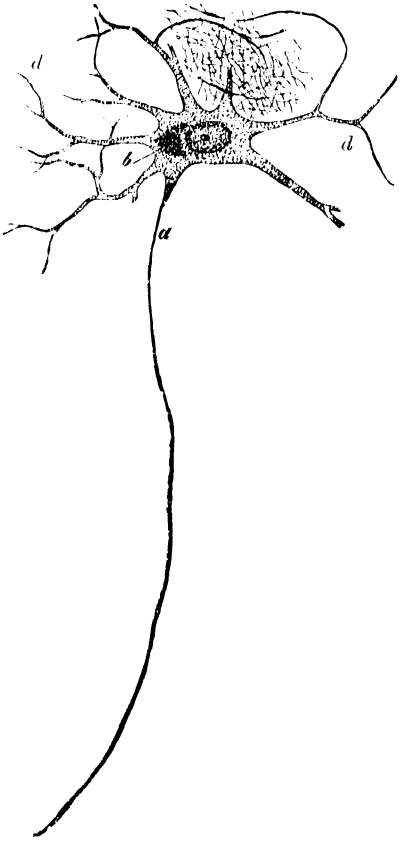


FIG. 319.—NERVE-CELL FROM VENTRAL HORN OF SPINAL CORD. (J. Gerlach.)

a, axon; *b*, cell-body with nucleus and clump of pigment-granules; *d*, *d*, dendrons.

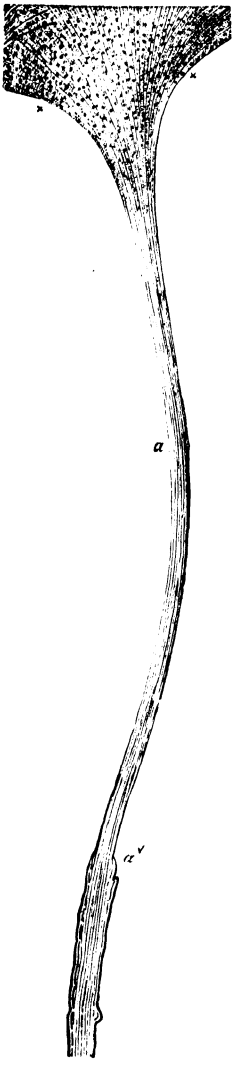


FIG. 320.—AXON ARISING FROM CELL-BODY OF A NERVE-CELL. (M. Schultze.)

a, axon; *a'*, appearance of medullary sheath; × ×, portion of nerve cell-body showing neuro-fibrils converging into axon.

Nerve-cells are found only in the grey matter of the nerve-centres and in the ganglia which lie outside the central nervous system, of which they form isolated

[1] Ranvier, Arch. de Physiol. 1893. [2] Retzius, Biol. Unters. v. 1893; vi. 1894.
[3] Amer. Journ. Anat. ii. 1902, iii. 1904.

extensions. On the other hand, the white matter of the nerve-centres is composed of medullated nerve-fibres which are processes of nerve-cells invested by a sheath of myelin (*medullary sheath*). These medullated nerve-fibres also occur in the nerve-roots and peripheral nerve-fibres, but here they have in addition an outer membranous sheath (*nucleated sheath, neurolemma*), enclosing the white or medullary sheath and conferring a certain amount of toughness upon the fibre. Every nerve-cell gives origin to at least one nerve-fibre (figs. 319, 320), and conversely every nerve-fibre is connected at one extremity to a nerve-cell of which it forms a direct prolongation. This has been recognised as a fundamental principle governing the structure of the nervous system ever since the continuity of nerve-cells with nerve-fibres was shown by Deiters[1]; it may be termed *Deiters' law*. But the complete establishment of the principle dates from the discovery by Golgi of the silver chromate method.[2] In his own hands and in those of Cajal, Kölliker, Retzius, and others the employment of this method has led to a complete revolution in our ideas regarding the construction of the grey matter of the nervous system, which before Golgi's observations was commonly regarded as formed by a network of nerve-fibrils.

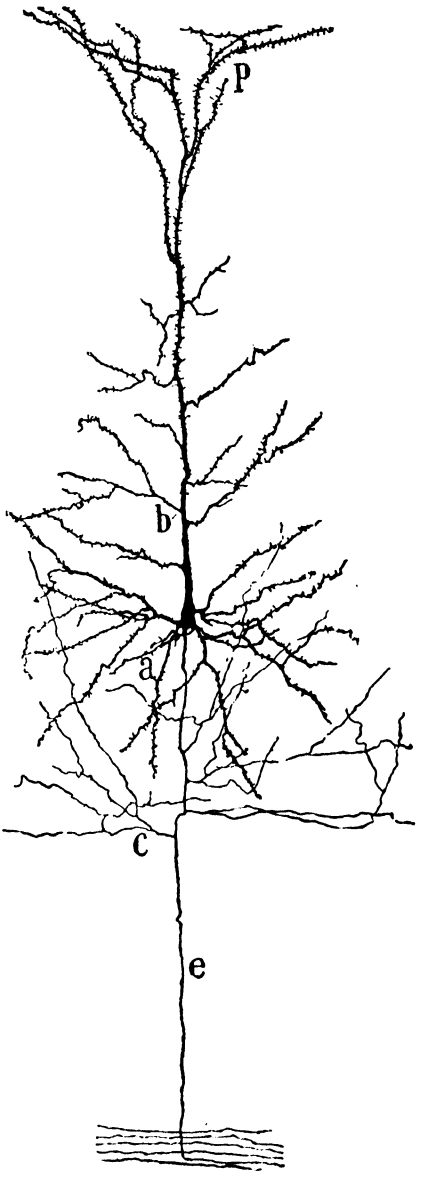


FIG. 321.—A NERVE-CELL FROM THE CEREBRAL CORTEX. Golgi method. (Cajal.)

a, basal dendrons; *b*, apical dendron; *c*, collaterals of axon; *e*, axon; *p*, apical dendrons ending in branches near surface of brain.

Nerve-cells vary greatly in size, shape, and structural appearance. Their one constant character is the possession of a process which becomes a nerve-fibre, or rather the central (axial) part of a nerve-fibre; this process of the cell is known as the *axon*.

The term 'neuron' would have been more appropriate to designate the nerve-fibre process,[3] but this word (or the similar word 'neurone') has come into use in a different sense, viz. to denote the nerve-cell itself, including all its processes (Waldeyer, 1891), which should rather, in accordance with the established principles of histological nomenclature, be termed 'neurocyte.' But the use of the word neuron or neurone for neurocyte has become so deeply rooted in the literature of the subject, that it would now be difficult to make a change. The term 'nerve-cell,' on the other hand, is sometimes used to denote merely the enlarged part or body of the cell which contains the nucleus (*perikaryon* of Sherrington): it is unnecessary to point out that such a restricted use of the term 'cell' is logically indefensible. Sanger Brown has suggested the use of the

[1] Unters. ii. Gehirn. u. Rückenm. 1865.
[2] Golgi, Gaz. med. lomb. 1873. See also his collected investigations, published in German in 1894.
[3] Schäfer, Brain, xvi. 1893, p. 134.

term 'cyton' to denote the nucleated cell-body. If this is adopted the neurone or neurocyte would be described as composed of cyton, axon, and dendrons.

The nerve-fibre process varies in length from a millimetre or less, as in some of the cells of the grey matter of the cerebral cortex, to more than a metre, as in the fibres of limb-nerves. It seems probable that in many cases the size of the cell-body bears a relationship to the length of the fibre which arises from it. The axon is always unbranched until it nears its termination; except that it may give off fine lateral offsets (*collaterals*) into the grey matter adjacent to the cell-body. In some nerve-cells the axon is the only process which the cell possesses, but most nerve-cells have other processes which begin to branch immediately on leaving the cell-body, like the roots or branches of a tree; these processes are known as *dendrons*

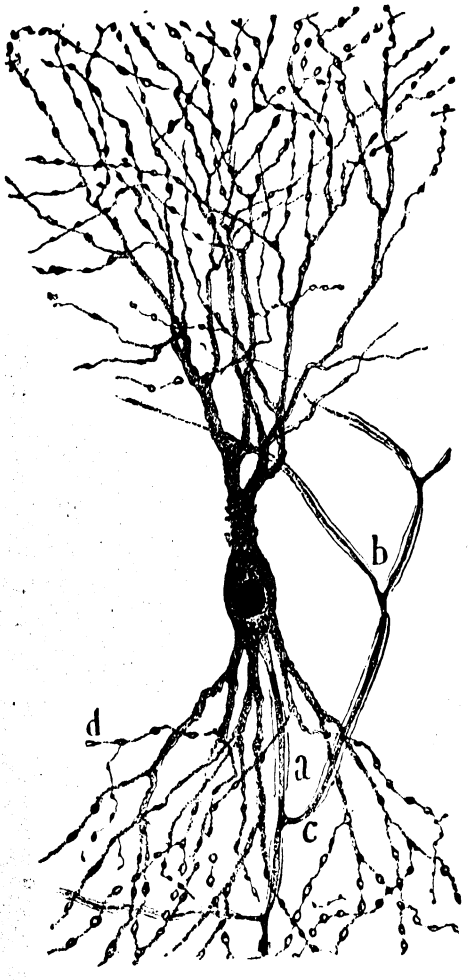


FIG. 322.—A NERVE-CELL FROM THE CEREBRAL CORTEX, SHOWING A VARICOSE CONDITION OF THE DENDRITIC PROCESSES. Methylene-blue preparation. (Cajal.)

a, axon, giving off at *c*, a branching collateral, *b*. All these possess a medullary sheath. *d*, ending of a dendron.

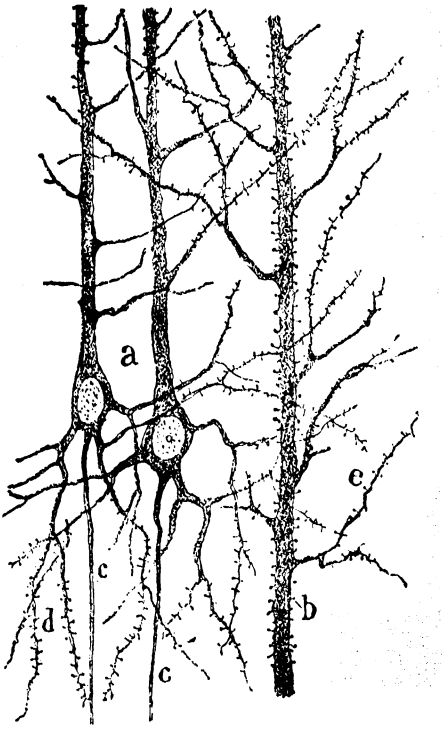


FIG. 323.—NERVE-CELLS OF CEREBRAL CORTEX SHOWING SPINES ON DENDRONS. Methylene-blue preparation. (Cajal.)

a, apical dendron of two cells; *b*, apical dendron of another cell which is not included in the figure; *c*, *c*, axons; *d*, *e*, terminations of dendrons.

or *dendrites*—they always terminate in the neighbourhood of the cell-body. The dendrons resemble the protoplasm of the cell-body in structure, and were accordingly termed by Golgi the *protoplasmic processes*[1]; the axon has a clearer, less

[1] Golgi at first supposed that the dendrons serve exclusively for the purpose of obtaining nutriment for the nerve-cell, like the roots of a tree. Whether they have such a function or not it is nevertheless certain that they conduct nerve-impulses. It has been suggested that the nerve-cell is capable of

granular appearance, and takes origin in a portion of the cell-body which is also free from obvious granules (*cone of origin of the axon*) (see Plate opposite p. 212). The dendrons usually branch in a spreading manner and with frequent bifurcations. Sometimes they may remain unbranched for a certain distance, as with the distal dendrons of many of the pyramid cells of the cerebral cortex. Occasionally they are beset with minute spinous projections (fig. 323), which are believed to make connexion with collaterals of other cells.[1] Sometimes they assume a moniliform character, but this may be the result of the mode of preparation. It is most frequently seen in preparations stained by Ehrlich's method (fig. 322). The dendrons usually conduct nervous impulses towards the cell-body and the axons conduct away from it, but the fibres of the dorsal roots form an important exception to this 'law of conduction.'

All nerve-cells have a relatively large and conspicuous nucleus, but the proportionate amount of basi-chromatin which the nucleus contains varies. The

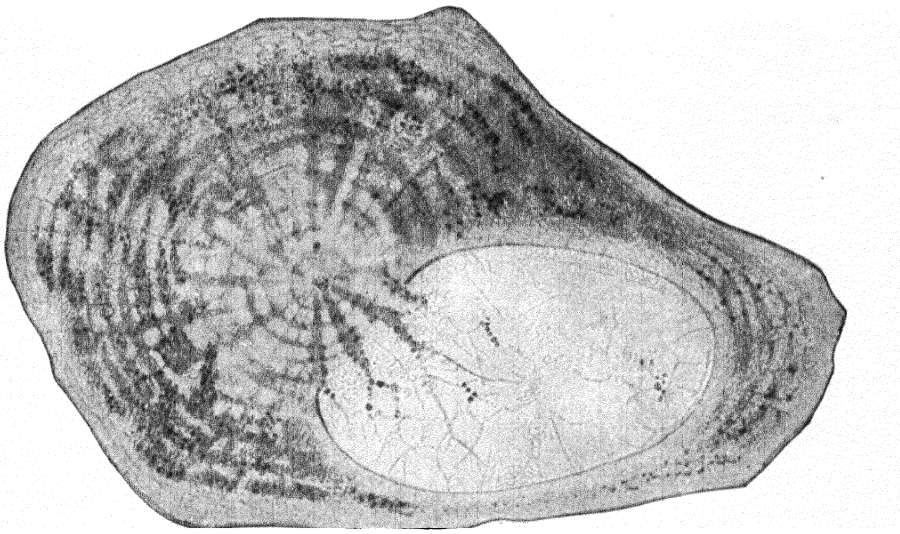


FIG. 324.—NERVE-CELL OF LOPHIUS WITH GAP IN MEMBRANE OF NUCLEUS OPPOSITE CENTROSOME. THE NISSL GRANULES APPEAR TO BE FORMING AT THIS PART. (Holmgren.)

nucleus is generally spherical and clear, with little or no obvious reticulum, but with a very distinct nucleolus, sometimes more than one. Appearances have been described which are interpreted as indicating an extension of nucleolar substance into the protoplasm.[2] Occasionally the nucleolus has been observed to be connected with a chromatin fibril (fibre of Roncoroni, 1885), extending into the cytoplasm.[3] The nucleus usually lies in the middle of the cell-body, which also contains a centrosome (fig. 324); sometimes more than one.[4] In many nerve-cells the protoplasm of the cell-body is markedly granular in appearance. This is due to the presence of angular groups of basiphil granules, which occupy the cytoplasm between the neuro-fibrils,[5] and which stain intensely with methylene blue (see

slightly withdrawing or projecting its processes, like an amœboid cell, and thus diminishing or increasing the capability of the synapses (see p. 213) for conduction (Rabl-Rückhard, Neurol. Centralbl. ix. 1890; Duval, C. r. Soc. biol. 1895). The suggestion is criticised by Kölliker (Würzburg Sitzungsb. 1895).

[1] Cajal, La Cellule, 1891; Berkeley, Anat. Anz. xii. 1896; A. Hill, Brain, xx. 1897.

[2] E. Holmgren, Anat. Hefte, xii. 1879; Page May and Walker, Quart. Journ. Exper. Physiol. i. 1908.

[3] E. Mencle, Arch. f. mikr. Anat. lxviii. 1906.

[4] Bühler, Würzburg Verhandl. xxix. 1895; Dehler, Arch. f. mikr. Anat. xlvi. 1895; v. Lenhossék, *ibid.*; M. Lewes, Anat. Anz. xii. 1896; E. Holmgren, Anat. Hefte, xii. 1899; Kolster, *ibid.* xvi. 1901; H. Fuchs, *ibid.* xxi. 1903; N. Van der Stricht, Bull. de l'acad. royale de médecine de Belgique, 1906.

[5] W. H. Cox, Anat. Hefte, x. 1898.

Plate): they are known as the *Nissl bodies* [1] and consist chemically of nucleoproteid containing organically combined iron.[2] The Nissl bodies may be scattered uniformly in the protoplasm or they may lie in two zones; one near the nucleus, the other near the circumference of the cell-body, leaving the intermediate part clear. If the centrosome is well marked the granules may be arranged concentrically to it. They extend into the dendrons, but do not occur in the axon or its cone of origin, and in some ganglion-cells there is a thin peripheral layer of the cell-body free from them.[3] They are found to vary with the functional condition of the nerve-cell and of its nucleus, which has been observed to exhibit amœboid projections abutting upon a small mass of Nissl granules or to have rows of chromatin-granules streaming out from it towards the centrosome [4] (fig. 324). In fatigued cells (fig. 325) the granules break up and gradually disappear; [5] whilst the cell-body correspondingly diminishes in size and the nucleus shrinks in bulk,[6] showing, however, a relative increase in the amount of chromatin.[7] The term *chromatolysis* (Marinesco) or *Nissl degeneration* is applied to these changes in the Nissl bodies.[8]

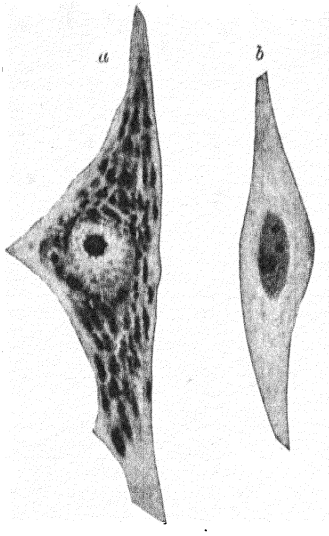
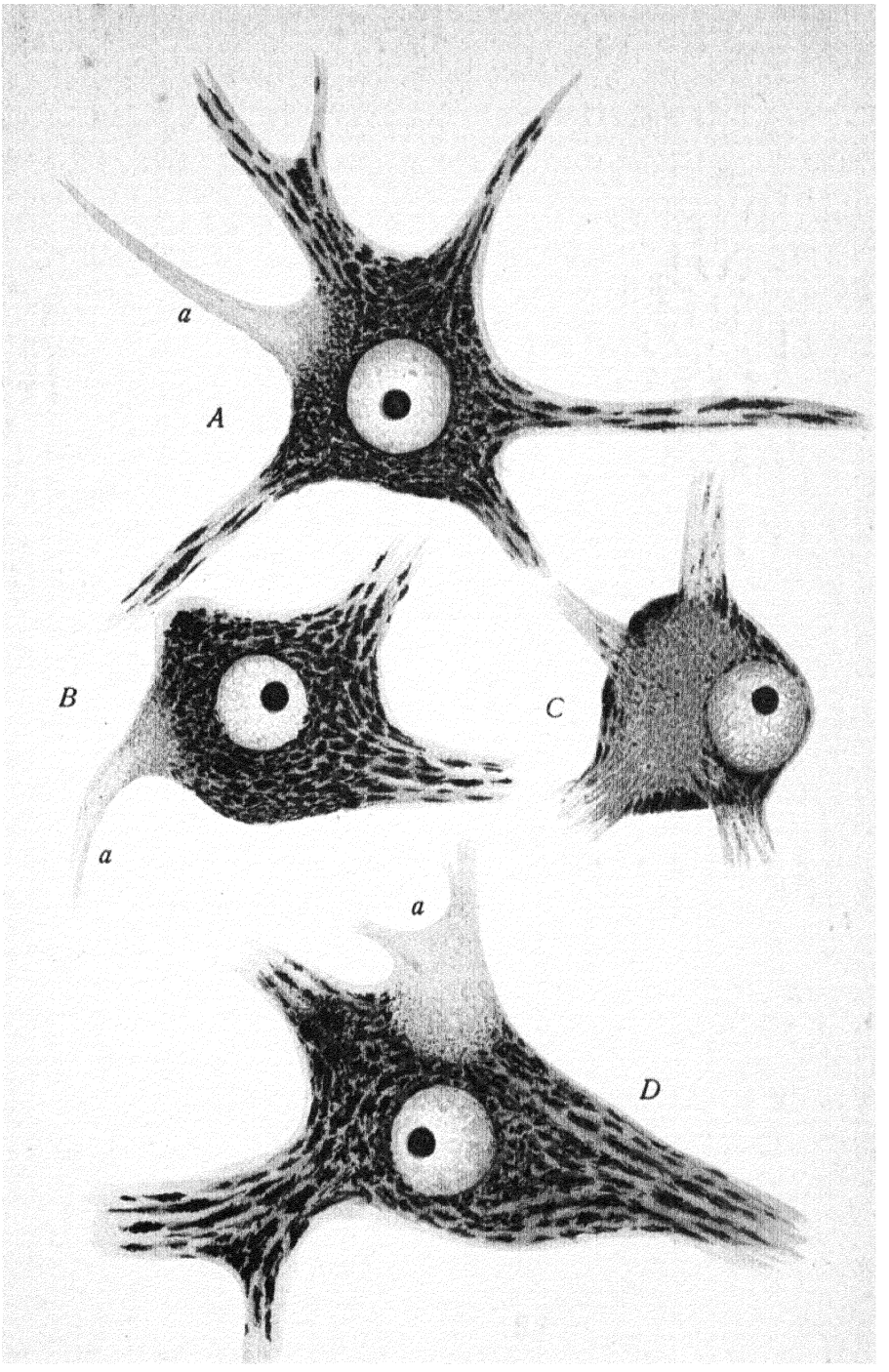


FIG. 325.—TWO MOTOR NERVE-CELLS FROM THE DOG.

a, normal; *b*, after a period of prolonged activity. (Photographed from preparations by Dr. Gustav Mann.)

Similar changes occur if the axon of a nerve-cell is cut,[9] whether near to or at a point far distant from the cell-body (*axon-reaction*) (see Plate, fig. c); the change begins 24 to 48 hours after the section and is completed in about 15 to 24 days. This fact is made use of to determine from which cells or groups of cells particular nerve-fibres originate.[10] Various poisons which affect the nervous system are also found to have marked effects in causing chromatolysis either in the nerve-cells generally or in those of special parts. This applies also to the poisons (toxines) which are produced in disease. With removal of the cause of degeneration a process of reparation may begin. If the degeneration has been caused by section of the axon the reparative process is very slow, so that it may be three or four months before it is completed. At the end of this time the nerve-cell bodies have resumed their original appearance even though reparation of the cut nerve may be incomplete. But in some instances regeneration of the cell-bodies does not take place; this seems to be the case with the cells of the vagus ganglion on cutting the peripheral nerve,[11]

[1] Nissl, Naturforscherversamml. z. Strassburg, 1884.
[2] A. B. Macallum, Journ. Physiol. xxxii. 1905.
[3] v. Lenhossék, Arch. f. Psych. xxix. 1897; G. Mann, Verh. d. Anat. Gesellsch. 1898, p. 39.
[4] E. Holmgren, Anat. Hefte, xii. 1899; xv. 1900.
[5] But with activity which is not excessive the chromatin may at first increase in amount (Dollay Amer. Journ. Physiol. xxv. 1909).
[6] Hodge, Journ. Morph. vii. 1892.
[7] G. Mann, Journ. Anat. and Physiol. xxix. 1894. See also F. H. Scott, Journ. Physiol. 1906.
[8] For the literature on this subject, see article on the Nerve-cell in Schäfer's Text-book of Physiology; also L. L. Barker's Nervous System.
[9] This statement does not apply to the centripetal axons of the cells of the spinal ganglia (Lugaro, Riv. d. patol. nerv. vol. i. 1896; Köster, Neurol. Centralbl. xxii. 1903); nor does section of these axons interfere with the development of the spinal ganglion-cells in the young animal, although section of their peripheral axons has a marked effect (H. K. Anderson, Journ. Phys. vol. xxviii. 1902).
[10] See especially Van Gehuchten, Anatomie du système nerveux, 1907.
[11] Van Gehuchten and Nélis, La Cellule, 1897.



Nerve-cells stained by Nissl's method, with toluidin blue.
Magnified 750 diameters. (Schäfer.)
A. From anterior horn of spinal cord, monkey.
B and *C*. From facial nucleus, dog.
D. From reticular formation of pons Varolii, dog.
C. Shows Nissl degeneration, consequent on section of the facial nerve 15 days previously. *a*. *a*. axons.

and also with the cells of Clarke's column in the spinal cord on cutting the fibres which emanate from them.[1]

Besides the basiphil granules of the Nissl bodies the cytoplasm of nerve-cells contains oxyphil granules,[2] which are not brought to view by the ordinary methods of staining, but are probably more constant in their occurrence than the basiphil granules. For, as has already been mentioned, the Nissl granules are by no means of constant occurrence in nerve-cells, a large number of these, especially in the cerebro-spinal centres, remaining unstained (except their nuclei) by Nissl's method.

The change known as 'Wallerian degeneration,' which occurs in the peripheral part of the nerve-fibre when it is severed from the central part and cell-body will be subsequently referred to (see p. 215).

Synapses. — Nerve-cells are not directly joined to one another by their cell-processes: indeed, there is strong evidence that every nerve-cell with all its processes is a distinct anatomical unit; this is the basis of the 'neurone-theory' of Waldeyer.[3]

The evidence is briefly as follows: (1) With certain methods of staining, especially that introduced by Golgi, and known by his name, a certain number of the nerve-cell bodies and all the processes which extend from them are intensely

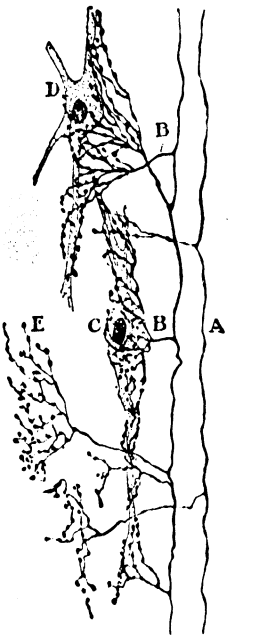


FIG. 326. — DORSAL ROOT-FIBRES (A) SENDING COLLATERALS (B) TO FORM SYNAPSES (C, D, E) AROUND CELLS IN DORSAL HORN OF GREY MATTER OF SPINAL CORD. (Cajal.)

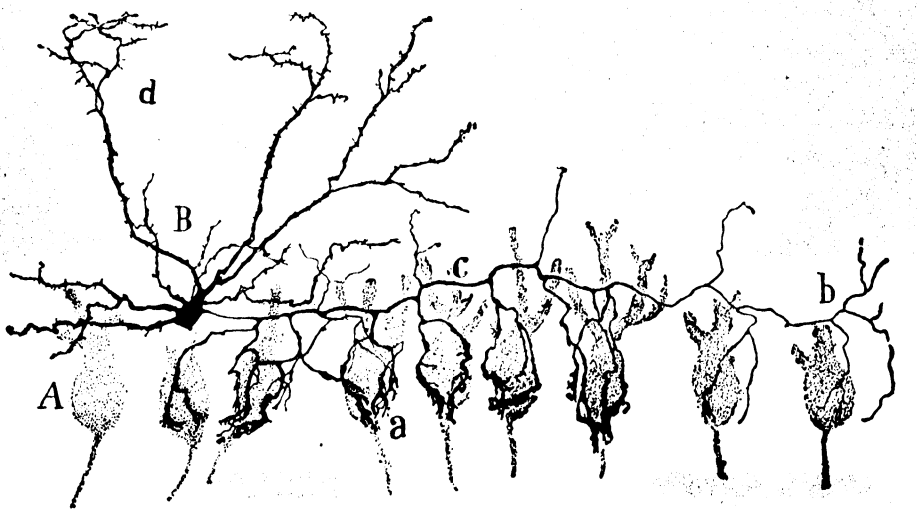


FIG. 327.—SYNAPTIC CONNEXIONS OF NERVE-CELLS OF CEREBELLUM. Golgi method. (Cajal.)

B, a nerve-cell with dendrons, *d*, and an axon, *b*, *c*. Numerous branches are given off from the axon to form synapses around the cell-bodies of the cells of Purkinje, A; *a*, axon processes of the cells of Purkinje: only a short length is represented.

[1] Loewenthal, Recueil zool. Suisse, 1886; Schäfer, Proc. Physiol. Soc. Journ. Physiol. xxiv. 1899.
[2] E. Holmgren, Anat. Hefte, xv. 1900. [3] *Op. cit.*

stained, but however far the processes are traced, they always appear to end in free ramifications and never become continued into a process from another nerve-

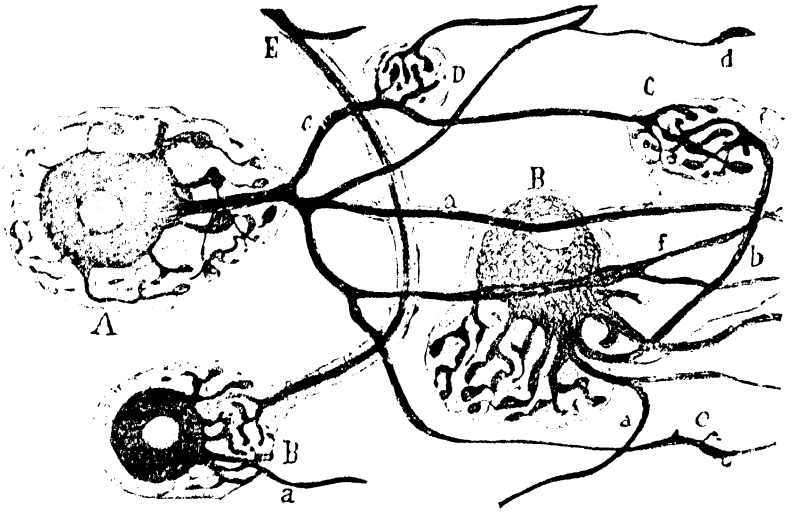


FIG. 328.—SYNAPTIC CONNEXIONS OF CELLS OF THE SUPERIOR CERVICAL GANGLION OF MAN. (Cajal.)
A, B, cells within capsules; *a*, their axons; *b*, *c*, *d*, *e*, *f*, extra-capsular dendrons; C, D, synapses between dendrons; E, a fibre forming a synapsis with intra-capsular dendrons.

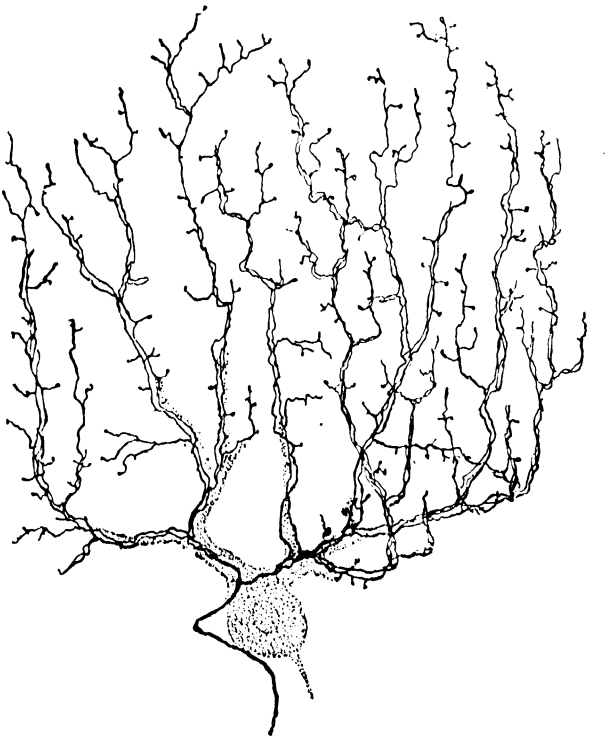


FIG. 329.—AN AFFERENT FIBRE BREAKING UP INTO RAMIFICATIONS AROUND THE DENDRONS OF A PURKINJE CELL OF THE HUMAN CEREBELLUM. (Cajal.)

cell, although they may come *in contact* with the cell bodies or processes of other cells. (2) It happens in certain diseases and injuries of the nervous system that

certain cells and cell-groups only are affected by a resulting process of degeneration. Such degeneration is confined to the limits of the cells and cell-groups affected; although it includes all their processes, however remote, it does not extend beyond

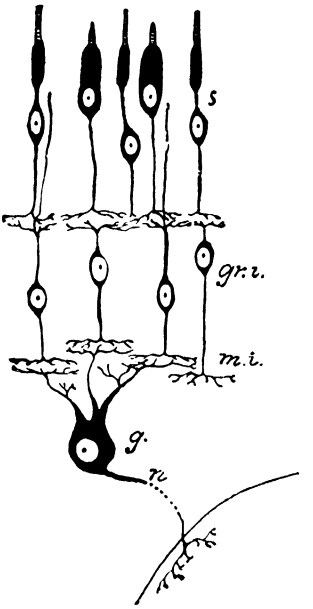


FIG. 330.—DIAGRAM OF SYNAPSES BETWEEN AXONS AND DENDRONS IN THE RETINA. (G. Retzius.)

g, ganglion-cell, with axon, *n*, and dendrons, the latter forming synapses in the inner molecular layer, *m.i.*, with axons of the bipolar nerve-cells, *gr.i.* External to (above) these are the synapses which their dendrons form with the axon-processes of the rod and cone elements.

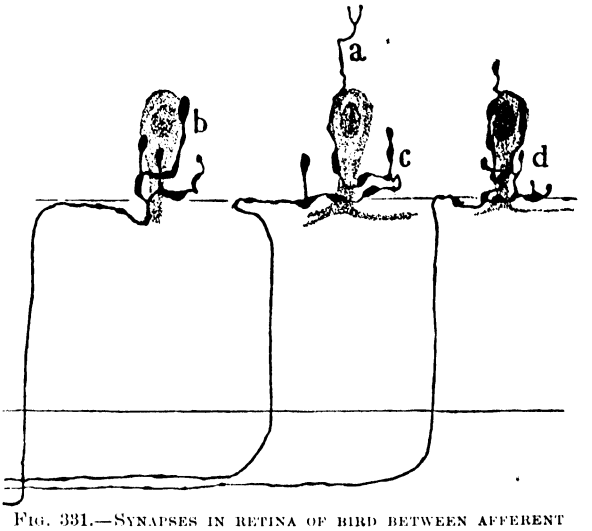


FIG. 331.—SYNAPSES IN RETINA OF BIRD BETWEEN AFFERENT NERVE-FIBRES AND NERVE-CELL BODIES. (Cajal.)

b, *c*, *d*, the synaptic endings; *a*, a fibril continued beyond one of these.

FIG. 332.—PECULIAR ENLARGED SYNAPTIC NERVE-ENDINGS OF NERVE-FIBRES AROUND THE CELL-BODIES OF THE VENTRAL ACOUSTIC NUCLEUS. (Cajal.)

In *a*, *b*, and *c* the cell-bodies are indicated; in *d*, *e*, and *f* they are omitted.

them, even to those cells and cell-groups with which they are in close physiological connexion. (3) The facts of development of nerve cells and fibres are strongly in favour of the doctrine that each cell with all its processes is a distinct anatomical unit.[1]

The axon of one nerve-cell may ramify around the cell-body of another cell (fig. 327) or around its dendrons (fig. 329). These ramifications come apparently in contact with the cell-substance of the second cell, but without continuity. Or the axon of one nerve-cell may form a closely ramified interlacement of fibrils with similarly ramified fibrils derived from the dendrons of other nerve-cells (fig. 328, B, and fig. 330). Or, again, but more

[1] Cf. Max Verworn, Das Neuron, Jena, 1900; L. L. Barker, Nervous System, 1899.

rarely, synapses may occur between dendrons (fig. 328). To such modes of contact between different nerve-cells (or in the usual parlance between different 'neurones') the term 'synapse' (M. Foster) has been applied. Synapses may be either 'investing' or 'interlacing' as in the instances above given, or the contact may be effected by the simple application of the branched or unbranched (and usually in that case dilated) extremity of an axon to the body of another nerve-cell. The calices described by Held in the trapezoid nucleus, and the somewhat similar enlargements of axons described by Cajal in the ventral acoustic nucleus (fig. 332) may be given as examples of this.[1]

The doctrine of contiguity without continuity of the anatomical units which compose the nervous system is not universally admitted, some observers holding that there is sufficient evidence to justify belief that the nerve-cells of a nerve-chain are continuous with one another —at least, so far as regards the neuro-fibrils.[2]

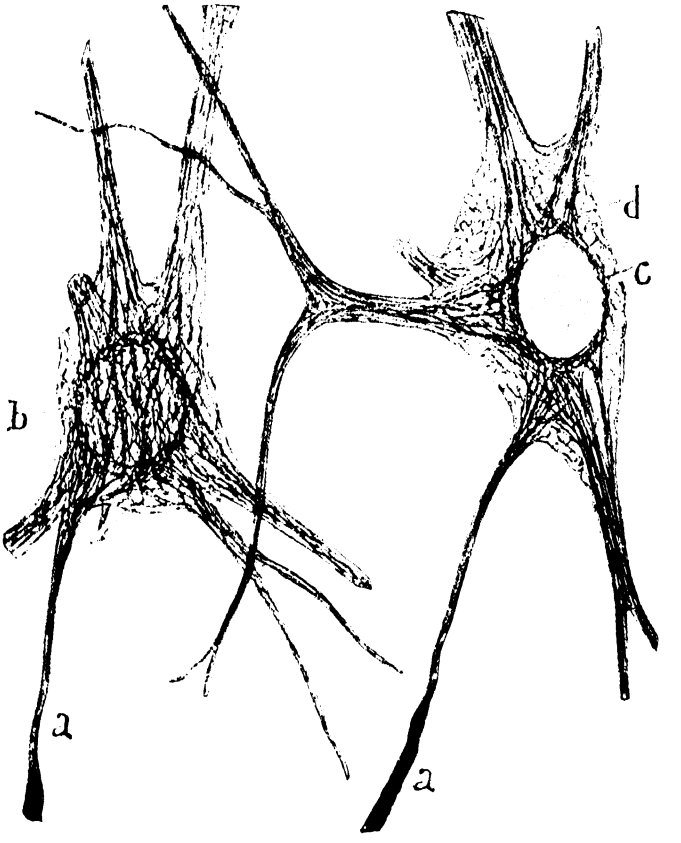


FIG. 333.—NEURO-FIBRILS IN NERVE-CELLS FROM ANTERIOR CORPORA QUADRIGEMINA OF KITTEN. (Cajal.)

a, axon; *b*, cell-body; *c*, nucleus; *d*, neuro-fibrils.

Neuro-fibrils.—A distinctive character of nerve-cells is the existence of fibrils which pass into and through the cell-body and extend into all the processes. These *neuro-fibrils* (figs. 333 to 336) were first described by Max Schultze: they

[1] Cf. Semi Meyer, Arch. f. mikr. Anat. xlvii. 1896, and liv. 1899; Vincenzi, Anat. Anz. xviii. 1900.

[2] Cf. Apáthy, Mitth. a. d. zool. Station z. Neapel, xii. 1897; Nissl, Münch. med. Wochenschr. xlv. 1898, Neurol. Centralbl. 1900, and Die Neurontheorie, &c. Heidelberg, 1903; Bethe, Arch. f. mikr. Anat. l. and li.; also Allgem. Anat. u. Physiol. d. Nervensystems, 1903; H. K. Anderson, Journ. Physiol. xxviii. 1902; H. Held, Arch. f. Anat. 1905.

appear to be of universal occurrence. They can be coloured *intra vitam* by methylene-blue,[1] and are also specifically stained *post mortem* by various methods.[2]

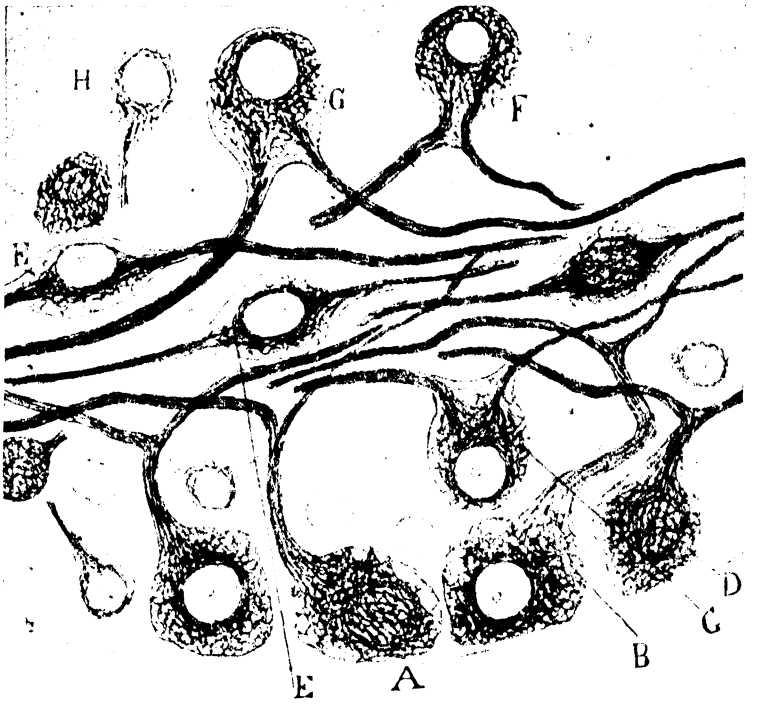


FIG. 334.—NEURO-FIBRILS IN SPINAL GANGLION-CELLS OF EMBRYO. (Cajal.)

A, B, unipolar cells; C, D, F, G, transitional cells; E, E, cells which are still bipolar; H, a cell with the neuro-fibrils as yet imperfectly developed.

The neuro-fibrils are traceable along the axis-cylinder of all nerves as far as their terminations; the ultimate ramifications of the axis-cylinder may end in what appear to be single fibrils. Some observers describe them as exhibiting junctions (anastomoses) throughout their course in the cell-body (figs. 333, 334, 335) and cell-processes.[3] This is, however, denied by others, who believe that the neuro-fibrils run distinct from one another in the nerve-

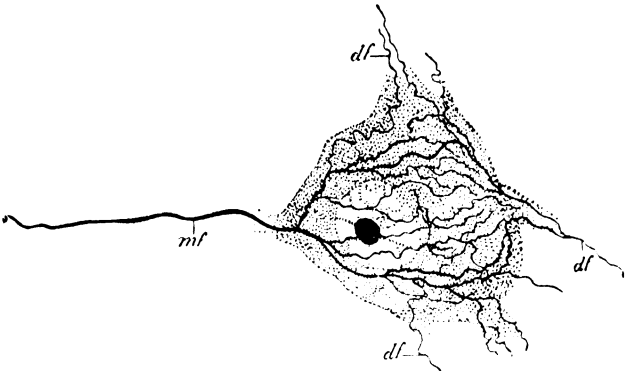


FIG. 335.—NEURO-FIBRILS IN NERVE-CELL OF ANNELID. (Apáthy.)

df, fibrils in dendrons; *mf*, a large fibril in the axon.

[1] Ehrlich, Deutsche med. Wochenschr. 1886.

[2] Růžička, Arch. f. mikr. Anat. liii. 1899; Mönckeberg and Bethe, *ibid.* liv. 1899; Bielchowski, Neurol. Centr. xxii. 1903; Donaggio, Gaz. med. ital. 1903, and Riv. sper. di fren. 1904; E. S. London, Arch. f. mikr. Anat. lxv. 1903; Cajal, Trabajos del labor. d. invest. biol. 1904; Tello, *ibid.*; Marinesco, Rev. neurol. 1904; Schiefferdecker, Arch. f. mikr. Anat. lxvii. 1906; Cajal and Illera, Trabajos del labor. d. invest. biol. 1907; Apáthy, Anat. Anz. xxxi. 1907; Idris, Bull. de l'acad. roy. de méd. xxi. 1907.

[3] Vincenzi, Anat. Anz. xxviii. 1906; Kató, Folia neuro-biol. iii. 1909.

cell and its processes.[1] The fibrils are said to vary in size according to the functional condition of the nerve-cell. Thus they are described by Cajal and Tello as being thicker and less numerous in the hibernating lizard during the winter sleep (fig. 336, B,C), and finer and more numerous during activity (fig. 336, A,D). It is commonly assumed that the fibrils are the essentially conducting part of the nervous element, but this is not easy of proof, and the opposite view was taken by Leydig,[2]

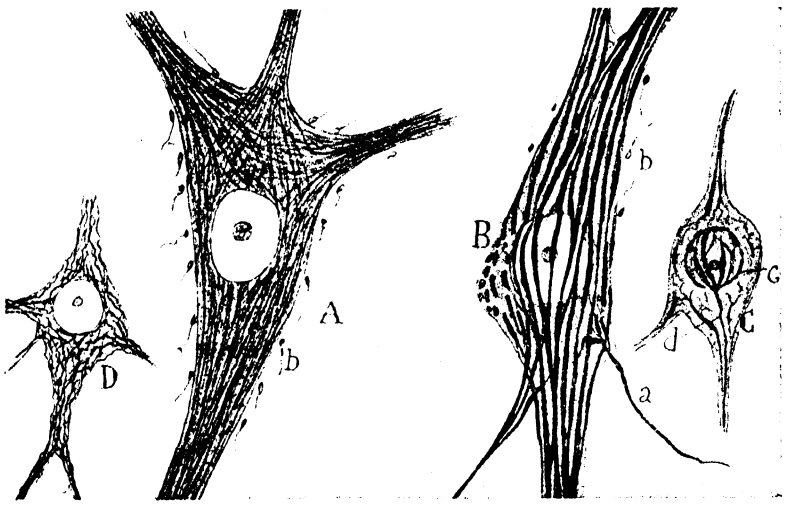


FIG. 336.—FIBRILS WITHIN NERVE-CELLS. (Cajal and Tello.)

who held that the interfibrillar substance is the true conducting material of nerve-fibres. Nor is it clear whether the fibrils are solid threads or hollow tubules occupied by fluid : this question will be discussed later (p. 235). In some invertebrates (Apáthy[3]) it appears as if the neuro-fibrils may extend through two or more nerve-cells without interruption ; this fact has been employed to throw doubt upon the doctrine of separate nerve-units. Similar conditions have been described by Bethe in vertebrates, but the evidence is not convincing. And even if such continuity of nerve-fibrils from cell to cell were found to be general, the fact that the direct trophic influence of the nucleus and cell-body is confined to the limits of its own cell-processes, and does not extend to those of other nerve-cells (see pp. 214, 215), sufficiently indicates that, from the point of view of nutrition at any rate, the doctrine of independent units must be looked upon as established.

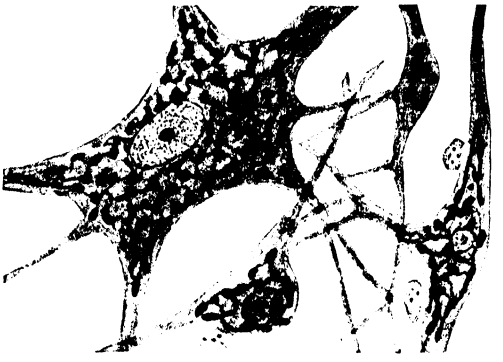


FIG. 337.—DEEP NETWORK OF GOLGI WITHIN CELLS OF SPINAL CORD. (Cajal.)

An internal reticulum unconnected with the neuro-fibrils and similar in character to that which has been found to be present in certain other cells (p. 25)

[1] Cf. Jäderholm, Arch. f. mikr. Anat. lxvii. 1906. For a summary of views held regarding neuro-fibrils, see Joris, Journ. de neurol. 1909.

[2] Arch. f. Anat. 1897.

[3] *Op. cit.*

has been described by Golgi [1] in the body of the nerve-cell (figs. 337, 338). This network appears to contain myelin; it is darkly stained by prolonged treatment with osmic acid.[2]

Golgi has also described in some nerve-cells a reticular investment [3] covering the cell-body which may extend a certain distance over the cell-processes (fig. 339). The exact nature of this investment is not clear. According to some authorities it is formed by an interlacement of the terminal ramifications of axons proceeding from other cells to form synapses with the cell-body (see p. 215). Others believe it to have a neuroglial origin.[4]

Another appearance which has been described within many nerve-cells, especially those of the spinal ganglia, consists of ramified canals, which are occupied, according to Holmgren,[5] by branching processes from the cells lining the capsule (trophospongium, see p. 27). Holmgren believes that these processes may be amœboid, and that the canals they occupy may therefore be constantly undergoing change.

Some nerve-cells also have in the immediate neighbourhood of the nucleus a clump of pigment-granules (fig. 340), yellow, brown, or black in colour. When present in many cells of the same locality they give a distinctive colour to the part, as in the *substantia nigra* of the mid-brain and the *locus cæruleus* of the fourth ventricle. The pigment contains lecithin. It tends to increase in amount with age, although it is already seen during the third year of life.[6] It is more extensively met with in man than in the lower animals.

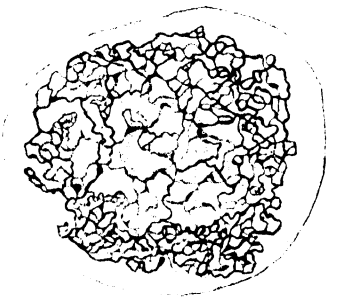


FIG. 338.—DEEP NETWORK OF GOLGI WITHIN A SPINAL GANGLION-CELL. (Golgi.)

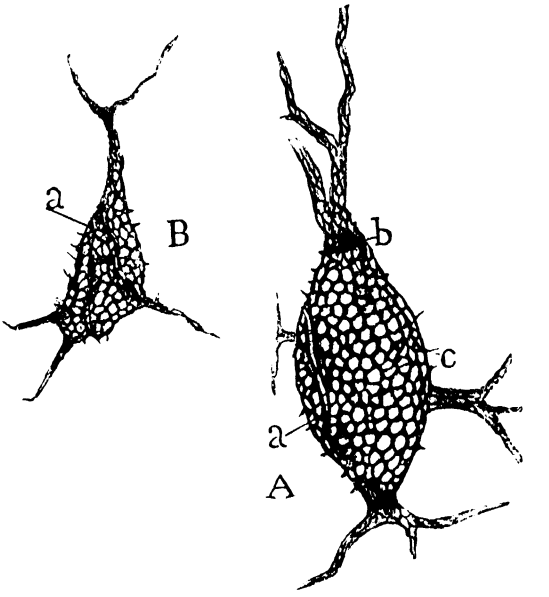


FIG. 339.—SUPERFICIAL NETWORK OF GOLGI OVER CELLS OF CEREBRAL CORTEX OF CAT. (Cajal.)

A, larger; B, smaller cell; *a*, *a*, folds in network; *b*, a ring-like condensation; *c*, projections from surface.

According to the number of processes which they possess, nerve-cells are termed *unipolar*, *bipolar*, or *multipolar*. Unipolar nerve-cells are met with in the

[1] Arch. ital. de biol. xxx. 1898; Verhandl. d. anat. Gesellsch., Anat. Anz. xviii. 1901. See also Rossi, Le Névraxe, vi. 1904.

[2] Kopsch, Sitz. d. preuss. Akad. xl. 1902. See also Misch, Int. Monthly Journ. of Anat. and Physiol. xx. 1903; v. Bergen, Arch. f. mikr. Anat. lxiv. 1904; and Sjövall, Anat. Hefte, xxx. 1906.

[3] Golgi, Arch. ital. de biol. xxx. 1898.

[4] H. Held, Arch. Anat. 1902; J. Turner, Brain, 1906.

[5] Anat. Anz. xvi. 1890; xviii. 1891; Arch. f. mikr. Anat. lx. 1903; Arch. f. Anat. 1904; Anat. Hefte, xxv. 1904. Nélis (Bull. acad. roy. de Belg. 1899) describes convoluted canals in the spinal ganglion-cells of the dog, but states that they do not anastomose like the canals described by Holmgren.

[6] Mühlemann, Arch. f. mikr. Anat. lxviii. 1901; Obersteiner, Arbeiten, x. 1903

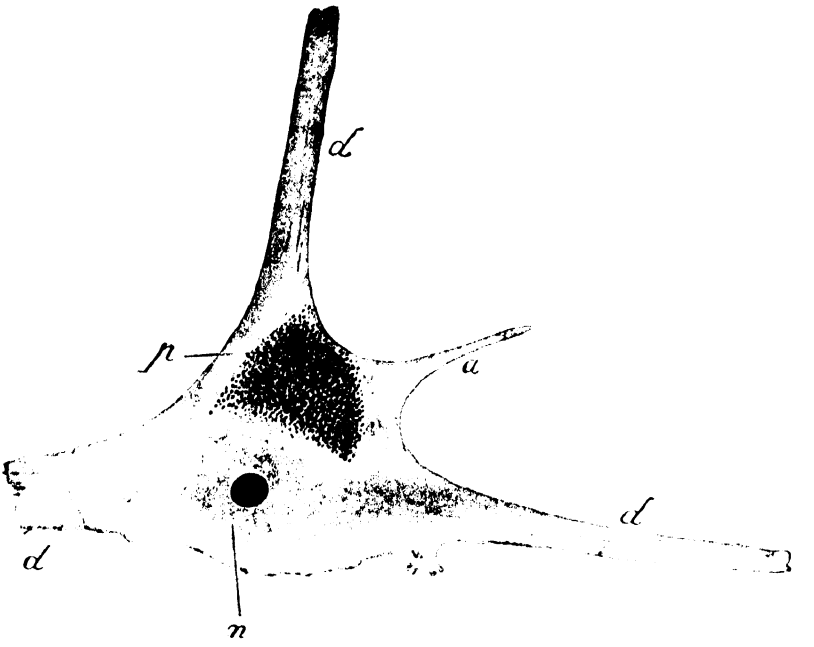


FIG. 340.—BODY OF A NERVE-CELL FROM THE SPINAL CORD (MAN).
(From Prenant, Bouin, and Maillard.)
a, axon; *d*, *d*, dendrons; *n*, nucleus with nucleolus; *p*, pigment.

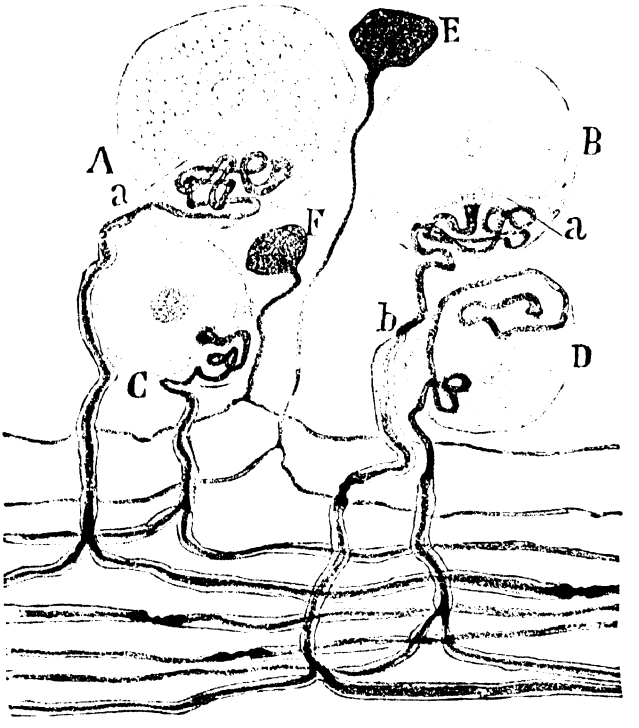


FIG. 341.—CELLS OF VAGUS GANGLION OF CAT. Ehrlich method. (Cajal.)
A, B, large clear cells with axon much convoluted near origin; C, D, smaller clear cells
E, F, smallest cells, staining darkly and without convolutions of axon.
a, indented portion of cell-body; *b*, commencement of medullary sheath.

cerebro-spinal ganglia (posterior or dorsal root-ganglia,[1] Gasserian ganglion, ganglion of the trunk of the vagus, &c.) and in the superior or accessory motor-nucleus of the fifth cerebral nerve. They are usually spheroidal in shape. The process which comes off from the cell is always an axon or nerve-fibre process, and receives a medullary sheath soon after leaving the cell. It is generally convoluted close to the cell-body and before emerging from the capsule (figs. 341, 342). After a short course as a single fibre it bifurcates, the branching being T- or Y-shaped (figs. 341 to 343). One branch (centripetal) passes towards the nerve-centre (posterior root-fibre, sensory root-fibre), where it ultimately terminates by fine ramifications within the grey matter; the other branch (centrifugal) passes peripherally and forms a sensory (afferent) fibre of a peripheral nerve. The spinal ganglion cells vary greatly in size and in

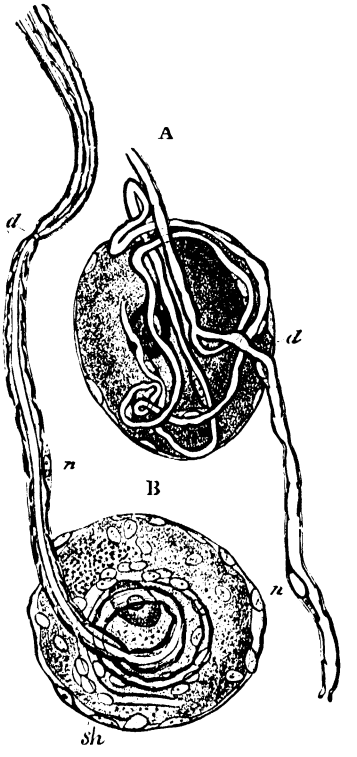


FIG. 342.—TWO NERVE-CELLS FROM A SPINAL GANGLION (HUMAN). (Retzius.)

sh, nucleated sheath; *n*, *n*, nuclei of the primitive sheath of the nerve. From each cell a fibre can be seen to arise, and, after a convoluted course on the surface of the nerve-cell, to bifurcate (opposite *d*); from which point the divisions pass either in the opposite direction to one another, as in A, or at first in the same direction as in B. The nuclei of the sheath of the nerve-cell are all represented in B, but only those seen in profile have been represented in A.

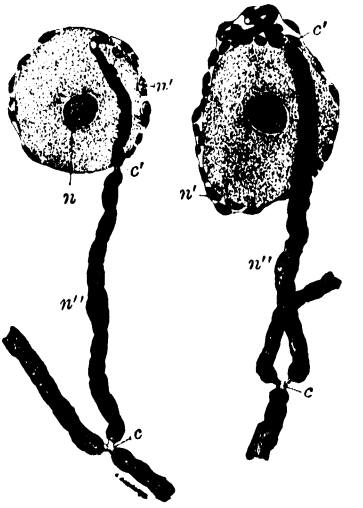


FIG. 343.—TWO SPINAL GANGLION-CELLS SHOWING BIFURCATION OF THE NERVE-FIBRE PROCESS. Osmic preparation. (Ranvier.)

n, nucleus of ganglion-cell; *n'*, nuclei of capsules; *n''*, nuclei of neurolemma; *c*, *c'*, constrictions of Ranvier.

appearance, some being clearer, others more granular (fig. 341). Most of them are large and conspicuous. Each cell is covered by a membranous sheath with nuclei upon its inner surface (fig. 342): this sheath is prolonged over the issuing fibre, and is continuous with the nucleated sheath of the fibre. Frequently a fine non-medullated fibre is seen within the sheath ramifying over the cell-body or around the issuing axon (fig. 344). This is derived either from some other cell

[1] Nerve-cells are in some situations met with among the fibres of the ventral roots of some of the spinal nerves. They are constant in the cat (Schäfer, Proc. Roy. Soc. 1880), and are also found occasionally in the lumbar and sacral nerves of man (Hoch, Beitr. z. Kenntn. d. anat. Verhaltens, &c. Heidelberg, 1891).

in the ganglion or from a cell of a sympathetic ganglion. Its function is unknown.[1] Some of the cells of the spinal ganglia have other processes besides the axon, but their nature is uncertain. They rarely extend beyond the capsule which encloses the ganglion-cell, and they have not the character of dendrons,

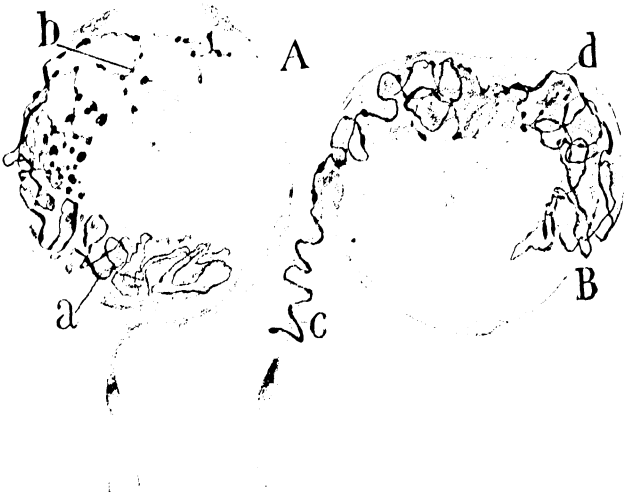


FIG. 344.—PERICELLULAR ARBORISATIONS IN SPINAL GANGLION-CELLS. (Cajal.)
In A the arborisation extends over the cell-body; in B it is limited to the axon. *a*, *b*, *c*, *d*, afferent fibres.

but rather resemble developing axons (fig. 345), being fine fibres which end in a marked enlargement. They were first noticed by Huber [2] in the frog, and have since been described in many situations by Cajal.[3] Nageotti [4] has suggested,

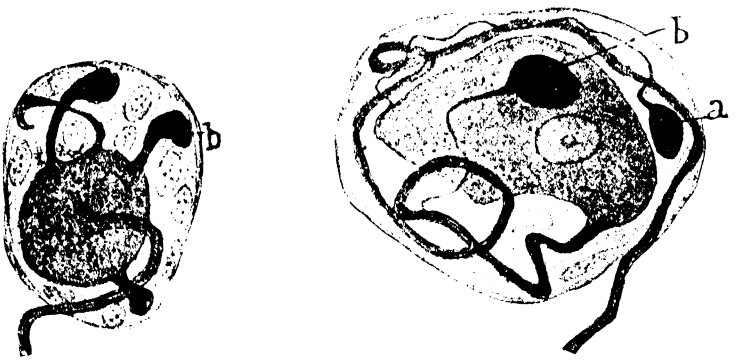


FIG. 345.—CEREBRO-SPINAL GANGLION-CELLS (MAN). (Cajal.)
a, *b*, intracapsular dendrons, with knobbed extremities.

with much probability, that the processes in question are aborted axons or their collaterals. They occur also in sympathetic ganglia (fig. 351).

In the early embryo the cells of the spinal ganglia are bipolar, a nerve-fibre process proceeding from each end of the elongated cell-body. The attachment

[1] G. Retzius, Biol. Unters. ix. 1900; Cajal, Textura del sist. nerv. 1904, and Ergebn. d. Anat. xiv. 1906.
[2] Anat. Anz. xii. 1886.
[3] Ergebn. d. Anat. xiv. 1906.
[4] Nouv. icon. de la Salpêtrière. See also v. Lenhossék, Arch. f. mikr. Anat. lxix. 1906, and Lewis, Anat. Anz. xxx. 1907. On the cells of spinal ganglia, see A. S. Dogiel, Bau der Spinalganglien, 1908.

of the two processes becomes gradually shifted as development proceeds (fig. 334), so that they presently are found to arise from the same point of the cell, and eventually the common attachment becomes lengthened out into a single axon. This bifurcates a certain distance from the cell-body, which has thus become unipolar. The bipolar condition is retained in the cells of the ganglion of the cochlea and the ganglion of Scarpa on the eighth nerve. It is also permanent

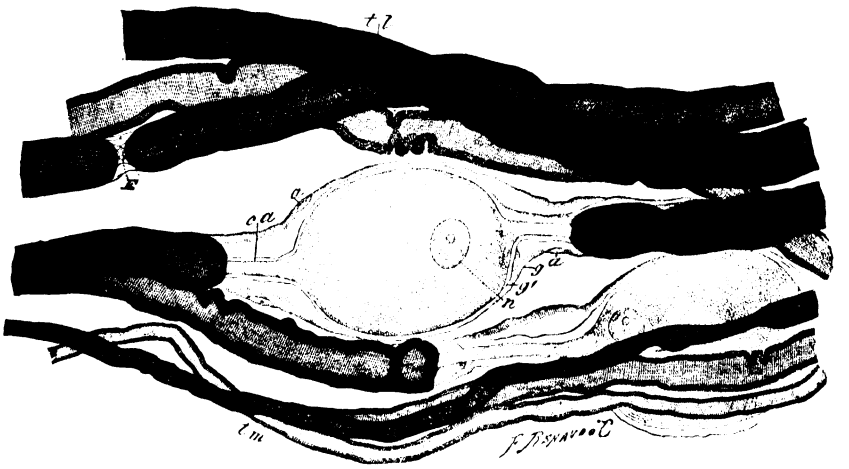


FIG. 346.—SPINAL GANGLION-CELLS AND FIBRES OF RAY Osmic preparation. (Ranvier.)

tl, *tm*, medullated fibres, large and medium-sized; *E*, constriction of Ranvier; *g*, sheath of ganglion-cell; *g'*, cell; *n*, nucleus; *ca*, axis-cylinder: another axis-cylinder is prolonged from the opposite end of the bipolar cell; *a*, *a*, nuclei of sheath. The medullary sheaths of the nerve-fibres are stained black by the osmic acid.

in the spinal ganglia of certain fishes (fig. 346). Occasionally a thin layer of myelin extends from the medullary sheath of the nerve-fibre over the cell-body of a bipolar cell (fig. 347).

Cells with processes extending from opposite poles of the cell-body occur in other situations than those above enumerated, as in the ganglion-cells and inner granules of the retina of the eye; but in these instances the two processes are

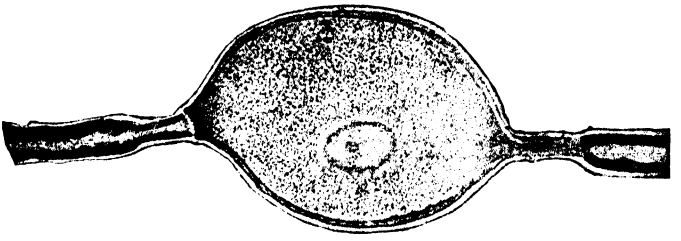


FIG. 347.—A BIPOLAR CELL FROM SPINAL GANGLION OF FISH, SHOWING THE MEDULLARY SHEATH OF THE NERVE-FIBRES CONTINUED AS A THIN LAYER OVER THE CELL-BODY. (E. Holmgren.)

different in character, the one being an axon and the other a dendron. In some of the sense-organs, as in the olfactory cells of the olfactory mucous membrane (fig. 348) and in the rod and cone cells of the retina (fig. 461), which are also bipolar, the central process is an axon, and the peripheral process is an unbranched projection from the cell-body specially modified to receive the physical or chemical stimulus which is converted by the cell into a nervous impulse. It is true that

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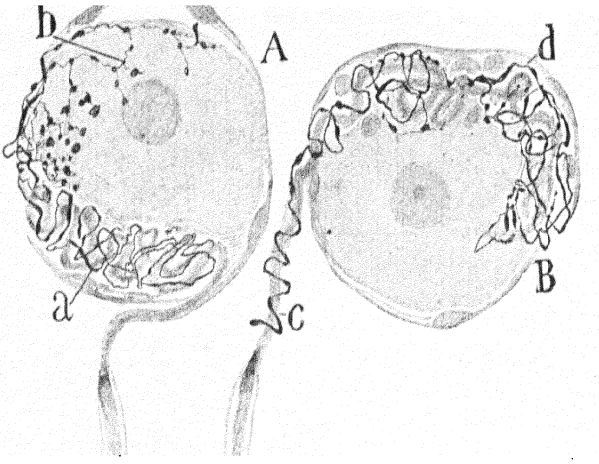

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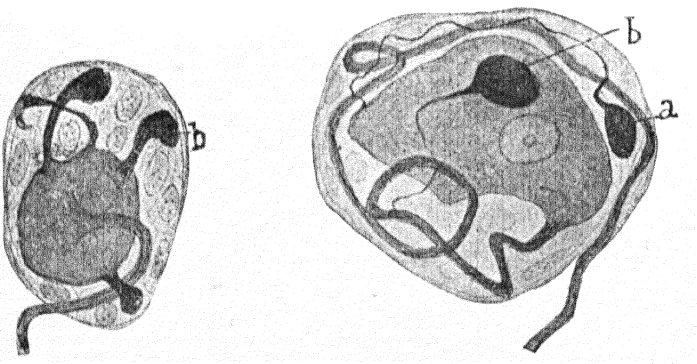

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[4] Nouv. icon. de la Salpètrière. See also v. Lenhossék, Arch. f. mikr. Anat. lxix. 1906, and Lewis, Anat. Anz. xxx. 1907. On the cells of spinal ganglia, see A. S. Dogiel, Bau der Spinalganglien, 1908.

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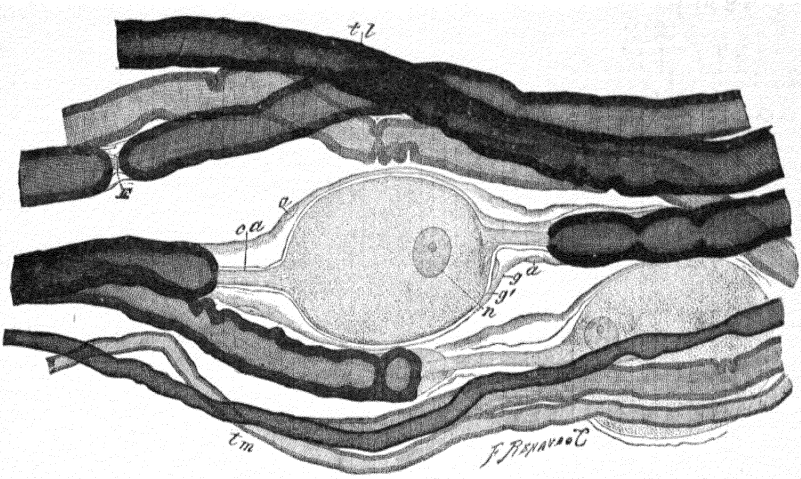

FIG. 346.—SPINAL GANGLION-CELLS AND FIBRES OF RAY Osmic preparation. (Ranvier.)

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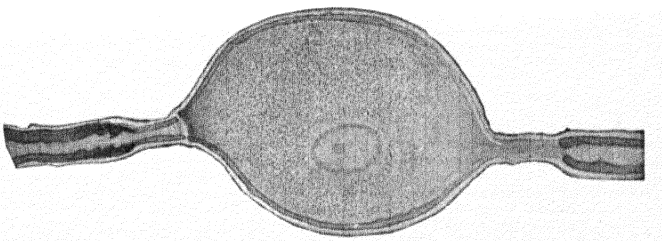

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these cells partake of an epithelial character, but similar cells occur in the epidermis of certain invertebrates (*e.g.* Lumbricus), which undoubtedly represent sensory nerve-cells (see p. 282, and Neurology, Part II. p. 359).

Most nerve-cells of the central nervous system are multipolar (see Plate opposite p. 212), having a single axon and two, three, or more dendrons. The number and relative size of the dendrons influence the general shape of the cell. If these are nearly equal and equally distributed, the cell-body is uniformly angular : if one or two dendrons are much larger than the rest, the cell-body tends to be drawn out in their direction : in this way nerve-cells become stellate, pyramidal, and assume many other forms. Most dendrons at once branch dichotomously, and rapidly decrease in size ; but in some cases the branching is less close to the cell-body. In the cells of Purkinje of the cerebellum the dendrons form a greatly extended arborescent mass (fig. 349). As already noticed (p. 211), some dendrons are closely beset with small lateral projections, the so-called 'spines' or 'thorns,' giving them a roughened appearance.

FIG. 348.—DIAGRAM OF THE ARRANGEMENT OF SENSORY NERVE-CELLS IN THE OLFACTORY MUCOUS MEMBRANE AND OLFACTORY BULB. (G. Retzius.)

n., *n*., axons of nerve-cells. The upper one comes from an olfactory cell and forms a synapse at *gl*. with one of the dendrons of a cell in the olfactory bulb.

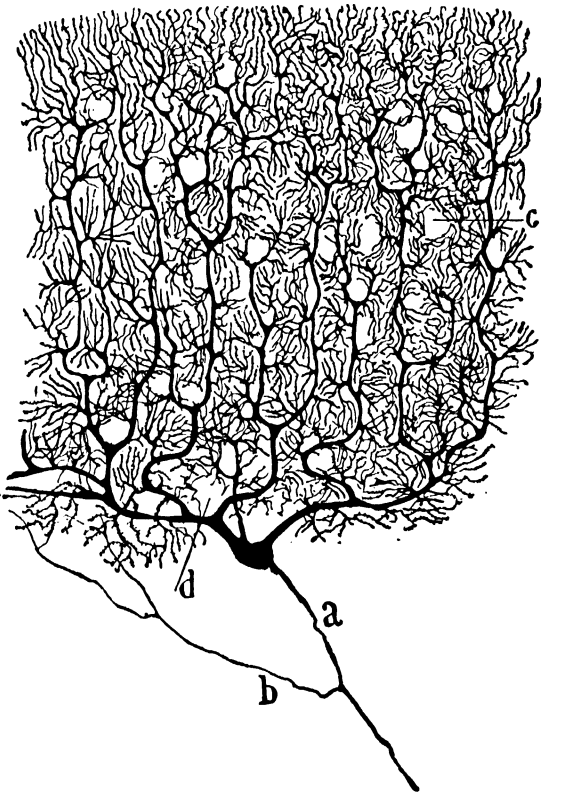


FIG. 349.—A CELL OF PURKINJE OF THE CEREBELLAR CORTEX. Golgi method. (Cajal.)

a, its axon; *b*, a collateral; *c*, *d*, the branching mass formed by its dendrons.

Although it is a general rule that the axon extends to some distance from the cell before terminating—and this fact constitutes an important difference between it and the dendrons—in a certain type of cells met with in the grey matter of the central nervous system the axon begins to break up into branches near the cell-body (fig. 350). These branches are, however, quite different from those of the dendrons and cannot be mistaken for them. Cells of the ordinary kind—the axons of which terminate at some distance from the cell-body—are known as cells of

type I. of Golgi; those of which the axon-terminations are close to the cell-body are known as cells of type II. of Golgi. But it cannot be doubted that every transition must exist between the extreme examples of these two types.

Some of the largest multipolar nerve-cells are those of the nuclei of origin of the motor nerves, and these contain the largest and most distinct Nissl bodies. Very large cells are also found in certain parts of the cerebral cortex (motor region) and in the cerebellar cortex (cells of Purkinje, cells of Golgi). On the other hand, the presence of a large number of very small nerve-cells ('granules')

FIG. 350.—A CELL OF GOLGI'S TYPE II. WITH AXON ENDING IN RAMIFICATION NEAR THE CELL-BODY. Golgi method. (Cajal.)
a, a', a'', axon; d, d, d, dendrons.

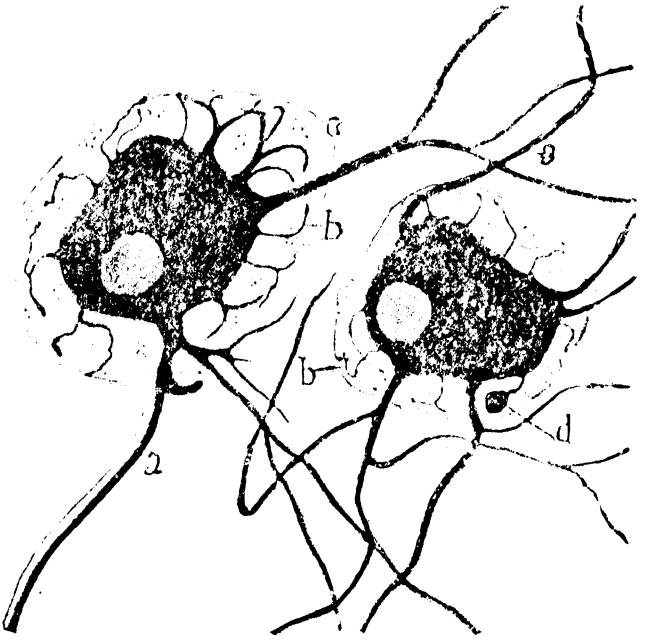


FIG. 351.—TWO SYMPATHETIC GANGLION-CELLS (MAN). (Cajal.)
a, a, axons; b, c, intracapsular processes; d, knob-like ending of an intracapsular process.

is characteristic of certain other areas of the cerebral cortex (sensory and association areas), and of the innermost layer of the cerebellar cortex (granule-layer). But every intermediate size occurs between the largest and the smallest nerve-

cells. The largest nerve-cells which are known are those which give origin to the electric nerves of Malapterurus. These are large enough to be easily visible with the naked eye, and the cell-body is excavated with hollows and passages into which blood-vessels for the nutrition of the cell penetrate.

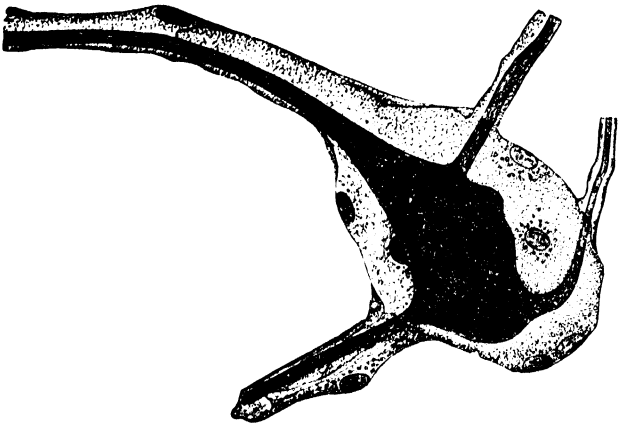


Fig. 352.—A ganglion-cell within its sheath: from the human sympathetic. (Key and Retzius.) Highly magnified.

The cells of the sympathetic ganglia of man and mammals are always multipolar,[1] with an axon and several dendrons. Occasionally, as in the spinal ganglia, there are also a number of short processes confined within the capsule (fig. 351). The cell-body is usually of an angular form with rounded angles. It is invested by a nucleated membranous sheath, which is continued over the issuing cell-processes (fig. 352). The axon is traceable to its termination as a pale (non-medullated) nerve-fibre: it sometimes, but rarely, becomes thinly medullated.[2] The cells vary greatly in size, probably in conformity with the length of their axons. In the rabbit, hare, and guinea-pig there are two nuclei in each sympathetic cell (Huber). The dendrons rarely extend beyond the confines of the ganglion in which the cell-body lies: they may end by ramifying around other cell-bodies in the ganglion. The cells of the sympathetic ganglia serve as distributing stations for the nerve-fibres which enter and end in the ganglia. The entering nerve-fibres are generally of the fine medullated variety; these are derived from cells of the lateral horn and neighbouring part of the grey matter of the spinal cord and corresponding situations in the grey matter of the medulla oblongata. On entering the ganglion in which they are to terminate they ramify amongst the

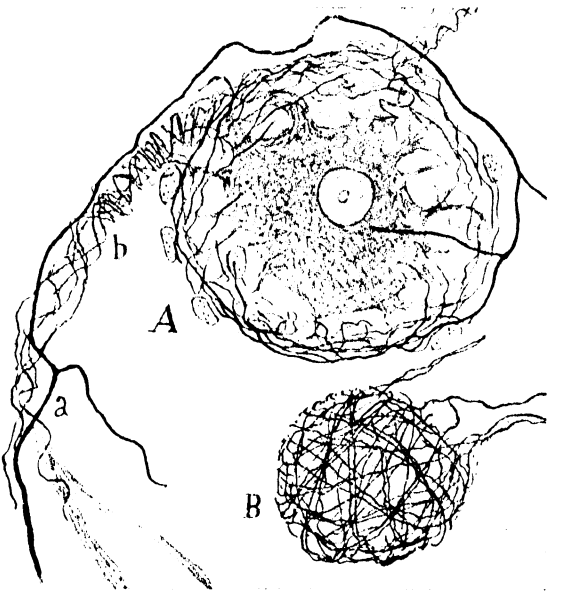


Fig. 353.—Two cells from a sympathetic ganglion of man, showing the ending of afferent fibres (*a*) around the cell-bodies and axons (*b*). (Cajal.)

[1] In amphibia they may be unipolar; L. Beale, Phil. Trans. 1863; Huber, Journ. Morph. 1889.
[2] Huber, *op. cit.*; Langley, Journ. Physiol. xx. 1896.

ganglion-cells, and their fine terminal fibrils form synapses around the cell-bodies (fig. 353).[1] The axons of the cells pass out from the ganglion towards the periphery as non-medullated fibres, and these non-medullated fibres end in connexion with the plain muscular and other tissues which are supplied by the sympathetic nerves.[2]

The nervous plexuses which occur in the wall of the alimentary canal, and which are offshoots of the sympathetic, contain small nerve-cells collected into small ganglia. In the plexus myentericus, as in most parts of the sympathetic, these cells are of two kinds (fig. 354) — viz. one with numerous short dendrons and a single axon, and another kind with numerous long processes extending far from the cell-body and distributed to the adjoining muscular tissue: in this second variety no clear distinction is evident between axons and dendrons. In the plexus submucosæ all the ganglion-cells are of this second type (fig. 355).[3]

Lastly it may be mentioned that at the termination of sympathetic nerve-fibres in other situations—*e.g.* in the mucous membrane of the small intestine and within the villi, as well as in the plexuses in which the nerve-fibres to blood-vessels and some other organs end, small multipolar cells occur (fig. 356),[4] which are believed to be of nervous nature, since they become stained by methods which are specially selective for nervous elements. According to Cajal they contain neuro-fibrils.

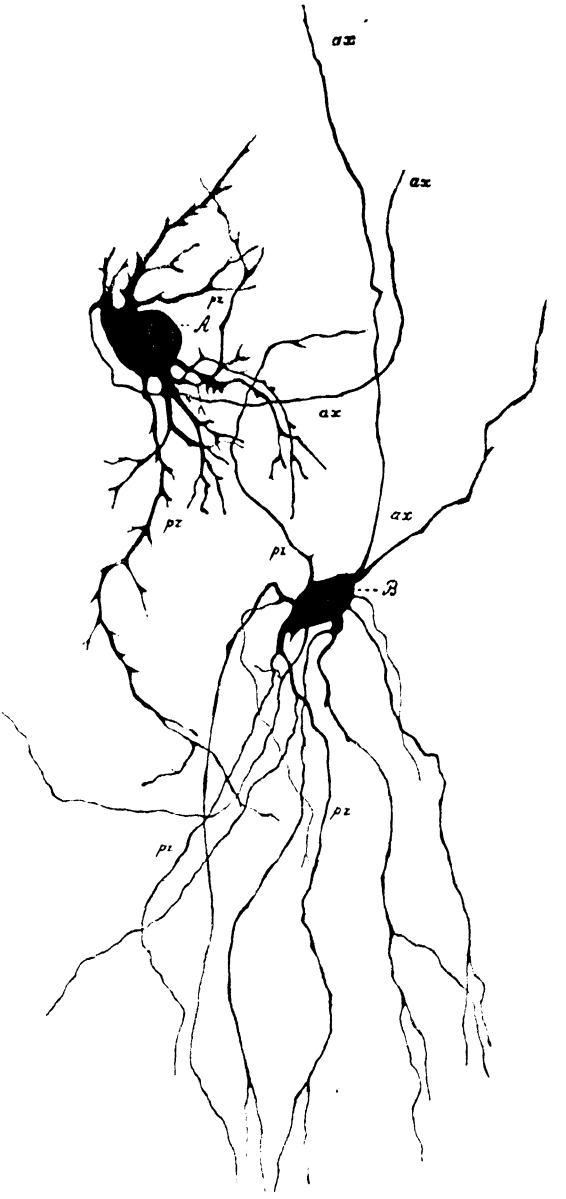


FIG. 354. — CELLS FROM THE SYMPATHETIC, SHOWING THE TWO DIFFERENT TYPES (A AND B) DESCRIBED IN THE TEXT. (Dogiel.)

ax, axons; *pz*, dendrons.

[1] Fibrils ramifying around the cell-body of the sympathetic ganglion-cell were described by A. Smirnow, but he regarded them as arising in the cell (Arch. f. mikr. Anat. xxxv. 1890). Their true nature has been shown by A. S Dogiel and Cajal.

[2] See on sympathetic nerve-cells, A. S. Dogiel, Arch. f. mikr. Anat. xlvi. 1895, and Anat. Anz. xi. 1896; Ramón y Cajal, *op. cit.*; Juschtschenco, Arch. f. mikr. Anat. xlix. 1897.

[3] La Villa, Riv. trimestr. 1898.

[4] Drasch, Sitzungsb. d. Wiener Akad. 1880; Cajal, 1889, Nuevas aplicaciones del método de Golgi, and Los ganglios y plexos nerviosos del intestino, 1895; Cajal and Sala, Terminacion de los nervios &c. 1891; G. Retzius, Biol. Unters. 1892; H. J. Berkeley, Anat. Anz. 1893; A. S. Dogiel, Anat. Anz. x. 1895.

Nerve-fibres.—As has already been explained, nerve-fibres always originate from nerve-cells, the axon of the nerve-cell forming the axial part (axis-cylinder)

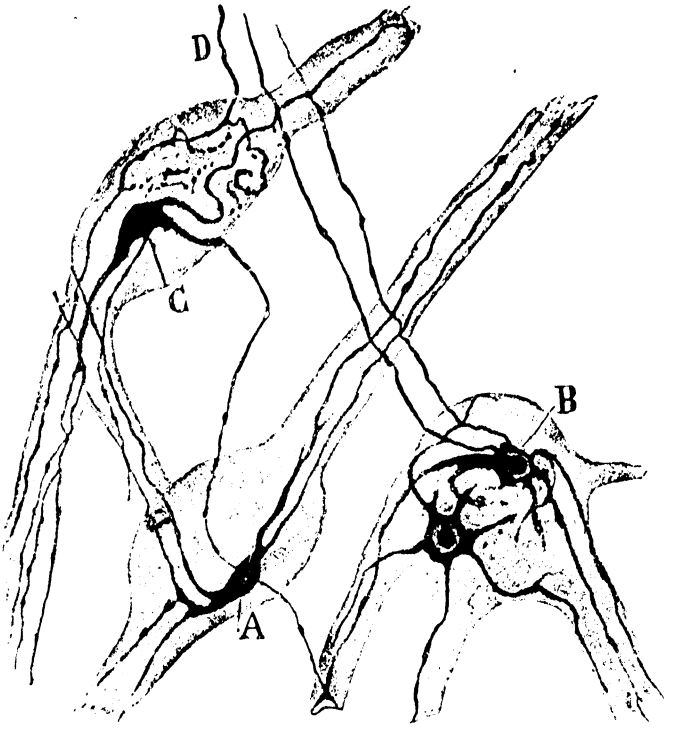


FIG. 355.—THREE SMALL GANGLIA OF THE PLEXUS SUBMUCOSÆ. (Cajal.)
A, B, C, cells with long axon-like dendrons; D, a fibre traversing one of the ganglia and giving off collaterals within it.

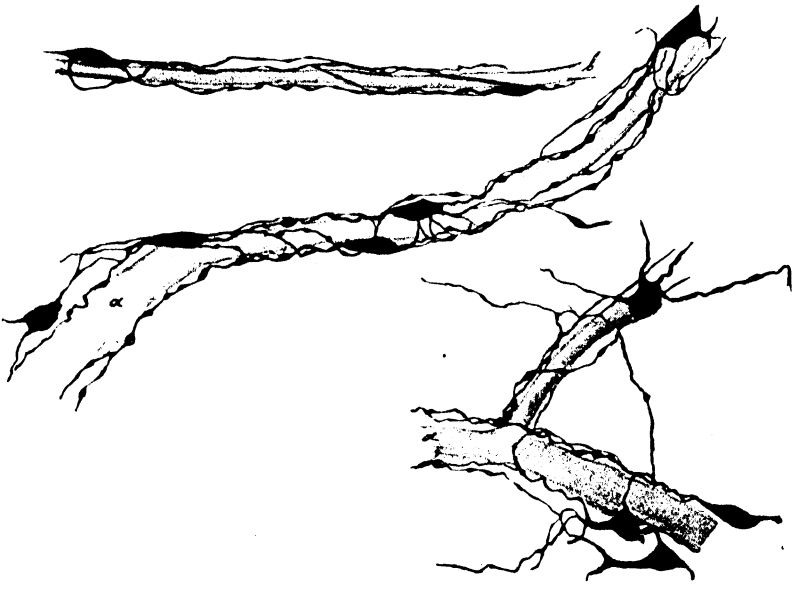


FIG. 356.—CELLS SITUATED UPON THE TERMINAL NERVE-PLEXUSES AROUND SMALL BLOOD-VESSELS. (A. S. Dogiel.)

of the nerve-fibre. Some nerve-fibres—*grey or non-medullated fibres*—are composed entirely of this axon, with perhaps a delicate (protoplasmic ?) sheath; these fibres exhibit elliptical nuclei at frequent intervals. Such non-medullated nerve-fibres occur only in the peripheral offsets from the sympathetic ganglia. All other nerve-fibres (*medullated fibres*) have a medullary or myelin sheath immediately surrounding the axis-cylinder, and those outside the central nervous system have in addition a membranous sheath external to the medullary sheath: this membranous sheath has nuclei at regular and somewhat distant intervals on its internal surface, partly imbedded in the medullary sheath; it is known as the *nucleated sheath of Schwann* or *neurolemma*.

Nodes or constrictions of Ranvier.—At equal regular intervals between the nuclei of the neurolemma occur interruptions or constrictions in the medullary sheath (fig. 357) which seem to be produced by the dipping in of the neurolemma towards the axis-cylinder, around which it appears to form a narrowed band, which was termed by Ranvier the *constricting band*. By these *constrictions of Ranvier* the nerve-fibre is divided up into a series of equal segments, each of which has a nucleus of the sheath of Schwann at about the middle of its length. On either side of each constriction the medullary sheath is usually somewhat swollen (fig. 365), giving a nodular appearance to the nerve-fibre at the constrictions, like the nodes upon a bamboo-stem: hence the name *nodes*, which has been applied to these parts of the fibre. Although the medullary sheath is interrupted at the constrictions, the axis-cylinder passes through uninterruptedly, and the neurolemma or sheath of Schwann is also continued over the node, although it is uncertain whether the continuity is not effected by the intermediation of cement-substance like that which connects together many epithelioid cells.

The chief reason for believing that this may be the case is the circumstance that the 'constricting band' is stained by nitrate of silver in the same way as the intercellular cementing substance of epithelial tissues (fig. 358). Staining fluids penetrate the nerve-fibre more readily at this point, and as the result of this penetration the axis-cylinder may become stained here whilst remaining unstained elsewhere. When this staining of the axis-cylinder at the node is effected by nitrate of silver, the result of the combination of the coloration of axis-cylinder and of constricting band is the production of the appearance of a cross at each node: an appearance sometimes known as the *cross of Ranvier*. If the coloration of the axis-cylinder by nitrate of silver is carefully observed with a high magnifying power it is often seen to

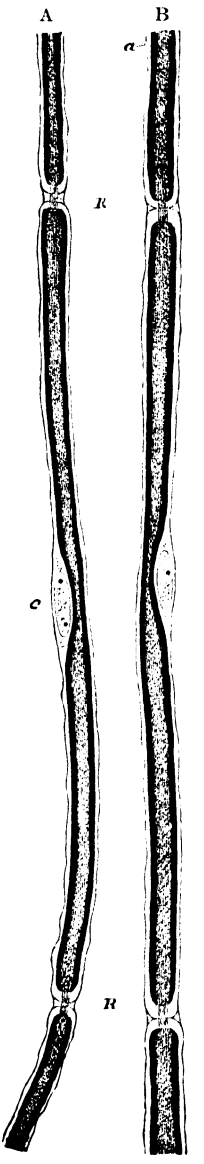


FIG. 357.—PORTIONS OF TWO NERVE-FIBRES STAINED WITH OSMIC ACID (FROM A YOUNG RABBIT). Diagrammatic. 425 diameters.

R, *R*, nodes of Ranvier, with axis-cylinder passing through; *a*, neurolemma; *c*, opposite the middle of the segment, indicates the nucleus and protoplasm lying between the neurolemma and the medullary sheath. In A the nodes are wider, and the intersegmental substance more apparent than in B. (Drawn by J. E. Neale.)

be in transverse bands with clearer intervals between them (fig. 358). This appearance, which is probably due to successive precipitations of silver chloride within the semi-fluid substance of the axis-cylinder, was first described by Frommann, and is known as *Frommann's striæ*.[1]

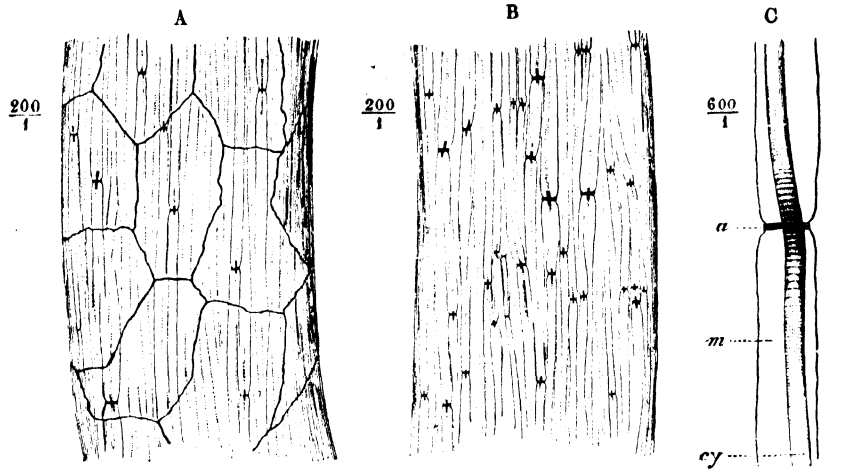


FIG. 358.—NERVES STAINED WITH NITRATE OF SILVER. (Ranvier.)

Small black crosses are seen upon the nerve-fibres at the nodes. In C it is evident that these are produced by staining of the axis-cylinders, *cy*, and of the constricting band, *a*. A shows markings due to a layer of epithelioid cells which covers the surface of the small nerve-bundle. In C, *m* denotes the medullary sheath.

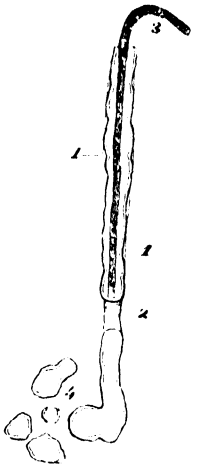


FIG. 359.—DIAGRAM TO SHOW THE PARTS OF A MEDULLATED FIBRE. (Sharpey.)

1, 1, neurolemma enclosing the doubly contoured medullary sheath. 2, a part where the white substance is interrupted, the outer sheath remaining. 3, axis-cylinder projecting beyond the broken end. 4, part of the substance of the medullary sheath escaped.

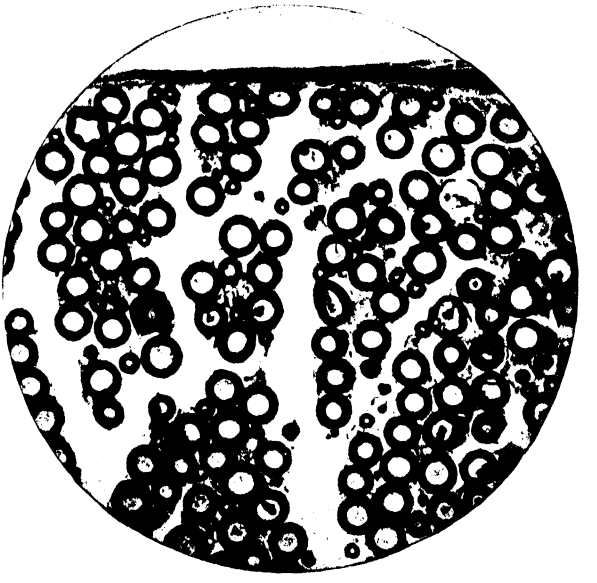


FIG. 360.—PHOTOGRAPH OF PART OF A SECTION OF THE SCIATIC NERVE OF A CAT. Osmic preparation. (Schäfer.) Magnified 300 diameters.

The medullary sheaths are black; the axis-cylinders appear colourless. Notice the variation in size of the fibres.

[1] For a possible explanation of the mode of formation of Frommann's striæ, see Macdonald, Proc. Roy. Soc. B. lxxvi. 1905, and lxxix. 1907; also Quart. Journ. Exp. Physiol. 1909, vol. ii. p. 51. Cf. Macallum and Menten, Proc. Roy. Soc. B. lxxvii. 1905.

From the above description it will be seen that a peripheral nerve-fibre consists of (1) the *axis-cylinder* or *axon* in the centre, (2) the *myelin* or *medullary sheath* next

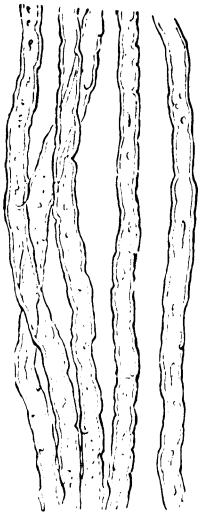


Fig. 361.

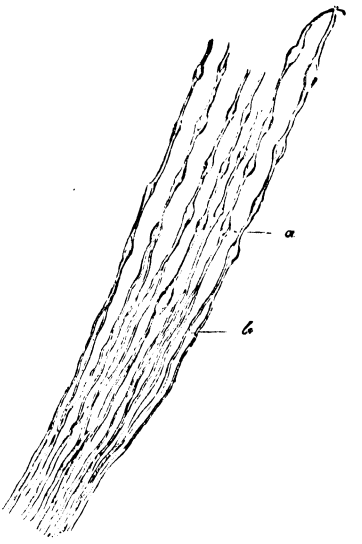


Fig. 362.

Fig. 363.

Fig. 361.—White or medullated nerve-fibres, showing the sinuous outline and double contours. (Bidder and Volkmann.)

Fig. 362.—Fine medullated fibres from the root of a spinal nerve. (Valentin.)
At *a* the fibres have been dragged upon in process of teasing and have become varicose.

Fig. 363.—A small part of a medullated fibre highly magnified. Half diagrammatic. (Schäfer.)

The fibre looks in optical section like a tube hence the term tubular, formerly applied to these fibres. Two partial breaches of continuity are seen in the medullary sheath, which at these places exhibits a tendency to split into laminæ. The neurolemma is here and there apparent outside the medullary sheath, and the delicate striæ which are visible in the middle of the fibre indicate the fibrillated axis-cylinder.

Fig. 364.—Portion of a fresh medullated nerve-fibre from sciatic of cat. (Schäfer.)
Magnified 600 diameters.

Three of Schmidt's intersegmental clefts are shown, and also the situation of a nucleus of the neurolemma (*n*).

to the axon,[1] and (3) the *nucleated membranous sheath* (*neurolemma*) most external (figs. 359 to 365). In the nerve-fibres which still lie within the nerve-centres, and which constitute the whole of the white substance of the brain and spinal cord, the membranous sheath is absent. These *alemmal* [2] myelinated fibres are far less tough, and therefore more difficult to isolate to any length than those of the nerve-roots and of the peripheral nerves, which are provided with neurolemma ;

[1] Donaldson and Hoke (Journ. Comp. Neurol. 1905) find that in every nerve the sectional areas of axon and medullary sheath are about equal to one another, coarser fibres having a thicker, and finer fibres a proportionally thinner sheath.

[2] α, privative ; λέμμα, sheath.

but, on the other hand, their axons are more easily displayed, because the myelin of the medullary sheath comes away from them more readily.

The *axis-cylinder* of the nerve-fibre, being in every case the axon of a nerve-cell, has the structure which has already been described for that process. It consists of a bundle of neuro-fibrils imbedded in a soft and probably protoplasmic matrix which fills the interior of the medullary sheath (fig. 363), but is liable to shrink after death (fig. 365). It is continued without interruption from its origin in a nerve-cell body to its termination in a peripheral organ, where it generally ends by branching dendritically, forming a terminal arborisation.

The size of nerve-fibres shows considerable variation (figs. 360 to 366). The largest (from 8 μ to 16 μ diameter) are those to the muscles of the limbs and skeletal muscles generally: most sensory fibres are also of large size, but those from the viscera are of smaller calibre. The smallest medullated fibres are those which belong to the autonomic system, passing from the spinal cord to the sympathetic ganglia (pre-ganglionic fibres of Langley). These are from

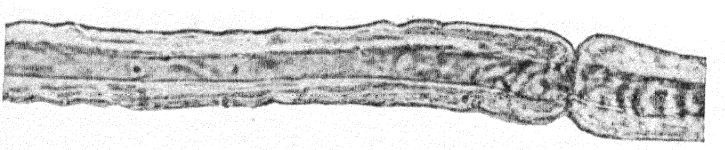


FIG. 365.—PORTION OF FRESH MEDULLATED NERVE-FIBRE IN WHICH THE AXIS-CYLINDER HAS BEGUN TO SHRINK, SO THAT IT IS CLEARLY DISTINGUISHABLE FROM THE MEDULLARY SHEATH. Photograph. (Schäfer.) Magnified 600 diameters.

A node of Ranvier is seen on the right.

1·8 μ to 3·6 μ. Fibres of intermediate size, both efferent and afferent, occur in some cranial nerves (fifth, seventh, ninth, tenth) and several spinal nerves.[1] The smaller medullated nerves are apt to become varicose on being teased in the fresh condition (fig. 362). Except in the autonomic system there seems to be some sort of relationship between the size of the nerve-fibres and the length of their course, but this does not follow any regular proportion.

The **medullary sheath** of the nerve-fibre in the living unaltered state appears structureless, except for the constrictions of Ranvier, which have already been described. These are, moreover, due to the presence of the neurolemma, for they are not seen in the alemmal fibres of the central nervous system. Various evidences of special structure have been from time to time described in the medullary sheath (see below), but there is abundant reason to believe that they are one and all the result of the action of reagents and of post-mortem coagulation upon the myelin of which this sheath is composed.[2] The myelin confers upon it a peculiar doubly-contoured appearance when examined at a certain focus. The presence of the myelin is also responsible for the dark ink-like staining which the medullated fibres undergo when treated with osmic acid. It is this sheath which shows the first signs of degeneration when the nerve-fibre is cut off from its cell of origin, the continuity of the myelin becoming interrupted at first only here and there, but after a short time at very frequent intervals, so that it becomes broken up into globular masses, and these ultimately into small globules and granules of fatty material (Wallerian degeneration, see p. 245).

The appearances in the medullary sheath which have been considered by various authors to represent a special structure invisible in living nerve-fibres are the following:

(*a*) The *conico-cylindrical segments* (Schmidt, Lantermann[3]). These are always seen in teased preparations of peripheral medullated nerve-fibres (figs. 363, 364) and are particularly

[1] On the size of nerve-fibres, see Gaskell, Journ. Physiol. vii. 1886; Edgeworth, *ibid.* xiii. 1892; J. Fischer, Anat. Anz. xxvi. 1905 (autonomic fibres).

[2] Cf. Pertick, Arch. f. mikr. Anat. xix. 1881.

[3] Arch. f. mikr. Anat. xiii. 1877.

conspicuous in osmic-acid-stained specimens (fig. 366). They have nothing in common with the regular segmentation of the nerve-fibre, which was described by Ranvier (see p. 229), but are produced by incomplete interruptions in the myelin of the medullary sheath, which are conical in form and are bridged across by fibre-like strands of the material composing the sheath (fig. 364). When the axis of the fibre is focussed the interruptions appear to run obliquely from

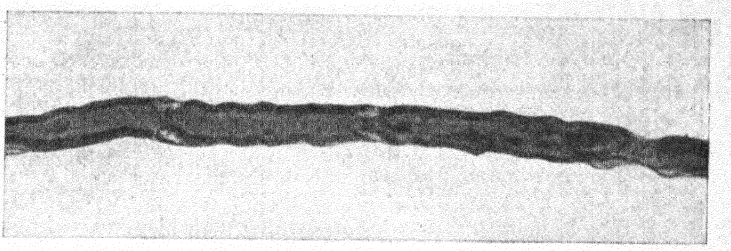


FIG. 366.—A PORTION OF MEDULLATED NERVE-FIBRE TREATED WITH OSMIC ACID. Photograph. (Schäfer.)

The medullary sheath is stained black. A node of Ranvier is seen on the right and two medullary clefts in the course of the fibres.

the neurolemma towards the axis-cylinder. The chief reasons for believing that these interruptions are artifacts are—

(1) They occur at very irregular intervals, so that the conico-cylindrical segments which lie between them vary greatly in length, some being short, others long; nor is there any constancy even in their irregularity.

(2) The less the nerve-fibres are mechanically injured, and especially pulled in the process of separating them, the fewer and less conspicuous are the oblique interruptions and the fewer the conico-cylindrical segments. On the other hand, their number and prominence can be greatly increased by manipulation of the fibres.

(3) They are not visible in fibres which are examined in intact transparent parts of living animals, such as the transparent tail-fin of small fishes.

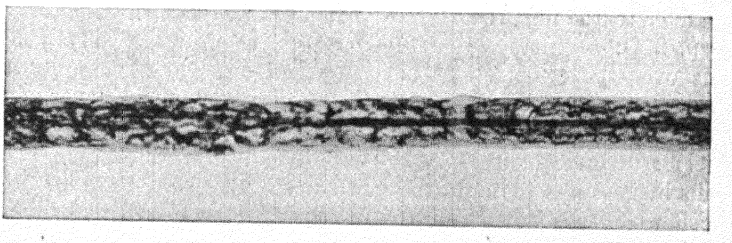


FIG. 367.—RETICULAR APPEARANCE (NEUROKERATIN) IN MEDULLARY SHEATH. Photograph. (Schäfer.) Magnified 600 diameters.

The axis-cylinder is coloured as well as the neurokeratin network.

(*b*) A *reticular structure* (*reticulum of the medullary sheath*), combined with which there may be an appearance of spiral fibres at the junction of the segments of Schmidt (fig. 367).[1] Various reagents, but especially alcohol and ether, produce this appearance of a reticulum or sponge in the myelin of medullated nerves. There is, however, reason to believe that the apparent structure is due to the way the myelin constituents have undergone coagulation and separation under the influence of the reagent. For (1) the size of the reticulum varies, even in the same nerve-fibres, with the strength of the reagent or reagents, and the rapidity with which they are allowed to act; (2) no trace of such a structure is visible in fresh nerve-fibres; (3) a similar reticular appearance can be produced in isolated drops of myelin.

The reticulum is probably due to the separating out in this form, under the influence of the coagulating reagents, from the complex material which forms the myelin, of a keratin-like substance (*neurokeratin*, Kühne). This, after such separation, is capable of being stained

[1] G. Sala (and Golgi) Verhandl. d. Anat. Gesell. 1901 (Anat. Anz. xviii.)

distinctively by carmine and other dyes, which entirely fail to affect it whilst it is still in combination in the myelin.[1]

(*c*) *A rodded structure.* This is seen after the action of certain reagents, especially picric acid. The medullary sheath of the fibres seems after this treatment to contain a large number of fine rods, which in transverse sections radiate out from the axis-cylinder towards the neurolemma like the spokes of a wheel (fig. 368), and in longitudinal view run perpendicularly between the axis-cylinder and neurolemma. The appearance is also, there can be little doubt, due to the peculiar manner in which the reagent has caused coagulation of the myelin of the medullary sheath, one of its constituents having become separated out in a semi-crystalline rod-like manner. No trace of such structure is visible in fresh nerve.

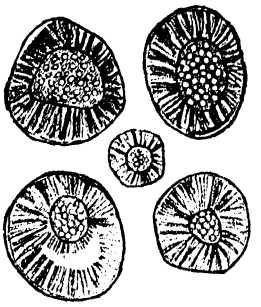


FIG. 368.—SECTION ACROSS PART OF A NERVE-TRUNK, SHOWING THE SECTIONS OF THE NERVE-FIBRES. From a photograph. (Schäfer.) $\frac{1000}{1}$.

The nerve was hardened in picric acid and stained with picrocarmine. The radial striation of the medullary sheath is very apparent. In one fibre the axis-cylinder is shrunken and the medullary striations are broken. The fibrils of the axis-cylinder are clear in section and suggest a tubular structure.

The **neurolemma,** which is also known as the *nucleated sheath of Schwann* and *primitive sheath*, forms the outermost stratum of the medullated nerve-fibre in peripheral nerves. It is a homogeneous membranous layer, very thin but somewhat tough, serving to contain the soft myelinic substance of the medullary sheath. As already mentioned, it is absent in the fibres of the substance of the brain and cord.[2] The oval nuclei which lie on the inner surface of this sheath, although imbedded in the myelin of the medullary sheath, undoubtedly belong to the neurolemma, for they are not seen in the alemmal fibres of the brain and cord: they appear to be the nuclei of the cells from which the primitive sheath was originally formed. Probably they represent cells which have wandered out in the embryo from the neural ectoderm and have undergone special modification to adapt them to the purpose of ensheathing the peripheral nerve-fibres (sheath-cells, see p. 243). Whether the membrane of the primitive sheath is actually continuous over the constrictions of Ranvier from segment to segment of the nerve, or whether the segmental portions of this sheath are merely united by cement-substance at the nodes, as the fact that it stains black when treated by the silver method seems to indicate (see p. 229), is not fully ascertained, but in any case there seems little reason to doubt that each segment of the neurolemma represents a single cell which has become enwrapped around the medullated fibre and has thereby imparted to this a segmented character. There is sometimes to be seen in the immediate neighbourhood of the nuclei a small amount of finely granular substance, which may be regarded as a remainder of the original protoplasm of the sheath-cell.

In the medullated nerves of osseous fish there may be several nuclei between each pair of nodes, and the protoplasm in which they lie may send processes through the medullary sheath towards the axis-cylinder.[3]

The **axis-cylinder** is the essential part of the nerve-fibre. At its origin from the cyton or nerve-cell-body the nerve-fibre consists only of axon without any sheaths, and at its termination in the periphery it is commonly found that the medullary sheath and neurolemma cease a short distance before the actual ending of the fibre,

[1] On the neurokeratin of the medullary sheath, see S. Hatai, Jour. Comp. Neurol. xiii. 1903.

[2] Bikeles found (in posterior roots of lumbar nerves) that Schwann's sheath is absent close to the cord, being there replaced by glia-cells, and that if the root be crushed regeneration of the nerve-fibres extends only as far as this point (Neurol. Centralbl. 1907).

[3] Nemiloff, Arch. f. mikr. Anat. lxxii. 1908. According to Nemiloff, both the neurokeratin network and also the septa between the conico cylindrical segments are occupied by these processes.

and that the nerve-fibre is continued to its termination by the axon alone, which is here usually branched. The axis-cylinder is therefore nothing but the axon of the nerve-cell, and its structure is the same therefore as that of this process, consisting of a bundle of fibrils (neuro-fibrils) which are imbedded in a homogeneous matrix (fig. 369). At the origin of the fibre in the body of the nerve-cell the neuro-fibrils tend to diverge towards all parts of the cell-body and towards and into the dendrons. At the termination of many nerves they also show a tendency to separate from one another, passing into the several ramifications of the nerve-ending, and eventually even running singly to their termination: here the individual fibrils are often themselves branched. But whether they branch in the actual course of the nerve-fibre is uncertain and difficult of determination. As already stated (p. 217), some authorities have held that these fibrils are in constant inter-

FIG. 369.—MEDULLATED NERVE-FIBRE OF FROG, SEEN IN TRANSVERSE AND LONGITUDINAL SECTIONS. Osmic acid and acid fuchsin preparation. (Biedermann.)

The longitudinal section shows a node of Ranvier and two clefts of Schmidt. Both sections exhibit the fibrils of the axis-cylinder.

communication throughout the length of the fibre, and have regarded them in the same light as the network of fibrils which has been described in many forms of protoplasm, but with the meshes of the network greatly drawn out in the direction of the length of the nerve-fibre. This was the view advocated by Frommann. On the other hand, Max Schultze, who first described these fibrils as definite constituents of the axis-cylinder, held that they are quite unbranched, and do not unite with one another throughout their whole course (fig. 320). This view is on the whole that which is supported by most authorities, although it must be admitted that the observations of Apáthy and others which have already been referred to seem to indicate that the isolation of the neuro-fibril is by no means an established fact. Moreover, an exception must in any case be made for the nerve-endings, where there is abundant evidence of the existence of branching and reunion.

It is stated by G. Mann [1] that the fibrils are the only parts of the nerve which are continuous at the nodes of Ranvier from segment to segment. But it is impossible to be sure there is no interfibrillar matrix between them: all that can be affirmed is that if present it is in much smaller amount here than elsewhere.

That the fibrils are not solid but of a semi-fluid nature is probable from the fact that they easily become varicose, with little beadlets or droplets upon their course: this is what one would expect with a viscous fluid, but not with a solid material. In transverse sections of the axis-cylinder the fibrils look like fine dots lying within a clear matrix: with a very high magnification the dots appear to be encircled by a differentiated outline, as if each fibril were a hollow tubule (fig. 368). The experiments of Carlson indicate that the conducting substance of nerve must be fluid.[2]

Some authors have described a special sheath (*sheath of Mauthner*) around the axis-cylinder separating it from the myelin, but there is no clear evidence of the existence of such a sheath, although, after death, the axis-cylinder may shrink away from the medullary sheath and leave a clear interval between. It seems highly probable that axis-cylinder and myelin sheath are originally parts of the same structure: the myelin being laid down or secreted by the protoplasm of the axis-cylinder; or, to put it in another way, that the original protoplasm which forms the axon of the nerve-cell undergoes differentiation in its external part to form the myelin sheath, which surrounds the central or internal part in which alone neuro-fibrils

[1] Verhandl. d. Anat. Gesellsch. 1898.

[2] A. J. Carlson, Journ. Exp. Zool. i. 1904; Amer. Journ. Physiol. xiii. 1905; Jenkins and Carlson, Journ. Comp. Neurol. xiii. 1903, and xiv. 1904.

become formed.[1] The alternative view, that the myelin is formed by the cells which produce the nucleated sheath or neurolemma, is less probable, since these cells do not exist in the substance of the brain and cord, although the fibres here are all myelinated. Further, all degenerative changes which occur in a nerve-fibre, whether in the central nervous system or at the periphery, are shared equally by the axis-cylinder and the surrounding myelin; in the latter they appear, in fact, to commence.

Non-medullated fibres.—These (figs. 370, 371) are exclusively connected with sympathetic ganglion-cells, of which they represent the axons. They have

FIG. 370.—NON-MEDULLATED NERVE-FIBRES. (Schäfer.) Magnified 400 diameters.

nuclei upon them at frequent intervals. These nuclei appear to be interpolated in the substance of the non-medullated fibre, although they have been thought to belong to a delicate sheath. It is, however, impossible to demonstrate the existence of such a sheath as distinct from the axon. Non-medullated fibres are destined for the plain muscular tissue of the viscera and blood-vessels, for the arrector muscles of the hairs (pilo-motor nerves), for the muscular tissue of the heart, and for the cells of secreting glands, and in all these situations they end by fine extended arborisations between the tissue-elements to which their twigs are applied, sometimes in the form of small dilatations. In some situations the endings have been described as continued into the interior of the cells, but whether this is so must be regarded as doubtful.

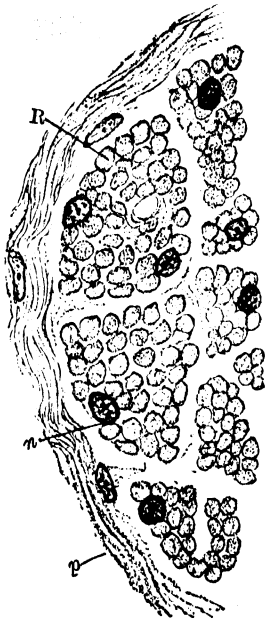


FIG. 371.—SECTION OF PART OF A SYMPATHETIC NERVE OF THE OX. (Cajal.)

p, perineurium; R, non-medullated fibres; *n*, a nucleus.

Although characteristic of sympathetic nerves, to which they impart when numerous a greyish appearance, non-medullated fibres are also found intermingled with the medullated in most peripheral nerves (to which they have passed from the sympathetic).[2] They are not found in the central nervous system, if we except those distributed to the blood-vessels of the brain and cord, nor in the nerve-roots except such fibres as may be passing along the roots to those blood-vessels. But in the anterior nerve-roots of all the thoracic and most of the lumbar nerves, in those of the second and third sacral, and in the roots of some of the cranial nerves (seventh, ninth, tenth, and eleventh) there occur amongst the ordinary large and medium-sized nerve-fibres a number of very fine medullated fibres which are usually collected in one or more distinct groups, and which are looked upon as belonging to the autonomic nerves.[3] In the case of the spinal nerves these fine medullated fibres pass to the nerve-root

[1] All protoplasm contains the constituents of myelin; probably that of the nerve-cell more than that of ordinary cells. Sometimes the body of a spinal ganglion-cell has an envelope of myelin (fig. 347)

[2] According to F. S. W. Ranson (Anat. Record iii. 1909), non-medullated fibres are much more numerous in ordinary nerves than has usually been supposed. He regards them as arising from the small ganglion-cells of the spinal ganglia, having found that after division of a nerve which contained only 1,500 medullated fibres, no fewer than 4,500 of the spinal ganglion-cells underwent Nissl degeneration (Journ. Comp. Neurol. xvi.).

[3] The autonomic system of nerves and ganglia includes not only what has hitherto been known as the sympathetic system, but also other nerve-fibres and ganglia which are distributed to the visceral and vascular system, such as the inhibitory fibres of the heart, the secretory fibres of the secretory glands, the vaso-dilator fibres of the pelvic viscera, &c. Langley, Schäfer's Text-book of Physiology. See also Schäfer and Symington's Neurology, Part I. (vol. iii. Part I. of this work).

from cells in the lateral horn (intermediolateral tract),[1] leaving the nerve-centre as the *white ramus communicans* and entering either one of the ganglia of the sympathetic chain or a ganglion nearer the periphery; they terminate by an arborescence of the axis-cylinder around

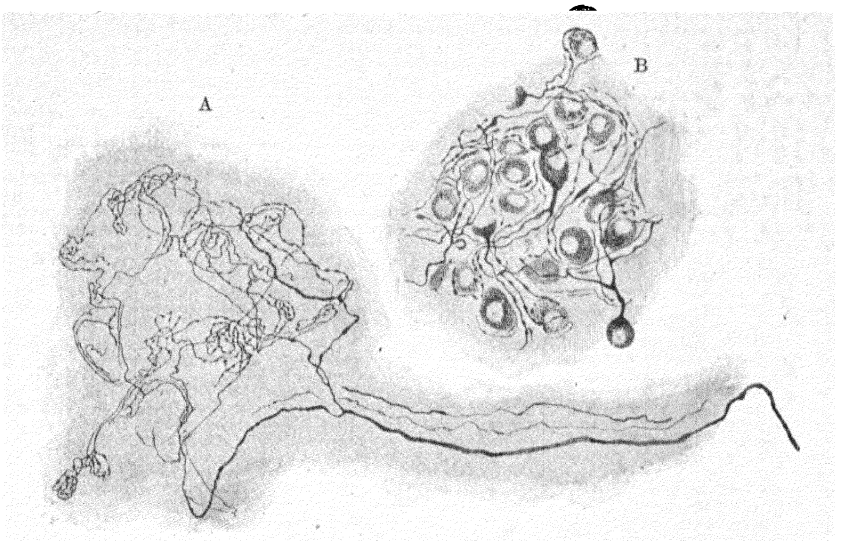


FIG. 372.—ENDINGS OF SYMPATHETIC NERVE-FIBRES IN SMALL GANGLIA OF HEART. Methylene-blue preparation. (A. S. Dogiel.)

In A the cells are omitted; in B they are shown.

the ganglion-cells. Since it is from these cells that the non-medullated fibres pass to the visceral and vascular systems, it is clear that the ganglia in question form an intermediate

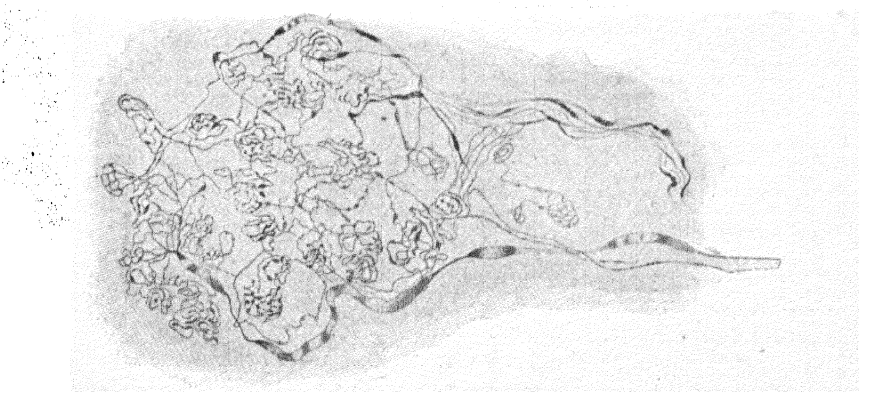


FIG. 373.—ENDING OF AUTONOMIC NERVES (PROBABLY FROM VAGUS) IN A SMALL PERIPHERAL GANGLION OF THE HEART. Methylene-blue preparation. (A. S. Dogiel.)

The cells are not represented; they occupy the spaces between the terminal ramifications of the nerve-fibrils.

station, in which one set of nerve-fibres of the nerve-chain ends and others begin. The cells of the sympathetic ganglia act, therefore, as distributing agents for the nerve-impulses which reach them from cells in the lateral horn of the spinal cord and from corresponding nerve-nuclei in the bulb.

[1] For the evidence on this point, see Biedl, Wien. klin. Woch. 1895; H. K. Anderson, Journ. Physiol. xxviii. 1902; P. T. Herring, *ibid.* xxix. 1903. See also Neurology, Part I. p. 81.

STRUCTURE OF THE NERVES AND NERVE-TRUNKS

The nerve-fibres in the peripheral nerves run together in small bundles, which are circular in section (fig. 374) and are named *funiculi*; these are gathered together to form the *nerve-trunks*. The funiculi are very variable in size, according to the number of fibres which they contain, and when there are several funiculi composing a nerve-trunk, they are constantly branching and uniting with other funiculi in their course along the nerve, so that it is impossible to dissect out a single funiculus for any distance. But while the funiculi thus branch and unite, the individual nerve-fibres which they contain run unbranched from the one funiculus to the other, and by this constant interchange the nerve-fibres, however various their origin, become, as a rule, thoroughly mixed up as they pass along the nerve-trunk.

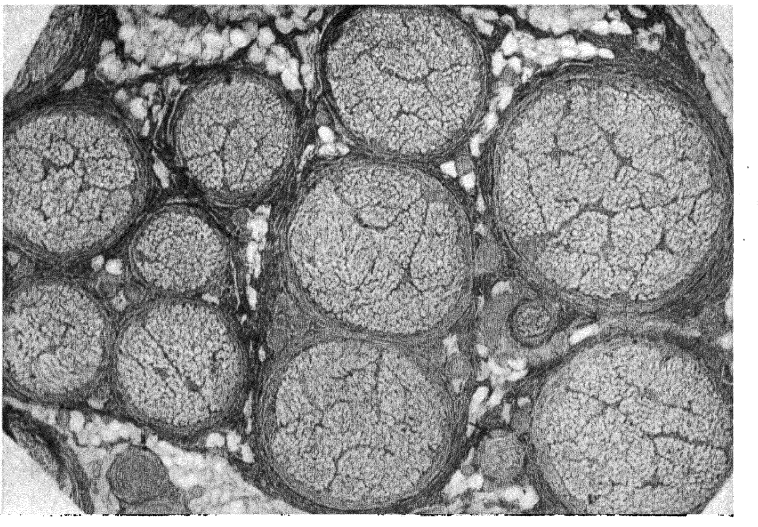


FIG. 374.—SECTION OF SCIATIC NERVE OF MAN. Low-power photograph. (Schäfer.)

Twelve funiculi of different sizes are included in the figure, each enclosed in its lamellar perineurium. The epineurium contains numerous fat-cells, which appear white in the photograph.

Exceptions are, however, found in which nerve-fibres of one origin remain within their own funiculus, which is merely attached, as it were, to another nerve, its fibres remaining unmixed with the fibres of the latter: an example of this is presented by the chorda tympani, which leaves the facial nerve in the aqueduct of Fallopius, and, passing across the cavity of the tympanum and through the Glaserian fissure, attaches itself to the course of the lingual branch of the fifth, by which it is conducted, without mingling with the true lingual fibres, towards the submaxillary and sublingual glands, and the tongue, to all of which it is eventually distributed.

Each funiculus is encircled by a sheath of connective tissue, which is termed the *perineurium* (Key and Retzius [1]) (figs. 374, 375). It is composed of very thin layers or lamellæ of white fibrous tissue, the fibres of which run circularly near the surfaces of the lamellæ. Intermixed with these in the thickness of each lamella are a certain number of fine elastic fibres, disposed in the form of a network. Each layer thus constituted is covered on its surfaces with flattened pavement-like (epithelioid)

[1] Studien in der Anat. des Nervensystems, 1896.

connective-tissue cells. Although the lamellæ are in contact with one another, it is possible to force injection material between them, and this may then find its way along the funiculus for a considerable distance. The intervals between the lamellæ represent, therefore, potential lymph-spaces, and it has been shown by Key and Retzius that at the nerve-roots, where these leave the skull and neural canal, the cerebro-spinal fluid, which fills most of the room within these cavities which is not occupied by the brain and cord, can pass into and along these clefts in the perineurium, and can thus drain slowly away towards the periphery along the nerves.

The regular arrangement of the lamellæ of the perineurium gives place within the funiculus to a looser tissue, which occupies the interstices between the nerve-

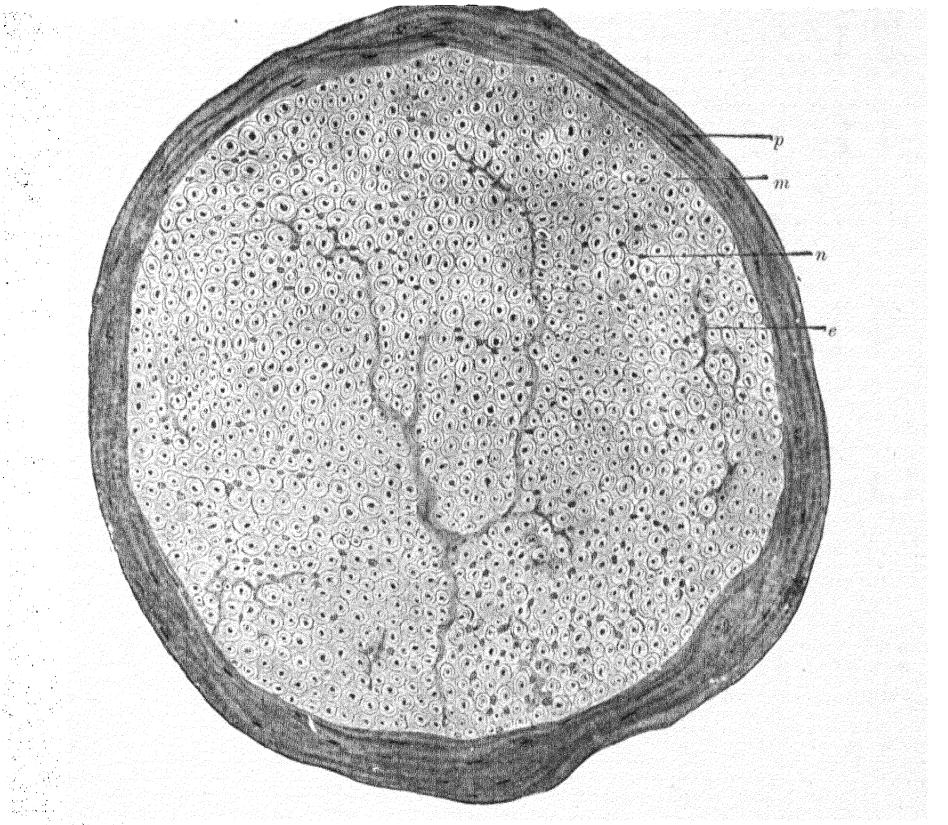


FIG. 375.—SECTION OF A FUNICULUS OF THE SCIATIC NERVE OF MAN.
(Prenant, Bouin, and Maillard.)
p, perineurium; *m*, transverse section of medullated nerve-fibre; *n*, non-medullated fibres; *e* endoneurium.

fibres. To this tissue the name of *endoneurium* has been applied. It consists in the main of fine longitudinally disposed white fibres running between and amongst the nerve-fibres, and serves to support these and to conduct amongst them the relatively small number of capillary blood-vessels which are supplied to the interior of each funiculus. There are also a few connective-tissue cells.

A nerve may consist of but a single funiculus, containing few or many nerve-fibres. Even nerve-fibres which are running singly to their destination are invested by a sheath which is continuous with the funicular sheath of the nerve-trunk or nerve-branch from which the fibre has been derived. Such a

sheath enveloping a single nerve-fibre is named *sheath of Henle*; it has the same structure as the perineurium, but with fewer lamellæ, and it encloses a prolongation of endoneurium. It takes a conspicuous part in the formation of the special organs in which nerve-fibres terminate, such as the Pacinian corpuscles and end-bulbs on many sensory nerves.

On the other hand, as has already been intimated, a large nerve may consist of several funiculi interlacing with one another in their course. Between the funiculi and also surrounding the whole nerve lies a considerable amount of loose areolar tissue, which conducts to the nerve the larger blood-vessels which are distributed to it, and also contains lymphatic vessels, and here and there sensory nerve-fibres (*nervi nervorum*) for the supply of the nerve-trunk itself and terminating in end-bulbs.[1] To this loose connective tissue outside and between the funiculi the name *epineurium* has been applied. It is continuous with the surrounding areolar tissue and forms a sort of tunica adventitia to the whole nerve. It often contains a large number of fat-cells (fig. 374).

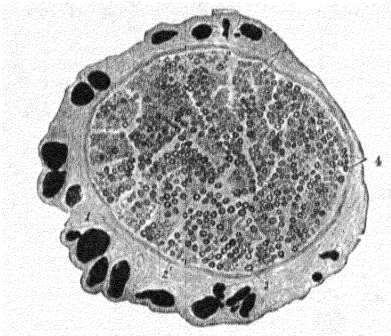


FIG. 376.—SECTION OF THORACIC SYMPATHETIC CORD OF CAT. Osmic preparation. (Fischer.)

The nerve is composed in almost equal parts of fine medullated fibres (3, 4) derived from ventral spinal roots, and of non-medullated fibres (5) derived from the cells of the sympathetic ganglia; 2, perineurium; 1, epineurium with fat-cells stained black.

The sympathetic nerve-trunks have the same general structure as the cerebro-spinal, but the funicular sheaths are thinner (fig. 376). In the section of the main nerves there is a considerable proportion of fine medullated fibres amongst the non-medullated, while in the peripheral branches of the sympathetic the relative number of medullated fibres is greatly reduced.

The optic nerves have a special structure, being enclosed by extensions of the brain membranes and divided up into angular bundles and not into cylindrical funiculi enclosed by perineurium (see Neurology, Part II., p. 220).

The amount of connective tissue in a nerve-trunk is altogether considerable. Ellison [2] found in the median nerve of the horse 63 per cent. of connective tissue; of the remaining 37 per cent. only 9 parts were occupied by axis-cylinder, the rest being medullary sheath.[3] The splenic nerve gave 61 per cent. of connective tissue and 39 per cent. nerve-fibre substance.

STRUCTURE OF GANGLIA.

Ganglia (figs. 377 to 379) are constructed somewhat similarly to the nerves upon which they occur, being enclosed by a firm connective-tissue covering which sends septa of the same tissue into the interior of the ganglion. But the distinctive funicular sheath or perineurium of the nerve-bundles is not seen in their progress through the ganglion, the bundles being much broken up as they enter it and gradually losing themselves amongst the groups of nerve-cells. Each cell of a ganglion is invested with a nucleated sheath continuous with the neurolemma of the nerve-fibres (fig. 378), and, in the case of the sympathetic ganglia, with sheaths which invest all the branches of the cell for a short distance (fig. 352). In the cerebro-spinal ganglia of vertebrates the nerve-cells are bipolar or unipolar; in the ganglia of the autonomic system they are multipolar, and in some animals they commonly contain two nuclei. In man the nerve-cells of the spinal ganglia and of the corresponding cerebral ganglia are

[1] Horsley, Brit. Med. Journ. 1884. See also Prees, Arch. slaves de biol. iv. 1888.
[2] Journ. Physiol. xxxix. 1910. [3] Cf. however Donaldson & Hoke, *op. cit.*

always unipolar, although in the early embryo they were bipolar (see p. 222). But the ganglia upon the vestibular and cochlear divisions of the eighth nerve

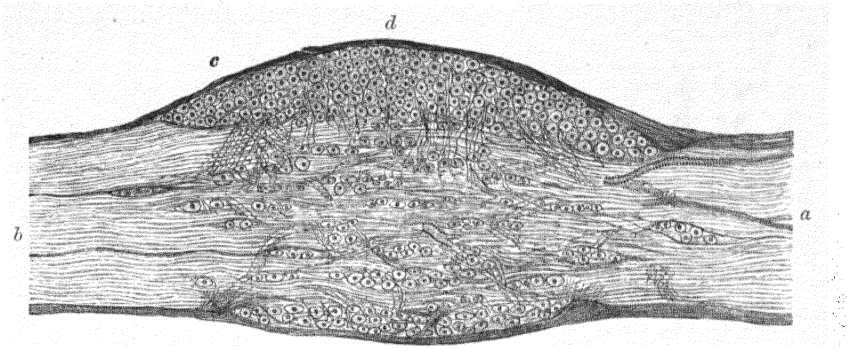


FIG. 377.—LONGITUDINAL SECTION THROUGH THE MIDDLE OF A GANGLION ON THE POSTERIOR ROOT OF ONE OF THE SACRAL NERVES OF THE DOG, AS SEEN UNDER A LOW MAGNIFYING POWER. (Schäfer.)

a, Nerve-root entering the ganglion; *b*, fibres leaving the ganglion to join the mixed spinal nerve; *c*, connective-tissue coat of the ganglion; *d*, principal group of nerve-cells, with fibres passing down from amongst the cells, to unite with the longitudinally coursing T-shaped nerve-junctions (see text).

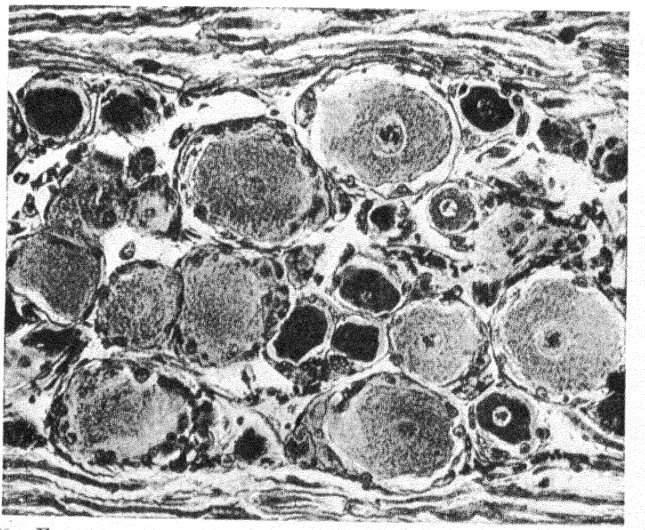


FIG. 378.—FROM A LONGITUDINAL SECTION OF SPINAL GANGLION OF DOG. (Schäfer.) Magnified 225 diameters.

The difference in size and appearance of the ganglion-cells is noticeable. The nuclei of the sheath-cells are also clearly visible.

(ganglion of Scarpa and ganglion of the cochlea) retain their bipolar condition throughout life.[1]

[1] The microscopical characters of the spinal-ganglion cells have already been considered (pp. 221, 222). For numerous details regarding them, see S. Hatai, Biol. Bull. iii. 1902; Decenn. Publ. of Univ. of Chicago, 1903; and Journ. Comp. Neurol. xii. xiii. and xiv. 1902 and 1903; Lugaro, Riv. d. pat. nerv. e ment. v. vi. vii. and viii.; Warrington and Griffith, Brain, 1904; Warrington, *ibid.* 1904; Cajal, Textura del sistema nervioso, 1904, and Trabajos, &c. iv. 1905; Hardesty, Journ. Comp. Neurol. 1905 (frog). According to Donaldson and Hatai, many of the cells of the spinal ganglia possess no processes; these are probably cells which have never become fully developed. A. S. Dogiel, who has published a monograph on this subject (Bau der Spinalganglien, Fischer, 1908), describes eleven types of cell in these ganglia, one being multipolar. He regards the free nerve-endings over the cells as the terminations of sensory or of sympathetic fibres.

HISTOGENESIS OF NERVES.

The embryonic development of the nerves has already been noticed (p. 203). It was there shown that all nerve-fibres and nerve-cells, whether belonging to the

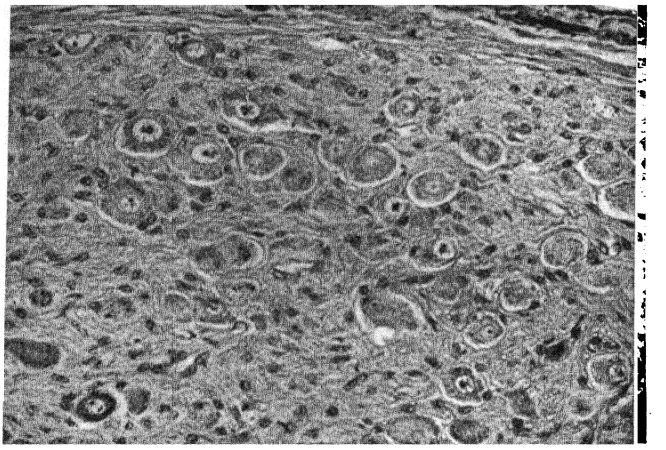


FIG. 379.—FROM A SECTION OF A SYMPATHETIC GANGLION OF DOG. (Schäfer.) Magnified 225 diameters.

The cells are smaller than those of the spinal ganglion, and the nerve-fibres are much smaller and more interwoven.

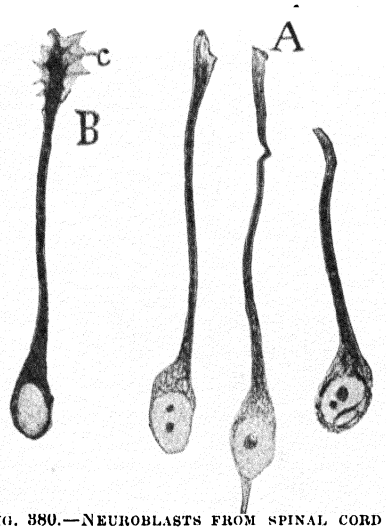


FIG. 380.—NEUROBLASTS FROM SPINAL CORD OF A CHICK DURING THE THIRD DAY OF INCUBATION. (Cajal.)

A, three neuroblasts stained by Cajal's method to show neuro-fibrils; B, a neuroblast stained by Golgi method; *c*, incremental cone.

central nervous system or to the peripheral and sympathetic nerves, are originally neuroblasts derived from the neuro-sensory ectoderm, and that in the case of the afferent nerve-fibres, such as those of the dorsal or posterior roots, the axis-cylinders grow from the neuroblasts of the neural crest (F. M. Balfour), which become separated off to form the spinal ganglia.[1] From these afferent or sensory neuroblasts growth takes place both centripetally into the nerve-centre and centrifugally towards the peripheral sensory parts; while in the case of the efferent nerve-fibres, those namely of the ventral or anterior roots, the axis-cylinders grow only centrifugally from their cells of origin, which here lie within the nerve-centre (neuroblasts of the nerve-centres), and thence eventually pass to and unite with the muscular fibres. It is a characteristic of all growing axons that their growing extremity is a protoplasmic expansion (fig. 380): this is known as the *incremental cone* (Cajal). A similar expansion is seen in regenerating nerves.

[1] R. G. Harrison (Amer. Journ. Anat. v. 1906) has shown that after removal of the neural crest in tadpoles the dorsal roots and ganglia fail to develop. The sympathetic ganglia are formed from off-shoots of the rudimentary spinal ganglia. Schenck and Berdsall, Mitth. a. d. embryol. Instit. in Wien, 1879; Onódi, Arch f. mikr. Anat. xxvi. 1886; W. His (junior), Sächs. Abhandl. 1891; Arch. f. Anat. 1897; S. Jean Meiklejohn, Journ. Physiol. xxxvi. 1908; Williamina Abel, Proc. Roy. Soc. Ed. xxx. 1910.

So far as is known, this is the only mode of development of nerve-fibres—viz. as outgrowths from neuroblasts—and they always, whether in the nerve-centres or in the nerve-trunks, at first appear as pale fibres, destitute both of neurolemma and of medullated sheath.

This doctrine of the outgrowth of nerve-fibres from neuroblasts was originally formulated by W. His, whose classical researches on the subject are well known,[1] and have been confirmed by nearly all modern investigators. F. M. Balfour[2] thought that the nerve-fibres are produced by the union of cells in chains, the cells passing out from the neural canal in a sort of bud-like growth. But it is now usually held that these are 'lemmal' or sheath-cells, and are concerned in the formation of the sheath of Schwann. Some observers[3] still think that the peripheral nerves are developed either from or within a syncytium of neuroblasts: Gurwitsch[4] believes the syncytium to be formed of mesoderm elements along which the axons of the neuroblasts grow, and which become the cells of Schwann's sheath. But the preponderance of evidence is in favour of an ectodermic origin, both of the axons (a point which is conceded by nearly all authorities) and of the sheath-cells. The mode of formation of Schwann's sheath

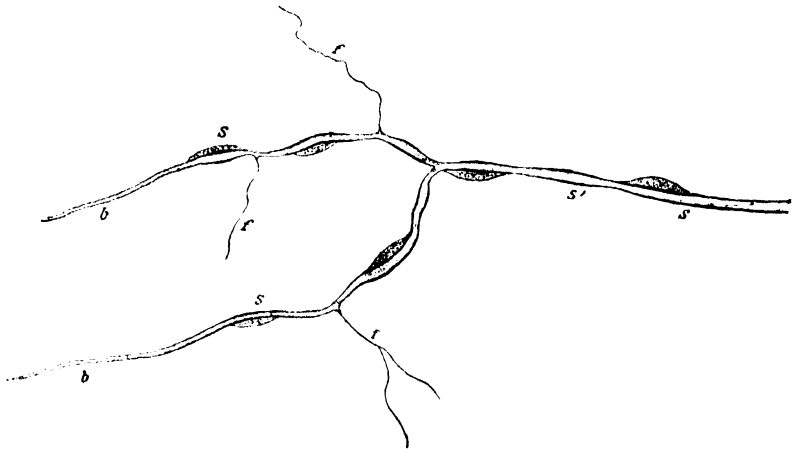


FIG. 381.—GROWING NERVE-FIBRES IN THE TAIL OF THE TADPOLE. (Kölliker.)
s, *s'*, sheath of Schwann with nuclei; *b*, growing ends of main branches of fibres; *f*, lateral fibrils.

from the sheath-cells has been studied by Bardeen.[5] According to Hardesty,[6] there are sheath-cells even within the central nervous system, although not apparent until the nerve-fibres are medullated. But since there is no sheath of Schwann on the fibres of the brain and cord, the cells described by Hardesty are probably of the nature of glia-cells. A few authors, however (amongst them Sedgwick,[7] Graham Kerr,[8] and Held[9]) still hold the opinion which was originally put forward by Hensen,[10] that the connexion between nerve-cell and muscle-fibre or other peripheral element is primary, and that the intervening nerve-fibre has become as it were spun out in the process of growth by the gradual separation from one another of the elements which it connects. But this view is not supported by the ordinary elective methods of staining nervous elements, and is at variance with many well-ascertained facts relating to the structure and functions of the nervous system. Recently Harrison has supplied an objective demonstration of the outgrowth of fibres from nerve-cells by the study of isolated neuroblasts of the tadpole in which he has been able to observe the growth of the axon proceeding under the microscope. It is also seen in the growth of nerve-fibres in the tail of the amphibian larva (fig. 381).[11]

[1] Unters. ii. d. erste Anlage d. Wirbelthierleibes, 1868; Abhandl. d. Königl. Sächs. Gesellschaft, 1886, 1888, and 1889; Arch. f. Anat. 1890.
[2] Phil. Trans. clxvi. 1875; and Comparative Embryology.
[3] O. Schultze, Arch. f. mikr. Anat. lxvi 1905; H. Held, Anat. Anz. xxx. 1907.
[4] Arch. f. Anat. 1900. [5] Amer. Journ. Anat. ii. 1902–3. [6] Amer. Journ. Anat. iv. 1905.
[7] Quart. Journ. Micr. Sci. xxxvii. 1894. [8] Trans. Roy. Soc. Edin. xli. 1903–4.
[9] Arch. f. Anat. 1907. [10] Virch. Arch. 1864.
[11] Proc. Soc. Exp. Biol. iv. 1907. Cf. also the same observer's experiments showing growth of nerve-fibres into grafted limbs (Amer. Journ. Anat. vi. 1907; Journ. Exper. Zool. iv. 1907).

The fibres which are thus first formed are axis-cylinders, or will become such. They are accompanied or followed by an outgrowth of the neural ectoderm, the cells of which form the sheath of Schwann.[1] They also become surrounded by cells from the adjacent mesoderm, which penetrate between them, and eventually produce the connective tissue of the nerve-sheath (epineurium, perineurium, endoneurium). In the nerve-centres very little connective tissue passes between the nerve-fibres, which are there supported by the spongioblasts (see p. 205). These are cells which have a common (ectodermic) origin with the neuroblasts, although their function, according to His, is early differentiated.[2] From the spongioblasts, neuroglia-cells appear ultimately to be produced, and these, within the central nervous system, take on much the same supporting function which is elsewhere fulfilled mainly by connective tissue.[3]

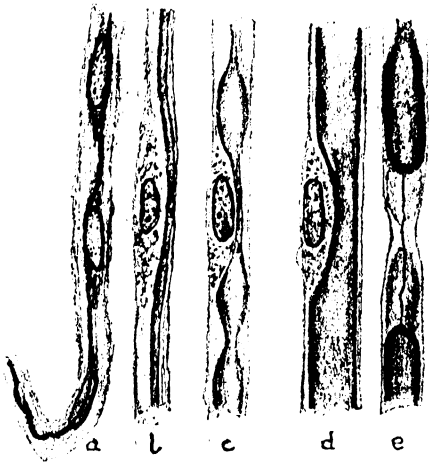


FIG. 382.—STAGES IN THE FORMATION OF THE MYELIN OF THE MEDULLARY SHEATH IN NERVE-FIBRES. (Bardeen.)

The neighbourhood of the nodes of Ranvier remains free from myelin later than the rest of the nerve-fibre.

The medullary sheath does not make its appearance until a comparatively late period of embryonic life, and there is some doubt as to its mode of formation. It first appears as a thin layer of myelin, not infrequently interrupted, which closely ensheaths the axis-cylinder, and is itself ensheathed by the nucleated neurolemma or sheath of Schwann (fig. 382). Some authors refer the formation of the medullary sheath to the cells which compose the nucleated sheath of Schwann, but it is more probable that it is actually formed by the axis-cylinder, or by the protoplasm which forms the peripheral layer of the axis-cylinder in its embryonic condition, and for the following reasons—viz. (1) that in the central nervous system the medullated nerve-fibres never at any time possess this nucleated sheath; (2) that in regenerating nerve-fibres, a thin medullary sheath appears around the growing axis-cylinders before these are surrounded by a nucleated sheath. The neurolemma or sheath of Schwann, on the other hand, appears certainly to be formed by cells which have applied themselves to and have become flattened out around the pre-formed axis-cylinder. Whether they are to be regarded as of mesodermic origin (Vignal,[4] Kölliker[5]), or whether they have been derived from

[1] Schaper (Arch. f. Entwickelungsgesch. v. 1897) distinguishes two kinds of migratory cells—viz. *sympathetic neuroblasts* and *indifferent cells*. R. G. Harrison (Arch. f. mikr. Anat. lvii. 1901) regards the migrating cells as probably forming the motor cells of the sympathetic ganglia. Kohn (Arch. f. mikr. Anat. lxx. 1907) and Carpenter and Main (Anat. Anz. xxxi. 1907) also suggest that some of these cells which wander out from the neural ectoderm may become motor sympathetic cells. Kunz (Anat. Record, iii. 1909) considers the migratory cells to be of two kinds, one forming the ganglion-cells of the sympathetic and the other being sheath-cells. Kunz (Anat. Anz. xxxv. 1909) describes a similar migration along the vagus nerve both from its ganglion and from the neural canal, the migratory cells forming ganglia in the viscera supplied by the vagus.

[2] Cajal, however, states that many of the neuroblasts are directly derived from cells which are identical with the spongioblasts of His.

[3] It is not certain that all neuroglia-cells are derived from ectoderm elements. Andriezen (Brit. Med. Journ. 1893) described two types of these cells, one with long unbranched fibre-like processes (spider-cells), the other with dendritic processes, and suggested that the latter may owe their origin to mesodermic elements (see also on this subject, Hatai, Journ. Comp. Neurol. xii. 1902).

[4] Arch. de physiol. 1883 and 1884. See also Boycott, Journ. Physiol. 1903.

[5] Gewebelehre.

the neural epithelium, and are therefore ectodermic in nature, is a question which requires further investigation; the latter appears the more probable hypothesis.[1]

The formation of the medullary sheath occurs, not simultaneously over the whole nervous system, but in regular order along definite tracts at different periods of late fœtal and early post-fœtal life; the knowledge of this in the hands of Flechsig has proved an important means of tracing the course of strands of fibres in the nervous centres.

The fact that the nerve-segments or internodes of the peripheral nerves are considerably shorter in the young animal points to the existence of an interstitial as well as a terminal growth of nerve-fibres. Besides such expansion of the internodes, Vignal has described another method of growth in length of nerve-fibres; cells similar to those which originally produced the nucleated sheath, applying themselves to the axis-cylinder at the nodes, and determining an increase in length of the nodal axis-cylinder, upon which a formation of myelin occurs, so that a short segment becomes intercalated at the node. These short segments soon grow so as to attain the length of the remaining segments of the nerve-fibre.

Neuro-fibrils appear comparatively early in the neuroblasts. They have been detected even before the axon-process begins to grow out from the cell-body, and increase in number as development proceeds.[2]

DEGENERATION AND REGENERATION OF NERVES

The divided ends of a nerve that has been cut across readily reunite by cicatricial connective tissue, but the cut ends of the fibres themselves do not thus unite. On the contrary, soon after the section, a process of degeneration begins in the peripheral or severed portion of the nerve. The medulla of the white fibres breaks up into a granular mass consisting of fatty globules, and is eventually totally removed, its place being taken by a mass of protoplasm; the axial fibre also early breaks up and disappears (fig. 383, A, B, and C). The nuclei become multiplied and the protoplasm about them largely increased in amount. To these changes in the nerve-fibre, and especially in the medullary sheath, the name of *Wallerian degeneration*[3] has been applied.

In regeneration the new fibres grow afresh from the axial fibres of the central end of the divided nerve-trunk (often more than one from each); and, penetrating into the peripheral end of the trunk, grow along this as the axis-cylinders of the new nerves, becoming after a time surrounded with medullary substance and a nucleated sheath of Schwann (fig. 383, D).

In warm-blooded animals the first degeneration-changes in the peripheral part of the nerve are seen twenty-four hours after section; in cold-blooded animals they take much longer to develop.[4] The nuclei underneath the neurolemma are everywhere found hypertrophied, the neurolemma is distinctly visible, and protoplasm is found to have accumulated at the expense of the medullary sheath, both in the immediate neighbourhood of the nuclei, at the nodes, and also at other points in the fibre.[5] Fifty hours after the section in the rabbit (but not till four days in the dog) the protoplasmic aggregations are found here and there altogether to interrupt the continuity of the medullary sheath, and they contain numerous

[1] On the histogenesis of nerve-fibres and the formation of myelin, see Bardeen, Amer. Journ. Anat. ii. 1903.

[2] Gerini, Anat. Anz. 1908.

[3] A. Waller, Phil. Trans. 1850.

[4] See footnote, p. 252.

[5] Mönckeberg and Bethe (Arch. f. mikr. Anat. liv. 1899) describe early changes in the fibrils of the axis-cylinder, both central and peripheral to the point of section. But the nerve-fibres retain their excitability (to artificial stimuli) and conduction for from two to five days after section (the period of retention of excitability varying with different kinds of nerve-fibre).

fatty granules, and sometimes droplets of myelin (fig. 383, A). About the fourth day the nuclei are seen to be multiplied,[1] but not to any great extent (C); and the whole of the myelin after four or five days is broken up into drops, some larger, some smaller. The axis-cylinder is also found to be interrupted at numerous places, and remains only in the shape of short fibres, often curled round at their broken ends, enclosed in the large drops of myelin (B). Eventually these portions

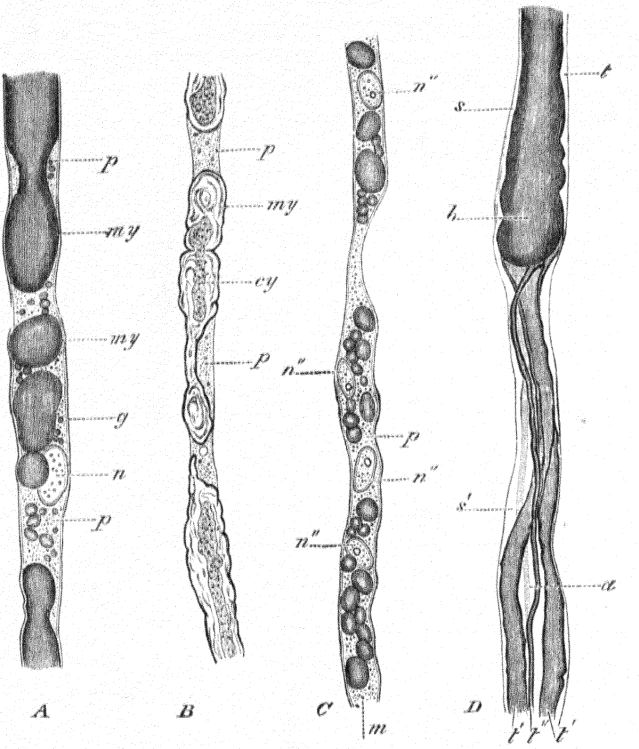


FIG. 383.—DEGENERATION AND REGENERATION OF NERVE-FIBRES IN THE RABBIT. (Ranvier.)

A, part of a nerve-fibre in which degeneration is commencing in consequence of section (fifty hours previously) of the trunk of the nerve higher up; *my*, medullary sheath becoming broken up into drops of myelin; *p*, granular protoplasmic substance which is replacing the myelin; *n*, nucleus, not yet multiplied; *g*, primitive sheath. B, another nerve-fibre in which degeneration is proceeding, the nerve having been cut four days previously. This specimen is differently prepared from the others, so as to exhibit the axis-cylinder (*cy*) also partly broken up into portions of different lengths, enclosed in the myelin, *my*. C, more advanced stage of degeneration, the medullary sheath having in great measure disappeared, while several nuclei (*n''*, *n''*) have been formed by division of the single nucleus of the internode. D, commencing regeneration of a nerve-fibre. Several small nerve-fibres (*t'*, *t''*), have sprouted out from the enlarged cut end (*b*) of the nerve-fibre (*t*); *a*, an axis-cylinder, which has not yet acquired a medullary sheath; *s*, *s'*, primitive sheath.

also may disappear. The myelin at length becomes almost entirely removed, probably through the agency of phagocytic leucocytes, until nothing remains of it except a few isolated drops, which escape absorption, and all that then remains of the original fibre is the neurolemma, which is occupied by a protoplasmic mass containing an increased number of nuclei. During the disappearance of the myelin from the nerve-fibres the cells of the tissue in the neighbourhood of the fibres become charged with fatty granules, which have probably become formed

[1] The multiplication is effected by karyokinesis, G. C. Huber, Arch. f. mikr. Anat. xl. 1892.

from the disintegrated substance of the medullary sheath. The fatty globules which result from the degenerating medullary sheath stain much more intensely with osmic acid, after fixation with bichromate of potash, than the unaltered myelin. On this fact depends Marchi's method for tracing degenerated fibres.[1]

These degenerative changes seem to occur almost simultaneously along the whole length of the nerve. In the nerves to voluntary muscles the end-plate is said to be the part first affected. The motor endings undergo degeneration earlier than the sensory endings in muscle, and their regeneration also takes place sooner.[2]

In the immediate neighbourhood of the section the appearances are somewhat modified by the escape of myelin from the cut ends of the nerve-fibre, and the infiltration of blood and lymph into the interior of the ends thus emptied of their contents. This change must, of course, occur in the central stump of the nerve as well as in the peripheral cut end: it does not often extend beyond the first node. Apart from such traumatic modification, true degenerative changes do not occur in the end of the nerve which is still in connexion with the centre, although proliferation of the nucleus in the first and second internodes near the cut may take place. The central cut end of the axis-cylinder does not become ostensibly altered; it undergoes a slight swelling, preparatory in all probability to the renewed growth by which the regeneration of the fibre is effected.

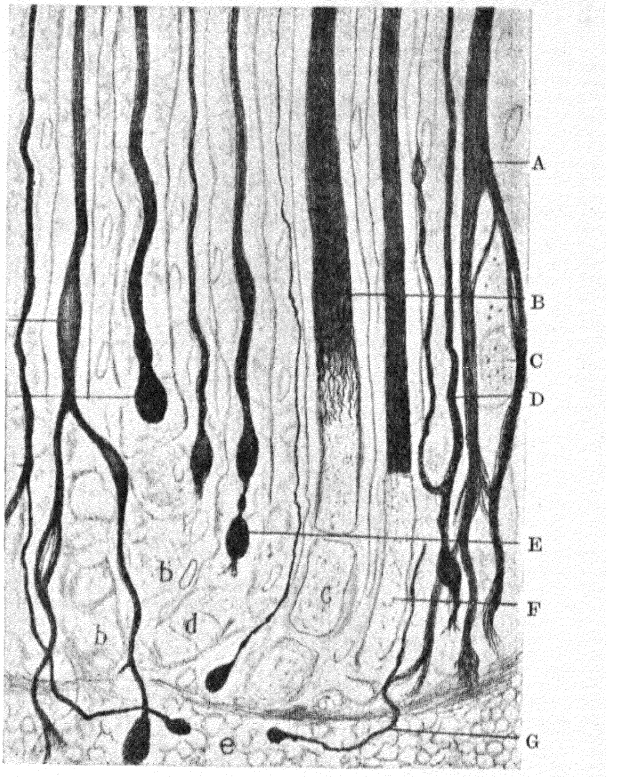


FIG. 384.—COMMENCING OUTGROWTHS FROM AXIS-CYLINDERS IN STUMP OF CUT NERVE. (Cajal.)

A, an axon bifurcating: its branches, which show clearly a fibrillar structure, pass on either side of a group of sheath-nuclei, C; B, another axis-cylinder with its end frayed into fibrils: this has not yet begun to grow out; D, an axis-cylinder, one branch of which has begun to grow upwards into the stump, instead of downwards towards the periphery; E, a growing axis-cylinder ending in a bulbous enlargement; F, an empty nerve-sheath; G, a fine axon growing into wound (with bulbous end); *b*, *c*, *d*, myelin fragments escaped from injured fibres; *e*, blood-clot.

Regeneration proceeds but slowly. Up to the twenty-eighth day after the section, or even later than this, there is still no trace of the new nerve-fibres in the peripheral part of the nerve. With the exception of a few fibres which, for some reason not well understood (probably because they are derived from an adjacent nerve which has not been cut), have not undergone degeneration, nothing is to be seen in a section of the nerve at this period, except the sheaths of the old fibres, filled with clear

[1] Riv. sper. di fren. 1885. On the chemical decomposition products of the medullary sheath of degenerating nerve-fibres, see Halliburton, Croonian Lectures, Brit. Med. Journ. 1901.

[2] G. C. Huber, Amer. Journ. Physiol. iii. 1900.

or finely granular protoplasm-like substance. If, however, a transverse section be made of the peripheral end considerably later than this (sixty or seventy days after the original section), it is found that within the tubes formed by the old neurolemmal sheaths, according to Vanlair[1] and Cajal also between them, small single fibres or groups of fibres, either pale or provided with a thin medullary sheath, are to be seen, besides here and there the altered drops of myelin which have remained unabsorbed from the medullary sheaths of the original fibres. On cutting out the central end of the nerve, together with the cicatrix, and separating its fibres, it is seen that the groups of small fibres noticeable in a transverse section are continuous with the central ends of the axis-cylinders of the original nerve (fig. 383, D). Either a bunch of small fibres may grow directly from the axis-cylinder of one fibre, or one or two only emerge from this (figs. 384, 385); but these may bifurcate, and, repeating this process again and

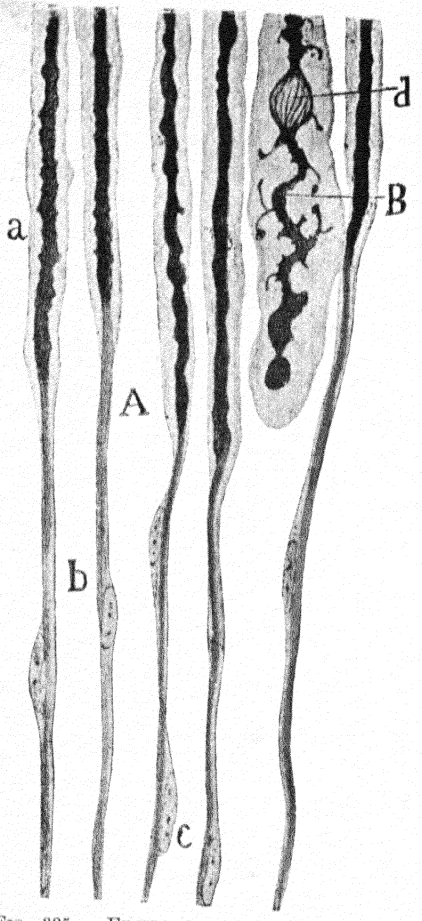


FIG. 385. — FIBRES FROM CENTRAL END OF SCIATIC OF YOUNG RABBIT, CUT TEN DAYS BEFORE DEATH. (Cajal.)

A, fibres showing downgrowth of axis-cylinder which is invested by a nucleated sheath; *a*, intact part of fibre; *b*, downgrowing fibres. B, a fibre the axon of which has not grown down with the rest, but is undergoing degenerative changes, as at *d*, and putting out abortive bud-like processes.

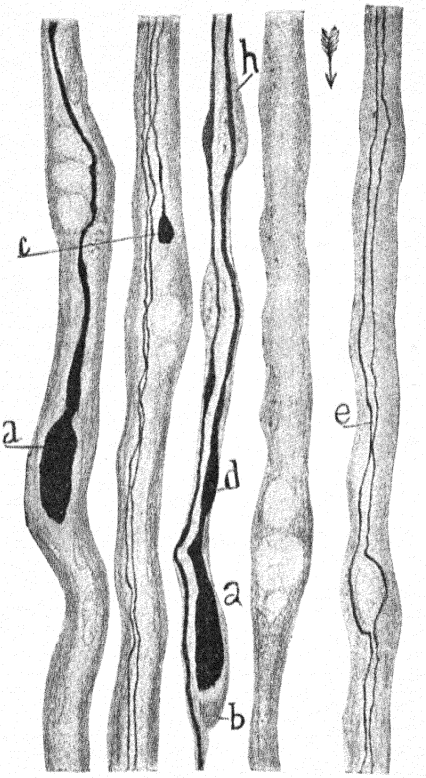


FIG. 386.—FROM THE PERIPHERAL END OF A NERVE CUT SEVENTY-EIGHT DAYS BEFORE DEATH.

a, *a*, *c*, enlarged ends of downgrowing axons, enclosed in the old neurolemma-sheaths, within which myelin drops are still visible; *h*, two fibres growing down interstitially (not in the old sheaths)—they show a new formation of nucleated sheath; to their right is an empty sheath; *e*, fine fibres within an old sheath: the growing ends of these are out of the field of view.

[1] Arch. de Physiol. 1886.

again, eventually form a considerable group. It would appear therefore that the regeneration of a cut nerve is effected by a growth of new fibres from the axis-cylinders of the central cut end, and that frequently many more such fibres are formed in the first instance than the old ones which have undergone degeneration. The growth from the old axis-cylinders usually occurs in the situation of a node—either the one nearest to the section or one somewhat higher up (Ranvier). The growing axons either find their way into the old neurolemmal sheaths or into the interstices between them (figs. 386, 387); in this case fresh nucleated sheaths become formed around them. The new fibres are at first pale, but subsequently acquire a medullary sheath, still later a neurolemma, with constrictions of Ranvier. These, as in young nerves, are placed at much more frequent intervals than in the old fibres, so that the segments are much shorter.

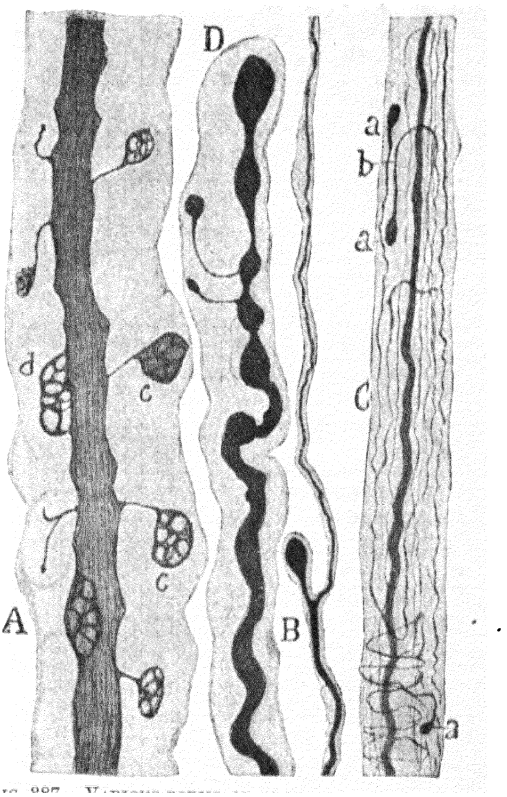


FIG. 387.—VARIOUS FORMS OF ABORTED AXIS-CYLINDER SPROUTS FROM A REGENERATING NERVE. (Cajal.)

A, a large fibre with numerous lateral buds (*c*, *c*, *d*) from axis-cylinder; B, a small fibre growing interstitially showing a lateral bulb-like sprout; D, an irregularly constricted axis-cylinder with a terminal bulb and two fine lateral fibrils each ending in a bulb-like enlargement; C, a fibre containing a large number of fine fibrils which have sprouted from the axis-cylinder and are growing in all directions within the sheath.

The fibres which grow thus in groups from the old axis-cylinders are often very irregular in their course, twisting around one another, and even looping back in some places for a considerable distance (fig. 387). In the cicatrix especially is this irregularity and obliquity of disposition noticeable, probably on account of the absence here of the guide formed by the sheaths of the original fibres. If the cut ends are brought by sutures into close juxtaposition regeneration is effected more quickly than if there is an obvious gap left between the ends. But the individual cut fibres never unite directly. In case a gap should be left between the cut ends, as, for example, when a piece of the nerve is actually excised, it is necessary to introduce into the interval some material which can act as a guide for the outgrowing fibres of the central cut end. Huber [1] found that the best guide-material was a piece of dead (and, of course, aseptic) nerve.

Restoration of function in the nerve may not occur for several months,[2] during which time it may be presumed the new nerve-fibres are slowly finding their way along the course of those which have been destroyed as a result of the section. Of the numerous fibres in the groups above described, no doubt a few only eventually assume the function of the fibres which they replace, but the later steps of the process of regeneration have not yet been fully followed out.

The ends of the growing axis-cylinders are characterised by a bulbous aspect, reminding one of the enlargement on the growing ends of the axon of the neuroblast (figs. 384, 386). Moreover, the regenerating fibres may fork or give off lateral buds, and these again may form a fine interlacement around the main outgrowing fibre. Such complications, however, all ultimately disappear as the regeneration of the nerve becomes complete.

[1] Journ. Morph. xvi. 1900.

[2] See the experiments of H. Head, Brain, xxviii. xxix. 1905; and of Trotter and Morriston-Davies Journ. Physiol. xxxviii. 1909

Except close to the actual place of section, where they are somewhat hypertrophied, the connective-tissue sheaths of the nerve remain unaltered. In the cicatrix the new nerve-fibres do not at first run in definite sheaths, but these become subsequently developed from the connective tissue around, so that at length the restoration of continuity of all the structures in the nerve becomes complete. Vanlair states that the outbudding of the axis-cylinders of the central end may occur as much as one or two centimetres from the point of section, and may involve at first only the peripheral fibres of a funiculus.

Ranvier looks upon the regeneration of a nerve by growth from the intact central ends of the fibres as illustrating the tendency which, he believes, all nerve-fibres exhibit, to grow continuously until a hindrance is met with, and he compares the result of cutting a nerve-fibre in causing the growth of a number of new fibres in place of the original one, to that produced when the leading shoot of a plant is removed, in causing the production of a number of lateral buds.

Some have thought that under favourable circumstances an immediate union between the ends of the nerve-fibres may happen after section; but considering the impossibility of procuring exact apposition of the individual fibres, end to end, as well as the inevitable extension of the effects of the mechanical injury caused by the section along the soft contents of the primitive sheath, it seems improbable that such direct union should ever occur.

Regeneration need not necessarily occur along the track of the original nerve, but can be made to take a different path. Thus if the vagus and sympathetic nerves in the neck (cat, rabbit) be both divided, and the central cut end of the vagus be sutured to the peripheral cut end of the sympathetic, all the effects of sympathetic excitation can be got after regeneration is complete by stimulating the central end of the vagus;[1] synapses between the vagus fibres and the cells of the sympathetic ganglion have become established. A similar result is obtainable by joining up the motor branch of the fifth with the sympathetic,[2] or a spinal nerve with the vagus, although in this case a long time is required for the downgrowing nerves to effect connexions in the heart.[3] On the other hand, two peripheral nerves can never be got to show any signs of regeneration if joined up together, nor is there any functional regeneration if afferent and efferent nerves are cut and joined together.[4]

Regeneration does not take place in the case of fibres crossing through the brain or spinal cord, so that a lesion of any part of these centres can never be made good.

The degeneration does not affect, as we have seen, the part of the nerve remaining in connexion with the nucleated cell-body, which maintains the nutrition of the nerve. The nucleated cell-bodies in the ganglia, as well as those in the grey matter of the brain and spinal cord, are centres of this influence. It is found that, in the central portion of a divided spinal nerve, while the fibres belonging to the anterior root owe their integrity to their connexion with the large cells of the anterior cornu, and, in the case of the fine medullated fibres, with the cells of the lateral cornu, those of the posterior root are similarly dependent on the nucleated cell-bodies within the ganglion; so that if the posterior root be cut between the ganglion and the spinal cord, not only will the fibres which pass from it into the trunk of the nerve beyond the ganglion remain unchanged, but also those above the ganglion, in the portion of the root left in connexion with it; whereas the fibres of the same root which remain connected with the cord but severed from the ganglion degenerate.

Various authors have believed that they have been able to show that regeneration of severed nerve-fibres may occur independently of the central end of the nerve in the degenerated portion peripheral to the injury (peripheral autogenesis). So far as the histological evidence is concerned, this opinion is based mainly upon the fact that a fibrillation may be exhibited within the sheaths of the degenerated fibres: this fibrillation has been regarded as due to the formation within these sheaths of neuro-fibrils, which are assumed to belong to axis-cylinders newly developing at the periphery. But the reasons for regarding these peripheral fibrils as neuro-fibrils is by no means convincing, and the evidence that the peripheral fibres are regenerated as outgrowths from the central stump of the divided nerve is so strong and fits so completely into the whole neuronal scheme of structure and development of the nervous system (and especially that

[1] Langley, Journ. Physiol. xxxiii. 1898. See also his article on the 'Sympathetic' in Schäfer's Text-book.

[2] Langley and Anderson, Journ. Physiol. xxxi. 1904, Braun, Harrison, and others.

[3] J. Erlanger, Amer. Journ. Physiol. xiii. 1905.

[4] Langley and Anderson, Journ. Physiol. xxx. 1904; W. A. Osborne, Proc. Physiol. Soc. in Journ. Physiol. 1908; Osborne and Kilvington, Journ. Physiol. xxxviii. 1909.

part of it which attributes the nutrition and therefore the growth of all the processes of the neurone to the nucleated cell-body) that it is impossible without far stronger reasons than have hitherto been brought forward to accept the presence of such fibrils as sufficient evidence of the doctrine of peripheral nerve-regeneration.

There is not space to deal with the very considerable volume of pathological and clinical evidence regarding this point, but it may be affirmed that the great bulk of such evidence is in favour of regeneration by cellulifugal outgrowth. Such instances as have been occasionally observed of immediate or very rapid recovery of function in the parts supplied by a cut nerve may without doubt be explained either by the overlap which often occurs in the peripheral distribution of neighbouring nerves, or by the fact that in such cases the cut nerve has received at some point peripheral to the point of severance a branch from an adjoining intact nerve, which has sufficed in some measure to replace the function of the cut fibres, or, in yet other cases, by an impression which has been applied to the skin having been conducted to the subjacent muscles or tendons in which the sensory nerve-fibres have remained intact, although the sensory fibres to the integuments have been severed.

Axon-reaction in body of nerve-cell.—As we have already seen (p. 212), there is always a change produced in the cell of origin when its axon is cut (*axon reaction, Nissl degeneration*), even although the stump of the nerve-fibre, which is still connected with the cell-body, shows no changes.

H. K. Anderson [1] experimenting upon young animals, finds that section of the sciatic nerve checks the development of the cells of the corresponding spinal ganglia, but that section of their central processes does not do so (although these processes themselves atrophy cellulipetally as well as cellulifugally). Section of the posterior roots causes no check in the development of the corresponding anterior roots.

With regard to the sympathetic he finds that section of the post-ganglionic branches of the superior cervical ganglion checks the development of the cells of that ganglion, and not only this, but also that of the fibres of the sympathetic which are passing up to the ganglion. On the other hand, section of the fibres of the cervical sympathetic, although producing Wallerian degeneration right into the ganglion and checking the development of the central part of the fibres and of their cells of origin in the lateral part of the grey matter of the cord, has no influence upon the cells of the superior cervical ganglion.

Thus the effect of the severance of an axon is not necessarily confined, at least in young animals, to the neurone to which it belongs, but it may influence the metabolism of other neurones belonging to the same neurone-chain. This fact was first taken advantage of by v. Gudden to investigate tracts in the central nervous system. v. Gudden found that removal of parts or organs belonging to or connected directly with the central nervous system in young animals was followed by far more extended atrophy along the nerve-tracts involved in conduction of impulses from the part investigated than if the extirpation had been performed in the adult animal. The method of investigation is known as *v. Gudden's method*.

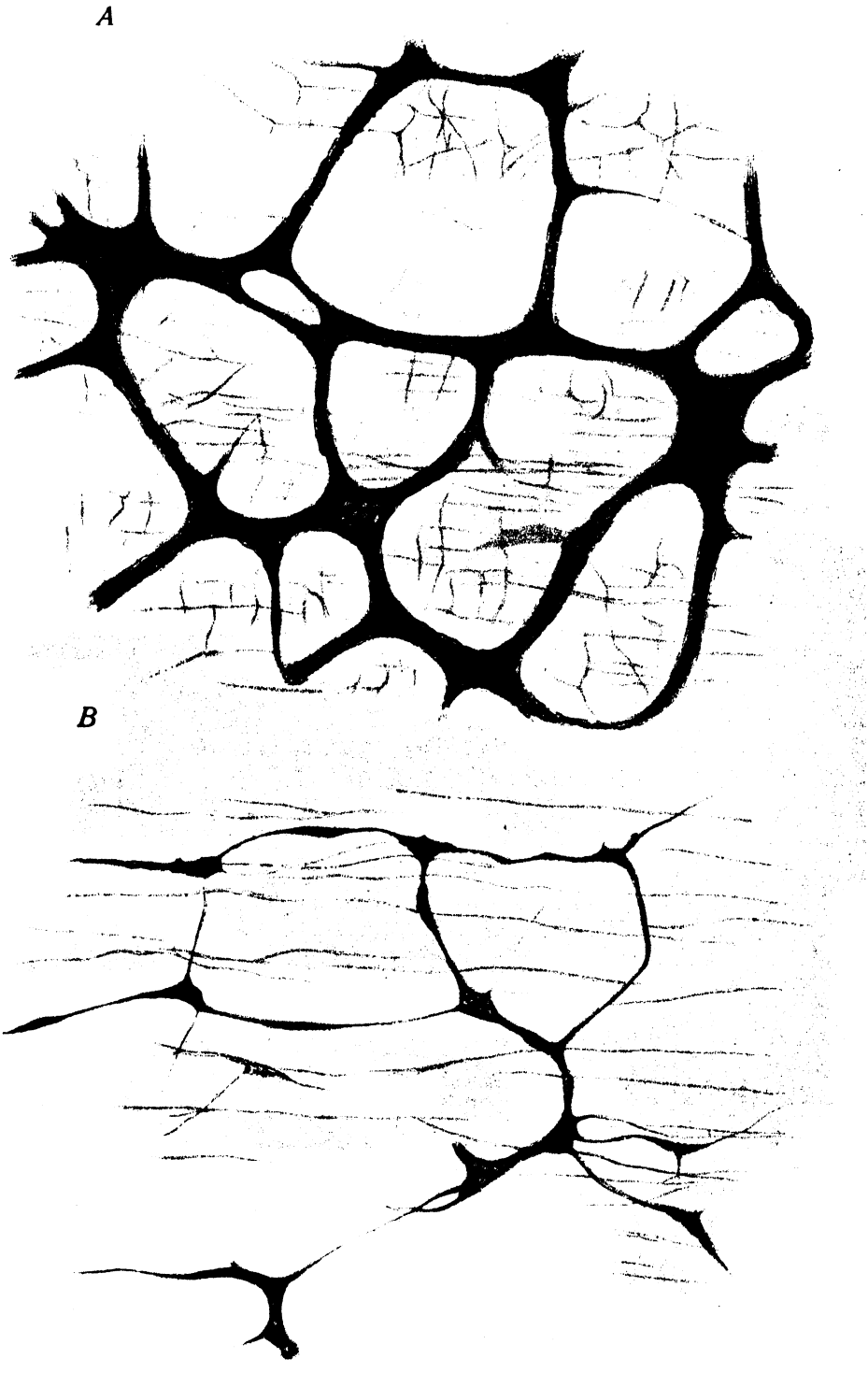
The latest and most complete histological account of nerve regeneration is that of Cajal (Trabajos, &c., 1905 and 1907), whose researches are entirely in favour of the outgrowth theory. Amongst others who uphold this view may be mentioned Langley,[2] Head,[3] Ladlum,[4] Marinesco,[5] Mott,[6] Halliburton,[7] Bikeles and Francke,[8] Lugaro,[9] Perroncito.[10] The chief advocate of peripheral autogenesis of late years has been Bethe,[11] whose views seem, however, to have undergone some modification.[12] Although the regeneration of the cut nerve-fibres seems to occur primarily by outgrowths from the central stump, there is some evidence of changes in the peripheral degenerated part of the nerve, preparatory to the appearance of the outgrowing axons.[13] These changes seem to have been sometimes looked upon as evidence of peripheral autogenesis of the fibres. See also the ' Neurology ' of this work (Vol. III. Part I.).

The degeneration of the peripheral end of a cut nerve and the breaking up of the substance of the medullary sheath were first noticed by Nasse in 1839. But the discovery by Augustus Waller of the dependence of the process upon isolation of the nerve-fibre from its nutritive

[1] Journ. Physiol. xxviii. p. 499, 1902.
[2] *Ibid.* xxx. 1904 (with H. K. Anderson).
[3] *Op. cit.*
[4] Referred to in Review of Neurol. 1905.
[5] Rév. neurol. 1906 (with Nimea).
[6] Proc. Roy. Soc. B. lxxviii. 1906 (with Halliburton and Edmunds).
[7] Brit. Med. Journ. 1907.
[8] Neurol. Centralbl. xxii. 1905.
[9] *Ibid.* xxiii. 1906.
[10] Ziegler's Beitr. xlii. 1907.
[11] Allgemeine Anat. u. Physiol. d. Nervensystems, 1903.
[12] Pflüger's Arch. cxvi. 1907.
[13] Cf. Halliburton, *op. cit.*

centre, and his application of this discovery to the tracing the course of nerve-fibres in peripheral parts (now known as the Wallerian method) first gave full interest and importance to the observation of Nasse. Stated briefly, the law may be formulated as follows: 'Degeneration occurs along the whole extent of any nerve-fibre which is cut off from the cell-body which governs its nutrition'; and this, as the observations of His have shown, is in every case the body of the cell from which the nerve-fibre has originally grown.[1]

[1] The nerves to blood-vessels offer an apparent exception to this rule. They were found by Langley in the frog (Journ. Physiol. xxxviii. 1909) not to degenerate after section, their nutrition being probably maintained, as suggested by Bethe, by peripheral cells (see p. 227). Langley found that the nerves to the skeletal muscles of the frog took forty days to undergo degeneration. The post-ganglionic fibres of the sympathetic showed degeneration soonest



Portions of longitudinal muscular coat and of submucous coat of intestine of guinea pig, prepared with gold chloride. Showing in *A* the *plexus myentericus* of Auerbach and in *B* the plexus of Meissner. Magnified 50 diameters. (Schäfer.)

TERMINATIONS OF NERVES.

It may be stated, generally, and apart from what may apply to special modes of termination, that, in approaching their final distribution, the fibres, medullated and non-medullated, usually divide into branches, the division in the case of medullated

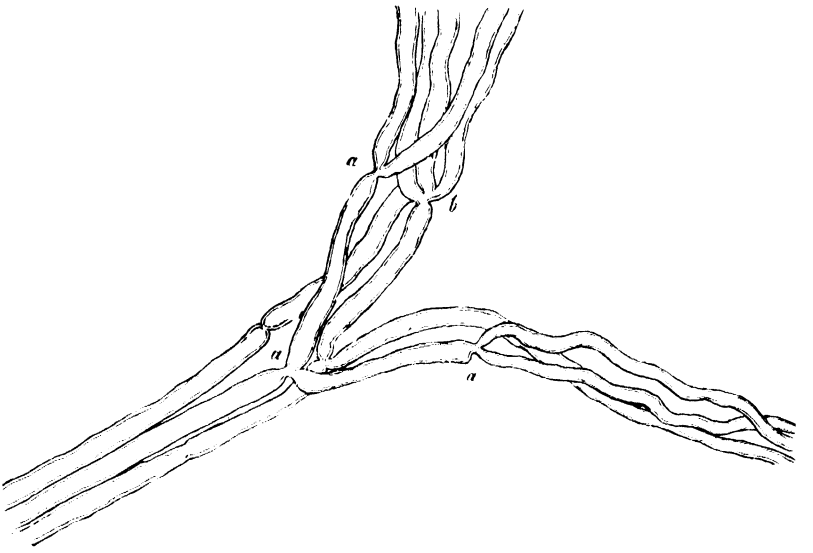


FIG. 388. SMALL BRANCH OF A MUSCULAR NERVE OF THE FROG, NEAR ITS TERMINATION, SHOWING DIVISIONS OF THE FIBRES. (Kölliker.) Magnified 350 diameters.

a, into two; *b*, into three.

fibres always occurring in the situation of a node of Ranvier (fig. 388). The axis cylinder participates in the division; and since the white fibres frequently lose their sheaths shortly before they terminate, they are then represented only by the axis-cylinder and its ramifications.

TERMINATIONS OF EFFERENT NERVES.

In many **involuntary muscles** such as those which constitute the muscular layers of the hollow viscera, the motor nerves, which are for the most part non-medullated with a small intermixture of white fibres, form complicated plexuses as they near their termination. At the junctions of the fine nervous cords which compose the plexuses groups of ganglion-cells, forming small ganglia, are in many parts met with; a well-known example of such a gangliated plexus being the *plexus myentericus* of Auerbach between the longitudinal and circular layers of the muscular coat of the intestine (see accompanying Plate). From these ganglia, it may be also indirectly from the nervous cords or directly from the incoming nerves, branches are sent off, which penetrate between the elements of the involuntary muscular tissue, coursing for the most part parallel with the muscular fibres. In some organs which are largely composed of involuntary muscle no such gangliated plexuses occur; the nerve-fibres pass directly to the muscular tissue. The nerve-fibres which are passing towards their terminations bifurcate and give off branches at acute angles at frequent intervals, and eventually become separated into fine filaments which may represent ultimate fibrillæ. The branches which are given off from these rarely, if ever, become united with those from adjoining nerve-fibres. The fine longitudinally coursing fibrils come into close relation with the

involuntary muscle-cells (fig. 389) and terminate by tapered or bulbous extremities which are applied to the surfaces of the plain muscle-cells (fig. 390).[1] The plain muscular tissue of the mucous membrane (muscularis mucosæ) is similarly supplied from a second gangliated plexus, known as the plexus of Meissner (see Plate, fig. B).

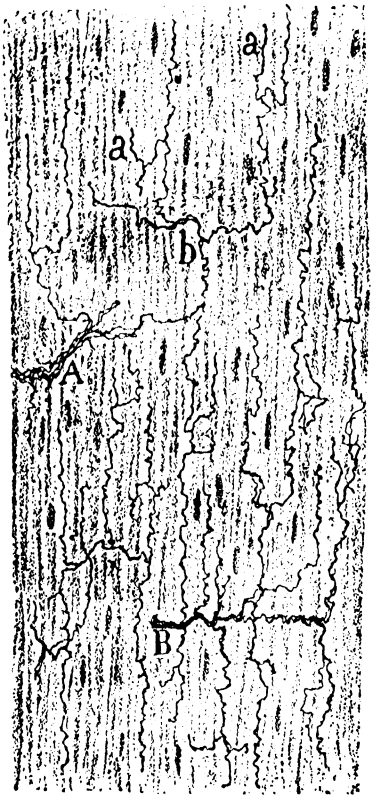


FIG. 389.—NERVE-FIBRES ENDING IN PLAIN MUSCLE, FROM INTESTINE OF GUINEA-PIG. (Cajal.)

A, B, larger branches; *a*, *b*, terminal twigs.

In **cardiac muscular tissue** the nerves, which are non-medullated in their branches of distribution, form plexuses with very long meshes. The fine nerve-fibres become closely applied to the muscular fibres, many appearing to end in small bulbous extremities, but they do not, it is believed, penetrate into the muscular fibres. According to Huber and de Witt,[2] and Smirnow[3] the (non-medullated) nerve-fibres end in fine fibrils which form free ramifications which are spread over a greater or less extent of each nucleated segment of the tissue (fig. 391). Motor end-plates, such as occur in voluntary cross-striated muscle, have not been found in the heart.

It is not known if there is any distinction between the mode of termination of the inhibitory and accelerator fibres of the heart. The vagal fibres pass to the ganglia of the auricles and some may extend to those at the base of the ventricles. There is little doubt that these pre-ganglionic fibres all terminate by synapses around the ganglion-cells, and that by the axons of these cells the nerve-path is continued to the muscle-fibres. On the other hand, there is some reason to believe that the accelerator fibres of the sympathetic (which are post-ganglionic) go directly to the muscle-fibres and not by the intermediation of peripheral ganglion-cells.

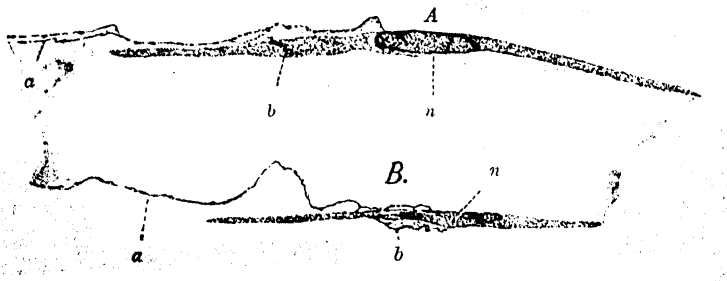


FIG. 390.—ENDING OF NERVE-FIBRES IN PLAIN MUSCLE. (Huber and de Witt.)

A and *B*, two plain muscle-cells with nerve-fibres, *a*, passing to them and ending at *b*, on the outside of the cell; *n*, cell-nucleus.

The **motor nerves of voluntary muscles** terminate in special expansions, to which the term *motor end-plates* has been applied. The term *motor end-*

[1] Huber and de Witt, Journ. Morph. vii. 1898. F. B. Hoffmann (Arch. f. mikr. Anat. lxx. 1907) describes them as ending in networks and loops, and not by free extremities.

[2] *Op. cit.* [3] Anat. Anz. xviii. 1901.

organ is however a more suitable one, for, as will immediately be explained, the termination of the nerve is rather of the nature of a flattened ramification than a continuous plate.

As was mentioned in the account of muscular tissue, the nerves in voluntary muscles form plexuses, of which the branches grow finer and the meshes closer as they advance farther into the tissue. The individual fibres, while still associated in small bundles, undergo division, and at length single dark-bordered fibres pass off to the muscular fibres

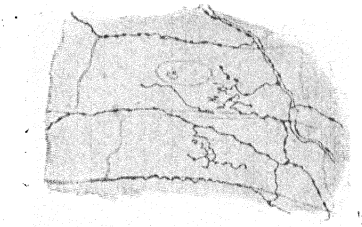


FIG. 391.—ENDING OF NERVE-FIBRES IN CARDIAC MUSCLE. (Smirnow.)

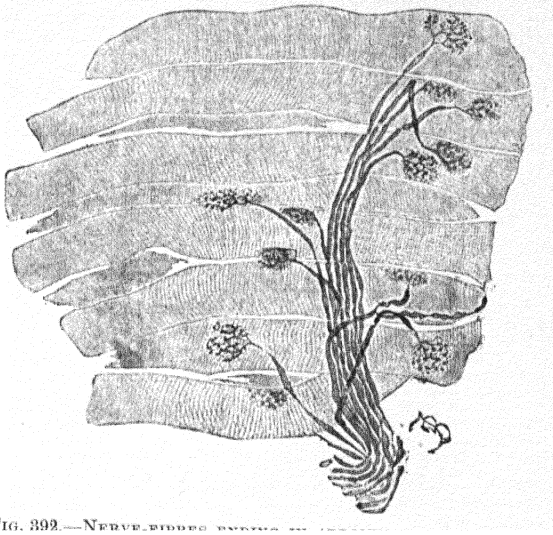


FIG. 392.—NERVE-FIBRES ENDING IN ABDOMINAL MUSCLES OF RAT. Gold preparation. (Szymonowicz.) Magnified 170 diameters.

(fig. 392). These nerve-fibres on approaching or reaching a muscular fibre often divide still further. The branches retain their medullary sheath until they reach the sarcolemma, when the white substance abruptly terminates, while the

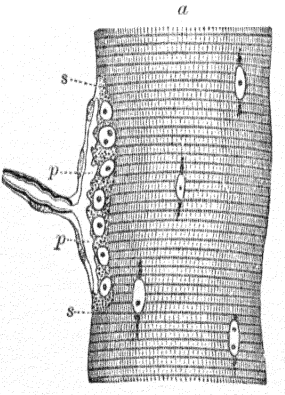


FIG. 393.—NERVE-ENDING IN MUSCULAR FIBRE OF A LIZARD (LACERTA VIRIDIS). (Kühne.) Highly magnified.

a, end-organ seen in profile; *b*, from the surface. *s*, *s*, sarcolemma; *p*, *p*, expansion of axis-cylinder. Beneath this is granular protoplasm containing a number of large clear nuclei and constituting the 'bed' or 'sole' of the end-organ. In *b* the expansion of the axis-cylinder appears as a clear network, branching from the divisions of the medullated fibre.

neurolemma becomes continuous with the sarcolemma (fig. 393, *s*). It would seem that the prolongation of the nucleated sheath of Henle is also continued over the end-organ, which thus receives a double covering to which the name *telolemma*

has been given by Kühne.[1] The axis-cylinder as it passes into the fibre forms a clear localised branched expansion (fig. 393, *p p*), which lies immediately under the sarcolemma, imbedded in a layer of protoplasmic matter, the 'bed' or 'sole' of

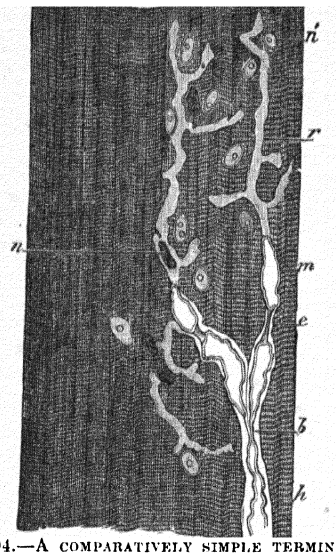


FIG. 394.—A COMPARATIVELY SIMPLE TERMINATION OF A NERVE IN A MUSCULAR FIBRE OF THE LIZARD (LACERTA VIRIDIS.) (Ranvier.) Highly magnified.

h, sheath of the nerve-fibre; *b*, bifurcation of the fibre; *e*, node; *m*, short segment beyond the node; *r*, terminal ramifications of the axis-cylinder; *n*, nuclei on the branches of the axis-cylinder; *n'*, nuclei in the granular substance of the end-plate. The granular substance lies in the intervals between the branches of the axis-cylinder; it is not seen in this figure.

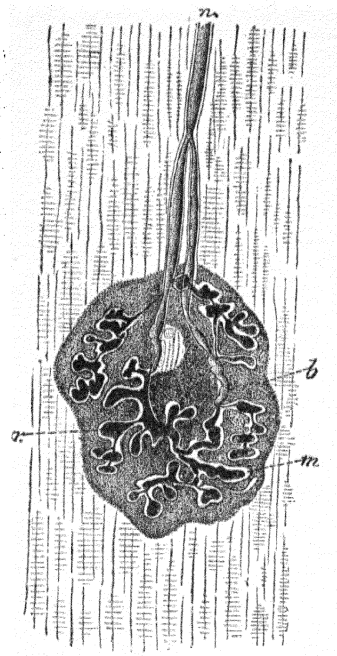


FIG. 395.—MOTOR END-ORGAN OF A LIZARD. Gold preparation. (Kühne.)

n, nerve-fibre; *r*, terminal ramification of axis-cylinder; *m*, clear substance surrounding the ramification (matrix); *b*, granular bed or sole of the end-organ.

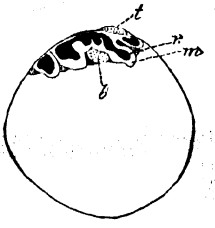


FIG. 396.—CROSS-SECTION OF MUSCULAR FIBRE AND END-ORGAN OF LIZARD. Gold preparation. (Kühne.)

r, terminal ramification of axis-cylinder; *m*, matrix; *b*, nucleus of bed; *t*, nucleus of telolemma.

FIG. 397.—MOTOR END-ORGAN OF HUMAN MUSCLE. Gold preparation. (Kühne.)

n, medullated nerve-fibre; *r*, terminal ramification of axis-cylinder.

the end-organ, which contains a number of large clear nuclei, each having one or more distinct nucleoli. The termination of the axis-cylinder is, as just explained, not a continuous plate, as was thought by Rouget, but appears when viewed from the surface in the form of an arborescent figure (figs. 394 to 397), the branches of

[1] Zeitschr. f. Biol. xxiii. 1886.

which do not anastomose (Ranvier). According to Kühne the branching figure which is formed by the axis-cylinder is composed of an axial part, staining darkly with gold, and a sheath, which remains unstained. Kühne regarded the axial part as representing the fibrils of the axis-cylinder, but it may be doubted whether the apparent differentiation into axial part and sheath is not due to the shrinking of the axis-cylinder under the influence of the reagent. The appearance of the two parts in gold preparations is well exhibited in fig. 395. Applied to the branches of the ramification small granular nuclei (fig. 394, *n*), are seen at intervals; these nuclei of the arborisation are different from the clear nuclei of the bed (*n*), and also from the flattened nuclei of the sheath which lie immediately under the sarcolemma covering the end-plate, and which resemble the nuclei of the sheath of Schwann of the nerve. The sarcolemma over the situation of the nerve-ending is often slightly raised above the general surface (fig. 393, *a*).

It would appear that in mammals each muscular fibre has but one end-organ, and receives consequently but one nerve-fibre. As, moreover, the fibres of a nerve undergo division, probably repeated division, before ending, it follows that one fibre in a nerve-root or -trunk supplies many muscular fibres. In reptiles and amphibia the longer muscular fibres may have two or more nerve-endings (fig. 398).

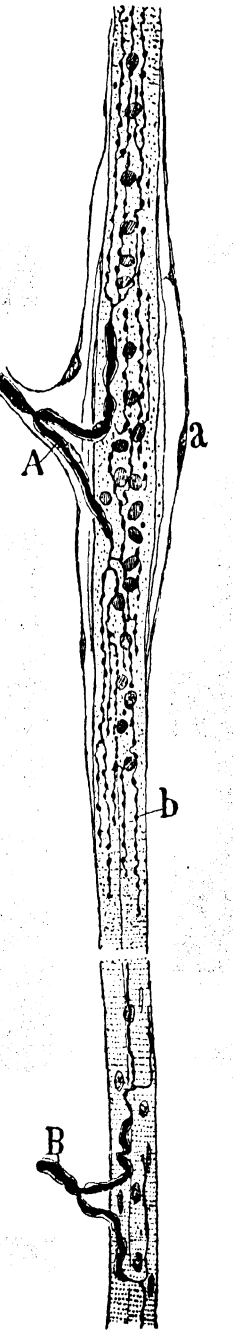


FIG. 398.—MUSCULAR FIBRE OF FROG SUPPLIED BY TWO NERVE-FIBRES. (Cajal.)

A, nerve-fibre inclosed by neurolemma and sheath of Henle, the latter of which expands to form an investment (*a*) to the muscle-fibre outside the sarcolemma. *b*, ending of nerve-fibrils. B, a second nerve-fibre with a somewhat less extensive distribution of its arborescent axis-cylinder.

The shape and extent of the terminal ramification of the axis-cylinder within the end-organ vary greatly, not only in different classes of animals, but also in animals belonging to the same class, and there is even some variation in individuals of the same species, as is evident from the various representations of the end-organs of the green lizard, which are here given (figs. 393, 394, 395). On the whole, it may be stated that the terminal ramification is most compact in mammals and reptiles and least so in amphibia (fig. 398), where there is no continuous protoplasmic bed with clear nuclei imbedded in it, and the ramifications of the axis-cylinder are extended over a much larger proportionate area of the fibre than in reptiles, birds, and mammals, so that the termination of the nerve is far less localised. The branches of the axis-cylinder in the frog run for a short distance parallel with the axis of the fibre between the sarcolemma and muscular substance, terminating abruptly by rounded extremities. They have here and there slight enlargements,

connected with which are seen, as in the end-plate of the lizard, elongated nuclei different in appearance from the proper nuclei of the muscle. In other animals, *e.g.* in snakes, there is a tendency for the branches of the ramification to become dilated at their termination into bulbous enlargements, which in a well-stained preparation gives an appearance like that of a bunch of berries. Many other variations are met with, but in no case is there a departure from the general rule that the ultimate termination is in the form of a ramification of the axis-cylinder on the surface of the fibre, but within the sarcolemma. The neuro-fibrils penetrate into all the branches of the axis-cylinder, and form networks within its expansions (figs. 399, 400). According to Boecke,[1] they are continuous with a reticulum in the sarcoplasm. Boecke also describes an accessory fibre as sometimes passing independently to the same 'bed.' These accessory fibres, which had previously been noticed by Perroncito and by Huber and de Witt, are non-medullated (fig. 400).

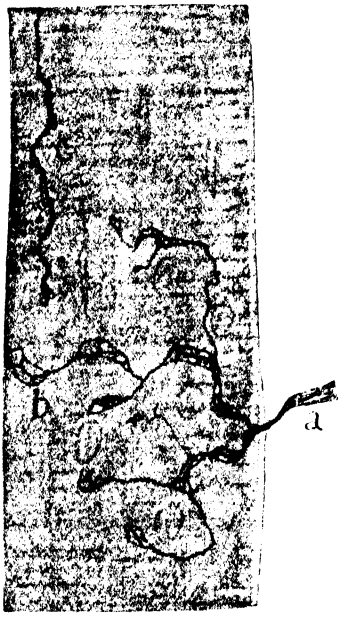


FIG. 399.—ENDING OF A MOTOR NERVE-FIBRE IN MUSCLE OF RABBIT. (Cajal.)

a, axis-cylinder of entering nerve; *b*, *c*, terminal ramifications with network of neuro-fibrils.

The termination of motor nerves in special granular expansions within the sarcolemma was first noticed by Doyére in insect-muscles. The arborescent termination of the axis-cylinder was discovered in the frog by Kühne in 1862. In the same year the end-plates were recognised by Rouget in the lizard, and in 1863 by W. Krause in mammals. The last-named observer was the first to describe the termination of the axis-cylinder as a ramified expansion imbedded in granular substance, but maintained that the whole structure lay outside the sarcolemma. In this opinion Krause was supported by Kölliker, but Kühne and the majority of observers have regarded the whole end-organ as hypolemmal in position.

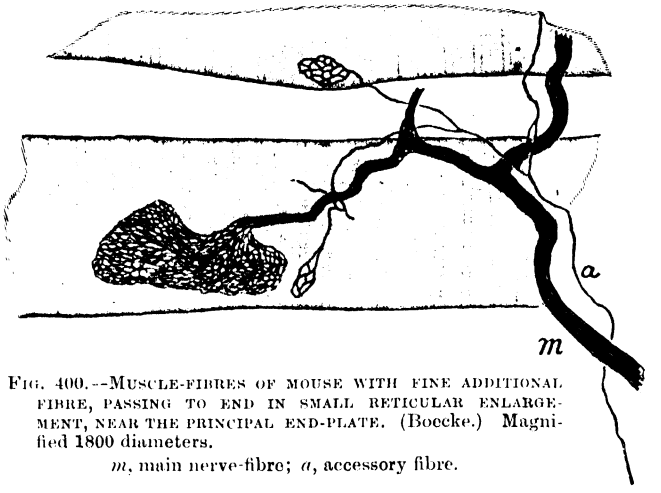


FIG. 400.—MUSCLE-FIBRES OF MOUSE WITH FINE ADDITIONAL FIBRE, PASSING TO END IN SMALL RETICULAR ENLARGEMENT, NEAR THE PRINCIPAL END-PLATE. (Boecke.) Magnified 1800 diameters.

m, main nerve-fibre; *a*, accessory fibre.

Development.—The development of motor end-organs has been investigated by Boecke[1] and Mays[2]: their degeneration and regeneration after section of the motor-nerve by Cajal and

[1] Anat. Anz. xxxv. 1910. [2] Zeitschr. f. Biol. xxix.

Tello.[1] The motor nerve-fibres reach the developing muscular fibre before the appearance of the sarcolemma and make contact with the muscle-substance, the nuclei of which are accumulated, together with a considerable amount of protoplasm, at the site of formation of the end-organ.

Tello found degeneration to begin twelve to fourteen hours after section: the degenerated remains are relatively soon absorbed, as compared with the rest of the nerve-fibre. In a young rabbit the regenerating fibres were found to reach the muscle two and a-half months after the operation, and on reaching the 'bed' to become ramified. The protoplasm and nuclei of the end-plate do not undergo degeneration: they are probably instrumental in absorption of the degenerated nerve-ending.

Nerve-endings in secreting glands.—The nerves to secreting glands and to secreting epithelium in general belong to the autonomic system, and leave the central nervous system as fine medullated fibres which end in the ganglia of the

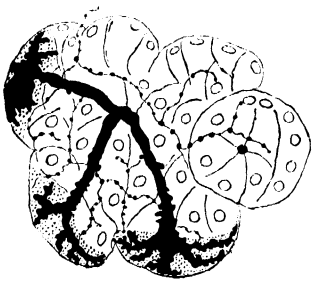


FIG. 401.—ENDING OF NERVE-FIBRILS AMONGST THE CELLS OF THE SUB-MAXILLARY GLAND OF A DOG. Golgi method. (G. Retzius.)

The nerve-fibrils are very fine and varicose. The lumen of the alveolus is also stained black and its extension into the crescents of Gianuzzi is shown.

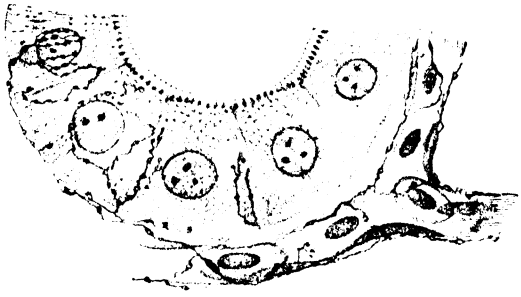


FIG. 402.—NERVE-FIBRILS ENDING OVER CAPILLARY BLOOD-VESSELS AND AMONGST THE EPITHELIUM-CELLS OF A CONVOLUTED TUBE OF THE FROG'S KIDNEY. (Smirnow.)

sympathetic chain or in peripheral ganglia. From the cells of these ganglia non-medullated fibres continue the chain and pass to their distribution amongst the cells of the glandular epithelium. Here they divide into fine varicose branches each representing not more than a single nerve-fibril, and these fibrils penetrate between and partly enwrap the secreting cells, to which they are closely applied, but apparently without entering them (figs. 401, 402).[2]

TERMINATIONS OF AFFERENT NERVES.[3]

The sensory or afferent nerves end either in cells or in free nerve-endings, which may be simple or plexiform, and may be enclosed by cells or connective tissue, or have an independent distribution. Of the sensory nerves which terminate in cells, the best recognised are those which are found in the organs of special sense. But some of these nerves may be regarded as taking origin in the sense-organ rather than ending in it, for if their development is studied it would appear, in the case of the olfactory and visual organs, that the nerve-fibres grow *from* the sense-organ towards the central nervous system and not centrifugally, as is the case with most other nerve-fibres. In the other sense-organs the nerve-terminations are not within, but between the sense epithelium-cells.

[1] Travaux du laboratoire de Cajal, v. 1907.

[2] For the nerve-endings in different secreting glands, see E. Müller, Arch. f. mikr. Anat. xl. 1890 (gastric glands and pancreas); G. Retzius, Biol. Unters. iii. 1892 (salivary); P. Korolkow, Anat. Anz. vii. 1892 (salivary); A. S. Dogiel, Arch. f. mikr. Anat. xlii. 1893 (lacrymal); H. J. Berkeley, Johns Hopkins Hospital Rep. v. 1894 (salivary).

[3] For an account of the literature of sensory nerve-endings, which is very extensive, the reader is referred to the articles by Kallius which have appeared from time to time in the Ergebnisse der Anatomie of Merkel and Schwalbe. The most recent account of the literature of the special tactile organs such as Meissner's corpuscles, Pacinian and Herbst corpuscles, and Grandry's corpuscles, will be found in a paper by E. Van de Velde, Int. Monatschr. f. Anat. u. Physiol. xxvi. 1909.

Of the ordinary sensory nerves, including those which are devoted to the perception of tactile sensations, some end as ramifications of the axis-cylinder, which resolves itself eventually into its ultimate fibrils, and thus penetrates between the epithelium-cells which cover the sensory surface, whilst others terminate in special organs composed of the connective-tissue sheath of the nerve-fibre. Of these end-organs, the best known are the *simple and compound end-bulbs* and *tactile corpuscles*, the *corpuscles of Grandry*, which occur in birds, the *corpuscles of Herbst*, also occurring in birds, and the *corpuscles of Pacini*; besides various similar structures, which are found chiefly in mammals and have received names according to their situation or from the observer who has first described them.

Tactile corpuscles or touch-bodies (*corpuscula tactûs*) (figs. 403 to 407). These were discovered by R. Wagner and Meissner in the papillæ of the skin of

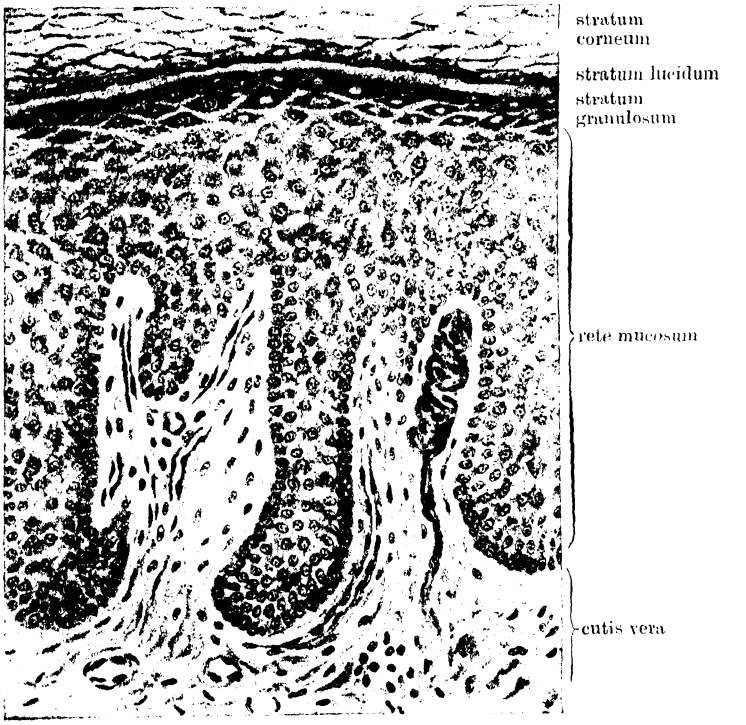


FIG. 403.—VERTICAL SECTION THROUGH THE SKIN OF THE PALMAR SIDE OF THE FINGER, SHOWING TWO PAPILLÆ (ONE OF WHICH CONTAINS A TACTILE CORPUSCLE) AND THE DEEPER LAYER OF THE EPIDERMIS. (Schäfer.) Magnified about 200 diameters.

the hand and foot, where they are of an oval shape, nearly 0·083 mm. ($\frac{1}{300}$ inch) long and 0·03 mm. ($\frac{1}{800}$ inch) thick. They may be found in the skin of all parts of the hand and foot (fig. 403) (including the bed of the nails), that of the volar surface of the forearm, in the skin of the nipple in both sexes, in the conjunctiva at the edge of the eyelids, in the skin of the lips and in the mucous membrane of the tip of the tongue (fig. 438). Similar corpuscles occur in monkeys, but they have not been found in animals lower in the scale. One, two, or more medullated nerve-fibres run to the corpuscle and either at once, or after winding round it two or more times, pass into its interior and become lost to view. The touch-body contains connective tissue, prolonged inwards from the capsule in

the form of imperfect membranous septa (figs. 405, 406, A, and 407), between which are supported the convolutions and ramifications of the nerves, and the enlarge-

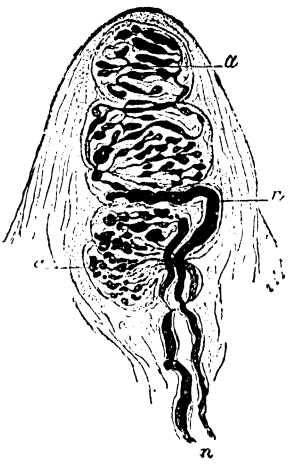


FIG. 404.—TACTILE CORPUSCLE WITHIN A PAPILLA OF THE SKIN OF THE HAND, STAINED WITH CHLORIDE OF GOLD. (Ranvier.) Highly magnified.

n, *n*, two nerve-fibres passing to the corpuscle; *a*, *a*, terminal varicose ramifications of the axis-cylinder within the corpuscle.

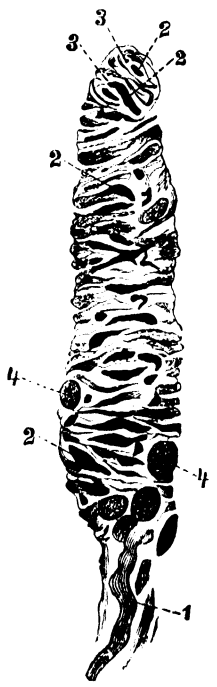


FIG. 405.—ANOTHER CORPUSCLE, TREATED WITH OSMIC ACID, SEEN IN LONGITUDINAL SECTION. (Flemming, from a preparation by Fischer.)

1, entering nerve-fibre, medullated; 2, 2, the same cut variously within the corpuscle; 3, 3, clear spaces around the fibre (perhaps homologous with the core of the cylindrical end-bulbs); 4, 4, nuclei of the transverse and spirally disposed cells of the corpuscle.

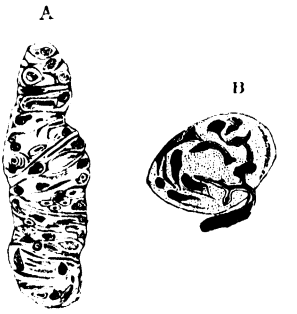


FIG. 406.—TACTILE CORPUSCLES FROM THE PALM OF THE HAND SEEN IN SECTION. (Merkel.)

A, longitudinal section showing the interior traversed by connective-tissue septa derived from the capsule; the nerve-fibres are cut across. B, transverse section at the point of entrance of a nerve-fibre, showing the axis-cylinder branching. Other nerve-fibres are cut obliquely.

ments in which the branches of the axis-cylinder eventually end (fig. 404). These terminal enlargements are usually near the capsule, and in small tactile corpuscles may occasionally project beyond it; (fig. 407). On entering the corpuscle the nerve-fibres for the most part lose their medullary sheath, but some retain it for a short while, or it may reappear here and there in the course of the fibres. The axis-cylinders, which are often varicose, have, as before intimated, a convoluted course before ending in their terminal enlargements (fig. 404). The core within which the axis-cylinder courses is composed of protoplasmic cells, mostly flattened. The enlargements of the axis-cylinder, both in its course and at its endings, contain a network of neuro-fibrils [1] (fig. 407).

[1] Van de Velde, *op. cit.*

FIG. 407.—A TACTILE CORPUSCLE FROM THE HUMAN FINGER, SHOWING CELLS OF CORPUSCLE AND NERVE-ENDINGS WITH NEUROFIBRILS. (Van de Velde.)

a, entering axis-cylinder; *b*, connective-tissue capsule; *c*, an extra-capsular nerve-ending.

Development.—Ranvier,[1] who studied the development of the tactile corpuscles, found that in the infant at birth they are represented by a bunch of bulbous nerve-endings immediately below the epidermis at the summit of a papilla and an island of specialised mesodermic cells lying just underneath the bunch of nerve-endings. Seven weeks after birth (fig. 408) these cells are found to have insinuated themselves between the mass of nerve-terminals, which are now much more numerous. The cells, as development proceeds, become flattened out and arranged so as to produce a lobulation of the corpuscle, with groups of the bulbous nerve-endings in each lobule. As growth proceeds, connective tissue is found between the lobules and also around the whole corpuscle in the form of a capsule, and the nuclei gradually pass to the periphery, so that in the adult they are rarely found in the middle of the corpuscle.

End-bulbs.—If the conjunctiva of the calf or of certain other animals is spread out and examined under the microscope, many of the medullated nerves which course in different directions in the membrane may be seen to end in very small oval or elongated corpuscles (fig. 409), into the interior of which the axis-cylinder of the nerve-fibre passes, surrounded by a core, which sometimes appears homogeneous, but more often shows nuclei scattered throughout its length; the axis-cylinder ends near the extremity of the core, with a rounded or dilated termination, and commonly gives off numerous lateral branches in its course. The dilatations

FIG. 408.—TACTILE CORPUSCLE OF CHILD OF SEVEN WEEKS OLD. Gold preparation. (Ranvier.)

n, afferent nerve; *a*, cells of nodule; *b*, ramifications of axis-cylinder with enlargements.

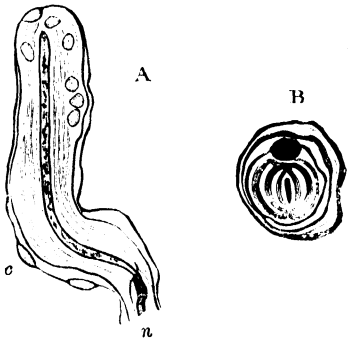


FIG. 409.—CYLINDRICAL END-BULBS FROM THE CONJUNCTIVA OF THE CALF. (Merkel.)

A, in optical longitudinal section; B, in transverse section; *n*, entering nerve-fibre; *c*, nucleated capsule.

contain a fine fibrillar network continuous with the fibrils of the axis-cylinder. The core with its contained fibre is enclosed in a nucleated capsule composed of flattened cells. The medullary sheath ceases abruptly at the entrance of the nerve, whereas the primitive sheath appears to be continued over the core, and to line the capsule. These *end-bulbs* were discovered by W. Krause. They are sometimes of a cylindrical form, sometimes more rounded, and they may occur singly or in small agglomerations. End-bulbs of a spheroidal form occur abundantly in men and monkeys in the conjunctiva (figs. 410, 411), and have also been found in man in the papillæ of the skin covering the lips, in the mucous membrane of the cheeks, soft palate, tongue, epiglottis, nasal cavities, and lower end of the rectum. Sometimes the medullated fibre which passes to each end-bulb divides into two or more branches before reaching the bulb, and the branches may be twisted around one another on their passage towards the organ. The capsule is continuous with the sheath of Henle of the nerve-fibre.

A form of end-bulb which is found in the human skin and which was described by A. S. Dogiel,[2] has a cylindrical form, sometimes bent, and is formed of a connective-

[1] Comptes rendus, December 27, 1880.

[2] Zeitschr. f. wiss. Zool. lxxv. 1903.

tissue capsule enclosing a core of cells. The entering nerve, which is large, loses its medullary sheath and is continued through the core as a broad flat axis-cylinder, which has a zigzag course and shows numerous enlargements. All of these, as well as the terminal expansions of the main fibre and its branches, show a network of neuro-fibrils (Van de Velde).

End-bulbs, simple and complex, occur in many other situations. Thus they are found in the

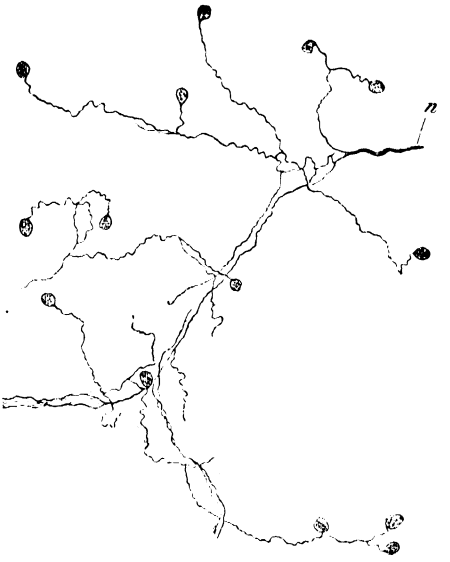


FIG. 410.—END-BULBS FROM THE HUMAN CONJUNCTIVA. (Longworth.)

Ramification of nerve-fibres in the mucous membrane, and their termination in end-bulbs, as seen with a lens.

FIG. 411.—END-BULB OF THE HUMAN CONJUNCTIVA, TREATED WITH 3 PER CENT. ACETIC ACID AND 1 PER CENT. OSMIC ACID. (W. Krause.)

peritoneum [1] (figs. 412, 413) and in the central tendon of the diaphragm (fig. 414), in other serous membranes, in tendons and ligaments, and in the connective tissue of nerve-trunks.[2]

FIG. 412.—A MEDULLATED FIBRE TERMINATING IN SEVERAL END-BULBS IN THE HUMAN PERITONEUM. Methylene-blue preparation. (Dogiel.) Low power.

Large end-bulbs of a rounded oval form have been found in the synovial membrane of certain joints in man (*e.g.* those of the fingers), and also in the articular synovial membranes of several mammals. They are somewhat flattened, have a

[1] A. S. Dogiel, Arch. f. mikr. Anat. lix. 1902; Ramström, Anat. Hefte, xxxvi. 1908.
[2] Horsley, Brit. Med. Journ. 1884.

large core composed of small cells, and receive from one to four medullated nerve-fibres, which terminate within them in fine convoluted and ramified non-medullated filaments (fig. 412). They are distinguished by the name of *articular end-bulbs.*

FIG. 413.—A DOUBLE END-BULB FROM THE HUMAN PERITONEUM. Methylene-blue preparation. (Dogiel.) High power.

a, medullated fibre; *b*, capsule of end-bulb; *c*, non-medullated fibres, probably destined for blood-vessels.

FIG. 414.—END-BULB FROM CENTRAL TENDON OF DIAPHRAGM OF DOG. Methylene-blue preparation. (Dogiel.)

Besides the main nerve-fibre, which is medullated, and ends in the core of the end-bulb in an arborescent manner, there is a second very fine medullated fibre in the outer part of the core.

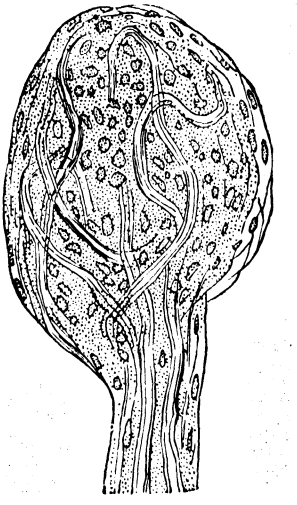


FIG. 415.—ARTICULAR END-BULB FROM PHALANGEAL JOINT IN MAN. Acetic-acid preparation. (Krause.)

n, two medullated nerve-fibres entering the corpuscle.

Another modification was discovered by W. Krause in certain parts of the external generative organs, both in the male and female (especially in the glans penis and clitoridis), and may be named *genital end-bulbs.* These corpuscles are usually subdivided by connective-tissue septa into from two to six knob-like portions, which gives the whole corpuscle a mulberry-like aspect. From one to four medullated fibres enter the genital corpuscle; their axis-cylinders for the most part break up within it into a large number of fine pale terminal fibres. Their size varies greatly, some of them being no larger than ordinary end-bulbs, others several times as large. In the simplest the axis-cylinder of the nerve-fibre entering at one pole of the somewhat oval corpuscle (fig. 416) may either pass straight or with one or two bendings through the corpuscle, and end by a tapering or by a dilated extremity near the opposite pole (often projecting beyond the general body of

the organ, as in B); or it may be much convoluted and ramified in its passage, so as to render it a matter of difficulty to trace its course and mode of termination (fig. 416 C, fig. 417). The arrangement of the cells in these corpuscles seems to vary. Generally they are chiefly collected at the exterior, leaving the part

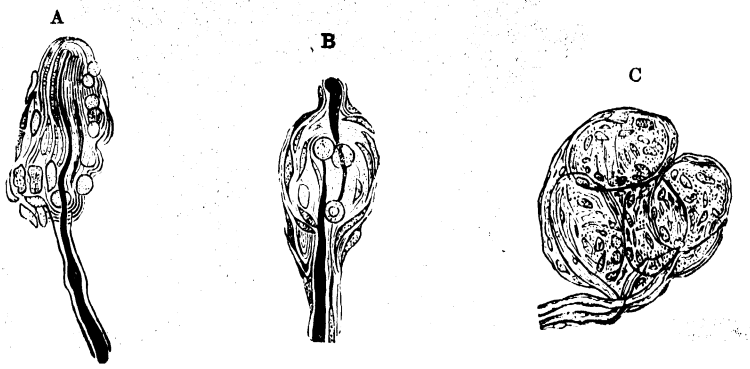


FIG. 416.—A AND B, GENITAL END-BULBS FROM THE CLITORIS OF THE RABBIT (Izquierdo); C, FROM THE HUMAN CLITORIS (W. Krause).

traversed by the axis-cylinder free from cells and of an obscurely fibrous appearance, concentrically striated in transverse section (G. Retzius); but in others such as the spheroidal end-bulbs of the human conjunctiva, an agglomeration of cells in the centre has been described; the existence of this is, however, denied by Retzius.

Corpuscles of Ruffini.—In the subcutaneous tissue of the finger, Ruffini [1] described a form of nerve-ending in connective-tissue bundles (fig. 418), which recalls the nerve-ending in tendon-bundles, described by Golgi and known by his name (see p. 279). Similarly in the Ruffini corpuscles one or more medullated nerve-fibres enter a connective-tissue bundle, their sheath of Henle becoming continued into the outer part of the bundle. Within the latter, which is somewhat swollen into an oval enlargement, the fibres, having lost their medullary sheath, break up into a close ramification, the branches lying in the interstices of and partly encircling the smaller bundles of connective tissue. Sometimes there are a number of these corpuscles of Ruffini in close juxtaposition, supplied by the divisions of a single nerve-fibre.

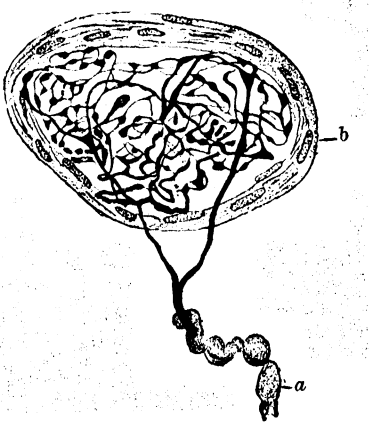


FIG. 417.—GENITAL END-BULB FROM GLANS PENIS. Methylene-blue preparation. (Dogiel.)
a, medullated nerve-fibre; *b*, capsule of end-bulb.

Corpuscles of Golgi-Mazzoni.—Golgi [2] and subsequently Mazzoni,[3] described a form of end-organ of spherical or cylindrical shape which is found on the surface of tendons, and similar corpuscles also occur according to Ruffini in the

[1] Arch. ital. de biol. xxi. 1894. [2] Mem. accad. d. sci. d. Torino, xxxii. 1880.
[3] Mem. accad. di Bologna, t. 50, 1891.

subcutaneous tissue of the finger. They are characterised mainly by the tendency which the branches of the axis-cylinder have to end in flattened expansions, often concatenated and lying, as in other end-bulbs, in a core. Each has a connective-tissue capsule, composed of several lamellæ like those of the Pacinian corpuscle (fig. 419). Ruffini [1] has found similar bodies in the connective tissue of the finger-

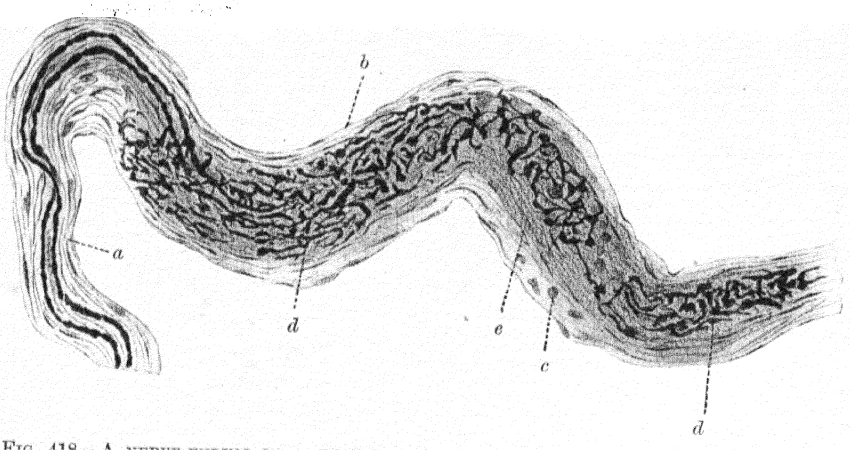


FIG. 418.—A NERVE-ENDING IN A SPECIAL CONNECTIVE-TISSUE ORGAN IN THE DEEPER PART OF THE CUTIS. Gold preparation. (Ruffini.) Magnified 320 diameters.

a, sheath of Henle of entering nerve; *b*, sheath of terminal organ; *c*, blood-capillaries; *d*, *d*, terminations of axis-cylinders; *e*, spindle-shaped connective-tissue core in which these terminations ramify.

pulp. These corpuscles have also been described by A. S. Dogiel [2] in other parts of the skin. They appear to be intermediate in complexity between the end-bulbs of Krause and the corpuscles of Pacini.

Corpuscles of Pacini.—In dissecting the nerves of the hand and foot certain small oval bodies like little seeds may be found attached to their finer branches as they pass through the subcutaneous fat on their way to the skin;

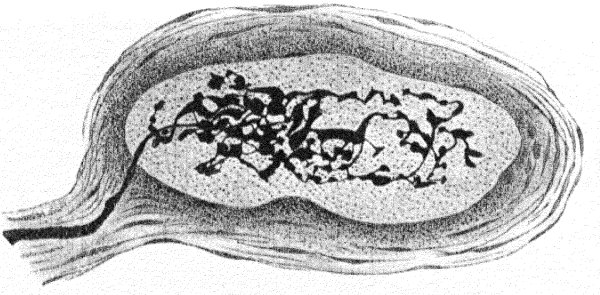


FIG. 419.—A GOLGI-MAZZONI END-ORGAN FROM THE SURFACE OF A TENDON. Gold preparation. (Ruffini.) Magnified 320 diameters.

each of these bodies receives a medullated nerve-fibre which terminates within it. The corpuscles referred to were described and figured by Vater in 1741, as attached to the digital nerves, but he did not examine into their structure, and his account of them seems not to have attracted much notice. In more recent times, their existence was again pointed out by Cruveilhier and other French anatomists, as well as by Pacini of Pisa, who appears to have been the first writer to give an account

[1] *Op. cit.* [2] Arch. f. mikr. Anat. xli. 1893

of the internal structure of these bodies, and to clearly demonstrate their essential connexion with nerve-fibres.

The corpuscles in question are, as already said, attached in numbers to the branches of the nerves of the hand and foot (fig. 420), and here and there they

FIG. 420.—A NERVE OF THE MIDDLE FINGER, WITH PACINIAN BODIES ATTACHED. Natural size. (After Henle and Kölliker.)

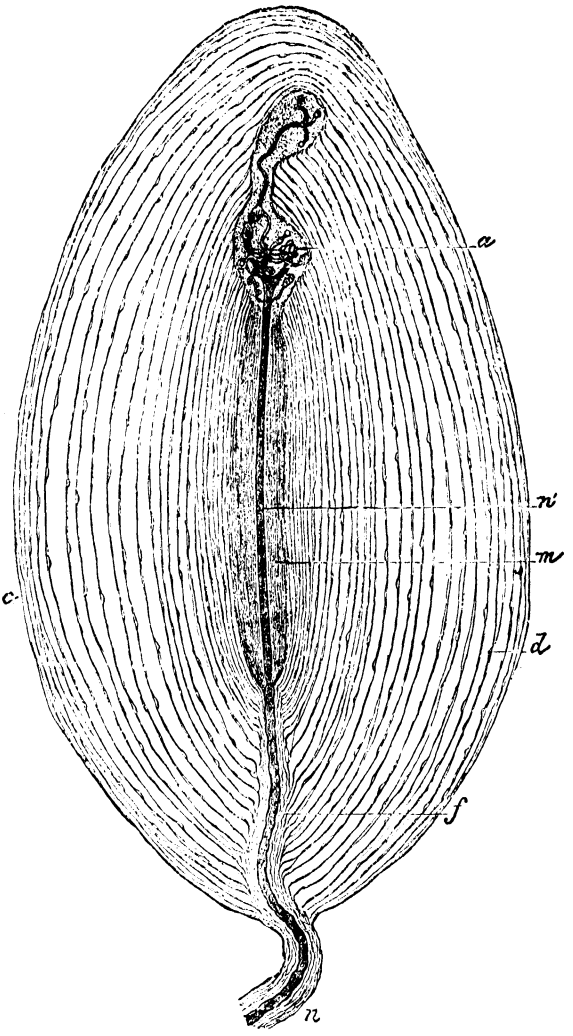


FIG. 421.—MAGNIFIED VIEW OF A PACINIAN BODY FROM THE CAT'S MESENTERY, AS SEEN IN LONGITUDINAL OPTICAL SECTION. (Ranvier.)

n, stalk with nerve-fibre enclosed in sheath of Henle passing to the corpuscle; *n'*, its continuation through the core, *m*, as a pale fibre; *a*, termination of the nerve in the distal end of the core. In the corpuscle here figured the termination is arborescent. *d*, lines separating the tunics of the corpuscle, often taken for the tunics themselves; *f*, channel through the tunics, traversed by the nerve-fibre; *c*, external tunics of the corpuscle.

are found on other cutaneous nerves. They have been discovered also within the abdomen on the nerves of the solar plexus, and on those of the parietal peritoneum.[1] They are nowhere more distinctly seen or more conveniently obtained for examination than in the mesentery of the cat, between the layers of which they exist abundantly. They have been found on the pudic nerves in the penis and clitoris, in the bulb and other parts of the urethra, on the intercostal nerves, sacral plexus, cutaneous nerves of the upper arm and neck, nerves of the nipple and mammary gland, and on the infra-orbital nerve. They have also been described on nerves to tendons and ligaments, more rarely on intra-muscular nerves, on the periosteal nerves, and, in considerable numbers, on the nerves of the joints. In many mammals they

[1] Ramström, Anat. Hefte, xxxvi. 1908.

occur in masses of from twenty to eighty corpuscles imbedded in the fat of the ball of the foot and also in the interosseous space between the radius and ulna, and between the tibia and fibula. They are found in individuals of all ages. The figure of these corpuscles is oval, somewhat like that of a grain of wheat—regularly oval in the cat, but mostly curved or reniform in man, and sometimes a good deal distorted. Their mean size in the adult is from $1\frac{1}{2}$ to $2\frac{1}{2}$ mm. long, and about half as broad. They have a whitish, opaline aspect: in the cat's mesentery they are usually more transparent, and then a white line may be distinguished in the centre. A slender stalk or peduncle attaches the corpuscle to the branch of nerve with which it is connected. The peduncle contains a single medullated nerve-fibre ensheathed in perineurium, with connective tissue and one or more fine blood-vessels; it joins the corpuscle at or near one end, and conducts the nerve-fibre into it. The corpuscle itself, examined under the microscope, is found to have a distinct lamellar structure (figs. 421, 422). It consists, in fact, of numerous concentric membranous tunics encasing each other like the coats of an onion. Surrounded by these tunics, and occupying a cylindrical space in the middle of the corpuscle, is the core, formed of transparent and seemingly homogeneous soft substance, along the middle of which the prolongation of the nerve-fibre runs. The number of tunics is various; from forty to sixty may be counted in large corpuscles. Those which are situated next to the core, and comprehending about half of the entire number, are thinner and more closely arranged than the exterior ones, seeming to form a system by themselves, which gives rise to a white streak often distinguishable along the middle of the corpuscles when seen on a dark ground. Outside of all, the corpuscle has a coating of ordinary connective tissue.

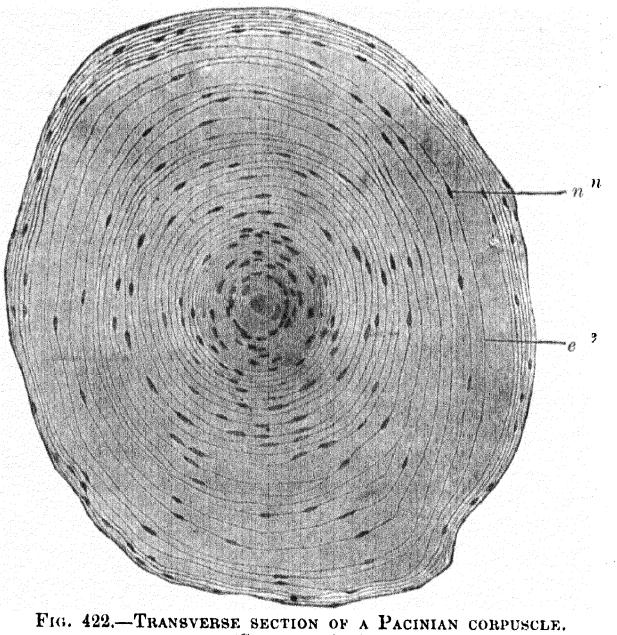


FIG. 422.—TRANSVERSE SECTION OF A PACINIAN CORPUSCLE. (Szymonowicz.)

e, one of the layers of epithelioid cells bounding the tunics; *n*, nucleus of an epithelioid cell. The axis-cylinder is seen in the centre; around this the core; then the closely arranged inner tunics; outside these and forming the greatest part of the thickness of the corpuscle, the more open outer tunics.

The lamellæ or tunics correspond very closely in structure to the lamellæ of the perineurium of a nerve. Each lamella (fig. 423) consists of a connective-tissue layer formed both of white fibres, which have mostly a transverse direction and are placed near its surfaces (*b*), and of elastic fibres, which pass in various directions, and (with occasional bands of white fibres) stretch across the thickness of the lamella from one surface to the other (*c*). Each surface of a lamella is covered with endothelial cells (*a*), which can be brought to view with nitrate of silver, and then their continuity with the similar cells in the perineurium is made manifest (fig. 424). The tissue of each lamella is lax as compared with that of the

layers of the perineurium, and the interstices between its fibres are occupied by a considerable quantity of lymph, and contain occasionally lymph-corpuscles. In the fresh state the delicate fibres of the lamellæ are difficult of observation, so that the adjacent layers of endothelial cells belonging to the successive lamellæ stand out sharply when the corpuscle is viewed in optical section, and these were long taken to represent the actual tunics of the organ. The layers are not everywhere in close juxtaposition, but are here and there separated from one another by interlamellar spaces which are occupied by lymph, and represent the lymphatic clefts between the layers of the perineurium of a nerve (p. 239).

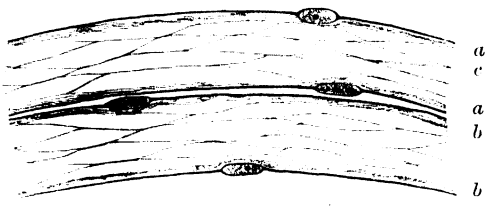


FIG. 423.—DIAGRAMMATIC REPRESENTATION OF TWO TUNICS OF A PACINIAN CORPUSCLE IN TRANSVERSE SECTION. (Schäfer.)

a, *a*, epithelioid layers; *b*, *b*, connective-tissue layer, more condensed near the surface; *c*, open network of fine elastic fibres in the substance of the lamella.

The nerve-fibre, the disposition of which may now be noticed, is conducted along the centre of the stalk, enters the corpuscle, and passes straight into the core, at the farther end of which it terminates. As shown by Pacini, the layers of the perineurium successively become continuous with, or rather expand into the tunics of the corpuscle. Since, however, in most Pacinian corpuscles there are many more tunics in the corpuscle than layers of the perineural sheath which invests the entering nerve, it is only a few of the tunics which are thus continuous; and it will be generally found that it is the outer ones which are so. A certain number of the inner tunics are superadded therefore, and when traced towards the nerve-fibres they may be seen to end with rounded margins bounding a canal in which the nerve-fibre runs. The latter is accompanied by a little endoneural connective tissue which generally contains a number of granular cells (fig. 425).

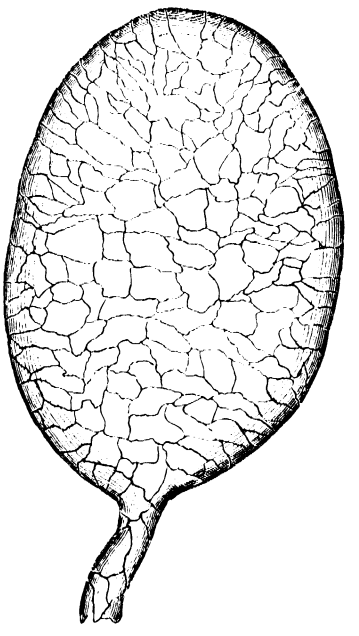


FIG. 424.—PACINIAN CORPUSCLE FROM THE MESENTERY OF THE CAT; STAINED WITH NITRATE OF SILVER. Magnified.

The epithelioid cells of the outermost tunic are shown, and their continuity, at the peduncle, with those of the corresponding layer of the perineurium. (From a drawing by G. C. Henderson.)

The nerve-fibre is single as it runs along the peduncle, unless when the latter supports two corpuscles; it retains the medullary sheath until it reaches the core, into which the axis-cylinder alone passes, freed from its neurolemma and medullary sheath. In its course through the core it is somewhat flattened, and presents the appearance either of a pale, finely striated, and very faintly outlined band or stripe, or of a darker and more sharply defined narrow line; differing thus in appearance according as its flat side or its edge is turned towards the eye. The contrast in the appearance of the fibre before and after entering the core is well exhibited after treatment with osmic acid, which stains the medullary sheath deeply, whereas the

axis-cylinder is far less stained. It sometimes happens that the fibre regains its double contour for a short space, and changes again before it terminates; this is especially liable to occur while it passes through a sharp flexure in a crooked core. The fibre usually ends by an enlargement at the farther extremity of the core, which is here itself somewhat dilated. The enlargement is formed by an expansion of the axis-cylinder, and is sometimes of considerable size. It may be of an irregular shape with processes branching outwards from the sides and ending in an arborescent manner in the core.[1] The axis-cylinder shows the usual longitudinal fibrillation as it passes through the core, and the fibrils become somewhat spread out as they pass into the terminal expansion, where they form a dense network [2] (fig. 426). In many

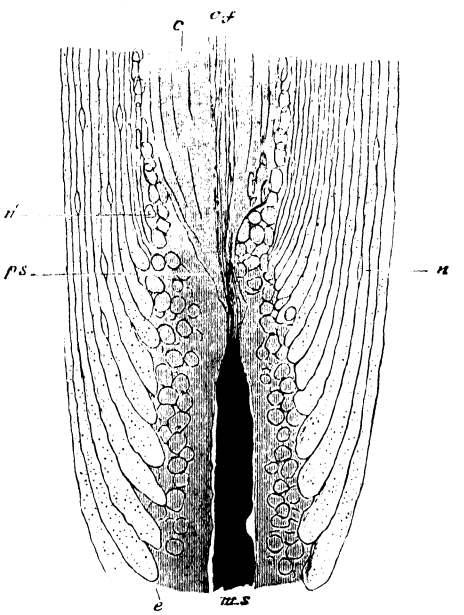


FIG. 425.—PART OF PACINIAN BODY, SHOWING THE NERVE-FIBRE ENTERING THE CORE. From an osmic-acid preparation. (Schäfer.)

ms, entering nerve-fibre, the medullary sheath of which is stained darkly, and ends abruptly at the core; *ps*, prolongation of primitive sheath, passing towards the outer part of the core; *c f*, axis-cylinder passing through the core as the central fibre; *e*, some of the inner tunics of the corpuscle, enlarged where they abut against the canal through which the nerve-fibre passes; *n*, nuclei of the tunics; *n'* nuclei of the endoneurium, continued by others in the outer part of the core.

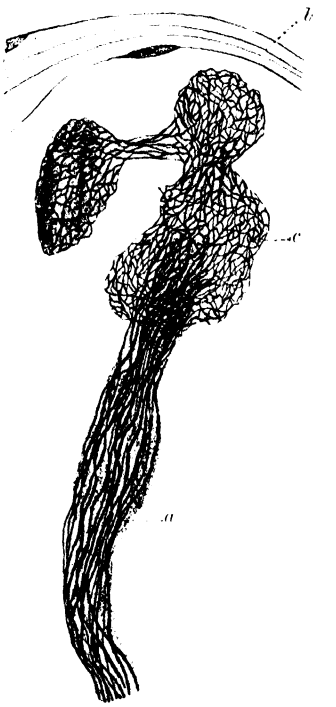


FIG. 426.—ENDING OF AXIAL FIBRE IN A PACINIAN CORPUSCLE FROM THE MESENTERY OF THE CAT, SHOWING THE NEUROFIBRILS. (Van de Velde.)

a, axis-cylinder; *c*, neuro-fibrillar network at its termination; *b*, some of the innermost tunics of the capsule.

cases the fibre, either immediately before terminating, or in its course through the core, divides into branches. In case of division of the fibre, the core is generally, but not invariably, divided in a corresponding measure, and the inner tunics present a figure in keeping with it. It is worthy of remark, that the nerve-fibre in its course along the core runs almost exactly in the axis of the latter, and it maintains this position even when passing through the abrupt flexures of an irregularly shaped core. It sometimes happens that a fibre passes quite through one corpuscle and terminates in a second, resuming its original size and dark outline while passing from the one to the other. A little artery enters the Pacinian body along with the

[1] Sala, Anat. Anz. xvi. 1900. [2] A. S. Dogiel, Anat. Anz. xxv. 1904; Van de Velde, *op. cit.*

nerve, and soon divides into capillary branches, which run up between the tunics. They then form loops, and return by a similar route into a vein corresponding to the artery: a single capillary usually accompanies the nerve as far as the core, and passes some way on the wall of the latter, sometimes with a spiral direction (Bowman). Occasionally a vessel enters the corpuscle at the distal end and passes towards the core, uniting the tunics in its passage.

Solokoff [1] describes a slender non-medullated fibre accompanying the medullated fibre, and ending over the surface of the core in an arborescent or reticular termination. A similar fibre has been described by A. S. Dogiel in the Herbst corpuscle.

The core is not structureless, as on superficial examination it seems to be, but exhibits in its outer part longitudinal striation and nuclei in variable number. In transverse section the striation in the outer part of the core is seen to be concentric, and is produced apparently by flattened nucleated cells, which are so arranged as to enclose the inner and more homogeneous portion. At the entrance of the nerve-fibre into the core the nucleated cells here spoken of are to all appearance continuous with cells in the endoneurium around the entering nerve-fibre, so that this outer part of the core, at least, may be regarded as formed by an expansion of endoneurium. The inner part, on the other hand—that, namely, which is in immediate contact with the axis-cylinder, appears structureless, but is developed as a mass of cells, the nuclei of which are seen at its periphery. The cells themselves seem to have become fused into a syncytium which envelops the terminating nerve-fibre.

TACTILE END-ORGANS OF BIRDS.

On account of the light which they throw upon the structure of the end-bulbs of mammals, a short description of certain tactile end-organs of birds may be given here.

Corpuscles of Grandry.—It was noticed by Grandry [2] that in the soft skin covering the bill of certain birds, such as the duck and goose, a peculiar form of end-organ exists consisting of two or more flattened cells, enclosed in a common capsule of connective tissue, and receiving between them the termination of an axis-cylinder (fig. 427). They are also found in great numbers in the mucous membrane of the duck's palate, along with the Herbst corpuscles to be immediately noticed.

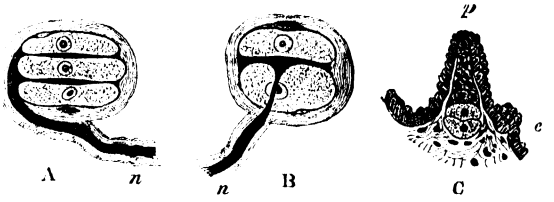


FIG. 427.—TACTILE CORPUSCLES FROM THE DUCK'S TONGUE. (Izquierdo.)

A, composed of three cells, with two interposed discs, into which the axis-cylinder of the nerve, *n*, is observed to pass; in B there is but one tactile disc enclosed between two tactile cells; C illustrates the development of a tactile corpuscle like the one shown in B; *e*, deeper cells of the epithelium covering the papillated surface of the tongue; *p*, apex of a papilla, in which there appears to be a downgrowth of epithelium-cells, the lowermost of which are becoming developed into tactile cells.

The cells which form a corpuscle of Grandry have the surfaces which are opposed to one another flattened or slightly hollowed. Their protoplasm is striated. There may be two only of these cells in a corpuscle of Grandry, or there may be three or four or even more, piled the one on the other. When numerous they may lose their regularity of arrangement. Occupying the interval between every two cells is a disc termed the 'tactile disc,' and according to the testimony of all observers the axis-cylinder of the entering nerve-fibre ends in these

[1] Anat. Anz. xvi. 1900.

[2] Journ. de l'anat. et de physiol. 1869.

tactile discs. The tactile cells and discs are enclosed in a common capsule of connective tissue continuous with the perineurium of the nerve. From the capsule incomplete septa pass inwards between the flattened cells, as far as the edges of the tactile discs so that the septa look as if they were perforated to receive the discs. Usually a single nerve-fibre passes to each corpuscle, and this may either lose its medullary sheath on entering the corpuscle or may retain it for some part of its course, although it eventually, in any case, becomes lost. The axis-cylinder, passing between the capsule and the tactile cells, divides into as many branches as there are tactile discs; in which, as already mentioned, it finally terminates. Within each tactile disc it breaks up into a large number of fibrils, which according to Dogiel penetrate into the adjacent cells. Dogiel also describes a second medullated fibre ending in a pericellular network within the capsule.[1]

When degeneration takes place as a result of the section of the nerve, the degenerative process extends not only to the tactile disc but also to the cells which cover it.

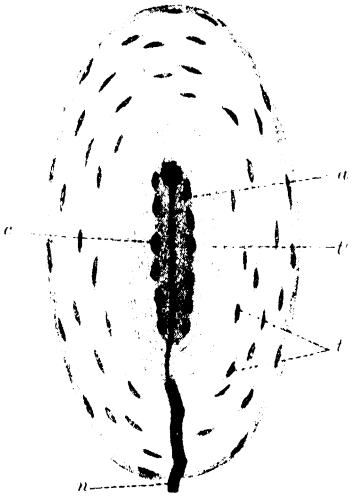


FIG. 428. — HERBST CORPUSCLE OF DUCK. (Sobotta.) Magnified 380 diameters.

n, medullated nerve-fibre; *a*, its axis-cylinder ending in enlargement at end of core; *c*, nuclei of core-cells; *t*, nuclei of outer tunics; *t'*, inner tunics.

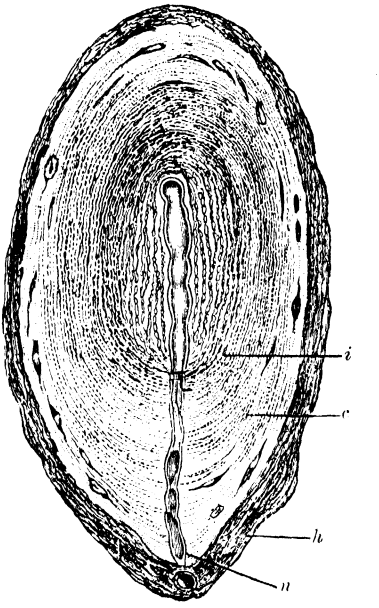


FIG. 429.—KEY-RETZIUS CORPUSCLE IN OPTICAL LONGITUDINAL SECTION. Bichromate preparation. (W. Krause.)

h, outer layer; *c*, *i*, concentric lamellæ of capsule; *n*, terminal nerve-fibre.

According to Izquierdo, these corpuscles are developed as a result of the multiplication and down-growth of some of the epithelium-cells which lie at the apex of a papilla (fig. 427, c). The growth becomes entirely cut off from the rest of the epithelium and surrounded by connective tissue, whilst the cells within it are converted into the flattened 'tactile cells,' and a prolongation of a nerve-fibre grows up into it. According to Szymonowicz,[2] the cells of both Grandry's and Herbst's corpuscles are of connective-tissue origin.

Corpuscles of Herbst (fig. 428).—These, which form the principal mode of nerve-termination in the bird's skin, and are also very abundant in the mucous membrane of the duck's palate, are in structure similar to large cylindrical end-bulbs. They have a core consisting of nucleated cells, which are disposed trans-

[1] A. S. Dogiel and Willanen, Zeitschr. f. wiss. Zool. lxvii. 1900; A. S. Dogiel, Arch. f. Anat. 1891, and Anat. Anz. xxviii. 1905. See also Geberg, Int. Monatschr. f. Anat. u. Physiol. x. 1893.

[2] Arch. f. mikr. Anat. xlvii. 1897.

versely, and through the middle of which the axis-cylinder passes, sometimes unbranched, sometimes branching once or twice. Each branch ends in an enlargement. The capsule is composed of an outer layer of longitudinal fibres, and an inner layer of strongly marked fibres of a brownish colour, running transversely or circularly. They most nearly resemble the innermost part of the Pacinian corpuscles—*i.e.* the core and the innermost lamella.

Certain corpuscles which are found in the bill of some water-birds exhibit so obviously a transition between the simple corpuscles of Herbst and the complex corpuscles of Pacini immediately to be described, that they may be especially mentioned here. These, which are sometimes named the *corpuscles of Key and Retzius* (fig. 429), differ from the corpuscles of Herbst in having a capsule composed of a large number of closely arranged lamellæ, similar to those of the inner or denser part of the Pacinian corpuscle, outside which is a single strong layer of longitudinally disposed fibrous tissue. The inner lamellæ are largely composed of circular or transverse fibres, but these lack the brownish tint of the fibres of the inner lamella of the Herbst corpuscle, nor do they exhibit the intra-lamellar fluid which is characteristic of most of the lamellæ of the Pacinian corpuscle.

Other modes of ending of afferent nerves.—Instead of ending in the special terminal corpuscles of different kinds which have been described in the preceding pages, many afferent nerves, as before stated, terminate in the form of fine ramifications of the axis-cylinder, which pass between the elements of the tissue to which the nerves are distributed. As they approach their termination the nerve-fibres, which are medullated, divide dichotomously again and again, retaining after all the earlier divisions both the medullary sheath and the neurolemma, and being accompanied by a prolongation of the sheath of Henle. Lower down this last-named sheath becomes lost, and a short distance farther on the medullary sheath and eventually also the neurolemma also disappear, the nerves being continued as axis-cylinders only; these can distinctly be seen in preparations stained with chloride of gold to be made up of fine varicose fibrils (fig. 430). At every division of the nerve some of these fibrils pass into each branch, and where, as often happens, the branches unite with one another to form a subterminal plexus, some of the fibrils pass across from one branch to another. By the time the terminal ramification is reached many of the branches may consist of ultimate fibrils (fig. 431). Whether these unite with one another so as to form an actual network is still doubtful.

FIG. 430.—DISTRIBUTION OF NERVES IN A PORTION OF THE CORNEA OF THE RABBIT. (Ranvier.)

The nerves are stained with chloride of gold. *p*, larger plexus of non-medullated fibres, made up of numerous fine fibrils; *a*, *a*, smaller fibres derived from them, and themselves giving off still smaller branches; *h*, varicose fibrils; *t*, junctional branches of the larger plexus.

A 'nervous network' is not to be confounded with a 'nervous plexus.' In the former an actual fusion of the fibres which result from repeated division of the nerves is assumed to take place, whereas in the latter, although there may appear to be an intimate union

between the different nerves which enter into the plexus, this union does not extend to the ultimate elements; in other words, although fibres or parts of fibres (fibrils) may be given and received by the several nerves to and from one another, these fibres (in the case of the larger plexuses) or fibrils (in the microscopic plexuses) remain completely distinct, although they

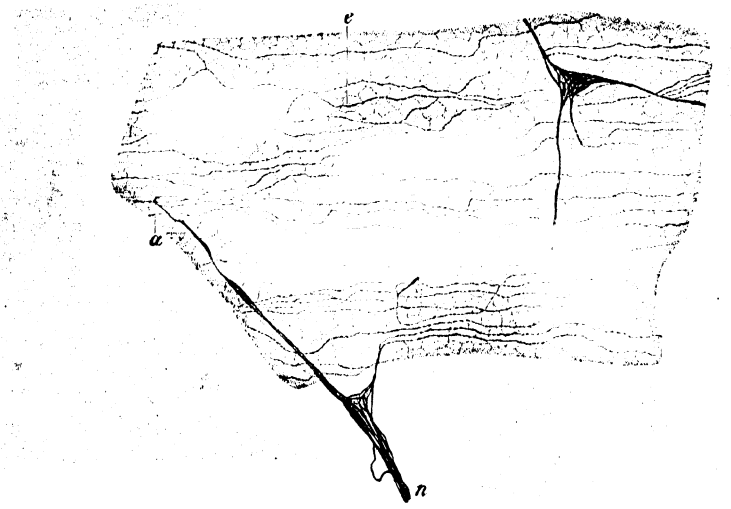


FIG. 431.—NERVE-FIBRILS PASSING TO THEIR TERMINATIONS IN THE EPITHELIUM COVERING THE CORNEA. (Ranvier.)

n, main branch of chief plexus; *a*, ending of secondary branch in a pencil of nerve-fibrils; *e*, intra-epithelial fibrils.

may run in close juxtaposition. Nervous plexuses are of very common occurrence, both those of the larger sort which have long been recognised by anatomists, and the smaller microscopic plexuses which are very often found near the endings, both of some centripetally conducting and of some centrifugally conducting nerves. Nervous networks are of less frequent occurrence,

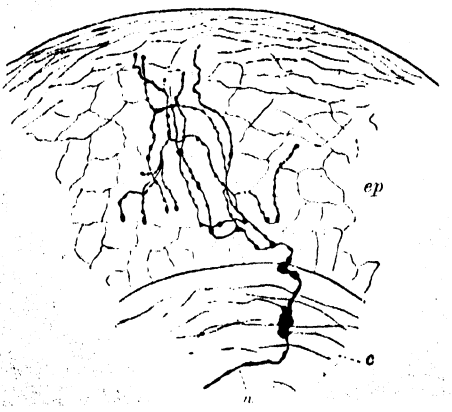


FIG. 432.—ENDING OF NERVE-FIBRILS IN A STRATIFIED EPITHELIUM (ŒSOPHAGUS OF RABBIT). (G. Retzius.)

n, nerve-fibre passing through corium, *c*, to terminate in a ramification of varicose fibrils in the epithelium, *ep*.

FIG. 433.—ENDING OF AN AFFERENT NERVE IN THE ENDOCARDIUM. (Dogiel.)

and indeed their existence has been doubted altogether by some histologists.[1] Recently, however, evidence has been accumulating in favour of the existence of a terminal network of neurofibrils from the same axis-cylinder, although networks formed by the union of branches of different axis-cylinders must still be considered as of doubtful occurrence.

[1] Compare Waldeyer, Ue. d. Endigungsweise der sensiblen Nerven: Archiv f. mikr. Anat. xvii. 367.

Nerve-endings of the above description are found in many parts of the body—*e.g.* the skin and mucous membranes, the cornea of the eye and serous membranes, and in intermuscular connective tissue. In the skin and mucous membranes the nerve-fibrils penetrate between the elements of the covering epithelium (fig. 432). In the cornea they may even reach the surface, but in the epidermis they are not

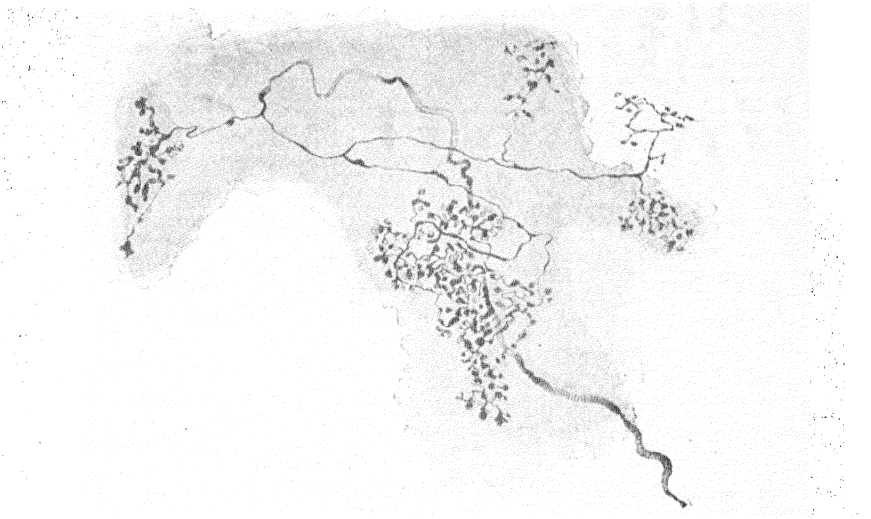


FIG. 434.—ENDING OF AFFERENT NERVE-FIBRES IN THE ENDOCARDIUM. (Dogiel.)

found beyond the limits of the Malpighian layer. The nerves destined for the epidermis and those for the end-bulbs of the skin are generally different, but occasionally a nerve-fibre passes through an end-bulb and then on to the epidermis. In serous membranes and in the endocardium, as well as in intermuscular septa, the terminal fibrils end in flattened expansions (figs. 433 to 436) which somewhat recall the appearances seen in the organs of Golgi (see pp. 278, 279).

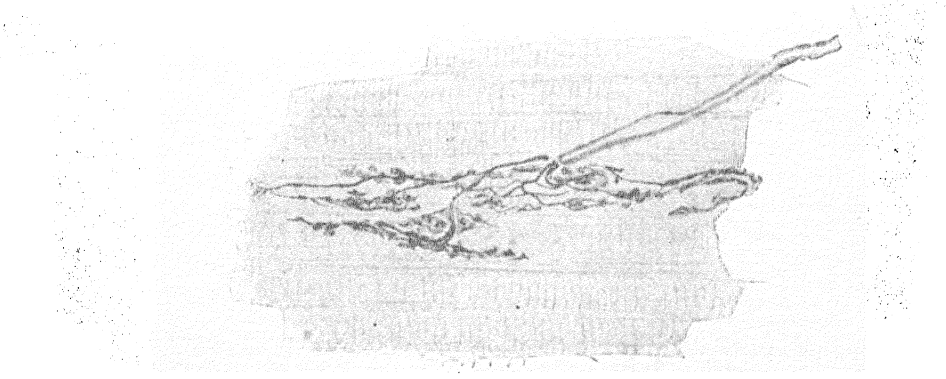


FIG. 435.—TERMINAL ARBORISATION FROM THE INTERMUSCULAR CONNECTIVE TISSUE OF THE RECTUS ABDOMINIS OF THE RABBIT. Methylene-blue preparation. (Dogiel.)

In the skin and mucous membranes the nerve-endings may exhibit a series of flattened leaf-like enlargements, presenting an appearance which has been compared by Ranvier to branches of ivy, and termed by him *hederiform nerve-endings*. Such occur in the most superficial layer of the derma in man, especially

in the immediate neighbourhood of the sweat-ducts (fig. 437), and in the mucous membrane of the tongue ; they may occur in these situations along with end-bulbs and other kinds of nerve-ending (fig. 438) ; and they are also found between the epithelial cells which constitute the outer root-sheath of certain of the hair-follicles of animals. In some other especially sensitive parts in animals the intra-

FIG. 436.—TERMINAL ARBORISATION FROM THE SUPERFICIAL LAYER OF THE PERITONEUM OF THE RABBIT. Methylene-blue preparation. (Dogiel.)

a, medullated fibre ; *b*, fibre connecting the arborisation with another one not here represented.

epithelial nerves are very numerous and exhibit a somewhat similar arrangement. This is the case in the epithelium covering the snout of the pig and some other mammals, where the branches of the axis-cylinders end in *tactile menisci* (fig. 439), which lie between some of the deeper cells (Ranvier). These menisci show a reticular structure (fig. 440). In the snout of the mole pencils of nerve-fibrils pass

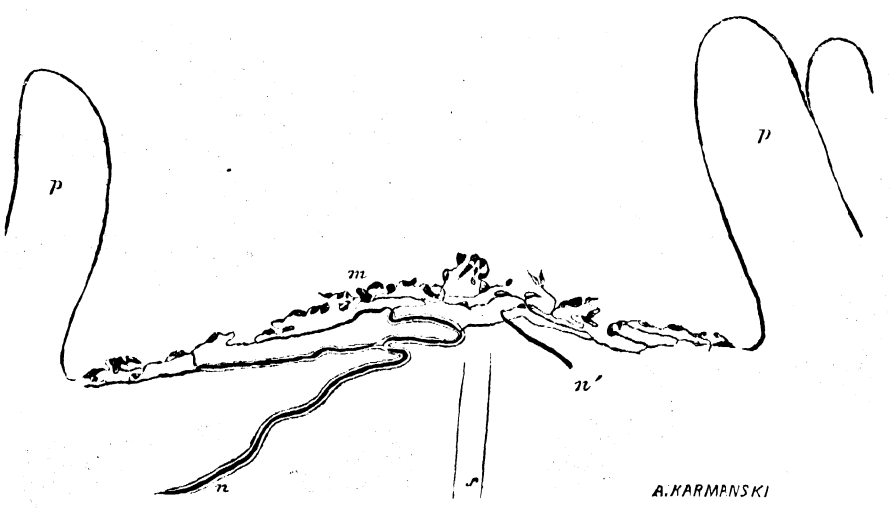


FIG. 437.—HEDERIFORM NERVE-ENDINGS IN THE CUTIS VERA. (Ranvier.)

n, *n'*, nerve-fibres; *m*, enlargements on terminal fibrils; *p*, papillæ; *s*, sweat-duct.

in great number vertically through the deeper layer of the epidermis to end freely beneath the horny stratum (Eimer).

Nerve-endings in a terminal ramification of fibrils are found in simple epithelia as well as in stratified. They have been described as passing between the cells of columnar epithelium and are also found ramifying amongst ciliated cells.[1] These

[1] A. Bethe, Arch. f. mikr. Anat. xliv. 1895. The nerve-endings in several mucous membranes have been described by G. Retzius (Biol. Unters.); in the mouth by E. Botezat (Anat. Anz. xxxi. 1907) and Ceccherelli, Int. Monatschr. f. Anat. u. Physiol. xxv. 1909. Botezat has also made a renewed study of the endings in the epidermis (Anat. Anz. xxxiii. 1908).

are doubtless of a sensory nature, for nerve excitation is not found to have any influence on the action of cilia.

Special modifications of the plexiform mode of ending of sensory nerves exist in various peripheral organs, amongst which the endings in tendons and muscles may be particularly described.

Nerve-endings in tendons.—Most of the nerve-endings in tendons seem referable to one or other of the end-organs which have already been described, although they present considerable modification of form. In some tendons end-bulbs like those in the conjunctiva are found, and small Pacinian corpuscles of simple structure occur occasionally in the areolar tissue sheaths of tendons and ligaments. But in many tendons, at their junction with the muscles, there occur, as was first shown by Golgi in 1878,[1] long spindle-shaped bodies composed of a number of tendinous bundles more or less fused, into which one or more medullated fibres pass. After dividing a certain number of times, their axis-cylinders spread themselves out between the smaller

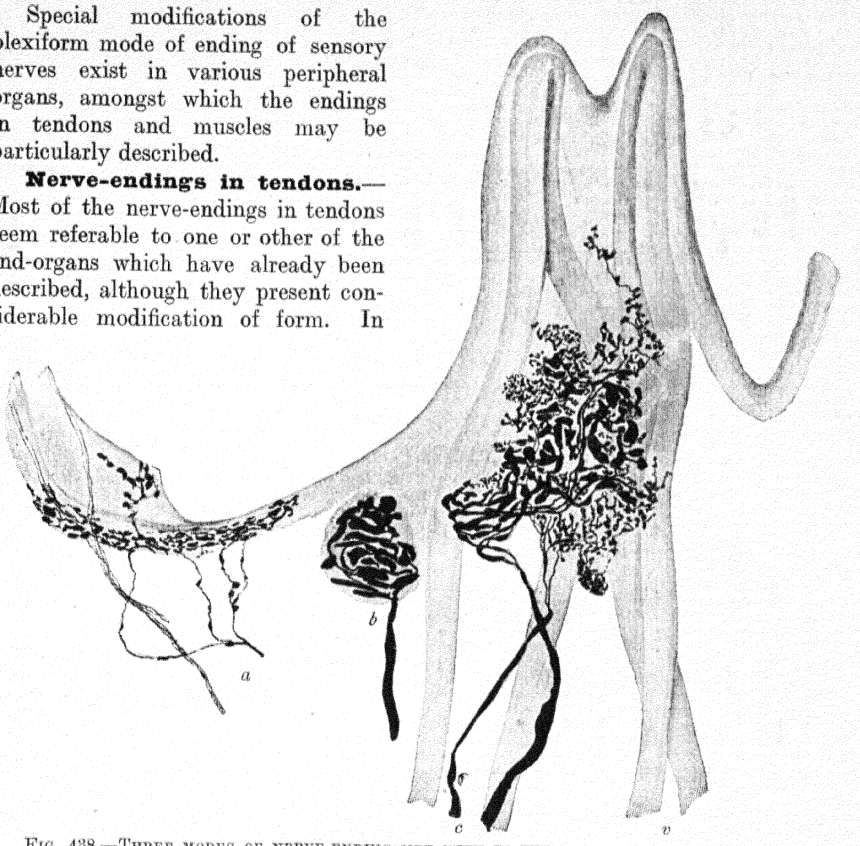


FIG. 438.—THREE MODES OF NERVE-ENDING MET WITH IN THE MUCOUS MEMBRANE OF THE TONGUE. Gold preparation. (Ceccherelli.)

a, nerve-fibre with hederiform ending; *b*, a fibre terminating in an end-bulb; *c*, nerve-fibres ending in close ramifications at the base of a double papilla; *v*, blood-vessels.

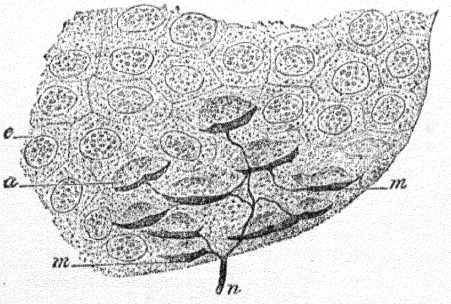


FIG 439.—ENDING OF NERVES IN TACTILE DISCS IN THE PIG'S SNOUT. (Ranvier.)

n, nerve-fibre; *m*, terminal menisci or tactile discs; *e*, ordinary epithelium-cell; *a*, altered epithelium-cell, to which the meniscus is applied.

[1] Gesammelte Unters. 1894; see also Ciaccio, Arch. ital. de biol. xiv. 1891.

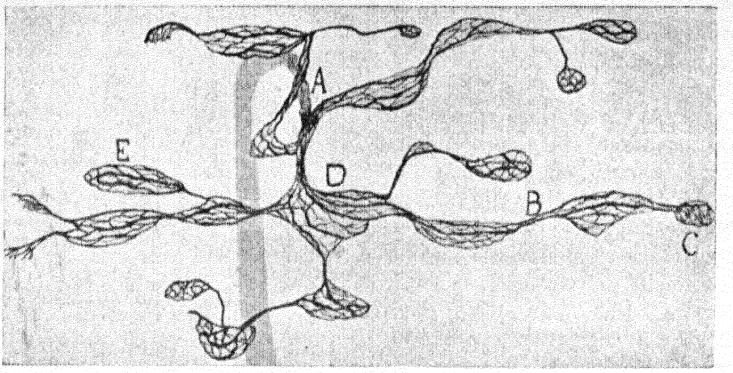


FIG. 440.—A NERVE-FIBRE ENDING IN TACTILE MENISCI. (Cajal.)
The neuro-fibrils are seen to form networks within the enlargements

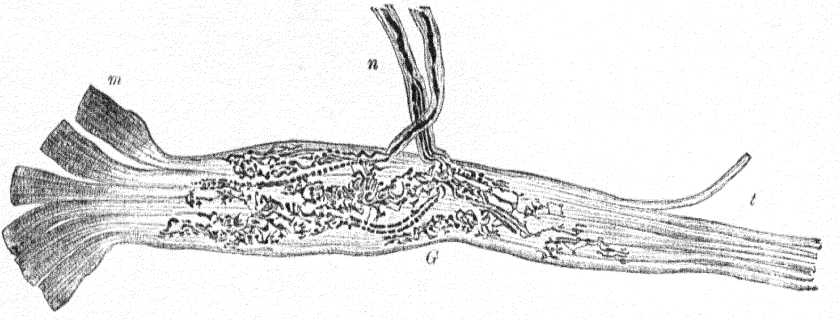


FIG. 441.—ORGAN OF GOLGI FROM THE HUMAN TENDO ACHILLIS. Chloride of gold preparation. (Ciaccio.)
m, muscular fibres; *t*, tendon-bundles; *G*, Golgi's organ with the axis-cylinder o the nerves, *n*, ramifying between the small connective-tissue bundles.

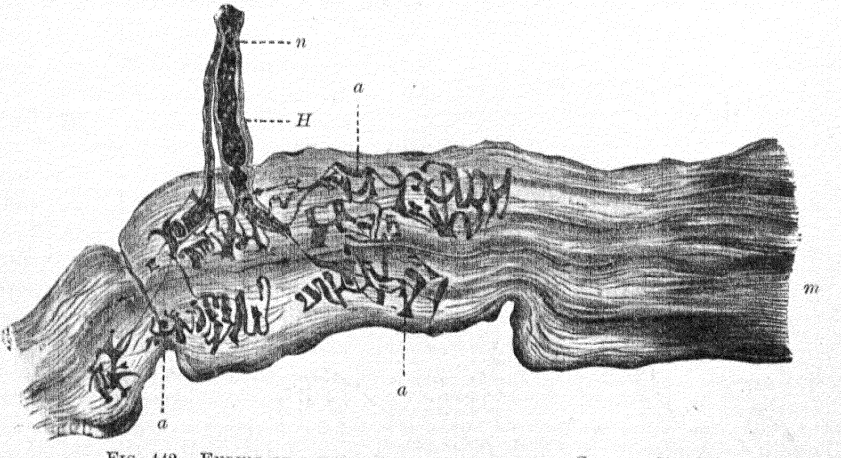
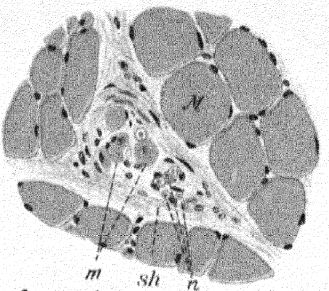
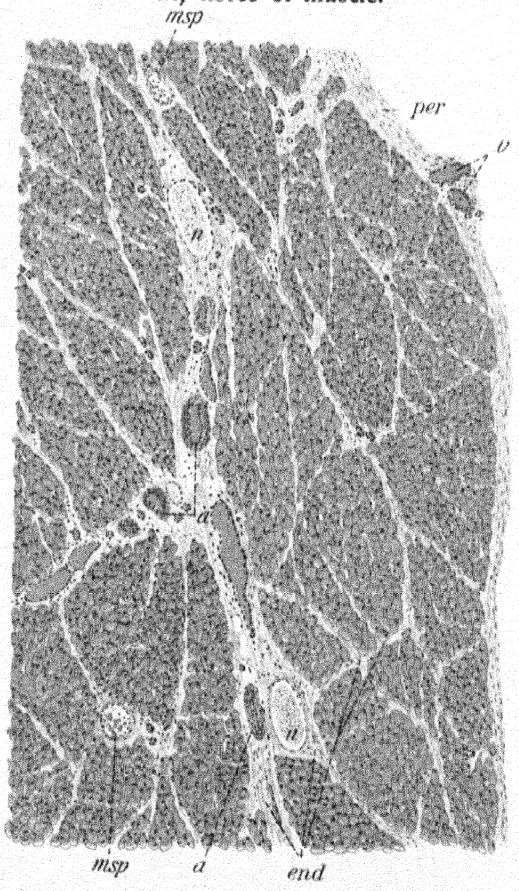


FIG. 442.—ENDING OF A NERVE-FIBRE IN AN ORGAN OF GOLGI. (Ciaccio.)
n, medullated nerve; *H*, its sheath of Henle; *a*, *a*, *a*, ramifications of its axis-cylinder between tendon-bundles; *m*, muscle-fibres.



Transverse section of muscle spindle, human (Sobotta). Magnified 40 diameters.

sh, sheath of spindle; *m*, muscle fibres of spindle; *n*, nerve-fibres of spindle; *M*, fibres of muscle.



Transverse section of omohyoid muscle, human, with blood-vessels injected (Sobotta). Haematoxylin-eosin.

msp, sections of two muscle-spindles in endomysium *(end.)*; *per*, perimysium; *a*, arteries; *v*, veins; *n*, nerves.

tendon-bundles, and collectively form a branched expansion which is not unlike that in which the sensory nerves to the muscles themselves end. The peculiar spindle-shaped thickening of the tendon which is thus provided with a rich nervous network is known as an *organ of Golgi* (figs. 441, 442). Various modifications of these have been described, but their fundamental structure appears to be the same in all vertebrates.

A. S. Dogiel[1] has shown that the nerve-endings in the organs of Golgi are fibrillar in structure, like those in the end-organs of the muscle itself.

Sensory nerve-endings in muscles: muscle-spindles. — In the voluntary muscles certain peculiar organs have long been known to occur amongst the ordinary fibres, consisting of a bundle of very fine cross-striated muscle-fibres enclosed in a loose capsule of connective tissue (see accompanying Plate and figs. 443 to 445). To these organs the name 'muscle-spindle' was attached, but their real meaning was until comparatively recent years a subject of conjecture. The histological researches of various authors, and particularly of Ruffini,[2] have however now completely elucidated the structure of the muscle-spindle. Ruffini showed that the nerves to the so-called 'intrafusal' muscle-fibres are not provided with the end-plates which are characteristic of motor-nerve endings, but terminate amongst the muscle-fibres of the spindle much in the same way that the nerve-fibres end between the tendon-bundles in the organs of Golgi. The positive proof that these nerve-fibres are afferent and not efferent was provided by Sherrington, who cut the ventral roots of the nerves of one of the limbs (in cat and monkey) and found that the intrafusal nerve-fibres did not participate in the Wallerian degeneration which affected all the motor nerves of the limb-muscles.

Muscle-spindles are, as their name implies, of a generally fusiform shape, larger

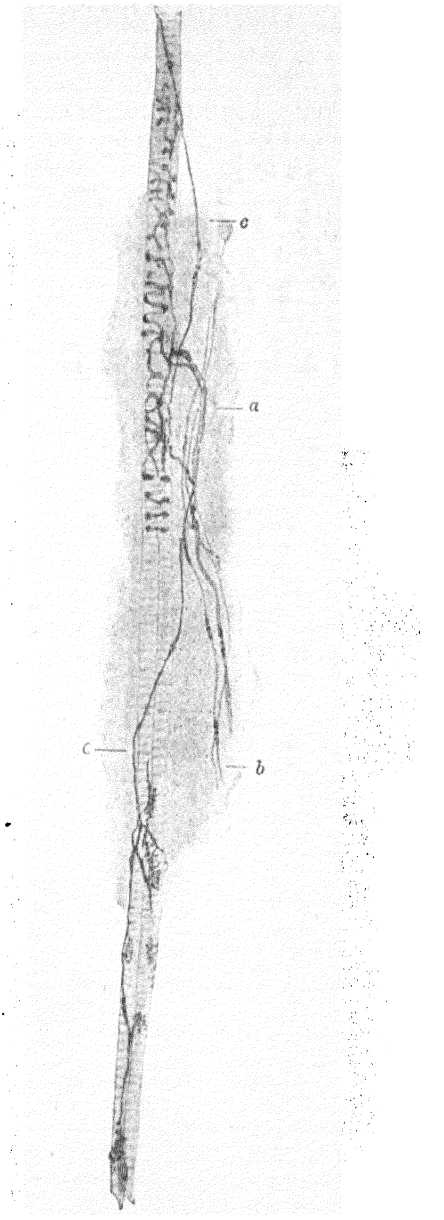


FIG. 443.—NERVE-ENDINGS UPON THE INTRAFUSAL MUSCLE-FIBRES OF A MUSCLE-SPINDLE OF THE RABBIT. Methylene-blue preparation. (Dogiel.) Moderately magnified.

a, large medullated fibre coming off from 'spindle' nerve and passing to end in an annulo-spiral termination on and between the intrafusal fibres; *b*, a fine medullated fibre coming off from the same stem and dividing. Its branches, *c*, pass towards the ends of the muscle-fibres and terminate in a number of small localised arborisations, like end-plates.

[1] Arch. f. mikr. Anat. lxvii. 1906.

[2] Arch. ital. de biol. xviii. 1893. See also Sherrington, Journ. Physiol. xvii. 1894; Sihler, Arch. f. mikr. Anat. xlvi. 1895; Huber and de Witt, Journ. Comp. Neur. vii. 1898; J. Baum, Anat. Hefte, xiii. 1900; A. S. Dogiel, Arch. f. mikr. Anat. lxviii. 1906.

in the middle and tapering to the ends. They vary greatly in number in different muscles, being fairly numerous in some, few in others, such as the eye-muscles, whilst in yet others their presence has not been detected. They are found in most if not in all vertebrates imbedded in the depths of the muscle-substance, and lying parallel with its fibres. They are more numerous in the limb-muscles than in those of the trunk, and in the distal than in the proximal part of the limb (Sherrington): most occur near the middle of a muscle.[1] They vary greatly in size, the extremes being from 0·75 mm. to 4 mm. in length and 0·08 mm. to 0·2 mm. in cross-section. Each is enclosed by a lamellated connective-tissue sheath, continuous externally with the intramuscular areolar tissue, and becoming somewhat looser towards the centre, where a lymphatic space (periaxial space) surrounds the muscle-fibres of the spindle: this space is bridged across by connective tissue here and there and by the entering nerve-fibres. Running through the axis of the spindle is the intrafusal bundle of muscle-fibres. These are much finer than the ordinary muscle-fibres, having, in fact, somewhat the appearance of embryonic muscle, and like this showing more numerous nuclei, especially near the middle of the spindle, and rather more protoplasm than the ordinary muscle-fibres. Moreover, each is found to split for the most part into two, at a short distance

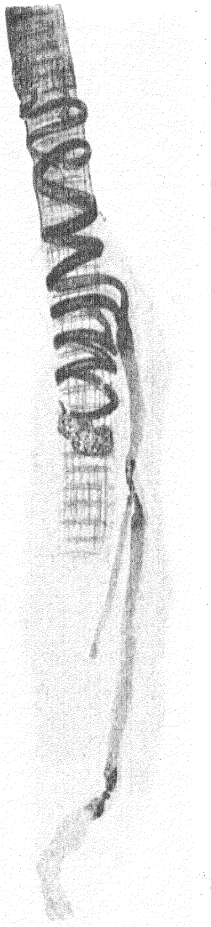


FIG. 444.—AN ANNULO-SPIRAL ENDING OF INTRAFUSAL FIBRE. Methylene-blue preparation. (Dogiel.) Highly magnified.

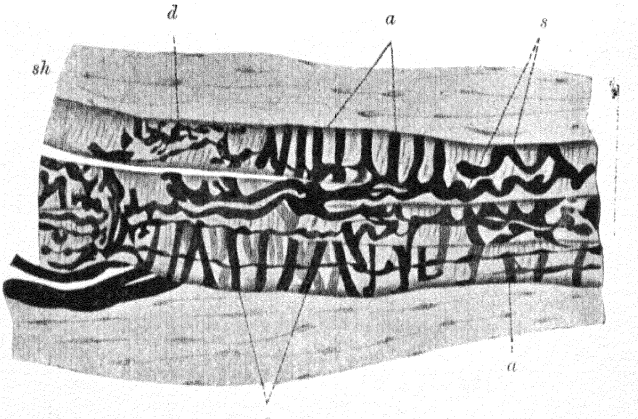


FIG. 445.—ENDING OF NERVE-FIBRES IN A MUSCLE-SPINDLE. (Ruffini.)

n, nerve-fibres passing to spindle; *a*, annular ending of axis-cylinders; *s*, spiral endings; *d*, dendritic endings; *sh*, connective-tissue sheath of spindle.

from the proximal end of the spindle, so that the middle and distal ends appear to contain more fibres than the proximal end. At these ends they pass into tendon-bundles, which are either continued into the intramuscular tissue or, if near the tendinous attachment of the muscle, into the tendon of the muscle itself.[2]

The nerve-fibres of the spindle are large medullated fibres, usually three or four in number (fig. 443). They divide on reaching the spindle and pass into the

[1] Gregor, Arch. f. Anat. 1904.

[2] These tendons frequently contain Golgi-organs (Sherrington).

intrafusal bundle, losing their medullary sheaths and being prolonged as axis-cylinders only, which run in an annular or spiral manner as flattened fibres around the muscle-fibres of the bundle, terminating with free, sometimes slightly enlarged, endings between the muscle-fibres (*annulo-spiral endings*) (figs. 444, 445). But they do not all terminate in this way, for some of the branches of the nerve-fibres are much finer than the rest, and these pass nearly straight along the muscle-fibres and terminate in an arborisation, the terminal twigs of which are applied to the surface of the muscle-fibre by means of finely branched localised expansions (*flower-spray endings*, fig. 443), not very unlike the 'end-plate' expansions of some motor-nerve endings. It is not, however, to be inferred from this that these represent motor-nerve fibres, for it would appear that they have their origin in common with the fibres of the annulo-spiral endings. Motor nerves and endings have also been described in the intrafusal muscle-fibres, but their presence here is somewhat doubtful.

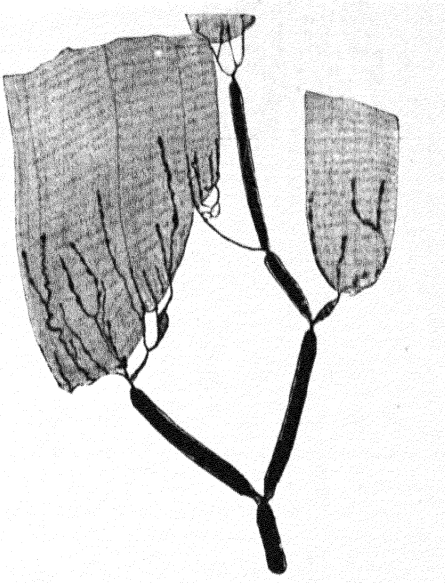


FIG. 446.—AN AFFERENT NERVE-FIBRE TERMINATING IN ARBORISATIONS AROUND THE TENDINOUS ENDS OF SEVERAL MUSCLE-FIBRES (TOAD). (Ceccherelli.)

It sometimes happens that two or three muscle-spindles are enclosed in a common sheath.

The nerves to the muscle-spindles are not the only sensory nerves of muscle. Giacomini,[1] Ceccherelli,[2] and A. S. Dogiel[3] have described in some animals fine fibrils (derived from branching medullated nerve-fibres) which form an arborescent investment to the ends of the muscle-fibres, close to their tendinous attachment (fig. 446). Similar ramifications occur in the tendon itself, close to the muscle; small Pacinian corpuscles are also found in this situation. All of these, as well as the organs of Golgi in the tendon-bundles, doubtless aid in ministering to the 'muscular sense,' although this is generally regarded as being mainly the function of the muscle-spindles.

ENDING OF NERVES IN ORGANS OF SPECIAL SENSE.

The special-sense organs show two main types of connexion of the sensory surface with the central nervous system (figs. 447, 448). One of these is in the main similar to the mode which has already been described in connexion with those sensory nerves of the skin which are distributed between the cells of the epidermis. Here the cell-body of the neurone is situated in a ganglion upon the nerve-root, and the nerve-cell-body from which the sensory nerve springs is in all cases originally bipolar, with two axons, one passing peripherally to ramify between the cells of the sensory surface and the other passing centrally to ramify in the grey matter of the adjoining part of the central nervous system, whether spinal cord, medulla oblongata, or pons. The gustatory and the auditory nerves conform to this type. In the other type, the nucleated cell-body of the sensory or recipient neurone is itself situated at the periphery between the cells of the sensory surface and sends its axon centrally towards the central nervous system, there to end by

[1] Monit. zool. ital. ix. 1898. [2] Anat. Anz. xxiv. 1904. [3] Arch. f. mikr. Anat. lxviii. 1906.

ramifying in the grey matter. The peripheral process is a part of the cell-body modified to receive the particular form of sensory impression which the sense-organ is adapted to convert into a nervous impulse. To this type the olfactory and visual sense-organs conform.

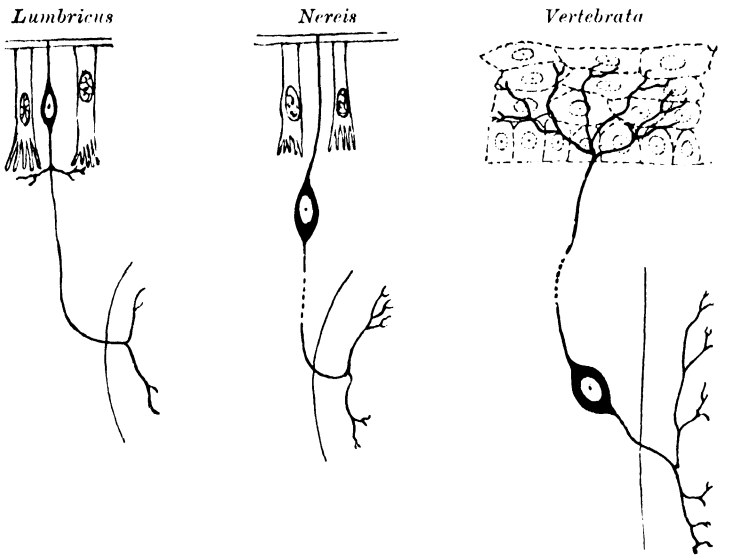


Fig. 447.—Diagrams showing the position of the sensory nerve-cell in Lumbricus, Nereis, and Vertebrata. (G. Retzius.)

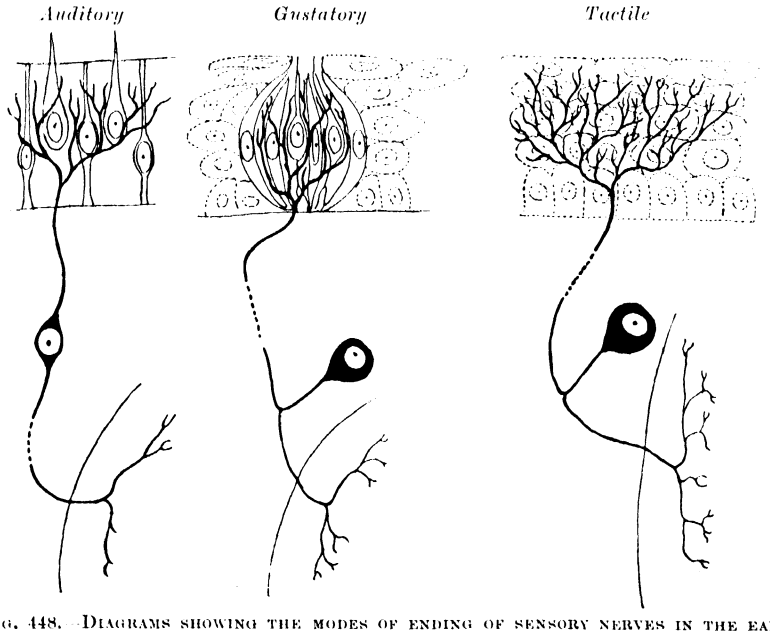


Fig. 448.—Diagrams showing the modes of ending of sensory nerves in the ear, taste-buds, and epidermis respectively. (G. Retzius.)

That the latter type is the more primitive is shown by the fact that it is met with in the lowest examples of Metazoa in which definite sensory nerves can be shown to exist. This is exemplified in the sensory organs (' eye-spots ') of medusæ,

and also in annelids such as Lumbricus, in which all the sensory cells of the integument lie amongst the ordinary epidermis-cells (fig. 447), with a short rod-like process extending towards the free surface and a relatively long nerve-fibre process (axon) passing into the gangliated cord which represents the central nervous system, and there ending in extended ramifications. In worms, such as Nereis, somewhat higher in the scale than the earthworm (fig. 447) the nucleated body of the sensory nerve-cell lies already below, *i.e.* deeper than the epidermis-cells, and its peripheral process is elongated to form a fibre which is inserted between those cells. It is only in vertebrates that the recipient sensory neurones for the general integument have their cell-bodies grouped into special ganglia lying close to the central nervous system.

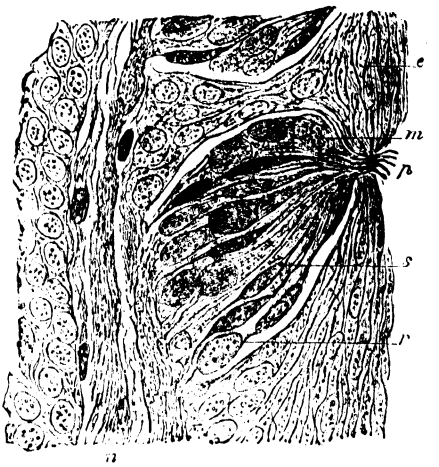


FIG. 449.—SECTION OF A TASTE-BUD OF THE RABBIT. (Ranvier.)

p, gustatory pore with hairlets; *r*, a sustentacular cell; *s*, a gustatory cell; *m*, a granular leucocyte; *n*, nerve-fibres; *e*, stratified epithelium.

Mode of ending of gustatory nerves.—The nerves which minister to the sense of taste terminate by arborisation amongst certain specially modified epithelium-cells in the lining membrane (mucous membrane) of the mouth and fauces. These specially modified cells are collected into bud-like masses (*taste-buds*) (fig. 449) which lie in and entirely fill cavities within the thickness of the stratified epithelium covering the mucous membrane. These cavities communicate with the interior of the mouth by a small aperture termed the 'gustatory pore,' and into this project minute rod-like processes from certain cells of the taste-bud which are known as the *gustatory cells*, and which mainly occupy the central part of the taste-bud, whilst the more superficial part is composed entirely of long tapered cells, somewhat flattened conformably to the external surface of the taste-bud, and termed the *covering* or *sustentacular cells*.

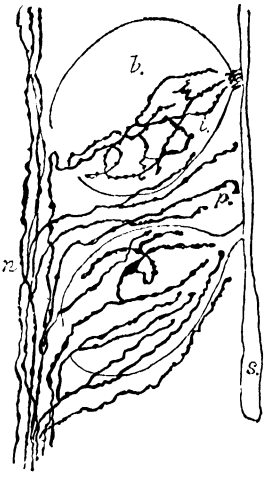


FIG. 450.—ENDING OF NERVE-FIBRES IN AND AROUND TWO TASTE-BUDS OF RABBIT. Golgi preparation. (G. Retzius.)

n, nerve-bundle; *b*, a taste-bud (the cells are not represented); *i*, ending of nerve-fibrils within taste-bud; *p*, ending of fibrils in epithelium adjacent to taste-bud; *s*, sulcus, on the sides of which the taste-buds are set.

The gustatory cells are long narrow cells with a prominent nucleus near the centre, a straight or slightly curved unbranched peripheral process terminating in the small rod just mentioned, and a fine centrally directed process which is often branched and which reaches the base of the taste-bud. It was at one time believed to be in continuity with the nerve-fibres of the taste-bud, but this is not the case. These nerve-fibres—which are mainly derived from the glosso-pharyngeal nerve, but some of which come from the chorda tympani of the facial and perhaps others from the fifth nerve—originate in ganglion-cells (like those of

the spinal ganglia) which are situated in the roots of the nerves just referred to, and they end peripherally, after losing their sheaths at the base of the taste-bud, by a fibrillar arborescence which lies amongst the gustatory cells (fig. 450). The centrally directed axon passes along the nerve-root to terminate in the grey matter of the pons. Taste-buds are found most abundantly in the tongue at the sides of the circumvallate papillæ and in the neighbourhood of these papillæ, but also in other parts of that organ, as well as on the under surface of the soft palate and on the posterior surface of the epiglottis. In the rabbit large numbers of taste-buds are found in the *papilla foliata* which lies on either side of the base of the tongue, and it is here that they are most easily studied.

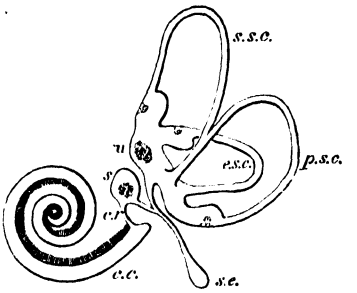


FIG. 451.—PLAN OF THE MEMBRANOUS LABYRINTH, SHOWING BY SHADING THE PLACES WHERE THE NERVE-FIBRES ARE DISTRIBUTED. (Schäfer.)

u, utricle with its macula; *s.s.c.*, *e.s.c.*, and *p.s.c.*, superior, external, and posterior semicircular canals, each with an ampulla; *s*, saccule; *s.e.*, saccus endolymphaticus; *c.r.*, canalis reuniens; *c.c.*, canal of cochlea.

Mode of ending of nerves in the organ of hearing. — In the two parts of the internal ear—viz. the cochlea and the vestibule, with its semicircular canals, the mode of ending of the nerve-fibres is, on the whole, similar to that described for the gustatory organ, the fibres terminating by a fibrillar arborescence between and around certain specially modified epithelium-cells.

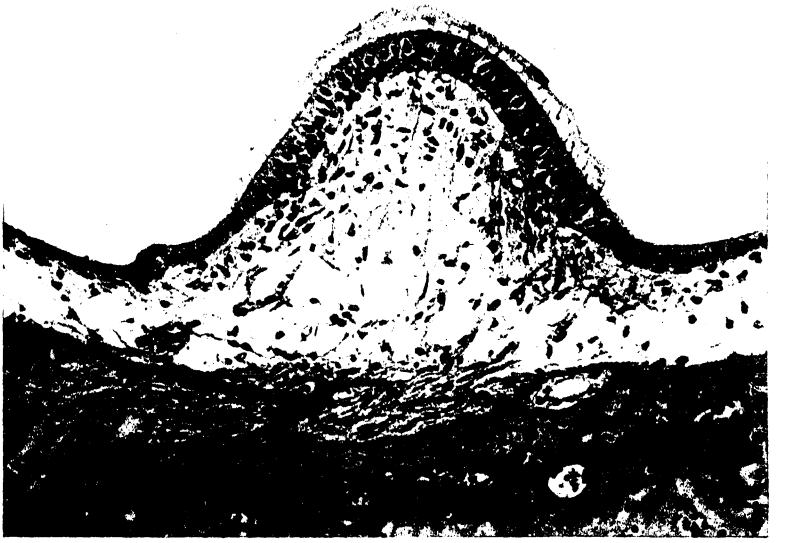


FIG. 452.—PHOTOGRAPH OF A SECTION THROUGH THE CRISTA OF AN AMPULLA OF THE GUINEA-PIG. (From a preparation by H. Pringle.)

In the lowest part of the section bundles of nerve-fibres are seen passing through the bone and turning up into the loose tissue below the crista. The epithelium-cells of the crista are pear-shaped, and are surmounted by hairlets which project into a mucinous material.

In the **vestibule (utricle and saccule)** and in the **ampullæ of the semicircular canals** there are certain patches (fig. 451) in the interior of the membranous labyrinth over which the somewhat flattened and simple

epithelium which elsewhere lines the membranous labyrinth undergoes a remarkable modification into columnar cells (fig. 452), each of which is terminated by a stiff-looking tapered hair-like process which projects into the endolymph which fills the membranous labyrinth. In the utricle and saccule these 'hairs' abut against a mucus-like mass containing numerous crystals of carbonate of lime (*otoliths*); in the ampullæ of the semicircular canals, where the macula takes the form of a crest-like projection into the interior, there are no otoliths, but a mucus-like mass is recognisable in the form of the so-called *cupula*. Between the hair-cells are other *sustentacular* or *fibre-cells* which extend through the thickness of the epithelium and form, at the free surface, a kind of cuticular membrane through which the 'hairs' of the hair-cells project. The nerve-fibres are derived from bipolar cells situated in a ganglion of the nerve-root (*ganglion of Scarpa*). The peripheral processes of these cells pass as medullated nerve-fibres to the maculæ, and here they lose their medullary sheath and end in a fibrillar arborescence amongst the hair-cells (fig. 453). The central processes of the bipolar cells (fig. 448) enter the grey matter of the medulla

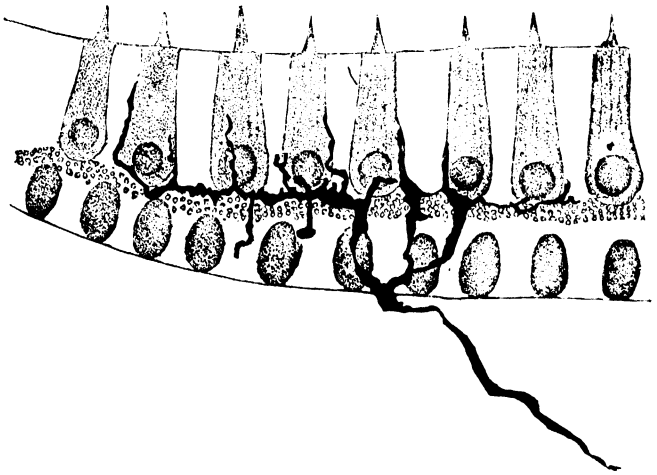


FIG. 453.—ENDING OF A NERVE-FIBRE AMONGST THE PEAR-SHAPED CELLS OF MACULA. Golgi method. (v. Lenhossék.)

oblongata as fibres of the vestibular division of the eighth nerve and terminate in its sensory nuclei.[1]

In the **cochlea** the epithelium, which is modified to receive the endings of the auditory nerve-fibres, forms part of the so-called *organ of Corti* (fig. 455). As in the vestibule, the membranous canal or duct of the cochlea, which is triangular in section, is lined by flattened epithelium-cells except at one part, the base of the triangle, where a fibrous membrane, the *basilar membrane*, stretches across the tube of the cochlea from the *spiral lamina* to the outer wall, and separates the endolymph of the duct of the cochlea from the perilymph of the scala tympani. The cells which form the organ of Corti rest on this membrane, and are covered by a soft pad-like projection from the thickened edge (limbus) of the spiral lamina: this projection is the *membrana tectoria*. Beneath its attachment the cells of the organ of Corti are continued as a pavement-epithelium over the limbus, and on the surface of a thin membrane (*membrane of Reissner*), which separates the endolymph of the membranous canal or duct of the cochlea from the perilymph of the scala vestibuli, and is stretched between the limbus and the outer wall of the cochlear

[1] See Neurology, p. 147, by Schäfer and Symington (Vol. III. Part I. of this work).

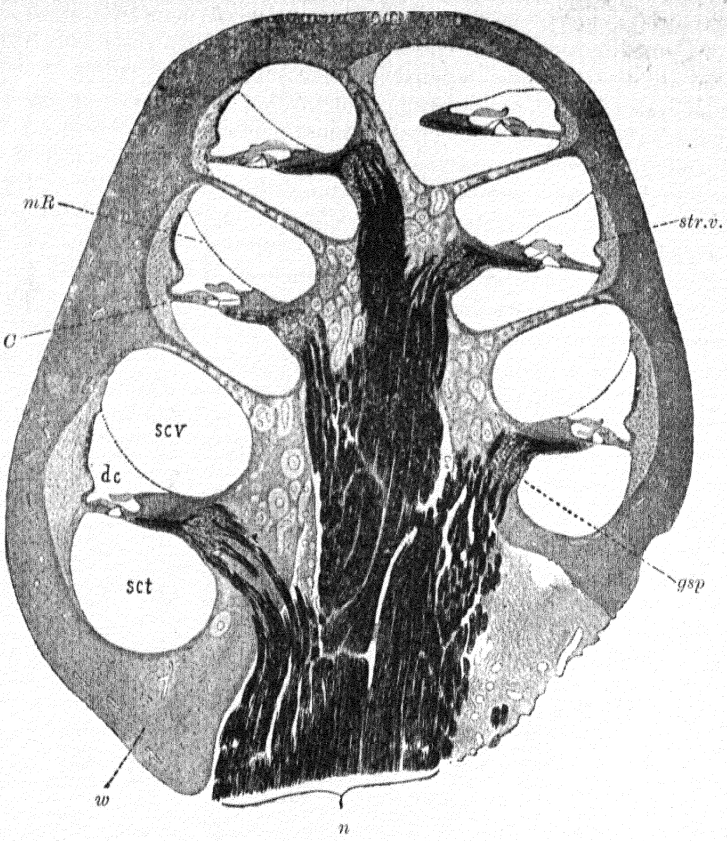


FIG. 454.—SECTION THROUGH THE COCHLEA OF THE CAT. (Sobotta.) ×25.

dc, duct of cochlea; *scv*, scala vestibuli; *sct*, scala tympani; *w*, bony wall of cochlea; *C*, organ of Corti on membrana basilaris; *mR*, membrane of Reissner; *n*, nerve-fibres of cochlear nerve; *gsp*, ganglion spirale; *str.v.*, stria vascularis.

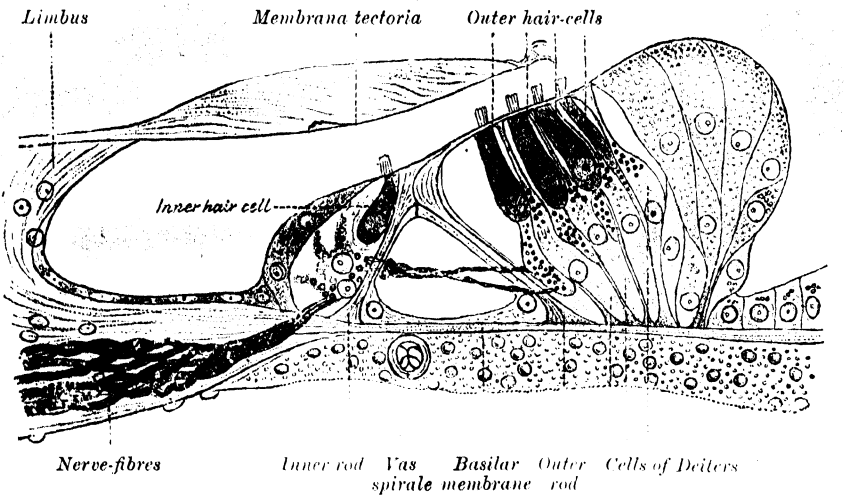


FIG. 455.—SECTION THROUGH THE ORGAN OF CORTI OF THE MIDDLE TURN OF THE HUMAN COCHLEA. (G. Retzius.)

tube. Finally this outer wall is lined internally by flattened or cubical cells which probably serve mainly to secrete the endolymph: at one part (*stria vascularis*) this epithelium of the outer wall is vascular and pigmented.

The organ of Corti is formed of (1) *sense epithelium-cells*, the so-called *hair-cells*; (2) *sustentacular cells* (*rods of Corti* and *cells of Deiters*); (3) the *membrana tectoria* already referred to; (4) a *reticular membrane* which overlies the hair-cells and is connected with the sustentacular cells; (5) the *endings of the auditory nerve fibres*.

The *hair-cells* (fig. 455) form in all four or five rows arranged in two series: one series (inner hair-cells) forms a single row near the spiral lamina, and the other series (outer hair-cells) forms three or four rows outside the rods of Corti. The hair-cells of the organ of Corti are somewhat similar to those of the maculæ of the vestibule, but the auditory hairs are comparatively short and stumpy, and are collected into a small group at the free surface of each hair-cell. The body of the hair-cell is columnar, being rounded below; this part, which contains the nucleus, is in contact with the terminal arborisations of the nerve-fibres. Separating the inner and outer series of hair-cells are the *rods of Corti*, which form a double row (*inner* and *outer*) of highly modified and peculiar-shaped cells, standing stiffly with an inclination towards one another upon the basilar membrane and having the reticular membrane attached to their free ends (heads). Lying between the outer hair-cells are the *cells of Deiters* which also extend stiffly from the basilar membrane to the reticular membrane, so that these stiff structures form a sort of framework to uphold and protect the more delicate hair-cells and nerve-fibres. Beyond the outer hair-cells the epithelium of the organ of Corti takes the form at first of columnar, then of cubical cells, which last are continued along the basilar membrane to the outer wall of the cochlea. The cells which are next to the inner hair-cells also become gradually shorter towards the limbus and pass into the ordinary lining cells of the membranous labyrinth. The *reticular membrane* is, as its name implies, a netlike cuticular thickening which is connected with the free ends of the rods of Corti and cells of Deiters, and has apertures through which project the 'hairs' of the hair-cells; these hairs abut against the under surface of the soft fibrous and pad-like *tectorial membrane*.

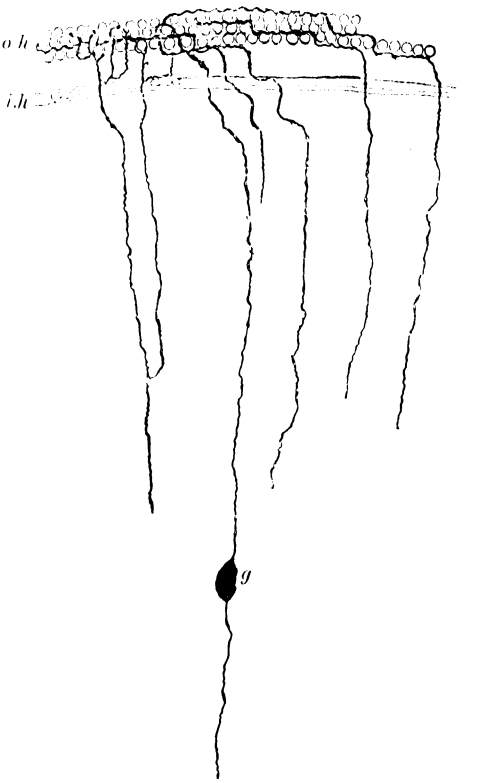


FIG. 456.—ENDING OF NERVE-FIBRES AMONGST THE HAIR-CELLS OF THE COCHLEA. Golgi preparation. (G. Retzius.)

g, cell of spiral ganglion; *i.h*, inner, *o.h*, outer hair-cells.

The *nerve-fibres of the cochlea* are derived from bipolar cells (fig. 456), forming a continuous spirally-arranged ganglion (*spiral ganglion, ganglion cochleæ*) at the

base of the spiral lamina (fig. 454). They pass through channels in the bony substance of the spiral lamina and enter the organ of Corti below the inner hair-cells. Some of them end amongst these, others pass across the arch or tunnel formed by the rods of Corti, and end amongst the outer hair-cells. In both cases the ending is a fibrillar arborescence of the axis-cylinders, the sheaths ceasing on entering the organ of Corti. The central axons of the bipolar cells of the spiral ganglion pass into channels within the central bony axis (*columella*) of the cochlea, and from these they are collected to form the cochlear division of the auditory nerve, which passes along with the vestibular division within the internal auditory meatus to enter the lateral aspect of the upper part of the medulla oblongata at its junction with the pons (see p. 302, and Neurology, p. 149).

Ending of the olfactory nerves.—The olfactory organ shows the primitive type of ending of special-sense nerves in its least altered condition. Here the cells which receive the sensory impression and which transmit the consequent nervous impulses to the central nervous system are situated at the periphery between the ordinary epithelium-cells of the olfactory mucous membrane. This membrane, which in primates and some other mammals (anosmatics) occupies only a comparatively small area at the uppermost part of the nasal passages, is much

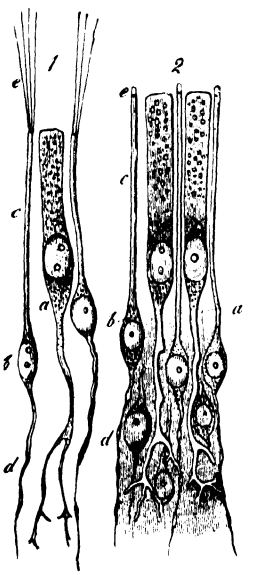


FIG. 457.—CELLS OF OLFACTORY MUCOUS MEMBRANE. (M. Schultze.)

1, From the frog; 2, from man.

a, sustentacular cell; *b*, olfactory cell; *c*, its peripheral process; *d*, its nerve-fibre process; *e*, hairlets.

FIG. 458.—AN OLFACTORY CELL, HUMAN. (v. Brunn.)

b, cell-body; *p*, peripheral process ending at *c* in hairlets, *h*; *n*, nerve-fibre process.

more extensive in most mammals (osmatics), in which a large part of the highly convoluted turbinate bones is covered by it. The epithelium of the membrane consists partly of columnar *sustentacular cells* (fig. 457, *a*), branched at the fixed end and terminating at the free end by a cuticular margin, partly of special *olfactory cells* (figs. 457 and 458, *b*) which lie between and are supported by the columnar cells, and which at their fixed or central end are continuous, in the form of delicate axons, with nerve-fibres (olfactory nerve-fibres). These pierce the cribriform plate of the ethmoid bone and enter the dilated extremity (*bulb*) of the *olfactory*

lobe. The free or peripheral end of each olfactory cell, *i.e.* the part which extends from the nucleated enlargement towards the surface, is a straight somewhat attenuated process which is terminated either by a single short filiform or hair-like projection (*olfactory hair*) or by a bunch of such 'hairs.' The nuclei of the olfactory cells occur at different levels in the thickness of the epithelium, so that the peripheral parts of the cells are of very varying length. The olfactory cells have a superficial resemblance to the gustatory cells, but differ from the latter in the fact that the central process becomes an actual sensory nerve-fibre which enters the central nervous system. Beneath the olfactory epithelium is a thick layer of serous glands (*glands of Bowman*) which pour out their secretion by ducts which open on the surface.

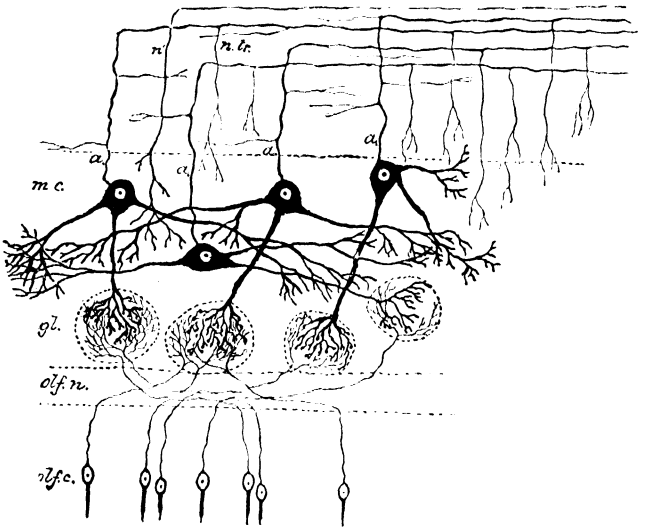


FIG. 459.—DIAGRAM OF CONNEXION OF OLFACTORY NERVES WITH CELLS IN OLFACTORY BULB. (Schäfer.)

olf.c., olfactory cells of nasal mucous membrane; *olf.n.*, nerve-fibres derived from these cells; *gl.*, olfactory glomeruli with synapses between the olfactory nerve-fibres, and dendrons of the mitral cells, *m.c.*; *a*, axons of mitral cells passing into the olfactory tract as nerve-fibres, *n.tr.*: these fibres give off collaterals to the olfactory bulb; *n'*, afferent nerve-fibre, ending in olfactory bulb.

It is clear that the olfactory cells are sensory neurones in the same sense as are the sensory cells of the integument of annelids. Their axons, as we have seen, enter the olfactory bulb, which is an extension of the brain; within this they form synapses with processes (dendrons) of certain of its nerve-cells (*mitral cells*), and these again send their axons by the *olfactory tract* towards the more central portions of the brain (fig. 459). The synapses in question are contained within small globular portions of grey matter, termed the *olfactory glomeruli.* The axons of the olfactory cells (fibres of the olfactory nerves) remain non-medullated throughout their course, although they possess a delicate nucleated sheath. The absence of medullary sheath furnishes an additional indication that these neurones have retained more than any other sensory nerve-cells the primitive condition.

Mode of ending of the visual (optic) nerve-fibres.—The retina or nervous tunic of the eyeball, which contains, besides various other kinds of nerve-cell, those neurones which receive impressions of light and which transmit the consequent nervous impulses towards the brain, is, as the study of its structure

and development abundantly shows, an extension, towards the periphery, of the lateral wall of the primitive brain (fore-brain). It is itself composed mainly of nervous matter, and most of its cells are unmistakable nerve-cells. The retinal elements are arranged in four series, viz.: (1) a layer of *pigmented epithelium-cells.* The protoplasm of these on the inner side, *i.e.* the side next to the following series (rods and cones), is loaded with pigment-granules (fig. 460, *a*). (2) A layer of palisade-like neurones which are termed, from the appearance of their peripheral

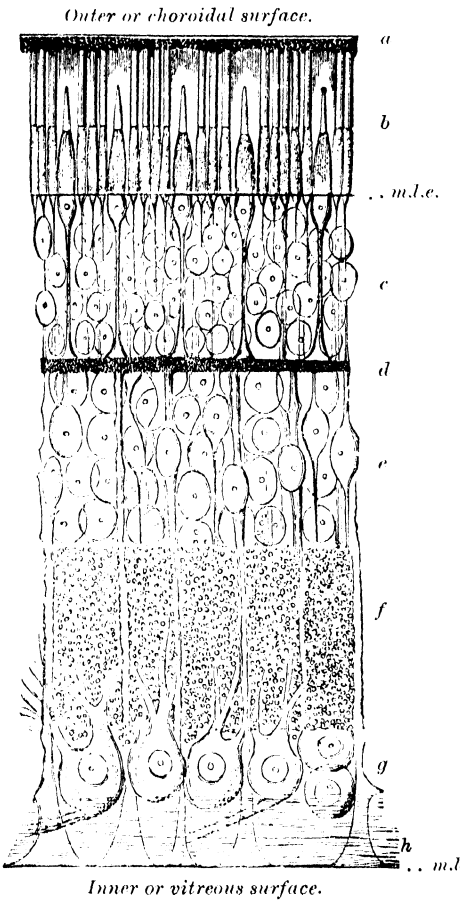


FIG. 460.—DIAGRAM OF A SECTION THROUGH THE RETINA. (M. Schultze.)

a, layer of pigment-cells; *b*, rod- and cone-layer; *c*, nuclei of rods and cones; *d*, outer molecular layer; *e*, layer of bipolars; *f*, inner molecular layer; *g*, nerve-cell layer; *h*, nerve-fibre layer; *m.l.i.*, membrana limitans interna; *m.l.e.*, membrana limitans externa.

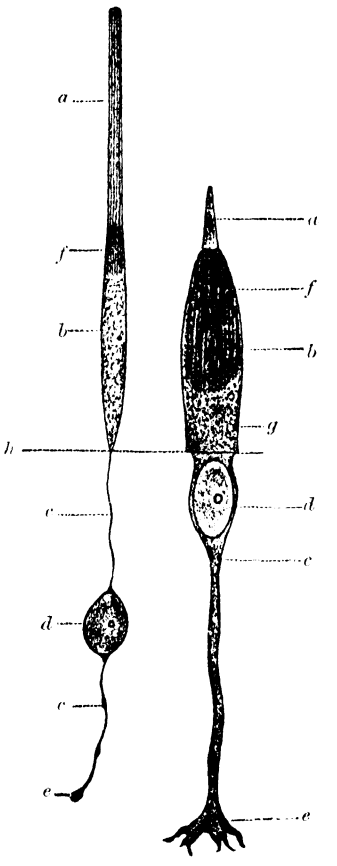


FIG. 461.—A ROD- AND CONE-ELEMENT FROM THE HUMAN RETINA. (Greeff.) Magnified 1,000 diameters.

a, outer segment; *b*, inner segment; *c*, rod- or cone-fibre; *d*, rod- or cone-nucleus; *e*, ending of fibre; *f*, ellipsoid; *g*, myoid; *h*, line of limitans externa.

processes, the *rod- and cone-cells* (rod- and cone-layer, fig. 460, *b*, *plus* outer nuclear layer, *c*). (3) A layer of small bipolar neurones termed the *inner granules* (inner nuclear layer, *e*). (4) A layer of comparatively large neurones, the axons of which become the axis-cylinder processes of the optic nerves (layer of ganglion-cells, *g*, *plus* nerve-fibre layer, *h*). Between the bipolar and the ganglion-cells layers and also between the bipolar and the rod- and cone-cell layers are the so-called *molecular layers* (*d*, *f*), outer and inner. These are mainly composed of interlacing arborescent nerve-fibres, which in these layers form synapses between

the bipolars and the rod- and cone-cells on the one side and the bipolars and ganglion-cells on the other.

The *rod- and cone-cells* (fig. 461) are the receptive sensory neurones. They are composed of a nucleated body (outer granule), an outer or peripheral process, and an axon or nerve-fibre process (central process, rod- or cone-fibre). The peripheral process is either rod- or cone-shaped, forming the so-called *rod* or *cone*, the rods being most numerous except at the central area of the retina (yellow spot): they are imbedded in the pigmented epithelial layer (fig. 460, *a*), which produces during life chemical changes in the rods (formation of visual purple): accompanying these chemical changes the pigmented part of the epithelium-cell moves nearer to the bodies of the rod- or cone-cells, or is withdrawn farther from them, according to whether light falls upon the retina or not (see p. 100). It is probably upon the *outer part or segment of the rod or cone* (which exhibits a special structure as if built up of minute superposed discs) that the light-waves impinge

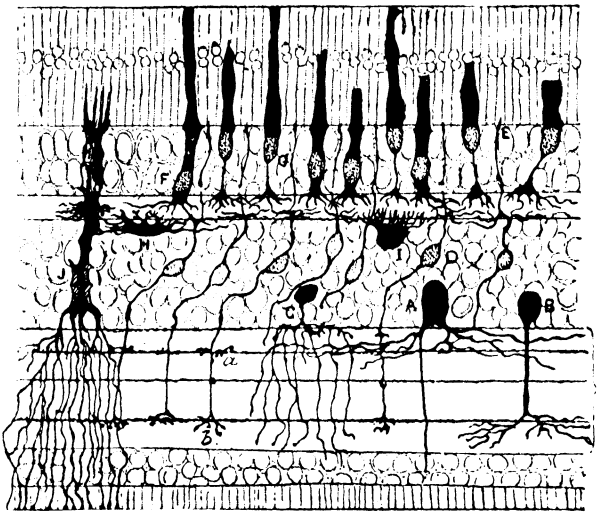


FIG. 462.—SECTION OF RETINA OF BIRD. Golgi method. (Cajal.)

A, B, C, spongioblasts or amacrine cells of inner molecular layer; D, bipolars, sending axons into inner molecular layer to form synapses, *a*, *b*, with dendrons of ganglion-cells (not represented), and dendrons sent into outer molecular layer to form synapses with the rod- and cone-fibres; E, a fibre continued beyond the outer molecular layer; F, G, rod- and cone-nuclei; H, I, spongioblasts of outer molecular layer; J, a fibre of Müller.

and set up the excitation which produces the nervous impulses. The *inner segment of the rod or cone* is fibrillated, the fibrils being perhaps neuro-fibrils. The *central process of the rod- or cone-cells* is a nerve-fibre (axon), itself fibrillated, which extends towards the bipolars to meet peripherally extending processes (dendrons) from those cells in the outer molecular layer; here the two sets of processes undergo synapsis (fig. 463). The *bipolars*, as their name implies, have two processes, one just mentioned, passing peripherally into the outer molecular layer, the other passing to the inner molecular layer and there forming a synapse with processes (dendrons) of the cells of the ganglionic layer (fig. 463); some pass through the inner molecular layer to apply themselves to the cell-bodies of the ganglion-cells. The *cells of the ganglionic layer*, much larger in most parts of the retina than the bipolars, have also two sets of processes: the one just mentioned forming synapses in the inner molecular layer with the axons of the bipolars, the other being a single axon from each cell, and forming one of the fibres of the innermost layer

of the retina (nerve-fibre layer). The fibres of the nerve-fibre layer, which in the retina itself are non-medullated, become collected at the colliculus (*optic disc*) or entrance of optic nerve (really the exit of the nerve-fibres) into a mass of fibres, circular in section. These fibres pierce the coats of the eyeball, in a number of bundles which receive strong sheaths from its outermost tunic, which also gives a general investment for the whole (optic) nerve as it leaves the globe of the eye. The fibres are conveyed along the optic nerves and optic tracts to the optic thalami (lateral geniculate bodies) and to the anterior corpora quadrigemina, where their axons end by arborising amongst the nerve-cells there situated.

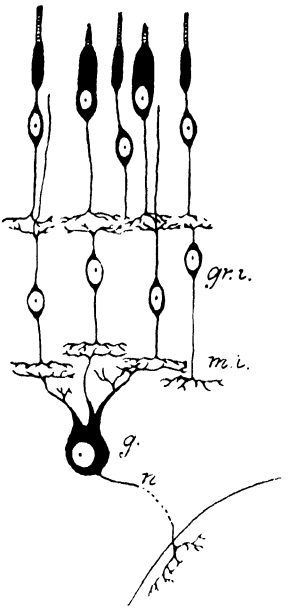


FIG. 463.—DIAGRAM OF THE CONNEXIONS OF THE RETINAL ELEMENTS. (G. Retzius.)

gr.i., inner granules (bipolars); *m.i.*, inner molecular layer; *g*, cell of ganglionic layer; *n*, nerve-fibre process passing towards brain.

The nervous elements proper of the retina (nerve-cells and their processes) are supported by a framework formed from certain cells which appear to be derived from the spongioblasts of the embryonic nervous system, and are perhaps homologous with the ependyma-cells of the adult brain and spinal cord (see p. 203). These cells take the form of elongated structures—the *fibres of Müller* (fig. 462, J)—which extend from the inner surface of the retina (where the base of the cell is represented by a

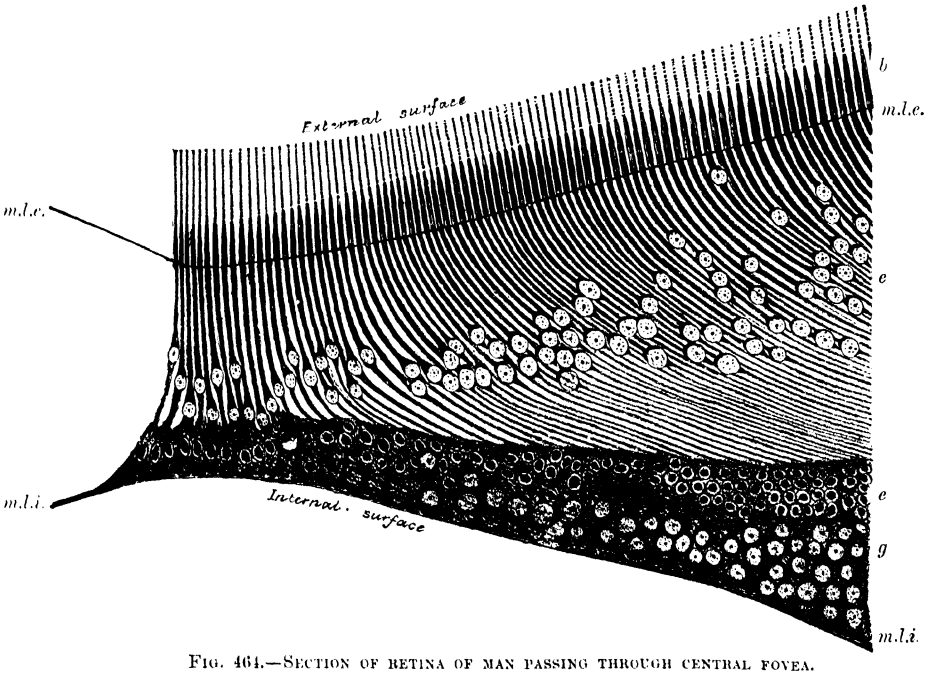


FIG. 464.—SECTION OF RETINA OF MAN PASSING THROUGH CENTRAL FOVEA.

From a preparation by C. H. Golding-Bird. Magnified 350 diameters.

b, cones; *c*, cone-fibres and -nuclei (fibrous layer); *e*, bipolars; *g*, ganglion-cell layer; *m.l.e.*, limitans externa; *m.l.i.* limitans interna.

somewhat conical 'foot' sometimes ramified), through all the retinal layers, as far as the rods and cones. Here the fibres of Müller end in a number of fine short fibrils which extend around and probably aid in supporting the inner segments of the rods and cones. At the level of the layer of inner granules each Müllerian fibre contains a nucleus.

Modifications of the above described arrangements of the retinal elements are met with in the central area (*macula lutea* and *fovea centralis*) and in the anterior or peripheral part, at the *pars ciliaris*.

In the *central fovea* (fig. 464) there are only cone-elements, rods being absent. These, however, begin to appear at the edges of the fovea, and soon become more numerous than the cones. The latter are much more slender in this part of the retina than elsewhere, and the fibres which come off from them run obliquely towards the bipolar layer, producing the appearance known as the fibrous layer of Henle.

At the *ora serrata* the retinal layers cease abruptly, at least so far as concerns the nervous elements. In front of the ora serrata the place of the retina is taken by a double epithelial stratum termed the *pars ciliaris retinæ*, the cells of the inner layer of which are long and columnar, those of the outer layer shorter and pigmented. These two layers are continued over and between the ciliary processes and on to the back of the iris, but here both strata are formed of pigmented cells (see fig. 167, p. 101).

An account of these modifications and full details regarding the structure of the retina and of the sense-organs generally will be found in the part of this work which deals with the sense-organs (Vol. III., Part 2).

ARRANGEMENT OF NERVOUS ELEMENTS IN THE CEREBRO-SPINAL NERVE-CENTRES.

The cerebro-spinal nerve-centres include the *spinal cord* (*medulla spinalis*), the *bulb* (*medulla oblongata*), the *pons*, the *cerebellum*, the *mid-brain*, and the *cerebrum*. A complete account of the structure of all these parts and of their relation to one another is given in the part of this work which deals with Neurology (Vol. III., Part 1). It will be sufficient to intimate here the main features of structure and the general arrangement of cells and fibres which characterise each of these parts.

In all sections of nerve-centres grey and white matter are distinguishable. In the spinal cord the grey matter is found exclusively in the more central parts of the section : in the medulla oblongata, pons, and mid-brain it becomes less confined to those parts and extends to other portions of the sectional area, so that the distinction between the grey and white matter is in many places confused ; in the cerebrum and cerebellum a sharp distinction between grey and white matter again shows itself, but the larger part of the grey matter lies at the periphery (cerebral and

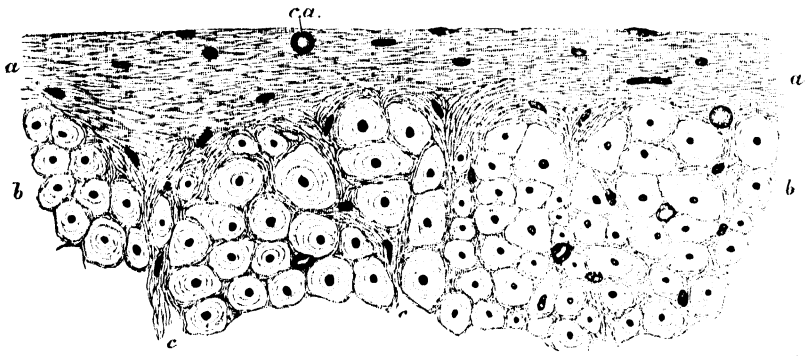


FIG. 465. —FROM A SECTION OF HUMAN SPINAL CORD SHOWING THE SUPERFICIAL NEUROGLIA. (Schäfer.)

a, *a*, superficial neuroglia, composed of a feltwork of fibres, with the nuclei of the cell-bodies interspersed amongst them; *b*, medullated nerve-fibres of the white substance, in section, with neuroglia between them, *c*, *c* ; *c.a*, corpora amylacea.

cerebellar cortex), a smaller portion being found near the centres of those organs, while the whole of the intermediate substance is formed of white matter.

In all parts of the cerebro-spinal centres the white matter is formed of medullated nerve-fibres, unprovided with a membranous sheath. The fibres run in definite directions in the white substance ; longitudinally for the most part in the spinal cord, bulb, pons, and mid-brain, but with many fibres crossing from side to side, usually in an arcuate manner ; radially in the cerebrum and cerebellum, where they diverge from the so-called peduncles of these organs towards the grey cortex. The nerve-fibres are supported by numerous neuroglia-cells and -fibres, which vary in arrangement in different parts. In most situations the neuroglia-cells are stellate, and give off long slender fibres which penetrate everywhere between the nerve-fibres. But near the surface of the cerebrum and cerebellum (fig. 315, p. 206), the neuroglia-cells and -fibres have a general direction vertical to the surface. And from the ependyma-cells of the central canal of the cord and ventricles of the brain fibres indistinguishable from neuroglia-fibres are continued for long distances through both the grey and white matter : in the embryo these fibres reach the surface (fig. 312). In many parts of the nerve-centres there is a thin layer of neuroglia formed by a feltwork of fibres immediately within the vascular membrane (pia

mater) which covers the surface ; this layer may be free from nerve-fibres : it is termed the superficial neuroglia (fig. 465).

The nerve-fibres of the white matter are also in part supported by connective tissue, which is prolonged into the centres from the pia mater, accompanying the blood-vessels which are supplied from this membrane to the nervous substance, but the actual amount of true connective tissue in the nerve-centres is very small.

From all parts of the white matter where it is adjacent to the grey substance fine medullated collateral fibres are given off : these pass into the grey substance and terminate in arborescences and synapses around its cells.

Spinal cord (medulla spinalis).—In the spinal cord the grey matter lies in the centre (fig. 466). In each lateral half of the cord it forms an irregularly crescentic mass—the grey crescent—which approaches the surface at its two horns

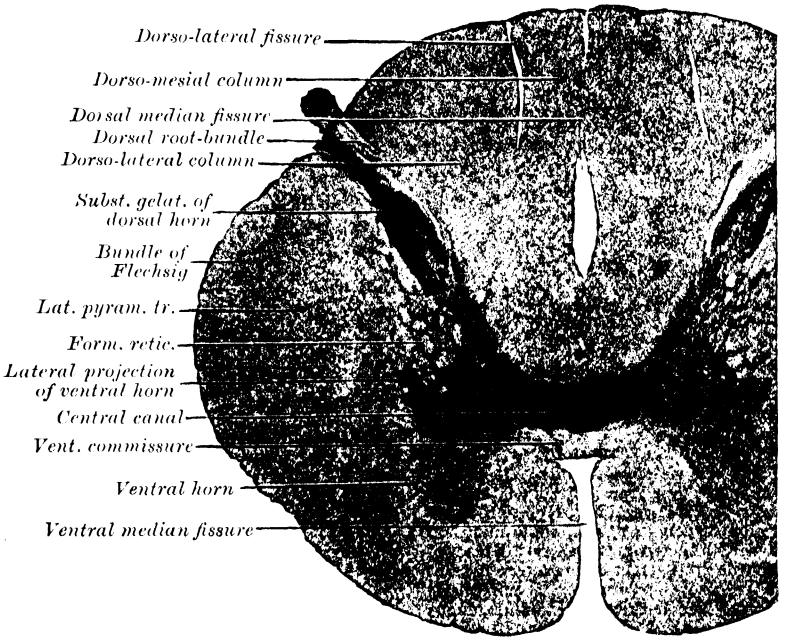


FIG. 466.—SECTION OF HUMAN SPINAL CORD FROM UPPER CERVICAL REGION. (Schäfer.)
Photograph. Magnified about 8 diameters.

—dorsal and ventral—and which is joined with its fellow of the opposite side by a bridge of grey matter in the middle of which is the central canal of the cord. The shape and amount of grey matter vary in the different regions. In the thoracic region the grey matter is relatively in least amount, corresponding to the fact that the nerve-roots which are connected with the thoracic cord are relatively small. But in the uppermost segment of the thoracic region and in most of the cervical region there is a considerable addition to the grey matter of the anterior horn, and the same is found to obtain from the penultimate thoracic to the third sacral segment. These additions contain the nerve-cells from which the motor nerves of the limb-muscles are derived, and mainly affect the ventral horn, but an increase of size occurs also in the dorsal horn and body of the crescent in the same regions.

The nerve-cells in the grey matter appear in transverse sections as if arranged in groups (fig. 467) ; in longitudinal sections the groups take the form of elongated

cell-columns—not closely packed, but with the cells of the group or column separated from one another by intercellular grey matter. Such groups are known as 'nuclei.' The best marked cell-groups are those of the ventral horn (*motor nuclei*); those of the middle part or body of the crescent (*middle nucleus*)—these have but little Nissl substance and are therefore less conspicuous; those of *Clarke's column or nucleus*, at the base of the dorsal horn, mesially; and those of the lateral horn (*intermediate cell-column*), lying in a projecting part of the middle of the crescent. There are, besides these, nerve-cells, small and large, scattered throughout other parts of the grey matter of the dorsal horn, and a large number of small cells in the gelatinous substance of Rolando, which forms a cap over the apex of the dorsal horn.

Clarke's column and the intermediolateral column are only found in the thoracic and lumbar portions of the cord. The cells of the first-named give rise to fibres which run up the lateral column on the same side of the cord and end in the cerebellum (spino-cerebellar fibres of the tracts of Flechsig and Gowers, fig. 469). Those of the intermediolateral column give origin to fine medullated fibres which leave the cord along with the large motor-fibres of the ventral roots and go to sympathetic ganglia (pre-ganglionic fibres of the sympathetic). The dorsal roots are not formed of fibres which originate in the cord. They have their cells of origin in the spinal ganglia (fig. 468). They enter the white matter of the dorsal columns of the cord close to the dorsal horn of grey matter and divide into ascending and descending branches, besides giving off numerous collaterals. Some of their branches pass into the grey matter at once, others are continued up (and some for a short distance down) the cord to end in its grey matter; many are prolonged up to end in the grey matter of the dorsal column of the bulb.

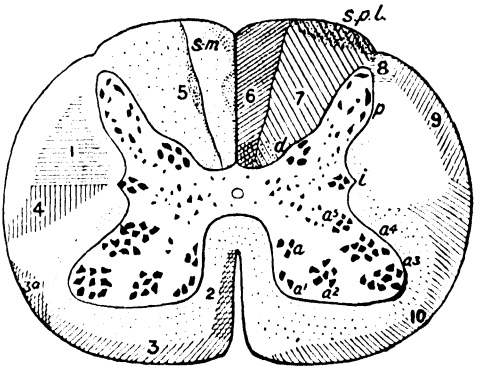


FIG. 467.—DIAGRAM SHOWING CELL-GROUPS IN GREY MATTER OF CORD AND NERVE-TRACTS IN WHITE MATTER. (Schäfer.)

Descending tracts shown on left side: 1, lateral pyramid tract; 2, anterior pyramid tract; 3, antero-lateral descending; 3*a*, Helweg's tract; 4, pre-pyramidal (rubrospinal); 5, comma; *s-m*, septo-marginal fibres. Ascending tracts shown on right side: 6, tract of Goll; 7, tract of Burdach; 8, tract of Lissauer; 9, tract of Flechsig; 10, tract of Gowers; *s.p.l.*, superficial postero-lateral fibres. The dots represent endogenous fibres, which are confined in their course to the cord itself. Cell-groups: a^1 to a^5, different groups in ventral horn; *i*, intermedio-lateral group; *p*, groups of dorsal horn; *d*, Clarke's column.

Besides these tracts of nerve-fibres which are derived from Clarke's column and from the dorsal roots, the white matter of the cord contains laterally a large bundle of fibres which are derived from cells in the motor region of the opposite cerebral hemisphere (*crossed pyramid tract*), and ventrally a certain number of fibres—most numerous in the upper part of the cord—which are derived from similar cells of the cerebral hemisphere of the same side (*direct pyramid tract*). Ventral to the crossed pyramid tract is another bundle of descending fibres. This is derived from the red nucleus in the mid-brain and is known as the *rubro-spinal tract*. In the ventro-lateral part of the white matter a number of fibres which arise in the pons and mid-brain run down the length of the cord (*ventro-lateral descending fibres* of the dorsal and ventral longitudinal tracts). All these tracts of white fibres send numerous collaterals into the grey matter to ramify

amongst its cells. Finally, immediately in contact with the grey matter in the ventro-lateral regions are many fibres which have originated in cells of the cord itself and are passing upwards or downwards to make connexions between the segment of the cord from which they originate and others above or below. These are termed *propriospinal fibres* to distinguish them from the fibres of longer course which have either their origin or destination in some other part of the nervous system.[1]

The spinal cord is closely covered externally by a vascular connective-tissue membrane which is known as the *pia mater*. Within this the arteries ramify, and from them numerous blood-vessels enter the white substance to supply this and in greater measure the grey matter with capillaries. Accompanying these entering vessels are septa of connective tissue, the largest of which passes in along the dorsal median

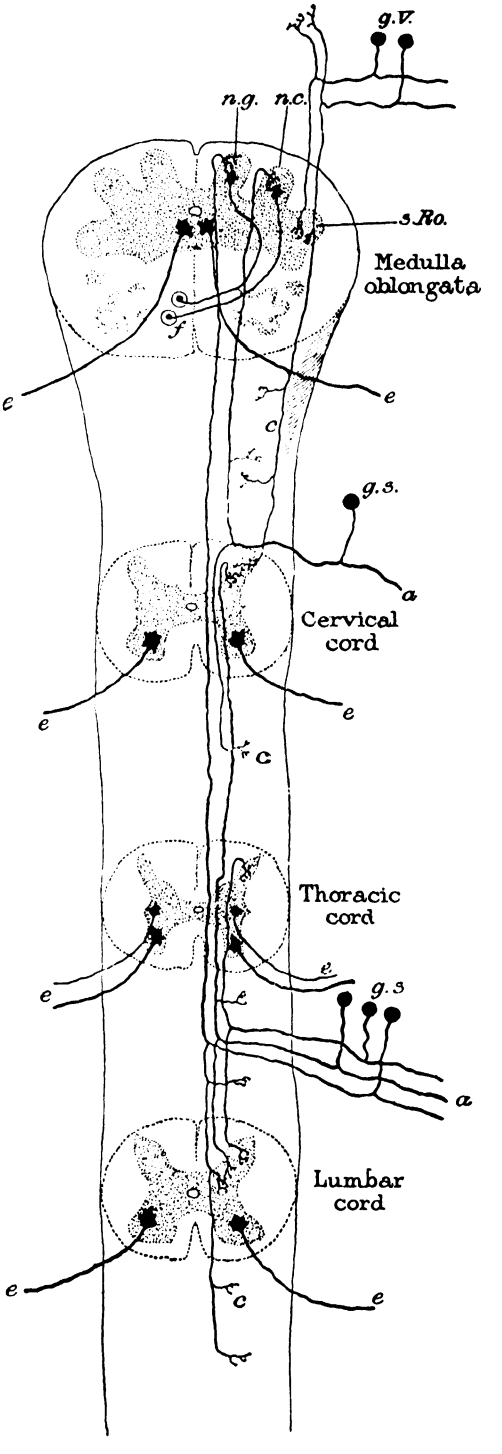


FIG. 468.—DIAGRAM TO SHOW COURSE OF FIBRES OF DORSAL ROOTS WITHIN CORD.

(Schäfer, modified from Cajal.)

a, afferent fibres passing through spinal ganglia, *g.s.*; *e*, efferent fibres arising in cells of ventral horn; *g.V.*, ganglion-cells of fifth cerebral nerve; *n.c.*, nucleus cuneatus of medulla oblongata; *n.g.*, nucleus gracilis; *f*, fibres of fillet arising from cells of these nuclei; *c*, descending branches of fifth and spinal nerves, giving off collaterals to dorsal horn and to the substantia Rolandi, *s. Ro.*

line, and separates the two dorsal columns of white matter. Along the ventral median line is a deep groove which is lined by a continuation of pia mater.

Outside the pia mater and separated from it by a considerable space containing cerebro-spinal fluid is a delicate non-vascular connective-tissue membrane known as the *arachnoid*. The space between it and the pia mater, which is bridged across here and there by trabeculæ of connective tissue, is the *subarachnoid space*. Outside the arachnoid and usually in close contact with it, but with a narrow capillary cleft (*subdural space*) between, which may become distended by the accumulation of cerebro-spinal fluid, is the thick fibrous *dura mater*. The dura mater contains some blood-vessels, but is not as vascular as the pia mater. It is not in close contact with the wall of the vertebral canal, but is separated from the

[1] The term *endogenous* is also employed to designate fibres which run up or down the cord and take origin in the spinal cord itself; those which have their cells of origin outside the cord (in the spinal ganglia or in higher parts of the central nervous system) being termed *exogenous*.

bone by areolar tissue containing a venous plexus, as well as some loose fat. There are openings in the dura for the nerve-roots, which receive a sheath from it. The dura mater and arachnoid are attached to the pia mater by the denticulations of the longitudinal membrane

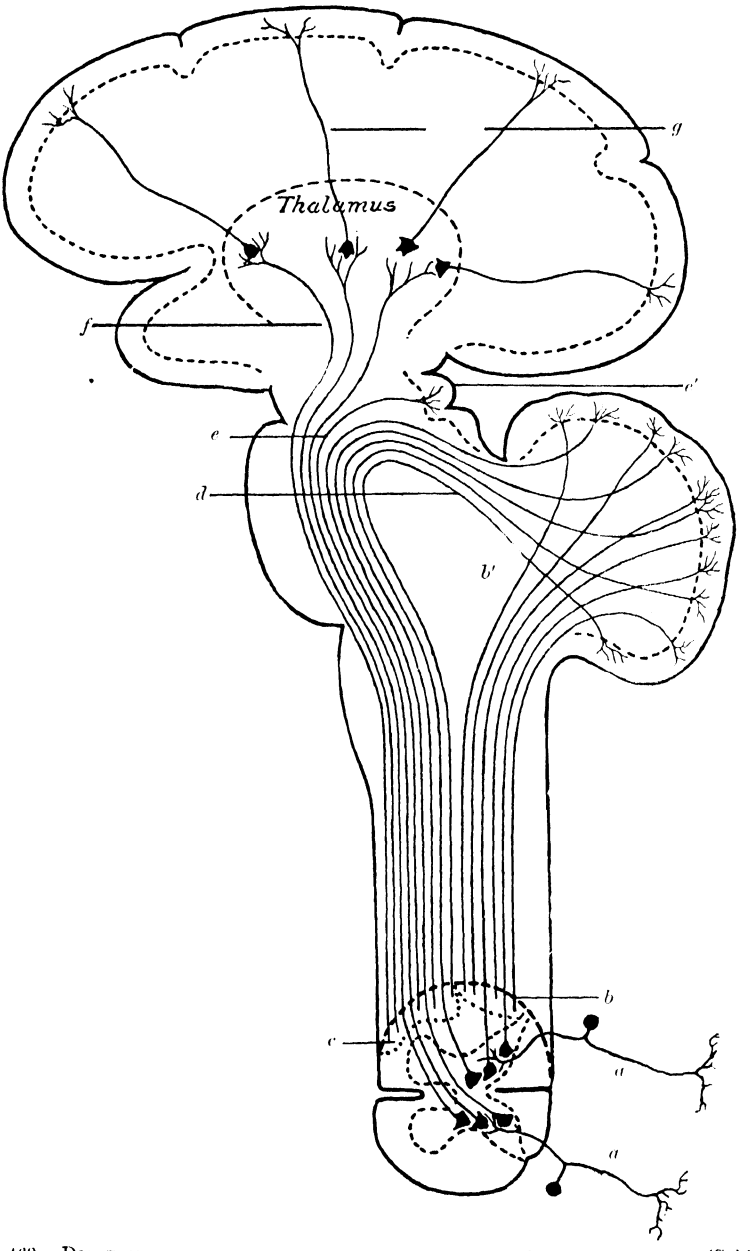


FIG. 469.—DIAGRAM OF SOME OF THE ASCENDING TRACTS OF THE SPINAL CORD. (Schäfer.)

a, dorsal root-fibres; *b*, fibres of Flechsig's tract, passing from cells of Clarke's column to cerebellum by inferior peduncle, *b'*; *c*, fibres of Gowers' tract, passing from cells of Clarke's column, partly to cerebellum, *d*, partly to corpora quadrigemina, *e*, and partly to thalamus, *f*; *g*, fibres continued from cells of thalamus to cortex centri.

known as the *ligamentum denticulatum*, which runs down the cord on each side. All the membranes contain elastic fibres, and their surfaces are covered with endothelium-like cells, similar to those of serous membranes.

Medulla oblongata or spinal bulb.—In the lower part of the medulla oblongata the arrangement of the grey matter has undergone a change as compared with that of the cord (fig. 470). The central canal is still present and surrounded with grey matter, but the motor or efferent nerve-cells are now situated close to the canal. Some of these cells lie ventro-laterally, others dorso-laterally, to the section of the canal: they give origin to the fibres of the hypoglossal and part of the spinal accessory nerves (fig. 470, N. XI., N. XII.). The ventral horn is cut off from the grey matter by the passage of bundles of nerve-fibres from the pyramids of the medulla oblongata to the lateral white column of the cord, and the middle part of the crescent is broken up into a reticular formation in which white bundles running longitudinally and transversely interlock with portions of the grey matter containing nerve-cells

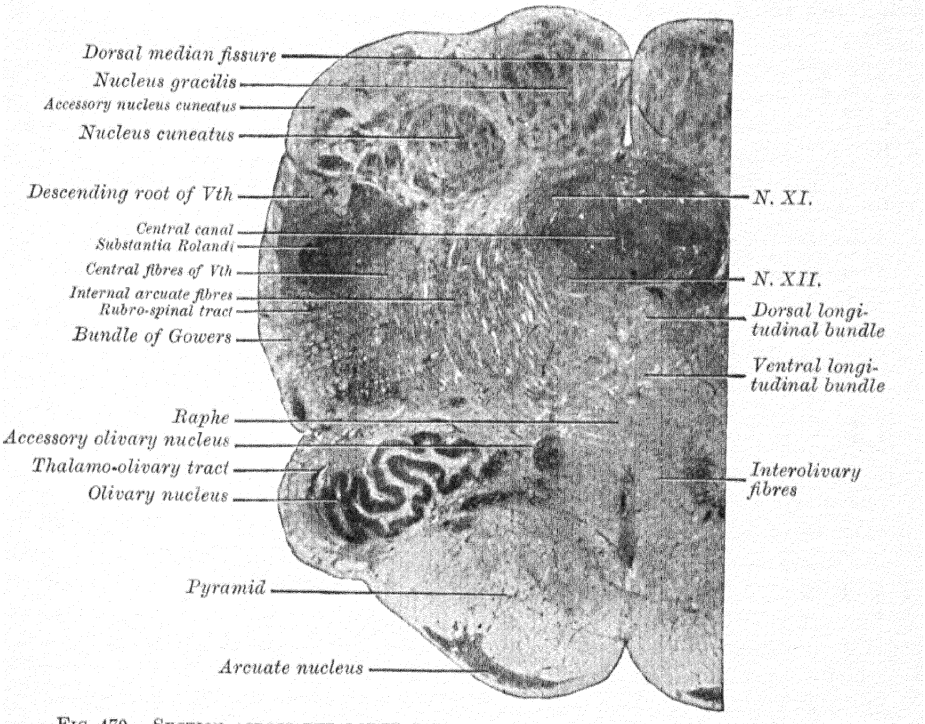


FIG. 470.—SECTION ACROSS THE LOWER PART OF THE MEDULLA OBLONGATA. (Schäfer.)
Photograph. Magnified about 6 diameters.

of different sizes. And whereas in the spinal cord the dorsal columns are entirely composed of white fibres, in the medulla oblongata grey matter is found to extend into them and soon entirely to occupy the columns, the white fibres which are prolonged up from the spinal dorsal roots becoming lost and ending in ramifications in this grey matter. From its cells, on the other hand, new fibres arise and run as *arcuate fibres* through the reticular formation. They cross the raphe (seam) which joins the two lateral halves of the bulb, and, becoming longitudinal on the opposite side, run upwards towards the cerebrum, where they ultimately end in the thalamus. These fibres, which are joined by others coming from other portions of the grey matter of the bulb and pons in which the sensory cerebral nerves end, and probably also by fibres derived from cells of the spinal cord, constitute collectively the great sensory tract known as the *main or lower fillet.*

The apex of the dorsal horn also is cut off from the central grey matter in the medulla oblongata. It becomes enlarged and approaches the surface, where it forms a mass of gelatinous-looking substance known as the *tubercle of Rolando*. This receives the central arborescent terminations of the sensory root of the *fifth* or *trigeminal nerve* and forms its 'nucleus.' A considerable bundle of fibres of this root runs down the medulla oblongata alongside of the tubercle of Rolando, into which the fibres send collaterals. Some of the fibres of this *descending root of the fifth* pass into the cervical part of the spinal cord, ending in the gelatinous substance of the apex of the dorsal horn.

The white matter of the medulla oblongata is characterised by the presence on each side of its ventral fissure of a prominent mass of longitudinal fibres termed the *pyramid*. Its fibres form the pyramid tract already noticed in the cord; at the lower part of the medulla oblongata they cross the middle line obliquely in bundles which decussate with bundles from the opposite pyramid to pass to the lateral column of the cord as the crossed pyramid tract. The fibres of the pyramid which remain uncrossed form the direct pyramid tract of the cord. The *spino-cerebellar tracts* are continued up from the spinal cord in the lateral column of the bulb: they separate at its upper end, one portion, the dorsal, passing to the cerebellum by its inferior peduncle; the other, the ventral, running farther up to reach the upper end of the pons and then turning back into the cerebellum along its superior peduncle. These are said by most authors to be distributed to the whole of the vermis of the cerebellum of the same side, a few fibres crossing the middle line; but Mott,[1] who is corroborated by Mackalty and Horsley,[2] could trace them only to the cephalic part of the vermis. The descending fibres of the antero-lateral column of the cord, which there forms two tracts, are resolved in the medulla oblongata into three, all of which have a deeper position here than in the cord. They are known respectively as the *dorsal and ventral longitudinal bundles* and the *bundle of Monakow* or *rubro-spinal tract*. They will be noticed again in the mid-brain and pons.

The *central canal* in the medulla oblongata gradually approaches its dorsal surface, and about the middle of its length opens into the lozenge-shaped *fourth ventricle of the brain* (fig. 471). The lower part of the lozenge lies dorsally to the medulla oblongata, the upper part dorsally to the pons. The cavity is roofed in by a thin layer of ependymal epithelium covered by pia mater; this membrane invaginates the roof on either side with a vascular thickening which forms the *choroid plexus* of the fourth ventricle. The opening out of the central canal throws the grey matter which surrounded it to the side of the middle line: it here forms the *grey matter of the floor of the fourth ventricle* and contains a continuation of the nuclei which gave origin below to fibres of the twelfth and eleventh nerves. In this part they still give origin to fibres of the twelfth nerve, but the eleventh is replaced by the tenth, or vagus, and higher up by the ninth, or glossopharyngeal. Other fibres of these nerves take origin from a small motor nucleus which lies in the reticular formation and is known as the *nucleus ambiguus*.

Still more laterally in the central grey matter than the motor nucleus of the ninth nerve there is seen in the uppermost part of the medulla oblongata—extending up into the pons—another nucleus which receives part of the eighth or acoustic nerve (see p. 303).

The *reticular formation* lies in this upper part of the medulla oblongata ventral to the grey matter of the floor of the ventricle. In the lateral part of the reticular formation the descending root of the fifth nerve and its gelatinous 'nucleus' is still seen, and near it another smaller circular white bundle, also in contact with

[1] Brain, xv. 1892. [2] *Ibid.* xxxii. 1909.

a small mass of gelatinous grey substance. This bundle—known as the *solitary bundle*—is a descending sensory root of the tenth and ninth nerves, and its grey substance is their sensory 'nucleus': it receives also the pars intermedia of the seventh nerve. Most ventral of all, as in the lower part of the bulb so also in this upper part, is seen the mass of fibres forming the *pyramid*. Between the pyramid and reticular formation another peculiarly shaped mass of grey matter has become developed—the *nucleus of the olivary body*. This appears in sections as a corrugated grey band containing numerous small nerve-cells. It is already seen in the lower part of the bulb, but is most developed in the upper or ventricular part. It produces an olive-shaped prominence—the *olive*—on the surface of the lateral column. The

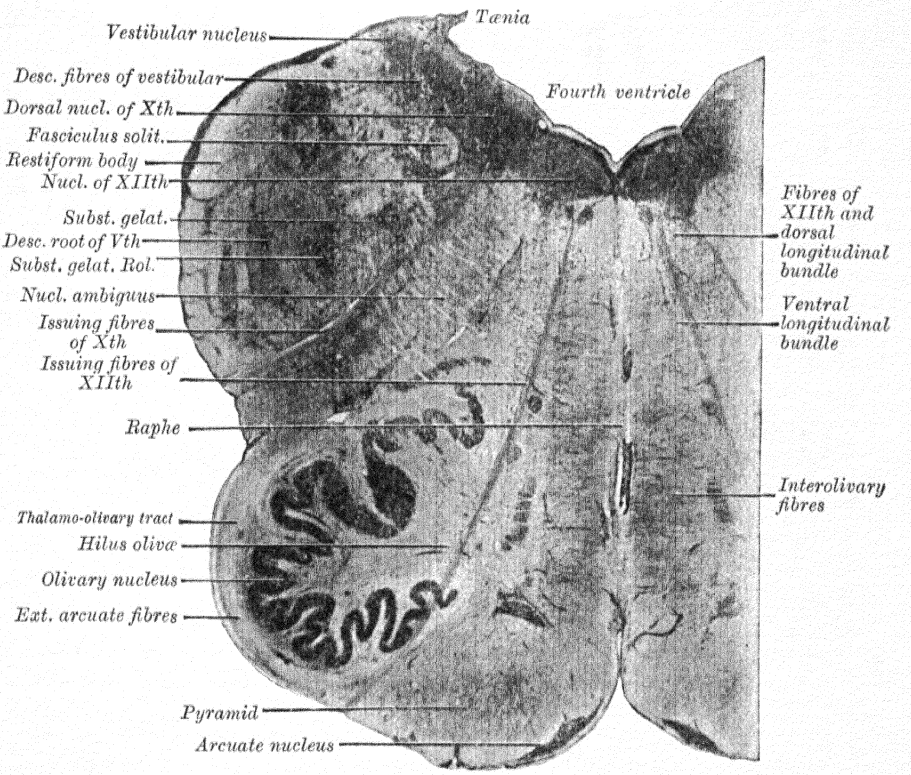


FIG. 471.—SECTION ACROSS THE UPPER PART OF THE MEDULLA OBLONGATA. (Schäfer.)
Photograph. Magnified about 6 diameters.

nucleus is open towards the raphe, and here numerous fibres pass out from its interior and, crossing the raphe, can be traced as *arcuate fibres* into the *inferior cerebellar peduncle*, and so to the cerebellar hemisphere of the opposite side. The dorsal spino-cerebellar fibres can also be seen, as already mentioned, to pass into this peduncle; some fibres from the ventral spino-cerebellar bundle also enter it.

Pons.—The structure of the pons is very similar to that of the uppermost part of the medulla oblongata, with which it is continuous. But the part which is continued up from the medulla oblongata is concealed from the ventral aspect by a large mass of fibres which have their origin in the ventral part of the pons in grey matter (*nuclei pontis*) situated around and between the longitudinally

running bundles into which the pyramids of the medulla oblongata have resolved themselves. These *ponto-cerebellar fibres* decussate in the middle line and course over to the opposite side to form the *middle peduncle of the cerebellum*, in the hemisphere of which they end. The part of the pons which adjoins the fourth ventricle consists of *grey matter of the floor of the ventricle*; ventral to this is *reticular formation*, and within or adjacent to this are certain longitudinally and transversely crossing nerve-bundles, which are continuous with tracts above and below. In the *grey matter of the floor* of the fourth ventricle there lies near its lateral angle a large-celled nucleus which gives origin to fibres of the *motor root of the fifth nerve*. Other fibres of this root arise from a nucleus of large spherical nerve-cells which

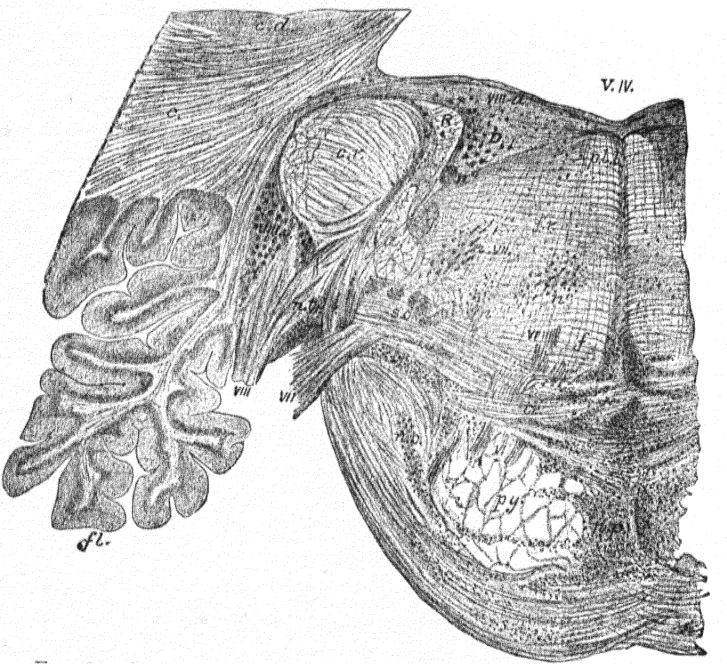


FIG. 472.—SECTION ACROSS THE LOWEST PART OF THE PONS. (Schäfer.)
Magnified about 4 diameters.

v.IV., fourth ventricle; *c*, cerebellum; *c.d.*, its corpus dentatum; *fl*, grey matter of flocculus; *c.r.*, restiform body; *R*, fibres of vestibular nerve; *D*, Deiters' nucleus; *VIII*, root of eighth nerve; *VIII.d*, *VIII.v*, its dorsal and ventral nuclei; *tr*, trapezium; *n.tr.*, its nucleus; *f*, fillet; *p.l.b.*, posterior (dorsal) longitudinal bundle; *f.r.*, formatio reticularis; *n*, *n'*, *n''*, nuclei within it; *V.a.*, descending root of fifth nerve; *s.g.*, substantia gelatinosa; *s.o.*, superior olivary nucleus; *VII*, root of facial nerve; *n.VII.*, its nucleus; *VI*, root-fibres of sixth; *py*, pyramid-bundles; *n.p.*, nuclei pontis.

lie in the central grey matter at the side of the ventricle and can be traced up also in its continuation at the side of the Sylvian aqueduct to the mid-brain (*accessory motor nucleus*). The large *sensory root of the fifth* enters the side of the pons, penetrating the bundles of the middle cerebellar peduncle. The sensory fibres partly end by ramifying in an extensive *sensory nucleus* of small cells near the motor nucleus, partly bend downward to be continued into the medulla oblongata as the descending root, the fibres of which terminate in the substantia gelatinosa of Rolando. Three other cerebral nerves are connected with the pons. One of these is the *fourth nerve* (see p. 305). Another, the *seventh nerve*, which has both efferent and afferent fibres, arises, as regards its efferent fibres, from a nucleus of medium-sized cells which lies in the reticular formation and corresponds in general situation and

structure to the nucleus ambiguus of the medulla oblongata which gives origin to part of the ninth and tenth. The fibres which arise from these nuclei are similar in their course, for they all pass from the nucleus towards the grey matter of the floor of the ventricle near the middle line, then run upwards in this for a short distance, and finally bend round and pass in a lateral and ventral direction to emerge at the side of the pons or bulb. The afferent fibres of the facial (*pars intermedia*) pass into the uppermost end of the solitary bundle (see p. 301), and terminate by arborescence amongst the cells of its attached grey matter.

Lastly, the fibres of the *eighth nerve* enter the nerve-centre just at the junction of the medulla oblongata and pons in two divisions, vestibular and cochlear. The *vestibular division* enters mesial to the inferior cerebellar peduncle, its fibres lose themselves partly in a mass of small-celled grey matter, the *main vestibular nucleus*, partly in a *descending nucleus* continuous with the main nucleus, which

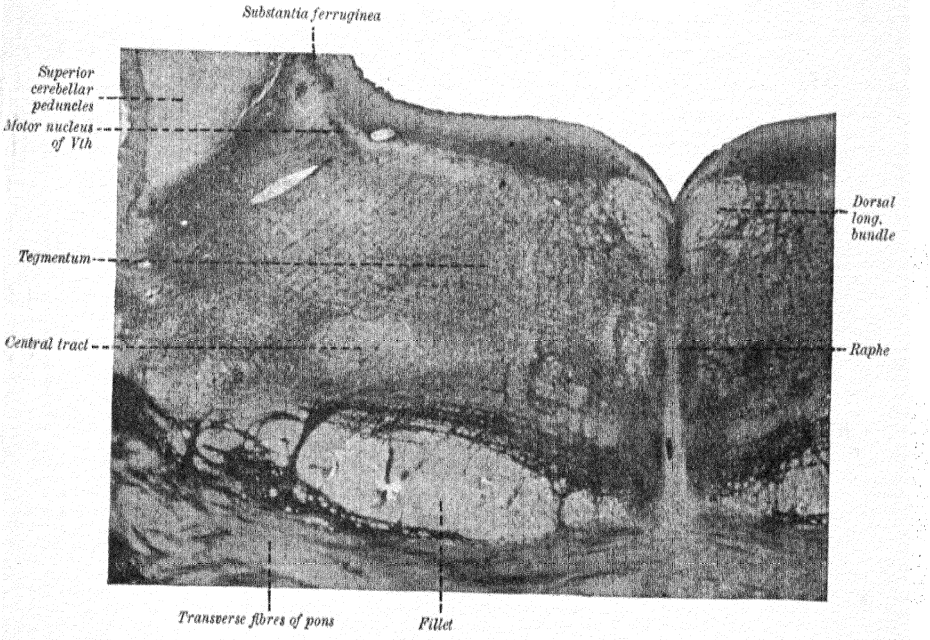


FIG. 473.—SECTION FROM THE MIDDLE OF THE PONS SHOWING THE PART ADJACENT TO THE FOURTH VENTRICLE. Photograph. (Schäfer.)

receives fibres from descending bundles of the nerve, and partly in certain large-celled nuclei (*nucleus of Deiters* and *nucleus of Bechterew*), which lie just below the grey matter of the floor of the ventricle: other fibres pass into the cerebellum. The *cochlear division* passes partly laterally to the inferior cerebellar peduncle, turning round it to end in a prominence of grey matter (*acoustic tubercle*, *dorsal nucleus*), which overlies it and extends to the floor of the ventricle; partly into a nucleus immediately ventral to the peduncle (*ventral* or *accessory nucleus*). From the cells of these nuclei fibres arise which form a tract known as the *trapezium*, passing transversely across the raphe to the opposite side, behind the longitudinal pyramid bundles. Its fibres are there connected with various nuclei (*superior olivary*, *trapezoid*, *nucleus of lateral fillet*), a description of which will be found in the part of this work devoted to Neurology. From these nuclei fibres are continued upwards towards the mid-brain (posterior corpora quadrigemina), forming the *lateral fillet* or *fillet of Reil*, which is visible at the side of the mid-brain.

Ventral to the reticular formation of the pons is a flattened mass of white fibres which is continued up from the tract of the fillet of the medulla oblongata; this is the *lower* or *main fillet*. Its fibres are largely derived from the nuclei of the posterior columns of the bulb, having crossed the raphe mainly in the middle and lower parts of the medulla oblongata. But this is not the only source of the fibres of the main fillet, for they receive accessions from all the sensory nuclei of the pons and bulb and probably also from fibres derived from the grey matter of the dorsal horn of the spinal cord. The main fillet passes up into the mid-brain, and for the most part goes past this to end in the thalamus.

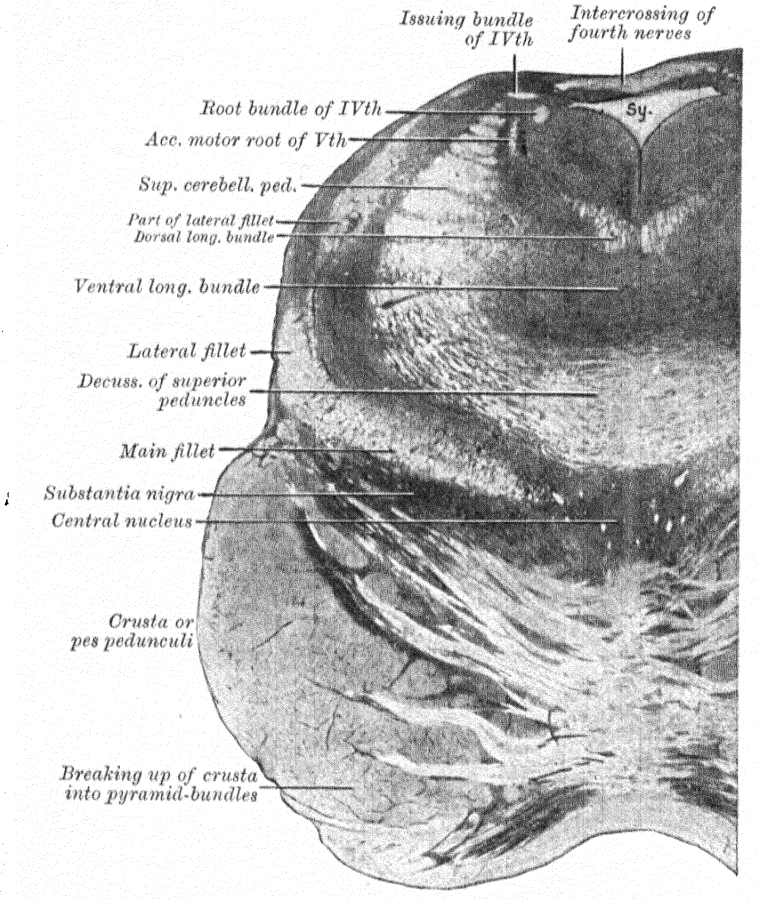


FIG. 474.—SECTION ACROSS UPPERMOST PART OF PONS. Photograph. (Schäfer.)

On each side of the narrowing upper end of the fourth ventricle are seen in sections across the uppermost part of the pons a considerable bundle of white fibres which, when followed downwards, is seen to be traceable out of a wavy nucleus (fig. 475 *n.d.*) of grey matter within the cerebellar hemisphere of the same side. This bundle is the *superior cerebellar peduncle*. Traced forwards it is found to dip gradually down until it comes to lie in the reticular formation ventral to the central grey matter, and here it is seen in the lower part of the mid-brain to decussate with its fellow in the middle line, forming a large round white bundle within

the tegmentum after the decussation is complete. Still farther forward—in the region of the anterior corpora quadrigemina—the fibres of this bundle lose themselves in a rounded mass of grey matter in the tegmentum, which is known as the *red nucleus* or *nucleus of the tegmentum* (fig. 482, *r.n*).

Lastly, above the roof of the ventricle, just below the junction of the pons and mid-brain, the two small *fourth nerves* are seen to come to the surface and to intercross over the middle line, each passing to the superior oblique muscle of the opposite side. The bundles of this nerve, which arise from the lower end of the *oculo-motor nucleus* of the mid-brain, pass at first a short distance downwards in the lateral wall of the narrow part of the fourth ventricle, and are seen in sections of the uppermost part of the pons (fig. 474).

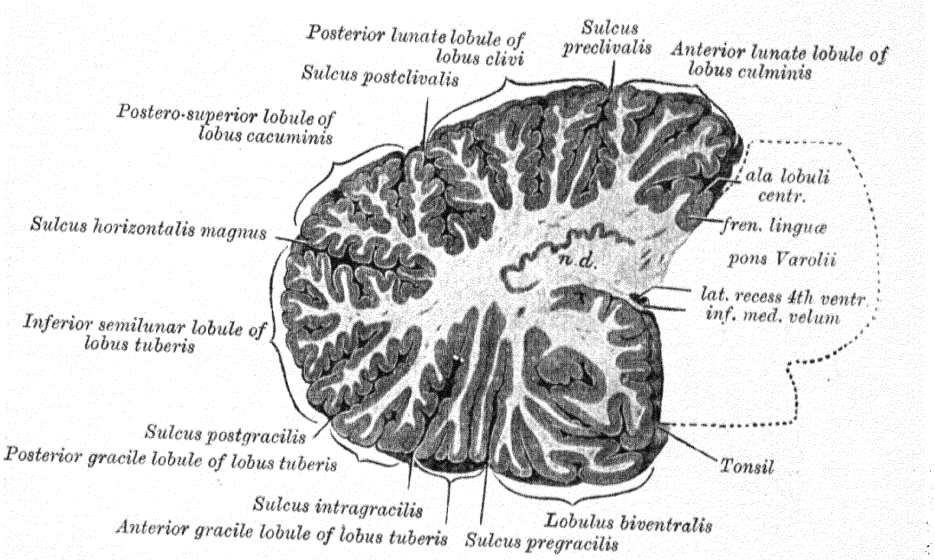


FIG. 475.—SECTION THROUGH ONE HEMISPHERE OF THE CEREBELLUM TO SHOW THE DISTRIBUTION OF ITS GREY AND WHITE MATTER. (Schäfer.) Natural size.

FIG. 475.—SECTION THROUGH ONE HEMISPHERE OF THE CEREBELLUM TO SHOW THE DISTRIBUTION OF ITS GREY AND WHITE MATTER. (Schäfer.) Natural size.

In this many of the fibres which have come down to the pons from the cerebral cortex terminate; those which are continued into the pyramids of the medulla oblongata give off many collaterals to this grey matter.

Cerebellum.—The cerebellum belongs anatomically to the part of the central nervous system which has just been considered, and its structure may therefore be noticed next. It is formed of a median part—the *worm*—and two lateral *hemispheres*. Its surface is corrugated by deep and ramified sulci, with laminæ between, and is covered by vascular pia mater. A section through it has a ramified appearance, which has received the name *arbor vitæ*. Within the pia mater is a continuous layer of grey matter, the *cortex*, and within this, in each lamina, a *white centre*. The white centres of the various laminæ unite to form a central white mass, much larger in the hemispheres than in the worm. Within this central mass, and quite near the fourth ventricle, which is covered in dorsally by the cerebellum, are certain nuclei of grey matter—viz. in the hemisphere, the wavy *nucleus dentatus*,

already mentioned as giving origin to the fibres of the superior peduncle; and in the worm, on each side, the *nucleus tecti*, the *nucleus globosus*, and the *nucleus emboliformis*. These all contain many small nerve-cells, and probably all receive fibres from the cortical grey matter.

The *grey matter of the cortex cerebelli* has its nerve-cells arranged to form three strata (fig. 476). The middle of these is formed by an incomplete layer of very large flask-shaped cells—the *cells of Purkinje*. These have large, greatly branching dendrons extending into the outer stratum, and an axon which extends through the inner stratum into the white centre: it gives off collaterals which run backwards into the outer stratum. The inner stratum, which lies between Purkinje's cells and the white centre of each lamina, is mainly formed of very small nerve-cells (*granule-layer*). These have short dendrons with moss-like endings, and axons which pass between Purkinje's cells into the outer stratum and there bifurcate; here they become fine medullated fibres which run parallel to the direction of the lamina, and are therefore cut across in sections transverse to the lamina (fig. 477, I.) and longitudinally in sections parallel to the direction of the lamina (fig. 477, II.). On the other hand the branches of the dendrons of Purkinje's cells spread out over a considerable area across the direction of the lamina, but not parallel to it.

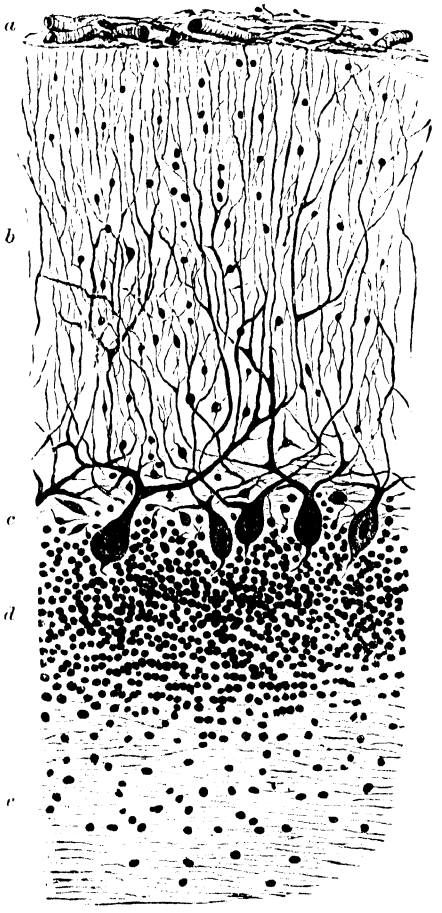


FIG. 476.—SECTION OF CEREBELLAR CORTEX. (Sankey.)

a, pia mater; *b*, molecular layer; *c*, cells of Purkinje; *d*, granule-layer; *e*, white centre.

Amongst the granules are some larger nerve-cells (*cells of Golgi*, fig. 479, G) with axons ending in numerous ramifications near the cell-body, and also the moss-like endings of afferent nerve-fibres, which form synapses with the dendrons of the small nerve-cells. Other afferent nerve-fibres pass through this layer and form synapses with the dendritic processes of Purkinje's cells (*climbing fibres*, fig. 479, *cl. f.*).

The *outer* or *molecular layer of the cerebellar cortex* is largely formed of the branching dendrons of Purkinje's cells and of the branches of the axons from the granules of the inner stratum. But it has in addition certain cells—the so-called *basket-cells*—which have dendrons spreading in the outer layer, but whose axons pass to the cell-bodies of Purkinje's cells and end in basket-like synapses around these and around the axons which are continued from them (fig. 478).

The vertical neuroglia-cells in the cerebellar cortex (fig. 479, gl^3) have already been noticed. It also contains neuroglia-cells of the 'spider' and 'arborescent' types (gl^1, gl^2)

Mid-brain.—The mid-brain (figs. 480, 482) is the direct continuation of the pons towards the cerebrum, but the transverse fibres of the middle cerebellar

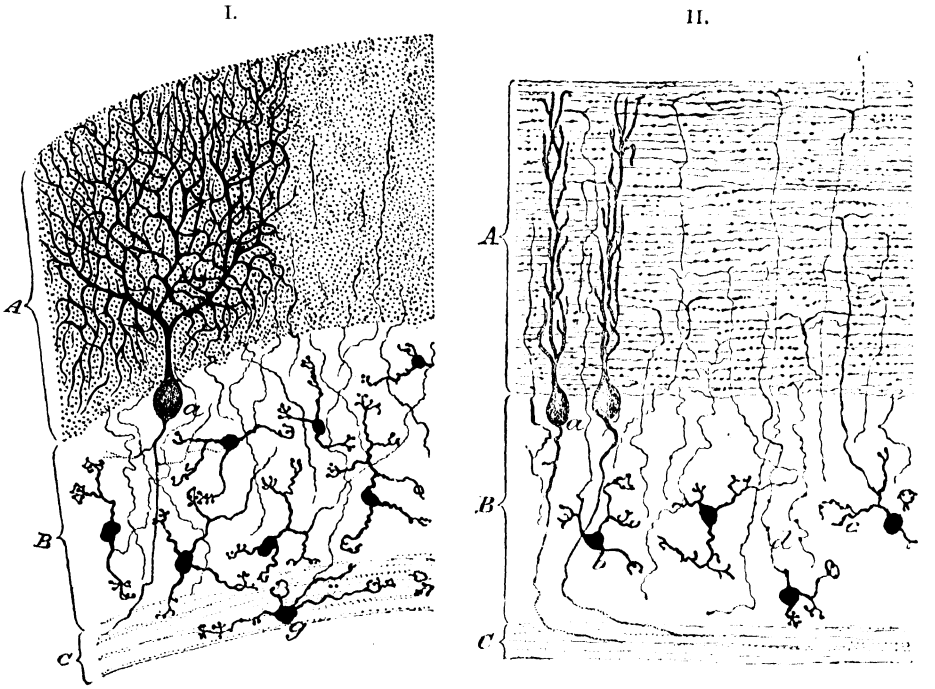


FIG. 477.—STRUCTURE OF CORTEX OF CEREBELLUM. Golgi method. (Cajal.)

I. Section across lamina. II. Section parallel to lamina.
A, molecular layer; B, granular layer; C, white centre.

a, bodies of cells of Purkinje; *b*, one of the granules; *c*, dendron of a granule; *d*, axon of another granule; *e*, an axon bifurcating in the molecular layer; *g*, a granule lying among the fibres of the white centre.

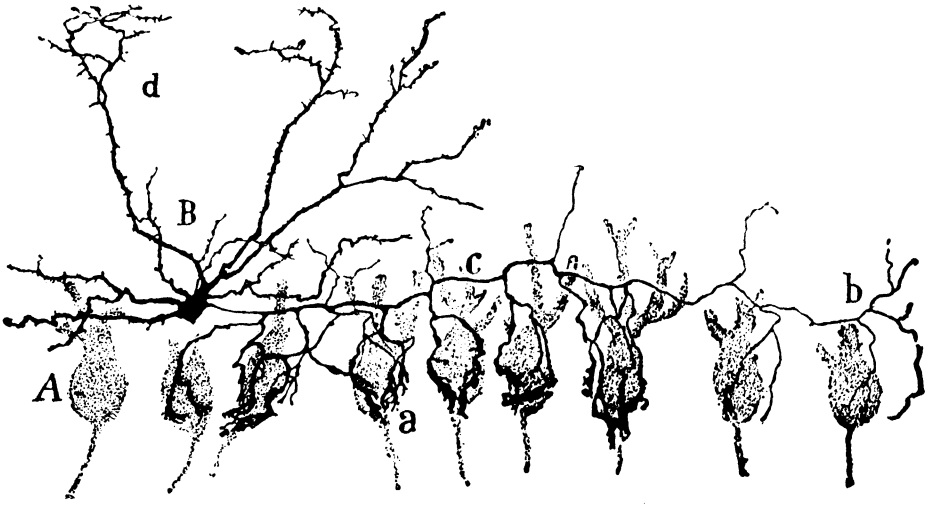


FIG. 478.—A BASKET-CELL FROM THE CEREBELLUM. (Cajal.)

A, Purkinje cells; B, basket-cell; *a*, *b*, terminations of its axon, *c*, in synapses around the Purkinje cells; *d*, one of its dendrons

x 2

peduncles which characterise and give its name to the pons have disappeared. The pyramid-bundles of the pons are collected in the ventral part of the mid-brain on either side of the middle line to form the *crusta* or *pes pedunculi*; the fourth ventricle is narrowed into the small *aqueduct*, which is surrounded by a continuation of *central grey matter*; below it is a continuation of the reticular formation of the pons, here known as the *tegmentum*; ventral to this is the main fillet, which is separated from the crusta by grey matter containing darkly pigmented nerve-cells—the

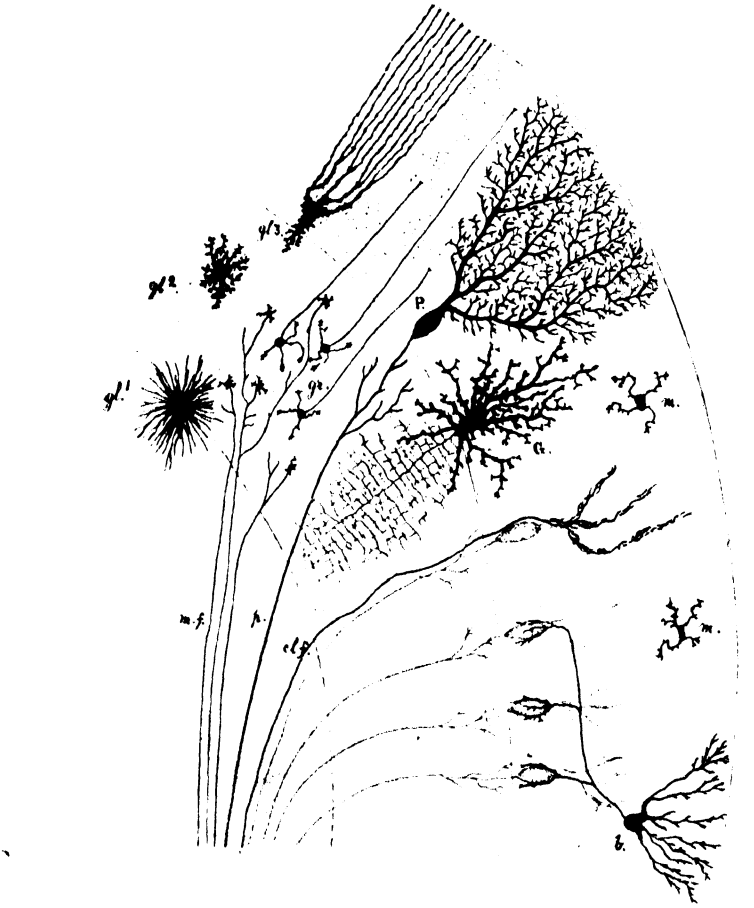


FIG. 479.—DIAGRAM OF ARRANGEMENT OF NERVE-CELLS AND FIBRES IN CEREBELLAR CORTEX. (Kölliker.)

P, cell of Purkinje; *p*, its axon, giving off collaterals near cell-body; G, cell of Golgi; *b*, basket-cell; *m*, *m*, small cells of molecular layer; *gr*, cells of granule-layer; *m.f.*, afferent fibres (moss-fibres) ending in granule-layer; *cl.f.*, a climbing afferent fibre ending in a synapse around the dendrons of a Purkinje cell; gl^1, gl^2, gl^3, three types of neuroglia-cells.

substantia nigra; within the tegmentum is the round bundle of the *superior cerebellar peduncle* in the lower part of the mid-brain and the *red nucleus* in the higher part; at the side of the tegmentum is the *lateral fillet*. Characteristic of this part of the brain are four prominent tubercles, two on each side, overlying the dorsal part of the central grey matter; these are the *anterior and posterior quadrigeminal bodies* (*anterior and posterior tubercles*). The nuclei from which the fibres of the third and fourth nerves originate lie in the central grey matter ventral to the aqueduct, on each side of the middle line. The fibres of the fourth nerve have

been seen in the pons; those of the third nerve pass ventrally to emerge, for the most part on the same side, opposite the situation of the substantia nigra, not far from the middle line. A well-marked feature of this part of the brain—seen also in the pons—is a longitudinal white bundle which runs on each side, just ventral to the central grey matter close to the middle line. This is the *dorsal longitudinal bundle* (figs. 480, 482, *p.l.b.*); its fibres originate from cells in the reticular formation of the pons and medulla oblongata (from the cells of Deiters' nucleus amongst others), and crossing the raphe divide on the opposite side into ascending and descending branches. These either end in or send collaterals to all the motor nuclei in succession from the oculo-motor down to the ventral-horn cells of the

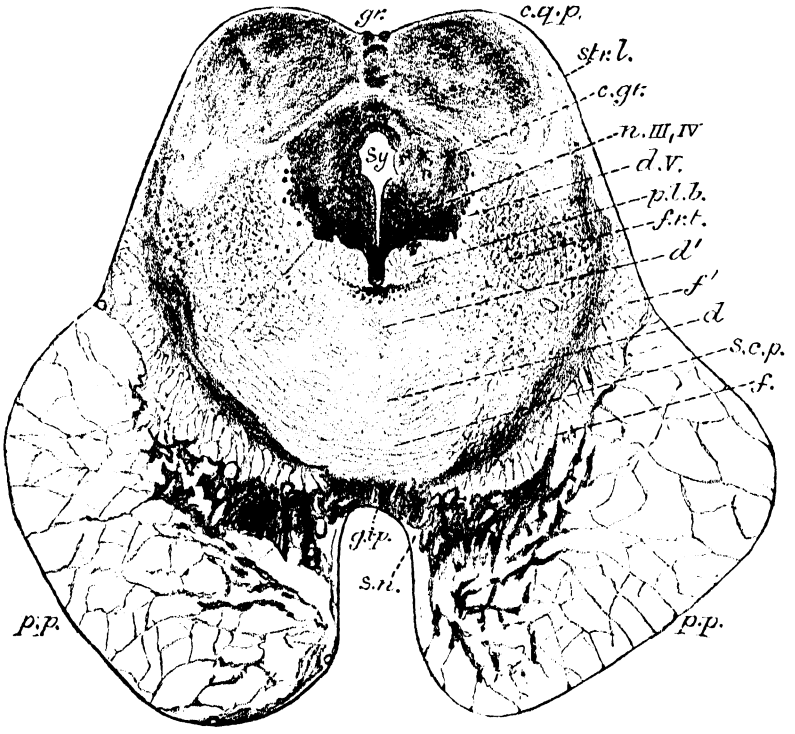


FIG. 480.—SECTION ACROSS THE MID-BRAIN, THROUGH THE POSTERIOR CORPORA QUADRIGEMINA. (Schäfer.)

gr, median groove; *c.q.p.*, posterior tubercle; *c.gr.*, central grey matter; *n.III, IV*, oculo-motor nucleus; *d.V.*, descending motor root of fifth nerve; *p.l.b.*, posterior or dorsal longitudinal bundle; *f.r.t.*, reticular formation of tegmentum; *d*, *d'*, decussating fibres of tracts in tegmentum; *s.c.p.*, decussation of superior cerebellar peduncles; *f.*, main fillet; *f'*, lateral fillet; *str.l.*, superficial layer of fillet over tubercle; *p.p.*, pes pedunculi; *s.n.*, substantia nigra; *g.i.p.*, interpeduncular ganglion; *Sy*, aqueduct of Sylvius.

lower part of the spinal cord. In the cord they form part of the ventro-lateral descending fibres, collaterals from which pass freely into the ventral horn. The dorsal longitudinal bundle receives an accession of fibres from a nucleus in the upper part of the mid-brain close to the uppermost limit of the bundle; this nucleus is known as the *nucleus of the dorsal longitudinal bundle.*

Ventral to the dorsal longitudinal bundle in the mid-brain is a less defined longitudinal white bundle, known as the *ventral longitudinal bundle.* Its fibres are also traceable down into the ventro-lateral column of the cord, and also communicate with the motor nuclei: they are believed to arise from cells in the opposite anterior tubercle of the mid-brain, but the cells from which they originate are not

definitely known. Still more deeply placed in the tegmentum is the superior cerebellar peduncle, which in sections through the posterior tubercles (fig. 480, *s.c.p.*) may be seen decussating with its fellow of the opposite side, and in sections through the anterior tubercles is observed to be continued into the red nucleus (fig. 482, *r.n.*). From the cells of the red nucleus on the other hand fibres arise, which cross the raphe again and pass downwards through the pons and bulb, eventually reaching the spinal cord, in which they can be traced in its lateral column, vertical to the crossed pyramid tract, finally ending in the grey matter of the lateral and ventral horns. The bundle which they form is termed the *rubro-spinal bundle.*

Structure of the corpora quadrigemina. — The substance of the corpora quadrigemina proper differs in structure in the two pairs of tubercles, posterior and anterior. That of the *posterior tubercle* (fig. 481) has a central nucleus of grey matter with a white layer superficial to it and another between it and the grey

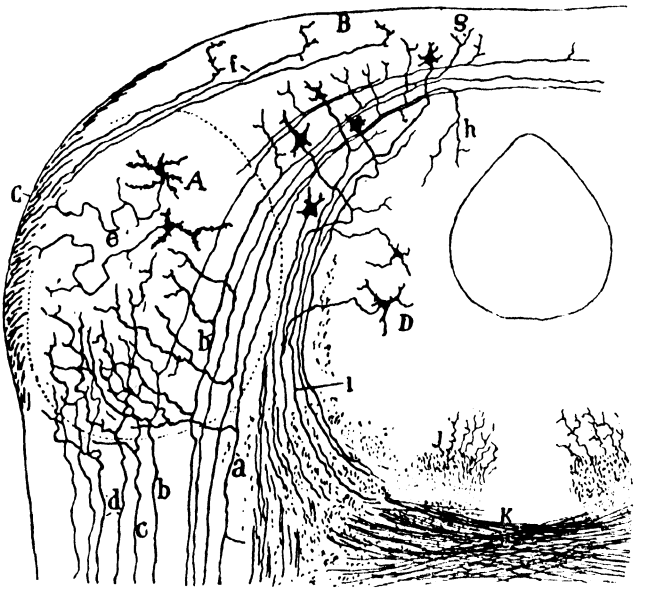


FIG. 481.—ARRANGEMENT OF CELLS AND FIBRES IN POSTERIOR CORPORA QUADRIGEMINA. (Cajal.)

A, principal nucleus; B, C, cortical white layer; D, grey matter around aqueduct; *a, b, c, d, g, h*, fibres of lateral fillet; *e*, axons of cells passing to brachium; *f*, fibres of brachium entering cortical layer; *j*, collaterals of dorsal longitudinal bundle passing to oculo-motor nucleus; *l*, deep white layer.

matter of the aqueduct. The cells of the grey nucleus send their axons chiefly into the superficial layer. The deeper white layer is largely composed of fibres from the lateral or acoustic fillet which end in the nucleus.

The *anterior tubercle* shows four layers of cells (fig. 483). Those of the superficial layer have for the most part a horizontal arrangement; those of the second a vertical arrangement; while in the third and fourth the cells are more irregularly placed. The substance of the third layer is largely formed, between its cells, of fibres derived from the *optic tract*; these run obliquely towards the surface and end by ramifying amongst the cells of the more superficial layers. The deepest layer contains some afferent fibres from the fillet, but most of its fibres are efferent, for the axons of many of the cells of the tubercle pass into it. Some of these axons are passing to form the ventral longitudinal bundle above referred to.

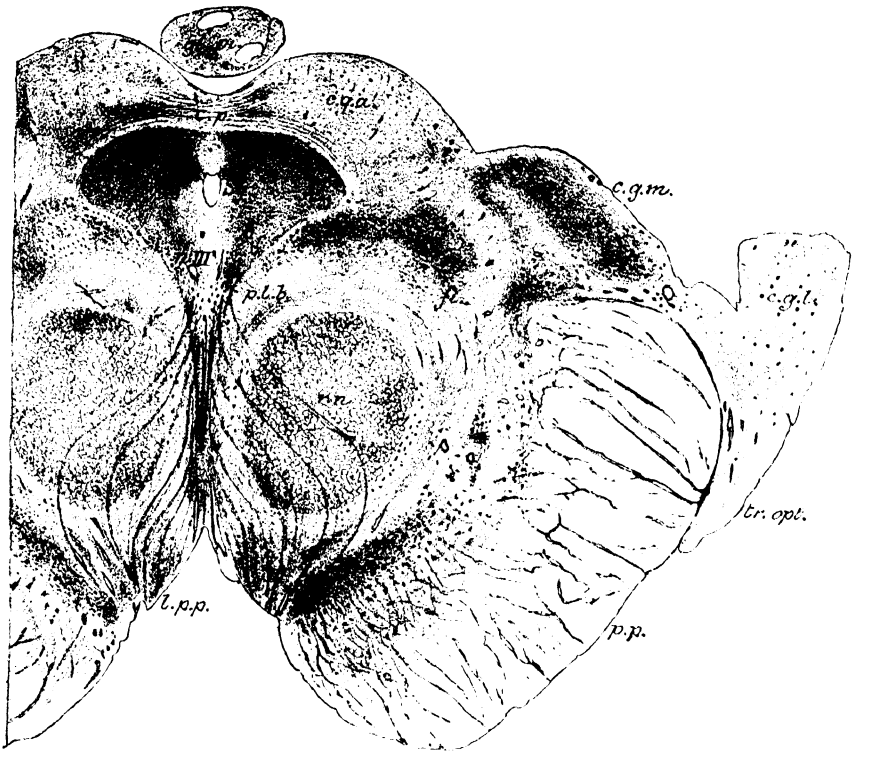


FIG. 482.—SECTION ACROSS THE MID-BRAIN, THROUGH THE ANTERIOR CORPORA QUADRIGEMINA. (Schäfer.)

c.q.a., grey matter of anterior tubercle; *c.g.m.*, mesial geniculate body; *c.g.l.*, lateral geniculate body; *tr.opt.*, optic tract; *gl.pi.*, pineal gland; *c.p.*, posterior commissure; *Sy.*, aqueduct of Sylvius; *n.III.*, nucleus of third nerve; *III.*, fibres of third nerve; *p.l.b.*, dorsal longitudinal bundle; *fi.*, upper fillet; *r.n.*, red nucleus; *p.p.*, pes pedunculi; *l.p.p.*, posterior perforated space.

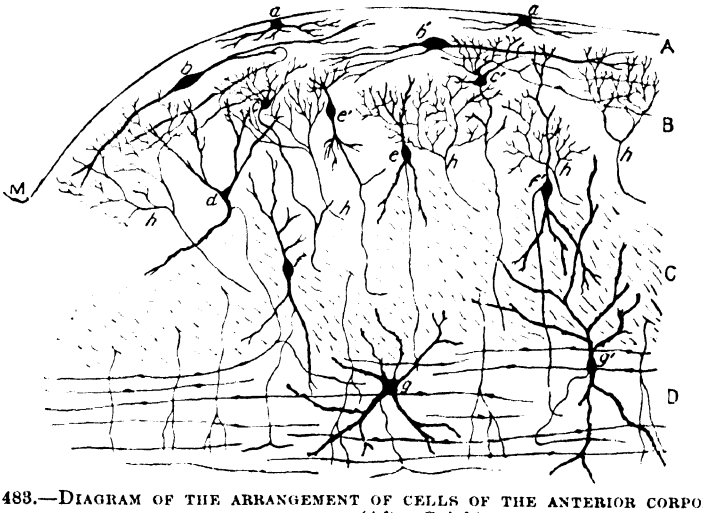


FIG. 483.—DIAGRAM OF THE ARRANGEMENT OF CELLS OF THE ANTERIOR CORPORA QUADRIGEMINA. (After Cajal.)

M, median groove; *A*, superficial white layer; *B*, grey cap; *C*, optic-fibre layer; *D*, fillet layer; *a* to *g*, types of cells of the several layers; *h*, optic nerve-fibres ending in surface layers

Cerebral hemispheres.—A section through the grey cortex of the cerebral hemispheres shows a less distinct stratification than one through that of the cerebellum. The general shape of the cells of the cerebral cortex is conical or pyramidal, and they are arranged vertically with the base towards the white centre, and the apex passing towards the surface (fig. 489). The apex is always a dendron; it usually remains unbranched for a short distance. It then bifurcates, and the branches again dividing similarly it becomes resolved into a spreading cluster of twigs, which interlace with those of other cells in the more superficial layers. From the body of each pyramidal cell other dendrons arise and ramify in the neighbourhood of the cyton. The axon arises from the base of the cell (sometimes from a dendron) and passes into the white centre: before it does so it gives off collaterals to the grey matter. In a few cases the axon turns up towards the superficial layers (*cells of Martinotti*). Certain cells are different from those described. Some have a pencil of dendrons proceeding from either end of the spindle-shaped cell-body (*double-brush cells*). Others are variable in shape (*polymorphous cells*) tending to be stellate: some of these belong to Golgi's second type, with the axon ramifying in the neighbourhood of the cell. The most superficial layer has characteristic horizontally disposed cells (*cells of Cajal*). In the rest of the thickness of the cortex the pyramidal cells increase in

FIG. 484.—TYPES OF CELLS OF THE CORTEX CEREBRI AND THEIR ARRANGEMENT. (From L. F. Barker, after Starr, Strong, and Leaming.)

a, *b*, *c*, horizontal cells of Cajal in superficial layer; *d*, *e*, small pyramids; *f*, a medium pyramid; *g*, *g*, large pyramids; *k*, *m*, *n*, cells of Golgi's second type, with axon ending in grey matter near cell-body; *m*, a cell sending its axon towards the surface; *p*, *q*, polymorphous cells; *r*, *r*, afferent fibres to cortex from white matter.

size in the successive layers reckoned from without in; small, medium, and large pyramids being distinguished and giving their names to the layers in which they

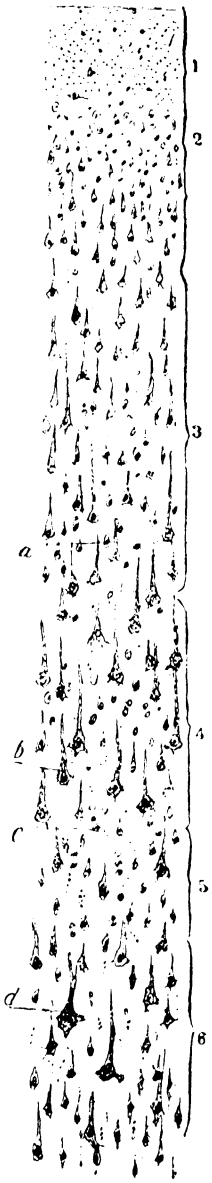


FIG. 485.—SECTION OF MOTOR CORTEX (PRECENTRAL GYRUS) OF MAN. Nissl method. (Cajal.)

1 to 6, successive layers of cortex; *a*, *c*, granules (small nerve-cells); *b*, large pyramids; *d*, a giant 'Betz' cell.

FIG. 486.—SECTION OF POST-CENTRAL GYRUS OF MAN. Nissl method. (Cajal.)

1, plexiform layer; 2, small pyramids; 3, medium pyramids; 4, large pyramids; 5, small cells (granules); 6, 7, deep medium and large pyramids; 8, fusiform and polymorphous cells.

are found most numerously. Bundles of nerve-fibres are seen passing from the white centre into the cortex. Some are efferent and are derived from the axons of the cortical cells; others are afferent and ramify among those cells.

In different regions of the cortex there is considerable variation in the size, form, and arrangement of the cells, the most striking differences being found in the motor cortex of the frontal lobe, and in the parts of the cortex concerned with reception of sensory impulses. The *motor cortex* (fig. 485) is characterised by the

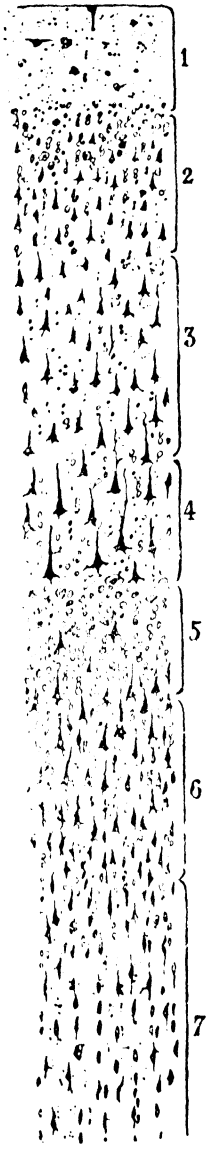


FIG. 487.—SECTION OF FIRST TEMPORAL GYRUS OF MAN. Nissl method. (Cajal.)

1, plexiform layer; 2, small; 3, medium; 4, large pyramids; 5, granular layer; 6, deep pyramids; 7, fusiform and polymorphous cells.

FIG. 488.—SECTION OF CALCARINE (VISUAL) CORTEX OF MAN. (Cajal.)

1, plexiform (molecular layer); 2, small pyramids; 3, medium pyramids; 4, large stellate cells (characteristic of this part of the cortex); 5, layer of small cells (granules) of stellate form; 6, layer containing pyramids; 6', large pyramids; 7, layer of small cells (granules) of pyramid form; 8, fusiform and polymorphous cells.

presence of very large 'giant' cells (Betz), amongst the larger ordinary pyramids: they are usually in small groups. They give origin to the fibres of the pyramid-tract and undergo Nissl degeneration when these fibres are severed. Most of the sensory and percipient parts of the cortex—parietal lobe (fig. 486), temporal lobe

(fig. 487), occipital lobe (fig. 488)—are noteworthy by reason of the fact that great numbers of small nerve-cells ('granules') are seen forming either one or two strata between those formed by the pyramidal cells. This is especially the case in the visual and auditory areas of the cortex, and it is amongst these 'granules' that

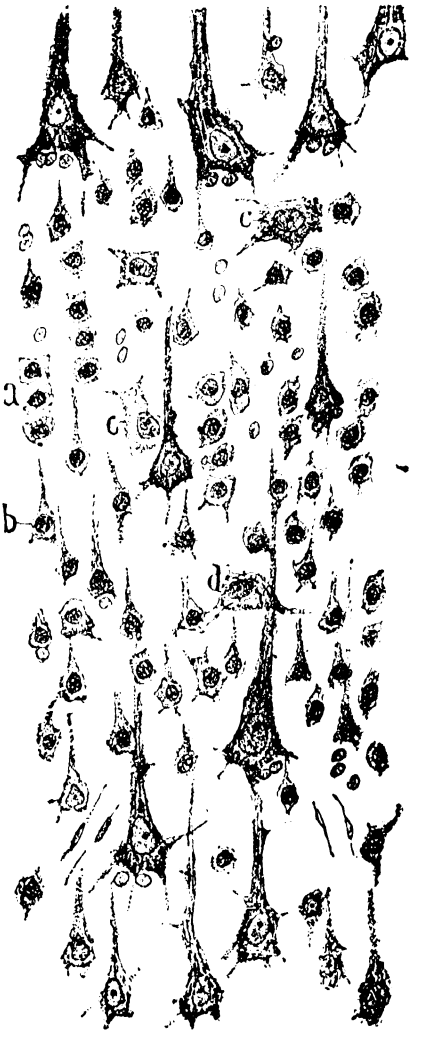


FIG. 489. — PART OF A SECTION OF POST-CENTRAL GYRUS[1] OF MAN. Nissl method. (Cajal.)

The section includes some of the large pyramid-cells, and part of the layer of small nerve cells or granules, which exhibit different forms as illustrated by *a*, *b*, *c*, and *d*.

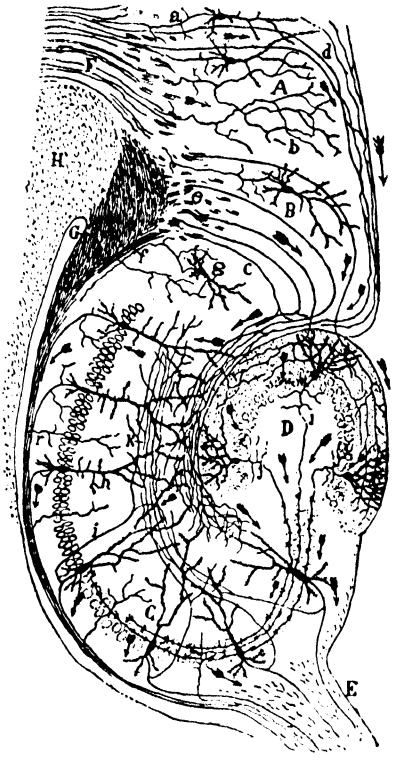


FIG. 490.—HIPPOCAMPAL REGION OF CORTEX. (Cajal.)

A, B, hippocampal gyrus; C, C, hippocampus; D, dentate gyrus; E, fimbria; F, white matter of hippocampal gyrus; G (in lateral ventricle), points to fibres which have crossed from hippocampal region of opposite side; H, fibres of corpus callosum cut across; *a*, axons of pyramid-cells of hippocampal gyrus; *b*, afferent fibres passing into grey matter of this gyrus; *c*, others passing to hippocampus and dentate gyrus; *d*, others at surface passing through and over hippocampal gyrus and entering hippocampus; *e*, fibres cut obliquely; *f*, fibres of alveus; *g*, *h*, pyramid-cells of hippocampus sending axons into alveus and towards fimbria; *i*, *k*, collaterals entering grey matter; *r*, collaterals of afferent fibres in alveus.

most of the afferent fibres to those parts of the cortex end in ramifications, producing one or two well-marked white lines in sections of the grey cortex, which are known as the *lines of Baillarger* (*line of Gennari* in occipital cortex). The olfactory area (hippocampal region) shows peculiarities of structure even more marked than those of the other sensory areas (fig. 490). It is on the whole simpler

[1] This region probably subserves tactile sensibility.

than the rest, and its pyramid-cells—at least those of the hippocampus proper—are in one layer only, as is the case in the whole of the cortex of the lowest vertebrata. In the dentate gyrus, which adjoins the hippocampus, all the cells are very small. But in the hippocampal gyrus, which bounds the hippocampus on the other side, and also belongs to the olfactory area, the layers of cells are much more numerous. This gyrus is characterised by the presence of groups or islets of cells in its more superficial layers (fig. 491). The structure of the olfactory bulb has already been noticed (fig. 459).[1]

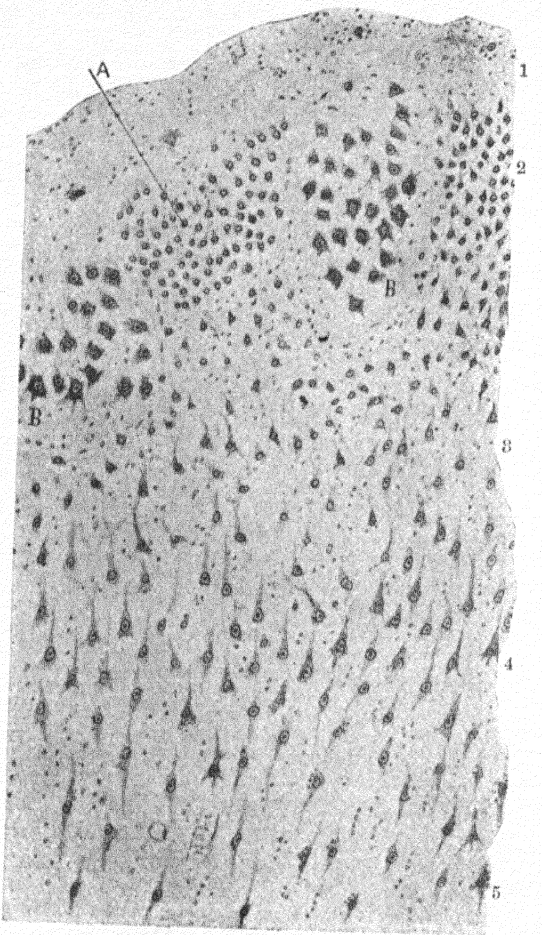


FIG. 491.—SECTION OF CORTEX OF HIPPOCAMPAL GYRUS, SHOWING THE CHARACTERISTIC ISLETS OF CELLS NEAR THE SURFACE. (Cajal.)

A, islet of small cells; B, islet of large cells; 1, 2, 3, 4, 5, successive layers of the cortex.

The fibres which arise from the cells of the cerebral cortex and pass into its white centre take various directions (fig. 492). Some go as *projection-fibres* into the internal capsule, and from this either into the grey masses of the corpus striatum and thalamus, or, passing through the internal capsule, are continued down in the crusta of the mid-brain. Some end in the grey matter of that part,

[1] A detailed account of the structure of the several areas of the cerebral cortex is given in Neurology (Vol. III. Part I. of this work).

others reach the grey matter of the pons and there terminate, and yet others pass down the medulla oblongata and spinal cord as the tract of the pyramid. Certain fibres of the cerebral cortex pass as *association-fibres* to other parts of the cortex, either of the same hemisphere, or, traversing the great longitudinal fissure in the commissure known as the *corpus callosum*, are distributed as *commissural fibres* to the cortex of the opposite hemisphere. The commissural fibres of the olfactory region pass across from one hemisphere to the other in the *anterior commissure.*

Corpus striatum and thalamus.—Two large masses of grey matter are situated in the white matter of the cerebral hemisphere near its base, and in close relationship to the lateral and third ventricles. They receive many nerve-fibres from the cerebral cortex, and on the other hand the axons of many of their cells pass to the cortex. Their cells are arranged in groups or nuclei, the connexions of which are as yet very imperfectly understood. The *thalamus* is undoubtedly a recipient of many fibres from afferent or sensory tracts (fig. 493). The bulk of the fibres of the upper fillet terminate in it, as do the secondary sensory tracts of the fifth and of

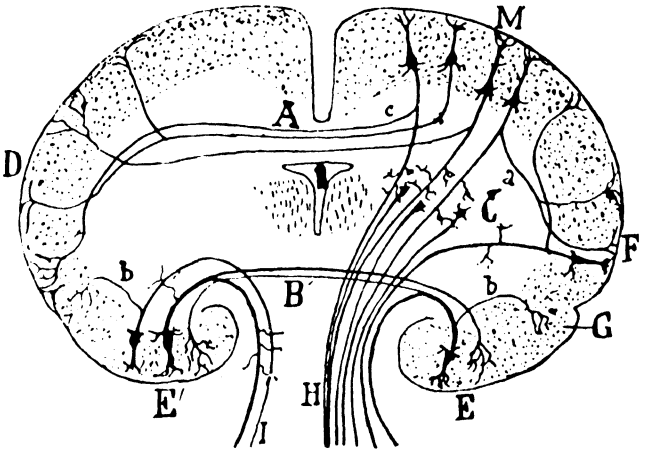


FIG. 492.—DIAGRAM SHOWING PROJECTION-, ASSOCIATION-, AND COMMISSURAL FIBRES ARISING FROM CELLS OF THE CORTEX CEREBRI. (Cajal.)

A, commissural fibres in corpus callosum; B, commissural fibres in anterior commissure; C, corpus striatum; D, ending of commissural fibres in grey matter of opposite hemisphere; E, hippocampal cortex; F, G, endings of association-fibres, derived from motor and hippocampal cortex; H, projection-fibres from cortex and corpus callosum; I, projection-fibres from hippocampal cortex; *a*, *b*, *c*, collaterals.

other sensory cerebral nerves. It also receives posteriorly (into the lateral geniculate body and the adjacent part of the thalamus) many fibres of the optic tract; and into the mesial geniculate body fibres connected with the secondary acoustic tract; while the nucleus of the mamillary body at its base receives fibres of the secondary olfactory tract. The nuclei of the thalamus are very numerous; their cells vary greatly in size and characters.

Below, the thalamus is continued into the *hypothalamus*, which is a direct anterior continuation of the tegmentum of the mid-brain. It contains the superior (anterior) end of the red nucleus, besides other nuclei, such as the *corpus subthalamicum* of Luys, peculiar to itself, as well as the continuation cerebral-wards of several of the tracts of the tegmentum.

The *corpus striatum* is formed of two parts. The part known as the *nucleus lenticularis* is separated from the other, termed the *nucleus caudatus*, and from the optic thalamus, by the flattened mass of white fibres of the internal capsule. These are for the most part, as already noticed, fibres which are passing between

the crusta of the mid-brain and the white centre and cortex of the cerebral hemisphere. In their passage they give off many collaterals to the nuclei on either side and also receive additions from those nuclei. Both nuclei of the corpus striatum contain many small nerve-cells of Golgi's second type, with their axons ending within the nuclei, and others of all sizes—some being large and with widely extended dendrons—of Golgi's first type, with the axons passing out from the nuclei (fig. 494). Many of the nerve-cells contain a considerable amount of reddish-yellow pigment in man.

The **membranes of the brain** are similar in general structure and arrangement to those of similar name of the spinal cord. The *dura mater* of the brain is, however, closely attached to

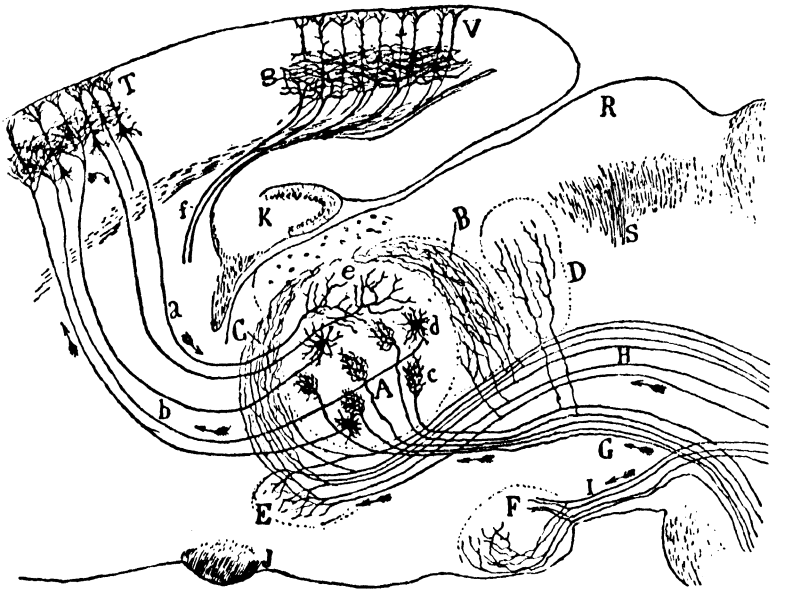


FIG. 493.—DIAGRAM OF THE CONNEXIONS OF THE THALAMUS WITH THE FIBRES OF THE SENSORY TRACTS AND WITH THE CORTEX CEREBRI. (Cajal.)

A, chief sensory nucleus; B, C, accessory (semilunar) nuclei; D, posterior nucleus; E, nucleus of zona incerta of hypothalamus; F, nucleus of mamillary body; G, fibres of upper fillet; *c*, their arborisation in the chief nucleus—collaterals are seen passing to the posterior nucleus; H, fibres of secondary or central tract of fifth nerve, passing to accessory nuclei and to zona incerta; I, fibres ending in mamillary body; J, optic chiasma; K, outline of hippocampus; R, outline of anterior colliculus of corpora quadrigemina; S, fibres of optic tract; T, cells of cortex, sending axons, *a*, to end in ramifications, *e*, in chief nucleus of thalamus; *b*, axons of thalamus cells, *d*, passing to end in cortex cerebri; V, visual cortex; *f*, afferent fibres passing from lateral geniculate body and thalamus and ending in visual cortex by arborisations in the stria of Gennari, *g*. The arrows indicate the course taken by nerve-impulses.

the inner surface of the skull, and furnishes it with periosteum. It is split at certain places to contain large venous sinuses, which convey blood away from the brain, and it sends between the two hemispheres a strong vertical fibrous septum, the *falx cerebri*, whilst between the cerebrum and cerebellum a horizontal septum, the *tentorium cerebelli*, extends, which is attached in front to the back of the falx cerebri; and below the tentorium, projecting downwards from its posterior border, is another, smaller, vertical septum, between the hemispheres of the cerebellum—the *falx cerebelli*.

The *arachnoid membrane* of the brain differs from that of the cord in being separated from the pia mater only in certain places. At these are considerable spaces, known as the *cisternæ arachnoidales*; so that in these situations the sub-arachnoid space is wide. But in other parts the arachnoid is closely applied to the pia mater, instead of to the dura mater as in the cord, and the subdural space is large. In other places it occupies an intermediate position. Between it and the pia mater are numerous connective-tissue trabeculæ. In the neighbourhood of the

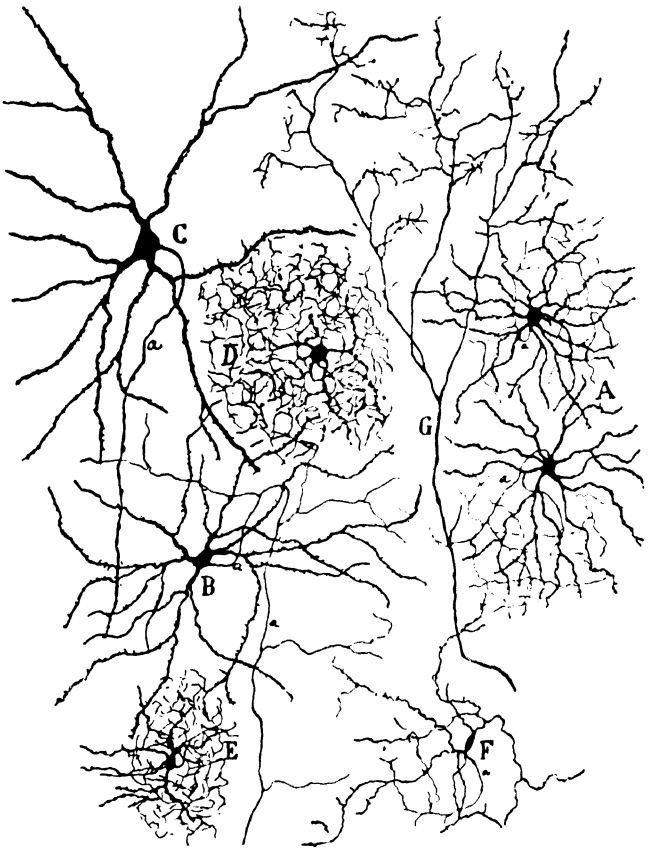


FIG. 494.—CELLS OF CORPUS STRIATUM. Golgi method. (Cajal.)
A, D, E, F, cells with axons ramifying near cell-body; B, C, large cells with long axons; G, an afferent nerve-fibre ending in the grey matter.

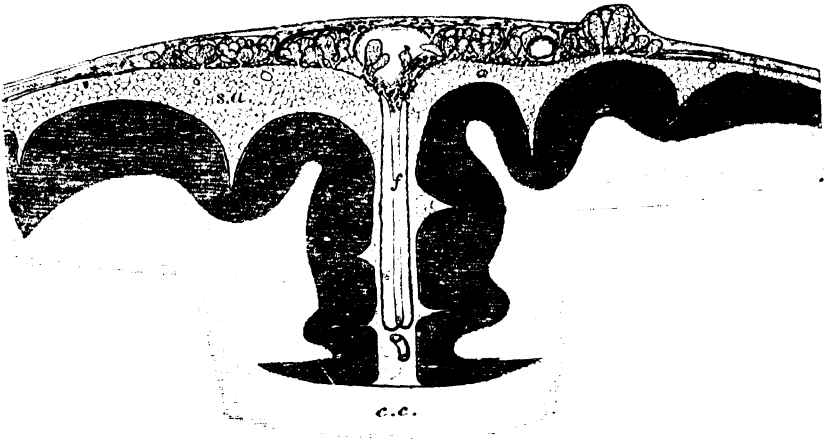


FIG. 495.—SECTION OF BRAIN AND MEMBRANES IN THE REGION OF THE SUPERIOR SAGITTAL SINUS. (Key and Retzius.)

c.c., corpus callosum; *f*, falx; *s.a.*, subarachnoid space, with fine connective-tissue trabeculæ. From the arachnoid fungiform projections (arachnoid villi) are seen projecting into the subdural space and into the venous sinus.

venous sinuses in the dura mater the arachnoid exhibits numerous villus-like outgrowths (arachnoid villi, Pacchionian granulations) (fig. 495) which project into the subdural space and even grow, covered with a thin layer of invaginated dura mater, into the venous sinuses of that membrane. These villi, although closed, appear readily to permit the filtration of cerebro-spinal fluid from the subarachnoid space into the subdural space and even into the venous sinuses. There are no lymphatic vessels in the central nervous system, and the only other path of exit for the cerebro-spinal fluid is along the sheaths of the nerve-roots and nerve-trunks, which are lamellated, with crevices between the layers, and are continuous with the membranes of the brain and cord.

The encephalic *pia mater*, which dips into all the sulci between the convolutions of the cerebrum and between the laminæ of the cerebellum, gives off its blood-vessels directly into the cortical grey matter. It is invaginated at the side of the brain into the lateral ventricles—but does not project naked into them, for it is covered with ependymal epithelium—and similarly over the third ventricle, forming the *velum interpositum* or *tela choroidea* and the *choroid plexuses* of those ventricles. It is also prolonged over the fourth ventricle, forming its choroid plexuses (p. 300). These plexuses, which are in all probability concerned with the secretion of cerebro-spinal fluid, are composed of close capillary networks, which are covered everywhere on the side of the ventricle with a prolongation of its ependymal epithelium, which is here of a flattened character and non-ciliated.

THE VASCULAR SYSTEM:

INCLUDING THE HEART, BLOOD-VESSELS, AND LYMPH-VESSELS.

By PROFESSOR GUSTAV MANN.

The vascular system, or circulatory system, consists of the heart and blood-vessels, which are lined by specially modified connective-tissue cells, mesodermal in origin, which form the endothelium. Vessels are classified into *arteries*, which come from the heart and are on their way to the tissues; *capillaries*, consisting of only a single layer of endothelium and in close contact with the tissue elements, which they nourish; and *veins*, by which the blood returns to the heart. From the veins are developed secondarily the *lymph-vessels*, as is more fully described later.

THE HEART.

Originally a single tube, the heart forms in the higher vertebrates an organ consisting of two auricles or atria and two ventricles, each of which has definite histological features. The heart is surrounded by a special serous cavity, the pericardial space, which is an enlarged lymph-space and is lined by a single layer of endothelial cells. The serous membrane is reflected over the heart and becomes so firmly attached to the outer surface of the latter as to seem to belong to it; it is called the *epicardium* (*visceral pericardium*). The bulk of the heart consists of muscle, called the *myocardium*; while its interior is lined, as already mentioned, by a single layer of endothelial cells belonging to the *endocardium* or membrane lining the cavities of the heart, continuous with the intima of the vessels springing from it.

Epicardium.—The epicardium (fig. 496) varies greatly in thickness according to position, being more developed along the course of the large coronary vessels, in which situation the adipose tissue also is especially abundant. Choosing a thin

Fig. 496.—Epicardium over left ventricle. (Mann.)

a, superficial endothelium; *b*, elastic fibres; from *a* to *b* tunica externa v. superficialis; *c*, tunica media, consisting of coarse tendinous bundles with a few elastic fibres; *d*, tunica profunda; *e*, blood-vessels, and *f*, fat-cells in the tunica profunda, which at *g* is continuous with the connective tissue of the myocardium, *i*. A small nerve, *h*, is seen in the tunica media.

part over the left ventricle we find externally a single layer of endothelium, and next to it a not very sharply defined layer of connective tissue; these form together the tunica externa. Between this layer and the tunica media, which contains small blood-capillaries, lymph-vessels, and nerves, is an ill-defined strand of elastic

fibres. The tunica profunda of the epicardium contains larger blood-vessels and fat-cells, and is continuous with the connective tissue found in the myocardium.

Myocardium.—The structure of heart-muscle has already been discussed (pp. 197 to 202). The arrangement of the fibres is complicated, passing, as they do, in different layers, obliquely, transversely, or vertically, and terminating in the fibrous tissue forming the annular rings at the base of the ventricles, and in the chordæ tendineæ of the papillary muscles. Many fibres are common to the two sides of the heart, passing across the median septum between the auricles and that between the ventricles. But on the other hand, at least in mammals, the fibres of the auricles are not continued into those of the ventricles except in the case of one small bundle—the auriculo-ventricular bundle [1]—although such continuity is extensive in lower vertebrates.[2]

The bundle in question consists of fibres which are more embryonic (less differentiated) than the cardiac fibres generally. They are gathered from various parts of the right auricle and auricular septum, but mainly from near the entrance of the coronary sinus, and becoming parallel run forwards into a nodular mass of plexiform structure (node of Tawara) which lies in the inter-auricular septum close to the septum fibrosum between auricles and ventricles. From this node the bundle passes downwards through the septum fibrosum to the upper part of the ventricular septum and divides into two branches which are distributed to the two ventricles, spreading out as they pass to their destination under the endocardium. In the sheep they are continuous with the fibres of Purkinje (Tawara).

Another plexiform mass of similar fibres lies in the wall of the right auricle close to the entrance of the superior cava (Keith and Flack). It is here that the cardiac contractions probably originate. It is richly supplied with nerve-fibres from both vagus and sympathetic.

Endocardium.—The endocardium (figs. 497, 498) forms a complete lining to the whole of the auricular and ventricular cavities, covering the valves, chordæ tendineæ, and papillary muscles. It may be compared to the wall of a vessel, such as the aorta, but with the additional development outside it of a muscular portion, the myocardium. It shows in some regions a division into three tunics—tunica intima, media, and adventitia. The intima is bounded on the side next the blood by a single layer of endothelial cells, which are much more isodiametric than are the corresponding cells in the blood-vessels, but a slight elongation may always be made out. The outlines of these cells are readily revealed by silver nitrate. Immediately external to the endothelium is a fine layer of delicate connective tissue, which abuts on the tunica media. The

FIG. 497.—ENDOCARDIUM OF RIGHT AURICLE. (Mann.)

a, endothelial lining of tunica intima; *b*, white fibrous tissue of tunica intima; *c*, elastic layer composed of very fine elastic fibres and membranes, collectively resembling the internal elastic lamina of medium-sized blood-vessels; *d*, tunica media with coarser bundles of white fibrous tissue than in the intima, with very few elastic fibres; *e*, outer elastic lamina; *f*, tunica adventitia, containing many coarse elastic fibres arranged in a definite layer around the muscle-bundles, *g*; *h*, perimysium internum.

[1] Stanley Kent, Journ. Physiol. xiv. 1893; W. His, jun. Arbeiten aus d. med. Klin. zu Leipzig, 1893; also in Wiener klinische Blätter, 1894; Retzer, Arch. f. Anat. 1904; Bräunig, Arch. f. Physiol. 1904 (Suppl.); Tawara, Zentr. f. Physiol. xix. 1905, and Das Reizleitungssystem des Säugethierherzens, 1906; Keith and Flack, Journ. Anat. and Physiol. xli. 1907; Wenckebach. Arch. f. Physiol. 1907; Wilson, Proc. Roy. Soc. lxxxi.B, 1909; Aschoff, Deutsche med. Wochensch. Nov. 1909; Cohn and Trendelenburg, Pflüger's Arch. cxxxi. 1910.

[2] Gaskell, Journ. of Physiol. v. 43.

tunica media contains elastic fibres which in parts somewhat resemble the elastic membranes found in the aorta (fig. 497, *c*). This description holds good especially for the auricular wall close to the auriculo-ventricular orifice, while on the ventricular side of this opening the elastic membranes are grouped so closely together as to give rise to an appearance resembling the internal elastic lamina of medium-sized blood-vessels. The tunica media contains in places scattered bundles of non-striped muscle, as first pointed out by Schweigger-Seidel. Outside the tunica media lies

FIG. 498.—ENDOCARDIUM OF RIGHT VENTRICLE COVERING ONE OF THE MUSCLE COLUMNS. (Mann.)
a, endothelial lining; *b*, combined tunica media and adventitia; *c*, myocardium.

the tunica adventitia, in which the elastic fibres are much coarser than in the media, a feature which reminds one of that seen in many vessels. Here also adipose tissue is frequently found. The amount of development of the endocardium is in inverse proportion to that of the myocardium, for in the right auricle the endocardium is four to five times thicker than in the left ventricle (v. Ebner); it is very thin over the musculi pectinati of both auricles and ventricles (fig. 498). Externally the endocardium is continued into the scanty connective-tissue framework of the myocardium, the so-called perimysium internum (fig. 497, *h*);

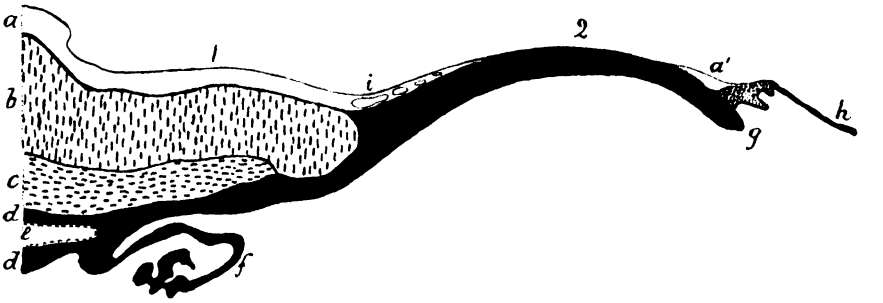


FIG. 499.—DIAGRAM OF SECTION OF MITRAL VALVE, YOUNG NEGRESS (Mann.)
1. Muscular portion. 2. Tendinous portion.
a, ventricular endocardium, thick over the muscular, and thin over the tendinous portion, except at *a'*, where the tunica adventitia contains many elastic fibres; *b*, myocardium; *c*, deep adipose portion of the endocardium, *d*, of the auricular surface; *e*, bundles of non-striped muscle in the tunica media; *f*, auricular fringe; *g*, free edge of the valve; *h*, tendinous cord; *i*, constrictor of the auriculo-ventricular opening composed of non-striped muscle (see fig. 500).

over the papillary muscles and the tendinous cords it is not only very thin but contains a relatively small amount of elastic tissue. On the auriculo-ventricular valves the endocardium is thicker on the auricular side, while on the semilunar valves it is thicker on the ventricular side (v. Ebner).

The auriculo-ventricular valves (fig. 499), in addition to being lined on both sides by endocardium, contain a middle lamella of connective tissue formed by the tunica adventitia of the auricular endocardium and by the terminations of the chordæ tendineæ. The elastic fibres are most abundant in the tunica adventitia on the ventricular side; on the auricular surface are one or two elastic laminæ close

to the endothelium. The greater part of the valve contains no elastic fibres. At the base of the tendinous portion (fig. 499, *a*, and fig. 500, *b*) is a mass of non-striped muscle, which may act as a constrictor of the orifice. The valves are joined to the wall of the heart by strands of connective tissue coming from the

FIG. 500.—THE REGION *i* OF THE PREVIOUS FIGURE MORE HIGHLY MAGNIFIED. (Mann.)
a, endothelial lining of the tunica intima; *b*, tunica media containing bundles of non-striped muscle cut transversely; *c*, part of tunica adventitia containing coarse elastic fibres.

ostia venosa; they contain a few blood-capillaries. The semilunar valves are thinner than the auriculo-ventricular valves, and contain at their base bundles of muscle continuous with the myocardium of the auricles; they are supplied with blood-vessels as far as these strands of muscle extend.[1] The aortic valves (fig. 501) are elastic on the ventricular and tendinous on the aortic surface. The elastic tissue of the heart has been especially studied by Seipp.[2]

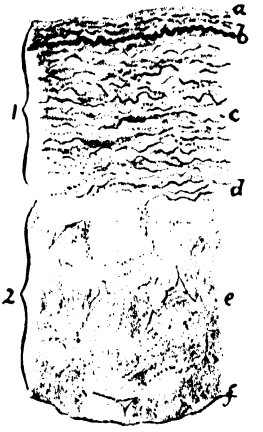


FIG. 501.—LONGITUDINAL SECTION OF HUMAN AORTIC VALVE, ABOUT ITS MIDDLE. (Mann.)
1. Ventricular (elastic) moiety.
2. Aortic (tendinous) moiety.
a, tunica intima of endocardium; *b*, elastic lamina; *c*, white fibrous tissue with large admixture of elastic tissue; *d*, junction of loose ventricular with dense aortic tissue; *e*, compact white fibrous tissue with very delicate elastic fibres arranged round the bundles; *f*, delicate elastic lamina immediately underneath the layer of endothelium on the aortic surface.

Blood-vessels and lymphatics. — The circulatory systems of the heart are represented by the blood-vessels, the lymph-vessels, and the paths along which tissue-lymph travels. The *blood-vessels* are derived from the coronary vessels, and are characterised by soon losing their adventitious coats and then forming a plexus of capillaries running parallel to the long axis of the columns of muscle-elements. Each column is in contact with two or three capillaries and with as many lymph-capillaries[3] (fig. 502). The veins arising from the capillaries retain for a long time the structure of capillaries, being, even in vessels measuring 0·25 mm., composed of a layer of endothelium only.

The *lymph-vessels* of the heart form two superficial plexuses, one under the visceral pericardium, and the other beneath the endocardium. The older histologists (Henle, Schweigger-Seidel) believed the lymph-vessels of the myocardium to be so numerous as to convert the latter into a 'lymphatic sponge'; all the clefts which one sees in sections were believed to represent lymph-vessels. Salvioli demonstrated by injection the existence of true lymph-vessels in the myocardium which are in continuity with those of the peri- and endo-cardium. Bizzozero and Salvioli found a large-meshed system of lymph-vessels in the connective tissue at the base, which open into the lymph-glands between the pleura and pericardium. The visceral pericardium, although considerably thinner than the parietal pericardium,

[1] Oehl (Mem. d. accad. d. sci. di Torino, xx. 1861) has described muscle-bundles, having a certain resemblance to muscle-spindles, in the longer of the chordæ tendineæ of the left auriculo-ventricular valves.

[2] Anat. Hefte, vi. 1896. Seipp finds elastic fibres most abundant in the myocardium of auricles and endocardium of ventricles.

[3] Bock, Anat. Anzeiger, xxvii. 1905.

contains a far more complex lymphatic system. The superficial plexus lies close under the endothelial membrane, being separated from the latter by only a few connective-tissue bundles; it is close-meshed and composed of fine lymph-vessels, and by short branches is in free communication with a second more deeply placed network built up of much larger vessels. The whole of the endocardium is also very rich in lymphatics; that of the papillary muscles especially so. There are more lymphatics in the ventricles than in the auricles, and those of the latter extend even as far as the middle of the atrioventricular valves.

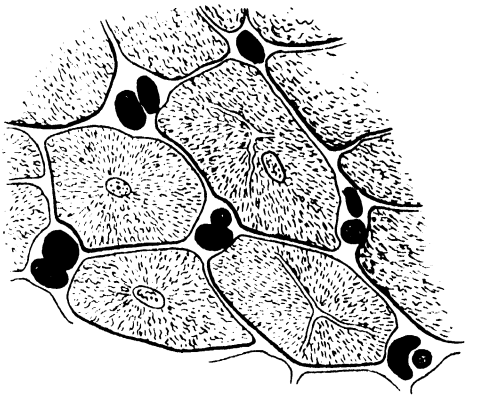


FIG. 502.—SECTION OF MYOCARDIUM WITH BLOOD-VESSELS (RED), AND LYMPHATIC VESSELS (BLUE) INJECTED. (Bock.)

By injecting living hearts, and allowing the heart to distribute the injection-mass by its own activity, Albrecht (quoted by Bock) showed that lymph-vessels pass from the interfascicular connective-tissue lymphatics to the intervals between the muscle-cells, where they form intermuscular capillaries; and Bock—by first kneading the warm heart in normal saline to remove all blood, then injecting the blood-vessels with carmine-gelatine through the coronary arteries, and finally filling the lymph-vessels from near the apex of the heart by means of puncture with Prussian blue—proved that lymph-vessels form as complete a plexus as do the blood-capillaries. Blood- and lymph-capillaries lie usually very close together in the interstices between the muscle-cells (fig. 502), running parallel with one another and occupying the spaces between neighbouring heart-cells, so that each capillary comes in close relation with several cell-units of heart-muscle, and each cell-unit with several capillaries. The lymphatics of the heart are closed vessels lined throughout by endothelium. This is denied by Nyström,[1] but Golgi's method, which he employed, will occasionally be found to have impregnated the whole of the lymph, whether contained in definite lymph-vessels or distributed in tissue clefts. Nyström (fig. 503) figures intracellular channels resembling those found in nerve-cells or liver-cells; this he interprets to indicate that each muscle-cell may have developed special intracellular channels for the ready interchange of fluids and substances in solution.

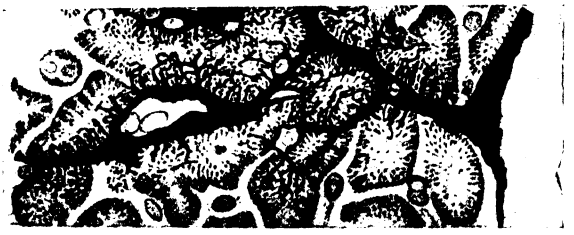


FIG. 503.—SECTION OF MUSCULATURE OF PIG'S HEART. Golgi method. (Nyström.)

The preparation shows intermuscular clefts connected with canaliculi which appear to lead from the interior of the muscle-fibres.

Nerves.—Three distinct systems are to be distinguished in the heart—namely, (1) efferent nerves which terminate in the cardiac ganglia or in the myocardium, (2) nerves which arise in the heart and pass to the cord, and (3) a sympathetic

[1] Arch. f. Anat. u. Physiol. Anat. Abtheil. 1897, p. 361.

ganglionic system. The sympathetic ganglion-cells were discovered by Remak in the heart of the calf in 1844; the distribution of the nerve-fibres has been recently studied by Dogiel,[1] Smirnow,[2] Valedinsky,[3] and Michailow.[4]

Afferent nerves run along the connective-tissue strands of the heart, and are especially abundant under the intima of the endocardium. A *subendocardial*

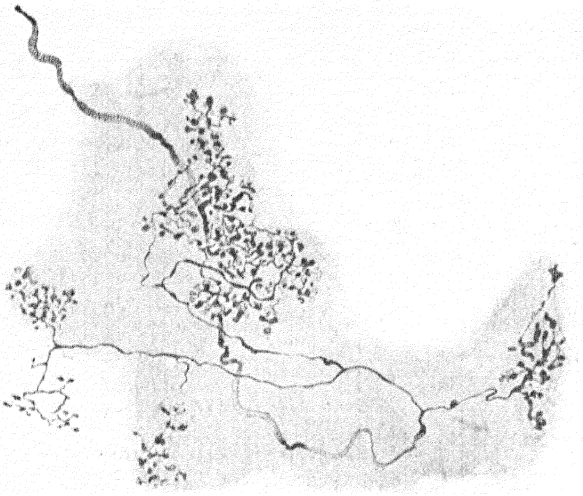


FIG. 504.—TERMINATION OF SENSORY NERVES IN HEART. (Dogiel.)

nerve-plexus lies next to the myocardium, and consists of bundles of fibres from which spring finer trunks containing one to four medullated or non-medullated fibres (usually the latter), which run towards the intima and there give rise to an *endocardial nerve-plexus*. This latter has many of its fibres in direct contact with the endothelial cells of the intima, and spreads into the auriculo-ventricular valves, being especially abundant where the septum passes into the atrium. From the subendocardial plexus arise medullated fibres, which terminate at different levels of the endocardium in special sensory plates after having given rise to numerous terminal non-medullated nerves. The sensory end-plates (fig. 504) are most abundant in the endocardium of the auricles and the auricular septum, but also occur in less complicated forms in the endocardium of the ventricles and in the ventricular septum. Special sensory nerve-terminations are also found in the chordæ tendineæ, while the semilunar valves do not possess sensory end-plates, but only fine fibres (Smirnow). The epicardium also is richly supplied with special end-plates (Dogiel), each of which according to its size may show three to sixteen nuclei which belong to peculiar star-shaped cells, characterised by a small amount of protoplasm, imbedded in which are fine granules. These specialised connective-tissue cells form the supporting framework of the end-plate (fig. 505). All the nerves in the epicardium are derived from

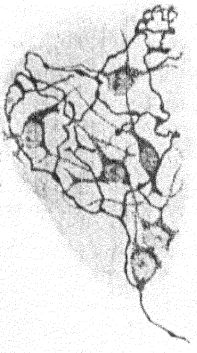


FIG. 505. — END-PLATE WITH STELLATE CELLS IN SENSORY ENDINGS OF HEART. (Dogiel.)

[1] Arch. f. mikr. Anat. liii. 1899. [2] Anat. Hefte, xxvii. 1904–5. [3] *Ibid.*
[4] Anat. Anz. xxxii. 1908.

medullated nerves, and the number of end-plates amounts to from about 100 to 300 per sq. cm., showing that the heart is supplied as abundantly with afferent nerves as is the most sensitive skin-surface.

The endings of the efferent nerves were first observed by Gerlach[1] in the frog, by the use of the gold method. In the interauricular septum they form a complete plexus from which fine fibres go to individual columns of muscle-fibres, and there end after having divided several times on the surface of the columns. Smirnow,[2] working with the methylene-blue method, found the nerve-terminations in fishes, amphibians, and reptiles to be distributed over the greater portion of the 'muscle-cell,' while in mammals the final branch is restricted to a comparatively small portion of the cell (fig. 506).

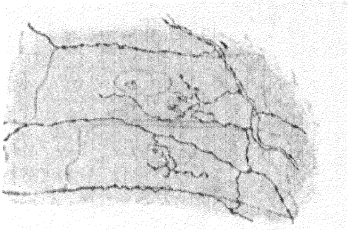


FIG. 506.—ENDINGS OF NERVE-FIBRES IN CARDIAC MUSCLE. (Smirnow.)

FIG. 507.—TWO NERVE-CELLS FROM BELOW THE EPICARDIUM OF THE MIDDLE THIRD OF THE LEFT VENTRICLE OF A NEW-BORN CHILD. (Smirnow.)

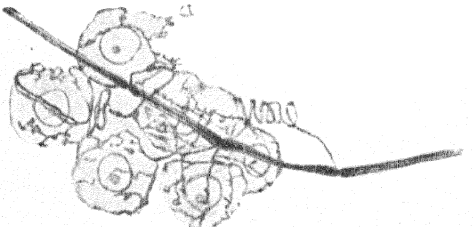


FIG. 508.—GROUP OF NERVE-CELLS, CONNECTED WITH BRANCHES OF A MEDULLATED NERVE-FIBRE, FROM THE OUTER PART OF THE MYOCARDIUM OF THE MIDDLE THIRD OF THE LEFT VENTRICLE OF A RABBIT. (Smirnow.)

Ganglia.—According to Schwartz,[3] the rat's heart shows four to five groups of ganglion-cells lying under the epicardium on the posterior wall of the auricles, more to the left than the right side of the interauricular septum. A similar description has been given for man by Eisenlohr, Ott, and W. His, jun.[4]

FIG. 509.—NERVES ENDING IN HEART GANGLION. (Dogiel.)

[1] Virchow's Arch. lxvi. 1876. [2] Anat. Anzeiger, xviii. 1900.
[3] Arch. f. mikr. Anat. liii. 1899.
[4] Eisenlohr, Über d. Ganglienzellen und Nerven d. menschlichen Herzens, Dissertation, München, 1886; Ott, Prager medizinische Wochenschrift, 1885; and W. His, jun., 'Die Entwickelung d. Herznervensystems bei Wirbeltieren,' Abh. d. math.-physik. Kl. d. K. Sächs. Gesell. d. Wissensch. 1893.

On the other hand, Valedinsky and Smirnow describe ganglion-cells along the course of the nerves down to the very apex of the heart (figs. 507 and 508). Valedinsky also found ganglion-cells to be present in the middle third of the ventricular septum. Dogiel finds numerous ganglia in the subpericardium of the auricles, while in the subpericardium of the ventricles ganglion-cells are rare.

These ganglion-cells, according to Dogiel, are connected with two distinct types of nerve-terminations. Those of the first type, derived from other ganglia, terminate by forming plexuses around both the nerve-cells and their processes,

FIG. 510.—ENDING OF NERVES IN HEART GANGLIA. (Dogiel.)

On the right is shown the terminal arborescence of a nerve-fibre; on the left a group of ganglion-cells belonging to type 2 of Dogiel's sympathetic cells.

but without the nerve-fibres piercing the capsule of the ganglion-cell (fig. 509). The second class of nerve-terminations is spinal-ganglionic in origin. These nerve-fibres are always medullated, but now and then lose their medullary sheath between two nodes of Ranvier. Each fibre supplies several ganglia, giving off two to three branches, which after repeated division pierce the capsule of the ganglion-cells and come thus to lie in direct contact with the cell-body, forming true pericellular nets (fig. 510).

From the small-celled type of ganglion-cells, which are most numerous, fine non-medullated nerve-fibres pass into the myocardium. Other cells serve by their processes to bring about communications with neighbouring ganglia.

BLOOD-VESSELS.

ARTERIES.

These vessels were originally supposed to contain air. This error, which had long prevailed in the schools of medicine, was refuted by Galen, who showed that the vessels called arteries, though for the most part found empty after death, really contain blood in the living body.

The total capacity of the blood-vessels is equal to holding from four to five times the amount of blood normally present, if we judge by the amount of

carmine-gelatine required to distend the blood-vessels until the finest capillaries are of such a diameter as to allow of the easy passage of red blood-corpuscles.

Mode of distribution.—The arteries usually occupy protected situations; thus, after coming out of the great visceral cavities of the body, they run along the limbs for the most part on the adductor side, so that when the limbs are flexed, all the main vessels are out of harm's way.

As they proceed in their course the arteries divide into branches; the division may take place in different modes. An artery may at once resolve itself into two or more branches, no one of which greatly exceeds the rest in magnitude, or it may give off several branches in succession and still maintain its character as a trunk. The branches come off at different angles, most commonly so as to form an acute angle with the further part of the trunk, but sometimes a right or an obtuse angle, of which there are examples in the origin of the intercostal arteries, and in the distribution of the vessels supplying the two muscular coats of the alimentary canal.

An artery, after a branch has gone off from it, is smaller than before, but usually continues uniform in diameter or cylindrical until the next secession; thus it was found by Hunter that the long carotid artery of the camel does not diminish in calibre throughout its length. A branch of an artery is less than the trunk from which it springs, but the combined area of the transverse sections or the collective capacity of all the branches into which an artery divides, is greater than the calibre of the parent vessel immediately above the point of division. The increase in the joint capacity of the branches over that of the trunk is not in the same proportion in every instance of division, and there is at least one case known in which there is no enlargement, namely, the division of the aorta into the common iliac and sacral arteries; still, notwithstanding this and other possible exceptions, as a general rule an enlargement of area takes place. From this it is plain that, since the area of the arterial system increases as its vessels divide, the capacity of the smallest vessels and capillaries will be greatest; and, as the same rule applies to the veins, it follows that the arterial and venous systems may be represented, as regards capacity, by two cones whose apices (truncated it is true) are at the heart, and whose bases are united in the capillary system. The effect of this must be to make the blood move more slowly as it advances along the arteries to the capillaries, like the current of a river when it flows in a larger channel, and to accelerate its speed as it returns from the capillaries to the venous trunks.

When arteries unite they are said to anastomose or inosculate. Anastomoses may occur in arteries of considerable size, as those at the base of the brain, those of the hand and foot, and the mesentery, but they are much more frequent in the smaller vessels. Such inosculations admit of a free communication between the currents of blood, and must tend to equalise distribution and pressure, and to obviate the effects of local interruption.

Arteries commonly pursue a more or less straight course, but in some parts they are tortuous. Examples of this in the human body are afforded by the arteries of the lips and of the uterus, but more striking instances may be seen in some of the lower animals, as in the well-known case of the long and tortuous spermatic arteries of the ram and the bull. In the peculiar arrangement of vessels named a 'rete mirabile' an artery suddenly divides into small anastomosing branches, which latter unite again to form one vessel. Of such *retia mirabilia* there are many examples in the lower animals, but the purpose which they serve is not always apparent. The best known instances are: the *rete mirabile of Galen*, which is formed by the intracranial part of the internal carotid artery of the sheep and several other quadrupeds, and the glomerular plexuses in the kidney.

Arteries possess considerable strength and a very high degree of elasticity, being extensible and retractile both in their length and their width. When cut across they present, although empty, an open orifice; the veins, on the other hand, if empty, collapse, unless when prevented by adhesions to surrounding rigid parts.

Structure.—In most parts of the body the arteries are inclosed in a sheath formed of connective tissue, which in its turn is continuous with the connective tissue of the neighbouring structures. The outer coat of arteries is connected to the sheath by filaments of the same tissue, but so loosely that, when the vessel is cut across, its ends readily shrink some way within the sheath. Some arteries lack sheaths, those for example which are situated within the cavity of the cranium.

Independently of this sheath, arteries (except those of minute size whose structure will be noticed afterwards) have been usually described as formed of three coats, named, from their relative position, internal, middle, and external (fig. 511, in section); and as this nomenclature is generally followed in medical and surgical works, and also correctly applies to the structure of arteries so far as it is discernible by the naked eye, it seems best to adhere to it as the basis of our description; although it will be seen, as we proceed, that some of these coats are found on microscopic examination to consist of two or more strata differing from each other in texture, and therefore reckoned as so many distinct coats by some authorities.

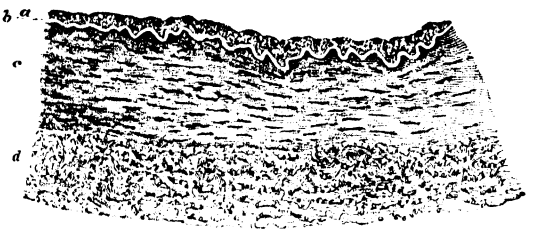


FIG. 511.—TRANSVERSE SECTION OF PART OF THE WALL OF THE POSTERIOR TIBIAL ARTERY, MAN. (Schäfer.)

Magnified 75 diameters.

a, endothelial and subendothelial layers of inner coat; *b*, elastic layer (fenestrated membrane) of inner coat, appearing as a bright line in section; *c*, muscular layer (middle coat); *d*, outer coat, consisting of connective-tissue bundles. In the interstices of the bundles are some connective-tissue nuclei, and, especially near the muscular coat, a number of elastic fibres cut across.

The structure of arteries of the same size varies very considerably according to the situation they are taken from, and this holds good especially for the smaller branches, and particularly as to the condition of the elastic tunics. On this account, after a general description of large and medium-sized arteries and veins, the special features of particular blood-vessels will be dealt with. In comparing vessels of different individuals due regard must be paid to sex, for in females the vessels are always smaller; and also to age, for with advancing years the vessels undergo definite changes. The last point to be kept in mind is the development of the vessels up to the time of maturity, for during this period what are ultimately large arteries pass through all the stages which subsequently, in the adult animal, are characteristic of the medium-sized and the small arteries. For descriptive purposes it is best to commence with the medium-sized arteries.

Medium-sized arteries.—Typical examples of these are the lingual, the tibial, and the renal arteries.

If arteries be fixed by injecting the fixing fluid under normal pressure through the aorta, transverse sections of the vessels will show a smooth inner surface; with the exception of the renal vessels, in which the elastic coat is especially developed. In fig. 512 is represented a transverse section of the renal artery of a dog. In this from within outwards will be seen firstly a dark sinuous line, which represents the elastic coat of the innermost membrane or *tunica intima*; then a broad pale band, representing the middle coat or *tunica media*, composed essentially of

non-striped muscular fibres arranged concentrically and broken up on its outer side into more or less distinct fasciculi. It will be noticed that the muscular coat is thicker on one side than on the other, a phenomenon quite common in many arteries, and to be discussed when describing the intracranial vessels. Outside the muscular coat is a broad, deeply stained band, containing a large number of elastic fibres held together by white fibrous tissue; this zone is called the *tunica externa* or *adventitia*. Still further outwards is the loose connective tissue by which the renal artery is fixed to neighbouring tissues, and here will be seen transverse sections of a number of nerves belonging to the vaso-motor system.

When examined under a higher power the following appearances are seen in a transverse section, say, of the posterior tibial artery.

Internal coat (*tunica intima*) (fig. 511, *a*, *b*).—This may be raised from the inner surface of the arteries as a fine transparent colourless membrane, elastic but very easily broken, especially in the circular or transverse direction, so that it

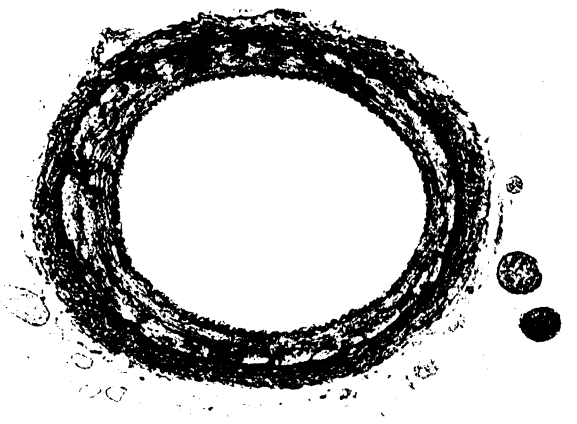


FIG. 512.—TRANSVERSE SECTION OF THE RENAL ARTERY OF A DOG. (Mann.)

Stained by Weigert's method to show the distribution of elastic tissue, and the formation of bundles of non-striped muscle where the media abuts on the externa. Outside the vessel are seen vaso-motor nerves in transverse section.

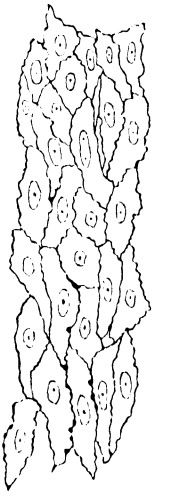


FIG. 513.—ENDOTHELIAL LAYER LINING THE POSTERIOR TIBIAL ARTERY OF MAN. Silver nitrate preparation. 250 diameters. (Schäfer.)

cannot be stripped off in large pieces. It is commonly corrugated with fine and close longitudinal wrinkles, caused by a contracted state of the artery after death. Such is the appearance presented by the internal coat to the naked eye, but by the aid of the microscope it is found to consist of three different structures, namely:

1. An *endothelial layer* (fig. 511, *a*, and fig. 513) forming the innermost part or ning. This is a simple layer of thin elliptical or irregularly polygonal cells, which are often lengthened into a lanceolate shape. The cells have round or oval nuclei, with nucleoli: the cell-outlines are often indistinct in the fresh state, but may be brought into view by means of nitrate of silver. When the vessels are empty and collapsed, the endothelium cells are less flattened, and the part of each cell which contains the nucleus may project somewhat into the lumen of the vessel.

2. A *subendothelial layer* (striated layer of Kölliker). This is composed of a finely fibrillated connective tissue with a number of branched corpuscles lying in

the cell-spaces of the tissue (fig. 514). This layer exists as a thin stratum in all medium-sized arteries.

3. An *elastic layer.* The elastic tissue is represented by one distinct lamina, which is separated from the endothelium by the subendothelial layer. It is, on its outside, in direct contact with the non-striped muscle of the middle layer. When discussing the small arteries the development of the elastic lamina will be gone into, and therefore it will suffice now to point out that this so-called 'internal elastic lamina' is membranous in character. The membrane is not, however, a continuous one as it appears to be in the section of the tibial artery of man (fig. 511), but is perforated by apertures, as shown in the microphotograph of the cutaneous artery of the dog (fig. 515, *a*). This 'perforated' or 'fenestrated' membrane of Henle closely resembles the elastic laminæ of the aorta, to be described hereafter.

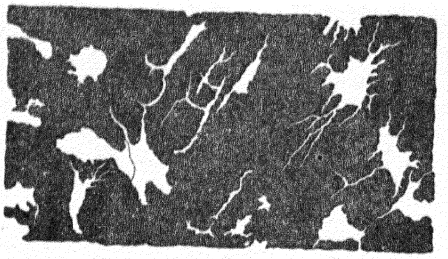


FIG. 514.—CELL-SPACES OF SUB-ENDOTHELIAL LAYER OF ARTERY (POSTERIOR TIBIAL). 250 diameters. (Schäfer.)

The ground-substance is stained by nitrate of silver, and the cell-spaces of the tissue are thus made manifest as white patches, the contained cells not being seen.

Middle coat (*tunica media*) (fig. 511, *c*, and fig. 515, *b*).—This consists of plain muscular tissue, in fine bundles, disposed circularly round the vessel, and consequently tearing off in a circular direction, although the individual bundles do not form complete rings. The considerable thickness of the walls of the arteries is due chiefly to this coat; in the smaller ones it is thicker than in the larger in comparison with the calibre of the vessel. In large vessels it is made up of many layers.

Although, generally speaking, the muscle-fibres are arranged transversely to the long axis of the vessel, one finds in certain situations, such as the lower reaches of the iliac arteries, and at the places where the abdominal branches of the aorta are given off, a number of oblique and occasionally even longitudinal fibres.

In addition to the non-striped muscle is also found white fibrous tissue which helps to bind the muscle-fibres together; also elastic tissue to a variable extent. Thus we find (fig. 515) one set of circular elastic fibres running parallel to the lumen of the vessel, and in addition to these a great many oblique fibres. Many of the apparent circular fibres are membranes which have been cut across, with ridges running partly longitudinally and partly transversely. The elastic fibres of the middle coat in many cases break up the muscular substance into distinct bundles (fig. 512).

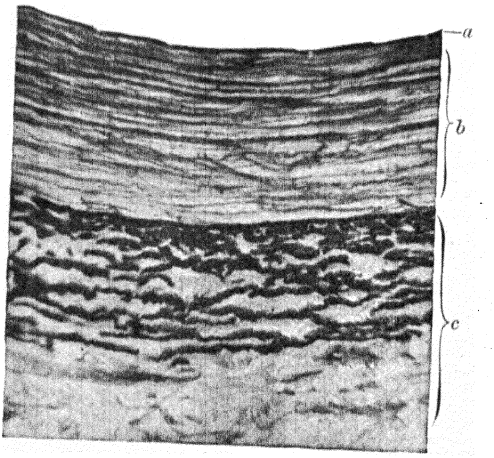


FIG. 515.—SMALL CUTANEOUS ARTERY, DOG. (Mann.)

Weigert's method for elastic fibres was employed.

a, the internal elastic lamina showing perforations. *b*, the tunica media with fine elastic fibres. At the junction of *b* and *c* is the external elastic lamina; *c*, the tunica adventitia with coarse elastic fibres.

By means of the oblique fibres the bundles of muscle-cells are firmly held together, and the whole system is rendered thereby more homogeneous.

Outer coat.—The *tunica externa* or *adventitia* (fig. 511, *d*, and fig. 515, *c*) is in middle-sized arteries largely formed of elastic tissue. Its thickness varies; in most, it measures from one-half to two-thirds that of the middle coat. In small arteries and arterioles the first indication of the presence of elastic tissue manifests itself in the deposit of elastic material in longitudinal strands immediately outside the muscular coat, between the latter and the white fibrous tunica adventitia. As in the case of the internal elastic lamina, so here the longitudinal elastic fibres may become converted into a distinct membrane, to form an 'external elastic lamina,' showing a number of apertures (fig. 515). The larger the vessel, excluding the very large ones, the greater is the number of elastic fibres developed on the external surface of the external elastic lamina. This arrangement serves to allow of a considerable enlargement of the vessel during systole.

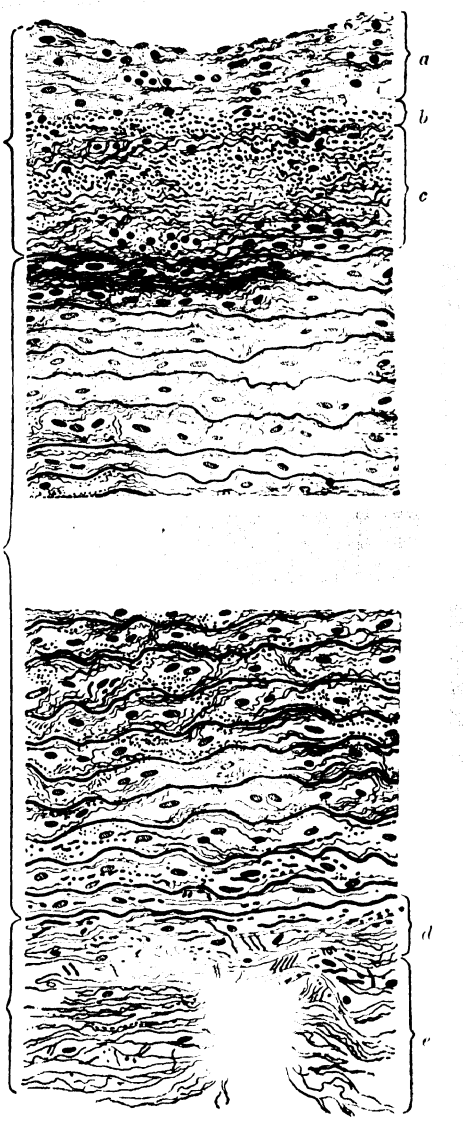


FIG. 516.—SECTION OF AORTA. (Grünstein.)

a, endothelium and subendothelial layers of intima; *b*, *c*, outer layers of intima, containing many fine elastic fibres; *d*, *e*, parts of adventitia.

Larger arteries.—These are represented by the aorta throughout its whole length: the innominate, the subclavian, the common carotid, and the common iliac arteries. Again three distinct coats may be seen.

Internal coat (fig. 516, *a*, *b*, *c*).—Innermost of all lies the endothelial covering which is characteristic of all vessels, but in the large vessels the endothelial cells are both relatively and absolutely shorter than in the medium-sized arteries. External to the endothelium is a well-developed subendothelial layer consisting for the greater part of white fibrous tissue and its cells. The elastic tissue of the inner coat varies very considerably according to the vessel examined. If the common iliac artery be examined in its lower regions the vessel shows two distinct elastic laminæ—namely, an internal elastic lamina like that of the smaller arteries, and a little external to this a second elastic lamina, which may be regarded as forming the inner boundary of the muscular coat. Between the two elastic laminæ just referred to is a quantity of connective tissue, containing numerous very delicate elastic fibrils running longitudinally, and also a few, equally fine, circular fibrils. The changes

which the inner coat undergoes when we pass from the iliac artery to the aorta affect essentially the yellow and the white fibrous elements. In the aorta (see fig. 516) the internal elastic lamina is no longer recognisable. Grünstein,[1] on making longitudinal sections through the iliac vessel where its lower reaches pass into the upper ones and the latter into the aorta, found the internal elastic lamina gradually to lose its membranous character by breaking up into numerous fine fibrils; while the second lamina found in the lower portions of the iliac artery, which is sometimes called the middle elastic lamina and counted as belonging to the tunica media (following the classification of Ranvier[2]), does not break up into fibrils but retains its membrane-like appearance.

The transition of the iliac artery into the aorta is further marked by a gradual increase in the amount of connective tissue between the internal elastic lamina and the endothelial layer, in addition to the increase of connective tissue between the internal and the second elastic lamina; this connective tissue forming the sub-endothelial layer. It is this increase of white fibrous tissue on the inside of the internal lamina which will engage our attention later when studying the changes the aorta undergoes during normal conditions as we pass from childhood to old age; the increase is also of importance in connexion with the pathological changes which are liable to occur in these arteries.

Middle coat.—While the external iliac artery still resembles the medium-sized vessels inasmuch as the non-striped muscle is arranged almost exclusively in a circular manner and is formed into bundles on the outer surface of the media where it abuts on the tunica adventitia, in the common iliac vessel, near the aorta, and in the aorta itself, the middle coat exhibits a definite lamellar arrangement owing to the development within it of a number of concentric elastic laminæ. The order of tissues in the tunica media is as follows, viz.:—a thick

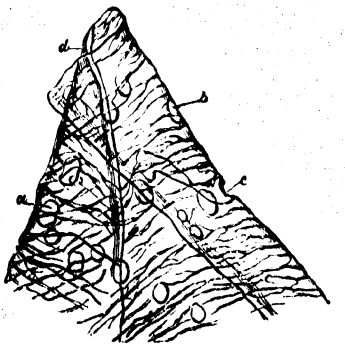


FIG. 517.—PORTION OF FENESTRATED MEMBRANE FROM THE FEMORAL ARTERY. (Henle.)
Magnified 200 diameters.
a, *b*, *c*, perforations; *d*, folds.

FIG. 518.—ELASTIC NETWORK OF ARTERY. (Toldt.)

elastic lamina; white fibrous tissue containing delicate elastic fibres running in different planes; non-striped muscle-fibres; white fibrous tissue with fine elastic fibres; a thick elastic lamina, and so on. The number of elastic laminæ varies from about forty in the new-born to about between fifty and seventy in the adult; this increase in number is itself considerable, and the thickness of each individual lamina is much greater in the adult than in the young. If a small shred of one of these laminæ be stripped off it is seen to have a remarkable tendency to

[1] N. Grünstein, 'Über d. Bau d. grösseren menschlichen Arterien &c.,' Arch. f. mikr. Anat. xlvii. 1896.
[2] Ranvier, Traité technique d'histologie, Paris, 1875 and 1889.

curl in at its borders, and roll itself up as represented in fig. 517. The films of membrane are marked by fine lines, following principally a longitudinal direction, and joining each other obliquely in a sort of network (fig. 518). These lines are reticulating fibres formed upon the membranous layer and continuous with the reticulating elastic fibres which pervade the muscular coat and with those which extend into the subendothelial layer. The elastic membranes are further remarkable by being perforated with numerous round, oval, or irregularly shaped apertures of different sizes. In some parts of the arteries the fenestrated membranes are very thin, and therefore difficult to strip off; in other situations they are of considerable thickness, consisting of several layers; in which case they tend in the outer layers to lose their membranous character: indeed, it must be borne in mind that every transition is met with between the fenestrated membranes and the longitudinal elastic networks.

The muscular fibre-cells of the middle coat of the arteries (figs. 519 and 520) are seldom more than from 0·16 mm. to 0·25 mm. long, and frequently, especially

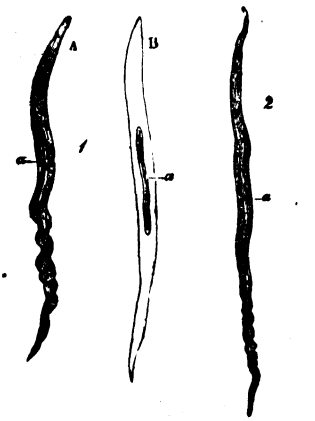


FIG. 519.—MUSCULAR FIBRE-CELLS FROM HUMAN ARTERIES. Magnified 350 diameters. (Kölliker.)

1. From the popliteal artery; A, natural; B, treated with acetic acid. 2. From a small branch of the posterior tibial. *a*, nucleus.

FIG. 520.—MUSCULAR FIBRE-CELLS FROM SUPERIOR THYROID ARTERY, MAN. (Schäfer.)

Magnified 340 diameters.

in those arteries in which the elastic tissue of the middle coat is most developed, present a very irregular shape with jagged extremities (fig. 520). Their nuclei are distinctly rod-shaped, are often slightly curved, and sometimes spirally wound during full contraction of the muscle-fibres.

As already remarked, bundles of white connective-tissue fibres also occur in the middle coat; the proportion increases considerably with the size of the artery. It is important to note that the muscular tissue of the middle coat is more pure in the smaller arteries, and that the admixture of other tissues increases in the larger-sized vessels; in these, moreover, the muscular cells are smaller. Accordingly, the contractility of the arteries, which depends on the muscular tissue of the middle coat, is little marked in those of large size, but becomes much more conspicuous in the smaller branches.

Although, because of the arrangement of the elastic laminæ, the muscle-fibres which originally formed a compact mass become broken up into lamellæ, they for the most part retain their circular direction in the tunica media; but in the laminæ nearest the tunica intima, impregnation with silver nitrate shows in the

aorta an exceedingly intricate arrangement of the muscle-fibres in vortices. Where the tunica media passes over into the tunica adventitia a number of longitudinal muscle-fibres belonging to the middle coat are also always seen in the aorta, but they are never so abundant as to form a definite layer.

External coat.—As in the smaller arteries, so in the very large ones we find, next the tunica media, a layer of elastic fibres running longitudinally and kept together by a few strands of white fibrous tissue; but in addition to this internal layer there appears an external one in which the elastic fibres run circularly.

In large and middle-sized arteries the bundles of white connective tissue chiefly run diagonally or obliquely round the vessel, and their interlacement becomes much more open and lax towards the surface of the artery, where they connect the vessel with its sheath or with other surrounding parts. Longitudinally arranged contractile fibre-cells have been described by various observers in the external coat of some arteries (*e.g.* the iliacs, superior mesenteric, splenic, renal, dorsalis penis, and the umbilical arteries of the fœtus). In the umbilical arteries (Eberth) a complete layer of longitudinal muscular fibres is also present in the middle coat, internal to the ordinary circular fibres; these peculiarities are more fully alluded to later.

Some arteries have much thinner coats than the rest, in proportion to their calibre. This is strikingly the case with those contained within the cavity of the cranium, and in the vertebral canal; the difference depends on the external and middle coats, which in the vessels referred to are thinner than elsewhere. The pulmonary arteries have also much thinner coats than those of the aortic system.

Changes in vessels during development and with advancing age.—The aorta undergoes during development the following changes:—At the end of the third month, in addition to the endothelium, a media is seen with irregular nuclei, and an adventitia, which is four to five times thicker than the media, and with the nuclei arranged longitudinally. At the commencement of the fourth month a membranous internal elastic lamina is distinct. During the fourth month the media grows rapidly and is broken up into lamellæ by about ten elastic laminæ, which communicate with one another by numerous offsets. In a somewhat older embryo, measuring 10 cm. from vertex to coccyx, the first traces of the white fibrous tissue of the internal coat appear. During the twentieth to the twenty-fourth week no elastic fibres are yet developed in the adventitia, but they appear during the seventh month. At birth about forty elastic laminæ are seen in the middle coat, and all of these are connected by longitudinal and oblique fibres. The changes which the different coats of the aorta undergo during extra-uterine existence are given in the accompanying table, in which the numbers indicate the thickness of the coats in micromillimetres.

Age	Intima	Media	Adventitia
New-born	6	650	1485
16-year boy	54	856	688
35-year man	124	996	—
50-year man	181	1075	—
70-year woman	190	1111	—

The first increase in the intima is due to the development of white fibrous tissue, the second to the deposit of elastic fibres. It will be seen from the table that the intima increases relatively more than the media.

With advancing age all vessels lose some of their elasticity owing to conversion of their *elastin* into a non-elastic substance, *elacin*. A vessel thus altered would have a tendency to become wider under the continued blood-pressure. In this way the

blood-stream through the aorta would be modified, were the diameter of the vessel not diminished by a special thickening which occurs in the intima (Thoma).

In the common iliac artery both the intima and the media increase in thickness, but the media increases faster than the intima at all ages.

VEINS.

Mode of distribution.—The veins are ramified throughout the body like the arteries, but in most regions and organs of the body they are more numerous and larger, so that the venous system is altogether more capacious than the arterial. The pulmonary veins form an exception to this rule, for they do not exceed in capacity the pulmonary arteries.

The veins are arranged in a superficial and a deep set, the former running immediately beneath the skin, and thence named subcutaneous, the latter usually accompanying the arteries, and named *venæ comites vel satellites arteriarum*. The large arteries have as a rule one accompanying vein, and the medium-sized and smaller arteries have two, but there are exceptions to this rule. The veins within the skull and spinal canal, and most of those belonging to the bones, as well as the pulmonary veins, run apart from the corresponding arteries.

The communications or anastomoses between veins of considerable size are more frequent than are those of arteries of similar calibre.

Structure.—The veins have relatively much thinner coats than the arteries, and hence collapse when cut across in the empty condition; whereas a cut artery presents a patent orifice. But, notwithstanding their comparative thinness, the veins possess considerable strength, more even, according to some authorities, than

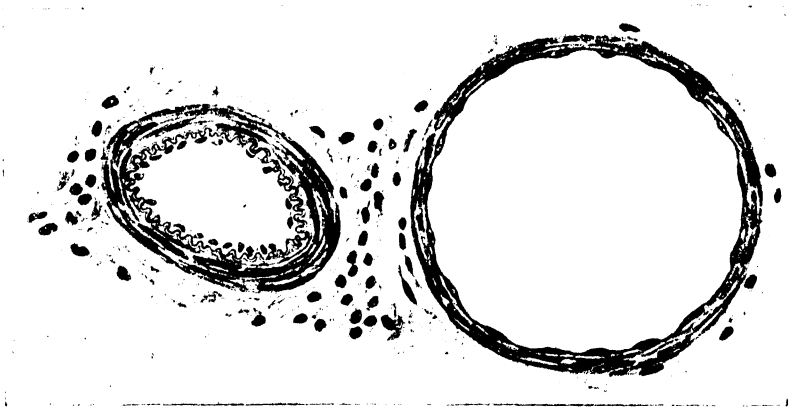


FIG. 521.—SECTION OF A SMALL ARTERY AND VEIN. (Schäfer.)

arteries of the same calibre. The number of their coats has been differently reckoned, and the tissues composing them differently described by different writers; this discrepancy of statement is perhaps partly due to the circumstance that all veins are not alike in structure. In most veins of moderate size, three coats may be distinguished, which, as in the arteries, have been named external, middle, and internal.

Internal coat.—This is more cohesive than that of the arteries, and therefore admits of being more readily peeled off without tearing; but in other respects the two are much alike. It consists in medium-sized and larger vessels of an

endothelium, a *subendothelial connective-tissue layer*, and a not very well marked *elastic layer* (fig. 522, *a*, *b*).

The endothelium of the veins is similar in character to that of the arteries, but the cells are shorter and broader. The subendothelial layer is less developed in most veins than in the arteries, and indeed is absent altogether in many. It is better marked in some of the medium-sized veins than in the larger trunks. The elastic tissue of the inner coat occurs as dense lamelliform networks of longitudinal elastic fibres, and but seldom as fenestrated membranes. Longitudinal muscular bundles, as well as isolated contractile cells, are found in the inner coat of some veins.[1]

Middle coat.—This tunic is thinner than that of the arteries, and has a much larger admixture of white connective tissue. It is pervaded by an elastic network, but this is less conspicuous in the veins than in the arteries. In the veins of the limbs (especially the upper limb) and in those of some other parts, the muscular fibre-cells have for the most part as in the arteries a transverse direction, although the layer which they form is not everywhere complete, being separated into bundles by the intervention of connective tissue (fig. 522, *c*). But in many veins some of the innermost fibres of the middle coat take a longitudinal course: this is the case with the iliac, crural, branches of the mesenteric, umbilical of the fœtus, and other veins (Eberth). The transition between the middle and the outer coat is more gradual than in arteries.

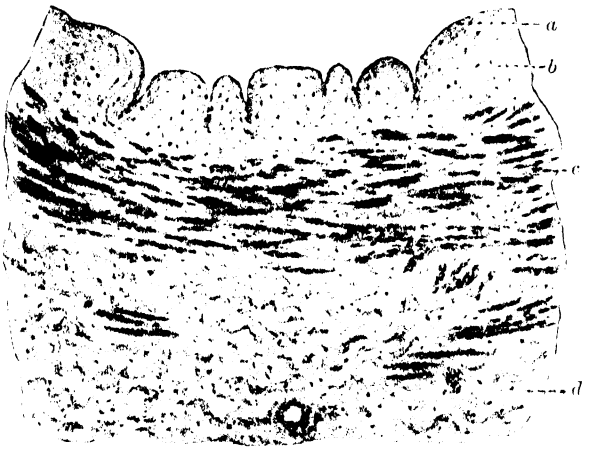


FIG. 522.—TRANSVERSE SECTION OF PART OF THE WALL OF ONE OF THE POSTERIOR TIBIAL VEINS, MAN. (Schäfer.)

About 200 diameters.

a, endothelial, and *b*, sub-endothelial layers of inner coat; *c*, middle coat consisting of irregular bundles of muscular tissue, alternated with connective tissue, and passing somewhat gradually into the outer connective tissue and elastic coat, *d*.

The middle coat is wanting altogether in the thoracic part of the inferior vena cava, but is well marked in the hepatic part: below the liver the muscularity of the middle coat is less developed.

External coat (fig. 522, *d*).—This is often thicker than the middle coat; but the line of junction between them is not sharply marked. It consists of dense areolar tissue and longitudinal elastic fibres. In certain large veins, as was first pointed out by Remak, this coat contains a considerable amount of plain or non-striated muscular tissue. Thus the muscular elements are well marked in the whole extent of the abdominal cava, in which they form a longitudinal network, occupying the inner part of the external coat; and they may be traced into the renal, azygos, spermatic and external iliac veins. The muscular tissue of the external coat is also well developed in the trunks of the hepatic veins and in that of the vena portæ (fig. 523), whence it extends into the splenic and superior mesenteric. It is found also in the axillary vein.

[1] Veins which are apparently healthy sometimes exhibit here and there well-marked thickenings of the inner coat; these thickenings may represent rudimentary valves (v. Bardeleben).

Muscular tissue is wanting, or very scanty, in the following veins: viz. (*a*) those of the maternal part of the placenta; (*b*) most of the veins of the pia mater; (*c*) the veins of the retina; (*d*) the venous sinuses of the dura mater; (*e*) the cancellar veins of the bones; (*f*) the venous spaces of the corpora cavernosa. In most of these cases the veins consist merely of an endothelium and a layer or layers of connective tissue more or less developed; in the corpora cavernosa the endothelium is applied to the trabecular tissue. It may be added that in the thickness of their coats the superficial veins surpass the deep, and the veins of the lower limbs those of the upper.

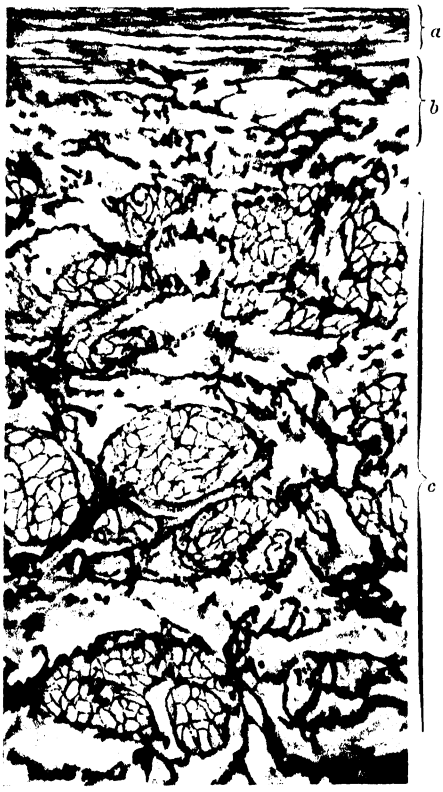


FIG. 523.—TRANSVERSE SECTION OF PORTAL VEIN OF DOG. (Mann.)

Stained by Weigert's method for elastic fibres.

a, tunica intima; *b*, tunica media; *c*, tunica adventitia, with large bundles of non-striped muscle cut transversely and imbedded in dense white fibrous tissue.

Valves. — Most of the veins, especially the superficial ones of the extremities, are provided with valves, a mechanical contrivance adapted to prevent the reflux of the blood. The valves are formed of semilunar folds of the internal coat, strengthened by included connective tissue, and projecting into the vein. Most commonly two such folds or flaps are placed opposite each other (fig. 524, A); the convex border of each (which, accord-

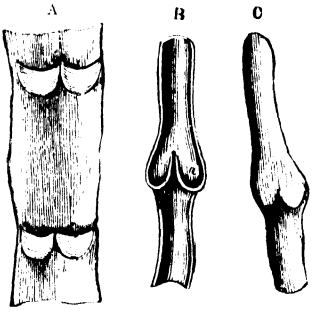


FIG. 524.—DIAGRAM SHOWING VALVES OF VEINS. (Sharpey.)

A. Part of a vein laid open and spread out, with two pairs of valves. B. Longitudinal section of a vein, showing the apposition of the edges of the valves in their closed state. C. Portion of a distended vein, exhibiting a swelling in the situation of a pair of valves.

ing to Haller, forms a parabolic curve) is connected with the side of the vein; the other edge is free, and points towards the heart, or at least in the natural direction of the current of the blood along the vessel, and the two flaps incline obliquely towards each other in this direction. Moreover, the wall of the vein immediately on the cardiac side of the curved line of attachment of the valves is dilated into a pouch or sinus (fig. 524, B), so that, when distended with blood or by artificial injection, the vessel bulges out on each side, and thus gives rise to the appearance of a knot or swelling wherever a valve is placed (as in fig. 524, C). From the above description, it is plain that the valves are so directed as to offer no obstacle to the blood in its onward flow, but that, when from pressure or any other cause it is

driven backwards, the refluent blood, getting between the dilated wall of the vein and the flaps of the valve, will press them inwards until their edges meet in the middle of the channel and close it up.

The endothelial cells differ in shape and arrangement upon the two surfaces of the valves. On the side which faces inwards, and past which the current of blood flows, the cells are elongated in the direction of the current, whereas upon the opposite side which, when the valves are thrown back, faces the wall of the vein, the cells are elongated transversely. The main substance of the valve consists of transversely arranged connective tissue, which is strengthened on the side of the valve not facing the sinus by an abundance of elastic tissue corresponding to the internal elastic lamina. The valve is thinner close to its attachment than elsewhere, and possesses in the ox, but not in man, a few transverse muscular fibres, while the whole of the non-striped muscle in the vessel wall in the neighbourhood of the valves has a longitudinal direction.

The valvular folds are usually placed in pairs as above described : in the veins of the horse and other large quadrupeds three are sometimes found, but this rarely occurs in the human body. On the other hand, the folds are placed singly in some of the smaller veins, and in large veins single valvular folds are not unfrequently placed over the openings of smaller entering branches ; also in the right auricular sinus of the heart there is a single crescentic fold at the orifice of the vena cava inferior, and another more completely covering the opening of the principal coronary vein.

Many veins are destitute of valves. Those which measure less than about 2 mm. in diameter rarely, if ever, have them. In the human subject, valves are wanting in the superior and inferior venæ cavæ, in the trunk and branches of the portal vein (except its gastric tributaries, Koeppe), in the hepatic, renal and uterine veins ; also in the ovarian veins of the female. In the male, the corresponding veins (spermatic) have valves in their course, and in each sex a little valve is occasionally found in the renal vein, placed over the entrance of the spermatic or ovarian. The pulmonary veins, those within the cranium and vertebral canal, and those of the cancellated texture of bone, as well as the trunk and branches of the umbilical vein, are also without valves. In the azygos and intercostal veins valves are not generally found, and when present are few in number. On the other hand, they are numerous in the veins of the limbs (and especially of the lower limbs), which are much exposed to pressure in the muscular movements or from other causes, and have often to support the blood against the action of gravity. No valves are met with in the veins of reptiles and fishes, and not many in birds.

Blood-supply of vessels.—The coats of arteries and veins are supplied with nutrient vessels, *vasa vasorum*, which may penetrate into the middle coat and even approach the inner surface. They are, however, only found in the largest vessels, and are not abundant in these.

Structure of Vessels in Special Situations.

Blood-vessels of the cranial cavity.[1]—The arteries which are supplied to the brain differ from others of the same size met with elsewhere in having a specially strongly developed inner elastic lamina ; a very slight development of elastic material in the muscular or middle coat ; and, finally, a remarkable absence of longitudinal elastic fibres. The internal elastic lamina is always fenestrated ; the fenestræ, oval in shape, with the long axis running longitudinally, are fewer and further apart in the larger vessels. This lamina is both relatively and absolutely thicker in cerebral vessels than in others, and shows the peculiarity that it has projections on its inner side in all the larger vessels, while in other arteries the

[1] H. Triepel, Anat. Hefte, vii. 1896–97, and *ibid.* xi. 1899 ; H. Schöppler, Anat. Hefte, xv. 1900.

thickenings of the elastic lamina are as a rule confined to its outer side. Further, the lamina is apt to split up into two or more layers whenever there is need for counteracting an excessive amount of pressure, as, for example, at points where branches are given off, or where two vessels come together as with the vertebral arteries, and also along the concave side of a bent vessel. The adventitia never possesses the elastic lamina which in other arteries separates the muscular middle coat from the fibrous outer coat (see fig. 515). In the larger vessels the adventitia is composed internally of dense circular connective tissue and externally of loose white fibrous tissue, with bundles of non-striped muscle running longitudinally.

The cerebral veins resemble one another in the following points: The endothelium cells have large nuclei, and lying immediately outside the endothelium is a thin structureless membrane which does not give the reactions of either elastin or elacin, and stains with both acid and basic dyes. The wall in all the veins is thicker on the side next to the brain than on that next to the arachnoid. The wall in the veins under the fornix is thicker next to that structure than next to the roof of the third ventricle. The larger veins may show from six to eight lamellæ of connective tissue running alternately longitudinally and transversely.

Smooth muscle-fibres occur in all the larger and middle-sized cerebral veins scattered about amongst the white fibrous bundles, especially in proximity to the internal elastic lamina, the direction of the fibres being either transverse or oblique. In the middle-sized veins only a few muscle-fibres are found, but they are present even in the vena terminalis; in veins within the brain-substance muscle is very rarely seen.

The elastic tissue is in the form of very fine fibres, forming in the middle coat a delicate network with no definite direction, the number of fibres being in inverse ratio to the muscle; the elastic fibres in the external coat are thicker, and run for the most part circularly. In the large superficial veins the wall abutting on the pia contains much less elastic material than does the other wall, while in the internal cerebral veins the side next to the ventricle is richer in elastic tissue than is the other side. Very little elastic tissue is present in the inferior cerebral veins, and still less in the vena terminalis, while in all the smaller vessels no elastic tissue is present, though the vessel may be surrounded by several layers of white fibrous tissue.

The dural sinuses exhibit on their inner aspect, outside the endothelium, a dense meshwork of elastic fibres, and have the white fibrous tissue united into thicker bundles. The vena cerebri magna has a well-marked network of elastic tissue, and contains in its wall a large number of vasa vasorum. The sinuses, especially the sagittal sinus, contain trabeculæ within the lumen.

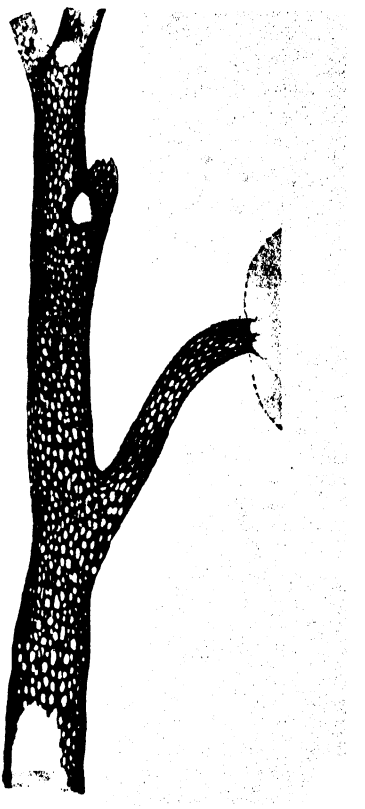


FIG. 525.—INTERLOBULAR ARTERY OF KIDNEY OF MONKEY, SHOWING THE ELASTIC TISSUE TO EXTEND UP TO THE GLOMERULUS, PART OF WHICH IS INDICATED BY THE DOTTED LINE (Mann.)

Weigert's method for elastic tissue.

Blood-vessels of the kidney.—The renal arteries are remarkable for the great development of their elastic tissue, and in animals injected with fixing fluids even slightly above normal blood-pressure, the renal artery is never found so completely dilated as to present a smooth inner surface (see fig. 512). This indicates a special mechanism for safeguarding the kidney against a sudden rise in blood-pressure, a conception which is still further supported by the fact that in the arterial system the internal elastic lamina is only represented up to the end of the afferent vessel in the glomerulus. There is not a trace of elastic material in the whole of the circulatory system in the cortex of the kidney beyond the afferent vessel referred to. Every provision is further made for the ready discharge of the blood which has passed through the glomerulus, the renal veins having relatively a very large lumen. The strong nature of the fenestrated internal elastic lamina of an interlobular renal artery is shown in fig. 525.

Blood-vessels of the lung.[1]—The bronchial arteries and veins show the same differences as those found in the rest of the body, but the pulmonary arteries and veins resemble one another more closely. The terminal arterioles of the lung, if compared with those of the kidney, show a remarkable difference. The internal elastic lamina of the adventitia is represented by fibrils running a separate course, and is therefore not a lamina at all. Moreover, the elastic fibres of the arterioles are continuous with the elastic fibres covering the air-sacs. By this arrangement, when the air-sacs are distended by an inspiration these elastic fibres are simultaneously put on the stretch, and in their turn pull on the walls of the blood-vessels and so help to dilate them. In the cat and monkey certain vessels may occasionally be found in which the only demonstrable elastic tissue is composed of circular fibres, which would naturally tend to counteract the pull exerted on the vessel-wall during inspiration. Except in these vessels, which are rare, the general arrangement in both the larger arterioles and venules is to have a longitudinal set of elastic fibres next to the lumen; then in the muscular coat a number of circular fibres, and, finally, in the external coat other longitudinal fibres.

Umbilical and placental vessels.[2]—The structure of these vessels varies considerably according to their situation, *i.e.* whether examined in parts which are within the embryo or in parts which lie outside it. The structure of the external umbilical arteries is very characteristic, for although large vessels they contain no elastic lamina in the intima. Immediately external to the endothelium is a layer of non-striped muscle running longitudinally, and outside the latter a circular coat of muscle. Such elastic tissue as exists is found scattered in the form of a few longitudinal and oblique fibres between the muscle-bundles. The inner longitudinal coat of muscle-fibres is especially rich in elastic fibres running longitudinally, and here elastic membranes may be present. The tunica media abuts directly upon Wharton's jelly, a tunica adventitia and vasa vasorum being absent. At birth the peculiar arrangement of the muscle-fibres and the absence of an elastic coat make it possible for the artery to become completely occluded on section or rupture; thereby preventing the new-born from bleeding to death.

The internal portion of the umbilical artery has Wharton's jelly replaced by the fibro-elastic mantle-zone of Herzog; the circular muscle-layer shows fewer and fewer elastic fibres, and the inner longitudinal elastic layer is gradually replaced by a true internal elastic lamina.

The umbilical vein differs from the arteries in remaining patent when the umbilical cord is severed. It possesses a well-marked internal elastic lamina next to the endothelium, and an enormously developed muscular coat, the fibres of which run in a longitudinal direction internally and externally, while most of the middle fibres run in a circular direction. The elastic fibres increase in amount as we trace them from within outwards. The internal division of the umbilical vein is sharply defined, for the internal elastic lamina of the outer division ceases suddenly; at the same time the white fibrous tissue between the muscle-fibres becomes more abundant. The muscle-fibres of the tunica media run mostly longitudinally; there are, however, a few circular fibres. The adventitia becomes gradually stronger and there are developed in it numerous coarse elastic fibres which run longitudinally.

The placental vessels differ from the umbilical in the following manner:—The superficial arteries contain fewer elastic fibres and membranes; the superficial veins possess no internal elastic lamina and only a few elastic fibres, and their muscular tissue is not arranged in bundles. Mechanical stimulation of the placental arteries leads to their dilatation.

Blood-vessels of domestic animals.—The axillary vessels in the domestic animals, on being compared with one another, show the following points.[3] The larger the animal the larger are the endothelial cells; elastic tissue is well developed in the intima of the horse, donkey, and ox, feebly developed in the pig, and absent in the dog; muscle-fibres occur in the intima, especially where branching of the vessels occurs. The internal elastic lamina of the arteries is developed in inverse proportion to the number of elastic fibres in the intima. From the shoulder to the elbow-joint elastic fibres are especially abundant in the tunica media, while from the elbow-joint to the digits the muscular tissue increases relatively more and more. But the alteration of the vessel-wall brought about by this decrease of the circular elastic tissue in the tunica media is counterbalanced by an increase of the longitudinal elastic fibres in the tunica adventitia. The muscle-fibres as a rule run circularly, but are arranged spirally in the subscapular artery of the horse; the external elastic lamina is absent in the horse, donkey, and ox, but well developed in the sheep and dog. The tunica adventitia is characterised by the longitudinal elastic fibres becoming more and more prominent as we pass from the central to the peripheral end of the arteries, and the increase in the elastic tissue of the tunica adventitia, as just pointed out, counteracts the diminished development of the elastic tissue in the tunica media.

[1] Linser, Anat. Hefte, xiii. 1900; J. Miller, Journ. of Anat. and Physiol. xl. 1905.
[2] B. Henneberg, Anat. Hefte, xix. 1902.
[3] Baum and Thienel, Arch. f. mikr. Anat. lxiii. 1904

CAPILLARIES.

That the blood passes from the extreme arteries into the veins was a necessary part of the doctrine of the circulation, as demonstrated by Harvey in 1628; but the mode in which the passage takes place was not ascertained until some time after the date of his great discovery. The finding of the capillary vessels, and of the course of the blood through them, was in fact one of the first fruits of the use of the microscope in anatomy and physiology, and was reserved for Malpighi in 1661.

When the web of a frog's foot is viewed through a microscope of moderate power (as in fig. 526), the blood is seen passing rapidly along the small arteries, and thence more slowly through a network of finer channels, by which it is conducted into the veins. The small vessels interposed between the finest branches of the arteries and the commencing veins are the capillary vessels. The course of the blood in these may also be conveniently seen in the lungs or mesentery of the frog, in the external gills and the tail of tadpoles; in the tail of small fishes; in the wing of the bat; in the mesentery of small quadrupeds; and generally in the transparent vascular parts of animals which can be brought under the microscope. These vessels can also be demonstrated by means of fine injections of coloured material, not only in membranous parts, such as those above mentioned, but also in sections of organs and tissues, which may be viewed as transparent objects, or which, if opaque injection-masses have been used, can be viewed in reflected light.

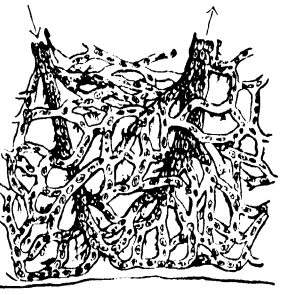


FIG. 526. — CAPILLARY BLOOD-VESSELS IN THE WEB OF A FROG'S FOOT, AS SEEN WITH THE MICROSCOPE. (After Allen Thomson.)
The arrows indicate the course of the blood.

The capillary vessels of a part are most commonly disposed in a network, the branches of which are of nearly uniform size, though not all strictly equal; and thus they do not divide into smaller branches like the arteries, or unite into larger ones like the veins. But the diameter of the tubes, as well as the shape and size of the reticular meshes which they form, differs in different textures. Their prevalent size in the human body may, speaking generally, be stated at from 7 to 8 micromillimetres as measured when naturally filled with blood. Animals injected under normal pressure with isotonic salt-solution, followed by 20 per cent. formalin in isotonic salt-solution, never show capillaries which are less in diameter than the red blood-corpuscles of the animal experimented on. The extreme branches of the arteries and veins in certain parts of the synovial membranes are connected by capillary loops which are considerably dilated at their point of flexure, and dilatations are also found upon the transverse capillaries of the red muscles of the rabbit.

There are great differences in the size or width of the meshes of the capillary network in different parts, and consequently in the number of vessels distributed in a given space, and the amount of blood supplied to the tissue. The network is very close in the lungs and in the choroid coat of the eye, and comparatively close in muscle, in fat, in the skin, and in most mucous membranes, as, for example, those of the mouth and nasal cavities; also in glands and other secreting structures, and in the grey matter of the brain and spinal cord. It has wide meshes and relatively few vessels in the ligaments, tendons, and other allied textures. In infants and young persons, the tissues are comparatively more vascular than in after-life.

The figure of the capillary network is not the same in all textures. In many cases the shape of the meshes is accommodated to the arrangement of the elements of the tissue in which they lie. Thus in muscle, nerve, and tendon, the meshes are long and narrow, and elongated in the direction of the fibres and fasciculi of these textures. In other parts, as in the lungs, in fat, and in secreting glands, the meshes are rounded or polygonal, with no one dimension greatly predominating. In the papillæ of the skin and mucous membranes the vessels of the network are often drawn out into prominent simple or ramified loops.

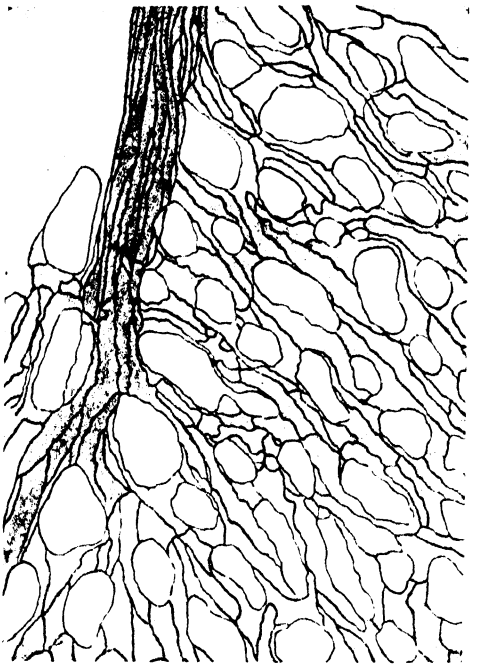


FIG. 527.—SMALL ARTERIOLE BREAKING UP INTO CAPILLARIES; FROM THE LUNG OF A FROG. THE OUTLINES OF THE ENDOTHELIAL CELLS ARE BROUGHT OUT BY SILVER NITRATE. (Mann.)

In addition to, or in place of, true capillaries some organs possess a lacunar system of vessels called sinusoids, which differ in size and in their mode of origin. These blood-sinusoids are met with in all blood-glands, and also in the liver; they will be discussed separately.

Structure of the capillaries.—The wall of the capillaries proper is formed entirely of a simple endothelial layer, composed of flattened lanceolate cells joined edge to edge, and continuous with the corresponding layer which lines the smallest arteries and veins (fig. 527). The outlines of the cells, or their lines of junction one with another, may in many regions be made apparent by silver nitrate; while in other regions silver nitrate does not produce this effect (see below). Their nuclei, which show a well-marked network, may be brought into view by any basic dye. Commonly there are not more than two or three cells in the cross section of the wall of a capillary. At the points of junction of the capillaries the cells are usually broader and not spindle-shaped, but radiate, with three or four pointed branches fitting in between the cells of the three or four adjoining vessels which meet at the spot (fig. 528, *c*, *c*, *c'*).

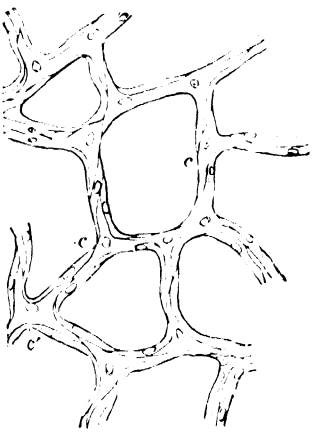


FIG. 528.—CAPILLARY VESSELS FROM THE BLADDER OF THE CAT. Magnified. (After Chrzonszczewsky.)

The outlines of the cells are stained by silver nitrate.

c, cells at junctions.

Silver nitrate does not show the outlines of cells in the capillary vessels of the villi of the intestine, the glomeruli of the kidney, the choroid coat of the eye, the hyaloid membrane of the frog, and in developing capillaries. In these situations treatment with silver solution produces a uniform brown staining.

The blood-channels of the liver of mammals after birth are quite distinct from all other blood-channels, for they are not lined by a continuous endo-

thelium, but their walls are partially beset by specially modified cells, the 'stellate cells' of v. Kupffer; these possess phagocytic properties. Where they are absent the blood comes in direct contact with the liver-cells. The vessels of the hepatic lobules are, however, not true capillaries, but sinusoids (see page 347). In the capillaries of the Fallopian tubes and in those of the uterus during gestation, the flattened endothelium-cells are replaced by cuboidal cells.

In capillaries which have been submitted to the action of silver nitrate, there is here and there to be seen between the cells of the capillary wall an increase in amount of the intercellular substance, appearing as an enlargement of the fine line of the silver deposit. To these gaps in the capillary wall J. Arnold has applied the term 'stigmata'; they are analogous to the 'pseudostomata' found between the endothelial cells of a serous membrane, and are doubtless artifacts. Besides these stigmata the white blood-corpuscles, when migrating from the blood-vessels and passing between the endothelial cells, give rise to the appearance of minute openings, the margins of which are stained by silver nitrate.

FIG. 529.—BRANCHED CONTRACTILE CELLS ENCIRCLING A CAPILLARY OF THE HYALOID MEMBRANE OF THE FROG. (From Tigerstedt, after Rouget.)

Capillaries may lie in direct contact with the most diverse tissues: thus, in the case of the palate of the frog, capillaries send diverticula between the epithelial cells; in Lophius, minute capillaries run right through the large ganglion-cells; in heart-muscle, and also in striped muscle, they lie in very close relationship to the contractile elements. In areolar tissue, branched cells of the surrounding areolar tissue are found connected intimately with the cells forming the capillary wall. This connexion occurs almost everywhere, but it is more obvious in parts which are pervaded by a supporting network of reticular connective tissue, such as the substance of the lymph-glands, the solitary and agminated glands and adjacent intestinal mucous membrane, where the small vessels and capillaries may even obtain a continuous covering from the reticulating processes of the cells. This coating was named by His, *adventitia capillaris*.

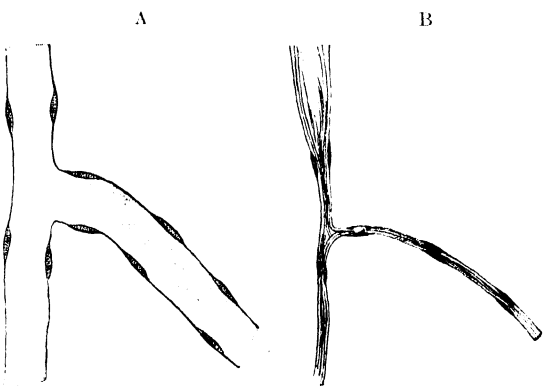


FIG. 530.—A LIVING CAPILLARY VESSEL.

A, previous to excitation; B, showing maximal contraction as the result of excitation. (From Tigerstedt, after Steinach.)

One type of capillary requires special mention — namely, that found in the hyaloid membrane of the frog's eye, lying between the vitreous humour and the retina—for the capillaries and larger blood-vessels in this situation possess no nerve-supply, and yet are contractile, as first surmised by Rouget and subsequently proved by S. Mayer. The capillaries here are peculiar in being surrounded by branched cells, the branches of which run right round the endothelial tube, and by their contraction diminish the lumen of the vessel (see fig. 529). The stimulus for contraction in this instance, and to a certain extent also in the following one, is perhaps given by alterations in the chemical composition of the blood-plasma. An actual diminution in the calibre of capillaries devoid of all non-striped muscle-fibres is readily seen in the nictitating membrane of the frog, if examined with its inner surface uppermost; also in those of the pericesophageal lymph-sac. By appropriate stimulation of the nerves of the part, or by applying electrodes to the margin of the preparation, a fully dilated capillary will frequently be seen to pass through all stages of partial contraction, until it ultimately

resembles a solid strand. This capillary contraction is by no means restricted to the cold-blooded animals, if we may judge by the fact that in the rabbit's mesentery successful impregnation with gold chloride has revealed every capillary to be supplied with a nerve running along it, these nerves forming complete loops corresponding to the capillary meshwork. Contraction both of the whole capillary wall, as well as of the individual cells of capillary vessels, has been described by Stricker, Tarchanoff, Rouget, and Steinach.

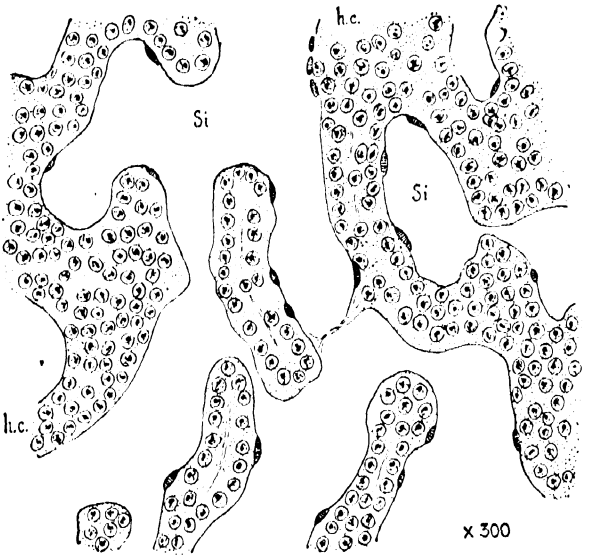


FIG. 531.—SINUSOIDS OF LIVER FROM EMBRYO CHICK, SHOWING LARGE BLOOD-SPACES INVADED BY CYLINDERS OF HEPATIC CELLS. (Minot.)

Si, sinusoids; *h.c.*, hepatic cylinders

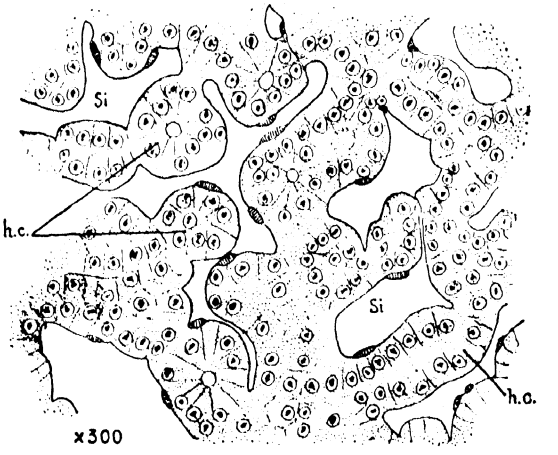


FIG. 532.—SINUSOIDS OF LIVER FROM EMBRYO CHICK MORE ADVANCED IN DEVELOPMENT. (Minot.)

Si, sinusoids; *h.c.*, hepatic cylinders.

SINUSOIDS.

This term was given by Minot[1] to a special form of blood-vessel occurring in the pro- and meso-nephros, the liver, the heart, suprarenal capsules, the parathyroid, carotid, and coccygeal glands; probably also in the lymph-glands, spleen, and thyroid glands of some animals, and perhaps in the 'cavernous' circulation of erectile tissue, and in the placenta.

Sinusoids differ from capillaries in considerably exceeding the diameter of a single red blood-corpuscle, while capillaries rarely allow more than one red corpuscle to pass at a time. Capillaries tend towards a cylindrical or subcylindrical form, while sinusoids have irregular shapes and numerous irregular connexions with one another. Capillaries are as a rule surrounded by connective tissue, while the endothelium of all embryonic sinusoids lies throughout its whole extent in direct contact with the parenchyma of the organ it occurs in; although in the adult condition a certain amount of connective tissue may make its appearance between the sinusoids and the rest of the organ.

According to Lewis, sinusoids may be either purely venous or purely arterial; while capillaries always form the link between the arterial and the venous systems. A sinusoid is formed by the mutual growing into one another (intercrescence) of the endothelium of a vessel and the parenchyma of an adjacent organ. 'The proliferating tubules or trabeculæ of an organ encounter a large vessel and invade its lumen, pushing the endothelium before them; the vessel, on the other hand, sends out branches to circumvent the tubules.'

Generally speaking, sinusoids are more characteristic in embryos than in adult animals. For example, 'the liver has its sinusoids rapidly transformed into capilliform vessels; in the heart, with the addition of the coronary arteries, the sinusoidal circulation is at least supplemented by the capillary.' In all such cases 'the higher forms have vessels of smaller calibre substituted for larger ones directly supplying the blood needs of the tissues' (Minot).

The gradual narrowing of the sinusoids during progressive embryonic development, and their general character of irregular spaces lined by endothelial cells in direct contact with the gland-substance, are well brought out in figs. 531, 532, which show two stages in the development of the liver sinusoids in the chick. In the adult liver, as has been already pointed out, the endothelium of the blood-channels is largely replaced by separate phagocytic cells, and the blood comes nearly everywhere in contact with the liver-cells. Thus its plasma can pass into fine canaliculi in the cell-protoplasm, which are capable of being easily injected from the portal vein by carmine-gelatine (see p. 26 and fig. 45).

SMALL ARTERIES AND VEINS.

In vessels a little larger than capillaries (fig. 533) there is added, outside the endothelial layer, a layer of smooth muscular tissue, in the form of the usual long contractile fibre-cells, which are placed circularly around the vessel. The elongated nuclei of these cells may be brought into view by means of acetic acid or by staining fluids (fig. 534). This layer corresponds with the middle coat of the larger vessels. In the smallest vessels in which it appears the muscular cells are few and apart, and a single long cell may turn spirally round the tube (Lister); in larger vessels, especially those of the arterial system, the muscular cells are more closely arranged. Outside the muscular coat is the areolar or connective-tissue coat, containing fibres and connective-tissue corpuscles, with longitudinally placed nuclei.

[1] C. S. Minot, Proceed. Boston Society of Natural History, xxix., 1900; F. T. Lewis, Anat. Anzeig. xxv., 1904.

In vessels of 0·3 mm. in diameter, the elastic layers of the inner coat may be discovered (fig. 534, A, δ), in the form of fenestrated membranes or of longitudinal reticulating elastic fibres.

At first all the membranes are of the nature of elastic fibres running longitudinally; later these fibres increase in thickness (see fig. 535). During the next stage more elastin is deposited in the same plane as delicate fibres between those already present; and this process is continued till there results a membrane

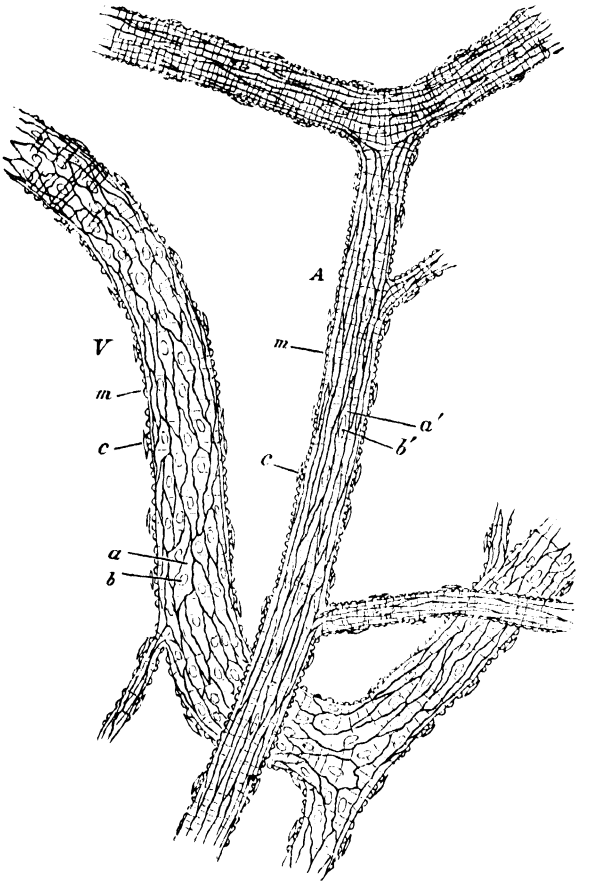


FIG. 533.—A SMALL ARTERY, A, AND VEIN, V, FROM THE SUBCUTANEOUS CONNECTIVE TISSUE OF THE RAT. Treated with nitrate of silver. 175 diameters. (Schäfer.)

a, *a'*, endothelium-cells with *b*, *b'*, their nuclei; *m*, *m*, transverse markings due to staining of substance between the muscular fibre-cells; *c*, *c*, nuclei of connective-tissue corpuscles attached to exterior of vessel.

consisting of the original fibres forming well-marked longitudinal ridges, and the secondarily and tertiarily developed elastin almost completely filling up the spaces between the ridges. There are, however, always apertures through which a free communication between the inner and outer divisions of a vessel is established. In the case of the kidney a close meshwork of fibres is deposited from the very first. These, with the increasing age and increasing diameter of the vessel, gradually become broadened out until a very even membrane with oval apertures results, as shown in the interlobular artery represented in fig. 525.

In the transverse section of the small artery represented in fig. 536, the elastic lamina has become corrugated owing to post-mortem contraction of the middle coat.

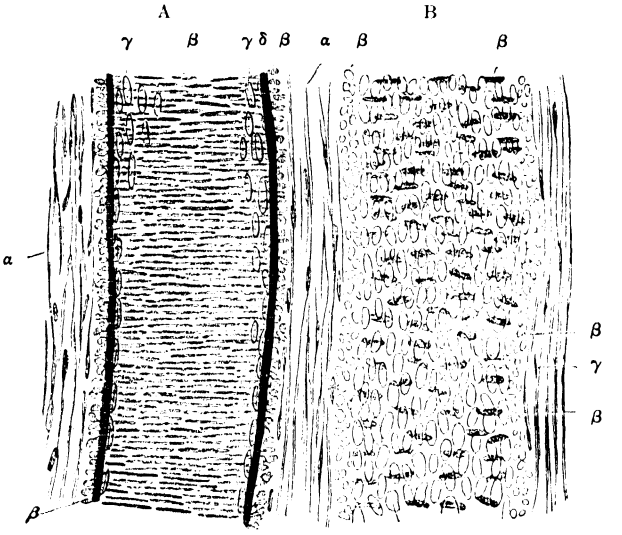


FIG. 534.—A SMALL ARTERY, A, WITH A CORRESPONDING VEIN, B, TREATED WITH ACETIC ACID, AND MAGNIFIED 350 DIAMETERS. (Kölliker.)

α, external coat with elongated nuclei; β, nuclei of the transverse muscular tissue of the middle coat (when seen endwise, as at the sides of the vessel, their outline is circular); γ, nuclei of the epithelium-cells; δ, elastic layers of the inner coat.

FIG. 535.—ELASTIC TISSUE OF TYPICAL SMALL ARTERY. THE DOTTED LINE INDICATES THE JUNCTION OF THE MIDDLE AND THE OUTER TUNICS. FROM THE DOG'S TONGUE. (Mann.)

Weigert's method for elastic tissue.

The small veins differ from arteries of corresponding size, chiefly in the inferior development of their muscular tissue; the lining cells of the arteries also are very

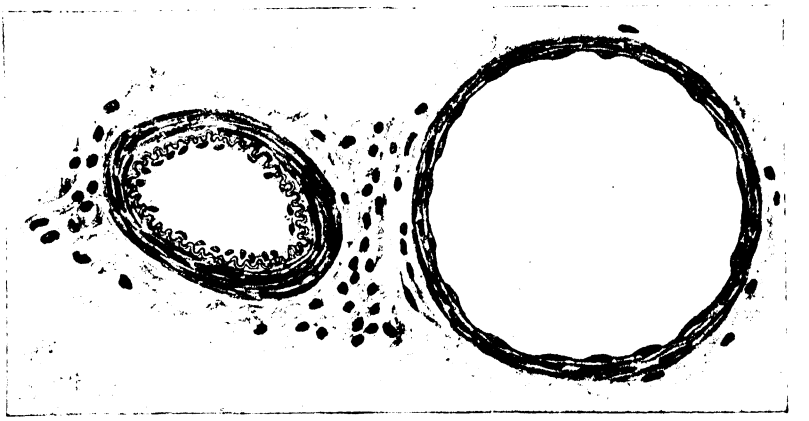


FIG. 536.—TRANSVERSE SECTION OF A SMALL ARTERY (ON THE LEFT) AND OF A SMALL VEIN (ON THE RIGHT). Magnified 250 diameters. (Schäfer.)

much longer and narrower than those of the veins. These differences, as well as the comparative size of corresponding vessels, are well shown in the accompanying figures (figs. 533, 534, 536).

A peculiar arrangement of non-striped muscle is found in the meshlike blood-vessels of the skate, in which the muscle, instead of forming a continuous coat, appears as well defined rings (P. Meyer) (fig. 537). In the mesentery of the macaque monkey, and occasionally also in the rabbit, the mesenteric veins show non-striped muscle arranged as a separate bundle running along one side of the vessel (fig. 539).

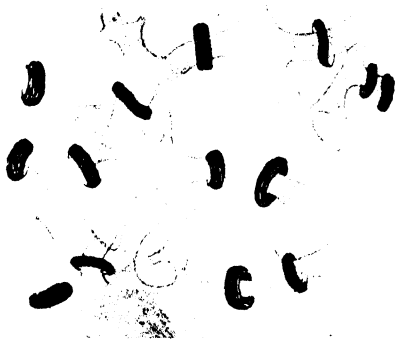


FIG. 537. — RING-LIKE ARRANGEMENT OF MUSCLE AROUND VESSELS OF SKATE. (Mann.) (From a preparation by P. Meyer.)

The only open communication between the arteries and the veins is by means of capillary vessels, and in certain cases by sinusoids, as above described; except that in the maternal part of the placenta, in the thoracic sympathetic ganglia (Ranvier) (fig. 539), and in the interior of erectile organs small arteries open directly into wide venous cavities without the intervention of capillaries; in the mesentery also small arteries may open directly into small veins. In the spleen (fig. 540), the arterial capillaries do not at once pass into the commencements of the veins, but

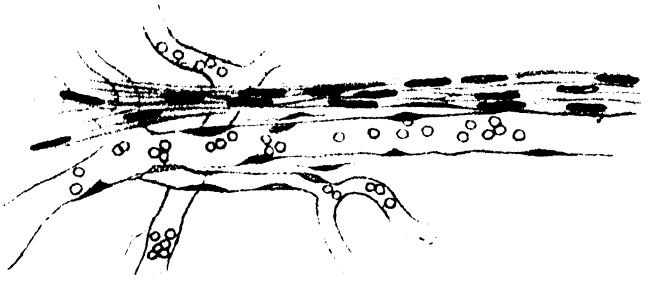


FIG. 538.—SMALL VENULE AND BLOOD-CAPILLARIES IN THE MESENTERY OF A MONKEY, SHOWING BAND OF NON-STRIPED MUSCLE RUNNING ALONGSIDE THE VENULE. (Mann.)

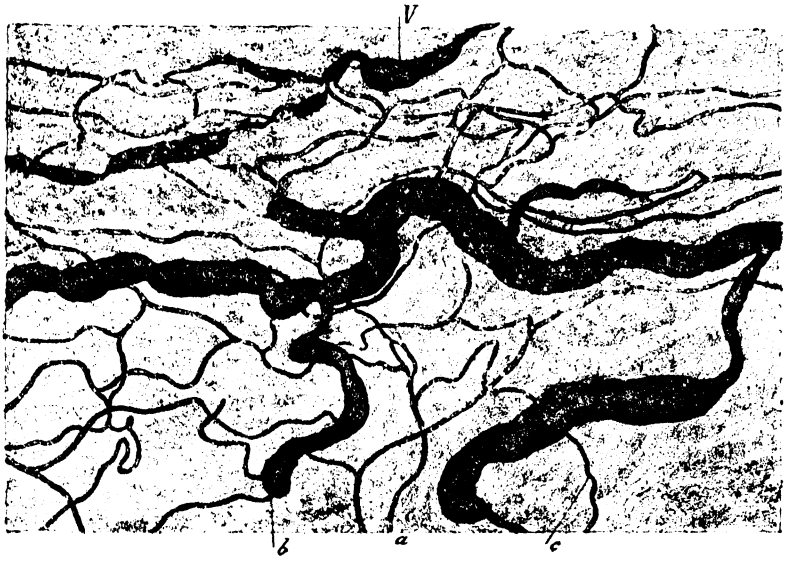


FIG. 539.—THIRD THORACIC GANGLION OF RABBIT, INJECTED WITH PRUSSIAN-BLUE GELATINE. (Ranvier.)

a, arteriole; *b*, capillary opening into a dilated terminal vein; *V*, a dilated venous sinus; *c*, a capillary.

open into the special blood-sinuses (ampullæ) of the organ, from which minute veins collect the blood.

In certain other parts of the body small arteries have been seen passing into small veins without the intervention of true capillaries (Hyrtl, Sucquet, Hoyer).

NERVES OF BLOOD-VESSELS.

That small groups of ganglion-cells occur along the course of the coronary arteries of the heart has already been mentioned, but these cells belong to the heart proper; and the ganglia described by Lehmann in the inferior vena cava may also be regarded as scattered extrinsic sympathetic cells not belonging to the vessel proper.

Both sensory as well as motor nerves are distributed to the coats of arteries. They form plexuses round the larger arteries, and run along the smaller branches in the form of fine bundles of nerve-fibres, which here and there twist round the vessel, and unite with one another in a plexiform manner. The fine motor branches destined for the artery penetrate to the middle coat; to the muscular tissue of which they are chiefly distributed.

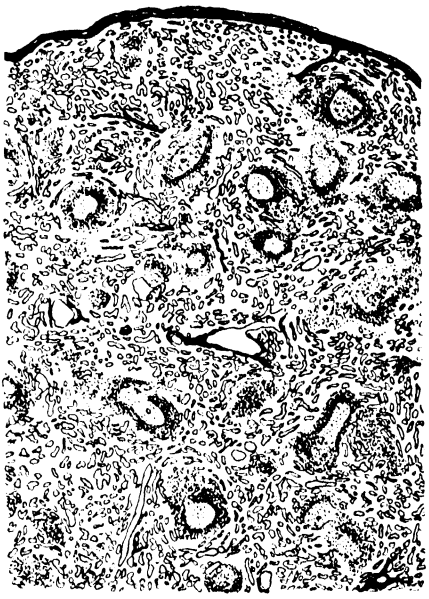


FIG. 540.—TRANSVERSE SECTION OF A MONKEY'S SPLEEN, FIXED BY INJECTING THE WHOLE ANIMAL FROM THE AORTA. THE VENOUS SINUSOIDS APPEAR AS IRREGULARLY SHAPED HOLES. THE GRANULAR MASSES ARE THE MALPIGHIAN CORPUSCLES.

Sensory nerves terminating in a kind of end-plate were described by Dogiel in the walls of small blood-vessels (fig. 541); they have also been found by others in the tunica intima of the aorta and pulmonary artery (Schemetkin), and of all cerebral arteries (Huber). In addition to these special sensory end-plates, Pacinian corpuscles have been found in the tunica adventitia of the abdominal aorta,

FIG. 541.—TERMINAL RAMIFICATIONS OF AFFERENT NERVE-FIBRES IN A SMALL BLOOD-VESSEL (A. S. Dogiel.)

especially close to the diaphragm, but also in the lower part as far down as the common iliac arteries; also in the inferior vena cava and in the thoracic portion of the aorta in animals, but not in man (Rachanow). While both sensory end-plates and Pacinian corpuscles occur in the adventitia of vessels, other fibres pierce the adventitia and media and terminate in the intima, the best example of

these being the fibres of the depressor division of the vagus (Küster and Tschermak). The ganglion-cells of this sensory nerve, being situated in the superior portion of the jugular ganglion of the vagus, send their peripheral processes to the aorta, where the medullated fibres terminate in the intima after having lost their medullary sheath in the media. Whether the delicate nerve-fibres accompanying blood-capillaries which possess no muscular coat are sensory or motor, it is difficult to say; for, as explained on p. 345, the presence of muscle is by no means essential for the contraction of capillaries.

Nerves as to the efferent nature of which there cannot be any doubt are found in vessels which contain definite non-striped muscle-cells. By means of Golgi's silver-chromate method it is easy, especially in the spleen, to demonstrate the repeated dendritic branchings of the nerve-fibres before they terminate on the surface of each separate muscle-cell.

Around the blood-vessels in the mucous membrane of the intestine it is possible to show by Ehrlich's *intra vitam* methylene-blue method, and also by modifications of Golgi's method (fig. 542), a plexus of fibrils which communicate with one another and probably also with fibres derived from the sympathetic. Their peculiar arrangement makes it likely that they serve

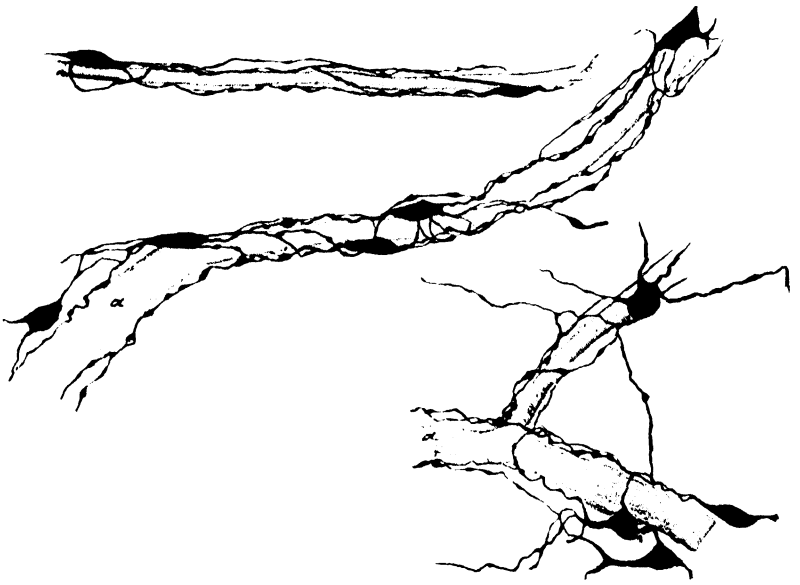


FIG. 542.—TERMINAL PLEXUSES AROUND SMALL BLOOD-VESSELS. (Dogiel.)
The plexuses show stellate enlargements here and there which are thought by Dogiel to be nerve-cells.

the same purpose as do the sensory spiral fibres which surround the muscle-fibres in muscle-spindles; just as contraction of the muscle-spindle puts the sensory fibre on the stretch and so stimulates it, so here dilatation of the blood-vessels may bring about a stimulation of the perivascular plexus.

DEVELOPMENT OF BLOOD-VESSELS.

The first vessels which appear in the ovum are formed in the mesoderm, and development subsequently goes on in the same layer and in its derivatives in all parts of the animal body. New vessels, also, are formed in the healing of wounds, in the restoration of lost parts, and in the production of adventitious growths.

The first vessels of the embryo, both of the chick and mammal, are formed in the vascular area, and originate from some of the cells of the mesoderm in that

situation (figs. 543, 544) which form a syncytium. Vacuoles are formed within this, and as they increase in size run together; a cavity filled with fluid is in this way produced in parts of the syncytium. The nuclei of the cells have meanwhile multiplied, and blood-corpuscles have become formed within the cavity in the manner to be described in connexion with blood-development. The cavities, while these changes are going on, increase largely in size, especially in the chick, where they form vesicles (fig. 543), visible to the naked eye as minute reddish specks, which have been known since the time of Pander as 'blood-islands.' The enlarged parts of the syncytium are united to one another by narrower parts, and after a time the cavities extend into the narrow portions so that a network of vessels is produced.

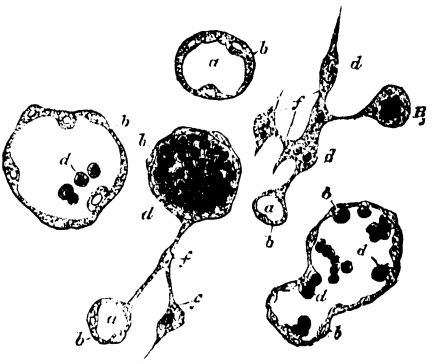


FIG. 543.—CELLS FROM MIDDLE LAYER OF CHICK'S BLASTODERM UNDERGOING DEVELOPMENT INTO BLOOD-VESSELS. Magnified. (E. Klein.)

a, cavity of cell; *b*, wall of cell; *f*, *f*, cells not yet hollowed out; *d*, blood-corpuscles.

The wall of these primary vessels is therefore composed at first merely of the protoplasm of the syncytium, with nuclei imbedded in it here and there. Subsequently the protoplasm becomes differentiated around the nuclei into the flattened cells which compose the wall of the capillaries, and which form the lining membrane of the arteries and veins; but this differentiation may not occur until comparatively late, and the capillaries of certain parts never show it (see p. 344). The remaining coats of the larger vessels are developed later, from other mesoderm-cells which apply

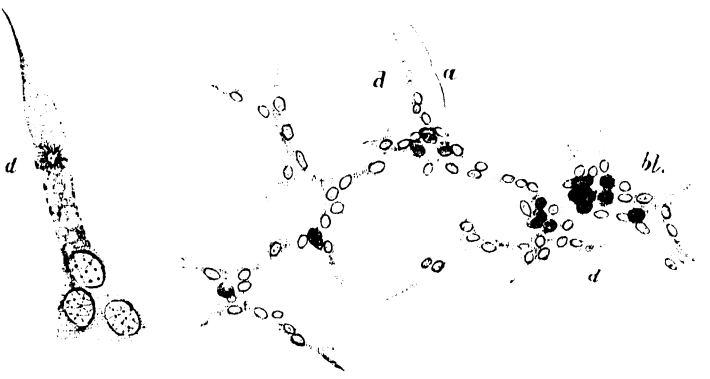


FIG. 544.—DEVELOPING BLOOD-VESSELS IN MESODERM OF VASCULAR AREA OF GUINEA-PIG. (Schäfer.)

bl, nucleated embryonic red corpuscles accumulating at the enlargements of a network of mesoderm-cells, which is becoming hollowed out at the enlarged parts. At *d*, *d*, division-appearances. The smaller figure on the left shows the part, *a*, of the larger figure more highly magnified.

themselves to the exterior of the previously simple endothelial tubes and produce the plain muscular and other tissues of which those coats consist. In many parts of the body of the embryo, vessels are formed in like manner from cells of the connective tissue, especially in rapidly growing vascular tissues.

Formation in connective tissue.—One of the most favourable objects for the study of the development of the blood-vessels is afforded by the subcutaneous tissue of the new-born rat, especially those parts in which fat is being deposited (Schäfer). Here we may observe that many of the connective-tissue corpuscles are much vacuolated, and that the protoplasm of some of them has a decided reddish tinge (fig. 545, *h*). In others the red matter has become condensed in

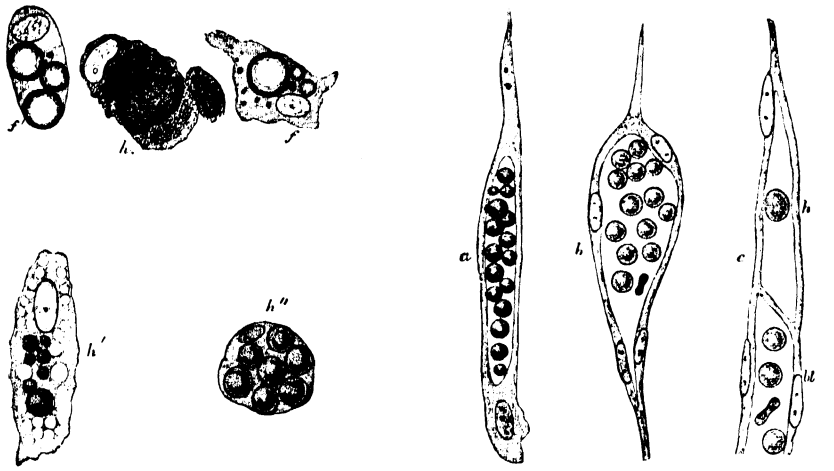


FIG. 545.—DEVELOPMENT OF VASOFORMATIVE CONNECTIVE-TISSUE CELLS INTO BLOOD-VESSELS. FROM THE SUBCUTANEOUS TISSUE OF THE NEW-BORN RAT. (Schäfer.)

h, a cell containing hæmoglobin in a diffused form in the protoplasm; *h'*, one containing coloured globules of varying size, and vacuoles; *h''*, a cell filled with coloured globules of nearly uniform size; *f*, *f'*, developing fat-cells; *a*, an elongated cell with a cavity in its protoplasm occupied by fluid and by blood-corpuscles which are still globular; *b*, a hollow cell the nucleus of which has multiplied: the new nuclei are arranged around the wall of the cavity, the corpuscles in which have now become discoid. In *c* is shown the mode of union of a vasoformative cell, which in this instance contains only one corpuscle, with the prolongation (*bl*) of a previously existing vessel. *a* and *c*, from the new-born rat; *b*, from the fœtal sheep.

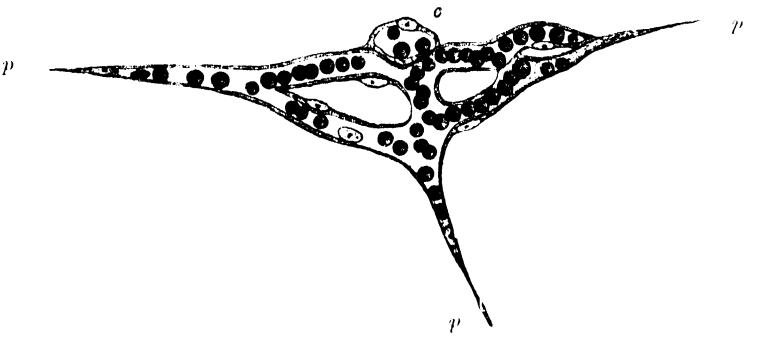


FIG. 546.—ISOLATED CAPILLARY NETWORK FORMED BY THE JUNCTION OF SEVERAL VASOFORMATIVE CELLS CONTAINING COLOURED BLOOD-CORPUSCLES IN CLEAR FLUID. (Schäfer.)

c, a hollowed-out cell which does not yet communicate with the network
p, *p*, pointed protoplasmic extensions growing out from the network.

the form of globules within the cells (*h'*, *h''*, &c.), varying in size from minute specks to spheroids of the diameter of a blood-corpuscle, or more. At some parts the tissue is completely studded with these cells, each containing a number of such spheroids, and forming groups or 'nests' of blood-corpuscles or minute 'blood-islands.' The cells become elongated and pointed at their ends, and send out

processes to unite with neighbouring cells. At the same time the vacuoles in their interior become enlarged, and coalesce to form a cavity within the cell (fig. 545, *a*), in which the reddish globules, which are now becoming disc-shaped (fig. 545, *b*), are found. Finally the cavity extends through the cell-processes into those of neighbouring cells and into those sent out from pre-existing capillaries (fig. 545, *c*), but a more or less extensive capillary network is often formed long before the connexion with the rest of the vascular system is established (fig. 546). As has been mentioned already, young capillaries do not exhibit the well-known lines when treated with nitrate of silver, for the differentiation of the hollowed cells and cell-processes into flattened cellular elements is a subsequent process.

The development of capillaries from 'vasoformative cells' has also been described in the great omentum of the cat and rabbit by Ranvier, and of the dog by Hayem; in the mesentery of the guinea-pig by Nicolaides; in the liver of the sheep-embryo by Kuborn; in the capsulo-pupillary membrane of embryos of rodents by Leboucq; and under pathological conditions by Malassez. Other authors (*e.g.* Spuler, Fuchs, Saxer, Pardi), without impugning the correctness of the observations, believe that the vasoformative cells are remnants of capillary vessels which are undergoing retrogression or atrophic change, the 'cells' in question representing nodal points in a capillary system in which the connecting vessels have disappeared. Spuler suggests that in many cases the vasoformative cells are still in connexion with existing patent blood-vessels, and that their apparently isolated position is due to a collapse of delicate capillaries which cannot be seen by ordinary methods. But while the possibility of occasional isolation of segments of a capillary system owing to degenerative changes is not denied, there can be very little doubt as to the real existence of vasoformative cells.[1]

Formation by outgrowths from existing capillaries.—It must not be supposed that new capillaries are in every case produced by vasoformative cells, for the common procedure in adult tissues, especially after injuries, consists in a budding of new vessels from older ones. This process is very readily studied in the tails of amphibians and in growing tissues generally. As described above, all blood-vessels are originally formed by mesoderm-cells which become converted into endothelial cells, and it is these which initiate the formation of new capillaries. At the place where a new capillary is about to be formed, an endothelial cell begins to lose its flattened character by giving rise to a solid process which penetrates into the surrounding connective tissue. This projection may occur close to its nucleus or some distance from it (Kölliker, Flemming[2]), and may be preceded, accompanied, or followed by a mitotic division of that nucleus. Since it is impossible to demonstrate in actively growing capillaries the outlines of endothelial cells by means of silver nitrate, we must regard the endothelial cell which has undergone nuclear division as part of a syncytium. The solid process thrown out by the cell in question is always, to begin with, destitute of a nucleus; but very soon one of the nuclei of the syncytium travels into the process, and presently undergoes further mitotic division. By this means the process gradually increases in length, and meets eventually with a similar process thrown out by another capillary. At this time the two capillaries are linked together by a protoplasmic bridge consisting of nucleated but as yet undifferentiated endothelium. This bridge becomes gradually hollowed out by the lumina of the original capillaries extending into it. In this way the cells become channelled out and converted into an endothelial covering. At first only blood-plasma enters the developing capillary, but later the red blood-corpuscles also pass along it.

[1] The recent literature on this subject is given in connexion with the development of the blood-corpuscles.

[2] Flemming, Arch. f. mikr. Anat. xxxv. 1890.

LYMPH-VESSELS OR LYMPHATICS.

A system of lymph-vessels is superadded to the sanguiferous in all classes of vertebrate animals, but this is not the case in the invertebrata; in many of these the blood-vessels convey a colourless or nearly colourless fluid, but no additional class of vessels is provided for conveying lymph or chyle.

Distribution.—Lymph-vessels are found in all the organs which receive blood, with the exception of the central nervous system, the globe of the eye and the internal ear. They are always conveyed in the connective tissue of the part. The larger lymphatic trunks usually accompany the deeply seated blood-vessels; they convey the lymph from the plexuses of origin towards the thoracic duct and right lymphatic duct. The lymph-vessels of a part anastomose or intercommunicate with each other much more frequently than do the veins alongside of which they run.

It not infrequently happens that a lymph-vessel, or a close interlacement of lymph-vessels, may ensheath an artery or vein either partially or wholly. In this case the lymphatic is termed 'perivascular.' In flat, membranous or expanded parts, the lymph-vessels usually form a network, which is situated either in a single plane, as in many parts of the serous membranes, or in two or more parallel planes united by intervening vessels, as in the skin and some mucous membranes. In the latter case the strata are generally composed of finer vessels and form a closer network the nearer they are to the surface of the membrane in which they are distributed, but even the most superficial and finest network is composed of vessels which are larger than the blood-capillaries.

In most parts of the body lymph-vessels are so delicate that they require a special method—namely, impregnation with silver nitrate according to the plan of v. Recklinghausen—for their demonstration. If we take a thin connective-tissue membrane, cover it with a solution of silver nitrate and, after rinsing with distilled water, expose it to the light, we find, after the tissue has become brown, a number of white areas, either quite separate or joined together (fig. 547, *c*). These white patches v. Recklinghausen took to be intercommunicating spaces; but we now know that each stellate area represents a connective-tissue cell, which remains white either because it does not contain chlorides for the silver salt to react with, or because the silver nitrate does not penetrate into the cells. And if we stain a silver-nitrate preparation of areolar tissue with any basic dye, such as toluidin-blue, each of the spaces is seen to contain a large nucleus. In fig. 547, in addition to the stellate cells (*c*), separated by a large quantity of deeply stained apparently homogeneous intercellular substance, are seen more regular cells (*d*) only separated by thin sinuous lines. These connective-tissue cells placed close together represent the endothelium of lymphatics, and here, again, each cell in the wall of a lymphatic may be shown to possess its own nucleus. Looking at v. Recklinghausen's figure one may readily see how he fell into the error of supposing lymphatic vessels to take their origin in tissue clefts (see p. 102). As far as we know to-day, the view of Langer and of Ranvier—namely, that lymph-vessels are formed as a closed system which ultimately opens only by the thoracic duct and right lymphatic duct into the venous circulation—is the correct one.[1] In most parts the actual origin of the lymphatics is in the form of a network or plexus of vessels of irregular size which here and there show blind root-like diverticula extending into the accompanying connective tissue; and we find analogous outgrowths in the lymphatics of the intestinal villi, which, although they form networks in the larger and broader villi, usually consist of a

[1] See pp. 361–364.

single vessel which begins with a blind or closed extremity at the free end of the villus, whence it passes to join the general plexus of the intestinal mucous membrane.

In the more solid organs, such as glands, the lymph-vessels are found in the interstitial connective tissue. In many cases they lose in great measure the character of distinct tubular canals, and appear simply as cleft-like spaces ; these are, however, always bounded by an endothelial layer, like that which lines the lymph-vessels elsewhere. This lacunar formation of lymphatics was first described in the testicle by Ludwig and Tomsa, and it is now known to be characteristic of most glandular

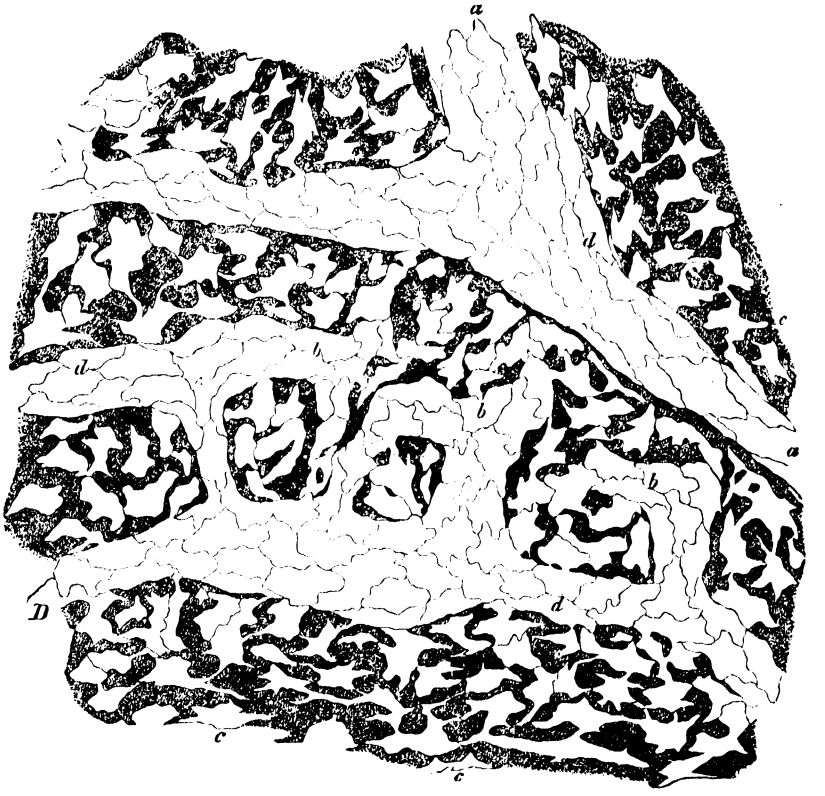


FIG. 547.—LYMPHATICS OF CENTRAL TENDON OF DIAPHRAGM OF RABBIT, PLEURAL SIDE: TREATED WITH NITRATE OF SILVER AFTER REMOVAL OF SUPERFICIAL ENDOTHELIAL LAYER. (v. Recklinghausen.)

c, *c*, connective-tissue cells which v. Recklinghausen mistook for empty spaces; *d*, *d*, lymphatic vessels, which appear to be in continuity with the 'cell-spaces' at *b*, *b*.

structures. Occupying everywhere the interstices of the penetrating connective tissue, the lymph bathes the exterior of the tubules or alveoli of the gland, in many parts even separating them from the capillary blood-vessels, so that the exchanges of material between the plasma of the blood and the secreting cells of the gland must be carried on through the intermedium of the lymph in these spaces.

Lymphatics, although developed originally from veins, are in open communication with the serous cavities, by means of orifices or *stomata*, which will be described with the serous membranes. These stomata allow of the passage of lymph from the serous cavities into the lymphatics. Owing to this the fluid which moistens them does not accumulate in the serous cavities under normal conditions. The

stomata are most readily seen in the peritoneal wall of the cisterna magna or great lymph-sac in the frog; the cells lining the stomata become ciliated during the winter season in female frogs and toads (Klein), so as to direct the lymph-flow from the big lymph-sac over the developing ova. Remak was the first to notice these cilia, but he mistook the stomata for vesicles.

In some of the lower animals the lacunar condition of lymphatics has been long known. Rusconi found that the aorta and mesenteric arteries of amphibia are enclosed in large lymphatic spaces. Johannes Müller recognised the spaces which so extensively separate the frog's skin from the subjacent muscles as belonging to the lymphatic system, and v. Recklinghausen showed that the subcutaneous lymph-spaces of the frog's leg communicate with lymphatic vessels which envelop the blood-vessels of the foot; also that milk injected into these spaces finds its way into the blood. The lymphatic system, with its lacunæ or interstitial receptacles, resembles the blood-vascular system of crustaceans and insects.

Structure.—The smallest lymph-vessels, as already mentioned, are larger than the blood-capillaries. The endothelial cells show a markedly sinuous outline, which is well seen in fig. 548.

Lymph-vessels differ from blood-vessels in that their diameter varies greatly within short distances—a very wide space may suddenly become narrowed down to a close passage, as is seen in figs. 548 and 549; and also in that their walls are thinner in proportion to their calibre and less systematically arranged into tunics.

In the larger vessels, from about 0.25 mm. upwards, there are present in the tunica intima, in addition to the endothelial lining, elastic fibres running longitudinally, forming a more or less complete network, which in the largest lymphatics may become membranous in character. Where, however, a great deal of elastic tissue exists in the surrounding tissues, as in the mesentery of mammals, the elastic tissue of the lymphatics is absent or greatly reduced.

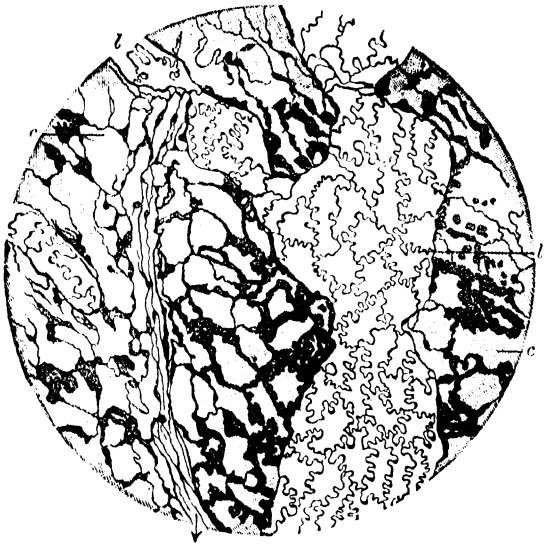


FIG. 548.—PART OF A LYMPHATIC VESSEL IN THE PLEURAL COVERING OF THE DIAPHRAGM. $\frac{1}{1}\frac{1}{8}$. (Ranvier.)

l, *l*, the lymphatic vessel with characteristic sinuous endothelium; *c*, cell-spaces of the connective tissue

In all large lymph-vessels, as in blood-vessels, three distinct tunics are met with. Outside the tunica intima is the tunica media, consisting of muscle-fibres running transversely and obliquely, strengthened by a few transverse elastic fibres. The outer coat (tunica externa seu adventitia) is, in the small lymphatics, the most characteristic; it contains amongst the longitudinally placed connective-tissue elements a considerable number of non-striped muscle-fibres running longitudinally and obliquely, a feature rarely met with in the blood-vascular system except in the large veins. Both large and moderate-sized lymphatics have blood-vessels ramifying in their outer coat.[1]

In the thoracic duct there is a subendothelial layer, as in the large arteries, and it also contains elastic fibres forming a longitudinal network. The tunica media has

[1] H. M. Evans, Amer. Journ. Anat. vii. 1907.

a larger number of circular non-striped muscles than a vein of similar size, but not as many as are found in a corresponding artery. The tunica externa contains connective tissue and a few longitudinal elastic and muscle-fibres. Nerve-fibrils are abundantly supplied to lymph-vessels.[1]

Gaskell described an attachment of elastic fibres to the walls of smaller lymphatics in some parts, and inferred that the patency of the lumen may by their means be restored after it has been temporarily obliterated by external pressure or by contraction of the muscular coat.

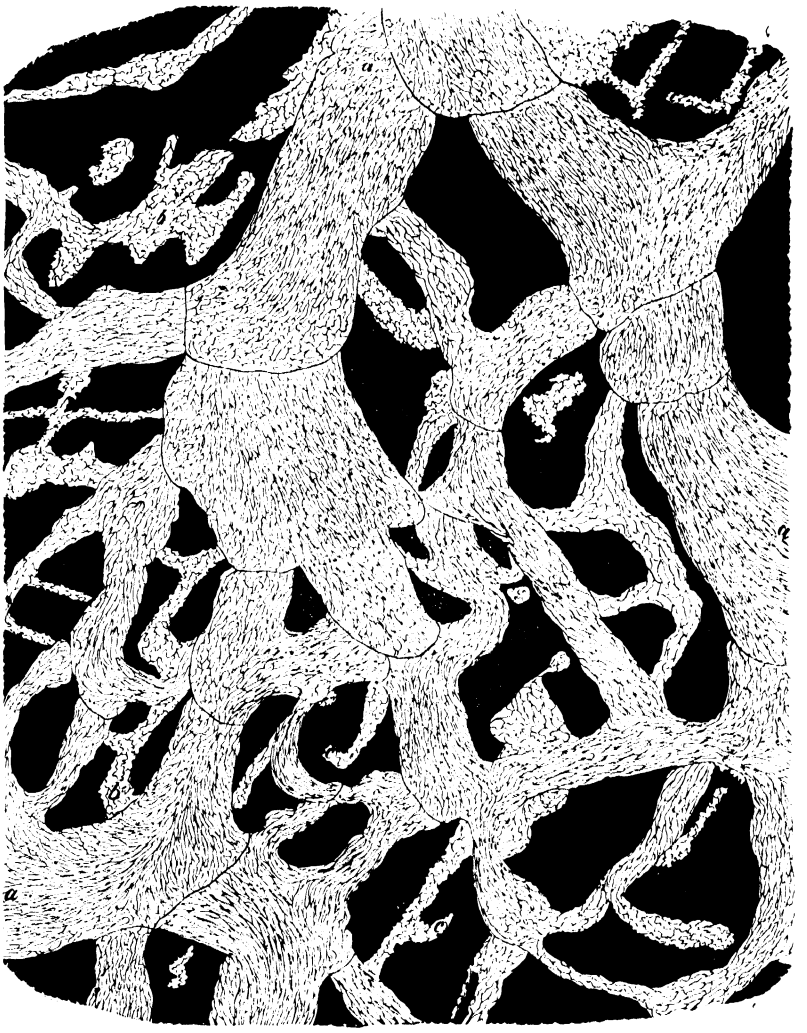


FIG. 549.—LYMPHATIC PLEXUS OF CENTRAL TENDON OF DIAPHRAGM OF RABBIT, PLEURAL SIDE. Magnified. (Klein.)

a, larger vessels with lanceolate cells and numerous valves; *b*, *c*, lymphatics of origin, with wavy-bordered cells. Here and there an isolated patch of similar cells is seen in the meshes of the network. The connective tissue cell-spaces are not represented.

Valves.—The lymphatics and lacteals are furnished with valves serving the same office as those of the veins, and for the most part constructed after the same fashion. These generally consist of two semilunar folds arranged in the same way as in the already described valves of veins, but deviations from the

[1] A. S. Dogiel, Arch. f. mikr. Anat. xlix. 1897.

usual structure occur here and there. A difference is noticeable in the endothelium upon the two surfaces of the valves similar to that which has been noticed in the valves of the veins (see p. 340).

Valves are not present in all lymphatics, but where they exist they follow one another at much shorter intervals than those of the veins, and give to the lymphatics, when distended, a beaded or jointed appearance (see figs. 548, 549). Valves are also placed at the entrance of the lymphatic trunks into the great veins of the neck. They are very abundant in the lymph-vessels of the mesentery. They are as a rule wanting or imperfect in the lacunæ and plexuses of origin; so that fluid injected into one of these vessels runs in all directions, filling to a greater or less extent the whole plexus, and then passing along the separate vessels which issue from the organ.

The lymphatics of fish and amphibia are in most cases destitute of valves, and may therefore be injected from the trunks; valves are also much less numerous in the lymphatics and lacteals of reptiles and birds than in those of mammals.

Terminations of lymphatics.—The absorbent system discharges its contents into the blood-circulatory system at two points, namely, on the left side (by the thoracic duct) at the junction of the subclavian and internal jugular veins, and on the right side (by the right lymphatic trunk) at the corresponding part of the venous system. The openings, as already remarked, are guarded by valves. It sometimes happens that the thoracic duct divides, near its junction with the veins, into two or three short branches, which open separately but near each other; more rarely a branch opens into the vena azygos—indeed the main vessel has been seen terminating in that vein. Again, it is not uncommon for larger branches, which usually join the thoracic duct, to open independently in the vicinity of the main termination; this is more apt to happen with the branches which usually unite to form the right lymphatic trunk. Notwithstanding these variations the junctions with the great veins are confined in man to the region of the neck; in birds, reptiles, and fishes, on the other hand, communications take place between the lymphatics of the lower part of the trunk and lower limbs and the sciatic or other veins of the abdomen or pelvis.

Lymphatic hearts.—J. Müller and Panizza, almost at the same time, but independently of each other, discovered that the lymphatic system of reptiles is furnished, at its principal terminations in the venous system, with pulsatile muscular sacs, which serve to discharge the lymph into the veins. These organs, which are named lymph-hearts, have now been found in all the different orders of reptiles and amphibia, and also in birds, but not in any mammal. In the frog and toad two pairs of lymph-hearts occur: a posterior pair, situated in the sciatic region, which pours its lymph into a branch of the sciatic or of some other neighbouring vein; and an anterior, more deeply seated pair, placed over the transverse processes of the third vertebra, and opening into branches of the jugular veins. The walls of these sacs are thin and transparent, but contain muscular tissue, which appears obscurely striated, decussating in different layers, as in the blood-heart. In their pulsations they are quite independent of the latter organ, and are not even synchronous with each other; their beats are dependent upon connexion with the spinal cord. In adult reptiles (lizards, serpents, tortoises, and turtles) only a posterior pair has been discovered, which agree in all essential points with those of the frog. In the goose, and in other species of birds belonging to different orders, Panizza discovered a pair of lymph-sacs opening into the sacral veins; and Stannius found that these sacs have striated muscular fibres in their walls. Some birds have an anterior as well as a posterior pair of lymph-hearts. Nerve-fibres, both dark-bordered and pale, have been observed in the lymph-hearts of the frog, and nerve-cells in those of the tortoise (Waldeyer).[1]

[1] Müller's description is to be found in the Philosophical Transactions for 1831; Panizza's, in a special memoir on the Lymphatic System of Reptiles, published in 1833. For an excellent account of the lymphatic hearts of the frog the reader is referred to the 'Leçons d'anatomie générale' delivered by Professor Ranvier in the Collège de France in 1877–78, and published in 1880 and to the 'Traité technique' of the same author, 2nd edition, published in 1889.

Development of lymph-vessels.—Until a few years ago little was definitely known as to the manner in which lymph-vessels are developed, but this question can now be regarded as being considerably more advanced towards settlement, owing especially to the researches of Florence R. Sabin [1] and F. T. Lewis.[2]

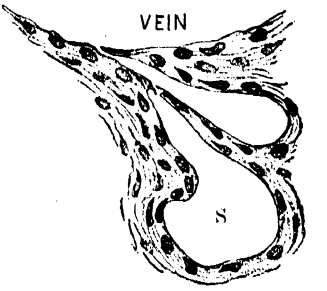


FIG. 550.—RELATION OF THE LYMPH-SAC AND DUCT TO THE CARDINAL VEIN IN A PIG-EMBRYO 14·5 MM. LONG. Magnified 170 diameters. (Sabin.)

S, lymph-sac, communicating through another vessel with the interior of the vein.

Langer [3] was the first to notice that in the frog lymphatics grow as blind sprouts in exactly the same manner as do blood-vessels. Ranvier,[4] later, described their development as centrifugal in the embryo pig: he further suggested that lymphatics take origin as outgrowths from veins. Ranvier stated that the thoracic duct throws out buds, which at first are solid, but later become converted into channels. Whenever a bud is formed it possesses a dilated end, and from this there arises a narrower bud which grows further into the surrounding tissue, and itself gradually becomes dilated. The dilated ends of the successive buds give rise to the valves of the lymphatic system. In the omentum of the newly born kitten there exist a large number of lymphatics ending in blind diverticula; these vessels completely disappear by the time the kitten is three months old.

Gulland,[5] on the other hand, thought that lymph-vessels arise at the periphery and grow towards the blood-vessels, finally opening into the latter. Gulland states that before definite lymphatic vessels are developed there appear in the subcutaneous connective tissue intercommunicating spaces between the lamellar connective-tissue cells and the white fibrous tissue to which the cells have given rise. The spaces are filled by fluid which has exuded from the

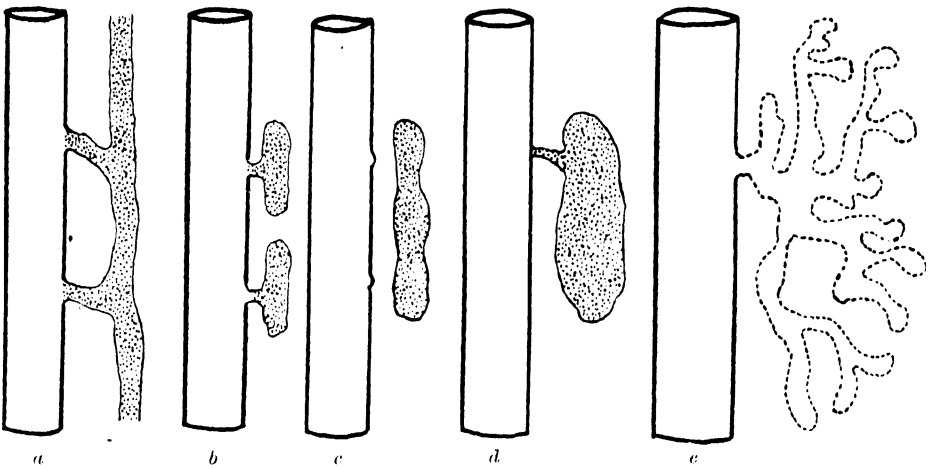


FIG. 551.—DIAGRAM OF THE MODE OF FORMATION OF THE LYMPHATIC FROM THE VENOUS SYSTEM. (Mann.)

a, a main vein with lateral branches; *b*, partial atrophy of the branches and formation of blind sacs communicating with the veins and filled with blood; *c*, loss of communication with the main vein, and blending of the sacs into a single closed sac, still occupied by blood; *d*, secondary connexion of the sac, which is now enlarged, with the main vein; *e*, budding out of lymph-vessels from the sac, the blood from which has been discharged into the vein.

blood-vessels, and which percolates along from the distal ends of the limbs to their proximal ends; in doing so it is supposed gradually to make for itself definite channels in the subcutaneous tissue; and the cells lining the ever-widening channel to become converted into flattened elements—the lymphatic endothelial cells. In the light of more recent researches Gulland's

[1] Amer. Journ. Anat. i. 1902; iii. 1904; iv. 1905; Anat. Record, ii. 1908; Amer. Journ. Anat. ix. 1909.
[2] Amer. Journ. Anat. v. 1905.
[3] Sitzungsb. d. k. k. Akad. d. Wiss. lviii. 1868.
[4] Comptes Rendus, 1895–1896; Arch. d'anat. micr. 1897.
[5] Journ. of Pathol. and Bact. ii. 1894.

view cannot be adopted, although some authors believe that intercommunicating spaces such as he describes may play a part in the formation of peripheral lymph-channels (see next page).

In mammals the lymph-vessels arise as six lymphatic sacs, one pair of which is found anteriorly in the neck, and another pair posteriorly in the groin. In addition to these paired sacs, two unpaired sacs occur—namely, one at the root of the mesentery and another behind the aorta ; this last sac becomes the receptaculum chyli. The anterior pair of sacs is developed about the level of the fifth cervical nerve along the dorso-lateral surface of the post- and pre-cardinal veins, opposite the duct of Cuvier (fig. 550). The sacs begin to appear in pig-embryos of 6·5 mm. ; they are fully formed in 16 mm. embryos. They correspond in situation to the anterior lymph-hearts of the lower vertebrata. In older embryos the anterior lymph-sac gradually differentiates into lymph-nodules. The mesenteric sac arises according to Baetjer from veins of the renal anastomoses,[1] while the sac which becomes the receptaculum chyli buds out dorsally to the aorta and adjacent to the azygos veins. Subsequently the mesenteric sac and the receptaculum chyli join and become connected with the thoracic duct, which has developed in connexion with the azygos veins.

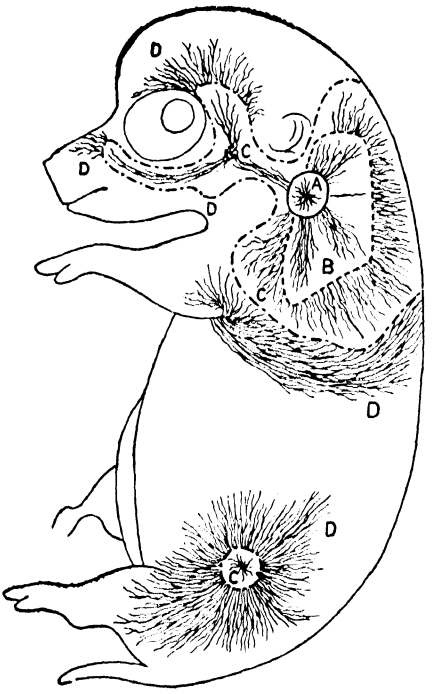


FIG. 552.—COMPOSITE DIAGRAM OF THE SPREADING OF THE SUPERFICIAL LYMPHATICS IN THE EMBRYO PIG. (Sabin.)

A, extent of area in an embryo 18 mm. long; B, extent of area in an embryo of 20 mm.; C, C, extent of areas in an embryo of 30 mm.; D, D, extent of areas in an embryo of 40 mm.

The general principle on which the sacs are formed is probably as follows (see diagram, fig. 551) :

In the regions where the lymph-sacs subsequently make their appearance, plexuses of small venous vessels, which open into a main vein (fig. 551, *a*), become formed. These plexuses become detached from the main vein and reduced to a smaller number of closed spaces lined with endothelium and filled with blood (fig. 551, *b* and *c*). These spaces fuse together to form the lymph-sac (fig. 551, *c*), which is at first filled with blood and is not in communication with the main vein. Later a connexion forms between the sac and the vein (fig. 551, *d*); into this the blood, which was contained within the sac, passes. Soon afterwards the sac gives rise by budding to true lymph-vessels (fig. 551, *e*). The latter start from the lymph-sac and invade the region of the embryo which adjoins the lymph-sac (figs. 552, 553). In this way each half of the embryo develops (1) an anterior lymph-sac from which the lymphatics of the corresponding head and chest region grow out, (2) a posterior sac from which those of the inguinal and leg region are formed, and (3) two unpaired mesial sacs, of which the retroperitoneal gives rise to the lymph-vessels of the intestine,[2] the other becoming the receptaculum chyli.

[1] Anat. Record, ii. 1908; Amer. Journ. Anat. viii. 1908. C. F. Silvester (Verhandl. d. anat. Gesellsch., Anat. Anz. 1910) describes a permanent lymph-vein-connexion at the level of the renal veins in South American monkeys.

[2] Heuer, Anat. Record, ii. 1908 Amer. Journ. Anat. ix. 1909.

According to this account lymph-vessels grow out from the lymph-sacs, which are themselves originally formed from venous plexuses; they are in no way assisted in their formation by pre-existing peripheral tissue-clefts. This view is not shared by Huntingdon,[1] who believes that the venous lymphatic outgrowths unite with lymphatic spaces independently developed in various parts of the mesenchyme in close proximity to embryonic veins. The balance of evidence appears, however, to favour the view that the lymphatic system is a series of vessels lined by endothelium which arise from separated portions of veins and eventually again open into the venous system.[2] The present tendency is to deny the incorporation of tissue-clefts into advancing lymph-vessels which have started at the lymph-sac, and the statements of Budge,[3] Gulland[4] and Sala,[5] all of whom affirmed the development of lymphatics from tissue-clefts, have fallen into discredit. Sala states that the posterior pair of lymph-sacs of the

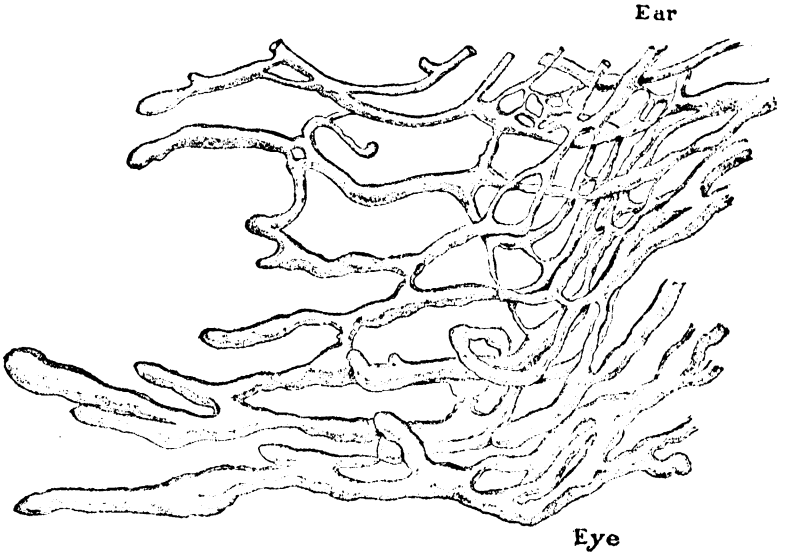


FIG. 553.—GROWING EXTREMITIES OF THE LYMPHATICS OF THE SKIN BETWEEN THE EAR AND EYE IN A PIG-EMBRYO 50 MM. LONG. Magnified. (Sabin.)

chick are derived from lateral branches of the first five coccygeal veins, and that later these become connected secondarily with lymph-vessels, formed by the union of spaces arising independently in the mesenchyme.

The following additional points may be mentioned as illustrating the centrifugal growth of the lymphatics. Knower[6] has shown that the subcutaneous lymph-sacs of the frog are derived from ramifications of simple tubular vessels of the lateral lymphatic trunks. Goldfinger found that the sacs of the posterior limbs have a similar origin. Rainer describes the lymphatics in the skin as developed in regular order, from within out—viz. first those of the subcutaneous tissue, then those of the cutis vera, and finally those of the papillary layer. In the lung, according to Flint,[7] the lymphatics are seen first at the hilum, whence they penetrate along the connective-tissue septa. Heuer[8] describes the growth of the intestinal lymphatics as follows: The primary lymph-vessels enter with the mesenteric artery; they pierce the muscular coats and form a system of loops in the submucous coat; these loops, by sending out lateral branches, gradually give

[1] Verhandl. d. anat. Gesellsch., Anat. Anz. 1910. See also Huntingdon and McClure, Anat. Record, i. 1907, and McClure, Anat. Anz. xxxii. 1908.
[2] Cf. F. R. Sabin, Anat. Record, ii. 1908, p. 51.
[3] Budge, Arch. f. Anat. u. Physiol., Anat. Abtheil. 1880 and 1887.
[4] Gulland, Journ. of Pathol. and Bacteriol. ii. 1894.
[5] Sala, Abstract in Arch. ital. de Biol. xxxiv. 1900
[6] Anat. Record, ii. 1908.
[7] Amer. Journ. Anat. vi. 1906.
[8] *Op. cit.*

rise to a coarse-meshed plexus of lymphatics; from this, at a later date, is derived a fine-meshed plexus on the inner side of the muscularis mucosæ, and from this plexus spring the lacteals which enter the villi; the muscular coat is mainly supplied from branches arising from the submucous plexus, while the plexus between the muscular and serous coat is the last to develop, arising from twigs given off by the main lymphatics before they enter the muscular coat. W. G. MacCallum[1] found that the lymph-vessels of embryo pigs between 5 and 15 cm. long are closed tubes unconnected with the connective-tissue spaces, and described them as growing by solid sprouts. Lastly, it may be mentioned that Clark,[2] studying the growth of lymph-vessels in the tail of the tadpole, states that they grow centrifugally as sprouts from pre-existing vessels,[3] the cells which form their growing extremities being phagocytic.

Huntingdon[4] has suggested that phylogenetically the circulation was originally of the lymphatic type, and that from this arose, secondarily, the hæmal or blood-circulatory system. In support of this view he quotes the work of Favaro, who found that in bony fishes certain vessels act alternately as blood- and as lymph-vessels. As we descend in the vertebrate series we find that the origin of the lymphatic system undergoes simplification, for in urodelous amphibians fourteen to sixteen veno-lymphatic hearts are found, while in anurous amphibians two posterior and two anterior hearts only are met with, and in adult reptiles the posterior alone occur. Most birds lose the anterior heart, but some retain it, whereas mammals are entirely devoid of contractile lymph-hearts, although retaining a double connexion between the venous and lymphatic systems.[5]

[1] Arch. f. Anat. 1902. [2] Anat. Record, iii. 1909. [3] Cf. Langer, *op. cit.*

[4] Anat. Record, ii. 1908. See also Anat. Anz. xxxix. 1911, where an extensive bibliography relating to the subject will be found.

[5] The description of the structure and development of the vascular system (including the lymph-vessels) has been furnished by Professor Gustav Mann of Tulane University.

THE BLOOD AND LYMPH.

THE BLOOD.

To the naked eye the blood appears opaque and homogeneous; but, when examined with the microscope, either within the minute vessels, or when spread out in a thin layer upon a glass slide, it is seen to consist of a transparent colourless fluid, named 'liquor sanguinis,' or 'plasma,' in which corpuscles are immersed. The most evident of these corpuscles are of two kinds, the coloured (*erythrocytes*) and the colourless (*leucocytes*). The former are by far the more abundant, and have been long known as the red or coloured corpuscles of the blood; the colourless, white, or pale corpuscles, on the other hand, being fewer in number and less conspicuous, were longer in being generally recognised. Of late years a third kind of corpuscle, much smaller than either of the other two, and far less conspicuous, has been recognised as a constant morphological constituent of blood. These corpuscles appear to be connected with the process of coagulation and are hence termed *thrombocytes*; from their small size and flattened shape they are also known as *blood-platelets*.

When blood is drawn from the vessels it undergoes coagulation, the plasma depositing fibrin, which appears under the microscope in the form of fine interlacing filaments; the colourless or yellowish fluid which remains is named *serum*.

In a cubic millimetre of normal human blood there are on an average 5,000,000 red corpuscles. The number of white corpuscles is about 10,000, but varies much more than that of the red; from 5,000 to 20,000 per cubic millimetre being met with even under normal circumstances. There are fewer red corpuscles in the female (4,500,000 per cubic millimetre). The number of blood-platelets is still more variable; it has been given at from 5,000 to 450,000 per cubic millimetre of blood.

The number both of erythrocytes and leucocytes is relatively higher in young children. According to the observations of H. H. Roberts,[1] the average number of erythrocytes per cubic millimetre of blood during the first twenty-four hours after birth is 6 millions. There is an increase during the first three days, then a gradual decrease, until during the second week there are about 5½ millions. There are usually some erythroblasts on the first day. The blood-platelets are fewer than in the adult. Leucocytes are also more numerous immediately after birth. On the first day they average 18,000 per cubic millimetre, and on the second day 16,000, but by the third day they are down to 11,000. The proportion of hæmoglobin in the red corpuscles is higher in the new-born than in the adult by 15 to 20 per cent.

FIG. 554. — HUMAN RED CORPUSCLES. Magnified about 420 diameters

Enumeration of the coloured blood-corpuscles is readily performed. A definite amount of blood, obtained by pricking the finger, is measured in a capillary tube, and is then mixed with a measured amount (100 times its volume) of dilute solution of sulphate of soda, or some other fluid which prevents coagulation and at the same time preserves the corpuscles; the latter can then be counted in a small known quantity of the mixture. This part of the operation is effected by placing a drop of the mixture in the middle of a glass 'cell' of a certain depth ($\frac{1}{10}$th of a millimetre), the bottom

[1] Thesis, Edinburgh, 1906 (unpublished). This is generally confirmatory of the older observations, especially those of Hayem (Recherches &c., Paris, 1878; also 'Du Sang,' &c., 1889).

of which is ruled in squares, of a definite dimension (usually $\frac{1}{10}$ mm.). If now a covering glass is placed over the cell so as to touch the drop, the latter will form a layer of the mixture $\frac{1}{10}$ mm. deep, and the part above each square will represent a cube of liquid the sides of which measure $\frac{1}{10}$ mm. By counting the number of corpuscles in ten such squares, after allowing them time to subside, and multiplying the result by 10,000, the number in a cubic millimetre of the blood is obtained. In the actual instrument the larger squares are subdivided into smaller for convenience of counting.

The methods of Hayem and Nachet, Gowers, and Thoma are based on the above principle.[1] The average results obtained by recent investigators agree closely with the original estimates of Vierordt and Welcker.[2]

For the enumeration of the leucocytes and thrombocytes special methods of preparation and staining as well as a less dilution of the blood are employed.

RED CORPUSCLES OF THE BLOOD: ERYTHROCYTES.

Shape and Size.—The human erythrocytes are not spherical, as the name 'globules,' by which they were formerly designated, would seem to imply, but

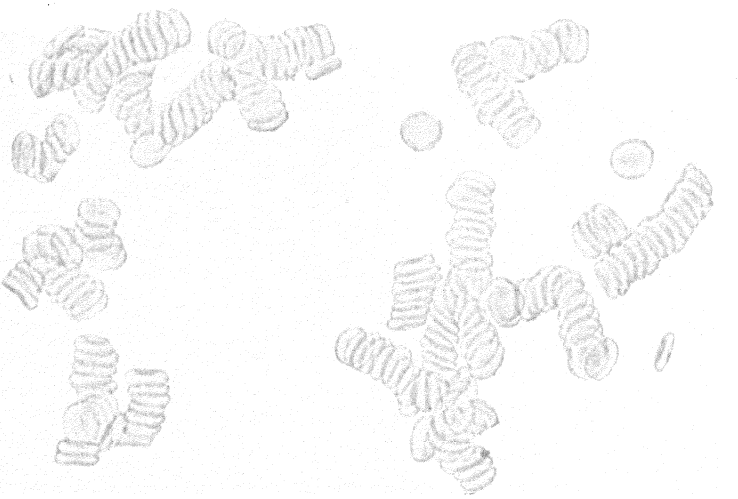


FIG. 555.—HUMAN RED BLOOD-CORPUSCLES. (Schäfer.) Photograph. Magnified 650 diameters.

flattened (fig. 554 and fig. 555), with a nearly circular outline, like a coin. When examined on a glass slide in the usual way they present a shallow cup-like depression or dimple on both surfaces; their usual figure is, therefore, that of biconcave discs. Sometimes they appear dimpled on the one surface and very slightly convex on the other (cup-shaped). According to Weidenreich[3] this is the normal condition in mammals: the biconcave shape being the result of evaporation of water during exposure in preparing the specimen. But this opinion, although shared by F. T. Lewis,[4] Radasch,[5] and a few other histologists, cannot be accepted,

[1] G. Oliver (Croonian Lectures, *Lancet*, 1896, vol. i.) has introduced a method of estimating the number of red blood-corpuscles without the labour of enumeration. Many valuable observations on the conditions affecting their number will be found in this article. See also 'The Blood and Blood-pressure,' London, 1901, by the same author. Other observations and references are collected in the article 'Blood' in Schäfer's Textbook of Physiology, 1898, by the editor, and in that on 'Blood and Lymph' by Boruttau in Nagel's Handbuch der Physiologie, 1910.

[2] P. B. Hawk (Amer. Journ. Physiol. x. 1904) found a higher number—viz., 5,600,000 per cub. mm.—as the blood-count of healthy young men taking regular exercise: he gives the mean blood-count for the leucocytes as 8,800, *i.e.* 1 to nearly 640 erythrocytes. The number of both was increased immediately after exercise (see footnote 1, p. 387).

[3] Ergebn. d. Anat. 1903, 1904, and 1909; Arch. f. mikr. Anat. lxi. 1903, lxix. 1906.

[4] Journ. Med. Research, x. 1904.

[5] Anat. Anz. xxviii. 1906. Radasch states that the erythrocytes of the child and embryo are mostly cup-shaped, but appears to have studied them chiefly in sections of fixed tissues.

for, on examining the circulating blood in the mesentery and other transparent parts of mammals, it is easy to observe that, with few exceptions, the erythrocytes are biconcave. This shape must therefore be regarded as the normal one.[1] Their magnitude differs somewhat even in the same blood, but the prevalent size is ·007 to ·008 millimetre[2] ($_{3}{}^{1}{}_{0}{}_{0}$th inch) in diameter, and about one-fourth of that in extreme thickness. A few may usually be found which are not more than one-half the normal size (microcytes), and others (macrocytes) which are rather larger (up to about ·0085 mm.); every gradation in size between these two extremes may be met with. In some diseases, especially pernicious anæmia, the relative number of microcytes is greatly increased.

In mammals generally the red corpuscles are shaped as in man, except in the

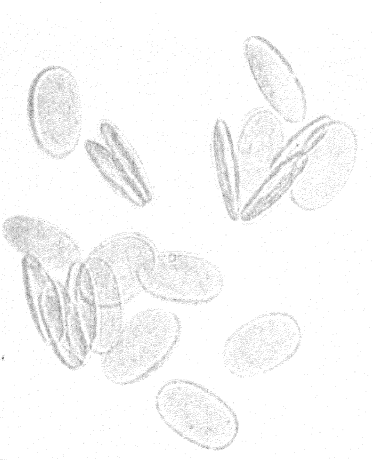


FIG. 556. — RED BLOOD-CORPUSCLES OF THE TOAD. (Schäfer.) Photograph. Magnified 450 diameters.

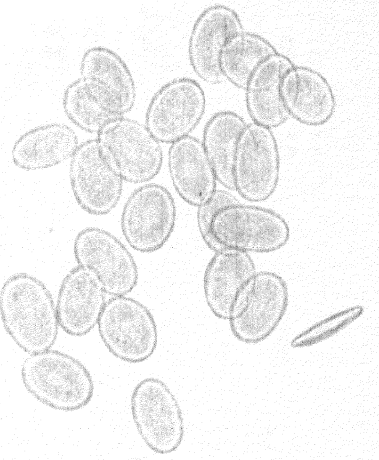


FIG. 557. — RED BLOOD-CORPUSCLES OF THE FROG. (Schäfer.) Photograph. Magnified 450 diameters.

camel tribe, in which they have the same shape[3] as in birds, reptiles, amphibia, and most fishes; in these they are elliptical discs with a central elevation on both surfaces (figs. 556 and 557). The height and extent of the elevation, as well as the proportionate length and breadth of the ellipse, vary, so that in some fishes the elliptical form is almost shortened into a circle.

The size of the erythrocytes differs greatly in the different classes of vertebrata; they are largest in amphibia. Thus in the frog they are about 25 μ long and 14·5 μ broad; in Proteus anguineus, 62·5 μ long and 34·5 μ broad; in Amphiuma tridactylum, where they are largest, the red corpuscles are one-third larger than those of Proteus. In birds they range in length from about 8·5 μ to 14·5 μ. Amongst mammals the elephant has the largest red blood-corpuscles (9 μ); those of the dog average 7 μ; those of the sheep 5 μ; the goat was long supposed to have the smallest (4 μ), but Gulliver found them about half this size in the Meminna and Napu deer.[4]

In observations upon the blood of different races of mankind, Richardson

[1] Schäfer (Anat. Anz. xxvi. 1905). A similar conclusion is arrived at by David (Arch. f. mikr. Anat. lxxi. 1907), by Jordan (Anat. Anz. xxxiv. 1909), and by Jolly, who observed the corpuscles in the vessels of the bat's wing (C. r. soc. biol. lviii. 1905; Arch. d'anat. micr. xi. 1909). Cf. also Orsós (Fol. hæmat vii. 1909) and L. Löhner (Pflüger's Arch. cxl. 1911).

[2] The one-thousandth part of a millimetre is known as a *micron*, and is represented by the Greek letter μ. The diameter of a red blood-corpuscle is therefore expressed as 7—8 microns (7 μ—8 μ).

[3] But not the same structure, for, as in mammals generally, the red corpuscles in the camel tribe are non-nucleated.

[4] Proc. Roy. Soc. 1842; Proc. Zool. Soc. 1873 and 1875.

found no constant difference, the average diameter of the erythrocyte being 7·8 μ. The corpuscles of many mammals, notably the dog among the common domestic animals, approach so nearly in size to the human blood-corpuscles as to be practically indistinguishable from them.

When viewed singly by transmitted light the erythrocytes do not appear red but merely of a reddish-yellow tinge, or yellowish-green in venous blood. It is only when the light traverses a number of corpuscles that a distinct red colour is produced.

In consequence of the concavity of the surfaces, the erythrocyte looks darker in the middle than at the edge when viewed with only a moderate magnifying power, or at a distant focus; but the middle of the corpuscle appears lighter than the periphery when a close focus or a very high magnifying power is employed.

FIG. 558.—RED CORPUSCLES COLLECTED INTO ROLLS. (After Henle.) Magnified about 420 diameters.

The erythrocytes, when blood is drawn from the vessels, sink in the plasma; they have a singular tendency to run together, and to cohere by their surfaces, so as to form cylindrical columns, like piles or rouleaus of money, and the rolls or piles themselves join together into an irregular network (figs. 555, 558). The corpuscles separate on slight movement of the fluid, and unite again when it comes to rest. The rouleau-formation will take place in blood which has been in any way brought to a standstill within the living vessels as well as in blood that has stood for some hours after it has been drawn, and also when the corpuscles are immersed in serum in place of liquor sanguinis.

It was shown by Norris [1] that discs which float completely immersed in any fluid will, when the fluid comes to rest, adhere together in the form of rouleaus provided that the surface of the discs is coated with a substance not wetted by the fluid in which they float. Thus cork discs which have been weighted so that they neither rise nor sink in water do not adhere together so long as they are freely wetted by the water, but if their surfaces are coated with a thin film of fatty substance the discs tend to run together into rouleaus. As it is probable (see next page, Structure of the Erythrocyte) that the red discs do actually possess a superficial film of fat-like substance, the facts pointed out by Norris suggest a reasonable explanation of the rouleau-formation which occurs in blood that has been allowed to come to rest.

Human erythrocytes, as well as those of mammals generally, often present deviations from the natural shape, which are due to causes acting after the blood has been drawn from the vessels, but which in some instances depend upon abnormal conditions previously existing in the blood. Thus, it is not unusual for many of them to appear shrunken and crenated, when exposed under the microscope (fig. 559, *f*), and the number of corpuscles so altered often increases during the time of observation. This is, perhaps, the most common change; it also occurs whenever the density of the plasma is increased by the addition of a neutral salt. On the other hand, a slight diminution in the density of the plasma causes one of the surfaces to be bent out, and the corpuscle then acquires a cup-like figure, which is sometimes seen in erythrocytes even within the blood-vessels (see pp. 366, 367).[2]

The corpuscles of the Mexican deer and some allied species present very singular

[1] Proc. Roy. Soc. 1862 and 1869. See also Physiology and Pathology of the Blood, 1882.

[2] It has been suggested by Rindfleisch (Arch. f. mikr. Anat. xvii. 1880) that the erythrocytes when first produced are cup-shaped, and that they become mechanically moulded into the biconcave form by impact against one another in the blood-vessels.

forms in consequence of exposure; the figures they assume are various, but most of them become lengthened and pointed at the ends, and often slightly bent, not unlike caraway-seeds (Gulliver).

Structure of the erythrocyte. — Each red corpuscle is formed of two parts, a coloured and a colourless. The former is mainly a solution of *hæmoglobin* in water, but containing also certain salts, those of potassium preponderating. Water constitutes about two-thirds of the corpuscles; if the water is driven off, about 90 per cent. of the dry residue is hæmoglobin. The colourless part of the corpuscle (the so-called *stroma* of Rollett[1]), which is in by far the smaller quantity, consists of a containing membrane, composed of various substances, chief among these being nucleo-proteids such as are found in ordinary cytoplasm. In addition there are always present lecithin and cholesterin, which are also constant constituents of cytoplasm. These are believed by Overton to form the surface-layer of cell-protoplasm through which osmotic effects are produced (see p. 11). In the erythrocyte there is reason to believe that they form a thin film on the surface of the membrane (see next page).

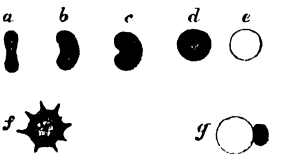


FIG. 559.—*a-e*, successive effects of water upon a red blood-corpuscle; *a*, corpuscle seen edgeways, slightly swollen; *b*, *c*, one of the sides bulged out (cup form); *d*, spherical form; *e*, decolorised stroma; *f*, a thorn-apple-shaped corpuscle (due to exposure); *g*, action of tannin upon a red corpuscle.

If water be added to a preparation of blood under the microscope, the water is imbibed and the concave sides of the corpuscle become bulged out so that it is rendered globular (fig. 559, *a–d*). By the further action of water the hæmoglobin is dissolved out of the corpuscle,[2] and the colourless part or stroma remains as a faint circular outline (*e*). This simple experiment conclusively shows that the corpuscle is composed of a membrane or external envelope with coloured fluid contents, for the above reaction is precisely the same as would occur by osmosis if a vesicle of the shape of the corpuscle covered by a semi-permeable membrane and filled with a solution containing electrolytes were placed in water. On the other hand it is inexplicable on the supposition that the corpuscle is composed of a uniform disc-shaped stroma permeated with coloured substance, which is the view originally advocated by Brucke and Rollett, and adopted until lately by nearly all writers on the subject; for if this were the case water should swell it out uniformly, as happens if a disc of gelatine is placed in water—the whole disc imbibing the water, and becoming increased in size while retaining its original shape.

Further indications of the above structure are provided by the effects of mechanical injuries. If the corpuscles are suddenly pressed they become ruptured and the hæmoglobin escapes, leaving the colourless part of the corpuscle as a mere outline. If blood is frozen the ice-crystals which form injure the envelope, and on thawing the hæmoglobin escapes into the serum. Electric shocks passed through blood, if sufficiently strong, also injure the delicate envelope of the corpuscles. Dilute acids act like water, but decompose the hæmoglobin into colourless protein (globin) and hæmatin, which are both dissolved by the acid. In the case of tannic acid, the products of decomposition are usually precipitated upon the envelope in the form of a small dark red coagulum[3] (fig. 559, *g*). Alkalies, even when very dilute, cause a complete disappearance of the red corpuscles, the membranes as well as the hæmoglobin being dissolved. Ether and chloroform also produce laking

[1] Article 'Blood' in Stricker's Histology, 1870.

[2] This passage of hæmoglobin out of the corpuscle, however produced, is termed 'laking' of the blood, in consequence of the distinctive colour which it produces in a sample of blood (see p. 371).

[3] W. Roberts, Proc. Roy. Soc. xii. 1862-3.

when shaken up with blood, but do not dissolve the envelope; they merely render it permeable to the hæmoglobin. The blood or serum of some animals produces decolorisation of the red corpuscles of others belonging to different genera. This is due to the presence of a special substance in the foreign blood (*hæmolysin*), the actual nature of which has not been determined definitely.[1] Immunity to the effect may be brought about by previous injections of the foreign blood into the living animal, an *antihæmolysin* being thus produced. Solutions of common salt, if stronger than 0·6 to 0·9 per cent. (according to the source of the blood), *i.e.* hypertonic solutions, produce, when added to blood, crenation of the red corpuscles. This is due to osmosis, the corpuscles losing water and thereby becoming shrunken.[2] Weaker solutions (hypotonic) tend to cause laking. The particular strength of solution which causes no alteration in the corpuscles is termed 'isotonic.'

The action of reagents seems to throw some light on the nature of the membrane of the erythrocyte. For it is not easy to understand why ether and chloroform should produce their particular effect unless the membrane were capable of being partly or entirely dissolved by them, and other reactions point to the fact that it is at least in part composed of lipoid substances, such as lecithin and cholesterin, having the physical characters of fats. It is probable that the composition of the envelope is similar to protoplasm, and that it is covered by a superficial layer of lipoid. The membrane of the erythrocytes becomes so altered by drying the corpuscles that they are then capable of being 'laked' by isotonic salt-solution.[3]

The suggestion that the external layer of the erythrocyte is formed of lecithin and cholesterin ('myelin') is due to Norris.[4] Norris showed that fluid droplets enclosed by myelin (lipoids) tend to take a flattened shape, whereas when enclosed by ordinary fats they are invariably globular.

Various other phenomena which have been noticed in connexion with the action of reagents and of varying external conditions upon the red corpuscles point to the same conclusion, viz. that the external pellicle of the erythrocyte is composed of a material having the character of lipoids. A heat of 52° C. causes the coloured corpuscles to extrude globular processes and beaded filaments which may attain a relatively considerable length, and eventually break off from the main substance of the corpuscle, forming coloured particles in the fluid. A further increase of temperature to 60° C. sets free the hæmoglobin, and produces the complete disappearance of the corpuscles. Here we may suppose the pellicle to become softened and eventually completely melted under the action of the increasing temperature, thus permitting of the partial and eventually of the complete flowing out of the contents.

Almost any fluid which has a solvent action upon lipoids also causes an extrusion of the hæmoglobin, sometimes with disappearance of the membrane; this is the case, for example, with solutions of the bile salts. Dilute alcohol in the form of sherry wine was noticed by Addison to produce at first the extrusion of filaments like those caused by heat; this may be supposed also to be due to its attacking the pellicle. The envelopes of the corpuscles, after complete decolorisation with water or dilute acids, stain faintly but characteristically of the presence of lipoid, when treated with osmic acid. Finally, the presence of such a pellicle would, as pointed out by Norris (see p. 368), furnish a sufficient explanation of the otherwise obscure phenomenon of rouleau-formation.

The envelope can be stained with magenta (Roberts) and with methyl violet (Schäfer). Its softness and elasticity is shown by the manner in which the corpuscles are distorted in shape by currents in the fluid in which they are immersed and the readiness with which they recover their

[1] According to Gottlieb and Lefmann hæmolysin is of the nature of a lipoid, which can be extracted by ether from the corpuscles (Med. Klinik, 1907).

[2] On the osmotic effects of various solutions see Hamburger, Arch. für Physiol. 1887 and 1898; Zeitschr. f. Biol. xxvi. 1898; Zeitschr. f. physik. Chemie, lxix. 1909. The action of many solutions upon the erythrocytes depends upon the permeability of the membrane of the latter to the different ions which the solutions contain. Other substances produce hæmolytic effects by entire or partial solution of or other direct action upon the superficial membrane, the permeability of which thus becomes altered.

[3] E. C. Guthrie, Amer. Journ. Physiol. vii. 1903.

[4] *Op. cit.*

form. Moving organisms in the blood (*e.g.* trypanosomes) may often be seen to indent the edges of the erythrocytes, doubling in the membrane, the shape being immediately recovered when the organism retreats.

It has been urged against the existence of a membranous envelope to the corpuscles that such an envelope when mechanically ruptured, as by pressure upon the corpuscles, should show signs of the gap through which the contents have escaped. This is by no means necessary, however, for in the case of a soft protoplasmic envelope coated with a superficial film of lipoid substance such as that the existence of which is here assumed, the edges would immediately tend to come together again after rupture, and would then show no indication of the breach of continuity. A similar explanation may be given of the fact that a corpuscle may sometimes be cut into two, as when a needle is drawn sharply across a preparation of newt's blood upon a glass slide, without the coloured contents escaping from the two separated parts; in this case the pressure of the needle-point has at the same time that it severed the corpuscle brought together the opposite edges of the cut envelope, and thus prevented the escape of the contents. The phenomena of a similar nature which are shown by soap-bubbles will be at once recalled in connexion with these characteristics of the envelope of the erythrocyte.

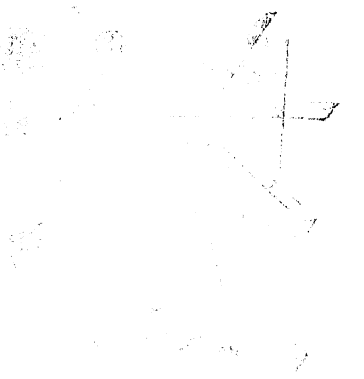


FIG. 560.—BLOOD-CRYSTALS, MAGNIFIED.
1, from human blood; 2, from the guinea-pig; 3, squirrel; 4, hamster.

Blood in which the hæmoglobin has been dissolved out from the corpuscles has lost its opaque appearance, and has acquired a transparent laky tint; the change depends upon the fact that the colouring-matter, when dissolved in the serum and forming a homogeneous layer, interferes less with the transmission of light than when occurring in scattered particles. If the erythrocytes are closely pressed together by very rapid centrifugalisation, the corpuscular mass may appear transparent and 'laky' even although the hæmoglobin is still within the corpuscles.[1]

Hæmoglobin after being separated from the blood-corpuscles is prone to undergo crystallisation. The crystals present various forms in different animals, but almost all (the hexagonal plates of the squirrel being alone excepted) belong to the rhombic system. From human blood and that of most mammals, the crystals are elongated prisms (fig. 560, 1), but they are tetrahedrons in the guinea-pig (2), and short rhombohedrons in the hamster (4). They are most readily obtained for microscopical examination from the blood of the rat, where they appear merely on adding a little water, and afterwards evaporating. The crystalline forms which may be obtained from various animals have been exhaustively studied, with the aid of photographs, by Reichert and Brown.[2]

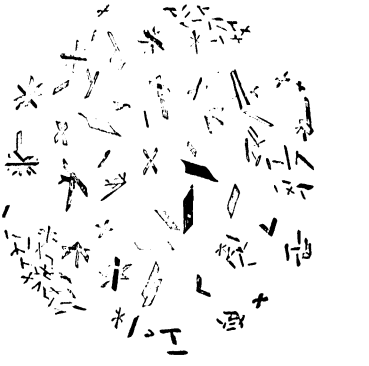


FIG. 561.—HÆMIN CRYSTALS, MAGNIFIED.
(From Preyer.)

Other coloured crystals which may be obtained from blood are the 'hæmin crystals' of Teichmann and the 'hæmatoidin' crystals of Virchow. The former are produced when hæmoglobin is warmed with a little salt and glacial acetic acid. On cooling, the hæmin crystallises out in minute reddish-brown acicular prisms (fig. 561), the demonstration of which affords a positive proof of the presence of blood-colouring matter. These crystals may readily be obtained from dried blood (which of course contains salt) merely by warming it with glacial acetic acid.

Hæmatoidin crystals are found within the body in old extravasations of blood. They are dark brown rhomboidal crystals having the chemical characters of bilirubin.

The amount of hæmoglobin in each corpuscle, which is liable to variation, may be approximately arrived at by determining both the number of corpuscles and the amount of hæmoglobin

[1] See on the laking of blood, G. N. Stewart, Journ. Physiol. xxiv. 1899.
[2] E. T. Reichert and Amos T. Brown, The Crystallography of Hæmoglobins, Philadelphia, 1909.

in a given volume of blood. The amount of hæmoglobin is estimated by diluting a sample of blood with a known quantity of water, and comparing the tint of the solution so obtained with that of a solution of hæmoglobin of known strength. A convenient means of quickly obtaining an idea of the amount of hæmoglobin in a sample of blood is afforded by the Gowers-Haldane hæmoglobinometer, which is arranged on the above principle.

Structure of the erythrocytes of the lower vertebrata. — The corpuscles of oviparous vertebrates differ from the mammalian corpuscles not only in their shape but also in the possession of a nucleus (figs. 556, 557). This is rather more than one-third the length of the corpuscle, but in the natural unaltered condition is visible with difficulty, owing to the fact that it possesses very nearly the same index of refraction as the rest of the corpuscle. The corpuscle is otherwise composed, like that of the mammal, of an envelope enclosing fluid coloured contents.

The effect of most reagents on the erythrocyte of ovipara is similar to that produced on the mammalian corpuscle. Hypertonic solutions of salt cause a manifest wrinkling of the envelope. Water causes both corpuscle and nucleus to swell up, the coloured part being eventually discharged. A dilute solution of acetic acid in an indifferent fluid also causes discharge of the colouring-matter, but the nucleus is shrunk and rendered very distinct (fig. 562, 3); if strong acetic acid be employed, the nucleus often acquires a reddish tint from deposition of hæmatin upon it. Alkalies, on the other hand, even when very dilute, rapidly dissolve both corpuscle and nucleus. Various reagents cause the coloured part of the corpuscle to become partly withdrawn from the envelope, and collected around the nucleus; this is especially the case with a solution of boric acid, which when mixed with newt's blood may eventually cause the coloured matter and nucleus (the so-called 'zooid' of Bruecke)[1] to be altogether extruded from the rest of the corpuscle ('oecoid').

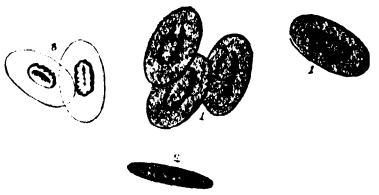


FIG. 562.—RED CORPUSCLES OF THE FROG (From Wagner.) Magnified 500 diameters.

1, shows their broad surface; 2, one seen edgeways; 3, shows the effect of dilute acetic acid; the nucleus has become distinct.

The envelope of the erythrocyte of oviparous vertebrates is much thicker and more distinct than that of mammals. In some forms it appears to be strengthened by a band of fibrils which extends round the circumference of the ellipse (fig. 563, A), just within the rounded angle formed by the junction of the biconvex surfaces of the corpuscle.[2] These fibrils can also be seen in sections across the corpuscle (fig. 563, B).[3]

The nucleus of the erythrocyte of ovipara resembles an ordinary cell-nucleus. It contains a close chromatin network (fig. 564). The erythrocytes of the adult appear to have lost the power of cell-division, but in larval amphibians mitotic division of the erythrocytes is frequent, and forms one of the best objects for the study of the process (see fig. 79, p. 47). According to Bryce, a centrosome only makes its appearance at the commencement of karyokinesis: it may, however, be present beforehand, concealed within the nucleus.

The view that the erythrocyte, both of mammals and oviparous vertebrates, is composed of a solid jelly-like *stroma* permeated with hæmoglobin was until recent years almost universally held, and the colourless portion, after extrusion of the hæmoglobin solution, is still often spoken

[1] Wiener Sitzungsb. 1867.

[2] Meves, Anat. Anz. xxiii. 1903; xxv. 1904; xxvi. 1905; and xxviii. 1906. See also A. Smirnow, *ibid.* xxix. 1906. Meves describes besides the circumferential fibrils a peculiar radial marking at the margin of the erythrocytes of some amphibia. The appearance of circumferential fibres has been also noticed by Dehler in the bird (Arch. f. mikr. Anat. xlvi. 1895), by M. Heidenhain in Proteus, and by Nicolas in reptiles and amphibians.

[3] T. H. Bryce, Trans. Roy. Soc. Edinburgh, 1904.

of under that name. But since the erythrocyte behaves in every way physically like a solution of hæmoglobin associated with electrolytes and enclosed by a semi-permeable membrane and in no way like a membrane-less jelly, the stroma theory must be definitely abandoned. The facts and arguments which have been given against this theory and in favour of the membrane hypothesis were originally stated in the 10th edition of this work (1891) and are discussed in connexion with the mammalian erythrocyte (pp. 369 to 371).[1] G. N. Stewart,[2] who admits a lipoid membrane, thinks the hæmoglobin is in form of a 'gel' in combination with the constituents of the 'stroma.' But if the erythrocytes are watched as they move along the capillaries or even as they are moved about in a microscopic preparation of blood, it is impossible not to conclude that their contents must be entirely fluid. This conclusion is strikingly confirmed in the corpuscles of ovipara by the readiness with which the nucleus becomes displaced even in a perfectly fresh preparation (fig. 584, p. 389).

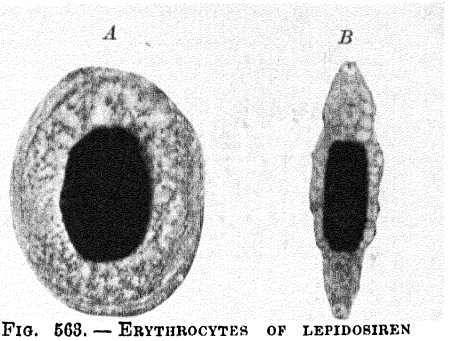


FIG. 563. — ERYTHROCYTES OF LEPIDOSIREN LARVA, FIXED WITH FLEMMING'S SOLUTION AND STAINED WITH IRON-HÆMATOXYLIN. (T. H. Bryce.)

A, as seen on the flat; *B*, in section. In *A* the fibrils around the edge are visible as fine lines parallel to the margin of the corpuscle. In *B* their sections are seen as fine points just within the thinnest part of the edge.

Formation of red blood-corpuscles.[3]—A. In the mesoderm of the early embryo. Blood-corpuscles make their appearance very early in the embryo, simultaneously with the formation of the earliest blood-vessels; they are in fact formed from some of the same cells (*angioblasts*) which produce the endothelium of the blood-vessels. These cells appear in the mesoderm of the yolk-sac, and groups of them are first visible to the naked eye as isolated reddish spots ('blood-islands' of Pander) which are seen in a circular area of the blastoderm (*area vasculosa*) surrounding the embryo, outside the body of which they are therefore first formed; later they make their appearance in the embryo proper. After a time the isolated spots are seen to have grown together to form a network of vessels in the vascular area, and this to have become connected with the simple tubular heart which by this time is developed at the head-end of the embryo. The angioblasts are at first branching cells, not unlike the rest of the mesoderm (mesenchyme) cells, with which, according to Maximow, they are identical (fig. 565). They unite with one another to produce an irregular protoplasmic network (syncytium, fig. 566). Their nuclei divide by karyokinesis, faster at some parts than others, and at such places the protoplasm accumulates around them and forms groups of rounded cells producing enlargements, usually at the nodes of the network. Within these enlargements the protoplasm of the accumulated cells becomes coloured by the formation of hæmoglobin, so that coloured nucleated cells (*primitive erythroblasts*) are thus produced (fig. 566). The rounded cells, whilst still colourless, are *primitive blood-cells* (*hæmoblasts*).

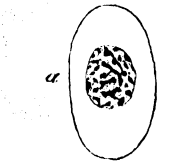


FIG. 564.—COLOURED CORPUSCLE OF SALAMANDER, SHOWING INTRA-NUCLEAR NETWORK. (Flemming.)

According to the account which Maximow[4] gives of the development of the blood in the rabbit-embryo, all the primitive blood-cells do not become primitive erythroblasts, but some remain uncoloured, and these, which are of the nature of lymphocytes (*primitive lymphocytes, lymphoblasts*), by division give rise both to other lymphocytes and primitive erythroblasts.

[1] Albrecht and others have arrived at a similar conclusion. See Weidenreich, Merkel and Bonnet's Ergebnisse der Anatomie, 1904, also Schäfer, Anat. Anz. xxvi. 1905.

[2] Amer. Journ. Physiol. viii. 1902.

[3] The following articles contain the literature of the subject up to their respective dates: A. Noll 'Formation and Regeneration of Red Corpuscles,' Ergebn. d. Physiol. 1903; J. Sieman, 'Die blutbildenden Organe' *ibid.* 1904; A. Goodall, Journ. Path. and Bact. xii. 1908.

[4] Arch. f. mikr. Anat. lxxiii. 1909.

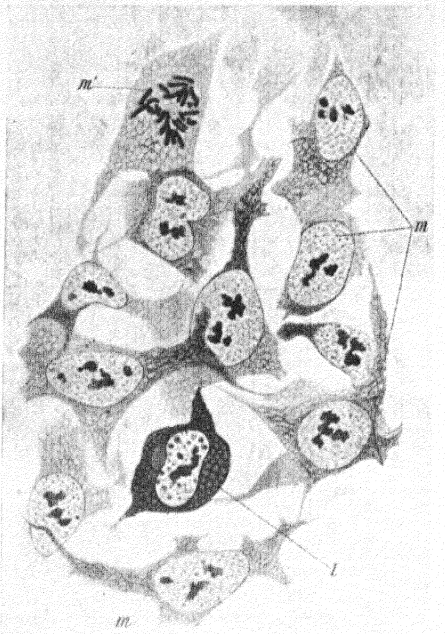


FIG. 565.—MESODERM OF RABBIT-EMBRYO AT THE TIME OF COMMENCING BLOOD-FORMATION. (Maximow.)

m, ordinary mesenchyme cells; *m'*, a cell in karyokinesis; *l*, a primitive blood-corpuscle.

Other lymphoblasts are said by him to be formed later by division of the endothelial cells of the vessels and of mesenchyme-cells outside the blood-vessels: these subsequently pass into the developing vessels. The lymphoblasts or primitive lymphocytes are of the large type, like the macrocytes of the adult (p. 389).

The protoplasmic network (syncytium) presently becomes hollowed out at the enlargements, and the newly formed corpuscles now lie bunched together in cavities occupied by clear fluid unconnected with neighbouring groups (fig. 567): this gives the appearance of 'blood-islands.' The hollowing out of the cell-network then extends along the communicating branches so that a vascular network is formed, and the nuclei of those angioblasts which are not formed into blood-corpuscles become nuclei of the endothelium-cells of which these primitive vessels are wholly composed. When a connexion is established with the developing heart the blood thus formed begins to circulate not only in the vascular area, but also in vessels which are similarly produced within the body of the embryo. In the circulating blood there are at first very few of the primitive blood-cells or hæmoblasts; they

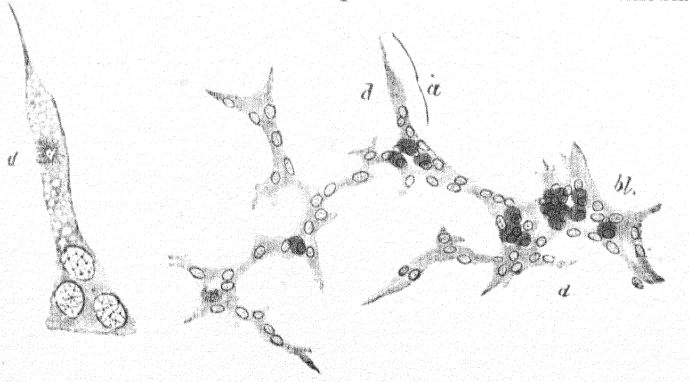


FIG. 566.—PART OF THE NETWORK OF DEVELOPING BLOOD-VESSELS IN THE VASCULAR AREA OF THE GUINEA-PIG. (Schäfer.)

bl, blood-corpuscles becoming free in an enlarged and hollowed-out part of the network. The smaller figure on the left represents *a* of the larger figure, more highly magnified; *d*, a nucleus undergoing division.

are stated to remain in the vessels of the vascular area and there to go on giving rise to other primitive erythroblasts, which pass into the circulation.[1]

The primitive erythroblasts which are thus produced themselves multiply within the vessels by karyokinesis. These are at first the only coloured cells in the blood,

[1] According to Maximow, the primitive blood-cells are phagocytic, and ingest and destroy some of the primitive erythroblasts.

but in the rabbit-embryo of thirteen or fourteen days (Maximow) they are accompanied by primitive disc-shaped erythrocytes which are said to differ in certain particulars of size, amount of hæmoglobin, &c., from the definitive red discs. Whether this is so or not, they are formed from the primitive erythroblasts in the same way as the definitive erythrocytes from their erythroblasts, viz. by loss of the nucleus and moulding of the corpuscle into the discoid shape. Later, erythroblasts of large size (*megaloblasts*, fig. 568, *a*, *a'*) and others which are smaller (*normoblasts*, *b*, *b'*), and are formed from the megaloblasts by division, make their appearance. The megaloblasts are developed from the primitive blood-cells or hæmoblasts. From the normoblasts, by atrophy or extrusion of their nuclei, definitive erythrocytes like those of the adult are produced. Having once appeared, these rapidly increase in number, and soon form the bulk of the red corpuscles. Before the end of intra-uterine life

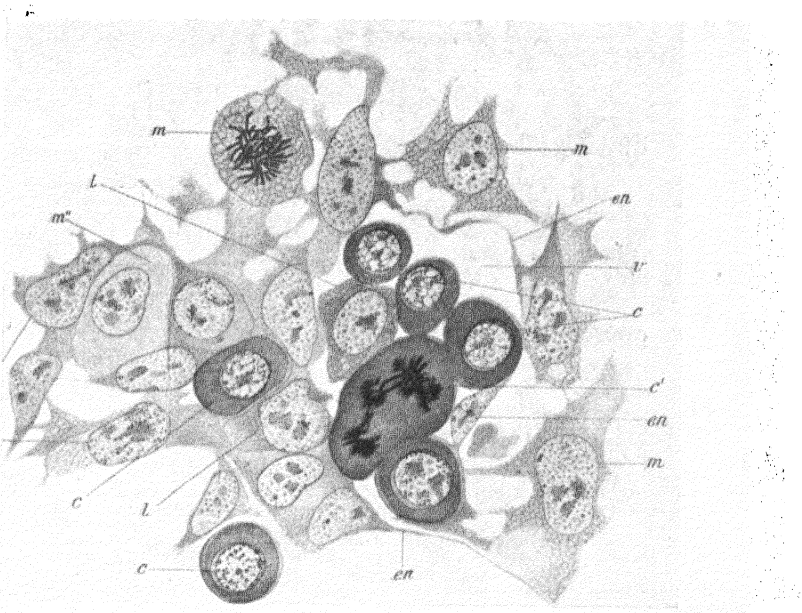


FIG. 567.—DEVELOPMENT OF BLOOD-CORPUSCLES IN VASCULAR AREA OF RABBIT. (Maximow.)

m, *m'*, *m''*, mesenchyme-cells (one shown in mitosis); *en*, endothelial cells; *v*, cavity of developing vessel; *l*, *l*, lymphoblasts; *c*, *c*, primitive erythroblasts; *c'*, a primitive erythroblast in mitosis. The cells described as lymphoblasts by Maximow in this and the succeeding figures are probably hæmoblasts.

erythroblasts have generally vanished from the blood and are restricted to the bone-marrow, as in the adult.

According to Grüneberg,[1] in the fœtus up to the seventh month there are still many erythroblasts (normoblasts) in the circulating blood, and karyokinetic figures are common within them. After the eighth month erythroblasts are rarely seen except in the blood-vessels of bone-marrow. Prior to the seventh month leucocytes are relatively abundant, and still consist mainly of lymphocytes. During the seventh month polymorph and granular leucocytes appear, and the former soon become numerous.

After the blood-vessels with their contained blood-corpuscles are once formed, they become extended by sprouts from the pre-existing capillaries. The sprouts are at first composed throughout of protoplasm, except that they may contain nuclei in process of karyokinesis. They become hollowed out by an extension into them of the lumen of the capillary from which they spring.

[1] Medic. naturwiss. Arch. i. 1908.

The development of blood-corpuscles in isolated patches in the vascular area of the chick was first recognised by Pander.[1] Remak[2] and Kölliker[3] described the first vessels in the vascular area of the chick as originating in the form of a solid cord of mesodermic cells, arranged so as to form a network; the peripheral cells of the vascular cords becoming flattened and forming the epithelium of the vessels, whilst the centrally placed cells become directly converted into blood-corpuscles, acquiring colour first of all at certain points—the blood-islands of Pander—and fluid accumulates between them to form the liquor sanguinis. W. His[4] stated that the blood-vessels within the body of the embryo originate as ingrowths from these vessels of the vascular area, which are themselves produced not from the ordinary cells of the mesoderm, but from special cells (parablast-cells of His) near the periphery of the blastoderm, which give origin not only to blood and blood-vessels, but to the connective tissues generally. Stricker[5] described

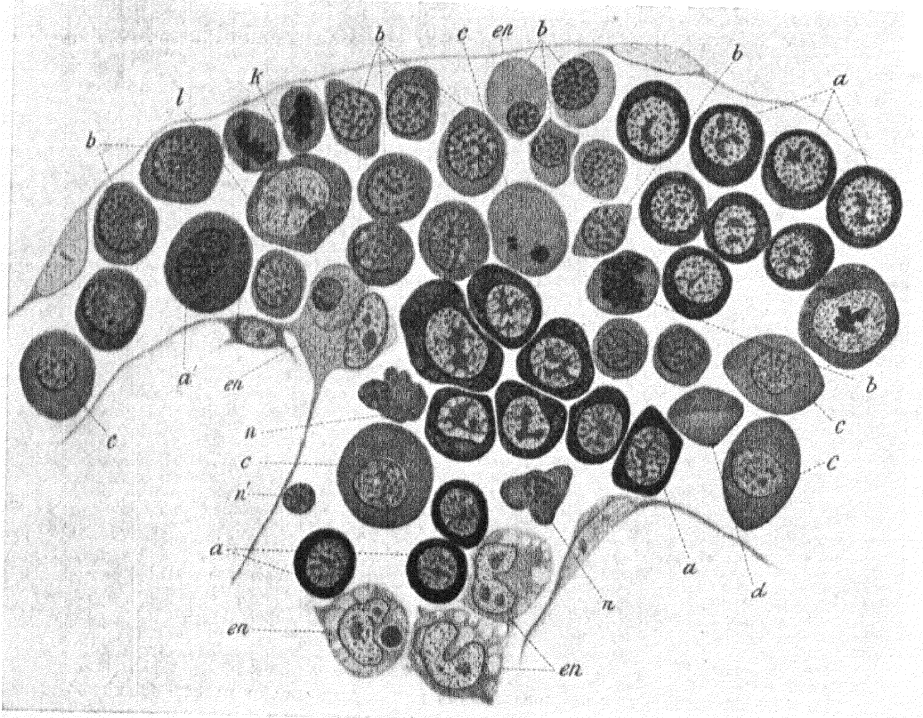


FIG. 568.—PART OF A BLOOD-VESSEL FROM THE YOLK-SAC OF THE RABBIT-EMBRYO, SHOWING THE CELLS WHICH ARE CONCERNED WITH THE FORMATION OF ERYTHROCYTES. (Maximow.)

a, megaloblasts; *a'*, one in mitosis; *b*, normoblasts, some becoming transformed into erythroblasts; *b'*, one in mitosis; *c*, erythroblasts: the nuclei of these are less chromatic and in one or two have almost disappeared; *d*, an erythrocyte fully formed but not discoid; *en*, endothelial cells; *l*, lymphoblasts; *k*, a divided erythroblast; *n*, erythroblasts somewhat shrunken and with atrophying nucleus; *n'*, a nucleus which has been extruded.

the formation of blood-vessels by the hollowing out of connective-tissue cells, and Afanasieff[6] and Klein[7] stated that the blood-islands of Pander are hollowed-out cells, in the interior of which blood-corpuscles make their appearance, and that the containing cells become the first blood-vessels. Klein's account was followed, and in some particulars modified, by F. M. Balfour.[8] A similar account of the formation of vessels and blood-corpuscles from a syncytium of mesenchyme-cells in the vascular area of mammals, derived from observations upon the embryo of the guinea-pig, was given in former editions of this work.

According to Maximow in the rabbit[9] and Dantschakoff in the chick,[10] the blood-islands

[1] Entwickl. d. Hühnchens im Ei, 1817.
[2] Entwickl. d. Wirbelth. 1851.
[3] Gewebelehre, Transl. by Busk and Huxley, 1853.
[4] Untersuchungen, &c., 1868.
[5] Wiener Sitzungsb. 1865–6.
[6] *Ibid.* 1866.
[7] *Ibid.* 1871; and Quart. Journ. Micr. Sci. 1872.
[8] *Ibid.* xiii. 1873.
[9] *Op. cit.*
[10] Anat. Hefte, xxxviii. 1909.

are formed originally of groups of mesenchyme-cells which are not at any time fused together into a syncytium. The central cells of the groups become primitive blood-cells; these multiply and give rise to erythroblasts (and to lymphoblasts, according to Maximow); the peripheral cells differentiate into endothelium. Some of the groups of erythroblasts which appear as blood-islands may not at first be enclosed by endothelium, but are said by Maximow to lie free in the mesoderm (fig. 570).

Primitive erythroblasts of megaloblastic type were noticed by Goodall[1] in the sheep-embryo, and found by him everywhere in the embryonic tissues, where they freely proliferate. He derives them as well as the primitive lymphocytes (which, as he believes, ultimately give origin to all varieties of leucocytes) from mesenchyme-cells. The primitive erythroblasts have in the rabbit, according to Maximow,[2] no genetic relation with the definitive erythroblasts and erythrocytes, which are produced in the following manner (fig. 568):

The definitive erythroblasts are developed from primitive lymphocytes or lymphoblasts which enlarge to form amœboid basophil lymphocytes; these divide two or three times. The resulting corpuscles when seen within the vessels of the vascular area are usually in groups of sister-cells (*a*), all very much alike, of spherical form, about 8–9 μ in diameter, without pseudopodia and with relatively large nuclei and little protoplasm, which is not now markedly basophil. The protoplasm becomes increased in amount and coloured by hæmoglobin, but not intensely—it is polychromatic; the nucleus has more chromatin than that of the primitive erythroblasts. In this condition the cells again multiply by mitosis. They resemble, in the appearance of their nuclei, in the polychromatism of their protoplasm, and in their relatively small amount of hæmoglobin, those cells of the bone-marrow which have been termed *megaloblasts*, although they are not necessarily of large size. By division they give rise to *normoblasts* (*b*)—cells which are somewhat less in size (7·5 μ), contain much more hæmoglobin and smaller, highly chromatic reticular nuclei, without nucleoli; these cells also exhibit typical mitoses (*k*). The cells produced by their division, of which the nuclei become much smaller and the protoplasm almost wholly converted into a solution of hæmoglobin, are the *primitive erythroblasts* (*c*). To produce the erythrocytes the erythroblasts lose their nuclei, which become atrophied and eventually extruded (fig. 569, *a*), whilst the coloured cytoplasm remains and becomes moulded to form the biconcave blood-disc. According to some authors[3] the nuclei are not extruded, but atrophy within the cell. The first embryonic blood-discs are rather larger than those of the adult and less regularly biconcave (fig. 568, *d*).

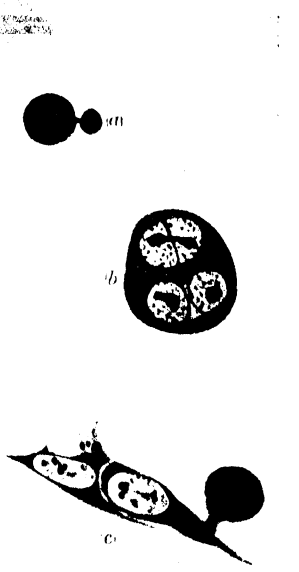


FIG. 569. — DEVELOPMENT OF BLOOD-CORPUSCLES IN RABBIT. (Maximow.)

a, an erythroblast, with the shrunken nucleus becoming extruded; *b*, an enlarged erythroblast, the nucleus of which is undergoing division into four; *c*, endothelial cells showing excrescences of protoplasm coloured by hæmoglobin.

The vessels within the embryo are formed independently of those of the yolk-sac, and are not merely, as was at one time supposed, an ingrowth from the vascular area. Within the embryo primitive hæmoblasts also develop, according to Maximow, from mesenchyme-cells, both inside and outside developing blood-vessels. From them are developed, as in the vascular area, lymphoblasts and erythroblasts, and from the latter erythrocytes.

In the guinea-pig the distinction which in the rabbit is found between primitive and definitive erythroblasts does not seem to obtain,[4] neither was it found by Dantschakoff in the chick.[5]

Some of the lymphocytes are stated by Maximow to become altered in structure and converted into polymorphs and myelocytes, but this is contested by other authorities, who hold that the granular blood-cells are developed from special mesenchyme-elements (myeloblasts), which later become restricted chiefly to bone-marrow.[6] Regarding the early appearance of leucocytes,

[1] Journ. of Path. and Bact. xii. 1908. [2] *Op. cit.*
[3] Nägeli, Verhandl. d. Kongr. f. inn. Med. 1906; Scott, Journ. Path. and Bact. 1906; Schridde, Ziegler's Beitr. xli. [4] Maximow, *op. cit.* [5] Anat. Hefte, xxxvii. 1908–9.
[6] Cf. Engel, Arch. f. mikr. Anat. liii. and liv. 1899; Gulland, Folia hæmatologia, iii. 1906; Nägeli, Verhandl. d. Kongr. f. inn. Med. 1906; Pappenheim, Folia hæmat. Bde. iii. iv. v. 1906–8; Schridde, Ziegler's Beitr. xli. 1907. See also p. 391.

differences seem to exist in different animals. The account above given mainly follows the observations of Maximow upon the development of blood-corpuscles in the rabbit-embryo. But Jolly and Acuna [1] found no leucocytes in the blood of guinea-pig embryos of less than sixteen days, and it is certain that erythroblasts make their appearance in the vascular area of these animals very early. In fact, the view has been held by most authorities that the white corpuscles of the blood are of later formation in the embryo than the (nucleated) red corpuscles, and that they are produced outside the vessels, into which they eventually penetrate by virtue of their amœboid activity.[2] Engel [3] found in the human embryo at first only erythroblasts in the vessels, lymphocytes appearing subsequently; and, about the third month, polymorphous leucocytes. Many of the erythroblasts have disappeared from the blood by the third month,[4] having given place to erythrocytes which are larger than those of the adult. Bryce describes in Lepidosiren [5] both leucocytes and erythroblasts as developing from primitive blood-cells, destitute of coloured protoplasm; and a somewhat similar account is given by Dantschakoff [6] for the chick. Similarly Dantschakoff [7] finds that in the reptile the primitive blood-cell in the vascular area is a hæmoblast, resembling a large lymphocyte, which gives origin to all blood-cells. But within the blood-islands only erythroblasts (and erythrocytes) are formed from this cell, the leucocytes being

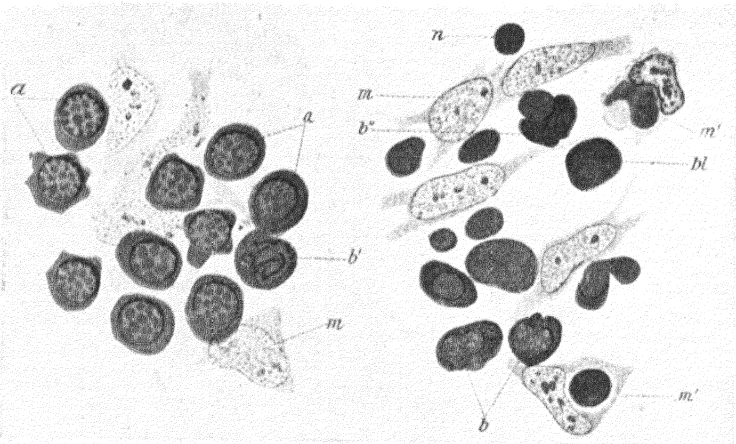


FIG. 570.—GROUPS OF PRIMITIVE ERYTHROBLASTS IN MESODERM OF EMBRYO-RABBIT. (Maximow.)

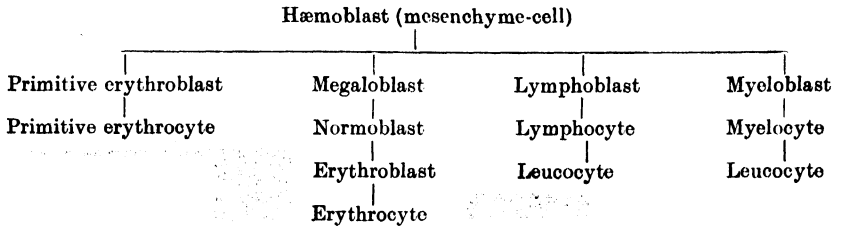
a, normoblasts; *b*, *b'*, erythroblasts; *b''*, extrusion of nucleus from an erythroblast; *m*, mesenchyme-cells; *m'*, mesenchyme-cells containing hæmoglobin; *n*, an extruded nucleus; *bl*, an erythrocyte.

produced outside the vessels and finding their way into them only later. This is like the account the same author gives of blood-formation in the chick, and is said by Maximow to be true also for Amphibia, although in Selachia he finds some of the cells in the blood-islands developing into leucocytes.

Schridde [8] describes the erythroblasts as appearing in the first instance in the form of megaloblasts (large cells containing relatively little hæmoglobin and a basophil protoplasm) from which by division other erythroblasts (normoblasts) become formed; he states very positively that in the process of conversion into erythrocytes the nucleus is not extruded but absorbed. Schridde denies that the primitive blood-cells are of the nature of lymphocytes, but regards them as myelocytes, and asserts that they give origin to all other kinds of leucocytes *except* lymphocytes, which according to him are formed later, after the development of the lymph-vessels, and by a process of budding from the endothelium of these vessels.[9]

[1] Arch. d'anat. microsc. vii. 1905. Also Jolly, *ibid.* ix. 1907.
[2] Cf. Kölliker, Handbuch der Gewebelehre, 1889; Van der Stricht, Arch. de biol. xi. and xii. 1891, 1892; C. r. soc. biol. 1895; Bull. de l'acad. roy. de Belgique, 1899. See also former editions of this text-book, where the earlier literature is referred to.
[3] Arch. f. mikr. Anat. liii. 1899.
[4] See, however, the statement of Grüneberg (p. 375).
[5] Trans. Roy. Soc. Edin. 1904.
[6] *Op. cit.*
[7] Verhandl. d. anat. Gesellsch., Anat. Anz. 1910.
[8] Centralbl. f. Path. xix. 1908.
[9] Cf. W. Türck, *ibid.*, and J. E. Jordan, Anat. Anz. xxxvii. 1910.

The genetic relationship which obtains between the blood-elements is tentatively shown in the following scheme:



B. Formation in the liver. When the liver begins to develop it becomes an important source of production of blood-corpuscles. These are formed (fig. 571)

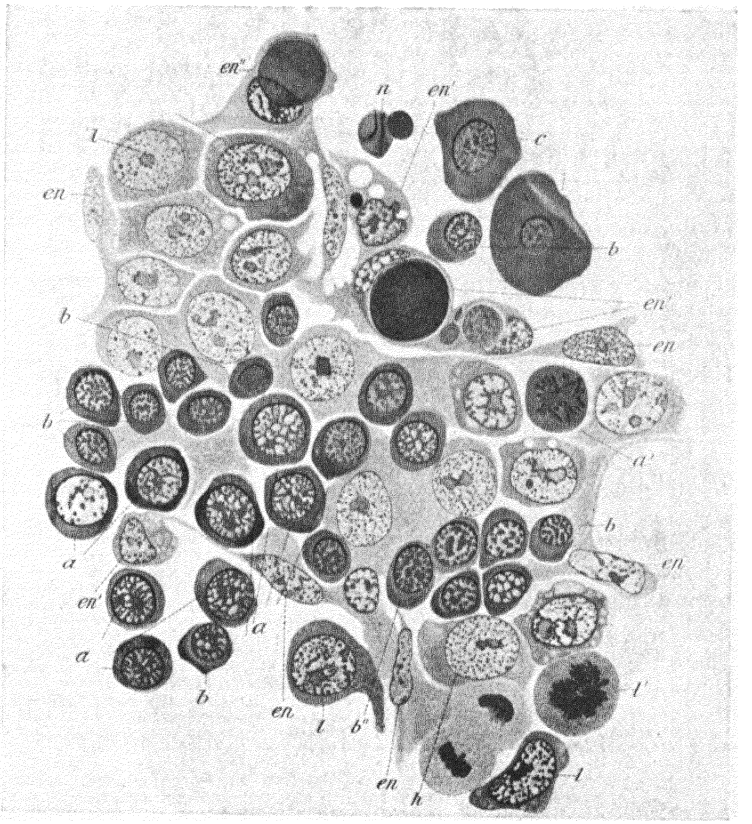


FIG. 571.—FORMATION OF ERYTHROBLASTS IN LIVER OF EMBRYO-RABBIT. (Maximow.)

en, *en'*, *en''*, endothelial cells of vessels (one of these, *en''*, contains a large hæmoglobin-coloured globule); *a*, megaloblasts; *a'*, megaloblast in mitosis; *b*, normoblasts; *c*, erythroblasts; *l*, lymphoblasts; *l'*, lymphoblast in mitosis; *h*, hepatic cell; *n*, a nucleus becoming extruded from a small erythroblast.

by multiplication of the hæmoblasts and erythroblasts which are circulating within its sinus-like vessels,[1] partly, perhaps, from primitive blood-cells which are derived from its mesenchyme and which wander into these sinuses and there undergo development into erythroblasts and leucocytes.[2] Some are described as

[1] Kostanecki, Anat. Hefte, i. 1891; Saxer, *ibid.* vi. 1896; Maximow, *op. cit.*; Jordan, *op. cit.*

[2] Maximow (*op. cit.*) states that such changes occur outside the vessels in the liver tissue. A similar statement is made by Mollier, Arch. f. mikr. Anat. lxxiv. 1909

budding off from the endothelium of the blood-channels. The development of blood-corpuscles in the liver ceases about fourteen days after birth.[1]

In the liver and other organs in which blood-corpuscles are being developed there are constantly found large nucleated giant-cells (megarokaryocytes) similar to those which are well known in bone-marrow;[2] their function is unknown. According to Kuborn[3] these giant-cells which are found in the embryonic liver play an important part in the formation of blood-corpuscles. Another common phenomenon is the appearance of masses of hæmoglobin within the protoplasm of the endothelium of embryonic blood-vessels and of certain mesenchyme-cells. This is generally explained by supposing that the hæmoglobin has been derived from erythroblasts or erythrocytes which have been taken into the cells in question by phagocytosis. But it is by no means certain that it has not become formed within the cells where it is found. One would expect hæmoglobin masses which have been phagocytically ingested and are in process of disintegration to exhibit signs of transformation into hæmatoidin, as is always the case when blood-corpuscles are ingested by phagocytic leucocytes (spleen, old extravasations), but such changes are not noticed in the embryo (see also on this subject p. 382). Moreover, it is difficult to see any reason for the occurrence of such phagocytosis in developing tissues, in which formation and not destruction of hæmoglobin is actively proceeding. On the other hand there is no improbability in supposing that in these situations other cells than those which are bodily transformed, with extrusion or atrophy of their nuclei, into erythrocytes, may share in the process of hæmoglobin formation, and the hæmoglobin-infiltrated cytoplasm may become budded off from the cell in which it has been produced. Such budding off of coloured cytoplasm from an endothelium-cell of a blood-vessel is depicted by Maximow in fig. 569, *c*, and fig. 571, *en''*.

C. Formation in the spleen. The embryonic spleen shows all the appearances of a hæmoblastic organ, although, according to Goodall,[4] at a later stage than the embryonic liver and marrow. Giant-cells are numerous in it, and lymphoblasts and erythroblasts—both frequently exhibiting mitoses—occur abundantly. As in the case of the liver, this hæmapoietic function—at least as regards the coloured blood-corpuscles—becomes lost after birth; but it has been shown that in some animals, after a severe hæmorrhage, the spleen may in part resume its property of acting as a nidus for the development of erythrocytes. On the other hand, the formation of lymphocytes by proliferation goes on throughout life in the Malpighian corpuscles (lymphoid tissue) of the organ, although as regards the erythrocytes the spleen-cells seem rather to have assumed a destructive *rôle*, as is evidenced by the inclusion within them of red corpuscles in every stage of disintegration.

D. Formation in connective tissue. In later embryonic life, after the disappearance of erythroblasts from the blood, the formation of erythrocytes may continue in the connective tissue, in the interior of cells which are in process of development into blood-vessels. But at this stage the erythrocytes are produced at once in a non-nucleated condition: they are formed within the protoplasm of the vaso-formative cell, which becomes coloured in places and differentiated into erythrocytes. The details of the process are as follows:

A part of the protoplasm of the cell becomes infiltrated with hæmoglobin (fig. 572, *h*), and after a time the coloured substance becomes condensed in the form of globules (*h'*) within the cells, varying in size from a minute speck to a spheroid of the diameter of a blood-corpuscle, or even larger; but gradually the size becomes more uniform (fig. 572, *h''*). Some parts of the embryonic connective tissue, especially where a vascular tissue, such as the fat, is about to be developed, are studded with cells like these, occupied by a number of coloured spheroids. After a time the cells become elongated and pointed at their ends, and processes grow out to join prolongations of neighbouring blood-vessels or of other similar cells. At the same time vacuoles form within the cytoplasm (fig. 572, *h'*), and becoming enlarged coalesce to form a cavity filled with fluid, in which the reddish globules, which are

[1] Kostanecki, Anat. Hefte, i. 1891.
[2] Saxer, Anat. Hefte, vi. 1896.
[3] Anat. Anz. v. 1890.
[4] *Op. cit.*

now becoming disc-shaped, float (fig. 572, *a*, *b*). Finally the cavity extends through the cell-processes into those of neighbouring cells, and a vascular network (fig. 572, *d*) is produced; this becomes eventually united with pre-existing blood-vessels, so that the blood-corpuscles which have been formed within the cells in the manner described, get into the general circulation.

This 'intracellular' mode of development of red blood-corpuscles ceases in most

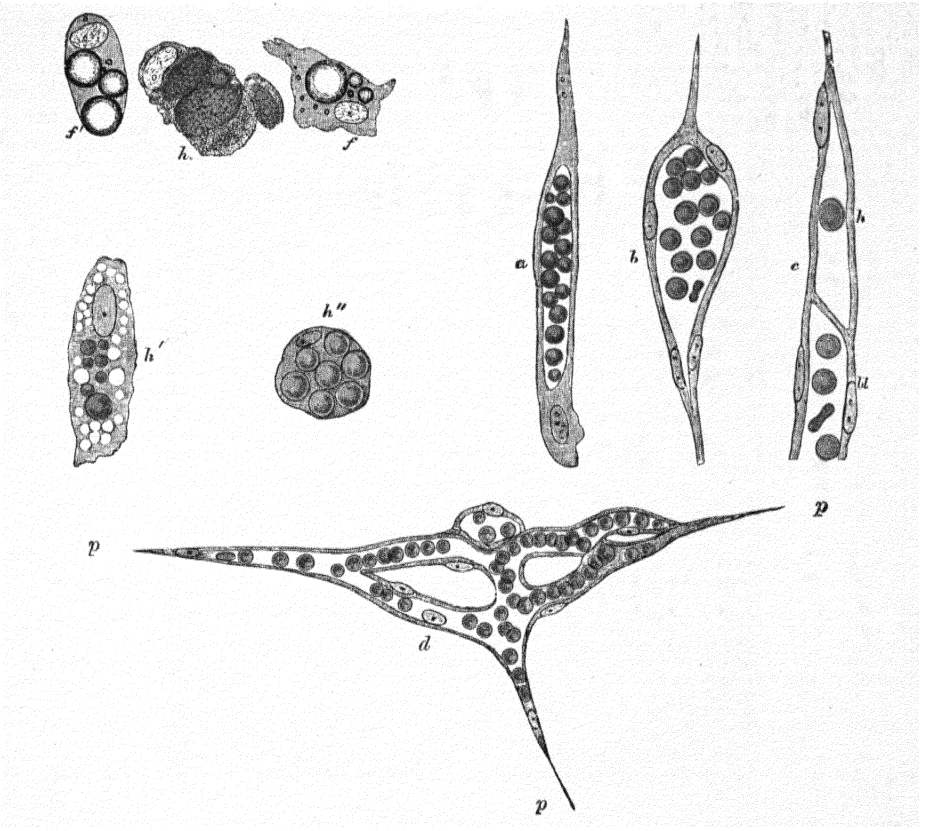


FIG. 572.—DEVELOPMENT OF VASO-FORMATIVE CONNECTIVE-TISSUE CELLS INTO BLOOD-VESSELS. (Schäfer.)

h, a cell containing hæmoglobin in a diffused form in the protoplasm; *h'*, one containing coloured globules of varying size, and vacuoles; *h''*, a cell filled with coloured globules of nearly uniform size; *f*, *f*, developing fat-cells; *a*, an elongated cell with a cavity in its protoplasm occupied by fluid and by blood-corpuscles which are still globular; *b*, a hollow cell, the nucleus of which has multiplied. The new nuclei are arranged around the wall of the cavity, the corpuscles in which have now become discoid; *c*, shows the mode of union of a 'hæmapoietic' cell, which in this instance contains only one corpuscle, with the prolongation (*bl*) of a previously existing vessel; *d*, isolated capillary network formed by the junction of several vaso-formative cells; *p*, *p*, protoplasmic extensions growing out from the network (*b*, from a fœtal sheep; the remainder from the new-born rat).

animals before birth, although in those which are born very immature it may be continued for a short time after birth. Subsequently, although new vessels are formed in the same way, blood-corpuscles are not produced within them.

The production of red blood-discs in the interior of cells of the connective tissue was first noticed in the subcutaneous connective tissue of the new-born rat, and subsequently in the embryos of a number of different animals.[1] Similar observations were made independently by Ranvier [2]—who termed the connective-tissue cells concerned in the process 'vaso-formative

[1] Schäfer, Proc. Roy. Soc. 1874.

[2] Arch. de Phys. 1874.

cells '—as well as by Lebouc[q] [1] and others.[2] It has been supposed by some recent writers on the subject, who have otherwise confirmed the observation,[3] that the intracellular formation of erythrocytes as above described is really an instance of the reverse process—viz. an atrophy of already formed blood-vessels and a breaking down of the contained blood-corpuscles by phagocytosis—and it is obvious that the series of appearances described can be read both ways. But there are difficulties in the adoption of this view. For, in the first place, the appearances are always seen where development is progressive and where blood-vessels need to be formed—as in growing adipose tissue—rather than where they are likely to be in process of removal. And, secondly, there is never to be detected within these vaso-formative cells any sign of the formation of crystals or of pigmentary matter, such as is always seen in cases of intracellular disintegration of erythrocytes—*e.g.* in the adult spleen.

E. Formation in bone-marrow. The marrow of the bones differs considerably in structure in different situations. Within the shaft of the long bones in

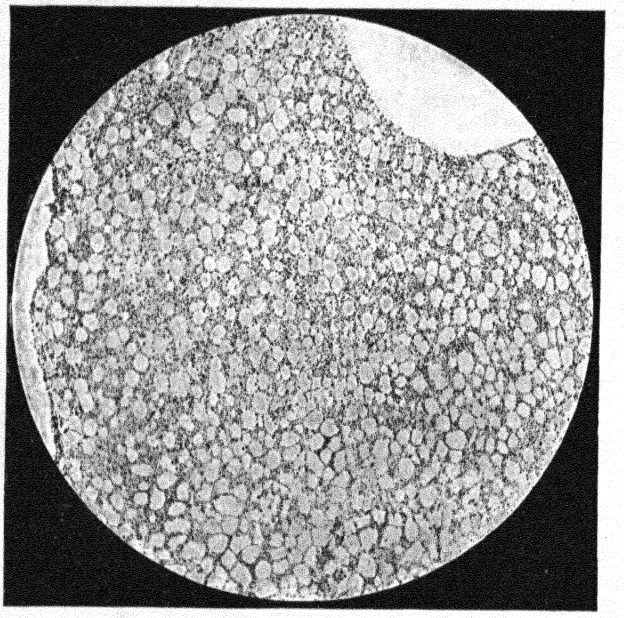
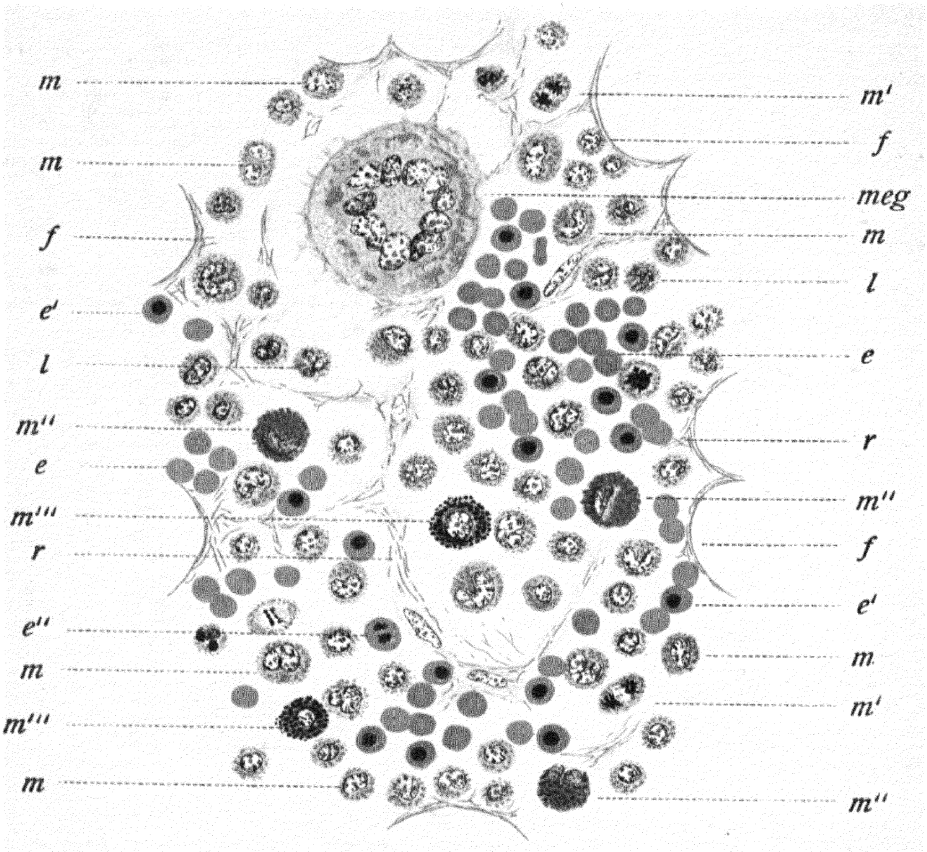


FIG. 573.—SECTION OF RED MARROW. (Carnegie Dickson.)
Magnified 45 diameters.

man it is largely composed of adipose tissue, but the fat-cells are supported by reticular tissue, and between them elements occur similar to those immediately to be mentioned in the red marrow. In many short bones, and cancellated ends of long bones, but especially in the cranial diploë, the bodies of the vertebræ, the sternum, and the ribs, the marrow is red or reddish in colour, and contains fewer fat-cells (figs. 573, 574, and accompanying Plate). While, however, the fat-cells are scanty in the red-coloured marrow, it contains numerous other cells—the *marrow-leucocytes* or *myelocytes* (*m*, *m'*, *m''* of accompanying Plate, and 23 to 26 on Plate opposite p. 387). These in general appearance resemble blood-leucocytes. Like blood-leucocytes they show variations in the granules contained in their cytoplasm. Some have only fine granules which are either neutrophil or oxyphil: these resemble the lymphocytes of the blood, and like them vary greatly

[1] Bull. d. l. soc. méd. de Gand, 1875.
[2] Wissosky, Arch. f. mikr. Anat. xiii. 1877; Kuborn (in liver), Anat. Anz. v. 1890; Nicolaides, Arch. f. Physiol. 1891.
[3] Spuler, Anat. Hefte, vii. 1896; Saxer, *ibid.* vi. 1896; H. Fuchs, *ibid.* xxii. 1903 (the literature is given in this article); F. Pardi, Arch. di Anat. e Embriol. viii. 1909.



Section of red marrow from femur of young rabbit. Haematoxylin-eosin. Magnified 400 diameters. (Schäfer.)

m, ordinary (amphophil) myelocytes; ***m'***, myelocytes in mitotic division; ***m''***, myelocytes with eosinophil granules; ***m'''***, myelocytes with basophil granules; ***meg***, a giant-cell or megakaryocyte; ***e***, erythrocytes; ***e'***, erythroblasts; ***e''***, erythroblast in mitosis; ***l***, polymorph leucocytes; ***r***, reticular tissue, at ***f, f***, outlining parts of fat-cells.

in size. Others have coarse oxyphil granules and others coarse basiphil granules like those in the mast-cells of connective tissue. There are also myelocytes which are highly amœboid and phagocytic: these have a lobulated nucleus and resemble the polymorph leucocytes of the blood. All the varieties of myelocyte are held by some authors to be derived from the blood-lymphocytes; others look upon them as independent, and as furnishing the source of the granular and polymorph blood-leucocytes.

Myelocytes have occasionally been noticed to contain one or more red corpuscles in their interior (Osler): these are phagocytic cells, and the erythroblasts within them are probably in process of transformation into pigment-granules. Cells containing reddish pigment-granules are, indeed, not uncommon.

There further occur in the marrow of growing bones numerous large multinucleated cells (*osteoclasts* of Kölliker) (figs. 259, 260), which appear to be more

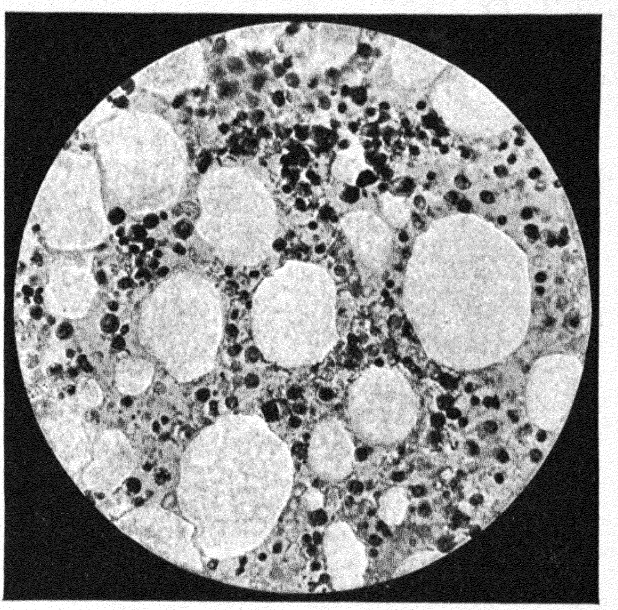


FIG. 574.—SECTION OF RED MARROW. (Carnegie Dickson.)
Magnified 300 diameters. The clear spaces are due to the presence of fat-cells.

especially concerned with the process of absorption of bone, under which head they have been already alluded to (p. 169). But in the adult marrow other giant-cells (myeloplaxes of Robin) are met with (see Plate), which vary much in size, but are always larger than the proper marrow-cells. Their nucleus is not usually multiple, but it is enlarged—hence the term *megakaryocyte* which has been applied to these cells—and presents indications of subdivision (fig. 575); it may even be so constricted as to exhibit an irregularly moniliform appearance. Frequently it is horseshoe-shaped, and not infrequently annular. The protoplasm of the megakaryocyte is usually oxyphil, and shows a differentiation into three zones (M. Heidenhain) (fig. 576). According to Schridde the megakaryocytes are amœboid, but not phagocytic, and the granules they contain are not identical with those of the leucocytic myelocytes. He believes that there is no genetic connexion between the giant-cells and leucocytes of marrow.

As M. Heidenhain has shown, the megakaryocytes have a number of centrioles, as well as a large number of nucleoli. Their centrioles may be accumulated

near together or distributed over a considerable area of the protoplasm. When the nucleus is annular they lie in the middle of the ring, when horseshoe-shaped, in the centre of the curve. These cells are generally stated to divide amitotically [1] and thus to break up into polymorph myelocytes, from which it is thought they have been originally derived.[2]

Giant-cells of this character are often met with in places where blood-corpuscles are in process of development, although it is not understood what relationship, if any, they bear to the process of hæmagenesis.

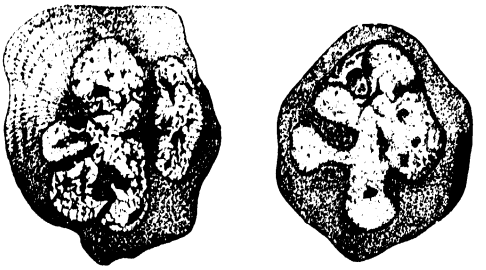


FIG. 575.—CELLS WITH IRREGULAR LOBED NUCLEI FROM BONE-MARROW OF RABBIT. (M. Heidenhain.)

Amongst the myelocytes and megakaryocytes are smaller cells which have a reddish colour, and resemble the primitive nucleated red corpuscles of the embryo (Plate, *e*, *e'* *e''*); these are the *erythroblasts*, which are concerned in the formation of the red blood-discs, and are perhaps themselves originally derived from colourless myelocytes.

The cells of the marrow are everywhere supported by a close network or feltwork of collagenous fibrils (fig. 201, p. 123), which constitute a sustentacular reticulum for its elements and blood-vessels. The reticulum also comprises some branched connective-tissue cells, which are more numerous in young marrow.[3]

There is reason to believe that apart from loss or destruction of erythrocytes due to accident or disease, and in the female accompanying menstruation, a regular destruction and reproduction of erythrocytes is always proceeding within the body. The evidence of destruction is derived partly from the continuous formation of pigments which are either certainly or probably derived from the hæmoglobin of blood-corpuscles — *e.g.* the bile-pigments and the pigment of the hairs and skin; partly from the histological evidence obtainable in such organs as the spleen and other blood- and lymph-glands, which contain cells enclosing erythrocytes in every stage of disintegration, from complete discs such as are found in the circulating blood to

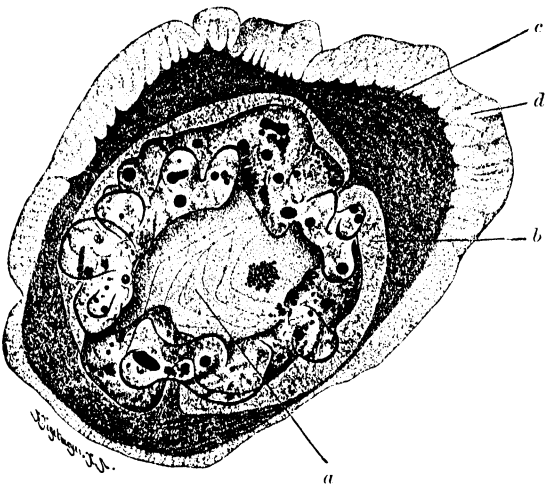


FIG. 576.—GIANT-CELL OF MARROW WITH MULTIPLE CENTRIOLES. (M. Heidenhain.)

a, *b*, *c*, *d*, various zones of the cytoplasm. The nucleus is very large and annular, with irregular lobes and numerous nucleoli.

[1] According to C. E. Walker they may also divide mitotically (Proc. Roy. Soc. B, lxxviii. 1906).

[2] See on the giant-cells of marrow, W. H. Howell, Journ. Morph. iv. 1890; M. Heidenhain, Arch. f. mikr. Anat. xliii. 1894; G. Retzius, Biol. Unters. x. 1902; Schridde, Anat. Hefte, xxxiii. 1907; A. Goodall, *op. cit.* A description of the cells met with in bone-marrow both in normal and pathological conditions will be found in the monograph by Carnegie Dickson, 'Bone-Marrow,' Longmans, London, 1908.

[3] C. M. Jackson, Arch. f. Anat. 1904.

amorphous or crystalline masses of pigment similar to hæmatoidin (see p. 371). Since the number of erythrocytes in the blood is on the whole constant, this regular destruction must be balanced by as regular a production.[1] Although this fact is fully recognised it was for a long time by no means clear what is the source of the newly formed erythrocytes, and conjecture centred itself upon the blood-leucocytes, which it was supposed might become transformed into erythrocytes; nor were observations lacking which seemed to point to the existence of forms intermediate between these and the red corpuscles. When the blood-platelets were discovered it was thought by some histologists that they might be regarded as precursors of erythrocytes. These conjectures have, however, for the most part been abandoned, since it was established, first by Neumann,[2] whose observation was confirmed by Bizzozero,[3] that the marrow of the bones always contains nucleated coloured corpuscles (the erythroblasts above mentioned) which are similar to the nucleated red corpuscles of the embryo, and which either have been derived from those corpuscles by direct descent, or formed from colourless hæmoblasts in the manner in which the erythroblasts are said to be formed in the embryo from hæmoblasts. These erythroblasts of the marrow multiply by mitotic cell-division, and from them are derived, with atrophy or extrusion of the nucleus,[4] discoid erythrocytes which pass into the blood-stream and supply the place of those which have disappeared. The erythroblasts of the marrow, like those of the embryonic mesoderm (p. 375), occur both as megaloblasts and as normoblasts, the latter representing a stage intermediate between the megaloblasts and the erythroblasts. Erythroblasts are produced from normoblasts by mitotic division and are converted with atrophy of their nuclei into discoid erythrocytes.

In this manner (in mammals) the erythrocytes are produced outside the blood-vessels in the tissue of the bone-marrow—especially in the red variety of marrow such as occurs characteristically in the ribs—and pass through the walls of the marrow-capillaries, which are very thin and possibly incomplete. Some erythroblasts (nucleated red cells) are also found within the vessels of the marrow, and they may sometimes be detected in the blood leaving the marrow.

The marrow undergoes a considerable accession of blood-forming activity after extensive hæmorrhage. Under these circumstances many more erythroblasts are seen, and transitional forms between these and erythrocytes are abundant. Occasionally when regeneration is in active progress portions of nuclear matter remain in some of the erythrocytes even in the circulating blood.[5]

It would appear from the observations of Bizzozero and Torre[6] that in birds the capillary walls are complete, and that all the erythroblasts are intravascular, *i.e.* are found within venous capillaries and not in the tissue of the marrow. These venous capillaries are relatively large, and the blood-stream in them must be slow. The fully developed red corpuscles lie in the axis of the vessel, the erythroblasts and hæmoblasts towards the periphery.

Denys,[7] who also subjected the marrow in birds to a careful examination, states that the coloured erythroblasts are derived from colourless corpuscles, *i.e.* hæmoblasts, lying next to the capillary wall, and that while this transformation into red corpuscles is going on within the vessels, the marrow-cells outside the vessels are multiplying and forming other hæmoblasts which pass into the capillaries. This would be very much the same process as goes on in the embryo mammal, where hæmoblasts are said to be formed both within and outside the vessels.

Morphology of the red corpuscles.—It is obvious from the study of the structure of the mammalian red blood-discs that, unlike those of ovipara, they are not morphologically to be regarded as cells. For they lack an important morphological constituent of the cell, viz. the nucleus,

[1] See on this subject W. Hunter, Brit. Med. Journ. 1887; Howell, Journ. Morph. iv. 1890.
[2] Centralbl. f. med. Wissensch. 1868.
[3] *Ibid.*
[4] Or, according to Rindfleisch, by a budding off of hæmoglobin-containing protoplasm (Arch. f. mikr. Anat. xvii. 1880).
[5] R. S. Morris, Arch. of Internal Medicine, 1909. Morris states that in the cat these particles often occur normally in the erythrocytes.
[6] Moleschott's Unters. xii. 1881.
[7] La Cellule, t. iv. 1888.

nor do they exhibit any centrosome or other internal sign of cell-architecture. Chemically they contain in their envelope (stroma) the nucleoproteids and lipoids which are characteristic of protoplasm, and these occur in about the same relative proportion as in protoplasm. But, although originally formed from and within protoplasm, they have lost all amœboid properties—in fact, the protoplasm from which they are produced has become transformed into little but a thin envelope enclosing a solution of hæmoglobin.

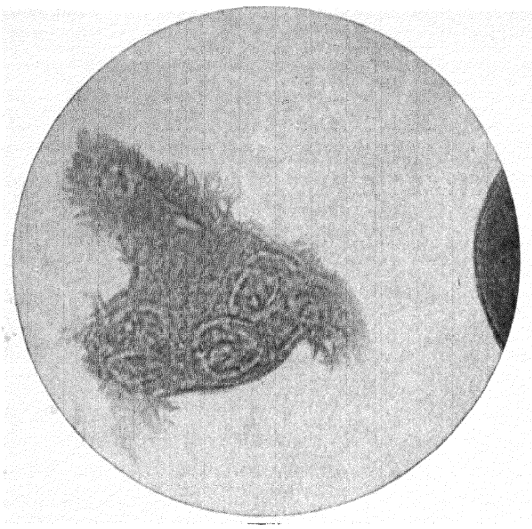


FIG. 577.—UNTOUCHED PHOTOGRAPH OF LIVING LEUCOCYTE OF TRITON, SHOWING RETICULAR STRUCTURE OF THE PROTOPLASM. (Schäfer.) Magnified 1360 diameters.

The photograph was taken in monochromatic light with Zeiss' 2 mm. apochromatic objective and projection eyepiece. The polymorph nucleus also exhibits a reticular structure.

The fact that the discoid erythrocyte may in some cases be formed by a transformation of a portion only of the protoplasm of a vaso-formative mesenchyme-cell, and may become free within such cell, and in other cases may be produced by transformation of the whole cytoplasm with separation of this from the nucleus, would not necessarily, as Minot[1] has supposed to be the case, constitute an essential morphological difference between the two kinds of erythrocyte, since in both cases the corpuscles are formed by modification of cytoplasm, and in both this modified cytoplasm separates itself from the cell-nucleus. In its definitive condition the mammalian erythrocyte cannot in any case be regarded as a complete cell.

The nucleated red corpuscle of oviparous vertebrates, on the other hand, is shown, both by its general structure and mode of development, to be morphologically a cell, although it has few of the functional characteristics of cells. In the adult condition it is incapable of undergoing division and multiplication, although the nucleus retains the structure and chemical composition which is typical of cell-nuclei. The cell-body, again, is wholly transformed into a thin envelope enclosing a solution of hæmoglobin. Some authors have described a reticular structure within these corpuscles, taking the form of fine intercommunicating threads extending from the nucleus to the envelope (see fig. 563), but we must bear in mind the ease with which such an appearance is produced by fixative reagents. These nucleated corpuscles of adult ovipara differ from the first formed erythroblasts of both the oviparous and of the mammalian embryo; for both megalo- and normo-blasts are complete cells, capable of division, and exhibiting amœboid phenomena; in short, they differ from a typical animal cell, such as the white corpuscle, mainly in the presence of hæmoglobin in their protoplasm. The erythroblasts of the marrow are in all respects similar to the embryonic erythroblasts.

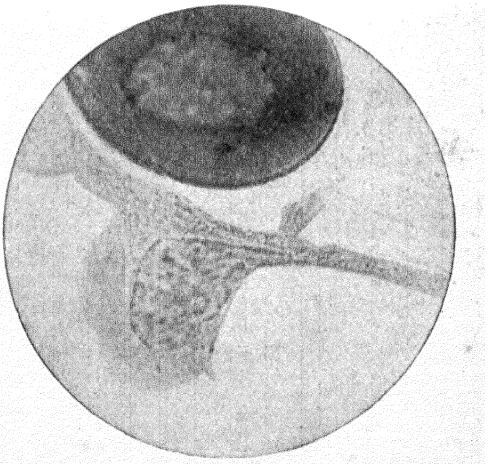
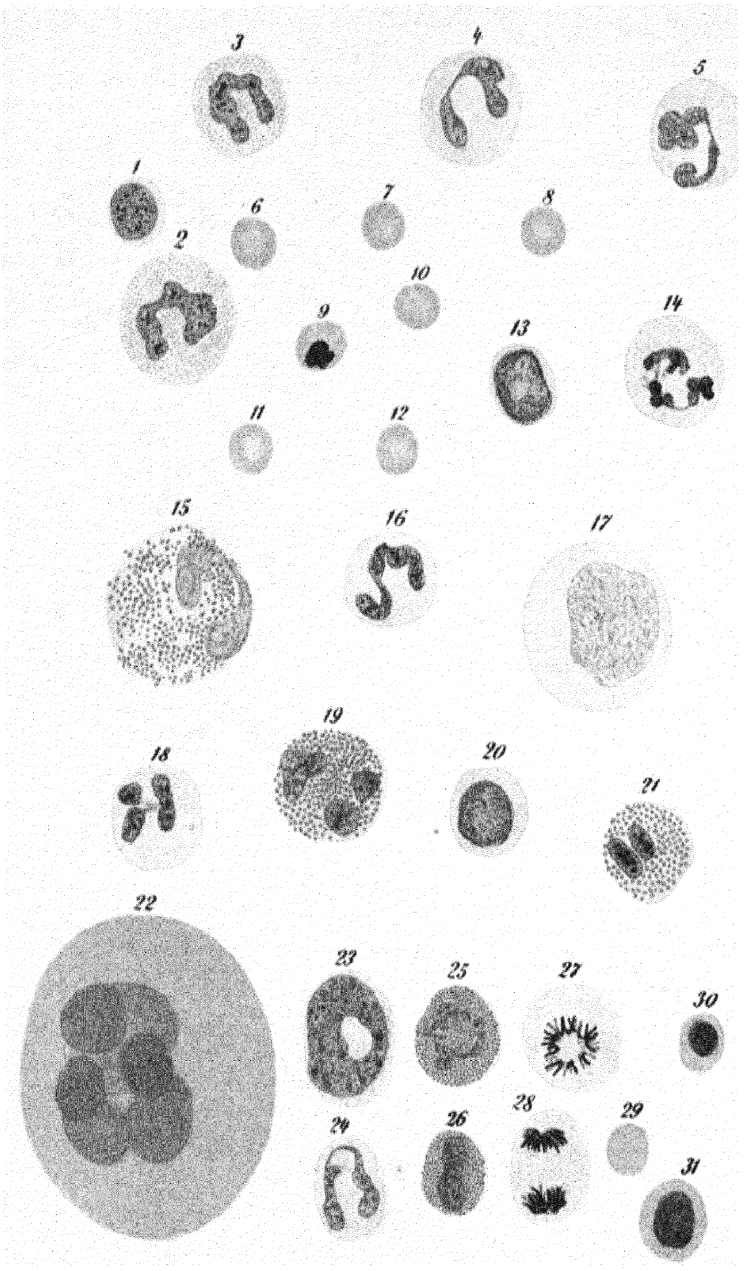


FIG. 578.—LACE-LIKE APPEARANCE OF LIVING PROTOPLASM OF A LEUCOCYTE OF SALAMANDER. (Schäfer.) Magnified 1200 diameters. Untouched photograph. The lace-like protoplasm is partly spread over an erythrocyte.

COLOURLESS CORPUSCLES: LEUCOCYTES.

The *colourless corpuscles* or *leucocytes* of man (and indeed of all animals) are protoplasmic cells. On account of their relatively small

[1] Anat. Anz. v. 1890.



Blood and marrow-cells (Sobotta) 700/1. (From film preparations.) *1—21*, from human blood films; *22—31*, from bone marrow of mouse. *6—12*, erythrocytes (*9* with remains of nucleus); *1*, lymphocyte; *2*, *3*, polymorph leucocytes with neutrophil granules; *4*, *5*, *14*, *16*, *18*, ordinary polymorphs; *15*, *19*, *21*, leucocytes with oxyphil granules; *17*, macrocyte; *13*, *20*, transitions betwen lymphocyte and macrocyte; *22*, giant cell of marrow; *23—26*, marrow-cells, the last two with oxyphil granules; *27*, *28*, marrow-cells in mitosis; *29*, erythrocyte; *30*, *31*, erythroblasts.

number (about 10,000 per cubic mm.), and their colourless protoplasm, they are at first a little difficult of recognition amongst so many erythrocytes (the proportion of leucocytes to erythrocytes averaging about 1 to 500).[1] They are specifically lighter than the erythrocytes, and therefore are usually found in the uppermost layers of a specimen of blood, immediately under and adhering to the cover-glass. They vary greatly in size in human blood, some being smaller and others larger than the erythrocytes: those which are most numerous average about 0·1 millimetre in diameter (10 μ or $\frac{1}{2500}$ inch), measured in the spherical condition.

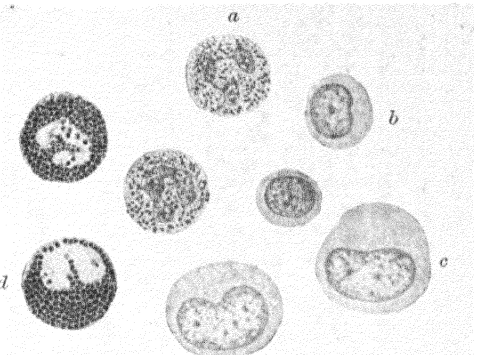


FIG. 579.—VARIOUS KINDS OF COLOURLESS CORPUSCLES, SHOWING THE DIFFERENT CHARACTERS OF THE GRANULES. (Schäfer.) (From a film preparation of normal human blood.)

a, polymorph; *b*, microcyte; *c*, macrocyte; *d*, oxyphil. Two of each kind have been drawn.

The nucleus of the leucocyte is difficult to observe in the fresh condition, but is strongly brought out after death and under the action of basic dyes or dilute acids. (See accompanying Plate and figures.) A centriole and attraction-sphere can be detected in the cytoplasm near the nucleus (fig. 580).

The protoplasm of the leucocyte has a distinct reticular appearance in the living condition (figs. 577, 578).[2] It contains granules which stain some with basic, others with acid, others with neutral, and others with both basic and acid dyes (fig. 579, and Plate); the granules being termed oxy-phil, baso- or basi-phil, neutrophil, or ampho-phil, according to their affinity for different kinds of stains. These terms have been extended to the cells which contain the particular kind of granule, so that oxy-phil (or eosinophil), basi-phil, etc., leucocytes are commonly spoken of.[3] Most leucocytes are highly amœboid,[4] but this property is only slightly marked in the small variety (lymphocytes), which contain very little cytoplasm. To their amœboid property leucocytes owe the faculty they exhibit of taking into their cytoplasm foreign particles which may be present in blood (*phagocytosis*). This faculty is also exhibited by leucocytes which have wandered out from the blood-vessels (the so-called *migratory* or *wander-cells*) and may serve to effect the piecemeal

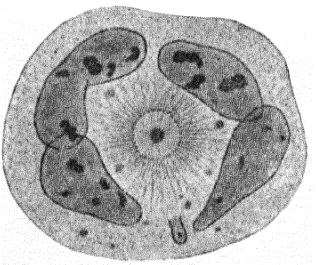


FIG. 580.—WHITE BLOOD-CORPUSCLE OF LEPIDOSIREN, WITH LOBED AND ALMOST ANNULAR NUCLEUS AND WELL-MARKED CENTROSOME.

(T. H. Bryce.)

[1] The relative and absolute number of leucocytes varies greatly with varying conditions of health and disease. Injections of certain substances (peptone, nuclein, etc.) also affect the relative proportions of leucocytes to erythrocytes and also the proportions of the different kinds of leucocyte (see below) to one another. Considerable variations in the number of leucocytes in blood drawn from a peripheral vessel may also occur as the result of taking food, of muscular exercise, and even of change of position of the body. These variations are probably to be explained as due for the most part to increase of activity of the heart or blood-circulation, in consequence of which leucocytes which were more or less stationary in the blood-vessels of the internal organs become dislodged and carried into the general circulation. Such increase in number usually lasts only for a short time. (Hasselbalch and Heyerdahl, Skand. Arch. f. Physiol. xx. 1908; Ellermann and Erlandsen, Arch. f. exper. Path. u. Pharm. lxiv. 1900). Increase of activity of the flow of lymph and chyle will also tend to wash more lymphocytes out of the lymph-glands.

[2] Schäfer, Quat. Journ. Exper. Physiol. iii. 1910.

[3] The staining of some cells has a diffuse appearance, which cannot, strictly speaking, be described as a staining of granules.

[4] The amœboid movements were first observed by Wharton Jones (Phil. Trans. 1846).

absorption of tissues which are undergoing degeneration and disintegration (Metschnikoff).[1]

Leucocytes are classified according to the special characters of their granules and the nature of their cytoplasm and nuclei, thus :[2]

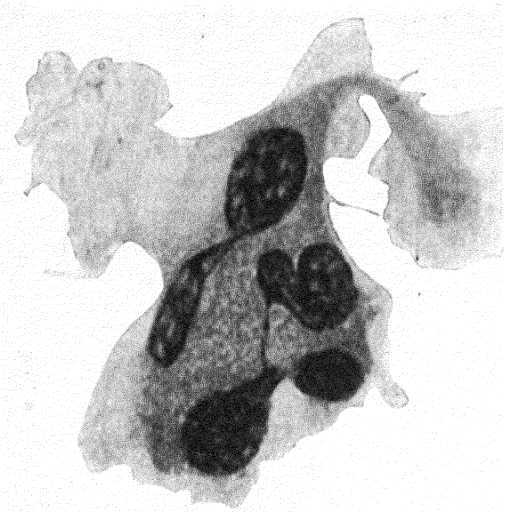


FIG. 581.—POLYMORPH LEUCOCYTE OF TRITON FIXED BY A JET OF STEAM AND STAINED WITH HÆMATOXYLIN. (Schäfer.) Magnified 1500 diameters. Untouched photograph.

The nucleus at first sight appears multiple, but on careful examination its several parts seem to be united by threads of basichromatin. These cannot all be seen in the figure, in which only one plane of the thickness of the corpuscle is shown.

1. **Polymorphocytes (polymorphous leucocytes).**[3]—These (fig. 579, *a*) are characterised by their relatively large amount of clear, highly amœboid protoplasm and the presence of a deeply lobed, or more commonly a multifid nucleus, the several parts of which look at first sight like so many smaller nuclei (fig. 581), although really united by fine threads of chromatin. They measure, when in the spherical condition, about ·01 mm. (10μ). The protoplasm contains very fine neutrophil or oxyphil granules,[4] staining with eosin. According to Phear they constitute 54 per cent. of the whole number of leucocytes. Carstanjen gives the percentage as from 57 to 69 in the adult, less in the child. The number is diminished after a meal. They are stated to be far more numerous immediately after birth than just before birth (in the rabbit).[5] In the dog and cat they are relatively more numerous than in man (70 to 90 per cent., Sherrington ; 75 per cent., Davis and Carlson). Similar cells are found in bone-marrow, and it is considered probable by many authors that the polymorphocytes of the blood are produced there. The polymorphocytes are highly amœboid (fig. 581) and phagocytic, and will continue for months to exhibit amœboid movement if the blood is preserved aseptically (J. Jolly).[6]

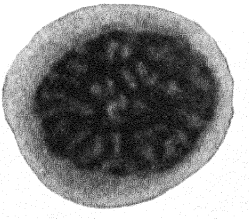


FIG. 582.—MICROCYTE FROM BLOOD OF TRITON, FIXED BY A JET OF STEAM, AND STAINED WITH HÆMATOXYLIN. Magnified 1500 diameters. (Schäfer.) Untouched photograph.

The nucleus exhibits a close and even network of basi-chromatin.

[1] Hamburger finds that phagocytosis is markedly increased by minute amounts of calcium (Trans. Internat. Congress of Physiology, Zentralbl. f. Physiol. xxiv. 1910) or of substances, such as chloroform, which have a solvent action on lipoids (K. Akad. Wetensch. Amsterdam, 1911).

[2] On the classification and numeration of leucocytes see Ehrlich, Arch. f. (Anat. u.) Physiol. 1879, and Zeitschr. f. klin. Med. i. 1880; Gulland, Laboratory Reports of the R. Coll. of Phys. of Edinburgh, 1891, and Fol. hæm. iii. 1906; Sherrington, Proc. Roy. Soc. lv. 1894; Kanthack and Hardy, Journ. Physiol. xvii. 1894; Hardy and Wesbrook, *ibid.* xviii. 1895; J. Jolly, C. r. soc. biol. xlix. 1897; Ehrlich and Lazarus, 'Norm. u. path. Histol. d. Blutes,' 1898; Phear, Med. Chir. Trans. 1899; Carstanjen, Jahrb. f. Kinderheilk. lii. 1900; Goodall and Paton, Journ. Physiol. xxxiii. 1905; Scott, Journ. Path. and Bact. xi. 1906; Goodall, Journ. Path. and Bact. xii. 1908; B. J. Davis and A. J. Carlson, Amer. Journ. Physiol. xxv. 1909.

[3] 'Polymorphonuclear' leucocytes of many authors.

[4] Kanthack and Hardy, *op. cit.*

[5] Tschistowitsch and Piwowarow, Arch. f. mikr. Anat. lvii. 1901.

[6] C. r. soc. biol. lxix. 1911.

2. **Microcytes (micro-lymphocytes).**—These (fig. 579, *b*) are characterised by their relatively small size, many of them being not much more than half the size of the polymorphocytes (·0065 mm.). They have, as already stated, very little protoplasm, and that hyaline and basiphil, staining with methylene-blue. The nucleus is simple and spheroidal or slightly indented. Its chromatin is reticular (fig. 582). The larger specimens of microcytes appear to be transitional to those of the variety next to be described. The microcytes constitute rather more than 20 per cent. (19 to 33, Carstanjen) of the total number of leucocytes in the adult, but are much more numerous in infancy. Their number is increased after a meal (lymphocytosis). They closely resemble the cells which form the bulk of lymphatic glands and other lymphoid tissue, and there is very little doubt they are directly derived from these. They are not actively amœboid or phagocytic.

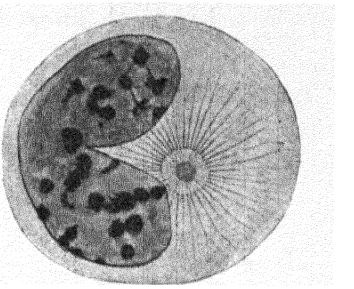


FIG. 583.—MACROCYTE OF LEPIDOSIREN, SHOWING LINES IN PROTOPLASM RADIATING FROM CENTRIOLE. (T. H. Bryce.)

According to Browning [1] the lymphocytes are not only the first of the leucocytes to make their appearance in the embryo, but are also the first to appear phylogenetically; the oxyphils are the next to show themselves.

3. **Macrocytes (macro-lymphocytes).**—These (fig. 579, *c*) are in general similar to the microcytes, containing a simple nucleus and a clear basiphil cytoplasm, but both nucleus and cytoplasm have a much larger volume, so that the cell itself is far larger. They form in fact the largest of all the blood-leucocytes. That they are derived from the micro-lymphocytes appears probable, seeing that all intermediate sizes may be found in blood. The nucleus is often indented or kidney-shaped (fig. 583). The cytoplasm is highly amœboid and phagocytic. The estimates of their number vary according as the intermediate forms between these and microcytes are included: if only the largest cells are enumerated, the number is less than 1 per cent. of the total number of the blood-leucocytes, whereas if the intermediate forms are taken in with them the percentage would amount normally to considerably more.

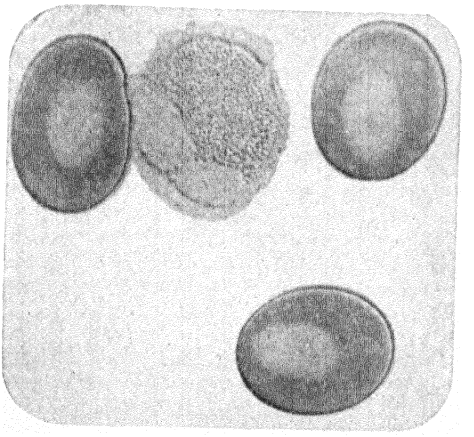


FIG. 584.—AN EOSINOPHIL LEUCOCYTE OF SALAMANDER BEGINNING TO ADHERE TO AN ERYTHROCYTE. (Schäfer.) Fresh preparation without addition of fluid. Untouched photograph. Magnified 600 diameters.

Two other erythrocytes are included in the field. Notice that the nuclei in these have undergone a change of position within the erythrocyte, showing that its contents must be completely fluid.

4. **Granular oxyphils.**—Leucocytes with a mass of coarse granules (fig. 579, *d*), staining with acid dyes such as eosin, sometimes filling the cytoplasm, sometimes leaving a part clear (fig. 584). The granules react for phosphorus. They are generally spheroidal, but in the cat are cylindroidal (Sherrington). The size of the granules varies in different species of animal. Ehrlich has suggested that these cells are secreting cells and the

[1] Journ. Path. and Bacter. x. 1905.

granules zymogen granules: they bear a resemblance to the zymogen granules of gland-cells.[1] In diameter the cells measure, when in the spherical state, about the same as the polymorphocytes. The nucleus is commonly horseshoe-

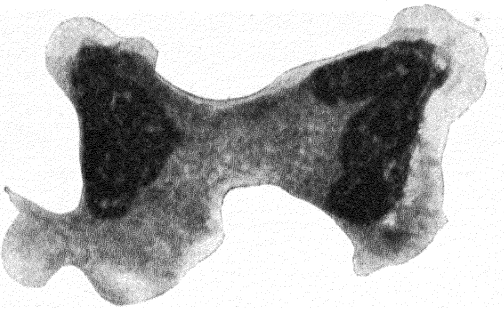


FIG. 585.—A POLYMORPH LEUCOCYTE OF TRITON FIXED BY A JET OF STEAM DURING WHAT APPEARS TO BE AMITOTIC DIVISION. (Schäfer.)
Magnified 1360 diameters. Untouched photograph.

shaped or bilobed, but not subdivided like that of the polymorphocytes. These leucocytes vary greatly in number in different individuals (1 to 11 per cent). They are amœboid, but less actively so than the polymorphocytes. Similar cells occur in bone-marrow, and this is probably their source: the granules of the oxyphil marrow-leucocytes having the same size and shape as those of the oxyphil blood-leucocytes of the same species of animal.

5. **Granular basiphils.**—Leucocytes with a mass of coarse granules, staining with basic dyes such as methylene-blue. These are not constant elements of normal blood, but occur occasionally. They are fairly numerous in bone-marrow and in the connective tissue of some parts, where they are known as 'mast-cells' (see p. 108). When present in blood they have probably passed into it from those tissues.

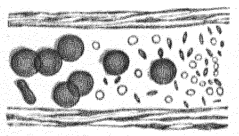


FIG. 586.—BLOOD-CORPUSCLES AND PLATELETS WITHIN A SMALL VEIN OF THE RAT'S MESENTERY. (W. Osler.)

The blood of lower vertebrates contains leucocytes having the same general characters as those of mammals, and of the same kinds, viz. polymorphs, lymphocytes, large and small, and granular oxyphil cells. In amphibians the leucocytes are considerably larger than in mammals and birds, although smaller than the erythrocytes.[2] Walker has described the leucocytes of Axolotl as undergoing a kind of conjugation, with exchange of nuclear material.

The leucocytes of Salamandra have been shown by Meves[3] to contain chondriosomes. These are not identical with Ehrlich's granules, although the latter have probably been formed from them. According to C. E. Walker the granules of these leucocytes are formed from the threads of their archoplasm.[4]

The exact nature of the granules of the leucocytes is not known. Some have been regarded as representing secretion-material within the protoplasm (see above). Attempts have been made, with more or less success, to prove that they possess digestive power, and Fiessinger and Marie[5] state that they have been able to obtain a tryptic ferment from centrifugalised leucocytes.

Formation and reproduction of leucocytes.—The formation of the leucocytes of the blood from primitive blood-cells or hæmoblasts has already been considered, as well as the possibility of the formation of the polymorph and the

[1] Weidenreich (Anat. Anz. xxxii. 1908, Verhandl. d. anat. Gesellsch.) makes the somewhat improbable suggestion that the eosinophil granules are derived from the hæmoglobin of ingested erythrocytes. Equally unlikely is the suggestion of Sacharoff (Arch. f. mikr. Anat. xlv. 1895) that they are formed from the extruded nuclei of the erythroblasts of bone-marrow.

[2] For a description of the leucocytes of the frog's blood, and the relative number of each kind, see Pentimalli, Intern. Monthly Journ. Anat. and Physiol. xxvi. 1909; and Freidsohn, Arch. f. mikr. Anat. lxxv. 1910.

[3] Arch. f. mikr. Anat. lxxv. 1910.

[4] Proc. Roy. Soc B. lxxix. 1907.

[5] Journ. de Physiol. 1909.

granular leucocytes from similar cells in bone-marrow. Many recent authorities[1] appear to be of opinion that the lymphocytes offer a common origin for all the varieties of leucocyte; but others, with Ehrlich, regard the lymph-cells as the

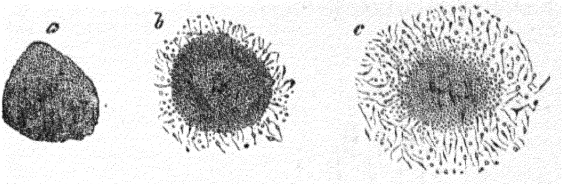


FIG. 587.—MASS OF BLOOD-PLATELETS, SHOWING THE DISINTEGRATION WHICH IT UNDERGOES AT ITS PERIPHERY WHEN OBSERVED IN SALT SOLUTION ON THE WARM STAGE. (W. Osler.)

source of the blood-lymphocytes (micro- and macrocytes) only, while the granular and polymorph cells are produced in the marrow.[2] Leucocytes have been described by several authors as undergoing multiplication by mitotic division.[3] This is easily seen in the lymphocytes of lymph-glands and the lymph-nodules of mucous membranes and of the spleen, but is rare in the blood itself in the adult condition, although amitotic division appears sometimes to occur, especially in the polymorph cells (fig. 585). Mitotic division is also seen in the leucocytes of bone-marrow.

BLOOD-PLATELETS: THROMBOCYTES.

Besides the erythrocytes and leucocytes, the blood contains a third corpuscular element consisting in mammals of minute circular discoidal particles, which were first described by Zimmermann[4] under the name *elementary particles*, and later by Bizzozero[5] under the name *blood-platelets*. This is the name by which they are now generally known, although the term *thrombocyte*, which was introduced by Dekhuyzen, is also frequently used for them.[6]

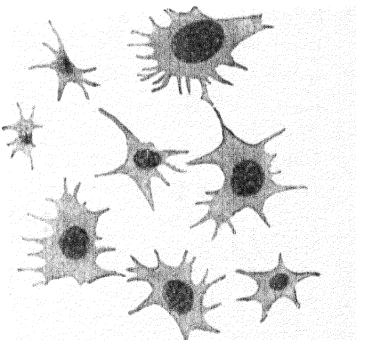


FIG. 588.—BLOOD-PLATELETS, HIGHLY MAGNIFIED, SHOWING THE AMŒBOID FORMS WHICH THEY ASSUME WHEN EXAMINED UNDER SUITABLE CONDITIONS, AND ALSO EXHIBITING THE CHROMATIC PARTICLE WHICH EACH PLATELET CONTAINS, AND WHICH HAS BEEN REGARDED AS A NUCLEUS. (After Kopsch.)

The **blood-platelets** in man are very small, the largest being less than one-third the diameter of an erythrocyte. In the living blood-vessels they are discrete (fig. 586), but in drawn blood they become clumped together into masses of varying size (fig. 587), lying here and there in the clear spaces of a microscopic preparation, between the rouleaus formed by the erythrocytes. Various views have been held regarding the nature of these particles, some having regarded them as representing a stage of formation of the erythrocytes, others as produced by the disintegration of leucocytes; while another opinion has been expressed that they represent merely a chemical precipitate from the plasma. But of late years there has been considerable advance made in the knowledge of these bodies.

[1] *E.g.* Saxer, *op. cit.*; Maximow, *op. cit.*; Bryce, Trans. Roy. Soc. Ed. xli. 1904-5; Weidenreich, Arch. f. mikr. Anat. lxxiii. 1909. See also 'Die Leukocyten' in Merkel and Bonnet's Ergebn. d. Anat. xix. 1909. Weidenreich believes that the small lymphocytes (microcytes) are derived from the larger ones by division, and themselves grow into larger ones (macrocytes).

[2] Cf. Schridde, Centralbl. f. allg. Pathol. xx. 1909. See further on this subject, Pappenheim, 'Atlas d. menschl. Blutzellen,' Jena, 1905, and Nägeli, 'Die weissen Blutkörperchen,' in Ehrlich and Lazarus' Die Anæmie, 2nd edition, 1909.

[3] Van der Stricht, Anat. Anz. 1891; C. E. Walker, *op. cit.*

[4] Virchow's Archiv, xviii. 1860. See also M. Schultze, Arch. f. mikr. Anat. i. p. 39.

[5] Virch. Arch. xc. 1882. One of the earliest and best accounts of these structures is that given by Hayem (Arch. de physiol. 1878 and 1879), who, however, supposed that they give rise to erythrocytes and termed them *hæmatoblasts*.

[6] For methods of examination of blood-platelets see Deetjen, Zeitschr. f. physiol. Chem. lxiii. 1909.

It has been found[1] that each possesses a chromatin mass (chromidium) which seems to represent a nucleus, and that under suitable conditions the cytoplasm exhibits changes of form comparable to the amœboid movements of protoplasmic cells (fig. 588). They may therefore be looked upon as minute cells,[2] and this conclusion seems to be borne out by their chemical composition, which resembles that of cells in general, consisting mainly of nucleo-proteins with some lecithin and cholesterin. They are readily destroyed by dilute alkalies,[3] and are stained by basic dyes, especially by methyl-violet. They vary greatly in number in different individuals, and in the same individual under different conditions: the number has been estimated by Brodie and Russell at from 5,000 to 450,000 per cubic millimetre.[4] The property which the blood-platelets possess of rapidly, almost explosively, throwing out processes and adhering together in masses when they come in contact with a foreign body has led to the supposition that these masses may serve the purpose of a plug at places where injuries to blood-vessels have occurred;[5] thus assisting to arrest hæmorrhage before the formation of a fibrin coagulum can occur to effect this object more completely. In this way they would resemble the action of the far larger cells in invertebrates, which produce a similar arrest of hæmorrhage by thrusting out processes and adhering firmly together as soon as the escaping blood comes into contact with injured tissue or foreign matter;[6] a kind of pseudo-coagulum being thus formed which produces the same result as that of an ordinary fibrin-clot, but much more rapidly. The view that this is

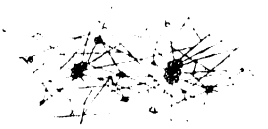


FIG. 589.—NETWORK OF FIBRIN, SHOWN AFTER WASHING AWAY THE CORPUSCLES FROM A PREPARATION OF BLOOD THAT HAS BEEN ALLOWED TO CLOT. (Schäfer.)

Many of the filaments radiate from small clumps of blood-platelets.

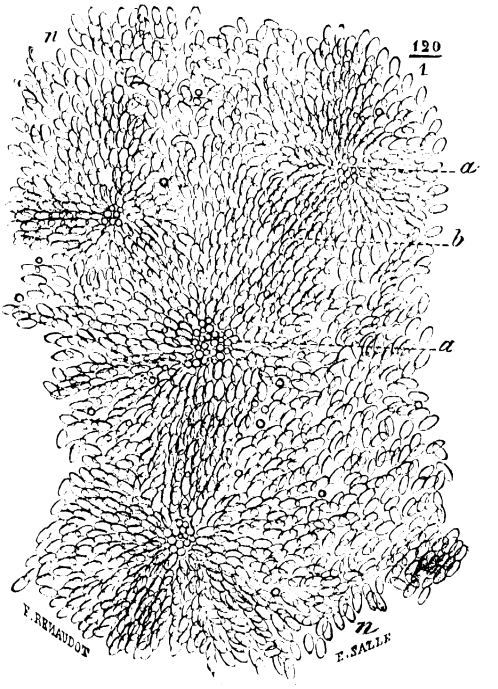


FIG. 590.—BLOOD OF FROG. (Ranvier.) Magnified 100 diameters. The preparation had been kept twenty-four hours.

a, *a*, rosetting of blood-corpuscles around clumps of blood-platelets; *b*, a strand of corpuscles joining two rosettes; *n*, *n*, loose corpuscles.

[1] Deetjen, Virch. Arch. clxiv.; Dekhuyzen, Anat. Anz. xix. 1901; Kopsch, *ibid.*

[2] Eisen (Journ. Morph. xv. 1899), who terms them plasmocytes, looks upon them as representing free centrosomes or centrioles of the erythrocytes. J. H. Wright (Virch. Arch. clxxxvi. 1906) states that they are produced by the megakaryocytes of bone-marrow, and can be seen on the warm stage to break off from these. Dantschakoff (Arch. f. mikr. Anat. lxxiv. 1909) and R. W. King (Journ. Med. Res. xxiv. 1911) believe that they are formed by the breaking down of the nuclei of the erythroblasts of the marrow. All of these suggestions seem improbable.

[3] Deetjen, Verhandl. d. path. Gesel. 1909.

[4] Journ. Physiol. xxi. 1897.

[5] It has been shown by Bizzozero (Virch. Arch. xc. 1882) and by Eberth and Schimmelbusch (Die Thrombose, etc., Stuttgart, 1888) that the white thrombus-formation of the pathologists is due to the accumulation and adhesion of blood-platelets to the diseased or injured vascular walls.

[6] L. Frederieq, Bull. acad. roy. de Belgique, xlvii. 1879; P. Geddes, Proc. Roy. Soc. xxx. 1879-80; W. B. Hardy. Journ. Physiol. xiii. 1892; Botazzi, Arch. ital. de biol. xxxvii. 1902; L. Loeb, Biol. Bull. iv. 1903; John Tait, Quart. Journ. Exper. Physiol. ii. 1909. The agglutinated corpuscles of the perivisceral fluid in echinoderms exude a coagulable material, no such material being present in the fluid itself (Schäfer, Proc. Roy. Soc. xxxiv. 1882).

the function of the blood-platelets has led to the name of thrombocytes being applied to them. It is believed that they contain *prothrombin*, which under the influence of the soluble lime-salts of the plasma becomes transformed into fibrin-ferment or *thrombin*, and it is probably on this account that fibrin-filaments are generally seen starting from the clumps of blood-platelets in a microscopic preparation of blood which has undergone coagulation (fig. 589).

The thrombocytes of oviparous vertebrata are very different in appearance from those of mammals. They take the form of colourless elongated corpuscles smaller than the erythrocytes and less numerous in proportion to these than are the thrombocytes of mammalian blood. They contain a distinct elliptical nucleus, and must certainly be regarded as cells: some authors have indeed been disposed to look upon them as representing a stage in the development of the nucleated erythroblast. But the observations of Hayem[1] and Meves[2] render it probable that these bodies fulfil the same functions as the thrombocytes of mammalian blood. Like the latter they undergo rapid changes (fig. 591) when the blood is drawn or when it comes in contact with an injured or foreign surface. The corpuscle itself, as well as its nucleus, becomes spheroidal and rapidly throws out bleb-like processes which extend some distance from the body of the thrombocyte. If two or more of these cells come in contact they adhere closely, and when there are many together they form a mass of cells, which, if accumulating at an injured spot in a vessel, may easily help to form a plug and impede the escape of the ordinary corpuscles. Presently bundles of fibrin-filaments may be seen in a microscopic preparation extending from the clumps

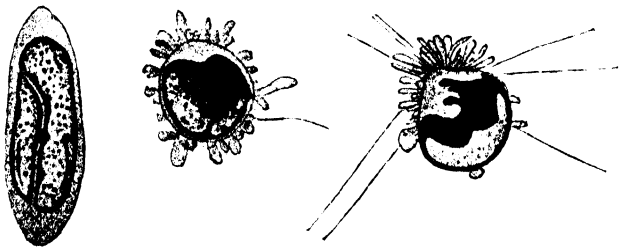


FIG. 591.—A BLOOD-PLATELET OF SALAMANDER, AND THE CHANGES WHICH IT UNDERWENT IMMEDIATELY AFTER WITHDRAWAL OF BLOOD FROM THE VESSELS. (F. Meves.)

of thrombocytes and passing between the clumps: these filaments adhere to erythrocytes which happen to be within their course; they appear to shrink later and thus to exert a pull upon the entangled erythrocytes (fig. 592) a peculiar rosetted appearance, being given to the groups of blood-corpuscles which are thus dragged upon (fig. 590). As with the mammalian thrombocytes, these seem thus to serve as centres for the deposition of fibrin, threads of which radiate in all directions from the metamorphosed thrombocytes.[3]

Nothing is positively known as to the origin of the blood-platelets, nor has it yet been exactly ascertained when they first make their appearance in the blood of the developing animal.

CORPUSCLES OF THE LYMPH AND CHYLE.

The corpuscles which are met with in lymph and chyle vary greatly in number. They consist almost entirely of the smaller lymphocytes, although there are a few somewhat larger,[4] with an occasional polymorph or oxyphil leucocyte. The lymphocytes are doubtless derived from the lymph-glands through which the

[1] Hayem, *op. cit.*

[2] Arch. f. mikr. Anat. lxviii. 1906. For various other observations upon the blood-platelets and the changes which they undergo after the blood is drawn see Deetjen, Zentr. f. Physiol. xxiii. 1909, and Zeitschr. f. physiol. Chem. lxiii. 1909. An article in Science Progress, 1906, by Buckmaster, contains information regarding them up to that date.

[3] See on the part played by thrombocytes in the arrest of hæmorrhage, Pringle and Tait, Proc. Physiol. Soc., June 18 and July 9, 1910, in Journ. Physiol. xl.

[4] B. F. Davis and A. J. Carlson, Amer. Journ. Physiol. xxv. 1909.

lymph which is collected from the tissues passes—very few are found before the lymph reaches a gland; the other occasional leucocytes are probably derived from the blood, having migrated into the lymphatics either near their origin in the connective tissue or within the lymph-paths of the lymph-glands.

The number of corpuscles in lymph is subject to great variation, being especially increased during digestion, when a large amount of fluid (chyle) is passing through the mesenteric lymph-glands.

Both lymph and chyle contain thrombocytes.

Chyle contains, in addition to the microscopic elements found in lymph, a vast number of minute globules of fatty matter, long known under the name of 'molecular base of the chyle.' This is derived solely from absorbed fat of the food, and is seen only in the mesenteric lymphatics (lacteals) and in the thoracic duct in which they terminate. It disappears, and with it the milky aspect of the contents of those vessels, when no food is given for some time (or food containing no fat).

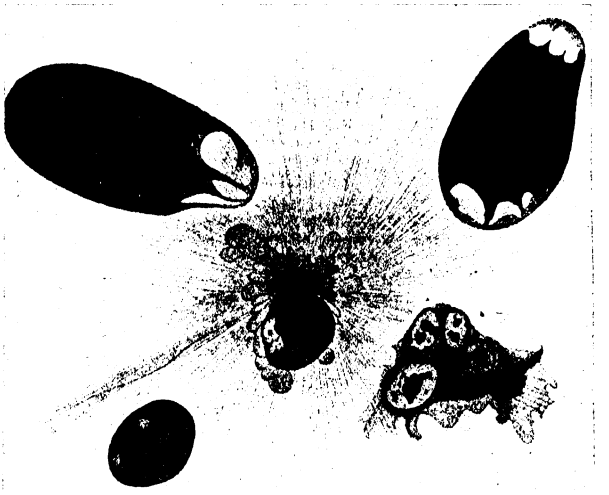


FIG. 592.—A BLOOD-PLATELET OF SALAMANDER, SHOWING ITS BLEB-LIKE PROCESSES AND ALSO THE FIBRIN-FILAMENTS RADIATING FROM IT AND ATTACHED TO ADJACENT ERYTHROCYTES. (F. Moves.)

Two erythrocytes, one free nucleus, and one polymorph leucocyte are included in the figure.

The number of lymphocytes which are passed into the blood by way of the lymph and chyle in twenty-four hours is considerable, and may be much greater than the number permanently present in the blood.[1] For the maintenance of the average number there must be an equivalent loss by disintegration either of these or of other leucocytes which are produced from them. Whether this disintegration occurs in the blood itself or, if not, in what tissues or organs it takes place, is unascertained, but there is some evidence that it may, in part at least, proceed within the mucous membrane of the alimentary canal. For as was first pointed out by Stöhr,[2] large numbers of leucocytes pass out through the stratified epithelium which covers the tonsils, and the same is the case wherever lymphoid tissue occurs in mucous membranes, as in the œsophagus, bronchial tubes, stomach, and intestine. The migrated leucocytes must certainly be disintegrated by the juices with which they are thus brought into contact. It cannot, however, be positively affirmed that these leucocytes are derived from the blood, for they may have been

[1] Davis and Carlson, *op. cit.*

[2] Virch. Arch. xcvii. 1884.

produced *in situ* within the lymphoid tissue underlying the epithelium through which they penetrate. The case of the villi of the intestine is perhaps different. In these, especially during digestion, great numbers of leucocytes are found, both between the epithelium-cells and also between those cells and the basement-membrane, as well as in the interstices of the reticular tissue, and even within the commencing lymph-vessel (lacteal) of the villus.[1] These leucocytes must mainly be derived from the blood circulating through the villus, for there is no evidence of their multiplication by division within the tissue of the villus.[2] Although they have not been observed, as with the leucocytes of the tonsils, to pass out on the free surface of the mucous membrane, there is reason to believe that during food-absorption they pass from the tissue of the villus into the commencing lacteals, and there undergo disintegration. It may also be the case that others become disintegrated outside the lacteals, although the occurrence of such disintegration in this situation would be difficult of detection.

[1] Schäfer, Proc. Roy. Soc. xxxviii. 1885; and Int. Monthly Journ. Anat. and Physiol. 1885.

[2] In the papers just referred to, it was assumed that the leucocytes within the villi might multiply by division. But it appears on the whole more probable that they are brought to the villi by the blood-vessels.

ORGANS CONCERNED WITH THE FORMATION OF LYMPH-CORPUSCLES.

THE organs and tissues which in the adult are concerned with the formation of leucocytes are the lymph-glands and other lymphoid structures, such as the lymphoid nodules which occur in the mucous membrane of the alimentary and pulmonary mucous membranes, the lymphoid tissue which forms the tonsils, the lymphoid tissue of the spleen (Malpighian corpuscles) and the lymphoid tissue of the thymus. Of these various hæmapoietic organs the lymph-glands, hæmal glands, and spleen will be here dealt with, the thymus, tonsils, and lymph-nodules of mucous membranes being described later.[1]

It is held by many authorities (p. 391) that the granular and the polymorph leucocytes have their seat of formation in bone-marrow; some of the cells of

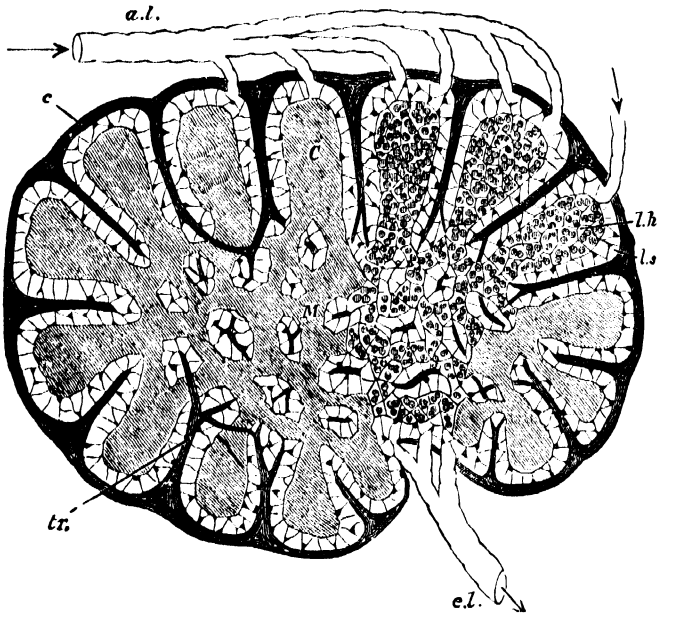


FIG. 593.—DIAGRAMMATIC SECTION OF LYMPHATIC GLAND. (Sharpey.)

a.l., afferent; *e.l.*, efferent lymphatics. C, cortical substance. M, reticulating cords of medullary substance. *l.s.*, lymph-sinus; *c*, fibrous coat sending trabeculæ, *tr.*, into the substance of the gland.

this tissue have been looked upon as a possible source of origin of thrombocytes also. If this is so, bone-marrow, especially the red variety, must be regarded as an organ-system adapted for producing all the different kinds of corpuscular elements found in blood.

As already mentioned, it is not certainly known where destruction of leucocytes mainly occurs, although many are lost by migration into the alimentary canal. But a certain number of leucocytes as well as of erythrocytes are destroyed by phagocytes in the spleen and hæmal lymph-glands; this may also happen in the ordinary lymph-glands.

[1] For an account of blood-forming organs in general see M. Löwit, Arch. f. mikr. Anat. xxxviii. 1891; Weidenreich, Ergebn. d. Anat. 1903, 1904, and Arch. f. mikr. Anat. lxv. 1905. For the lymph-glands in particular see Bertel and Stein, Arch. f. Anat. 1905 and 1906; for hæmal glands the various papers mentioned in footnote 2 on page 402. For a discussion of the relation of bone-marrow to leucocyte production see R. Muir, Journ. Path. and Bact. vii. 1901.

LYMPH-GLANDS: LYMPHATIC GLANDS.

Lymph-glands or **lymphatic glands,** formerly named also *conglobate glands,* and by modern French writers *ganglions lymphatiques,* are small solid bodies, placed in the course of the lymph-vessels and lacteals, through which the contents of these vessels have to pass in their progress towards the thoracic duct or the right lymphatic duct. These bodies are collected in numbers along the great vessels of the neck, and also in the thorax and abdomen, especially in the mesentery and alongside of the aorta, vena cava inferior, and iliac vessels. A few, usually of small size, are found on the external parts of the head, and considerable groups are situated in the axilla and groin. Some three or four lie on the popliteal vessels, and usually one is placed a little below the knee, but none farther down. In the arm they are found as low as the elbow-joint.[1]

Lymph-glands occur in all mammals, but only a few are found in birds, and these, of a comparatively simple structure, lie near the root of the neck and at the upper part of the thorax. No vertebrates below birds possess lymph-glands.

The lymph of some lymph-vessels passes through two, three, or even more lymph-glands before reaching the thoracic duct, whilst, on the other hand, there are lymph-vessels which enter the thoracic duct without having traversed any gland.

The size of lymph-glands is very various, some being not much larger than a hemp-seed, while others are as large as an almond or a broad-bean, or even larger than this. In shape, too, they present differences, but most of them are round, oval, or kidney-shaped.

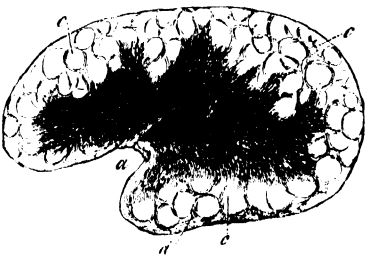


FIG. 594.—SECTION OF A MESENTERIC GLAND FROM THE OX, SLIGHTLY MAGNIFIED. (Kölliker.)

a, hilum; *b*, medullary substance; *c*, cortical substance with indistinct alveoli; *d*, capsule.

The lymphatics or lacteals which enter a gland are termed its afferent vessels (*vasa inferentia seu afferentia*), and those which issue from it the efferent vessels (*vasa efferentia*). The afferent vessels (fig. 593, *a.l*), on approaching a gland, divide into many small branches, which enter the surface; the efferent lymphatics commonly leave the gland at a depression (*hilum*) on one of its sides; and at a little distance beyond it, sometimes even before issuing from it, unite into one or more trunks (*e.l*), usually larger in size than the afferent vessels.

A lymph-gland is covered externally with a *capsule* (figs. 593, 595, *c*) of connective tissue (white and elastic), mixed, in most animals, with many plain muscle-cells. This capsule dips into the interior of the gland at the place where the larger blood-vessels and the efferent lymphatics pass into and out of the organ; this is the part of the gland, which often has a depression, above referred to as the hilum (fig. 594, *a*). The proper substance of the gland consists of two parts, the *cortex* (fig. 594, *c*), and within this the *medulla* (*b*). The cortex occupies all the superficial part of the gland, except at the hilum, and in the larger glands may attain a thickness of one or two millimetres. The medullary portion occupies the centre and extends to the surface at the hilum. It is most developed in the inwardly seated glands, such as the lumbar and mesenteric, whilst in the subcutaneous glands it is more encroached upon by the connective tissue which enters with the larger blood-vessels at the hilum, and which surrounds them, together with the lymph-vessels, in the centre of

[1] Rainer has described a small lymph-gland at the base of the heart, under the epicardium and close to the root of the aorta (Anat. Anz. xxxi. 1907).

the gland; so that in these the medullary part is reduced to a layer of no great thickness bounding inwardly the cortical part.

Throughout both its cortical and medullary parts the gland is pervaded by a trabecular framework which serves to support the proper glandular substance. The trabeculæ pass inwards from the capsule (figs. 593, 595). They consist, in the ox and most animals, chiefly of plain muscular tissue; in man, where they are much more delicate, of connective tissue, sparingly intermixed with plain muscle-cells. In the cortical part they are mostly lamellar in form, and partially divide the cortex up into separate nodules from 0.5 mm. to 1 mm. in diameter; these nodules communicate laterally with each other through openings in the imperfect septa between them (fig. 595, A). On reaching the medullary part the trabeculæ take the form of flattened bands and angular cords, and by their conjunction and reticulation form a freely intercommunicating meshwork throughout the interior. (In fig. 595 they are represented mostly as cut across.) In the interstices of the framework which is thus formed by the capsule and trabeculæ is included the

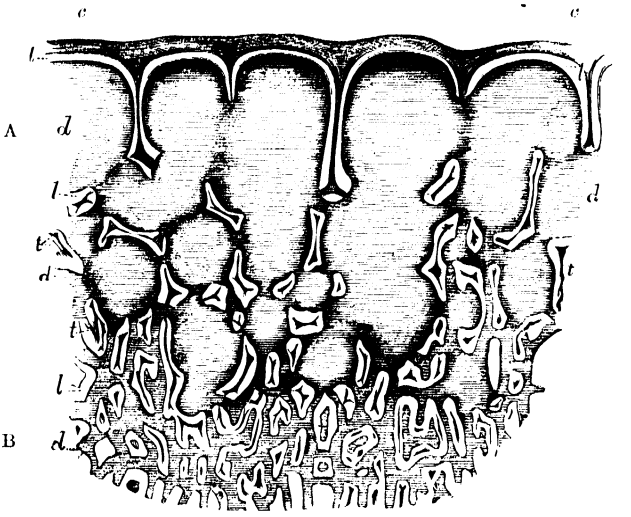


FIG. 595.—SECTION OF A MESENTERIC GLAND OF THE OX. (After His.) Magnified 12 diameters.

The section includes a portion of the cortical part, A, in its whole depth, and a smaller portion of the adjoining medullary part, B; *c*, *c*, outer coat or capsule sending partitions into the cortical part, eventually forming the trabeculæ, *t*, *t*, which are seen mostly cut across; *d*, *d*, the lymphoid tissue forming nodules in the cortical part, A, and reticulating cords in the medullary part, B; *l*, *l*, lymph-sinus or lymph-channel, left white.

proper *glandular substance*, which appears as a tolerably firm pulp, composed of masses of lymphocytes supported by reticular tissue, the two together forming the *lymphoid tissue* of the gland. In the cortex this tissue occurs, as we have seen, in the form of rounded nodules (*cortical nodules* or *follicles*) (fig. 595, A); in the trabecular meshes of the medullary part it takes the shape of rounded cords (*lymphoid cords*) joining in a corresponding network (fig. 595, B); and, as the containing meshes of the framework inter-communicate, so the contained gland-pulp is continuous throughout. But both in the cortical and the medullary parts, a narrow space (white in the illustrations, fig. 593, *l.s*; fig. 595, *l*, *l*) is left all round the gland-pulp, between it and the trabeculæ, such as would be left had the pulp shrunk away from the inside of a mould in which it had been cast. This space forms a channel of passage for the lymph that goes through the gland; it is named the *lymph-sinus*, or *lymph-channel* (fig. 593). It is traversed by somewhat coarser reticular tissue than that which is seen in the pulp. The reticulum in some glands is rather a spongework than a network;

it may have some elastic fibres amongst the white fibrils of which it is mainly composed.[1] The reticulum of the lymph-sinus is partly covered in the natural condition by ramified cells. The lymph-sinus is occupied by lymph, containing many lymph-corpuscles. These may be washed out from sections of the gland, so as better to show the sinus, while the corpuscles in the firmer gland-pulp tend to be retained in place. The finer reticular tissue of the lymphoid nodules and cords (fig. 596, *a*; fig. 597) communicates with that of the surrounding lymph-sinus, but is marked off from it by somewhat closer reticulation at their mutual boundary; not so close, however, as to prevent lymph-corpuscles from passing from the one to the other. The lymphoid tissue is otherwise made up, as already mentioned, of densely packed lymphocytes, occupying the interstices of its supporting reticular tissue, and usually exhibiting, especially at the centre of the nodules, abundant evidence of the process of division and multiplication by

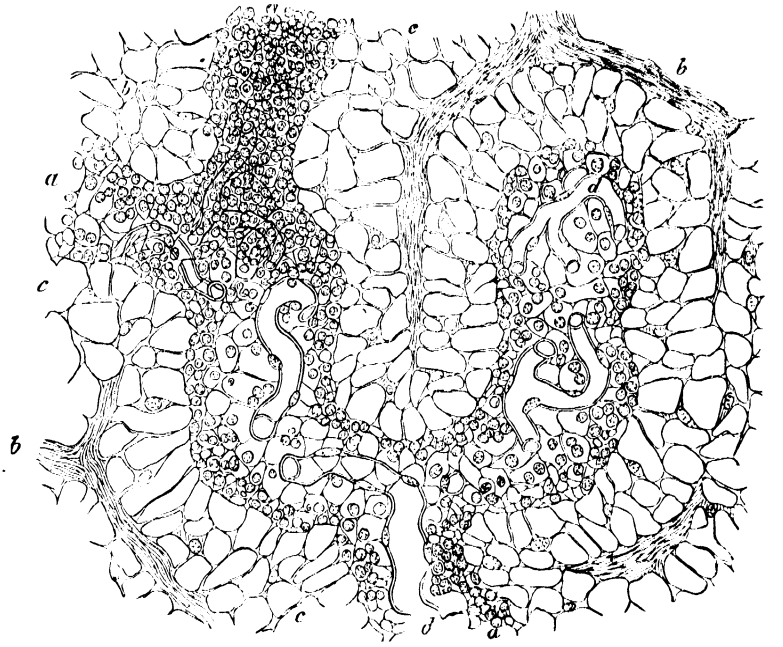


FIG. 596.—SECTION OF THE MEDULLARY SUBSTANCE OF A LYMPHATIC GLAND (OX). (v. Recklinghausen.) Magnified 300 diameters.

a, *a*, *a*, follicular or lymphoid cords; *b*, *b*, trabeculæ; *c*, lymph-sinus; *d*, *d*, blood-vessels.

mitosis (*germ-centres* of Fleming[2]). These germ-centres are only found in the cortical nodules, which have probably been produced by the accumulation of cells which results from frequent division. The multiplication of cells in the medullary cords is either too infrequent or too irregularly dispersed to produce a similar appearance. The germ-centres are not distinct in young animals—probably because the multiplication is less localised in them—nor in very old ones.[3] The lymphoid tissue is traversed by a network of capillary blood-vessels (fig. 596, *d*, *d*), which run throughout the proper glandular pulp, both cortical and medullary, but do not pass into the surrounding lymph-sinus. Although most of the cells of the glandular pulp are similar to the smaller lymphocytes of blood, larger cells of the character of macrocytes are here and there found.

The ramified cells which cover the reticular tissue of the lymph-sinus often

[1] Bunting, Journ. Anat. and Physiol. xxxix. 1904–5. [2] Arch. f. mikr. Anat. xxiv. 1885.
[3] Baum and Halle, Anat. Anz. xxxii. 1908.

contain a considerable number of pigment-granules, especially in the medulla of the gland (fig. 591). These reticulum-cells are phagocytic,[1] and have been noticed to contain, besides pigment, erythrocytes in stages of disintegration;[2] but it is

Fig. 597.—Lymphoid tissue from medulla of lymph-gland of dog. (Schäfer.)
The trabeculæ and the fibres of the reticular tissue are stained dark, the lymphocytes are only faintly stained.

doubtful if this is a normal condition, for since there are no blood-vessels in the sinus, blood-corpuscles which may have passed into it must have got by accident into the lymph. The phagocytes take up any foreign matter which is brought to the

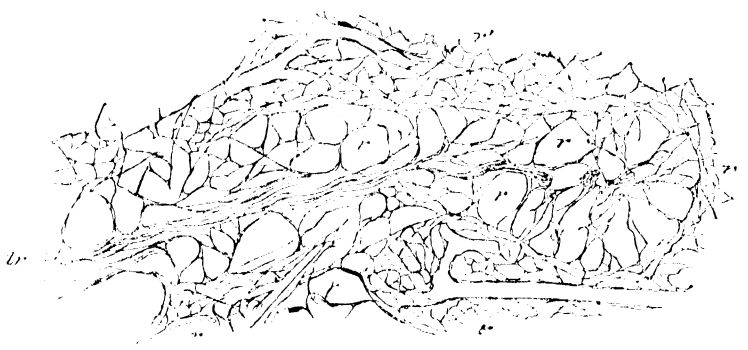


Fig. 598. Reticulum from the medullary part of a lymphatic gland. (Schäfer.)
tr, end of a trabecula of fibrous tissue; *r*, *r*, open reticulum of the lymph-path, continuous with the fibrils of the trabecula; *r'*, *r'*, denser reticulum of the medullary lymphoid cords. The cells of the tissue are not represented, the figure being taken from a preparation in which only the connective-tissue fibrils and the reticulum are stained.

gland by the lymph-vessels; *e.g.* those of the glands at the roots of the lungs almost always contain soot-particles which have been inspired and brought to them in the lymph. The trabeculæ have a covering of endothelium-cells, which on the side

[1] H. Hoyer, Arch. f. mikr. Anat. xxxiv. 1889.
[2] Schumacher, Arch. f. mikr. Anat. xlviii. 1897; Thomé, *ibid.* lii. 1898.

turned towards the lymph-channel are provided with processes to anastomose with those covering the retiform tissue. The inner surface of the capsule is also lined with endothelium-cells, which are continuous at the entrance and exit of the lymphatics with the endothelium of those vessels.

Blood- and lymph-vessels and nerves.—*Arteries* enter and *veins* leave the gland at the hilum, surrounded, in some glands, as already said, with a dense investment of connective tissue. The arterial branches go to the lymphoid tissue, but are conducted at first along the trabeculæ, and some branches may remain within the trabeculæ and pass to the capsule of the gland to be there distributed. As the arterioles pass to the proper glandular substance, the connective tissue of the trabeculæ which ensheaths them merges gradually into the lymphoid tissue of the pulp, so that this at first appears as a sheath to the arterial branch (as in the spleen). The arteriole soon, however, breaks up into capillaries, which ramify in the gland-pulp, supported by its pervading reticular tissue; this forms an additional adventitious coat around the minute vessels. The veins pass along the trabeculæ to the hilum, there uniting into one or two efferent veins. The gland receives a few small arterioles at its general surface, but nearly all the blood-supply enters and leaves at the hilum.[1]

FIG. 599. END OF A FIBROUS TRABECULA FROM THE SAME PREPARATION, SHOWING THE CONTINUITY OF THE CONNECTIVE-TISSUE FIBRILS WITH THE RETICULUM (Schäffer.) Highly magnified.

tr, trabecula; *r*, reticulum.

As to the *lymphatics* of the gland, the afferent vessels, after ramifying upon and in the tissue of the capsule, send their branches through it to open into the lymph-sinus of the cortex, and the efferent lymphatics begin by vessels which lead from the lymph-sinus of the medullary part, and form at the hilum a dense plexus of tortuous and varicose lymph-vessels: from these, larger vessels proceed to form the efferent trunks. The lymph-sinus, therefore, forms a path for the passage of lymph, interposed between the afferent and efferent lymphatics, communicating with both and maintaining the continuity of the lymph-stream. The afferent and efferent vessels, where they open into the lymph-sinus, lay aside all their coats, except the endothelial lining; this is continued upon the interior of the capsule and over the trabeculæ.

The *nerves* which pass to lymph-glands are distributed chiefly to the plain muscular tissue of the gland and of its blood-vessels.

Variations in structure.—The chief differences of structure seen in lymph-glands depend upon the relative amount and nature of the framework. Thus whereas in some animals both the capsule and the trabeculæ are strong and muscular, in others they are less developed and contain but little plain muscular tissue. In some the trabeculæ are almost or entirely absent, and the interior of the gland then looks in section like a continuous mass of lymphoid tissue, traversed by clearer lymph-channels. This is the case in some lymph-glands in the human subject[2] (fig. 600).

Function.—Within the lymphoid tissue of the lymph-gland a production of new lymphocytes is constantly proceeding. This is evidenced by the numerous mitoses seen in that tissue, especially at certain places, the germ-centres, as has

[1] On the distribution of the blood-vessels to lymph-glands see Calvert, Johns Hopkins Hosp. Bull. xii. 1901.

[2] For the differences in structure of lymph-glands in domestic animals see J. Richter, Arch. f. mikr. Anat. lx. 1902.

already been mentioned.[1] As the newly formed corpuscles accumulate in the middle of the lymphoid tissue, they tend to push out into the lymph-sinus the lymphocytes which are already formed. These pass into the lymph-sinus, so that fresh corpuscles are thus added to the lymph as it traverses the gland. As a consequence, it is found that the corpuscles are much more abundant in the lymph or chyle after it has passed through a lymph-gland.

HÆMAL LYMPH-GLANDS AND HÆMAL GLANDS.[2]

Both in man and other mammals glands are constantly found which have the general appearance of lymph-glands except that they are of a red colour and that on section the sinuses—or parts of them—are found to be occupied by blood instead of lymph (see accompanying Plate). When parts of the sinuses are occupied by

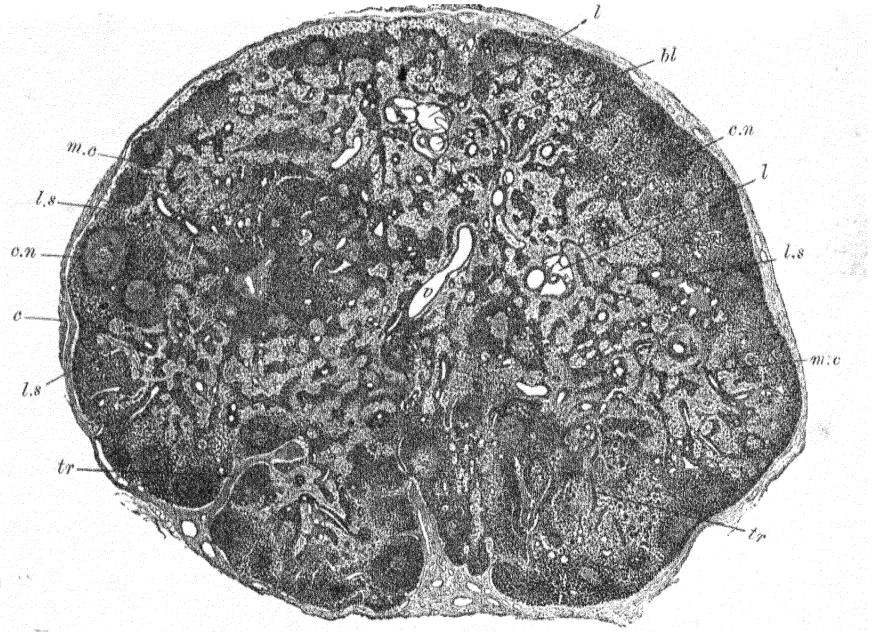


FIG. 600.—SECTION OF A LYMPH-GLAND FROM THE NECK OF AN EIGHT-YEAR-OLD CHILD. (v. Ebner.) Magnified 13 diameters.

c, capsule; *c.n*, cortical nodules of lymphoid tissue, some with germ-centres (lighter in central part); *m.c*, medullary cords of lymphoid tissue; *l.s*, lymph-sinus (the more lightly shaded part of the section); *tr*, trabeculæ; *l*, lymph-vessels; *bl*, blood-vessels; *v*, vein.

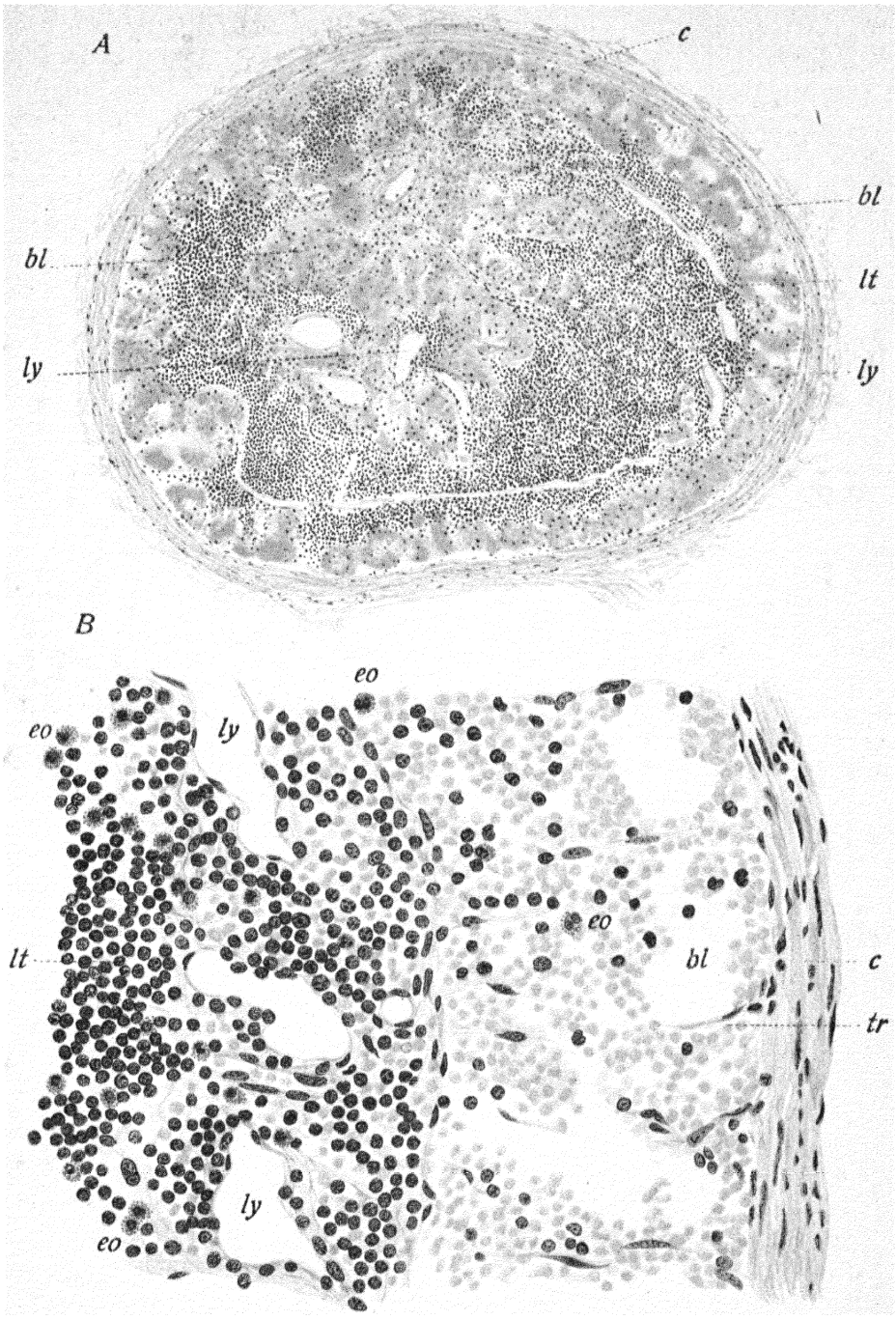
lymph these glands are termed *hæmal lymph-glands* (Robertson), when all are occupied by blood they are known as *hæmal glands*; it is stated that these purely hæmal glands have no relation to lymphatics, neither receiving nor giving off any lymph-vessels.[3] The blood-sinus in the hæmal glands is sometimes very large and may occupy the greater part of the interior.

The blood-corpuscles penetrate amongst the lymphoid cells of the lymphoid

[1] Flemming (Arch. f. mikr. Anat. xxiv. 1885) described in the lymphocytes of the germ-centres certain peculiar particles staining readily with basic dyes, which he termed the 'stainable particles.' They are possibly extruded portions of nuclear chromatin, but their real nature is unknown.

[2] The following are some of the chief papers on hæmal glands: Heneage Gibbes, Quart. Journ. Micr. Sci. xxiv. 1884, Amer. Journ. Med. Sc. 1898; Drummond, Journ. Anat. and Physiol. xxxiv. 1900; Clarkson, Brit. Med. Journ. 1891, Text-book of Histology, 1896; Robertson, Lancet, 1896; Vincent and Harrison, Journ. Anat. and Physiol. xxxi. 1897; Vincent, Proc. Phys. Soc. Journ. Physiol. xxii. 1898; Warthin, Boston Journ. Med. Sci. v. 1901, Amer. Journ. Anat. i. 1901; T. Lewis, Intern. Monthly Journ. Anat. and Physiol. xx. 1902, Journ. Anat. and Physiol. xxxviii. 1904; K. Helly, Ergebn. d. Anat. xii. 1902; Weidenreich, Arch. f. mikr. Anat. lxv. 1905.

[3] Weidenreich, *op. cit.*



Haemal lymph gland: haematoxylin-eosin. (Schäfer.)

The upper figure *(A)* shows a complete section through a small haemal lymph gland, magnified 60 diameters; the lower figure *(B)* a portion of the cortex of the same, magnified 400 diameters.

c, capsule, containing smooth muscle fibres; *tr.* fine trabeculae passing in from capsule; *bl,* blood sinuses full of red blood corpuscles, which are also seen in the interstices of the lymphoid tissue, *lt*; *ly,* lymph sinuses; *eo,* eosinophil cells.

tissue bounding the blood-sinuses; and phagocytosis of erythrocytes, with breaking down of their hæmoglobin into pigment, is a common phenomenon in these glands. The phagocytes are mostly large uninucleated cells (macrocytes); but the endothelial cells of the sinus and reticular tissue appear also to be phagocytic. Polymorphous leucocytes, rare in ordinary lymph-glands, are common in these; oxyphils also occur numerously, and basiphils are found occasionally; all of these being perhaps brought to the gland by the blood. Giant-cells with large lobed nuclei similar to the megakaryocytes of bone-marrow are also found in some of these glands. The blood-sinuses appear to be in communication on the one hand with the arterial capillaries and on the other with the veins of the gland, the arrangement in the hæmal glands and in the hæmal part of the hæmal lymph-glands being somewhat similar to that which obtains in the spleen. Indeed, these organs, the microscopic structure of which has been elucidated only within recent years, were probably often considered to be small accessory spleens.

The lymphatic part of the hæmal lymph-gland is precisely like that of the ordinary lymph-gland. According to some authors communications may be found between the blood- and lymph-sinuses in the mixed glands.

Some of the hæmal lymph-glands are said to resemble red marrow in structure. These have been termed by Warthin 'marrow lymph-glands'; they are characterised by smaller blood-sinuses, numerous basiphil cells and occasional giant-cells. Hæmal lymph-glands are found in man in the abdomen (behind the peritoneal cavity), in the neck, and in the thorax. They vary considerably in size, some being only just visible in a dissected part, others as large as a broad-bean. They are still more numerous in the sheep, and in the rat (Lewis), but less easily found in the dog and cat. Hæmal lymph-glands occur in birds (Vincent and Harrison), although these animals possess few lymph-glands of the ordinary type.

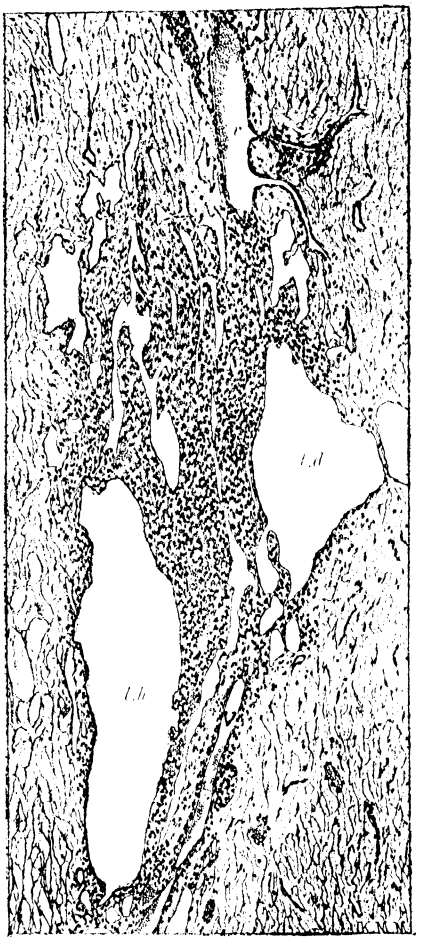


FIG. 601. DEVELOPING LYMPH-GLAND FROM A TRANSVERSE SECTION OF THE NECK OF A PIG EMBRYO 49 MM. LONG. (Sabin.) Magnified 44 diameters.

The top of the figure is in the position of the future hilum of the gland.

l.h, lymph-heart; *l.d*, afferent lymph-duct; *c*, vein.

Development of lymph-glands.— The first appearance of these organs is seen (in the human fœtus of 1¼ inch) in the form of a plexus of lymph-vessels amongst which masses of lymphoid tissue accumulate and eventually form intercommunicating columns (see figs. 601, 602, 603, from the pig). Blood-vessels penetrate into these columns,[1] and the whole becomes

[1] According to Gulland (Journ. Path. and Bact. ii. 1894; cf. also Saxer, Anat. Hefte, vi. 1896, and Ketterer, Journ. de l'anat. 1901) the blood-vessels are developed first and the lymph-cells are brought by these and form lymphoid tissue in the meshes of the vascular plexus, which is at first surrounded by a sinus-like lymph-space; the lymph paths within the gland are formed at a subsequent stage.

invested by mesenchyme, which forms a fibrous and muscular capsule surrounding the plexus and sends trabeculæ into the interior of the developing gland; from these trabeculæ fibrillar extensions pass into the lymphoid tissue to form its reticulum. The vessels of the lymphatic plexus become dilated to form the lymph-sinuses; into the spaces thus produced mesenchyme penetrates and forms the reticulum which bridges across the sinuses. The mesenchyme-cells and some of the endothelial cells remain as branched cells: these in places cover the reticular tissue in the fully formed organ. The cortical nodules become produced, as already mentioned, by an increased proliferation in the situation of the future germ-centres (fig. 603), but the latter are not distinct during fœtal life.[1] They also disappear in old age.

FIG. 602. DIAGRAM OF A DEVELOPING LYMPH-GLAND IN A PIG EMBRYO 70 MM. LONG. (Sabin.) Magnified 33 diameters.

The lymphatics are in solid black; the connective-tissue bridges are dotted.

Kling[2] describes the lymphatic vessels in the human embryo as growing into the vascular blastema of the developing gland at the future hilum and there forming plexuses, which become dilated into sinuses in its interior and a marginal sinus at the circumference, while the vessels at the hilum retain their plexiform and tubular character and become the efferent vessels of the gland.

The first glands to appear are those of the groin, axilla, and neck. Others appear later at the elbow, knee, along the course of the aorta and at the root of the mesentery.[3]

In the embryo of the pig Miss Sabin[4] finds the first sign of the development of lymph-glands in connexion with the sac-like dilatations (p. 362) near the four original points of outgrowth of the lymphatics from the venous system (fig. 550, S; fig. 601, *l.h*). These dilatations are homologues of the lymph-hearts of lower vertebrates, but do not pulsate.[5] The primitive lymph-glands develop in connexion with a close plexus of lymph-vessels that make their appearance at the apex of each of these dilatations.

According to Miss Sabin three types of lymph and hæmal glands become eventually formed, viz.: (1) those which are formed of a mass of lymphocytes supported by a reticulum and collected around a capillary network which is furnished with an artery and vein (lymph-nodules); (2) those in which this vascular lymphoid tissue is enclosed by a lymph-sinus (lymph glands); and (3) those in which it is enclosed by a blood-sinus. The last form the hæmal glands; the spleen is similar in mode of origin.

Lewis, who investigated the development of the lymphatic system, chiefly in rabbits, describes more numerous connexions with the venous system than are admitted by Miss Sabin.[6] He states that the first lymph-glands develop along the course of cutaneous veins, and are superficial, the deep glands at this stage being represented merely by lymphoid

FIG. 603. DIAGRAM OF DEVELOPING LYMPH-GLAND FROM A PIG EMBRYO 130 MM. LONG. (Sabin.) Magnified 33 diameters.

Four follicles are shown. Each is supplied by a separate branch of the artery which is furnishing capillaries to the follicles.

a, artery; *a.l*, afferent lymphatics; *e.l*, efferent lymphatics; *f*, follicles.

[1] Baum and Hille, Anat. Anz. xxxii. 1908.
[2] Arch. f. mikr. Anat. lxiii. 1904.
[3] Gulland, *op. cit.* See also Rep. Coll. of Phys. Edin. 1891.
[4] Amer. Journ. Anat. iv. 1904, and ix. 1909.
[5] This opinion is contested by F. T. Lewis (Amer. Journ. Anat. v. 1905). See also Anat. Record, iii. 1909.

trabeculæ. Lewis found at this time no sign of lymphoid tissue in the spleen or thymus and no lymphocytes in the blood.

Accumulations of lymphoid tissue occur later in different parts (*e.g.* in the mucous and serous membranes) in connexion with the formation of a reticulum of branching mesenchyme-cells, either outside of or within a sinus-like lymph-vessel, a network of blood-capillaries becoming developed within the reticular tissue (fig. 604) (Klein).[1]

THE SPLEEN.

The spleen has two membranous investments—a *serous coat* derived from the peritoneum, and a *fibrous coat*, or *tunica propria*. The soft substance (*pulp*) of the organ is supported by a reticular framework of fibrous and muscular bands (*trabeculæ*).

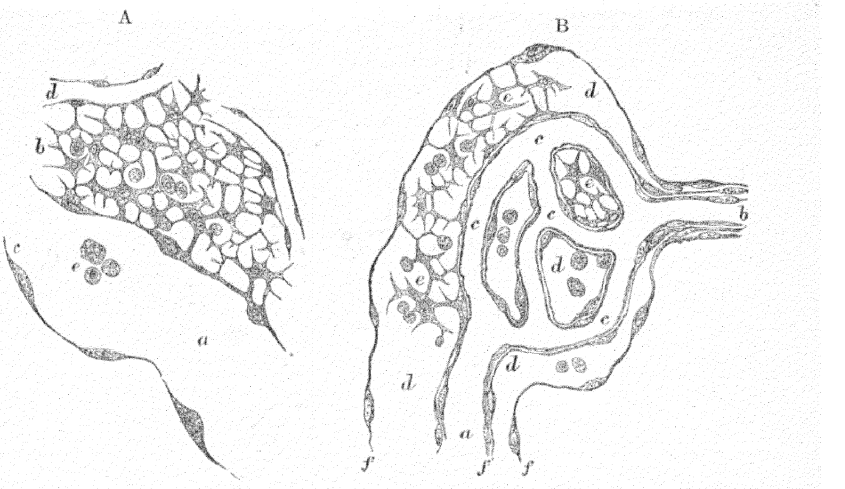


FIG. 604.—DEVELOPING LYMPH-NODULES FROM THE GUINEA-PIG'S OMENTUM. (Klein.)

A, formation of lymphoid tissue outside a sinus-like lymph-vessel.

a, lumen of vessel; *c*, its endothelium; *e*, lymph-corpuscles within it; *d*, blood-vessels; *b*, lymphoid tissue consisting of branched connective-tissue cells, attached to the endothelium and containing lymphocytes in the meshes of the reticulum which they form.

B, formation of lymphoid tissue in the interior of a lymph-sinus.

a, *b*, *c*, venule, arteriole, and capillary network, all enclosed within the sinus; *d*, lumen of sinus; *e*, lymphoid tissue within the sinus; *f*, endothelium of sinus.

The **serous coat** is thin, smooth, and firmly adherent to the tunica propria beneath. It closely invests the surface of the organ, except where it is reflected to adjacent organs, and at the hilum.

The **tunica propria** or **capsule** (figs. 605 to 607), much thicker and stronger than the serous coat, is whitish in colour and highly elastic. It is composed of fibrous and muscular tissue with many elastic fibres, and at intervals gives off trabeculæ into the interior. Along the hilum the proper coat is reflected into the interior of the spleen in the form of large trabeculæ, which support and ensheath the blood-vessels and nerves entering here, and ramify along with the blood-vessels, as far as their finer subdivisions. These trabeculæ, which pass in at the hilum, become continuous in the interior of the organ with the numerous trabecular processes which, as already stated, pass in from the whole inner surface of the capsule. This arrangement of the sheaths and trabeculæ may be easily displayed in the spleen of the ox by pressing and washing out the pulp from a thick section;

[1] For the mode of regeneration of lymph-glands after partial excision see Meyer, Johns Hopkins Hosp. Bull, xvii. 1906.

they are then seen to form a close reticulation through the substance of the spleen. Thus, the capsule, the sheaths of the vessels, and the trabeculæ, all of a highly elastic nature, constitute an extensible and contractile framework, containing in its interstices the red pulp. The framework is composed of interlaced bundles of areolar tissue with a large amount of fine elastic tissue, and a few plain muscular fibres. In the spleen of the pig, the dog, and the cat, and to a smaller extent in that of the ox and sheep, there is a more abundant admixture of muscular elements. The spleen exhibits a regular rhythmic contractility, contracting and dilating about once a minute.[1] This action is readily increased by drugs and many animal extracts and is also influenced through the central nervous system.[2]

The **pulp** of the spleen is of a dark reddish-brown colour: when pressed out from between the trabeculæ it resembles clotted blood, and, like that, acquires a brighter hue on exposure to the air. In fact, what is thus pressed out from the

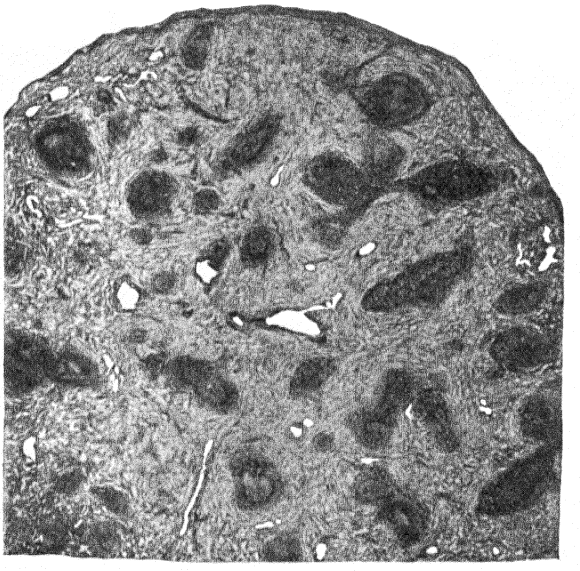


FIG. 605.—SECTION OF SPLEEN, SOMEWHAT MAGNIFIED. (G. Mann.)

The section was stained, and therefore the Malpighian corpuscles appear darker than the pulp. The venous sinuses show as clear spaces. The larger veins are contained in the trabeculæ.

dead spleen is mainly clotted blood which fills the interstices of the pulp and the venous sinuses which everywhere pervade it.

When a thin section which has been treated with dilute alkali or subjected to tryptic digestion and stained by iron hæmatoxylin is examined under the microscope, the pulp is seen to be everywhere pervaded by a reticulum of fine fibres continuous with the tissue of the trabeculæ (figs. 608, 609). These fibres are in the natural condition covered over and concealed by branched connective-tissue corpuscles. These are of various forms and sizes; in some parts little but the intercommunicating branches remaining, in other parts the cells being large and flat and in closer connexion. The corpuscles in question, which may be termed the *reticulum-cells* (fig. 610, *c*), contain each a round or oval nucleus, like that of a connective-tissue cell; and in teased-out preparations of the fresh spleen-substance it is not uncommon to find within them yellowish pigment-granules of various

[1] Roy, Journ. Physiol. iii. 1881. [2] Schäfer and Moore, Journ. Physiol. xx. 1896.

sizes. The interstices between the reticulum-cells are, in sections of the hardened organ, always found to be occupied by blood (fig. 610, *a*), white corpuscles occurring in larger proportion than in ordinary blood, especially in the neighbourhood of the Malpighian corpuscles to be immediately described. In close relation to the reticulum-cells, and occupying some of the smaller interstices between them, rounded, unbranched cells are seen, larger than white blood-corpuscles, but otherwise much resembling them (*spleen-phagocytes*, fig. 610, *d*). These cells are highly amœboid and phagocytic, and, as well as the reticulum-cells, often contain both red blood-corpuscles in various stages of disintegration, and clumps of pigment-granules. The phagocytes are also seen in the venules (fig. 610, *b*). Some observers have noted the presence of nucleated red corpuscles or erythroblasts (similar to

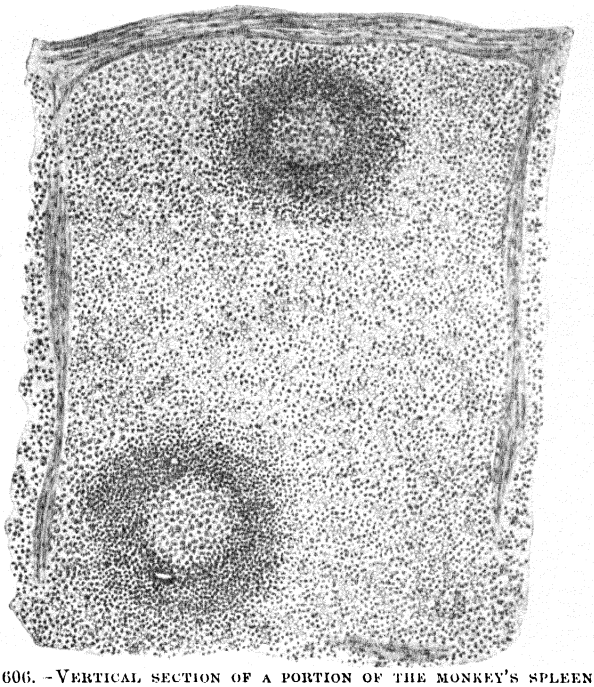


FIG. 606.—VERTICAL SECTION OF A PORTION OF THE MONKEY'S SPLEEN, AS SEEN WITH A LOW POWER. (Schäfer.)

those found in marrow) both in the splenic pulp and in the blood of the splenic vein; but these are difficult to find except in young animals or in animals which have a short time previously lost much blood. Giant-cells, with numerous or multi-lobed nuclei like those of bone-marrow, are also found in the pulp of fœtal and young animals (fig. 611).

Blood-vessels.—The splenic artery and vein, alike remarkable for their great proportionate size, having entered the spleen at the hilum by six or more branches, ramify in its interior, enclosed within the trabecular sheaths already described.

The smaller branches of the arteries have an adventitia derived from the trabeculæ, and pass into the proper substance of the spleen, dividing into small tufts of arterioles arranged in pencils (fig. 612). But before they thus terminate, the adventitious fibrous coat which is prolonged over them from the trabeculæ becomes transformed into lymphoid tissue, which forms a comparatively thick sheath along each. This lymphoid sheath is abruptly dilated here and there into small oval or spheroidal enlargements, measuring on an average 0.36 mm. in diameter, but varying in size from much smaller than this up to 1 mm., and closely

resembling the lymphoid follicles met with in the intestine and elsewhere. These lymphoid expansions may be seen on the surface of a fresh section of the organ as light-coloured spots scattered in the dark substance composing the pulp (but of a darker colour than the pulp in stained sections of the organ), and have been long noticed and described as the *Malpighian corpuscles* of the spleen (figs. 605 to 607 and 612). In some cases the corpuscle is developed only on one side of the arterial wall, upon which it then appears to be sessile; whilst in other instances—and this is the most frequent in the human subject—the expansion surrounds the vessel, which on section is seen to occupy a central or slightly excentric position within the corpuscle. In either case the artery sends off branches which supply capillaries distributed in the corpuscle.

In the guinea-pig the lymphoid tissue around the arteries is not swollen out into spherical Malpighian corpuscles, but its enlargement is uniform over a considerable length of the artery.

As just stated, the Malpighian corpuscles are localised expansions of the lymphoid tissue of which the external coat of the smaller arteries of the spleen is

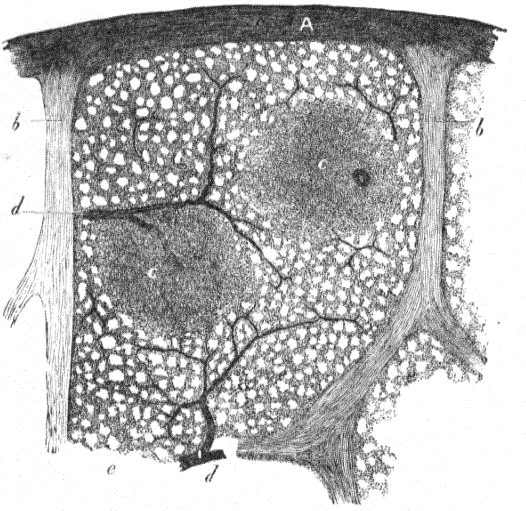


FIG. 607.—VERTICAL SECTION OF A SMALL SUPERFICIAL PORTION OF THE HUMAN SPLEEN. (From Kölliker.) Magnified with a low power.

A, peritoneal and fibrous covering; *b*, trabeculæ; *c*, *c*, Malpighian corpuscles, in one of which an artery is seen cut transversely, in the other longitudinally; *d*, injected arterial twigs; *e*, spleen-pulp. The clear spaces within this are the venous sinuses.

formed, and have apparently been produced, like the nodules found in lymph-glands and in other lymphoid organs, by increased multiplication of lymph-cells at certain spots (*germ-centres*, Flemming); the stainable particles of Flemming (see footnote 1 on p. 402) also occur in them. The reticulum of the lymphoid tissue is comparatively open, being almost absent towards the centre of the corpuscle: at the confines it becomes closer; there is, however, no distinct boundary separating it from the reticular tissue of the pulp. The tissue is densely packed with lymph-corpuscles, and traversed, as already stated, by capillaries.

The small arteries, shortly after leaving the Malpighian corpuscles, lose their lymphoid sheath and break up into branches. Structures described under the name 'ellipsoids,' which are formed of condensations of the reticular tissue of the spleen-pulp not loaded with leucocytes as in the Malpighian corpuscles, are found encircling the terminations of the arterioles. They are stated by W. Müller (bird) and

Whiting (cat) to be surrounded by a special sinus, but this is denied (for the cat) by Carlier. The arterioles end in the capillary vessels of the pulp. These capillaries soon

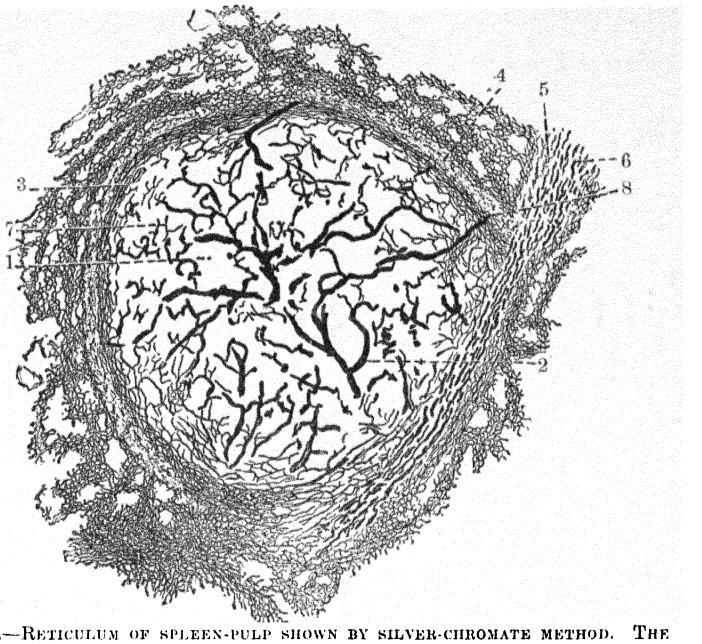


FIG. 608.—RETICULUM OF SPLEEN-PULP SHOWN BY SILVER-CHROMATE METHOD. THE CAPILLARIES OF A MALPIGHIAN CORPUSCLE ARE ALSO SEEN. (Oppel.)

1, Malpighian corpuscle; 2, small artery supplying it; 3, condensed reticulum around margin of corpuscle; 4, more open tissue outside this; 5, 6, wall of artery on which the corpuscle is seated; 7, capillaries of corpuscle; 8, branch of artery passing from Malpighian corpuscle to pulp.

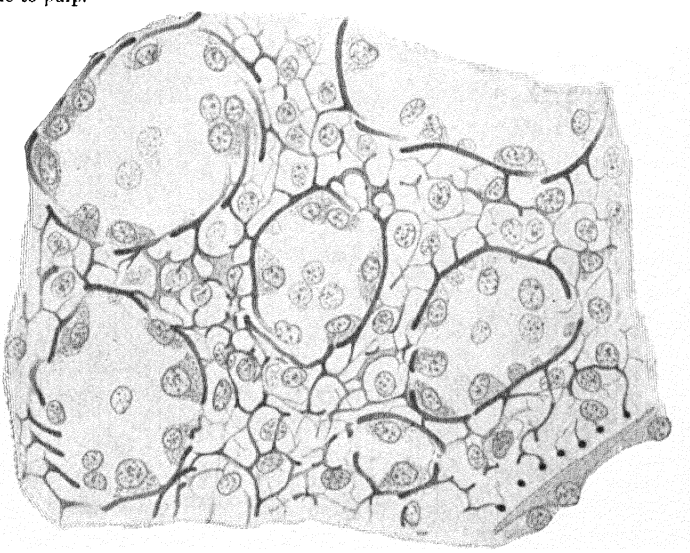


FIG. 609.—SMALL VEINS OF SPLEEN-PULP WITH RETICULAR TISSUE. (Hoyer.)

The veins, which are invested by encircling fibres, show gaps in their walls whereby they communicate with the interstices of the pulp.

lose their tubular character; the cells which compose their walls become partially separated from one another by elongated clefts; those at the extremity of the

capillary have branching processes and are united by these with the branched reticulum-cells of the pulp. In this manner the blood can flow directly into the

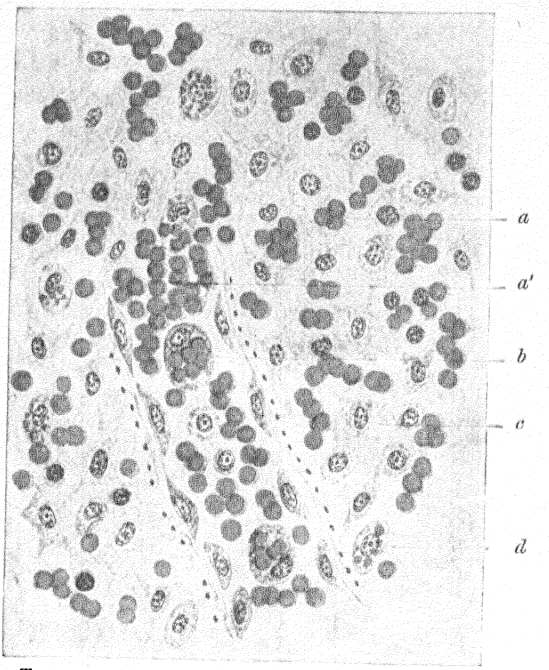


FIG. 610.—THIN SECTION OF SPLEEN-PULP OF CHILD, HIGHLY MAGNIFIED, SHOWING THE ORIGIN OF A SMALL VEIN IN THE INTERSTICES OF THE PULP. (Schäfer.) Magnified 400 diameters.

a, blood in pulp; *a'*, blood in vein; *b*, phagocyte in vein; *c*, reticulum-cell of pulp; *d*, phagocytic spleen-cell.

interstices of the pulp-tissue. The veins, which form a network of intercommunicating sinus-like spaces within the pulp (fig. 613), commence in the same manner as the capillaries terminate (figs. 609, 610); that is to say, the layer of endothelium no longer forms a complete tube, but gaps are left between the cells, the size of these gaps doubtless varying with the state of distension of the organ. The endothelium-cells of the venous sinuses appear ribbed longitudinally with fibres derived from the reticulum (fig. 614). The cell-bodies with their nuclei project somewhat into the lumen of the sinuses (fig. 615). In the human spleen, and in that of the monkey, the sinuses are encircled by ring-like anastomosing fibres (fig. 613) which are in continuity with the fibres of the pulp-reticulum, and according to S. Mollier the ring-fibres are conjoined to the longitudinal fibres just mentioned as producing a longitudinal ribbing on the endothelium; in this manner the reticulum of the pulp and the endothelial cells of the venous sinuses are intimately connected. The tissue of the pulp may be compared to a

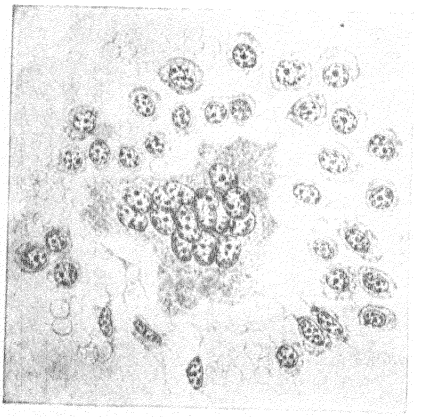


FIG. 611.—A GIANT-CELL FROM THE SPLEEN OF A KITTEN. (Schäfer.) Magnified 400 diameters.

sponge, with innumerable irregular interstices and larger channels—the venous sinuses—grooved out in it and leading into commencing veins.

The regular longitudinal and circular arrangement of fibres in the walls of the

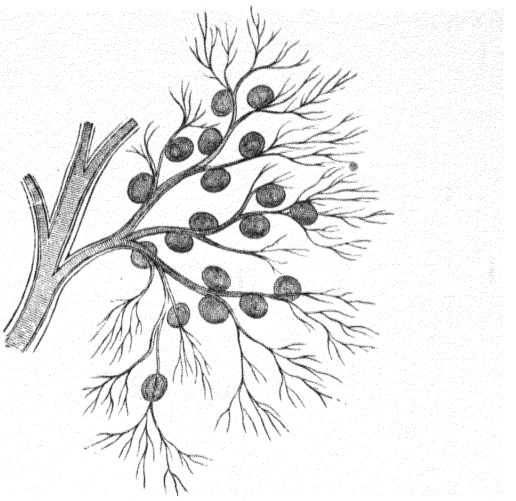


FIG. 612.—SMALL ARTERY FROM THE DOG'S SPLEEN WITH MALPIGHIAN CORPUSCLES ATTACHED. (Kölliker.) Magnified 10 diameters.

sinuses is seen in man and quadrumana (figs. 614, 615). In most other animals the arrangement is for the most part that of a uniform reticulum; although in

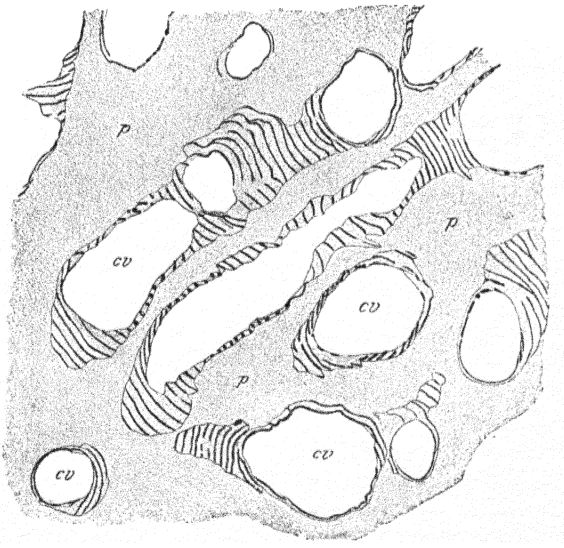


FIG. 613.—VENOUS SPACES OF SPLEEN PULP, SHOWING THE ENCIRCLING FIBRES IN THEIR WALLS. (v. Ebner.)

cv, capillary veins; *p*, pulp (the tissue-elements are not represented).

some there is displayed a tendency to such transverse and longitudinal arrangement (S. Mollier).

The small veins take a different course from the arteries, for they soon pass to the trabeculæ and are conducted upon and within these, freely joining and

anastomosing; whereas the arteries appear to have few or no anastomoses within the substance of the organ.

From the description above given, it would appear that the blood in passing through the spleen is brought into immediate relation with the elements of the pulp, and no doubt it undergoes important changes in the passage; in this respect resembling the lymph as it passes through the lymph-glands. Two modifications which are probably effected in it may be here pointed out. In the first place the lymphoid tissue ensheathing the arteries, together with that composing the Malpighian corpuscles, would appear, like the same tissue in the lymph-glands and other parts, to be the seat of the production of lymphocytes. At the circumference of this tissue, these can pass into the interstices of the pulp, and so into the blood. It is found, in fact, that the blood of the splenic vein is extremely rich in lymphocytes. In the second place, red blood-corpuscles may be taken up

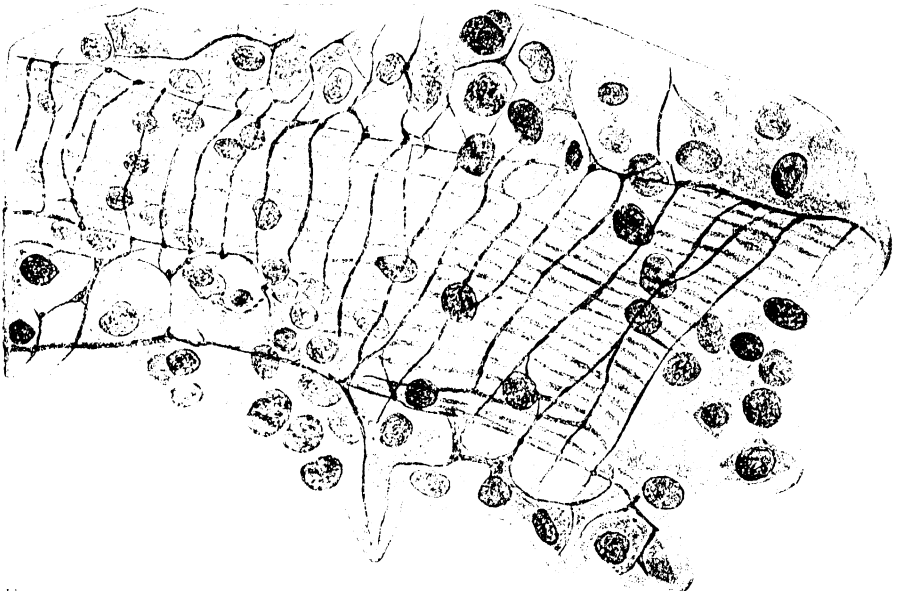


FIG. 611. SURFACE VIEW OF A VENOUS SINUS FROM SECTION OF PULP OF SPLEEN OF MONKEY. (S. Mollier.)

The longitudinal fibres of the wall of the sinus and the transverse fibres of the reticulum which encircle the sinus are well shown.

by the pulp-cells, their colouring-matter being transformed into pigment. The splenic cells have, indeed, been noticed, when examined on the warm stage, to take red corpuscles into their interior. Lastly, if it be the case that nucleated red corpuscles occur normally in the spleen, it may also be a seat of formation of coloured blood-corpuscles, at least in some animals.

According to F. P. Mall[1] the spleen may be regarded as composed of a great number of lobules about 1 mm. in diameter, imperfectly marked off from one another by the network of the trabeculæ. He describes each of these lobules as receiving a terminal arteriole, the capillary branches of which end in small expansions with incomplete walls, and the blood extravasates through side openings in them into the interstices of the pulp. The small veins, which form a plexus within the lobule, have similar lateral openings, so that on contraction of the organ the blood passes into them out of the pulp interstices.

The description of an interstitial circulation in the spleen was originally given by Stieda and was strongly advocated by W. Müller.[2] Previous to Müller most authorities considered that the

[1] Johns Hopkins Hospital Bulletin, ix. 1898, also Amer. Journ. Anat. ii. 1902.
[2] Article 'Spleen' in Stricker's Handbook of Histology, 1871.

extravasation of blood into the pulp is artificial, and that there is a closed circulation in the organ. This opinion is still held by some modern writers on the spleen.

The **lymphatics** of the spleen form two systems, a *trabecular* and a *perivascular*. The vessels belonging to the former system run in the trabeculæ and are in communication with a superficial network in the capsule. The perivascular lymphatics take origin in the lymphoid tissue which has already been noticed as ensheathing the smaller arteries, and forming the Malpighian corpuscles. After leaving the

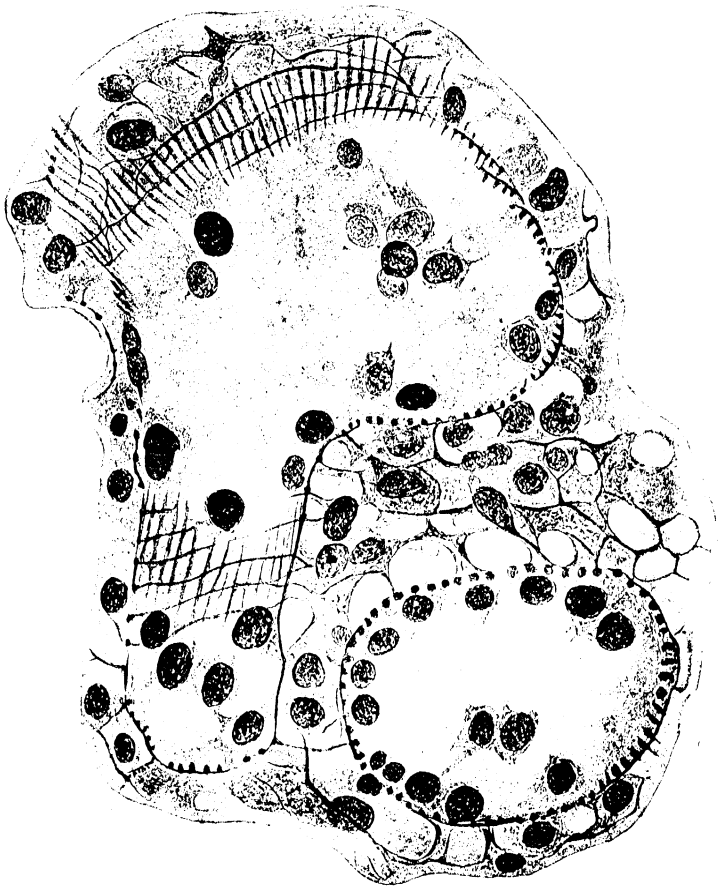


FIG. 615. FROM A SECTION OF SPLEEN OF MONKEY, SHOWING THE LONGITUDINAL AND CIRCULAR FIBRES OF THE WALLS OF THE VENOUS SINUSES OF THE PULP. (S. Mollier.)

Two sinuses are shown as well as some of the reticular cells and fibres of the pulp. One of the sinuses is cut obliquely, and a branch from it is partly seen in longitudinal section; the other one is cut almost exactly transversely, so that the longitudinal fibres of its wall are cut across and appear as a row of dots. Notice the prominent nuclei of the endothelium-cells.

lymphoid tissue the lymphatics commonly run in pairs, one on either side of an artery, uniting over it by frequent anastomoses, and sometimes partially or wholly enclosing it. At the hilum the two sets of lymphatics join one another and proceed along with the main blood-vessels, ultimately passing into lymph-glands at the back of the abdomen.

The above description of the course of the lymphatics applies rather to the spleen of animals than that of man, in which lymphatics have not been followed into the interior of the organ, except near the hilum.

The **nerves,** which are almost entirely non-medullated, are derived from the solar plexus. They surround and accompany the splenic artery and its branches and are distributed to the vessels of the organ and to the plain muscular tissue of the framework, but their precise mode of termination here has not as yet been worked out. The preganglionic nerves to the spleen are derived from the thoracic ventral roots from the third downwards and from the first lumbar on both sides, but more from the left spinal roots than from the right.[1]

The following additional articles on the spleen may be mentioned: Billroth, Virch. Arch. xx. 1861; Denys, Bulletin de l'académie royale de médecine de Belgique, 1888 (destruction of blood-corpuscles); Boehm, Kupffer Festschrift, 1899; v. Ebner, Anat. Anz. xv. 1899; Bannwarth, Archiv f. mikr. Anat. xxxviii. 1891; A. Oppel, Anat. Anz. vi. 1891 (reticulum); Eliasberg, Inaug. Diss. Dorpat, 1893 (formation of blood-corpuscles); Fusari, Arch. ital. de biol. xix. 1893 (nerves); H. Hoyer, Anat. Anz. xvii. 1900, and Morphol. Arbeit. iii. 1894; A. Koelliker, Sitzsb. d. Würzb. phys.-med. Ges. 1893 (nerves); Carlier, Journ. of Anat. and Physiol. vol. xxix. 1895 (reticulum); Kulschitzky, Arch. f. mikr. Anat. xlvi. 1895: Schumacher, Arch. f. mikr. Anat. lv. 1900 and Anat. Anz. xviii. 1900 (elastic tissue); Keyes, Amer. Journ. Anat. i. 1901 (framework); Weidenreich, Arch. f. mikr. Anat. lxviii. 1901, and Ergebn. d. Anat. 1903, 1904; Helly, Arch. f. mikr. Anat. lix. 1901, lxi. 1903, lxx. 1907 (closed vascular system); Janošik, Arch. f. mikr. Anat. lxx. 1907 (closed vascular system); T. Lewis, Int. Monthly Journ. Anat. and Physiol. xx. 1902; A. Noll, Ergebn. d. Phys. 1903 (formation and regeneration of red corpuscles); G. Retzius, Biol. Unters. iii. 1892; J. Seeman, 'Die blutbildende Organe,' Ergebn. d. Phys. 1904; Marigubi-Kudrjavtzewa, Anat. Hefte, xxxix. 1909; S. Mollier, Arch. f. mikr. Anat. lxxvi. 1911.

[1] Schäfer and Moore (in the dog), *op. cit.*

SEROUS MEMBRANES.

The **serous membranes** are so named from the apparent nature of the fluid with which their surface is moistened. They line cavities of the body which have no obvious outlet. The chief examples are, the *peritoneum*, the largest of all, lining the cavity of the abdomen; the two *pleuræ* and the *pericardium* in the chest; and the *tunica vaginalis* surrounding each of the testicles within the scrotum.

Form and arrangement.—In all cases a serous membrane has the form of a closed sac, one part of which is applied to the walls of the cavity which it lines, the *parietal* portion; whilst the other is reflected over the surface of the organ or organs contained in the cavity, and is therefore named the *reflected* or *visceral* portion of the membrane. Hence the viscera in such cavities are not contained within the sac of the serous membrane, but are really placed external to it; seeming to

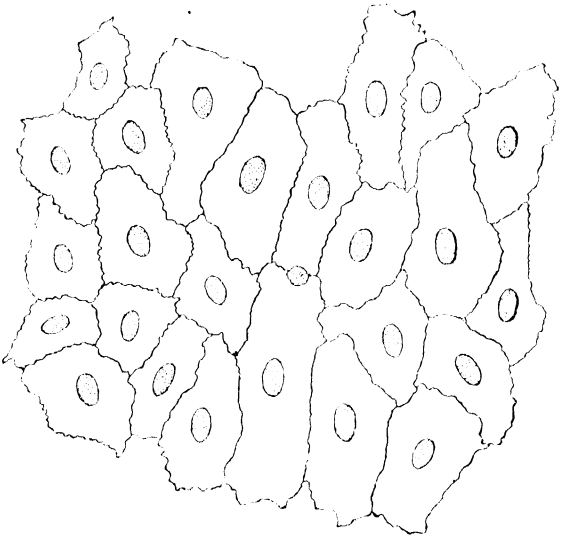


FIG. 616.—PAVEMENT EPITHELIUM (ENDOTHELIUM) FROM THE OMENTUM OF THE RABBIT. Nitrate of silver staining. (Schäfer.)

push inwards the part of the membrane which immediately covers them, some organs receiving in this way a complete, and others only a partial investment.

In passing from one part to another the membrane frequently forms folds, as, for example, the folds (or 'ligaments') of peritoneum passing between the liver and the parietes of the abdomen. Such folds are sometimes designated by special names, *e.g.* the mesentery, the mesocolon, and the omentum.

The peritoneum in the female sex is an exception to the rule that serous membranes are perfectly closed sacs, inasmuch as it has two openings by which the Fallopian tubes communicate with its cavity.

A serous membrane sometimes lines a fibrous membrane, as in the case of the parietal pericardium. Such a combination has been named a *fibro-serous* membrane.

The inner surface of a serous membrane is free, smooth, and polished; and, as would occur with an empty bladder, the inner surface of one part of the sac is applied to the corresponding surface of some other part; a small quantity of fluid, usually just sufficient to moisten the contiguous surfaces, being interposed.

The parts situated in a cavity lined by serous membrane, being themselves covered by it, can thus glide easily against its parietes or upon each other, and their motion is rendered smoother by the lubricating fluid.

The outer surface most commonly adheres to the parts which it lines or covers, the connexion being effected by means of areolar tissue, named therefore 'subserous,' which, when the membrane is detached, gives to its outer and previously adherent surface a flocculent aspect. The degree of firmness of the adhesion is very

Fig. 617. Endothelium-cells of serous membrane, seen in profile view, showing protoplasmic bridges stretching across the intercellular spaces.

(M. Heidenhain.)

various: in some parts the membrane can scarcely be separated; in others its attachment is so lax as to permit easy displacement.

Structure and properties.—Serous membranes are thin and transparent, so that the colour of subjacent parts shines through them. They are tolerably strong, with a moderate degree of extensibility and elasticity. They are lined on the inner surface by a simple layer of clear flattened irregularly polygonal cells (*serous endothelium*, (fig. 616), each of which contains a round or oval nucleus with one or two nucleoli, and an intranuclear network. The outlines of the cells may readily be

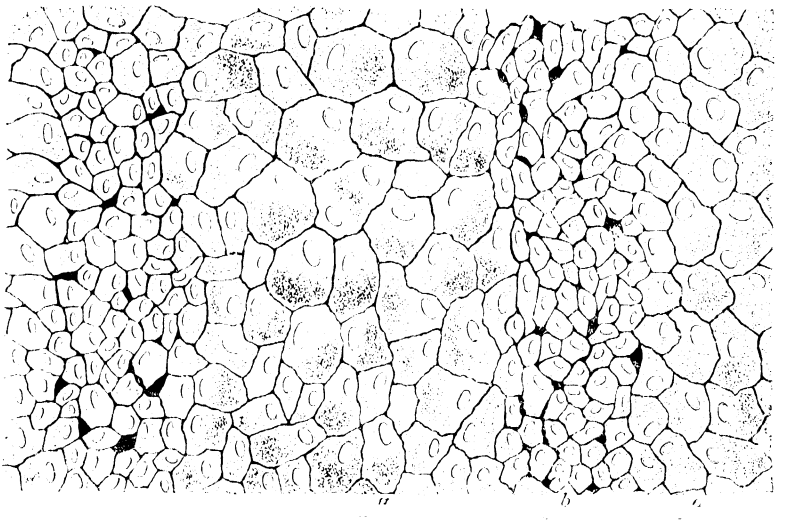


Fig. 618. Portion of endothelium of peritoneum from the under surface of the rabbit's diaphragm. (Klein.)

a, larger cells; *b*, small ones, with here and there a pseudostoma between.

brought into view by treatment with nitrate of silver. The intercellular lines of junction which are thus made evident may be straight and even, but are most commonly slightly jagged or sinuous. They are not everywhere completely separated from one another by cement-substance, but may be interconnected by protoplasmic bridges (fig. 617), which stretch across the intervals between adjacent cells.[1] According to Kolossow there is a thin cuticular layer on the free surface of the endothelium-cells of serous membranes. This cuticle may show vertical striations.[2]

[1] A. Kolossow, Arch. f. mikr. Anat. xlii. 1893. [2] Cf. v. Brunn, Centralbl. f. Path. xi. 1900.

The endothelium-cells of a serous membrane are connective-tissue cells of the lamellar type. In some situations they are the only cells in the tissue. This is the case, for example, in the omentum of the cat.[1]

Here and there between the cells apertures are to be seen, which are of two kinds. The smaller (fig. 618), which are also the more numerous, are occupied either by an accumulation of the intercellular substance or by processes sent up to the surface of the membrane from more deeply lying cells (*pseudostomata* of Klein and Burdon-Sanderson): the larger ones, on the other hand, are true apertures (*stomata*), around which the endothelial cells have a tendency to a radial arrangement: they are in some situations surrounded by a ring of small cubical cells (fig. 619, *s*, *s*). The true stomata always open into a subjacent lymphatic vessel, either directly or by the medium of a short canal lined with cubical cells. The surface cells of the serous membrane are not everywhere uniform in size, but patches are here and there met with in which they are small and granular in appearance, and it is in these parts that the stomata and pseudo-stomata are most frequently seen (figs. 618, 619).

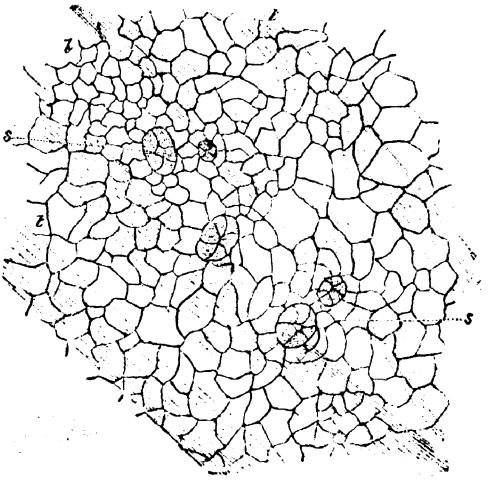


FIG. 619.—SMALL PORTION OF PERITONEAL SURFACE OF DIAPHRAGM OF RABBIT. (Klein.) Magnified.

l, lymph-channel below the surface, lying between tendon-bundles, *t*, *t*, and over which the surface-cells are seen to be relatively smaller, and to exhibit five stomata, *s*, *s*, leading into the lymphatic. The epithelium of the lymphatic channel is not represented.

The stomata were discovered in the peritoneal covering of the central tendon of the diaphragm by v. Recklinghausen, who found that milk-globules could be made to pass through them into the lymphatics. Similar apertures were found by Ludwig and Dybkowsky in the pleura of mammals, and by Schweigger-Seidel and Dogiel in the septum between the peritoneal cavity of the frog and the great lymph-sac (cisterna magna) behind it (fig. 620). They have since been described on the omentum by Klein, and have also been recognised in the pericardium. They are not always easy to find,[2] but their existence can readily be shown by introducing fluid containing very fine granules in suspension into the peritoneal cavity of a living animal, and examining the lymphatics of the central tendon after the lapse of an hour or two. They are very easily seen in microscopic preparations of the dorsal peritoneum of the frog.

Underneath the endothelium the membrane is composed of a connective-tissue ground-substance in which are fibres, both white and elastic. The elastic fibres in many serous membranes, as remarked by Henle, are principally collected into a reticular layer near the surface (fig. 621), although they also pervade the rest of the thickness of the membrane. The bundles of white fibres are also arranged in a reticular manner, frequently uniting with one another, and the meshes of the reticulation which they form are occupied by the ground-substance of the membrane, and bridged over by the flattened cells of the general surface. In some of the folds formed by serous membranes and especially in the great omentum of many animals, including man, the meshes of the reticulation have become open in many parts owing to the absorption of the intervening ground-substance and the

[1] Gronroos, Anat. Hefte, xxii. 1903.
[2] A. W. Meyer, Studies from the Anat. Depart. of the University of Wisconsin, 1900.

perforation of the cells covering it, so as to allow of a free communication between the two sides of the fold of membrane. In the thicker parts of a serous membrane, the ground-substance contains blood-vessels and lymphatics, often with lymphoid and adipose tissue; besides connective-tissue corpuscles with their corresponding cell-spaces (fig. 547), which in the serous membranes are very often collected into endothelium-like patches. In parts of the membrane in which the connective-tissue cells are more thinly scattered, they possess branching processes, some of which intercommunicate with those of neighbouring cells: others may pass up to the surface of the membrane as pseudo-stomata and others again become connected to the walls of the lymphatics and blood-vessels.

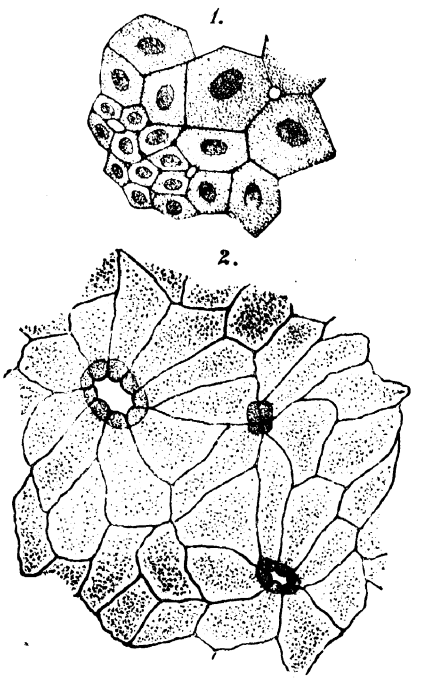


FIG. 620.—1. EPITHELIUM FROM THE POSTERIOR PART OF THE FROG'S PERITONEUM, SHOWING THREE STOMATA LEADING INTO THE CISTERNA LYMPHATICA MAGNA. (v. Ebner, after Schweigger-Seidel and Dogiel.)

2. A PORTION OF EPITHELIUM FROM THE PERITONEAL SURFACE OF THE RABBIT'S DIAPHRAGM. THREE PORES ARE VISIBLE BETWEEN THE EPITHELIUM-CELLS. (v. Ebner, after Ludwig and Schweigger-Seidel.)

In the human subject, the serous membranes are bounded under the epithelium by a basement-membrane (Bizzozero).

The **blood-vessels** of the membrane end in a capillary network with comparatively wide meshes, which pervades the subserous tissue and the tissue of the serous membrane. The vessels are much more numerous in the nodules and tracts of lymphoid tissue (see below) as well as in the adipose tissue, which is found largely developed in the serous membranes of fat animals.

The **lymphatics** of the serous membranes are abundant. Their relation both to the cell-spaces of the tissue and to the surface of the membrane, as well as their general arrangement, has been already noticed (p. 356).

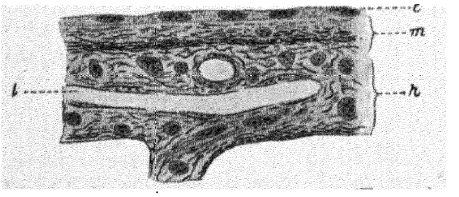


FIG. 621.—SECTION OF PLEURA OX. (Favaro.) Magnified 270 diameters.

e, endothelium; *m*, substance of membrane with numerous elastic fibres; *h*, hypo-pleura; *l*, lymph-vessel.

Nodules of lymphoid tissue may occur in the substance of the serous membranes, but they are never sharply circumscribed. More generally the lymphoid tissue takes the shape of elongated tracts which follow the course of the small blood-vessels, receiving from the latter branches which divide to form a capillary network. Lymph-vessels run in these tracts alongside the blood-vessels, and often partially enclose them. These lymphoid nodules and tracts are more numerous in the young animal; in the adult their place is frequently taken by lobules and tracts of adipose tissue.

The **nerves** of serous membranes are partly destined for the blood-vessels and for the most part accompany these in their course. Some fibres, however, are distributed to the substance of the membrane, in which they form a plexus with large meshes: from the branches of this plexus fibres may be traced which unite

into a somewhat finer plexus near the surface, where the nerve-fibres end in terminal ramifications and in end-bulbs. In the deeper parts of some serous membranes Pacinian corpuscles occur. These terminations have already been considered (pp. 263, 267, 275, and figs. 412, 413, 421, and 436).

Development of the serous membranes.—The serous cavities are all developed from the cœlomic split which occurs in the lateral mesodermic sheet at an early stage of embryonic history. The mesoderm-cells which line the cavity of the intra-embryonic cœlom [1] become the endothelium of the serous membrane and the adjoining mesoderm becomes developed into the connective tissue of the serous membrane. The connexion of the cavities of these membranes with lymph-vessels, which, as well as blood-vessels and nerves, penetrate freely into the serous membrane and ramify near its free surface, is established later by the formation of stomata. The serous cavities, therefore, although moistened with a fluid of the general nature of lymph, are not strictly speaking to be regarded as enlarged lymph-spaces like those which occur so extensively under the skin of the frog.

[1] An account of the formation of the cœlom and the subsequent changes which occur in it and result in its subdivision into the several serous cavities will be found in the part of this work (Vol. I.) which deals with Embryology.

Synovial membranes are connective-tissue membranes which are found surrounding closed cavities in connexion with movable structures in certain parts, such as the joints, the elongated sheaths in which some tendons glide, and at various situations between the skin and bony prominences below it. Synovial membranes are distinguished by the nature of their secretion, which is not lymph, like that moistening the serous membranes, but a viscid glairy fluid resembling the white of an egg and named *synovia*. From its nature it is well adapted for diminishing friction and thereby facilitating motion.

If a drop of synovial fluid is examined microscopically, it is found to contain (in addition to fat-molecules) a few amœboid corpuscles (leucocytes), as well as detached cells similar to those which occur on the projections of the membrane.

The different synovial membranes of the body are referred to three classes, viz. *articular*, *vaginal*, and *vesicular*.

1. *Articular synovial membranes*, or *synovial capsules of joints*.—These by their secretion lubricate the cavities of the diarthrodial articulations—that is, those articulations in which the opposed surfaces glide on each other. In these cases the membrane may be readily seen covering internally the surface of the capsular and other ligaments which bound the cavity of the joint,

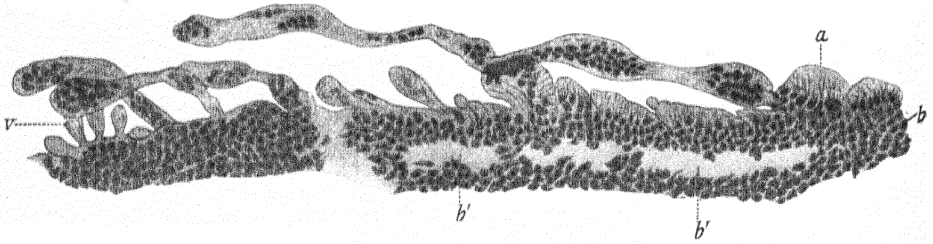


FIG. 622.—HAVERSIAN FRINGES SEEN AT THE EDGE OF A FOLD OF SYNOVIAL MEMBRANE. (Hammar.)
a, free surface of the membrane with long and short villi (*V*), some of the shorter villi being free from cells; *b*, portion of membrane closely packed with cells; *b*,' *b*,' portions without cells.

and affording also an investment to any tendons or ligaments which pass through the articular cavity, as in the instance of the long tendon of the biceps muscle in the shoulder-joint. On approaching the articular cartilages the membrane does not pass over them, but terminates after advancing but a little way on their surface, with which it is here firmly adherent. The synovial membranes, therefore, do not form closed bags lying between the articular cartilages, as was supposed by the older anatomists, for the main part of the surfaces of the joints is not covered at all by the membrane, nor even by a layer of epithelium-cells, prolonged from the membrane, as some have described.

In several of the joints, folds of the synovial membrane pass across the cavity; these have been called synovial ligaments. Other processes of the membrane simply project into the cavity at various points. These are very generally cleft into fringes at their free border (fig. 622), upon which their blood-vessels, which are numerous, are densely distributed. The larger folds and processes often contain fat, and then are sufficiently obvious; but many of the folds are small and inconspicuous.

The fringed vascular folds of the synovial membrane were described by Havers in 1691, under the name of the *mucilaginous glands*; he regarded them as an apparatus for secreting synovia. Rainey found that these *Haversian fringes*, as they are sometimes called, may exist in all kinds of synovial membrane, and that from the primary vascular fringes other smaller secondary processes are sent off, into which no blood-vessels enter.

2. *Vaginal synovial membranes*, or *synovial sheaths*.—These are adapted to facilitate the motion of tendons as they glide in the fibrous sheaths which bind them down against the bones in various situations. The best-marked examples of such fibrous sheaths are to be seen in the hand and foot, and especially on the palmar aspect of the digital phalanges, where they confine the long tendons of the flexor muscles. In such instances one part of the synovial membrane forms a lining to the osseo-fibrous tube in which the tendon runs, and another part affords a close investment to the tendon. The space between these portions of the membrane is lubricated

with synovia and crossed obliquely by one or more folds or duplications of the membrane, named "frœna," which in some parts inclose a considerable amount of elastic tissue (J. Marshall).

3. *Vesicular* or *bursal synovial membranes, synovial bursæ, bursæ mucosæ.*—In these the membrane has the form of a simple sac, interposed, so as to prevent friction, between two surfaces which move upon each other. The synovial sac in such cases is flattened and has its two opposite sides in apposition by their inner surface, which is free and lubricated with synovia, whilst the outer surface is attached by areolar tissue to the moving parts between which the sac is placed.

In regard to situation, the bursæ may be either deep-seated or subcutaneous. The former are for the most part placed between a muscle or its tendon and a bone or the exterior of a joint, less commonly between two muscles or tendons: the bursæ situated in the neighbourhood of joints not infrequently open into them. The subcutaneous bursæ lie immediately under the skin, and are found in various regions of the body interposed between the skin and some firm prominence beneath it. The large bursa situated over the patella is a well-known example of this class. Similar though smaller bursæ are found over the olecranon, the malleoli, the knuckles, and various other prominent parts. It must, however, be observed that among these subcutaneous bursæ are reckoned some which do not always present the characters of true synovial sacs, but look more like mere recesses in the subcutaneous areolar tissue, larger and more defined indeed than the neighbouring areolæ, but not bounded by an evident synovial membrane. These may be looked on as examples of less developed structure, forming a transition between the areolar-tissue spaces and perfect synovial cavities; indeed it may happen that what

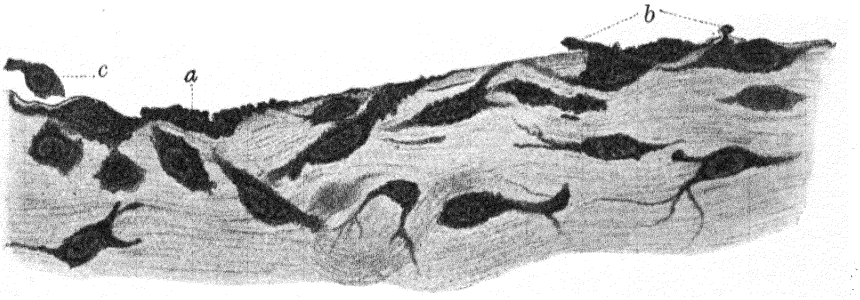


FIG. 623.—SECTION OF A SYNOVIAL MEMBRANE. (Hammar.) Highly magnified.
a, a superficial cell, lying on the inner surface; *b*, other superficial cells partly embedded in the membrane, but with projections beyond the surface; *c*, a detached cell within the cavity.

is a well-developed synovial bursa in one subject is merely an enlarged areola in another. Many of the bursæ do not appear until after birth, and they are said to increase in number as age advances.

Structure of synovial membranes.—The synovial membranes are composed entirely of connective tissue with the usual cells and fibres of that tissue. Some of the cells near the surface of the membrane exhibit peculiarities of staining reaction which, according to Hammar,[1] entitle them to the specific designation of 'synovial cells,' but in general appearance all closely resemble branched 'lamellar' connective-tissue cells (fig. 623). It was formerly stated, and is still asserted by some authors, that synovial membranes are lined with an endothelial layer of flattened cells, similar to those lining the serous membranes, but, as was shown by Hüter, there exists no complete lining of the kind. Here and there, it is true, patches of cells may be met with which present an epithelioid appearance (fig. 624, *e*), as, indeed, we know to be the case in the connective tissue of other parts; but most of the surface-cells of the synovial membranes are of the irregularly branched type (fig. 625), the surface of the membrane between the cells and sometimes also over them being formed by the ground-substance of the connective tissue, whilst here and there small blood-vessels come close to the surface from subjacent parts. The cells are in many places smaller than in connective tissue generally. They vary much in shape in different situations, sometimes forming a network in the tissue by the anastomosis of their ramifying processes, in other parts being rounded, and more

[1] Arch. f. mikr. Anat. xliii. 1894.

closely arranged. As Hammar has shown, some parts of the membrane are much richer in cells than others. Many of the smaller synovial villi (see below) contain very few cells, or even none at all (fig. 622).

The cells of a vaginal synovial membrane are often slightly elongated in the direction of the axis of the tendon.

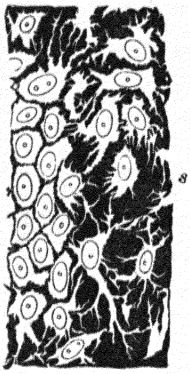


FIG. 624.—PORTION OF THE SURFACE OF A VAGINAL SYNOVIAL MEMBRANE, AFTER TREATMENT WITH NITRATE OF SILVER. (Reyer.) 250 diameters.

The cell-spaces of the tissue and the nuclei of the contained cells only are represented.

e, epithelioid arrangement of cells; *s*, ramified cells.

FIG. 625.—RAMIFIED CONNECTIVE-TISSUE CORPUSCLES, FROM ARTICULAR SYNOVIAL MEMBRANE OF OX. Chloride of gold preparation. (Reyer.) 250 diameters.

The articular synovial membranes pass, as before said, a certain distance over the cartilages of the joints. They do not, however, end abruptly, but shade off gradually into the margin of the cartilage, the fibrous tissue becoming fibro-cartilage and the cells gradually losing their processes and becoming transformed into cartilage-cells

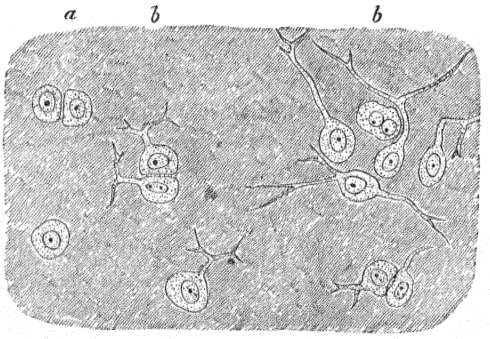


FIG. 626.—TRANSITION OF CARTILAGE-CELLS INTO CONNECTIVE-TISSUE CORPUSCLES OF SYNOVIAL MEMBRANE. FROM HEAD OF METATARSAL BONE, HUMAN. (Schäfer.) About 340 diameters.

a, ordinary cartilage-cells; *b*, *b*, with branch processes.

(fig. 626), so that it is difficult to say where the one structure begins and the other ends. This portion of the synovial membrane, or of the cartilage, is known as the 'marginal zone'; it is best marked around the convex heads of the bones, and is especially well seen near the lower margin of the patella (Hüter).

The Haversian folds, at least the larger ones, agree in general structure with the rest of the tissue of the synovial membrane, being vascular folds of that membrane, the largest of them usually containing fat; their surface layer consists for the most

part of irregularly stellate cells, except over the fat, where there is occasionally to be observed a true epithelioid covering like that of a serous membrane. The smaller folds are less liable to contain fat and are highly vascular. Their capillaries form loops near the margin. They are beset, as already stated, with non-vascular *secondary fringes* (Rainey) or *synovial villi* (Luschka). These (fig. 622) are small, variously shaped processes—often fungiform, sometimes finger-shaped, occasionally having the form of a thickened leaf—projecting from the margins of the folds, and consist for the most part of a strand of connective-tissue fibrils (fig. 627); they also contain groups of small rounded cells with granular protoplasm and in some cases a few cartilage-cells. The vascular folds are most common near the attachment of the membrane to the edge of the articular cartilage.

Vessels and lymphatics.—The blood-vessels in and immediately beneath the synovial membrane are numerous in most parts of the joints. They advance but a short way upon the cartilages, forming around the margin a vascular zone, named by William Hunter 'circulus articuli vasculosus,' in which they end by loops of vessels dilated at the bent part greatly beyond the diameter of ordinary capillaries (Toynbee). In the fœtus these vessels advance further upon the surface of the cartilage than in the adult. The vessels of the vaginal synovial membranes are less numerous than those of the synovial membranes of the joints.

The synovial cavities do not have the same relation to the lymphatic system as the serous. For although lymphatic vessels have been described by Tillmanns and others in the synovial membranes, they have not been shown to communicate by stomata with the cavities, nor do they as a rule lie near the free surface. In this respect they differ from the blood-capillaries, which come close up to the inner surface of the membrane.

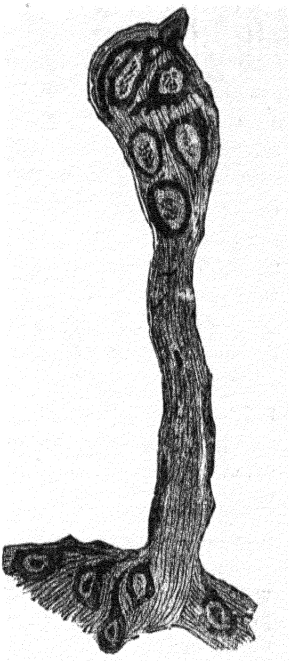


FIG. 627.—VILLUS OF SYNOVIAL MEMBRANE. (Hammar.) Highly magnified.

Nerves.—W. Krause described the nerves of the synovial membranes (at least those of the joints) as terminating in peculiar corpuscles (articular end-bulbs) (p. 263, and fig. 415). Nicoladoni traced nerves into a plexus of pale fibrils lying close under the surface of the membrane. Pacinian corpuscles have also been noticed under the synovial membranes in many places.

Development.—At the time of the formation of a joint by cleavage the tissue around it forms, in its outer part, the fibrous capsule of the joint; in its inner part, the commencement of the synovial membrane. The cartilage-cells on the surfaces of the newly formed joint are at first, like those of the embryonic cartilage generally, placed closely together without matrix or intercellular substance; after a time this appears in fine lines between the cells, so that in silvered preparations an epithelioid appearance is presented. By a further development of intercellular substance the superficial cells become more separated from one another, and now possess an irregularly branched shape with communicating processes. Near the edge of the cartilage this condition is permanent, so that the marginal zone of the synovial membrane is formed *in situ* from what was originally cartilage. Nearer the centre of the articular surface, a further change takes place in the progress of development. The cells lose their processes and acquire the characters of ordinary cartilage-cells, whilst the matrix between them becomes increased, and forms also a thin layer covering their surface. In some places, *e.g.* the glenoid cavity of the articulation of the lower jaw, the transformation into ordinary cartilage-cells may be incomplete, so that the synovial membrane extends over a larger extent of the articular surface than usual.

SECRETING GLANDS.

A secreting gland is an organ the cells of which produce substances destined to serve some purpose useful to the organism or to remove substances which would be harmful (excretion). The cells obtain from the lymph- or blood-plasma the materials which furnish the products of their secretion, and either pour out such products by means of a duct upon an internal or external surface, or again discharge the elaborated products into the lymph- or blood-vessels. Those which discharge these secretions by means of ducts are distinguished as *externally secreting glands*, or frequently as 'secreting glands' simply; those which pass their secretion into the lymph- or blood-vessels are known as *internally secreting glands*, or, from being unprovided with a duct, as 'ductless glands.' But this last name has been used to include organs that are not, strictly speaking, secreting glands at all, such as the spleen and lymph-glands, which are now known to have totally different functions, connected with the formation or destruction of the morphological constituents of the blood. It will therefore be better to discard the use of the term 'ductless glands' and to speak of the organs which were formerly grouped under that head either as 'glands of internal secretion' or as 'lymph-glands' and 'hæmal glands,' according to their respective functions. Of these the lymph- and hæmal glands have already been described. The glands of internal secretion differ so much from one another in the details of their structure that no general description is applicable to them. This is, however, not the case with the externally secreting glands, the general features of which may first be noticed.

The reproductive glands—ovary and testicle—represent a different class from any of the other externally secreting glands, for their secretion-products, although discharged by a duct on a free surface, do not consist merely of substances formed in and extruded from cells, but of complete cells, which become detached as such from the organ that forms them, and carried away from it along with fluid likewise produced by the gland.[1]

Some of the externally secreting glands have as a second function the production of materials which pass into the blood and serve to produce changes in other organs. Thus the pancreas produces a material which, after its passage into the blood, exercises an important influence on the metabolism of carbohydrates both in the liver and elsewhere, and the generative glands produce substances which enter the blood and affect the growth of a variety of organs, the secondary sexual characters being thereby mainly produced. Such glands must be reckoned as internally secreting as well as externally secreting organs.

EXTERNALLY SECRETING GLANDS.

These organs vary enormously in size and complexity of structure, but they all agree in being composed of epithelial cells, the secretion of which is conveyed away from the gland by a duct or ducts opening either upon the surface of the skin or on some internal surface (such as that of the alimentary canal) lined by mucous membrane and communicating with the exterior. In some situations secreting cells are not accumulated into a compact organ, but merely cover or line a secreting surface (which may, however, be increased by being thrown into folds, as in the case of the serous and synovial membranes, and the choroid plexuses within the ventricles of the brain). This is also the case with the layer of cells which covers many mucous surfaces within the body, the mucus moistening such surfaces being in many cases produced not by special glands, but by some (or all) of the covering epithelial cells; whereas in other situations the membrane is covered by a non-secreting stratified epithelium, and the mucous or serous secretion, as

[1] The reproductive glands are classed by Minot along with the organs which produce erythrocytes and leucocytes under the general head of *cytogenic glands* (Amer. Journ. Anat. iv. 1905).

the case may be, is entirely formed and poured out upon the surface by glands which lie beneath the mucous membrane and send their secretion to the surface by ducts which penetrate the epithelium.

The principal externally secreting glands are :

(A) Glands of the alimentary canal, viz. : (1) the small mucous or serous glands which occur under the mucous membrane throughout the whole extent of the nose, mouth, throat, and gullet, and in the trachea and bronchi ; (2) the salivary glands, including the parotid, submaxillary, and sublingual in man, and the infraorbital and retrolingual in animals ; (3) the gastric glands ; (4) the glands of Brunner and the crypts of Lieberkühn of the small intestine ; (5) the liver ; (6) the pancreas ; (7) the crypt-like glands of the large intestine ; (8) the small mucous glands of the anus.

The lungs may also be reckoned amongst the glands which open into the alimentary canal, for they resemble secreting glands both in the general features of their structure and in their mode of development.

(B) Glands of the urino-generative apparatus, viz. : (1) the kidneys ; (2) the ovaries and testicles ; (3) the small glands of the uterus ; (4) Cowper's glands ; (5) the glands of Bartholin ; (6) the seminal vesicles ; (7) the glands of the prostate and urethra.

(C) Glands, the secretion of which is conducted to the surface of the skin, viz. : (1) the sudoriparous or sweat-glands ; (2) the sebaceous glands ; (3) the Meibomian glands of the eyelids ; (4) the ceruminous glands of the external auditory canal ; (5) the mammary glands ; (6) the lacrymal glands.

Modifications in form of the secreting surface.—A secreting apparatus effectual for the purpose it is destined to fulfil may be said essentially to consist of a layer of secreting cells covering a free surface, whilst a layer of finely ramified blood-vessels is generally spread out close to the attached ends of the cells, with sometimes a basement-membrane between the two. But whilst the structure may remain essentially the same, the configuration of the secreting surface presents various modifications in different secreting organs. In some cases the secreting surface is plain, as in various parts of the serous, synovial, and mucous membranes, which may be looked on as examples of comparatively simple forms of secreting apparatus ; but, in other instances, and particularly in the special secretory organs named glands, the surface of the secreting membrane is variously folded and involved. An obvious effect of this complication is to increase the extent of the secreting surface in a secreting organ within a given bulk, and thus augment the quantity of secretion yielded by it. No connexion has been clearly shown to exist between the *quality* of the secretion and the particular configuration, either internal or external, of the organ ; on the other hand, we know that the same kind of secretion that is derived from a complex organ in one animal may be produced by an apparatus of most simple form in another.

There are two principal modes by which the surface of a secreting membrane is increased in extent, namely, by rising or protruding in form of a prominent fold or some otherwise shaped projection, or by retiring, in form of a recess.

The first-mentioned mode of increase, that by *protrusion*, is not the one most generally followed in the body ; still it is not without example, and as instances may be cited the Haversian fringes of the synovial membranes and the choroid plexus of the brain. In these cases, the membrane assumes the form of projecting folds, which, for the sake of further increase of surface, may be again plaited and complicated, or cleft and fringed, at their borders.

The augmentation of the secreting surface by *recession* or *inversion* of the membrane, in the form of a cavity, is, with few exceptions, that generally adopted in the

construction of secreting glands. If the recess is simple its blind termination, which is often enlarged, is spoken of as the 'fundus' of the gland. If compound, its terminations are known as 'alveoli' or 'acini.' In a *simple gland* the shape of the cavity may be tubular or saccular: of these two kinds of simple gland the former is by far the more common. Examples of simple saccular glands are found in the skin of the frog (fig. 628), of simple tubular glands in the alimentary canal (fig. 629). The secreting surface may be increased, in a simple tubular gland, by mere lengthening of the tube, in which case, however, when it acquires considerable length, the tube is coiled up into a ball so as to take up less room, and adapt itself to receive compactly ramified blood-vessels. The sweat-glands of the skin are instances of simple glands formed of a long convoluted tube. But the chief means of further increasing the secreting surface is by subdivision, as well as extension, of the cavity, and when this occurs the gland is said to be *compound*. There is, however, a condition sometimes met with, in which the sides or extremity of a simple tube or sac merely become pouched or loculated, in which case the tube is termed the gland-duct, as in the Meibomian glands of the eyelids; in some cases, as in the small mucous glands generally, the pouchings

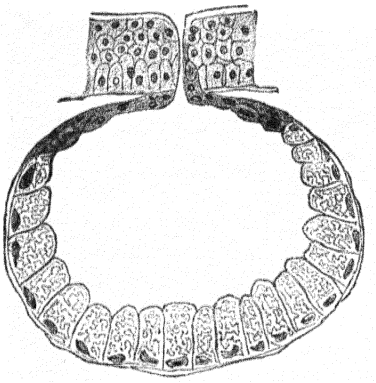


FIG. 628.—SIMPLE SACCULAR GLAND FROM THE AMPHIBIAN SKIN. (Flemming.)

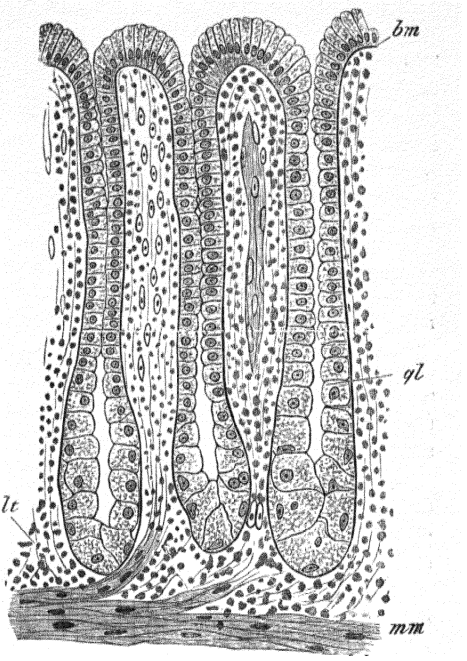


FIG. 629.—THREE SIMPLE TUBULAR GLANDS; FROM A SECTION OF THE KANGAROO'S STOMACH. (Schäfer and Williams.)

bm, basement-membrane; *gl*, epithelium of gland; *lt*, lymphoid tissue of mucous membrane; *mm*, muscularis mucosæ.

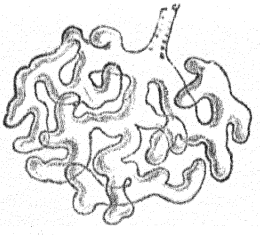


FIG. 630.—DIAGRAM OF SMALL ACINOUS GLAND FORMED OF A SIMPLE DUCT-SYSTEM. (Flemming.)

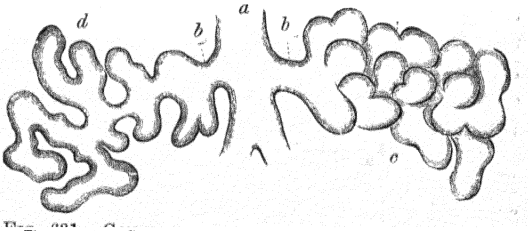


FIG. 631.—CONSTRUCTION OF A LOBULE OF AN 'ACINOUS' GLAND. (Kölliker.)

a, duct; *b*, *b*, branches of duct; *c*, alveoli as they lie together in the gland; *d*, the same unravelled, showing their connexion as an irregular tube.

or loculations may grow out into irregular tubular alveoli (fig. 630); the gland is however still regarded as simple, since all the alveoli open into a single duct (Flemming).[1]

In the compound glands, the divisions of the secreting cavity may assume a tubular or a saccular form, and this leads to the distinction of these glands into 'tubular' and 'acinous' or 'racemose.' The latter were so termed from the superficial resemblance which they bear, when examined with a lens, to a bunch of grapes. But it is found in many cases, when their subdivisions are unravelled, that the apparent saccules are merely dilatations in the course of somewhat irregularly branching tubules (fig. 631); such glands are hence named 'tubulo-racemose,' or 'acino-tubular.'

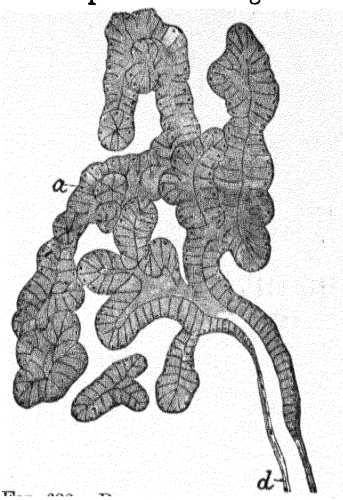


FIG. 632.—PART OF A SMALL MUCOUS GLAND, SHOWING THE TUBULAR CHARACTER OF THE ALVEOLI. (Flemming.)
a, alveoli; *d*, duct.

The disuse of the term racemose or acinous, as applied to any of these glands, was advocated by Flemming on the ground that the terminal alveoli are not merely dilatations grouped around the endings of the ducts, but are distinctly long and tubular in character (fig. 632); he proposed accordingly to term them all compound tubular glands. But since, as Chievitz has shown, the salivary and all other similar glands exhibit at an early condition of development a markedly saccaluted character, the ultimate alveoli, which may be tubular in character, being formed later as outgrowths of the saccules (whereas the tubular glands proper, such as the kidney, never exhibit this sacculated character), it appears desirable still to use a

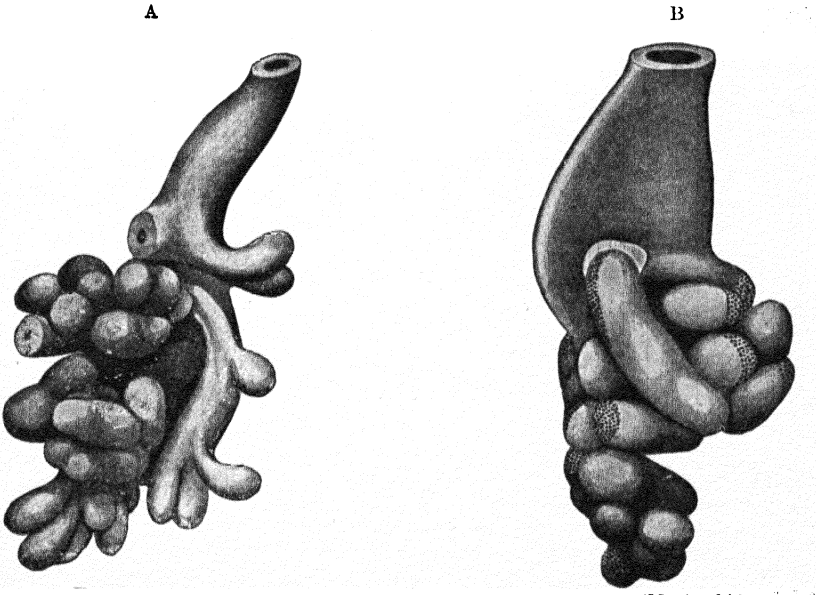


FIG. 633.—RECONSTRUCTED MODELS OF SECRETING GLANDS. (Maziarski.)
A, a small tubulo-racemose mucous gland from the epiglottis; B, a small muco-serous gland, with 'crescents' (the dotted parts of the alveoli).

term which recognises a morphological difference between the two classes of glands. And, as will immediately be explained, later investigations have shown that a true racemose character is met with in many of the glands which Flemming proposed to term tubular.

[1] Arch. f. Anat. 1888.

The actual shape of the alveoli of a compound gland is not easily determined by the examination of sections. But Maziarski,[1] by the use of the reconstructive method, and Peiser,[2] by the examination of teased-out glands, have succeeded in accurately portraying in various glands the shape and arrangement of the alveoli and the ducts which immediately lead from them. Their figures, some of which are here given (figs. 633 and 634), show a considerable variation in the shape and arrangement of the alveoli, even in glands which are otherwise nearly allied in structure. The alveoli of serous glands in general are distinctly racemose in type,[3] the somewhat globular alveoli or acini which represent the individual berries of the raceme being connected with the efferent duct that

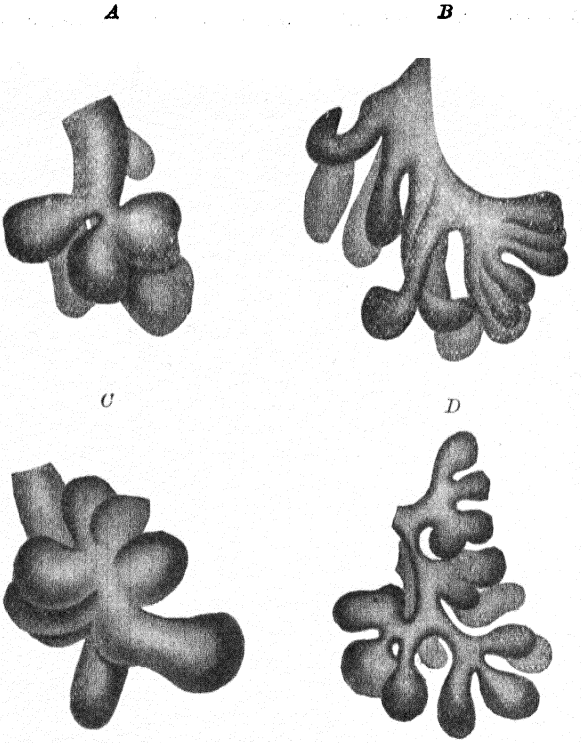


FIG. 634.—ISOLATED PORTIONS OF VARIOUS GLANDS. (Peiser.)
Magnified 300 diameters.

A, from one of the glands of the lip; *B*, from one of the glands of v. Ebner (serous gland) of the tongue; *C*, from the mucous portion of the human submaxillary gland; *D*, from the serous portion of the human submaxillary gland.

leads away from the group of alveoli (lobule) by comparatively narrow stalk-like ductules, which expand abruptly into the acini. These efferent ducts are continued into larger ducts, which meet with others of the same character, and the resulting tubes eventually pour their secretion into the main duct of the gland. These are true *racemose* or *acinous glands*. The mammary gland belongs to this type, although offering many points of difference in the details of its structure. Other glands, *e.g.* many of those which secrete mucus, have alveoli scarcely more dilated than the ductules which open out from them and convey their secretion into the efferent duct of the lobule. The ductules are relatively large, and form, with the alveoli that beset them, small groups or lobules, each

[1] Anat. Hefte, xviii. 1902. [2] Arch. f. mikr. Anat. lxi. 1903.
[3] R. Metzner, Zentr. f. Physiol. xxiii. 1909, p. 286.

of which has an efferent lobular duct, and these again join with others in the manner just described for the racemose type. When the lobules are unravelled the glands in question show a generally tubular character, although the expansions which form the alveoli are in some cases better marked than in others. When examined without unravelling, the lobules have a racemose appearance (fig. 631, *c*); accordingly, as already stated, they have been termed *tubulo-racemose glands*. Some serous glands, such as the lacrymal and the glands of Ebner of the tongue, are constructed on this type.

In a third type of compound gland the alveoli are represented by long tubules without any sign of sacculation or expansion beyond the diameter of the ducts which lead from them, although the tubules may vary in diameter in different parts of their course. This type is represented by the kidney and testicle, although the last-named organ is of a different nature from ordinary secreting glands, since its products, as already explained, are morphological (spermatozoa) rather than chemical, as is the case in the ordinary secreting gland. It is, however, built up like a gland, and is furnished with a duct, the vas deferens, which carries its secretion towards the exterior. Even the ovary, which appears, when fully formed, as a solid mass of vascular connective tissue containing vesicles—the Graafian follicles—lined by epithelium-cells, and enclosing the ova, displays at an early stage of its development an obscurely tubular structure, its epithelial cells being arranged in cylindrical columns extending in from the surface, near which they may even exhibit a lumen; although eventually these cell-columns ('egg-tubes' of Pflüger) become separated into islands or nests of cells to form the Graafian follicles. The ovary, however, is not directly connected with its duct, which is represented in the mammal by the Fallopian tube leading to the uterus; for this duct opens by a funnel-shaped enlargement provided with a fringed ciliated border into the peritoneal cavity near the ovary, and the ova, which are discharged from the latter by the bursting of the follicles containing them, are caught upon this expansion of the duct and conveyed down it into the uterus by the action of cilia.

Another gland, the study of whose ontogeny and phylogeny shows it to be essentially of a tubular type, is the liver. In the adult mammal the liver is composed of innumerable small solid masses of cells, the hepatic lobules, about a millimetre in diameter and imperfectly isolated from one another by connective tissue. Each lobule represents a miniature gland, and is provided with a duct or ducts which lead away through the liver-substance and unite with others to form, eventually, the hepatic duct. The ducts of the lobule do not, however, arise from the interior of alveoli, but from minute channels (bile-canaliculi) which run everywhere between the cells of the lobule and collect the secretion from them. The lobule is also traversed everywhere by blood-channels of a sinusoid character (Minot). The walls of these are incomplete, so that the cells are directly bathed by the circulating blood, an arrangement which obtains in no other secreting gland. Indeed the relationship between blood- and liver-cell is even more intimate, for the liver-cells are themselves excavated by a network of fine canaliculi into which the blood-plasma, and even on occasion blood-corpuscles, can penetrate.

Nevertheless, different as the structure of the liver appears from that of tubular glands in general, a study of its development shows that it must be classed along with them. It grows out as a protrusion from the entoderm of the alimentary canal, and from this protrusion there extend intercommunicating strands or trabeculæ of cells, which invade the lumen of the large sinus-like veins (omphalo-mesenteric and allantoic) that pass towards the sinus venosus of the heart. These trabeculæ are ultimately reduced to a network of cell-columns, in the meshes of which the blood in the venous sinuses circulates. The cell-columns presently

show a narrow lumen, which is continuous with the branches of the hepatic duct, and the liver at this stage is a tubular gland with anastomosing tubules (fig. 635). In certain fishes, in amphibians and in some reptiles, the trabeculæ are hollow from the first, and in cyclostomes the arrangement is precisely that of a tubular gland, the tubules being separate and not joined into a network. (See Embryology, Vol. I. pp. 173–175.)

Arrangement of blood-vessels, lymphatics and connective tissue.— In all glands, with the exception of the liver, the alveoli are supplied with nutrient plasma through the medium of the lymph which bathes the exterior of each alveolus and penetrates the basement-membrane to reach the cells which line it. This nutrient plasma is exuded from the blood-vessels of the gland, which form a capillary network in each lobule between and around the alveoli, but nowhere coming in contact with the basement-membrane, and nowhere, therefore, except in the liver, penetrating between the secreting cells. Capillaries are also distributed to the gland-ducts, and to the connective-tissue framework.[1] The blood-vessels and lymph-vessels

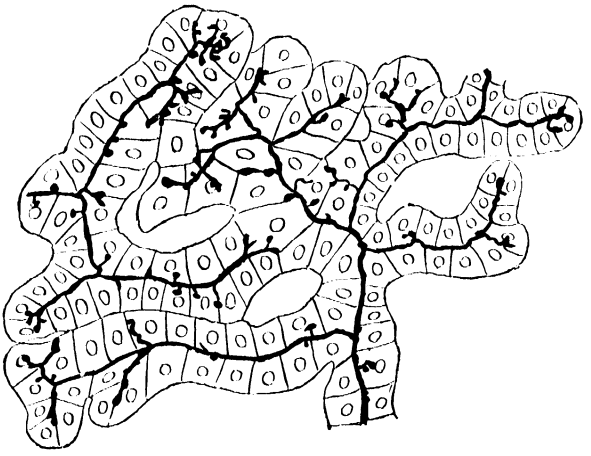


FIG. 635.—FROM A CHROMATE OF SILVER PREPARATION OF THE LIVER OF A SIX MONTHS' FŒTUS. (G. Retzius.)

The bile-canaliculi are represented black. It is seen that at this stage of development they do not anastomose. They appear to give minute offsets, which end between and within the liver-cells in small enlargements.

are supported by connective tissue (fig. 636), which penetrates into the lobules of the gland between its alveoli, and is found in larger amount between the lobules, binding them together, in some cases firmly and in others loosely, to form the whole mass of the gland. The connective tissue of glands is closely allied in its character to reticular tissue. It forms a close reticulum around the alveoli and ducts, coming into connexion with their basement-membranes. The smallest lobules are united by it into larger ones, and these again into still larger, a peculiar 'lobulated' appearance being in consequence exhibited by the gland both superficially and on dissection. Moreover, it is seen on unravelling the gland that the lobules are held together not only by the connective tissue and blood-vessels which penetrate between them, but also by their ducts, which are continually joining one another as they pass towards the main duct, much in the same way as the individual grapes of a bunch are held together by the junction of the smaller stalks into larger ones, and these eventually into the main stalk. The lymphatics form a network of cleft-like spaces in the connective and reticular tissue of glands; their efferent vessels for the most part accompany the blood-vessels.

[1] J. M. Flint, Amer. Journ. Anat. ii. 1903.

Basement-membranes of glands (*membranæ propriæ*).—In most glands the secreting cells of the alveoli and also the cells which line the ducts are bounded externally, *i.e.* are separated from the connective tissue of the gland, by a thin membrane, which is sometimes continuous, sometimes interrupted, and which has nuclei scattered here and there upon it (fig. 637). This is the basement-membrane, and, as the presence of the nuclei indicate, it is composed of more or less fused flattened cells of connective-tissue nature, which are sometimes united edge to edge, sometimes connected only by branched processes, so as to form a sort of flattened basket-work around the alveoli. Even in this case the meshes of the basket-work are not quite empty, being occupied by a delicate filmy membrane, which, according

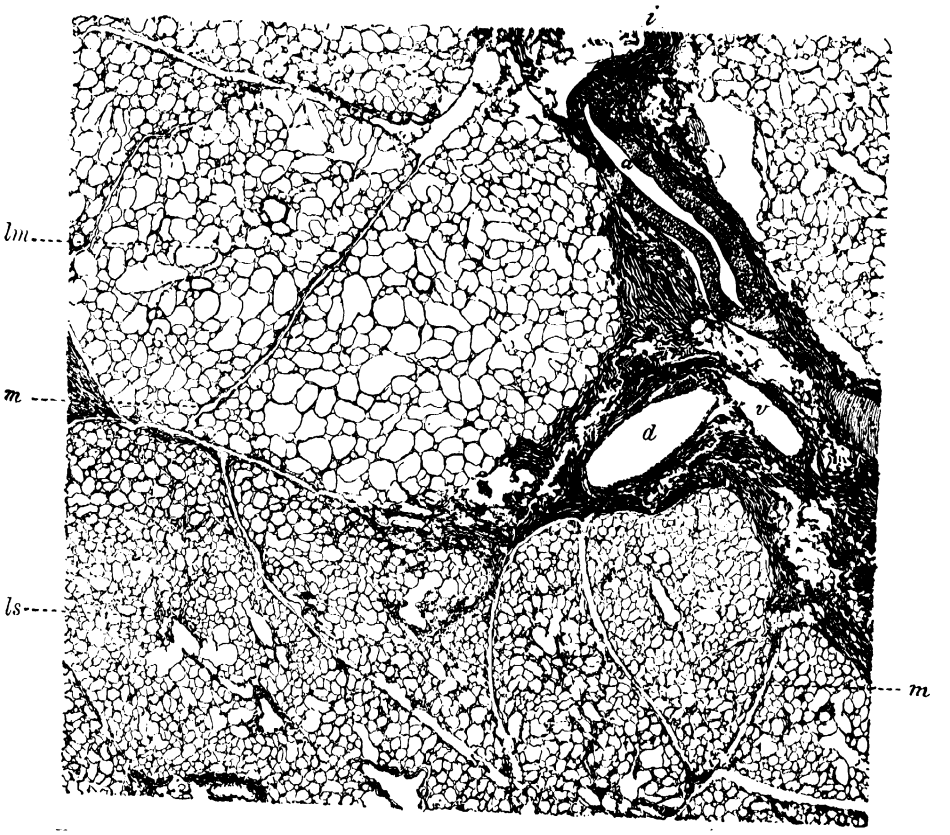


FIG. 636.—CONNECTIVE TISSUE OF A SALIVARY GLAND (SUBLINGUAL, MAN), DISPLAYED AFTER REMOVAL OF THE GLAND-CELLS AND OTHER TISSUES BY TRYPTIC DIGESTION. (J. M. Flint.) Magnified 28 diameters.

The gland is of the mixed type, one part being composed of mucous alveoli, the other part of serous alveoli.

a, artery; *v*, vein; *d*, main duct; *i*, connective tissue accompanying the vessels and duct; *lm*, a lobule of the mucous portion; *ls*, a lobule of the serous portion (with smaller alveoli); *m*, *m*, interlobular septa.

to Flint,[1] is a condensation of the reticular connective tissue. The basement-membrane cells may also send flattened branches into the interior of the alveolus, penetrating between the secreting-cells and helping to keep them in place (Boll, v. Ebner). Processes which actually penetrate into the protoplasm of the cells are also described by Holmgren (*trophospongium*, see p. 26).

[1] Arch. f. Anat. 1903. See also Amer. Journ. Anat. i. 1901 and ii. 1902.

Nerves.—It has been shown for many glands, and is probably true for most, that both the blood-vessels and cells of the gland are provided with nerve-fibres. The nerves to the blood-vessels are of two kinds—viz.: nerves which cause constriction and nerves which cause dilatation; in this way the blood-supply is com-

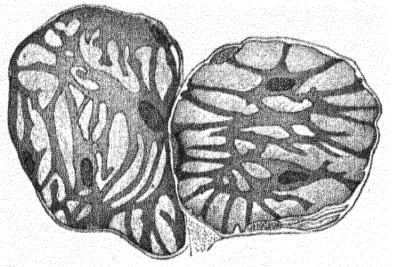


FIG. 637.—MEMBRANA PROPRIA OF TWO ALVEOLI OF A RACEMOSE GLAND. (v. Ebner.) Magnified 600 diameters.

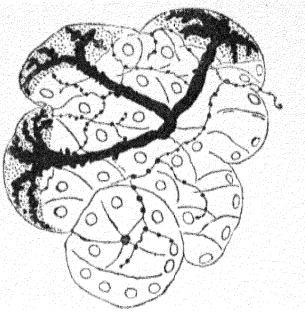


FIG. 638.—ALVEOLI OF THE SUBMAXILLARY GLAND OF THE DOG. (G. Retzius.) Golgi method.

The extensions of the lumen into the crescents of Gianuzzi are shown, and also the endings of nerve-fibrils.

pletely controlled through the nervous system. In some glands these differently acting vascular nerves take altogether different paths to reach the gland. Thus the submaxillary gland and the salivary glands generally are supplied with vaso-constrictors through the cervical sympathetic, and with vaso-dilators through one of the cranial nerves; in the case of the submaxillary and sublingual these arise with the facial and pass to those glands with its chorda tympani branch; in the case of the parotid they arise with the glosso-pharyngeal and reach the gland through the tympanic plexus, otic ganglion, and auriculo-temporal branch of the fifth nerve. The nerves which pass to the secreting cells are also of two kinds—at least this has been shown to be true for the salivary and some other glands. Those of the one kind (trophic fibres) chiefly cause, when excited, an increased formation of the products of secretion within the cells; these nerve-fibres, although not identical with the vaso-constrictors, reach the salivary glands along the same path. Those of the other kind cause a rapid discharge of secretion from the gland (secreting fibres): they are found in the case of the salivary glands to take the same path as the vaso-dilator fibres. The nerves which pass to the alveoli may be seen, in appropriately stained specimens, penetrating as fine branching fibrils between the secreting cells (fig. 638).[1]

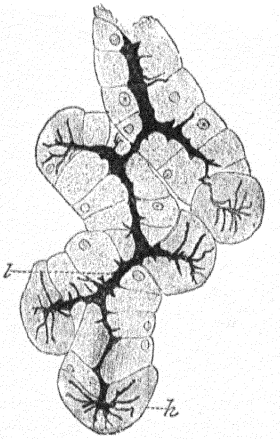


FIG. 639.—ALVEOLI OF HUMAN SUBLINGUAL GLAND PREPARED BY GOLGI METHOD. (E. Muller.)

l, lumen stained, with lateral diverticula passing between mucus-secreting cells; *h*, longer diverticula penetrating into the 'crescent' cells.

Secretory canaliculi.—It has long been known (see p. 569) that the bile is collected from the liver-cells by extremely fine canals which penetrate from the

[1] On the nerve-terminations in glands see Retzius, Biol. Unters. iii. 1892; C. Huber, Journ. Exper. Med. i. 1896.

interlobular bile-ducts between the secreting cells of the liver-lobule, and it has been affirmed by Kupffer and others that these bile-canaliculi even communicate with minute channels, temporary or permanent, penetrating into the interior of the cells themselves. It has since been established that such penetration of secretory canaliculi between the secreting cells of the alveoli is a constant feature in many racemose and tubular glands (fig. 639), especially those in which the character of the secretion is of a watery or serous type.[1] The canaliculi in question can be displayed either by injection from the ducts or by tracing some colouring substance previously introduced into the blood, such as sulphindigotate of soda, in the course of its removal from the body by these glands (fig. 640), or, more easily, by employing the Golgi method of staining. This method serves not only to display nerve cells and fibres, but also gland-ducts to their finest ramifications; by it secretory canaliculi have been traced between the cells of the parotid and of most serous glands;

FIG. 640.—SECRETION OF COLOURED MATERIAL BY THE CRESCENT-CELLS OF THE DOG'S SUBMAXILLARY. (R. Krause.)

In the right-hand figure the colouring-matter is seen in the form of droplets within the cells, and in the left-hand figure to be collected from these and to pass along fine canaliculi towards the lumen of the alveolus.

between the cells of the crescents of the salivary glands (fig. 638); around and even into the interior of the acid-forming cells of the gastric glands; and between the alveolar cells of the pancreas.[2]

Muscular tissue of glands.—Muscular tissue of the plain variety is found, disposed circularly, in the wall of the larger ducts of most if not all glands. In

[1] See on gland-cells and secretion-canaliculi, Langley, Journ. Physiol. ii. 1879-80, Phil. Trans. 1881, and Article 'Salivary Glands' in Schäfer's Text-book of Physiology, 1898; Cajal, Nuevas applic. d. met. d. color. d. Golgi, 1889; G. Retzius, Biol. Unters. iii. 1892; Laserstein, Pflüger's Arch. lv. 1894; E. Müller, Verhandl. Biol. Ver. Stockholm, iv. 1892, Om inter- och intracellulära Körtelgånger, Akadem. Afhandl. Stockholm, 1894, Arch. f. mikr. Anat. xlv. 1895, and Zeitschr. f. wiss. Zool. lxiv. 1898; R. Krause, Arch. f. mikr. Anat. xlv. 1895, xlix. 1897, and lix. 1902; P. Stöhr, *ibid.* xlvii. 1896; Zimmermann, Arch. f. mikr. Anat. lii. 1898; J. Arnold, *ibid.* lxv. 1905; Noll and Sokoloff, Arch. f. Physiol. 1905. According to Stöhr the mucous cells of the salivary glands and even the rodded epithelium of their ducts have secretory canaliculi; but if this is so, they are far less developed than are those to the serous cells. Several of the above papers deal with the formation of granules in the secreting cells.

[2] According to Rubaschin (Anat. Anz. xxix. 1906) the secretion capillaries are formed during the passage of the secretion, and are therefore not to be looked upon as permanent structures; but this view is improbable, at least in many cases.

some cases the muscular layer is comparatively thick, but more commonly it is little developed. The lobular ducts and the alveoli are usually unprovided with muscle, but an exception is found in the case of the sweat-glands, the convo-

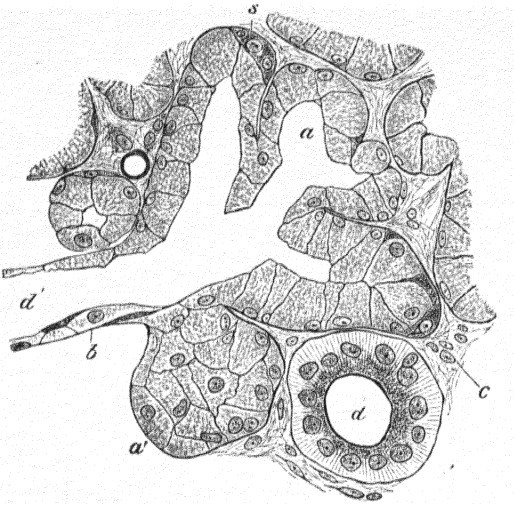


FIG. 641.—SECTION OF THE SUBMAXILLARY GLAND OF THE DOG, SHOWING THE COMMENCEMENT OF A DUCT IN THE ALVEOLI. (Schäfer.) Magnified 425 diameters.

a, one of the alveoli, several of which are in the section shown grouped around the commencement of the duct *d'*; *a'*, an alveolus, not opened by the section; *b*, basement-membrane in section; *c*, interstitial connective tissue of the gland; *d*, section of a duct which has passed away from the alveoli, and is now lined with characteristically striated columnar cells; *s*, crescentic group of darkly stained cells at the periphery of an alveolus.

luted secreting tubules of which have a layer of longitudinally disposed plain muscular fibres between the secreting epithelium and the basement-membrane. A

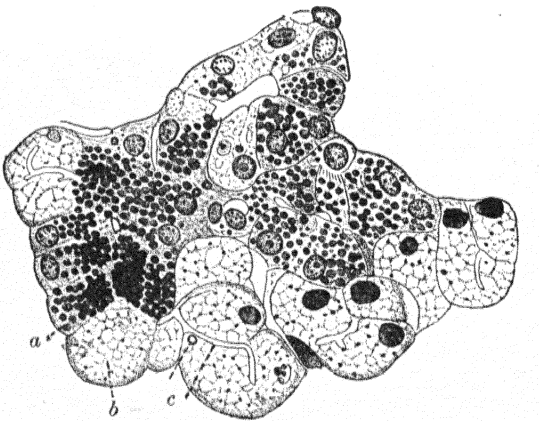


FIG. 642.—GRANULES AND SECRETORY CANALICULI OF SUBMAXILLARY GLAND OF RABBIT. (E. Müller.)

The cells, which are serous, are in different functional states, as indicated by the condition and staining of the granules. *a*, cell filled with darkly staining granules; *b*, clear cell; *c*, secretory canaliculi penetrating into the cells.

similar layer is found surrounding the saccular cutaneous glands of amphibia, and plain muscle has also been described around the alveoli of the mammary gland.

Characters of the secreting cells of glands and the changes which are observed in them during secretion.—The cells by the activity of which

the secretion of a gland is prepared, vary greatly in form in different glands and even in different parts of the same gland. Thus they may be columnar, cubical, ovoidal, polyhedral, or flattened. In many instances they have acquired the shape of a many-sided pyramid, the apex of the pyramid, which is blunted, being directed towards and even projecting into the lumen of the alveolus, while the base rests upon the membrana propria. This shape of a truncated pyramid is common in the saccular alveoli of racemose and racemo-tubular glands, while in glands the alveoli of which assume a more tubular character, and in the ducts of glands generally, a

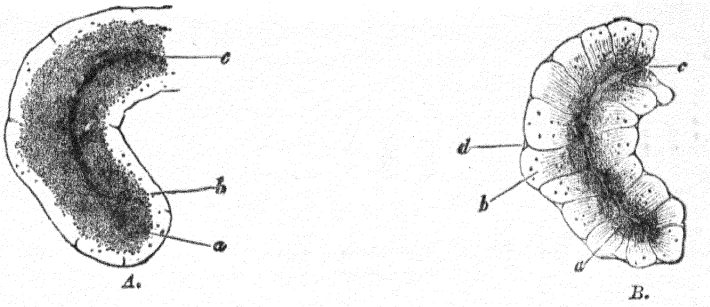


FIG. 643.—PART OF AN ALVEOLUS OF THE RABBIT'S PANCREAS. *A*, AT REST; *B*, AFTER ACTIVE SECRETION. (From Foster, after Kühne and Lea.)

a, the inner granular zone, which in *A* is larger and more closely studded with granules than in *B*, in which the granules are fewer; *b*, the outer transparent zone, small in *A*, larger in *B*, and in the latter marked with faint striæ; *c*, the lumen, very obvious in *B*, but indistinct in *A*; *d*, indentation at the junction of two cells, only distinct in *B*.

wedge shape is superimposed upon a columnar form, so as to adapt the cells to the curve of the cylindrical tubules. Like cells in general, those of secreting glands are composed of protoplasm containing a centrosome and a nucleus; the latter may occupy the centre of the cell, but in many cases lies in its basal part near the membrana propria. This is generally the case when the cell is filled with secretory products; after these have been discharged the nucleus usually moves nearer to the middle of the cell.

The most characteristic feature of the cells of secreting glands is the presence of secretory granules (fig. 642), no matter what may be the kind of secretion

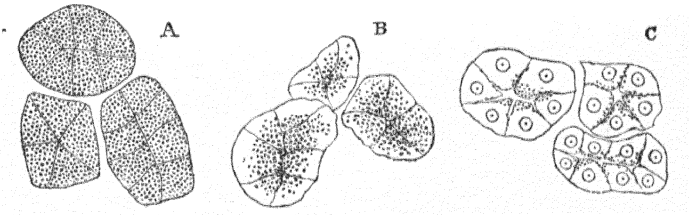


FIG. 644.—ALVEOLI OF SEROUS GLANDS. A, AT REST; B, AFTER A SHORT PERIOD OF ACTIVITY; C, AFTER A PROLONGED PERIOD OF ACTIVITY. (Langley.)

furnished by the gland. They have been found in serous glands such as the pancreas and parotid, in all mucous glands, in the lacrymal gland, in the gastric glands, in some cells of the intestinal glands and in the cells of the convoluted tubules of the kidney. The granules differ in size and appearance and in chemical reactions in different glands. In the cells of mucous glands they are large and, when stained, are conspicuous; they are usually smaller but still very distinct in those of serous glands (where they are easily seen in the fresh condition) and in the chief or pepsin-forming cells of the glands of the fundus of the stomach; in the

acid-forming cells of the fundus glands and in the pepsin-secreting glands of the pyloric part of the stomach they are still finer. That the granules are directly related to the process of secretion was first rendered evident by the observations of Langley[1] on the parotid and those of Kühne and Lea[2] upon the cells of the pancreas in living animals. In these cells the granules occupy the zone adjoining the lumen of each alveolus, the outer or basement zone being clear or occupied only by very fine granules, probably of a different nature (fig. 643, A). After a prolonged period of rest from secretion the inner zone of granules occupies about half or in some animals rather more than half the thickness of each cell. But if the gland be stimulated to activity the clear outer zone increases in size at the expense of the inner zone, the granules of which are evidently passed in a state of solution into the lumen of the alveolus along with the flow of secretion (fig. 643, B).

These observations have been confirmed by Langley and others for the alveoli of the pancreas and of all the salivary glands both serous and mucous (figs. 644, 645), for the gastric glands in mammals and œsophageal glands of the frog, for the lacrymal, for the cells of the salivary ducts (fig. 33), and for various other glands.[3]

The arrangement into granular and non-granular zones is not general in resting glands. It occurs in the gastric fundus-glands as well as in the pancreas; but in others, such as the salivary glands, the whole cell tends during a prolonged period of rest to be filled with secreting granules (Langley); during secretory activity these become discharged, so that at first the basal zone, and subsequently nearly the whole of the protoplasm, may become free from granules. But this last condition is brought about only as the result of excessive secretion, such as is produced by the action of pilocarpine (fig. 644, C), or in the salivary glands as the result of the continued secretion which follows section and degeneration of the cerebral nerves to those organs.

The granules in mucin-secreting cells and also in many gland-cells which do not secrete mucin are readily swollen and eventually dissolved by the action of most fixing reagents containing water, and even by alcohol. On this account they for a long time escaped observation. But they can, as already stated, be seen in many glands in the fresh condition, especially if it is possible, as with the pancreas and parotid of some animals, to examine thin portions of the gland during life with the circulation still proceeding. Even normal salt solution and serum tend to destroy the granules in mucin-secreting cells, and to see them in the fresh cell it is necessary, as Langley has shown, to examine the cells in 2 per cent. to 5 per cent. NaCl solution. Sections of glands fixed by ordinary hardening reagents and examined (after staining) in Canada balsam or damar show no sign of the secreting granules, but the cell-protoplasm looks clear with a faint indication of a fine network—a condition brought about by the swelling and disappearance of the granules. They can, however, in some cases be preserved by the use of osmic-acid solution, or better of osmic-acid vapour; or a mixture of equal parts of osmic acid (5 per cent.) with saturated solution of potassium bichromate (Altmann's mixture), the solution of osmic acid being made with 3 per cent. NaCl (Metzner). A saturated solution of picric acid fixes them in certain glands; but owing to the fact that they differ in chemical composition in different organs no one fixative is universally applicable.

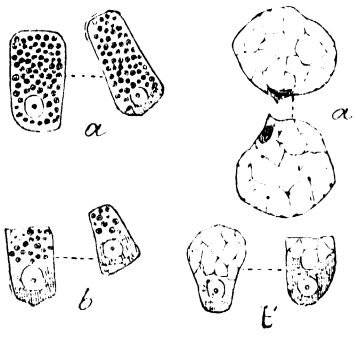


FIG. 645.—ISOLATED MUCIN-SECRETING CELLS FROM THE SUBMAXILLARY GLAND OF A DOG. (Langley.)

a and *b*, isolated in 2 per cent. salt solution; *a*, from loaded gland; *b*, from discharged gland; *a'*, *b'*, similar cells after treatment with dilute acid.

The secretion-granules may differ in their characters in different cells of the same gland or alveolus (fig. 642), and even within the same cell. This is due to the fact that they are not all in the same stage of development. They first appear within

[1] Journ. Physiol. ii. 1879–80. [2] Heidelberg Untersuch. 1882.

[3] A compendious account of the history of this subject is given by R. Metzner in Nagel's Handbuch der Physiologie des Menschen, 1906–7, to which article the reader is referred for the literature to that date.

the protoplasm as small granules, and gradually acquire the size and characters which distinguish them when ripe and ready for extrusion from the cell (figs. 646, 647). But even in the mature state their chemical characters may differ from those of the substance which represents them in the extruded secretion; this is shown, *inter alia*, by their varying behaviour to stains. A difference of this nature was found by Klein to obtain with the granules in mucin-secreting cells, and he accordingly termed these granules 'mucinogen,' as giving rise on extrusion to mucin.

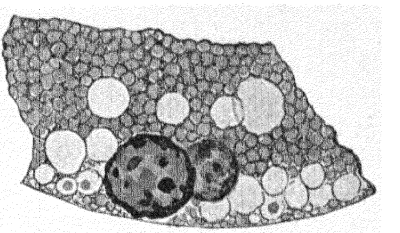


FIG. 646.—A CELL FROM THE POISON-GLAND OF A SALAMANDER-TADPOLE, FILLED WITH SECRETION-GRANULES. (Gurwitsch.) Highly magnified.

Some of the granules are swollen out into globules.

There is not sufficient evidence that the granules multiply by fission, as Altmann supposed to be the case. Altmann indeed looked upon cell-granules in general as being themselves minute organisms ('Die Elementar-organismen,' 1890) capable of growth and multiplication more or less independently of the cell as a whole; this view has not been widely accepted.

The changes undergone by secretion-granules are readily studied in mucin-secreting cells and especially in the so-called 'goblet-cells' which occur as isolated elements amongst the ordinary cells of columnar and ciliated epithelium (fig. 648). 'Goblet-cells' are in fact unicellular glands such as occur not infrequently in the integument of certain invertebrate animals. In these cells, as a rule, only the

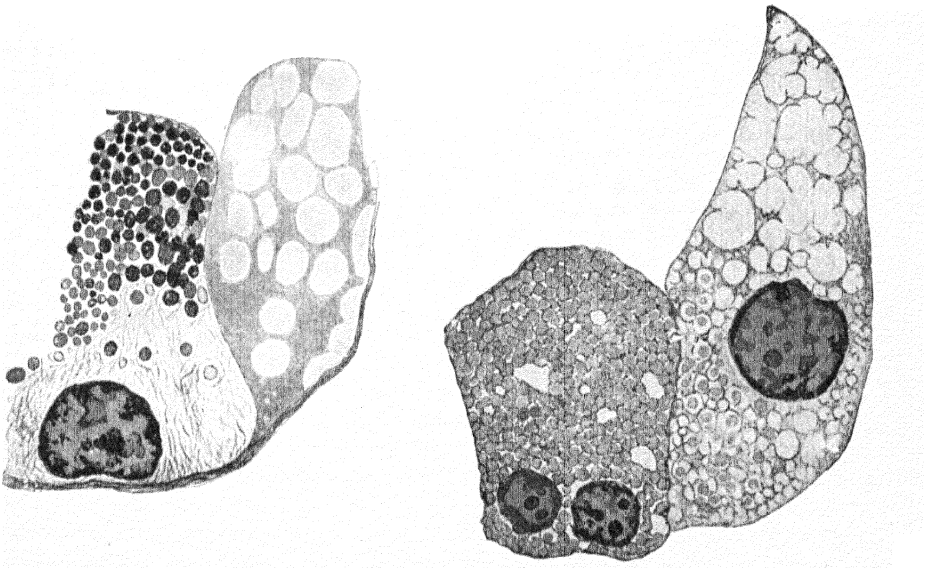


FIG. 647.—CELLS FROM POISON-GLAND OF SALAMANDER-TADPOLE, SHOWING SECRETION-GRANULES IN DIFFERENT STAGES OF FORMATION AND OF TRANSFORMATION INTO DROPLETS. (Gurwitsch.) Highly magnified.

One of the cells has two nuclei; in another the nucleus is not seen.

half directed to the free surface becomes occupied with the secretion-granules, the basal part, containing the nucleus, remaining free from distinct granules; although, as with all protoplasm, it may have a finely granular appearance. The mucin-granules which first make their appearance in the free half of the cell

are small, and their property of imbibing the specific stains for mucin is little marked. But as they gradually increase in size this property becomes more distinct, and the part of the cell containing them becomes swollen out (fig. 649). When the secretion is to be extruded, either by a contraction of the cell-protoplasm or, more probably, by a determination of watery fluid from the blood and lymph through the cell, the granules or globules of mucin are passed out at the free surface; here they are immediately swollen up and dissolved by the watery solution already present or simultaneously poured out, and are converted into an issuing plug-like drop of mucus, which in some cases may be seen protruding from the goblet-cell. When all the secretion is discharged the part of the cell which contained it looks almost empty. But it still contains a fine network of protoplasm; this grows so as again to fill the empty space, and within it granules of secretion again form.

A similar process takes place in serous glands except that in many of these,

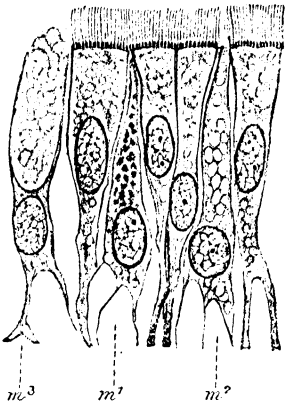


FIG. 648. — EPITHELIUM-CELLS FROM THE TRACHEA OF THE RABBIT, WITH THREE MUCUS-SECRETING CELLS AMONGST THE CILIATED COLUMNAR CELLS. (Schäfer.) Highly magnified.

m^1, m^2, m^3, mucus-secreting cells seen in various stages of mucin-formation.

FIG. 649. — GOBLET-CELL OF SALAMANDER LARVA, WITH ITS FINE END SWOLLEN OUT BY THE MUCIN-CONTENTS. (Gurwitsch, after Joseph.)

A diplosome (double centriole) with a filament extending from each particle is seen within the mucin-containing part of the cell.

as in some mucous glands, the secretion-granules are formed throughout the whole cell. But in the serous glands the granules are not so large, and the extrusion at the free surface produces less disturbance of the general form of the cell; the secretion-granules are also for the most part passed out into the lumen of the alveolus in a dissolved condition, although they are sometimes seen there in an undissolved form. In most glands it is only as the result of excitation through the nervous system, or by chemical agents (hormones) circulating in the blood, that the secretion-granules are extruded from the cell, but the process of formation of fresh granules is not arrested during such extrusion; indeed, it probably goes on even more rapidly than during rest. There is in fact reason to suppose that *behind* the already formed secretion-granules in process of extrusion there always proceeds within the protoplasm a new formation of granules, which are to take the place of those that are being extruded. Thus the excitation not only effects discharge of secretion but also the production of fresh secretion-granules to take the place of those which are discharged. But it may happen that if the gland is over-excited—as by pilocarpine—the discharge becomes more rapid than the production, and the cells are gradually depleted of secretion-granules.

In goblet-cells, as well as in the cells of certain glands, such as the sebaceous glands of the skin, the Harderian gland found in many mammals, and the poison-glands of the amphibian integument, the secretion-granules become discharged by the breaking down either of the whole cell or of the part next to the free surface, in which the secretion is for the most part accumulated, rather than by the discharge of the individual granules from that surface, whether whole or in a dissolved form.

Although the term 'granules' has been here used in speaking of the particles seen in secreting cells, it must be borne in mind that they are not necessarily of a solid nature, but may be liquid or semi-fluid. In such cases the term 'globules' would seem more appropriate. In the lacrymal gland they sometimes have a crescentic form.[1]

The relationship of the granules formed within secreting cells to the mitochondria, which have been shown to be intimately concerned with the differentiation of fibrils and other intracellular structures, has not as yet been worked out, but it is not improbable that some secretion-

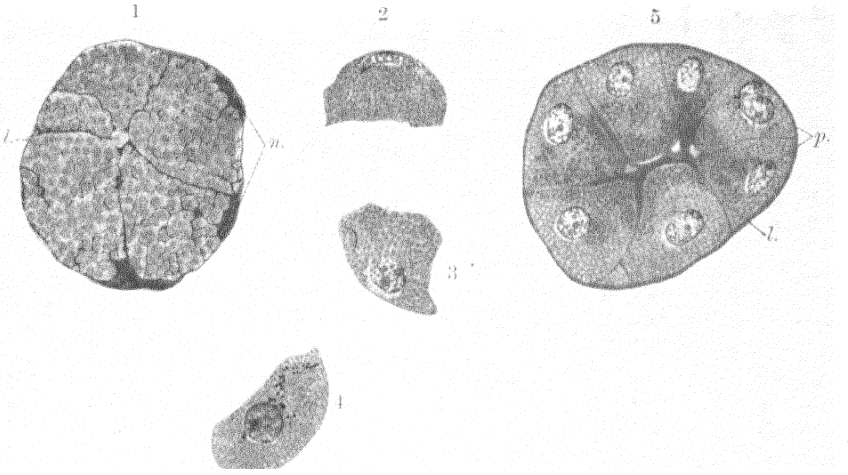


FIG. 650.—ALVEOLI AND SEPARATED CELLS FROM SALIVARY GLANDS OF THE DOG. (A. Maximow.) The preparations were stained with 'light green' and saffranin (red).

1, A mucous alveolus from the submaxillary; 2, 3, 4, isolated cells from 'crescents' of the submaxillary; 5, a serous alveolus from the retrolingual gland; *l.*, lumen of alveoli; *n.*, nuclei of mucous cells flattened against basement-membrane; *p.*, particles of chromatin extruded from nucleus. Similar particles are seen in 4.

granules are produced by or from these particles, which are now known to be an important constituent of the protoplasm of most, if not of all cells, either throughout their life or at some period of their existence.[2]

Influence of the nucleus upon the formation of secretion-products: the paranucleus.—We have already seen (p. 59) that in many secreting cells the nucleus appears to take on a special activity. Although it has not been proved that the participation of the nucleus is a general phenomenon, there is, nevertheless, a considerable amount of evidence to show that this constituent of the cell may play an important part in the formation of secretion-products.[3] This it appears to do by giving out into the adjacent protoplasm a portion of its chromatin (fig. 650) (which may take the form of nucleolar material) to furnish the basis from which the secretion-granules are gradually evolved in the metabolism of the cell. The substance extruded may for a time remain in the protoplasm as an independent mass of chromatic

[1] B. Fleischer, Anat. Hefte, xxvi. 1904.
[2] See on this subject H. Hoven, Anat. Anz. xxxvii. 1910.
[3] Matthews, Journ. Morph. xv. 1899 (suppl.); Carlier, La Cellule, xvi. 1899; Maximow, Arch. f. mikr Anat. lviii. 1901; Walker and Tozer, Quarterly Journal of Experimental Physiology, ii. 1909.

matter ; which in some cases seems to be made up of granules, in others to be drawn out into threads, often spirally wound. The mass in question is known as a paranucleus, and was first described for the secreting cell by Gaule [1] and Ogata [2] and by Nussbaum [3] in the pancreas, but has since been noticed in the salivary and lacrymal glands and elsewhere.[4] Apart from the question of the extrusion of a portion of its chromatin, the nucleus almost invariably undergoes enlargement during the activity of the secreting cell ; an observation which indicates an access of metabolic activity. On the other hand the testimony of all observers is clear that there is no special tendency to nuclear and cell division during glandular activity ; this fact renders very improbable the bodily destruction of gland-cells as a concomitant of secretion—a supposition which was at one time prevalent, especially in regard to mucus-secreting glands. It is possible, however, that it may still apply to the sebaceous glands of the skin.

[1] Centralbl. f. d. med. Wissensch. 1881.
[2] Arch. f. Physiol. 1883.
[3] Arch. f. mikr. Anat. xxi. 1882.
[4] Garnier, Journ. de l'Anat. et de la Physiol. xxxvi. 1900. See on the subject of the paranucleus, this volume, p. 59.

MUCOUS MEMBRANES.

These membranes, unlike the serous, line passages and cavities which communicate with the exterior, as well as recesses, ducts, and receptacles of secretion, which open into such passages. They are habitually subject either to the contact of foreign substances introduced into the body, such as air and aliment, or of various secreted or excreted matters, and their surface is coated over and protected by mucus, a fluid of a more consistent and tenacious character than that which moistens the serous membranes.

The mucous membranes of several different or even distant parts are continuous, and they may nearly all be reduced to two great divisions, namely, the *ventro-pulmonary* and *genito-urinary*. The former covers the inside of the alimentary and air-passages as well as the less considerable cavities communicating with them. It may be described as commencing at the edges of the lips and nostrils, where it is continuous with the skin, and proceeding through the nose and mouth to the throat, whence it is continued throughout the whole length of the alimentary canal to the termination of the intestine at the anus, there again meeting the skin; and also along the windpipe and its numerous divisions as far as the air-cells of the lungs. From the nose the membrane is prolonged into the lacrymal passages, extending up the nasal duct into the lacrymal sac and along the lacrymal canals until, under the name of the conjunctival membrane, it spreads over the fore part of the eyeball and inside of the eyelids, on the edges of which it meets with the skin. Other offsets from the nasal part of the membrane line the frontal, ethmoidal, sphenoidal and maxillary sinuses, and from the upper part of the pharynx a prolongation extends on each side along the Eustachian tube to line that passage and the tympanum of the ear. Besides these there are offsets from the alimentary membrane to line the salivary, pancreatic, and biliary ducts, and the gall-bladder. The *genito-urinary* membrane invests the inside of the urinary bladder and the whole tract of the urine in both sexes, from the interior of the kidneys to the orifice of the urethra, also the seminal ducts and vesicles in the male, and the vagina, uterus, and Fallopian tubes in the female.

By one surface the mucous membranes are attached to the parts which they line or cover, by means of areolar tissue, named 'submucous,' which differs greatly in quantity as well as in consistency in different parts. The connexion is in some cases close and firm, as in the cavity of the nose and its adjoining sinuses; in other instances, especially in cavities subject to frequent variation in capacity, like the gullet and stomach, it is lax and allows some degree of shifting of the connected surfaces. In such cases as the last-mentioned, the mucous membrane is accordingly thrown into folds when the cavity is narrowed by contraction of the exterior coats of the organ, and of course these folds, or *rugæ* as they are named, are effaced by distension. But in certain parts the mucous membrane forms permanent folds, not capable of being thus effaced, which project conspicuously into the cavity which it lines. The best-marked example of these is presented by the *valvulæ conniventes* seen in the small intestine. These, as is more fully described in the special anatomy of the intestines, are crescent-shaped duplicatures of the membrane, with connecting areolar tissue between their laminæ, which are placed transversely and follow one another at very short intervals along a great part of the intestinal tract. The chief use of the valvulæ conniventes is doubtless to increase the surface of the absorbing mucous membrane within the cavity.

In most situations the mucous membranes after death are nearly opaque or only slightly translucent. They possess no great degree of tenacity and but little elasticity, and hence are readily torn by a moderate force. The red or pink colour which they exhibit during life, and may retain in greater or less degree in various parts after death, is due to the blood contained in their vessels. The degree of redness is greater in the fœtus and infant than in the adult. It is greater too in certain situations; thus, of the different parts of the alimentary canal, it is most marked in the stomach, pharynx, and rectum.

Structure.—A mucous membrane is composed of a connective tissue *corium* lined by *epithelium*. Many mucous membranes have also at their attached surface a layer of plain muscle known as the *tunica muscularis mucosæ*, which may be considered to belong to the corium.

The **epithelium** varies in its characters. It may be stratified as in the mouth and throat, transitional as in the bladder, columnar as in the intestine, or ciliated as in the respiratory tract and uterus. When a mucous membrane is covered with an epithelium of the stratified variety, the mucus moistening its surface is derived from glands in or beneath the membrane, which are lined with secreting cells; but when a columnar epithelium or a ciliated epithelium covers the surface, mucus is formed in cells within this layer, and the glands of the membrane may also secrete mucus or may be devoted to the elaboration of some special secretion.

As has been already explained in dealing with secreting glands, the cells which are concerned in the production of mucus often become greatly distended with the accumulated granules or droplets of secretion and take the shape of a goblet or chalice. In many such cells the secretion may be seen to have become exuded from the free and apparently open end of the cell as a droplet of mucus. A certain number of these *goblet-* or *chalice-cells* are almost always to be found in the columnar or ciliated epithelium which covers mucous membranes. After discharge of their secretion their cavity becomes again filled with secretion-granules. The cells in question are analogous to the unicellular glands met with in the integument of some invertebrate animals.

The **corium** of a mucous membrane consists mainly of connective tissue, either areolar or reticular. It is often bounded next to the epithelium by a basement-membrane, and is separated from the submucous tissue by the *muscularis mucosæ*.

A *basement-membrane* is not everywhere demonstrable, but where it is well marked it appears in section as a thin line immediately underlying the epithelium. Viewed on the flat and with the superjacent epithelium removed, the membrane in question seems at first sight homogeneous; but treatment with nitrate of silver sometimes brings to view the outlines of flattened cells of which it is in part composed. In some places these cells, instead of adhering closely by their edges, intercommunicate by branching processes so as to form a network instead of a continuous membrane. Besides such flattened cells, which cannot always be seen, the basement-membrane is formed of a layer of connective-tissue ground-substance which is in many cases pervaded by closely reticulating fibres. The basement-membrane follows all the eminences and depressions of the surface of the mucous membrane, dipping down to take part in the formation of the wall of the glands, and passing over the raised villi and other prominences.

The *muscularis mucosæ* forms the deepest part of the corium, but it is not everywhere present. It is best developed in the mucous membrane of the alimentary canal, in some parts of which it may consist of two layers, in the outer of which the fibres are longitudinal, in the inner circular in direction. From its inner surface muscular bundles bend inwards into the thickness of the mucous membrane, passing between the glands contained within it, and even into its prominences, so as in many cases to reach and become attached to the basement-membrane covering them (as in the villi of the small intestine). The muscularis mucosæ is a part therefore of the mucous membrane, and is not to be confounded with the muscular coat proper, which forms a separate layer in most of the hollow viscera.

The *connective-tissue* of the corium varies much in structure in different parts. In some situations, as in the gullet, bladder, and vagina, fibrous connective tissue is abundant, and extends throughout its whole thickness, forming a continuous and tolerably compact web, and rendering the mucous membrane of

those parts comparatively stout and tough. In the stomach and intestines, on the other hand, where the membrane is pervaded by tubular glands, the tissue between these is chiefly reticular and lymphoid tissue, and in these situations the membrane, although it may be thicker, is far less firm and tough than in parts where much of the ordinary connective tissue is found. In other mucous membranes transitions are met with between these extremes.

It frequently happens that in certain circumscribed places the lymphoid tissue is greatly increased in amount, and becomes densely packed with lymphocytes. In this way the so-called *solitary glands*, *lymph-follicles* or *lymph-nodules* are produced. They resemble the cortical nodules of the lymph-glands, and are sometimes partly encircled by a sinus-like lymph-vessel. If there are many lymphoid nodules adjacent to one another, so as to make up a localised patch, a so-called *agminated gland* is formed, or if massed together more thickly, a lymphoid organ like the *tonsil*. These collections of lymphoid tissue, which may, if large, extend, on the one hand down into the sub-mucous tissue, and on the other upwards into the epithelium, will be more particularly described when the several parts in which they occur come under consideration. The lymph-cells of the lymphoid tissue migrate between the cells of the epithelium which covers the surface, and may even become free in considerable numbers in the fluid which moistens the surface. The purpose served by this emigration of lymph-cells is not understood.

Blood-vessels are abundant in most mucous membranes. The branches of the arteries and veins, dividing in the submucous tissue, send smaller branches into the corium, which then break up into a network of capillaries. This capillary network lies immediately beneath the epithelium, or beneath the basement-membrane when this is present, advancing into the villi and papillæ to be presently described, and surrounding the tubes and other glandular recesses. The **lymphatics** also form networks of cleft-like vessels in the mucous membrane, which communicate with plexuses of larger valved vessels in the submucous tissue ; they commence either by blind diverticula, as in most villi, or in the form of a superficial network, which is almost always more deeply placed than the network of blood-capillaries.

The **nerves** of mucous membranes are largely distributed to the muscularis mucosæ, where this exists. Before proceeding to their destination they are in many parts collected together to form a gangliated plexus in the submucous tissue, such as the plexus of Meissner in the alimentary canal. Some nerves pass to the epithelium and terminate between the epithelial cells.

Papillæ and villi.—The free surface of mucous membranes is in some parts plain, but in others is beset with little eminences named *papillæ* and *villi*. The largest papillæ occur on the tongue ; there they are small prominences of the corium, containing blood-vessels and nerves, and covered with stratified epithelium. Some are small and simple, others large and covered with secondary papillæ. Papillæ similar to those of the skin (p. 454) occur in the mucous membranes of the mouth, pharynx, and gullet, and generally where stratified epithelium is met with. They serve various purposes ; some of them no doubt minister to the senses of taste and touch, many appear to have chiefly a mechanical office, while others would seem to give greater extension to the surface of the corium for the production of a thick coating of epithelium. Villi are met with on the mucous coat of the small intestines. Being set close together like the pile of velvet, they give to the parts of the membrane which they cover the aspect usually denominated ' villous.' They are minute elevations or processes of the corium, covered with columnar epithelium, and containing blood-vessels and lacteals, which are thus favourably disposed for absorbing nutrient matters from the intestine.

In some few portions of the mucous membranes the surface is marked with fine ridges which intersect each other in a reticular manner, and thus inclose larger and

smaller polygonal pits or recesses. This peculiar character of the surface of the membrane, which has been termed 'alveolar,' is seen very distinctly in the gall-bladder, and on a finer scale in the vesiculæ seminales; still more minute recesses with intervening ridges may be discovered with a lens on the mucous membrane of the stomach; the recesses here are the orifices of the closely set gastric glands.

Glands of mucous membranes.—Many, indeed most, of the glands of the body pour their secretions into the great passages lined by mucous membranes; but there are certain small secreting glands which may be said to belong to the membrane itself, inasmuch as they are found in numbers over large tracts of that membrane, and yield either mucus or special secretions known to be formed in particular portions of the membrane. Omitting local peculiarities, the glands referred to may be described as of two kinds, viz.:

Simple tubular glands or crypts.—These are minute tubes formed by recesses or inversions of the basement-membrane, and lined with epithelium. They are usually placed perpendicularly to the surface and often very closely together, and they constitute the chief substance of the mucous membrane in those parts where they abound, its thickness depending on the length of the tubes, which differs considerably in different regions. The tubes open by one end on the surface; the other end is closed, and is either simple or cleft into two or more branches. Such tubular glands are abundant in the stomach, and in the small and large intestines, where they are comparatively short and are known as the crypts of Lieberkühn. They exist also in considerable numbers in the mucous membrane of the uterus, where they are longer and tend to be convoluted.

Small racemose glands.—Under this head are here comprehended minute glands of the racemose and tubulo-racemose kind, which open on the surface of the membrane by a longer or shorter duct. Numbers of these, yielding some a mucous, others a more albuminous or serous secretion, open into the mouth. When the mucous membrane of this cavity is dissected off, these glands are seen on its attached surface as small solid bodies, often of a flattened form, but varying much both in shape and size, and placed at different depths below the mucous membrane, on which their ducts open. They are also met with throughout the pharynx and gullet and in the larynx, trachea, and bronchial tubes; in all these parts their secretion is of a purely mucous character. The glands of Brunner, which occur in the submucous tissue of the duodenum, near its junction with the stomach, also bear a superficial resemblance to the racemose mucous glands, and in minute structure are not unlike them, but the nature of their secretion appears to be different.

The skin (cutis, δέρμα) consists of the cutis vera or corium, and the cuticle or epidermis. The cutis vera is a vascular connective-tissue membrane of considerable thickness; it is this part of the skin which is converted into leather in the process of tanning. The epidermis is entirely composed of epithelium-cells arranged in a number of layers. It is derived from the ectoderm of the embryo, whilst the cutis vera is a derivative of the mesoderm. In the European races the skin is for the most part white, with, in a few parts, a brownish coloration due to pigment (area round nipples, parts of external generative organs, neighbourhood of anus); during life the blood within its vessels gives it a more or less distinct reddish tinge, varying directly with its vascularity and inversely proportional to the thickness of the epidermis. At the apertures of the mouth, nostrils,

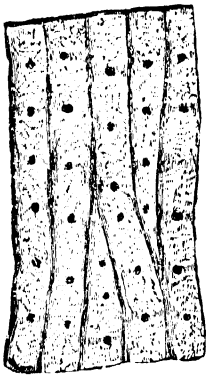


FIG. 651.—MAGNIFIED VIEW OF FOUR OF THE RIDGES OF THE EPIDERMIS, WITH THE OPENINGS OF THE SUDORIFEROUS DUCTS. (After Breschet.)

FIG. 652.—SECTION OF SKIN OF HEEL. (Blaschko.) Low power.

ep., epidermis; *c.*, cutis vera; *d*, *d*, ducts of sweat-glands; *d'*, *d'*, their openings at the surface of the papillary ridge; *r.m.*, Malpighian layer of epidermis; this is thickened opposite the papillary ridges, where it dips down into the cutis vera (at *r.'m.'*) leaving prominences of the cutis between.

rectum, and vagina the skin is continued into the mucous membranes which line those parts. The appendages of the skin are the nails, hair, and cutaneous glands. These are all of ectodermic origin, and of epithelial structure. Their description may conveniently follow that of the epidermis and cutis vera.[1]

EPIDERMIS.

The **epidermis, cuticle,** or **scarf-skin** belongs to the class of stratified epithelia, the general nature of which has been already considered. It forms a protective covering over every part of the true skin. The thickness of the cuticle varies in different parts of the surface, measuring in some places not more than 0.03 mm., and in other parts as much as 1 mm., or even more in some individuals. It is thickest in the palms of the hands and soles of the feet, where the skin is much exposed to intermittent pressure, and it is not improbable that such pressure may serve to stimulate the adjacent true skin to a more active formation of epidermis; but the difference does not depend immediately on external causes, for it is well marked even in the fœtus.[2]

[1] For details regarding the structure of the skin and its appendages, and an extensive bibliography to that date, see v. Brunn, Article 'Haut' in v. Bardeleben's Handbuch der Anatomie, 1897.

[2] For measurements of the thickness of the epidermis and its parts in different regions of the body see Drosdoff, Arch. de physiol. 1879.

In those parts of the skin where the papillæ are arranged in rows, the epidermal layer is thickened over the rows, the thickening appearing as ridges of the surface, upon which at regular intervals are seen small notches where the sweat-ducts open (fig. 651). The Malpighian layer participates in this thickening, and opposite the surface ridges dips deeper into the corium (fig. 652).[1]

The more firm and transparent superficial part or *horny layer* (*stratum corneum*) of the epidermis may be separated after maceration from the deeper, softer, more opaque and recently formed part, which constitutes the *Malpighian layer* (*stratum germinativum*) or *rete mucosum*.

The under or attached surface of the cuticle is moulded on the adjoining surface of the corium, and, when separated by maceration or putrefaction, presents impressions corresponding exactly with the papillary or other eminences, and the furrows or depressions of the true skin; the more prominent inequalities of the latter are marked also on the outer surface of the cuticle, but less accurately. Fine tubular

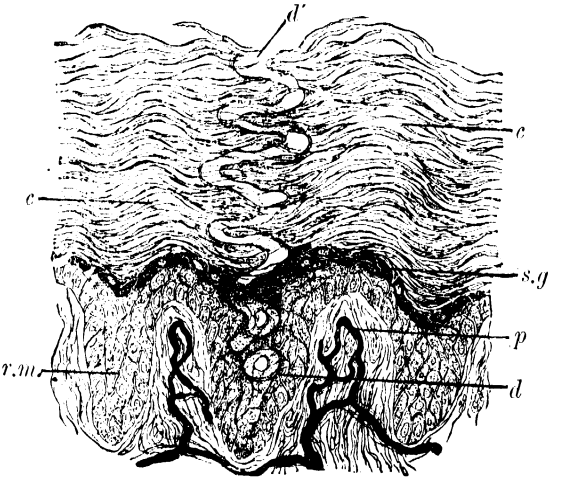


FIG. 653.—SECTION OF HUMAN EPIDERMIS WITH TWO VASCULAR PAPILLÆ OF THE CORIUM. (Heitzmann.) Magnified 200 diameters.

p, loop of capillary vessels in papilla; *r.m.*, rete mucosum; *s.g*, stratum granulosum; *c*, stratum corneum; *d*, *d'*, duct of sweat-gland passing through the epidermis.

prolongations of the cuticle are continued into the ducts of the sweat-glands, and are often partially drawn out from their recesses when the cuticle is detached, appearing then like threads proceeding from its under surface.

Structure.—The cuticle is made up of cells packed together in many irregular layers (figs. 653, 654). The deepest cells are elongated, and placed perpendicularly on the surface of the corium; they are denticulate at their lower ends, and fit into corresponding fine denticulations of the corium. The perpendicular cells generally form one stratum; above them are strata of cells of a more rounded or polyhedral shape. The cells have fine intercellular clefts or channels between them, bridged across by fibrils which pass from cell to cell (fig. 655), as in all stratified epithelia. The bridging fibrils run through the cell-bodies, in which they intercross, forming a kind of regular felt-work (fig. 656). The parts of the fibrils which bridge across the intercellular spaces exhibit nodular enlargements resembling the 'equatorial plates' of dividing cells (see p. 46).[2] These so-called 'spinous cells' form several strata; above, they become gradually

[1] See Blaschko, Arch. f. mikr. Anat. xxx. 1887; M. Heidenhain, Anat. Hefte, xxx. 1906.

[2] According to Rosenstadt (Arch. f. mikr. Anat. lxxv. 1910) the nodules are in reality crossing fibrils seen in optical section.

more flattened, conformably to the surface, until a layer, often incomplete, is reached in which the cells have a markedly granular appearance (Langerhans[1]). This has been termed the *stratum granulosum* (fig. 654). The granules in the cells are composed of a peculiar matter (*eleidin* of Ranvier,[2] *keratohyalin* of Waldeyer[3]), staining deeply with carmine and hæmatoxylin (fig. 657), and they are believed to have some connexion with the formation of the horny substance in the more superficial cells, since they occur the more abundantly the thicker the stratum corneum covering them (Klein). In places where the epidermis is thin, the stratum granulosum may be inconspicuous or absent. But a genetic relation between eleidin and keratin is rendered improbable if the statement which has been made by some

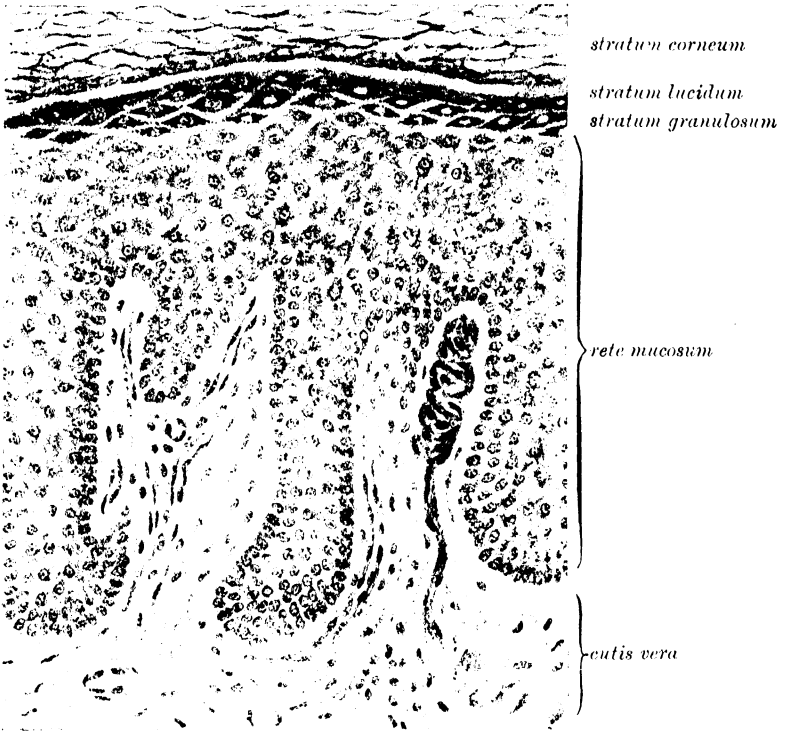


FIG. 654.—VERTICAL SECTION THROUGH THE SKIN OF THE PALMAR SIDE OF THE FINGER, SHOWING TWO OR THREE PAPILLÆ (ONE OF WHICH CONTAINS A TACTILE CORPUSCLE) AND THE DEEPER LAYERS OF THE EPIDERMIS. (Schäfer.) Magnified about 200 diameters.

authors is correct, that in some parts of the epidermis where a large amount of keratin is produced eleidin granules are not formed within the cells of the rete mucosum.

The chemical reactions of the eleidin or keratohyalin granules have been investigated by Waldeyer, who finds that the substance composing them is insoluble in water, alcohol, ether and acetic acid, but soluble in caustic alkalis and in mineral acids. Ranvier was unable to find eleidin in birds, reptiles, and amphibia, although he found it in all stratified epithelium in mammals. In the nail-matrix it is, however, replaced by a somewhat different material; and in other keratin-forming epithelia, substitutes may also occur.

According to Rabl[4] the keratohyalin-granules are derived from material furnished by the nucleus, but not from its chromatin. The granules do not appear to be transformed into

[1] Arch. f. mikr. Anat. ix. 1873
[2] Travaux, 1884.
[3] Henle Festschrift, 1882.
[4] Arch. f. mikr. Anat. xlviii. 1897.

keratin, but rather to run together as the cells pass into the succeeding more superficial layer, in which they form distinct drops of fluid (fig. 657, *b*).

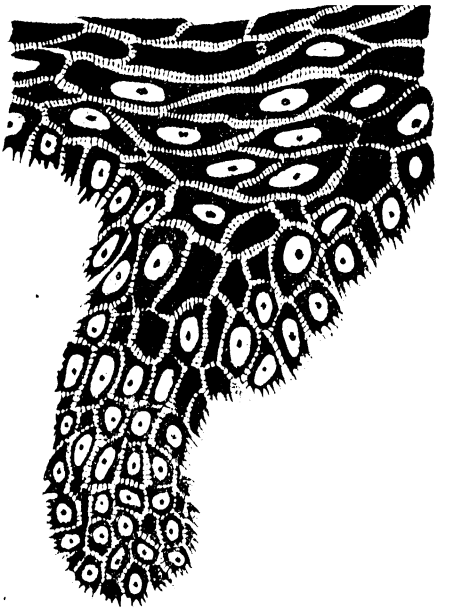


FIG. 655.—SECTION OF EPIDERMIS OF CAT'S FOOT SHOWING FIBRILS BRIDGING ACROSS THE INTERCELLULAR SPACES OF THE RETE MUCOSUM. THE DENTICULATIONS OF THE DEEPEST LAYER ARE ALSO SHOWN. (Kolossow.)

Immediately above the stratum granulosum is a clear-looking layer in which the outlines of the cells are somewhat indistinct. This layer, which is not always

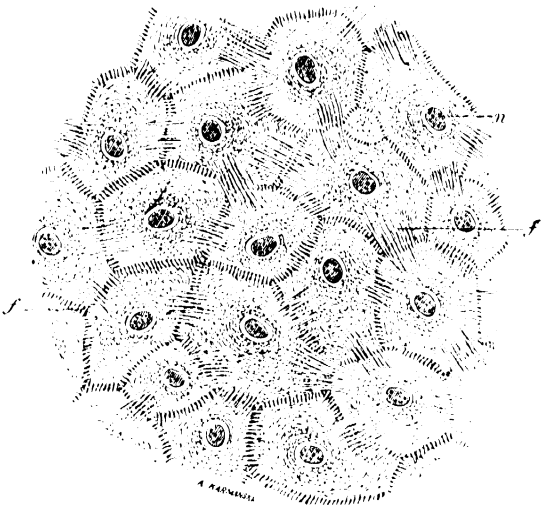


FIG. 656. FROM A SECTION OF THE RETE MUCOSUM OF THE EPIDERMIS SHOWING FIBRILS PASSING FROM CELL TO CELL ACROSS THE INTERCELLULAR SPACES. (Ranvier.)

n, a cell-nucleus; *f*, *f*, fibrils.

sharply marked off from the one superficial to it, has been termed *stratum lucidum* (fig. 654), and may be looked upon as transitional between the Malpighian and the horny layer of the epidermis. Its cells are not keratinised and the eleidin within

them is in a fluid condition. Superficial to it is a stratum which in some parts of the skin is of considerable thickness, and in which the cells are much enlarged, and the nuclei in many cases no longer visible: still nearer the surface this passes into a stratum of hard flattened scales which are constantly being thrown off by desquamation. As the cells change their form, their contents undergo chemical and physical changes; for in the rete mucosum they consist of a soft, fibrillar, protoplasmic matter, whilst the superficial cells are transparent, dry, and horny. These dry hard scales may be made to reassume their cell-form by exposure for a few minutes to a solution of caustic potash or soda, and then to water. Under this treatment they are softened by the alkali, and distended by imbibition of water.

As Zander [1] pointed out, there are two types of horny layers in the epidermis. The epidermis covering the greater part of the surface of the body has a stratum

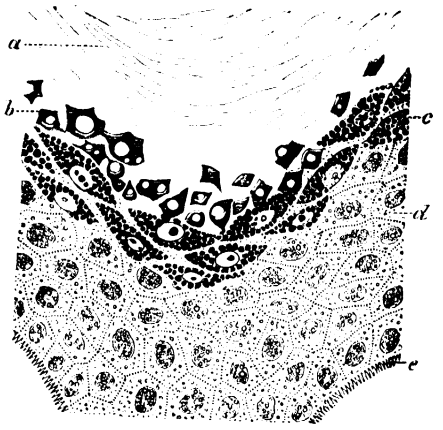


FIG. 657.—SECTION OF EPIDERMIS FROM THE SKIN OF THE FINGER, COLOURED BY PICROCARMINE. (Ranvier.)

a, stratum corneum; *b*, stratum lucidum, some of the cells of which are filled with eleidin; *c*, stratum granulosum, full of eleidin granules or droplets; *d*, spiny cells of rete mucosum; *e*, denticulations of deepest cells, for attachment to cutis vera.

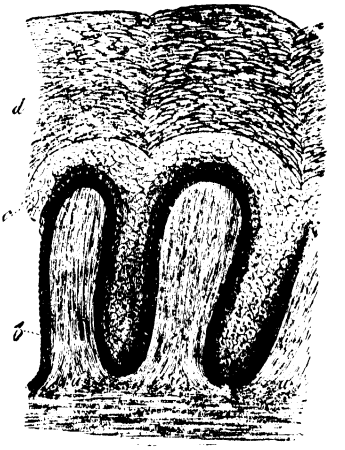


FIG. 658.—SKIN OF THE NEGRO, VERTICAL SECTION. (Kölliker.) Magnified 250 diameters.

a, *a*, cutaneous papillæ; *b*, undermost and dark-coloured layer of oblong vertical epidermis-cells; *c*, Malpighian layer; *d*, horny layer.

corneum composed exclusively of thin flattened scales which have lost all appearance of structure, although on treatment with dilute caustic alkali they swell up and assume the appearance of small vesicles; this is probably an indication that only the external layer of each cell is fully keratinised. On the other hand the horny stratum covering those parts of the skin which have a thicker epidermis and are not provided with hairs, is mainly composed of large swollen-out cells, with a central cavity representing the nucleus. These cells are permeated by a feltwork of fine fibrils which intercross in every direction. The cells in question appear to represent the epitrichial layer which during a certain period of fœtal development covers the whole surface of the body, but is thrown off where the hairs become developed (see next page).

The keratinisation process in the epidermis seems to involve the part of the cytoplasm between the cell-fibrils.[2] According to Weidenreich [3] the interfibrillar substance of the cells of the horny layer is altered eleidin (pareleidin), and the keratin is confined to the membranous outer layer. In the scaly cells at the surface the fibrillar structure is more difficult to demonstrate, but is probably present.

[1] Arch. f. Anat. 1888.

[2] Apolant, Arch. f. mikr. Anat. lvii. 1901.

[3] *Ibid.* lvi. 1900, and lvii. 1901.

Many of the cells of the cuticle contain pigment-granules, and in parts give the membrane more or less of a tawny colour, even in the white races of mankind; the blackness of the skin in the negro depends entirely on pigment in the cuticle. The pigment is contained principally in the cells of the deepest layer of the rete mucosum (fig. 658), but even the superficial part possesses a certain amount.

In the intercellular channels of the Malpighian layer stellate cells (probably leucocytes) are occasionally observed (Langerhans), and these, in animals, may also contain pigment-granules.

Development.[1]—The epidermis is derived from the cutaneous ectoderm. During the second month of intra-uterine life it consists of two layers of protoplasmic cells, of which the deeper are smaller and cubical, soon becoming columnar, the more superficial larger and flattened, soon becoming polygonal. The latter multiply, and by the second month are two or three cells deep; the most superficial cells are now clearer and more swollen, and stain less deeply with basic dyes, than the deep layer of cells. Between the second and third month, according to the observations of Minot [2] and Bowen,[3] the most superficial layer of the epidermis is formed by a complete stratum of these enlarged, swollen-out cells (fig. 659). These were noticed by Zander upon the fingers and toes of embryos of about thirteen weeks or more, and were termed by him 'bladder'-cells. The layer increases for a time in thickness, so as to be several cells deep (fig. 660), or even in certain parts, *e.g.* over the situation of the developing nails and on the palmar surface of the hands and plantar surface of the feet, to acquire a considerable thickness. Here the stratum seems to persist, but it disappears over the body of the nail, and also over the remainder of the surface of the skin, so that by the sixth month it is only found near the free border and root of the nail, and perhaps forming the thick horny layer of the palms and soles, which belongs to the second type of horny layer of Zander. This layer of bladder-like cells appears to correspond with an epithelial membrane which was first noticed by Welcker in a sloth-embryo, covering the surface of the body and lying over the developing hairs, hence named by him *epitrichium*. It has accordingly been termed the *epitrichial layer*, and has been shown to be of wide occurrence in the embryos of mammals and birds, and also to be represented in reptiles.[4]

FIG. 659.—SECTION OF EPIDERMIS FROM THE OCCIPUT OF A FŒTUS OF 2½ MONTHS. (Bowen.)

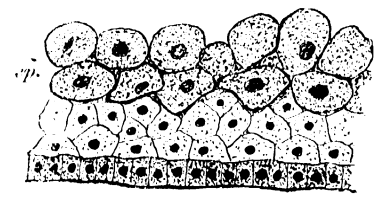


FIG. 660.—SECTION OF EPIDERMIS FROM THE PALM OF A 3 MONTHS FŒTUS. (Bowen.)

ep., epitrichial layer.

The cells of the fœtal epidermis underneath this epitrichial layer form the rete mucosum or Malpighian layer. The more superficial cells of the rete mucosum develop granules of eleidin and eventually become keratinised, so that a stratum corneum is produced. After the throwing off of the epitrichial layer, the superficial cells of the stratum corneum are also gradually cast off, whilst others pass from the rete mucosum to replace them. The cast-off scales, mingled with

[1] On the development of the epidermis and its appendages see W. Krause in Hertwig's Handbuch der vergl. Entwickelungsgesch. ii. 1906.

[2] Amer. Ass. for the Adv. of Science, 1885. [3] Anat. Anz. iv. 1889.

[4] On the epitrichium in the bird-embryo see E. G. Gardiner, Arch. f. mikr. Anat. xxiv. 1884; B. Rosenstadt, Arch. f. mikr. Anat. xlix. 1897. Rosenstadt finds the epitrichium-cells in the bird-embryo to be full of keratohyalin granules, which are derived from the nuclei. He considers the presence of these granules to be typical of epitrichium-cells, and states that these cells contain no keratin.

secretion of the cutaneous glands, form a yellowish caseous layer covering the surface of the fœtus (smegma embryonum, vernix caseosa), and occur also in flakes in the amniotic fluid.

The pigmentation of the Malpighian layer in the coloured races of mankind is frequently not superficially manifest until a day or two after birth: being con-

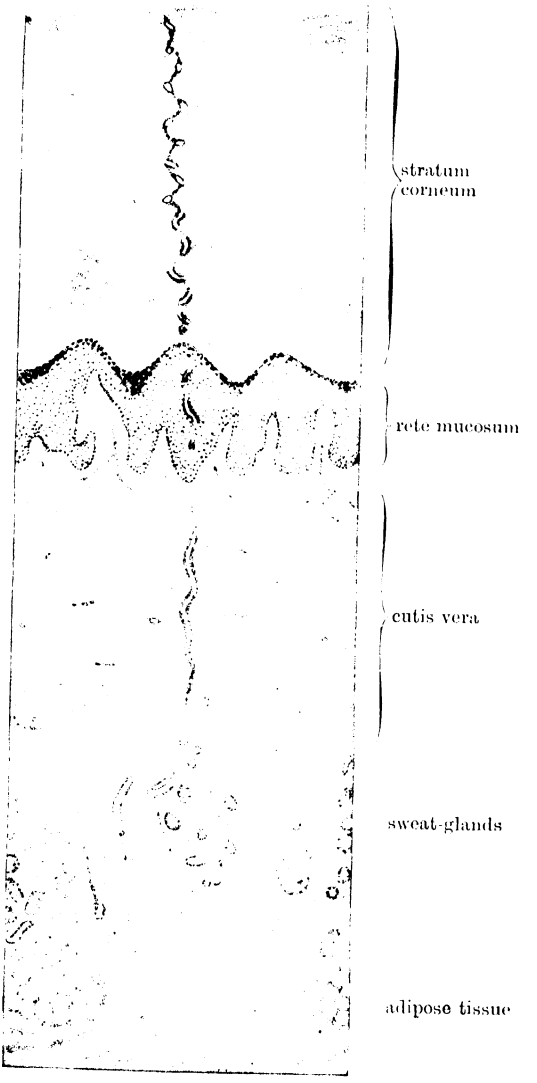


FIG. 661.—VERTICAL SECTION THROUGH THE SKIN OF THE SOLE OF THE FOOT. (Schäfer.) Magnified about 25 diameters.

cealed by the moist and therefore opaque epidermis over it. In the negro fœtus the pigment is present some weeks before term.

Growth.—The growth of epidermis continues throughout life. The cells of the rete mucosum are constantly multiplying,[1] and the new cells thus produced push outwards those previously formed. The more superficial cells of the Malpighian layer are thus continually passing on to reinforce the horny layer, the

[1] Hence also termed *stratum germinativum* (Flemming, Arch. f. mikr. Anat. xxiii. 1884).

cells as they proceed outwards becoming flattened and transformed into horny matter. This change seems to occur quite abruptly at the stratum lucidum; superficial to this the cells again swell out somewhat, until on reaching the layers nearest the surface they are entirely transformed into structureless horny scales which are constantly undergoing desquamation.

Regeneration.—When a portion of epidermis has been removed by a blister or wound of any kind, there is reason to suppose that its regeneration, like its growth, takes place only from cells of the Malpighian layer. If the whole of the epidermis over an extensive surface has been destroyed or removed, the process of regeneration is very slow, since the new covering has to grow in from the epidermis at the margins of the wound. But if the deeper cells have not been wholly removed, the regeneration may start from the places where any of them still remain, and the formation of the new covering is proportionately quicker. In the operation of 'skin-grafting' the surgeon endeavours to transplant from a healthy portion of skin small pieces of the epidermis, including its deeper layers, to the denuded surface: if the operation succeed, each such graft acts as a centre from which the new formation of epidermis may spread, and in this way the raw surface may be much more speedily covered.

CUTIS VERA.

The **true skin, cutis vera,** or **derma** is a sentient and vascular fibrous membrane. It is covered and protected, as already explained, by the non-vascular cuticle, and is attached to the parts beneath by a layer of areolar tissue, named 'subcutaneous,' which, except in a few parts, contains fat, and has therefore been also called the 'panniculus adiposus' (fig. 661). The connexion is in many places loose and movable, in others close and firm, as on the palmar surface of the hand and the sole of the foot, where the skin is fixed to the subjacent fascia by numerous stout fibrous bands (*retinacula cutis*), the space between being filled with a firm padding of fat. In some regions of the body the skin is moved by striated muscular fibres, which may be unattached to fixed parts, as in the case of the orbicular muscle of the mouth, or they may be attached beneath to bones or fasciæ, as is the case with the other cutaneous muscles of the face and neck, and the short palmar muscle of the hand.

Structure.—The cutis vera is made up of an extremely strong and tough framework of interlaced connective-tissue bundles. Its fibres are chiefly of the white variety, such as constitute the main part of the fibrous and areolar tissues; the bundles are stout and arranged loosely, except near the surface; where the texture becomes finer and closer. The principal bundles of the corium do not run anyhow, but have a regular average direction in different parts of the body (Langer), the direction being for the most part transverse to that of the subjacent muscles. With these are mixed elastic fibres, which vary in amount in different parts. Elastic tissue occurs in all parts of the cutis vera and of the subcutaneous tissue. It is extensively developed in some of the superficial fasciæ—such as that of the abdomen—where it forms close networks, almost amounting to continuous membranes (Kölliker). Its fibres are very fine in the papillary part of the cutis and in the papillæ themselves, where they have a vertical arrangement; whereas in the reticular layer they are not only much coarser, but their general arrangement is parallel to the surface. Many elastic fibres also accompany the blood-vessels, and enter into the formation of the connective-tissue sheaths of the hair-follicles and the connective-tissue investments of the sweat-glands and their ducts.

The cutis vera contains numerous branched connective-tissue corpuscles, mostly of the lamellar variety; many of them lie in the interstices of the white bundles, against which they are flattened. Other kinds of connective-tissue cells

are not absent, clasmocytes being especially numerous in the deep subcutaneous tissue; here also mast-cells may occur, in some parts in considerable numbers. Wander-cells are found in all parts of the cutis, and may even penetrate into the deeper layers of the epidermis.

Pigmented cells, although occurring in the cutis vera of the negro, are in the white races constantly found only near the anus; the deeper layer of the epidermis also contains pigment in this situation. Abnormally branched cells containing pigment occur in the white races in the bronzed patches which are seen in Addison's disease; here also there is pigment in the epithelium. It is possible that the branched pigmented cells in these cases are wander-cells conveying the pigment-granules to or from the epidermis.[1]

Towards the attached surface the texture of the cutis vera becomes much more open, with larger meshes, in which lobules of adipose tissue and the sweat-glands are lodged (fig. 661); thus the fibrous part of the skin, becoming more and more lax and more mixed with adipose tissue, blends gradually with the subcutaneous areolar tissue. In consequence of this gradual transition of the cutis vera into the subjacent tissue, its thickness cannot be assigned with precision. As a general rule, it is thicker on the posterior aspect of the head, neck, and trunk, than in front; and thicker on the outer than on the inner side of the limbs. As well as the cuticle, it is remarkably thick on the soles of the feet and palms of the hands. The skin of the female is thinner than that of the male.

Bundles of plain muscular tissue are distributed in the substance of the derma wherever hairs occur; their connexion with the latter will be afterwards explained. Plain muscular bundles are also found in the subcutaneous tissue of the scrotum, of the penis (glans and prepuce), of the perineum, and of the areola of the nipple, as well as in the nipple itself. They commonly join to form reticular layers, attached to the under-surface of the corium.

For convenience of description it is not unusual to speak of the derma as consisting of two layers, the 'reticular' and the 'papillary.' The reticular, the more deeply seated, takes no part in the construction of the papillæ, but contains in its meshes hair-follicles, sweat-glands, and some adipose tissue. The papillary is extended to form the papillæ, and receives the upper portions of the hair-follicles and gland-ducts, together with the terminal expansion of the blood-vessels.

The cutis vera is generally said to measure from $\frac{1}{50}$th of an inch to nearly one-eighth of an inch (·5 to 3 millimetres); but, as has been pointed out by Warren, that on the back and shoulders may be as thick as 5 or 6 mm. Here it is almost entirely formed of dense anastomosing bundles of connective tissue, on the one hand sending down fibrous prolongations through the subjacent panniculus adiposus, and on the other hand being penetrated obliquely by columns of fat-cells, which extend from that layer to the bases of the small hair-follicles, and conduct blood-vessels to these and to the surface of the skin.

Superficial markings.—The free surface of the cutis vera is marked in various places with larger or smaller furrows, which also affect the superjacent cuticle. The larger are seen opposite the flexures of the joints, as those so well known in the palm of the hand and at the joints of the fingers. The finer furrows intersect each other at various angles, and may be seen almost all over the surface; they are very conspicuous on the back of the hands. Fine curvilinear ridges, with intervening furrows, mark the skin of the palm and sole; these correspond in general arrangement to the rows of papillæ, to be immediately described: they form

[1] See on the pigment-cells, Waldeyer, Virch. Arch. 1870; Schäfer, reported in Greenhow's Croonian Lectures on Addison's Disease, 1875, p. 137; Ehrmann, Viertelj. f. Dermat, 1885; Unna, Monatschr. f. prakt. Derm. iv. 1885; Karg, Arch. f. Anat. 1888, Kölliker, Zeitsch. f. wiss. Zool. xlv. 1887, and Gewebelehre, 1889; List, Anat. Anz. iv. 1889; Rabl, Ergebn. d. Anat. vi. 1896 (with literature to that date); Meirowsky, Monatschr. f. pract. Derm. xlii. 1906, and Zeitschr. f. Pathol. ii. 1909. Meirowsky claims to have obtained pigment-formation in minute excised portions of skin, kept for some days under aseptic conditions in a moist chamber at body temperature.

definite patterns, characteristic of each individual, but capable of being classified under a relatively small number of heads. Moreover, these patterns are permanent and do not alter as growth advances, the impression obtained from the hand of a young child being identical even in the most minute details (although of course somewhat less displayed) with that obtained from the same individual when grown up (F. Galton).[1]

Ridges and papillæ.—The surface of the cutis vera shows ridge-like projections of its substance into the under surface of the epidermis, which in some parts run parallel with one another (although here and there joined by a cross ridge), while in others they have a somewhat reticulated arrangement (owing to a multiplicity of such cross ridges). The ridges have an uneven surface, this unevenness taking the form, in many parts, of prominent finger-shaped

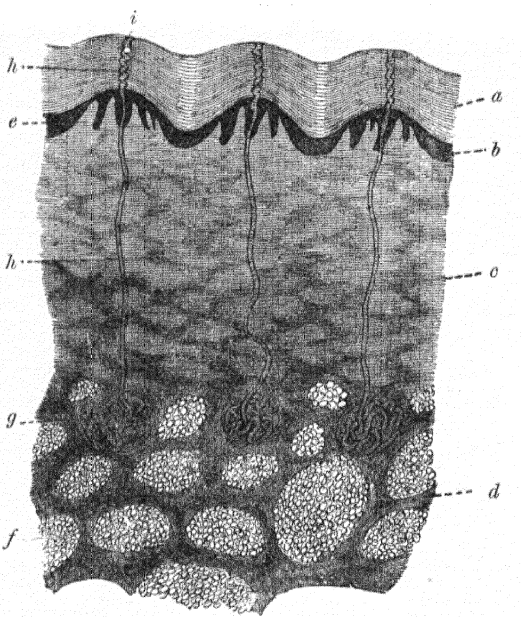


FIG. 662.—VERTICAL SECTION OF THE SKIN AND SUBCUTANEOUS TISSUE, FROM THE END OF THE THUMB, ACROSS THE RIDGES AND FURROWS. (Kölliker.) Magnified 20 diameters.

a, horny, and *b*, Malpighian layer of the epidermis; *c*, corium; *d*, *panniculus adiposus*; *e*, papillæ on the ridges; *f*, fat-clusters; *g*, sweat-glands; *h*, sweat-ducts; *i*, their openings on the surface.

eminences known as *papillæ*, which fit into corresponding pits in the deeper part of the epidermis. The papillæ are probably of use in bringing the superficial blood-vessels of the cutis into closer connexion with the epidermis, and thus minister to its nutrition, but they must also contribute to the functions of the skin as a tactile organ, seeing that some of them contain special sensory nerve-endings and that they are well developed where the sense of touch is well-marked. Both ridges and papillæ are prominent where the epidermic covering is thickest: thus we find the ridges well developed under the nail, and the papillæ longest and most closely arranged on the palmar surface of the hand and fingers, and on the corresponding parts of the foot. In these parts the ridges which bear the papillæ

[1] See on this subject Lewinsky, Virch. Arch. xcii. 1883; F. Galton, Phil. Trans. 182 B, 1891; and Finger Prints, London, 1892. On the development of the papillary ridges of the skin, see J. E. Evatt, Journ. of Anat. and Physiol. xli. 1906. The markings appear in the cutis of the human embryo at eleven weeks, and show on the surface of the epidermis at eighteen weeks. W. Kidd (*ibid.*) finds that in many parts the papillary ridges tend to be somewhat imbricated.

are ranged in parallel curved lines, as has already been mentioned.[1] As M. Heidenhain has pointed out, the *superficial* ridges do not necessarily correspond exactly with the uppermost parts of the laminæ, but often with the *spaces* between the laminæ. The papillæ are of a conical figure, rounded at the top and sometimes cleft into two or more points (see fig. 654). In structure they resemble the rest of the superficial layer of the corium, and consist of a finely fibrillated tissue, with a few elastic fibres. The bundles of fibrils chiefly run parallel to the axis of the papilla and the fibrils appear to end near its surface, which has a somewhat corrugated aspect. On the palm, sole, and nipple, where they are mostly of the compound variety, they measure from 0·125 to 0·25 mm. in height. On the ridges, the papillæ are placed commonly in double rows, with a space free from papillæ

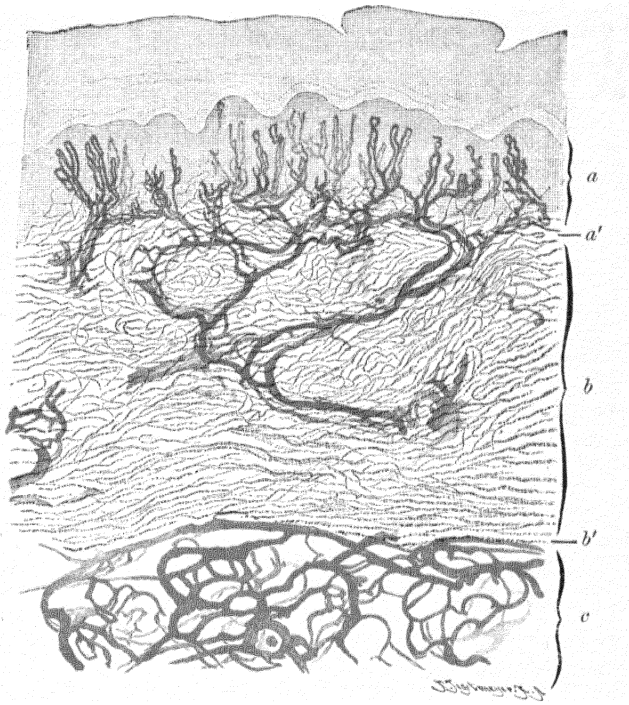


FIG. 663.—SECTION OF SKIN WITH BLOOD-VESSELS INJECTED. (v. Brunn.)

a, papillary layer of cutis vera; *a'*, subpapillary plexus; *b*, reticular layer of cutis vera; *b'*, subcutaneous plexus; *c*, panniculus adiposus.

between them (fig. 662); there are no papillæ in the grooves between the ridges. The ridges which are seen at the surface of the epidermis are marked at short and tolerably regular intervals with notches or short transverse furrows, in each of which, about its middle, is the minute funnel-shaped orifice of the duct of a sweat-gland. In other parts of the skin the papillæ are broader, shorter, fewer in number, and irregularly scattered. On the face they are only from ·003 mm. to ·005 mm. in height; here they disappear altogether in parts, or are replaced by slightly elevated reticular ridges. Fine blood-vessels enter most of the papillæ, forming either a simple capillary loop in each, or dividing into two or more capillary branches, according to the size of the papilla and its simple or composite form. Other papillæ receive nerves, and contain tactile corpuscles (fig. 654).

[1] On the relative development of the ridges and papillæ of the cutis see Blaschko, Arch. f. Anat. u. Physiol. 1884 and 1885, and Arch. f. mikr. Anat. xxxi. 1887.

Blood-vessels and lymphatics.—The *arteries* (fig. 663) divide in the sub cutaneous tissue (*subcutaneous plexus*), and, as their branches pass from this deep expansion towards the surface of the skin, they supply offsets to the fat-clusters, sweat-glands, and hair-follicles.[1] They divide again and anastomose near the surface (*subpapillary plexus*), and at length, on reaching it, form a network of capillaries, with polygonal meshes. Fine looped branches pass from the superficial arteries into the papillæ, as already mentioned. The *veins* accompany the arteries, but form more distinct anastomoses and plexuses; four venous plexuses may in some parts be recognised lying in successive planes parallel with the surface of the cutis.

Lymphatics are found in all parts, although probably not everywhere in equal number; they are abundant and large in some parts of the skin, as on the scrotum and round the nipple. They form at least two networks, one superficial and another more deeply situated, which intercommunicate by uniting vessels, whilst the deeper

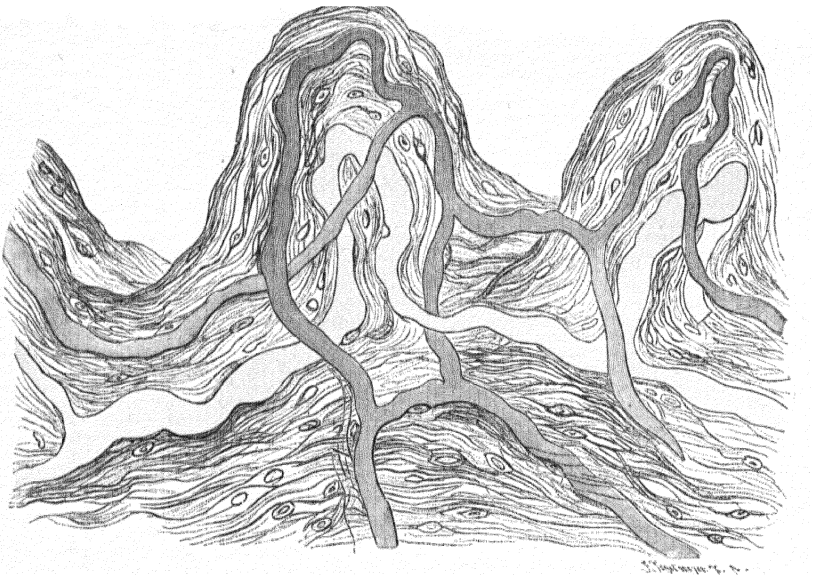


FIG. 664.—TWO PAPILLÆ FROM THE SKIN OF THE FINGER OF A NEW-BORN CHILD; INJECTED BLOOD-VESSELS RED, LYMPHATICS YELLOW. (v. Brunn after J. Neumann.)

network is joined with the lymphatics of the subcutaneous tissue. According to Klein there is a continuous plexus through the whole thickness of the corium, and all the vessels possess valves. The most superficial network, although close to the surface of the corium, is beneath the net of superficial blood-capillaries; its constituent vessels are much larger than the blood-capillaries. In certain parts on the palm and sole lymphatics pass into the papillæ, but do not reach their summits (fig. 664). The efferent lymphatics accompany the blood-vessels, two passing commonly with each small artery and vein, and joining and anastomosing over the vessels.[2]

As in other kinds of connective tissue, the lymphatics of the skin may be said to originate in the cell-spaces of the tissue, and since the cells lie for the most part in rows between the bundles, the combined spaces form interfascicular clefts. When these are injected the fluid passes into the lymphatics. The superficial cell-spaces communicate with the intercellular channels of the epithelium, and these also are thus brought into connexion with the lymphatics.

[1] See on the blood-vessels of the skin, Tomsa, Beitr. z. Anat. u. Phys. d. Haut, 1873; W. Stirling, Arb. a. d. Physiol. Anst. zu Leipzig, 1875; Journ. Anat. and Physiol. x. 1876; Spaltcholtz, Arch. f. Anat. 1893.

[2] On the lymphatics of the skin see Unna, Arch. f. mikr. Anat. lxxii. 1908.

Nerves.—Fine varicose nerve-fibrils pass up into the epidermis, penetrating between the cells of the Malpighian layer (fig. 665), where they undergo a certain

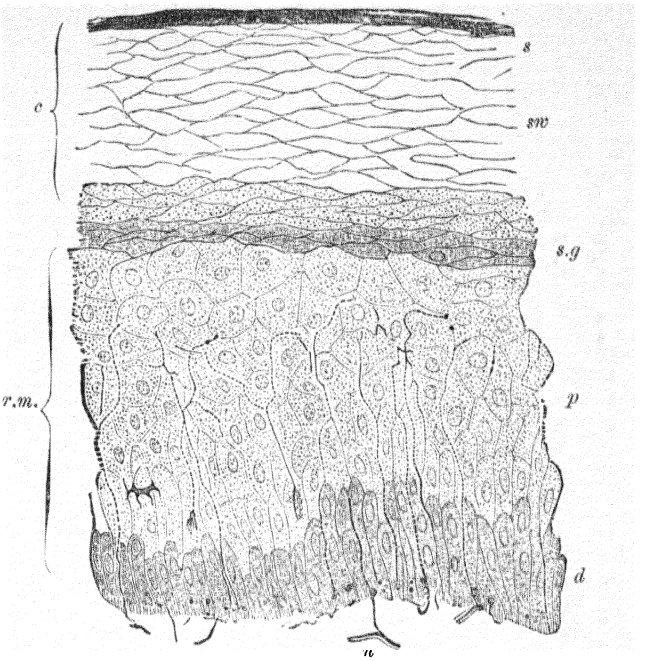


FIG. 665.—SECTION OF EPIDERMIS FROM THE HUMAN HAND. (Ranvier.) Highly magnified.

c, horny layer, consisting of *s*, superficial horny scales, and *sw*, swollen-out horny cells; *s.g*, stratum granulosum; *r.m.*, rete mucosum or Malpighian layer, consisting of *p*, prickle-cells, several rows deep, and *d*, elongated cells forming a single stratum near the corium; *n*, part of a plexus of nerve-fibres in the superficial layer of the cutis vera: from this plexus, fine varicose nerve-fibrils may be traced passing up between the cells of the Malpighian layer.

amount of ramification. The branches do not unite with one another to form a network, but end in knob-like swellings or varicosities. With the growth and displacement of the cells between which they are placed, these varicosities become, according to Ranvier, continually detached from the end of the fibrils, the latter meanwhile growing constantly to supply the place of the detached portions.

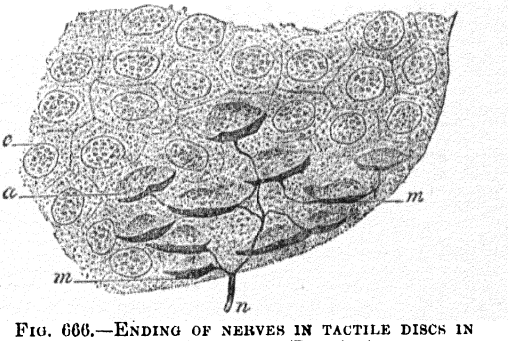


FIG. 666.—ENDING OF NERVES IN TACTILE DISCS IN THE PIG'S SNOUT. (Ranvier.)

n, nerve-fibre; *m*, terminal menisci or tactile discs; *e*, ordinary epithelium-cell; *a*, altered epithelium-cell to which the meniscus is applied.

In the skin covering the snout of certain animals (*e.g.* mole) the nerves end in peculiar terminal organs (Eimer), formed of thickenings of the epidermis; the nerve-fibres pass as an elongated bunch of closely set, somewhat zigzag, varicose, unbranched fibrils between the epidermis-cells. Besides these fibrils there are others at the periphery of the organ which are less closely arranged, and terminate in branched extremities as in other parts of the epidermis. In the snout of the pig the branched axis-cylinders pass partly into concavo-convex enlargements between the deeper epithelium-cells (tactile menisci of Ranvier) (fig. 666). Similar arrangements obtain in the epidermis of the dog's nose.[1]

[1] E. Botezat, Anat. Anz. xxxiii. 1908. The literature of the distribution of nerves in the epidermis is given in this paper.

Merkel has described the nerves of the epidermis as ending in pyriform 'tactile' cells placed between the ordinary epithelial cells, and Langerhans thought that the nerves could be traced to stellate cells in the interstitial spaces; but improved methods of staining render it probable that the termination of the nerve-fibrils in the cuticle is as above described, *between* the cells, not actually within them. In many places, however, the cells against which the enlarged endings of the nerve-fibres (menisci) are applied, differ in appearance from the other epithelium-cells, and although the nerve-fibres do not enter them they may be regarded as tactile cells.

Nerves are supplied in very different proportions to different regions of the true skin. They pass upwards towards the papillary surface, where they form plexuses, of which the meshes become closer as they approach the surface, and the constituent branches finer. From the most superficial or subepithelial plexus, which lies immediately under the epithelium, delicate non-medullated fibrils pass off and ramify immediately beneath the epidermis, where they form the so-called *hederiform nerve-endings* (fig. 667). Many of the nerves of the cutis vera terminate in end-

FIG. 667.—HEDERIFORM NERVE-ENDINGS IN THE CUTIS VERA. (Ranvier.)
n, *n'*, nerve-fibres; *m*, enlargements on terminal fibrils; *p*, papillæ; *s*, sweat-duct.

bulbs, tactile corpuscles, and Pacinian bodies, the last-named being seated in the subcutaneous tissue. Here also occur corpuscles of Ruffini and Golgi-Mazzoni endings. The tactile corpuscles of the skin are found most numerously in certain papillæ of the palm and sole, more sparingly in those of the back of the hand and foot, the palmar surface of the fore-arm, and the nipple. Such papillæ commonly contain no blood-vessels, and are named 'tactile,' as distinguished from 'vascular' papillæ. The structure of these different terminal corpuscles has been already described (pp. 260 to 271). Many of the nerve-fibres, chiefly the non-medullated, are supplied to the plain muscular tissue of the minute hair-muscles and of the blood-vessels.

NAILS.

The nails are thickenings of the deeper part of the horny layer of the epidermis, overlying a well-marked Malpighian layer, but not covered in the fully formed condition by epitrichium or by the superficial horny scales which characterise the rest of the epidermis. The cells of which they are formed are very closely conjoined to form the dense keratinised structure which constitutes the nail proper.

The posterior part of the nail, which is concealed in a groove or sulcus of the skin, is named its 'root' (fig. 668, *a*); the uncovered part is the 'body'; it terminates in front by the 'free edge.' A portion of the nail near the root,

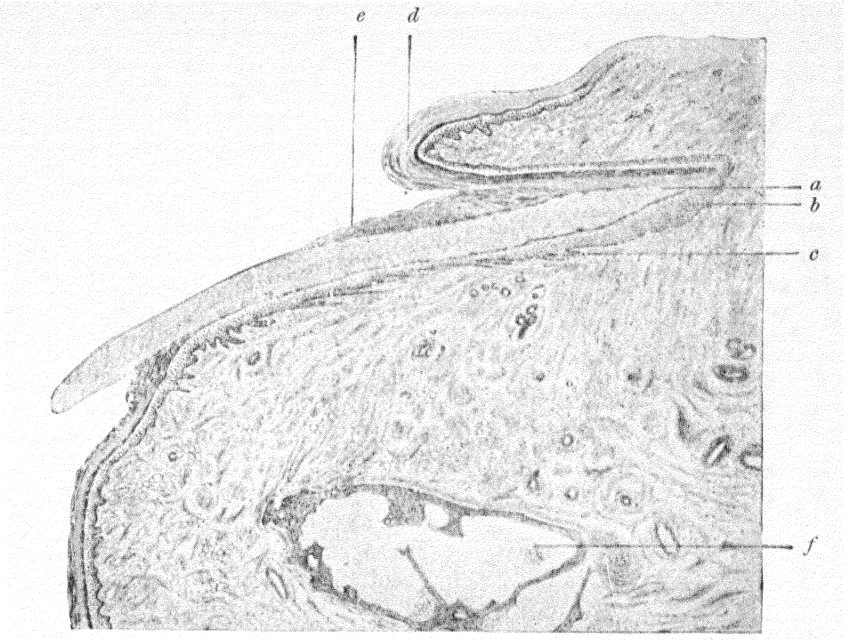


FIG. 668.—LONGITUDINAL SECTION THROUGH THE ROOT OF THE NAIL AND ITS MATRIX. (Schäfer.) Magnified about 10 diameters.

a, root of nail; *b*, Malpighian layer of matrix; *c*, ridges in dermis of nail-bed; *d*, epitrichial layer of epidermis; *e*, eponychium; *f*, bone (terminal phalanx) of finger.

named from its shape the 'lunula,' is whiter than the rest. This is largest on the thumb and is usually absent on the little finger. The appearance is commonly ascribed to the substance of the nail at this point possessing a greater degree of

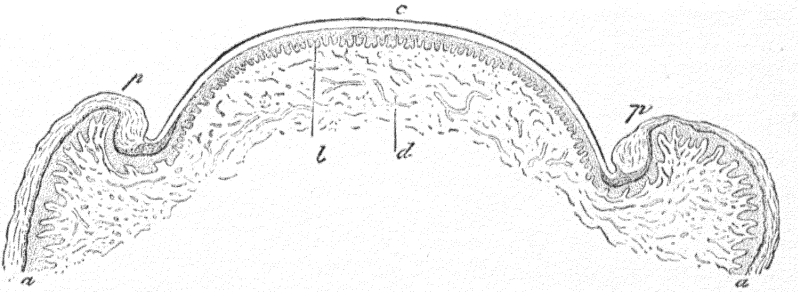


FIG. 669.—SECTION ACROSS THE MIDDLE OF THE NAIL OF A CHILD OF 8 DAYS. (Ranvier.)

c, body of the nail; *l*, nail-bed with its papillated ridges and rete mucosum; *d*, corium under nail-bed; *p*, fold at edge of nail: here the horny layer is separated from the mucous layer by a well-marked stratum granulosum, which is altogether lacking over the nail-bed; *a*, skin of finger at side of nail.

opacity in consequence of its being covered with a thick layer of the rete mucosum, the cells of which are in active process of division (Toldt), but according to Unna the opacity is due to the presence of keratohyalin (or onychogenic substance)

in considerable amount, and according to v. Brunn to the fibrous structure of the cells, which are undergoing keratinisation.

The part of the corium to which the nail is attached, and by which in fact it is generated, is named the *matrix* [1] or *nail-bed* (fig. 669). This portion of the skin is highly vascular, and ridged longitudinally over the greater part of its extent. In front, where the free edge of the nail begins to project, the ridges give place to large papillæ, which are continued forwards into a thickening of the ordinary epidermis. Posteriorly the matrix forms the crescentic groove already noticed (deep in the middle but getting shallower at the sides) which lodges the root of the nail. The matrix is closely attached, by means of dense connective-tissue bundles having a vertical arrangement, to the periosteum covering the ungual process of the terminal phalanx. The part of the matrix nearest the groove is covered with low papillæ having no regular arrangement. These papillæ become less marked and eventually disappear at about the middle of the lunula, the surface of the nail-bed here becoming flat for a certain space. The remaining surface of the matrix and nail-bed, situated in front of this and supporting the body of the nail, is marked with longitudinal ridges, more numerous but small and low behind, and becoming prominent in front, where, however, they

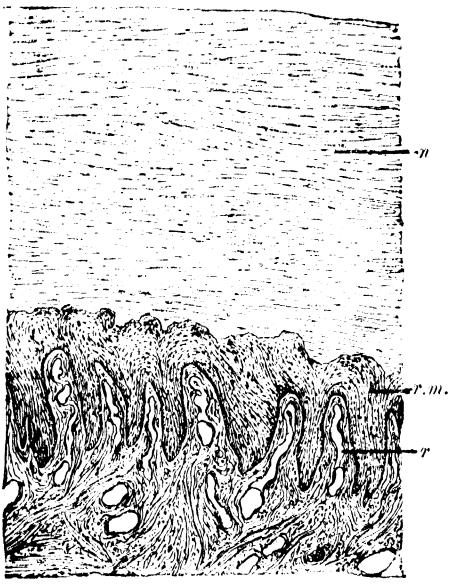


FIG. 670.—SECTION ACROSS THE NAIL AND NAIL-BED. (Heitzmann.)

r, ridges of cutis in section; *r.m.*, rete mucosum; *n*, nail.

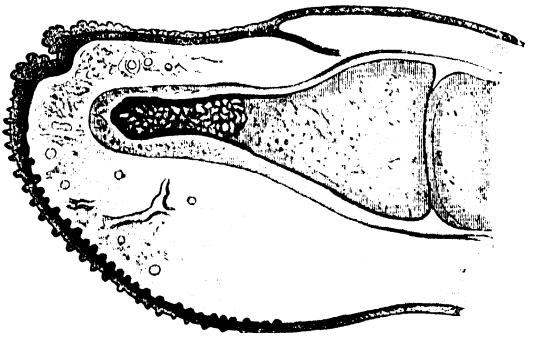


FIG. 671.—SECTION THROUGH END OF FINGER OF HUMAN EMBRYO AT THE TIME OF THE COMMENCEMENT OF FORMATION OF THE NAIL. (Kölliker.)

Notice the ossification of the terminal phalanx beginning at the tip of the cartilage. In the thickened epidermis over this the commencing nail is seen as a dark line.

are fewer in number. These ridges may be cleft at their summits; those towards the sides are directed obliquely. The ridges fit into corresponding furrows on the under-surface of the nail-epidermis.

[1] The term matrix is sometimes confined to the posterior part of the nail-bed; sometimes (*e.g.* by v. Brunn) to the rete mucosum of the epidermis of the part from which the root of the nail actually grows.

The ridges and papillæ are highly vascular, and have also an abundant nerve-supply. The nerves of the papillæ end in free ramifications, as well as in end-bulbs and tactile corpuscles. Ruffini corpuscles occur in the ridges; rarely Pacinian corpuscles; free endings are also found here.[1]

The nail, as already mentioned, is made up of a large number of horny epithelial cells which are broad and hard, but at the same time very thin, and so intimately connected together that their respective limits are scarcely discernible. They form the horny part or nail proper, cohering in parallel and sometimes slightly curved strata.[2] Air is sometimes developed between the strata, and gives the appearance of white specks in the substance of the nail. Below them are cells which are softer and of a polygonal shape. The deepest layer differs somewhat from the others in having its cells elongated and arranged perpendicularly, as in the case of the epidermis. Thus under the nail proper (fig. 670, *r.m.*) is a layer of cells corresponding with the rete mucosum of the epidermis, whilst the nail proper corresponds with a portion of the horny layer. The most superficial cells of the Malpighian layer of the nail have a granular aspect; this is due—not to the presence of eleidin but to the spiny processes which unite them to one another. As

FIG. 672.—APPEARANCE OF NAIL-SUBSTANCE IN THE FORM OF GRANULES OF ONYCHOGENIC MATERIAL IN SOME OF THE CELLS COVERING THE NAIL-BED. (Kölliker.)

in the case of the ordinary epidermis, the hardened scales of the nails may be made to reassume their cellular character by treatment with caustic alkali, and afterwards with water: it is then seen that they still retain an appearance of nuclei.

Formation and growth of the nails.—In the third month of intra-uterine life, the part of the embryonic corium which becomes the matrix of the nail is marked off by the commencing curvilinear groove, which limits it posteriorly and laterally. Part of the epidermis on the matrix then begins to assume, in the middle of its thickness, the characters of a nail (fig. 671); this is at first imbedded in the embryonic cuticle, in which it occupies the position of the stratum lucidum, and is covered by a thick layer of more loosely arranged scales, to which the name of *eponychium* has been applied (corresponding to the epitrichium of the general surface of the epidermis). The nail rudiment, which is preceded by and formed from granular cells somewhat similar to those of the stratum granulosum of the epidermis (fig. 672), first appears near the posterior part of the matrix, and from this point is developed forwards over the bed and backwards into the groove.[3] After the end of the fifth month it becomes free at the anterior border, breaking through the thick layer of epidermis which covers it superficially. The remains

[1] A. S. Dogiel, Arch. f. mikr. Anat. lxiv. 1904; Vitali, Internat. Monatschr. f. Anat. u. Physiol. xxiii. 1906.

[2] For variations in the arrangements of the strata and a discussion of the manner in which they are caused, see v. Brunn in v. Bardeleben's Handbuch der Anatomie, 1897.

[3] Zander, Arch. f. Anat. 1886; Kölliker, Zeitschr. f. wiss. Zool. xlvii. 1888. See further on the structure and growth of the human nail, Branca, Annales de dermat. et syphilis, 1910.

of this eponychium continue throughout life partly covering the lunula. At the anterior edge of the developing nail, the eponychium or epitrichial layer is greatly thickened (figs. 673, 674); below this epitrichial thickening is a well-marked stratum lucidum and stratum granulosum, continuous with the corresponding layers of the adjacent epidermis. At birth the free end of the nail is thin, being manifestly the earlier formed part, which has been pushed forward. As the infantile nail

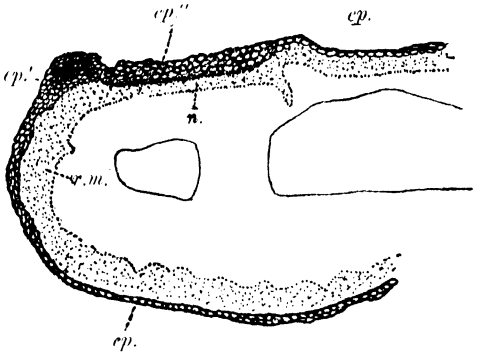


FIG. 673.—LONGITUDINAL SECTION OF THE TERMINAL PHALANX OF THE THIRD FINGER OF AN EMBRYO OF THE THIRD MONTH. (After Bowen.)

ep., epitrichial layer, greatly thickened at the nail-edge *ep.'*, and forming the eponychium *ep.''* above the nail formation, *n.*; *r.m.*, rete mucosum.

continues to grow, its flattened cells, at first easily separable, become harder and more coherent, as in after-life.

The average rate of growth of the nails is half a millimetre a week (W. Krause), but varies, being faster on the fingers than on the toes and faster in summer than in winter. According to Bloch[1] the rate varies at different ages. The growth is effected by a constant generation of the cells of the rete mucosum at the root. These cells in their more superficial layers acquire brownish granules, which are not

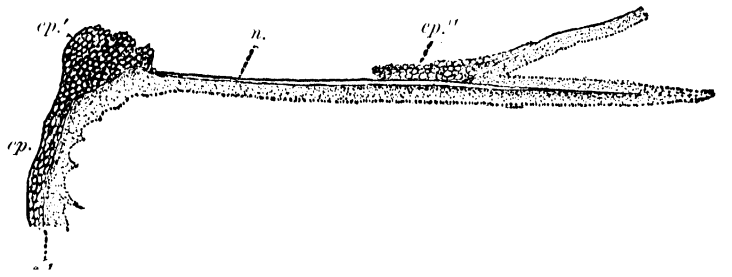
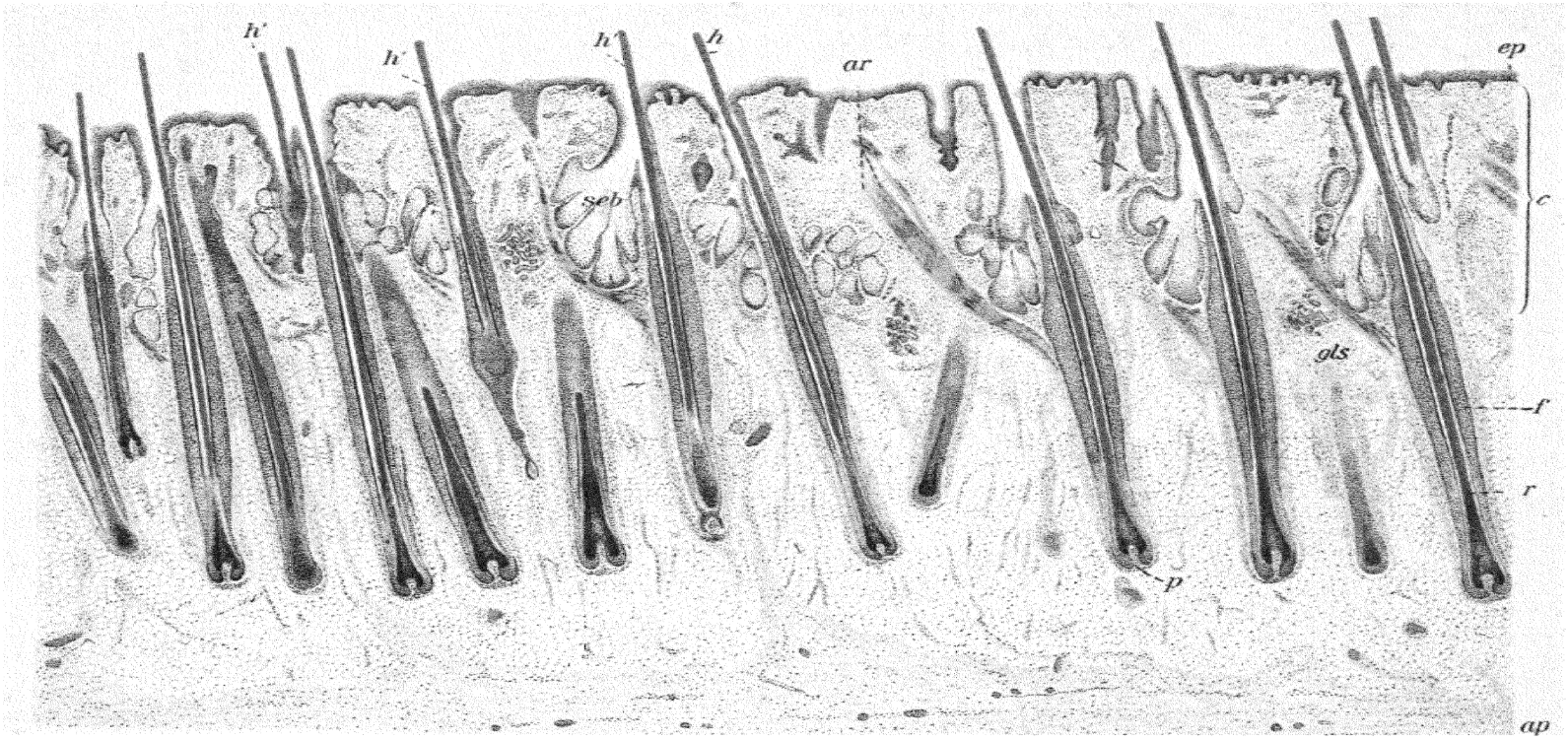


FIG. 674.—LONGITUDINAL SECTION OF THE GREAT TOE OF AN EMBRYO OF THE FIFTH MONTH. (After Bowen.)

ep., epitrichial layer of epidermis at end of finger; *ep.'*, thickening of epitrichium at the nail edge; *ep.''*, remains of eponychium; *n.*, nail; *s.l.*, stratum lucidum of epidermis.

identical with eleidin granules, and are termed by Ranvier *onychogenic substance* (*onychin*, Apolant). This substance stains brown with carmine instead of red, as do the eleidin granules; a similar brown-staining substance occurs in the fibrous substance and cuticula of the hairs. According to v. Brunn, any new onychogenic material formed after the sixth month of intra-uterine life is fibrillated, and is not composed of granules; its keratinisation takes place therefore

[1] C. r. soc. de biol. 1908.



Section of human scalp (Sobotta). Magnified 15 diameters. Haematoxylin-eosin.
h, ordinary hair; *h'*, club-hairs; *ar*, arrector pili; *f*, hair-follicle; *r*, root of hair; *p*, papilla of hair; *ep*, epidermis; *c*, cutis vera; *ap*, aponeurosis; *gls*, sweat glands; *seb*, sebaceous glands.

within fibrils which occupy the cell-protoplasm. In this respect it agrees in structure with the horny layer of the epidermis (see p. 449), and with the fibrous layer of the hairs. The fibrils of the nail-cells disappear, however, as the conversion into keratin is completed. Each successive series of these cells being followed and pushed from their original place by others, they become flattened out and transformed into the dry, hard, and inseparably coherent scales which characterise the nail-substance. By this addition of new cells at the posterior edge, the nail is made to advance, and by the apposition of similar particles to its under-surface at the lunula, it grows in thickness; so that it is thicker at the anterior border of the lunula than nearer the root. It does not appear to increase in thickness while passing over the bed. When a nail is thrown off by suppuration, or pulled away by violence, a new one is produced in its place, provided any of the cells of the Malpighian layer of the epithelium are left in the groove.

HAIRS.

A **hair** consists of a root, which is fixed in the skin, and a shaft or stem (see accompanying Plate). The stem is generally cylindrical, but may be more or less elliptical or even irregular in section: when the hair is uncut, it tapers gradually towards the point. The part nearest the root is also finer than the main stem. The length and thickness vary greatly in different individuals and races of mankind as well as in different regions of the body.[1] The finest are the so-called lanugo-hairs of the general surface, which may be no more than 5μ thick, while the hairs of the beard may be as thick as 200μ. But even in the same region, *e.g.* the scalp, the hairs vary in diameter from about 11μ to 160μ (Falck). In the straight-haired races (*e.g.* Mongolian), the individual hairs are coarser and thicker and the section more circular than in the crisp-haired races (negro), in which the section is smaller and oval, the hairs being sometimes markedly flattened. The section is largest in the North-American Indians, Chinese, and especially in the Japanese. Light-coloured hair is usually finer than black.

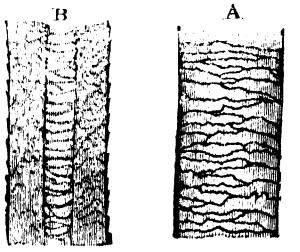


Fig. 675.—Human hair. (Schäfer.)

A, the surface of the hair focussed to show the cuticular scales. *B*, optical section. The medulla looks clear, the air having been expelled from it by Canada balsam.

The stem is covered with a coating of finely imbricated scales, the upwardly projecting edges of which give rise to a series of fine, waved, transverse lines, which may be seen on the surface of the hair with the microscope (fig. 675, *A*). Within this scaly covering, called the *hair-cuticle*, is a *fibrous* or *cortical substance*, which in all cases constitutes the chief part and often the whole of the stem; but in many hairs the axis is occupied by a substance of a different nature, called the *medulla* or *pith* (fig. 675, *B*). The *fibrous substance* is translucent, with short longitudinal opaque streaks of darker colour intermixed. It is formed of straight, rigid, longitudinal fibres, which again may be resolved into flattened cells of a fusiform outline; they are marked with ridges and furrows, and united to one another by fibrils, as in the deeper cells of stratified epithelium.[2] The colour of the fibrous substance is caused by oblong patches of pigment-granules, and generally diffused colouring-matter of less intensity. Very slender elongated nuclei are also discovered in the cells by means of reagents. Dark specks or marks often noticeable in the fibrous substance are occasioned by minute irregularly shaped cavities containing air; most

[1] Cf. Waldeyer, Atlas d. menschl. u. thier. Haare, 1884.

[2] Waldeyer, *op. cit.*; Reinke, Arch. f. mikr. Anat. xxx. 1887; Retterer, C. r. soc. de biol. lxiv. 1908; Branca, Annales de dermat. et syphilis, 1910.

of these are in the intercellular substance. The air-lacunules are abundant in white hairs, and are best seen in them, there being no risk of deception from pigment-specks; indeed they may be altogether wanting in very dark hairs. Viewed by transmitted light they are dark, but brilliantly white by reflected light. When a white hair has been boiled in water, ether, or oil of turpentine, these cavities become filled with fluid, and are then quite pellucid; but when a hair which has been thus treated is dried, the air quickly finds its way again into the lacunæ, and they resume their original aspect.

The *medulla* or *pith* does not exist in all hairs in the human subject. It is wanting in the fine hairs over the general surface of the body, and is not commonly met with in those of the head, nor in the hairs of children under five years. When present it occupies the centre of the shaft and ceases towards the point. It is composed of rows of cells, differing in shape, but generally angular, and in many animals exhibiting regular patterns. When viewed by transmitted light, it is black; by reflected light, on the other hand, it is white, its colour being due to the contained air-particles which lie in spaces between the cells, but in the hairs of a few animals within the cells. They are produced by the drying of the originally soft cells of the medulla on exposure of the growing hair to the atmosphere. The medulla may be interrupted at parts for a greater or less extent. In the latter case, the axis of the stem at the interruptions is fibrous like the surrounding parts.

The white colour which hair assumes with age is chiefly due to the absence of pigment in the fibrous part, allowing the white air-particles both of this, and especially of the medulla, to become manifest. If there is no medulla, as is the case in some individuals, the hair never becomes fully white with age, but merely grey.[1]

The **root** of the hair is lighter in colour and softer than the stem; in young and growing hairs it swells out at its lower end into a hollow bulbous enlargement or knob (see *h*, *h*, of Plate), but in older hairs which have ceased to grow and are in process of being shed, the termination of the root is not hollow but solid. Its extremity appears expanded, but in place of overlying a papilla it has a ragged termination amongst the cells of the root-sheath. These hairs are termed *non-papillated* or *club hairs* to distinguish them from the *growing* or *papillated hairs* just mentioned (*h'*, *h'*). The root of the hair is received into a recess of the skin named the *hair-follicle*, which, when the hair is of considerable size, reaches down into the subcutaneous fat.

The substance of the hair, of epidermic nature, is, like the epidermis itself, quite extravascular, but, like that structure also, it is organised and subject to internal organic changes. Thus, in the progress of its growth, the cells change their figure and acquire greater consistency. In consequence of their elongation, the hair, bulbous at the commencement, becomes reduced in diameter, and cylindrical above. But it cannot be said to what precise distance from the root organic changes may extend. Some have imagined that the hairs are slowly permeated by a fluid from the root to the point, but this has not been proved. The sudden change of the colour of the hair from dark to grey, which sometimes happens, has never been satisfactorily explained: it is usually supposed to be due to the development of air between the elongated cells composing the hair.

The rate of growth of hair is about half an inch a month.

Hairs are found on nearly all parts of the skin; the exceptions being the palms of the hands and soles of the feet, the whole surface of the third phalanges of the fingers and toes, and the flexor and lateral surfaces of the other phalanges; they are also absent on the glans penis, and on the inner surface of the prepuce and of the labia majora. They are most numerous on the scalp, where there are 200 to 300 or more per square centimetre; on the chin there are about 44 in the same area; on the back of the forearm 24, and on the back of the hand 18 (v. Brunn). On the scalp they are set in groups of three to five; over the rest of the skin grouping is for the most part not so evident, but it is generally present, although there may be only two or three hairs in each group. The lower ends of the follicles are not so manifestly grouped as the hairs them-

[1] On the loss of pigment in hairs see Stieda, Anat. Hefte, xl. 1910.

selves, and a tangential section through the deeper part of the integument shows them more evenly scattered; the follicles therefore converge somewhat towards the surface. Except those of the eyelashes, which are implanted perpendicularly to the surface, the follicles slant, the direction of slant being constant in the same parts. In the negro the hair-follicles have been found to be curved, so that the papilla may look in a direction parallel to or even away from the surface of the skin (Stewart). Pinkus[1] has pointed out that the skin undergoes a curious modification in the neighbourhood of the hair-groups (fig. 676). On the side towards which these slope there is a disc-like patch of cutis, the papillæ of which are enlarged (hair-disc, fig. 676, *d*); the epidermis is thickened over this, and receives an unusually large number of nerve-fibres (*n*). On the opposite side of the hair-group the surface of the cutis over a small area is flat, and is

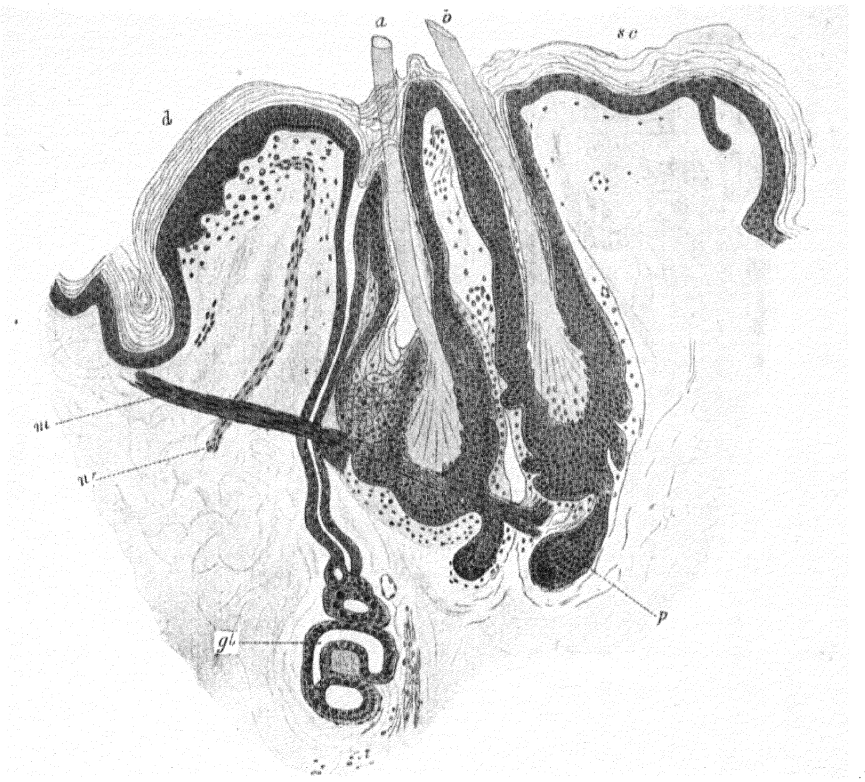


FIG. 676.—DIAGRAMMATIC SECTION OF A HAIR-AREA OF CYNOCEPHALUS, MADE FROM A RECONSTRUCTION. (F. Pinkus.)

a and *b*, two (club) hairs out of a group of four; *p*, new hair-rudiment; *m*, arrector muscle; *d*, hair-disc; *n*, nerve-fibres passing to hair-disc; *sc*, thickened scale-like portion of epidermis; *gl*, sweat-gland.

covered by a scale-like thickened epidermis (*sc*), which Pinkus believes to be the homologue of the reptilian scale.[2]

The slope of the hairs takes different directions in different regions of the skin. Along certain lines the hairs incline away from one another; these lines have a spiral arrangement, so that the hairs appear to diverge in *whorls*. The whorls are definitely and symmetrically placed; all being paired except that on the vertex. There are also secondary lines of divergence between the whorls. The whole constitutes a general hair-pattern over the surface, which is generally well seen in the lanugo of the fœtus, and in some individuals can be recognised throughout life.[3]

[1] Arch. f. mikr. Anat. lxv. 1904.

[2] This was originally a suggestion of Weber based on the mode of arrangement of the hairs. See also Stöhr, Anat. Anz. xxx. 1907 (Verhandl. d. Anat. Gesel.)

[3] On the hair-slope in man see W. Kidd, Journ. of Anat. xxxv. 1901; also v. Brunn, *op. cit.*

With the exception of the bones and teeth, no tissue of the body withstands decay after death so long as the hair, and hence it is often found preserved in sepulchres, when nothing else remains but the skeleton.

Structure of the hair-follicle.—The follicle may be described as consisting of a *mouth* and *body*: the latter being the part below the orifice of the sebaceous glands (fig. 677). The wall of the follicle consists of an outer coat continuous with the corium, and an epidermic lining continuous with the cuticle.

The *dermic coat* is thin but firm. It is not very distinct around the mouth of the follicle, but elsewhere it consists of three layers. The external layer is formed of connective tissue in longitudinal bundles, with many elastic fibres, but with few corpuscles. It is highly vascular, and provided with nerves. It may be

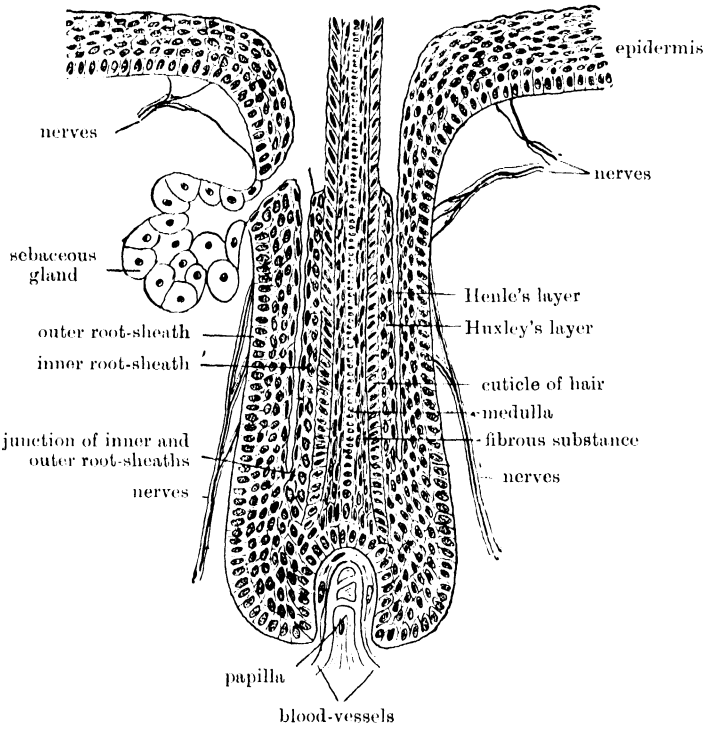


FIG. 677.—DIAGRAM OF A HAIR-FOLLICLE. (Maurer.)

regarded as being continuous above with the corium. The internal layer (*hyalien layer*, Kölliker) (fig. 678, i, *hy*) is a transparent homogeneous membrane, marked transversely on its inner surface with raised lines. It does not reach as high as the mouth of the follicle, and varies greatly in thickness at different levels of the follicle. According to Stöhr [1] the stratum next to the root-sheath is composed of a very fine membrane of epithelial origin. The middle layer of the dermic coat, of which it forms the thickest part, is composed of a fibrous matrix, tearing transversely, with transversely disposed connective-tissue corpuscles, with long nuclei. This layer corresponds with the papillary part of the cutis vera, and its blood-vessels are continuous above with those of that layer.

The *epidermic coat* of the follicle adheres closely to the root of the hair. It commonly separates, in great part, from the follicle and abides by the hair when the

[1] Anat. Hefte, xxiii. 1903.

latter is pulled out; hence it has been named the 'root-sheath.' It consists of an outer, softer, and, in the fresh condition, more opaque stratum next to the dermic coat of the follicle, and an internal more transparent layer, next to the hair. The former, named also the *outer root-sheath*, and in most parts of the follicle much the thicker of the two, corresponds with the rete mucosum of the epidermis in general. It is formed of protoplasmic cells, of polygonal form, but flattened tangentially in places; they include pigment-granules in the coloured races. They are distinctly

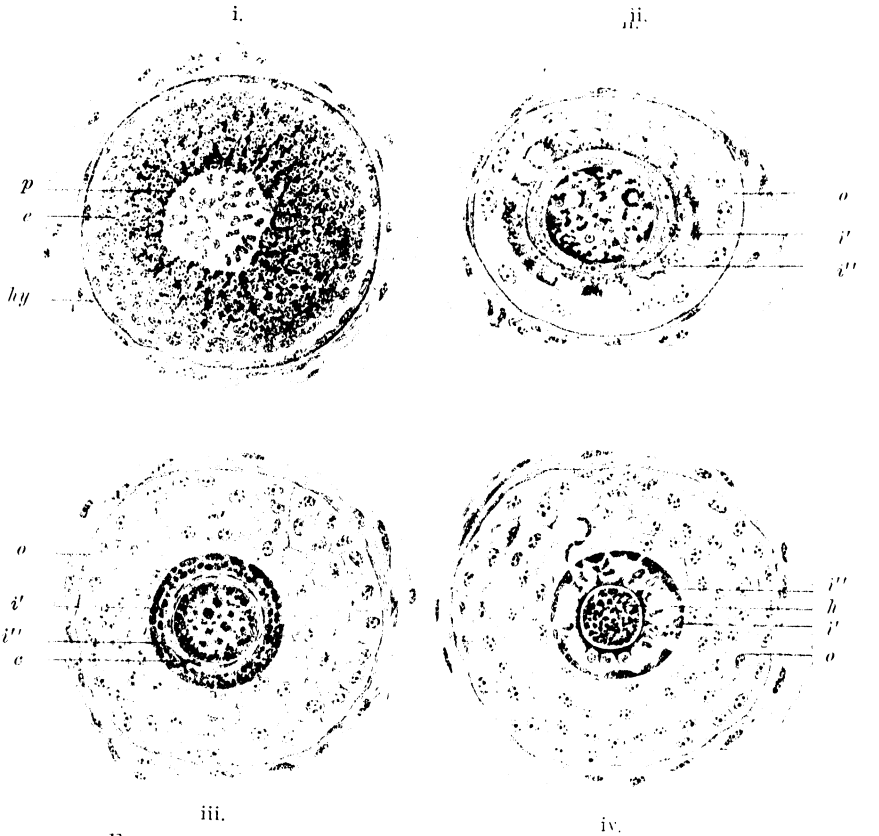


FIG. 678.—SECTIONS ACROSS HAIR-FOLLICLES FROM THE SCALP OF AN INFANT. (Schäfer.)

i. Through papilla. ii. Just above papilla. iii. About middle of follicle. iv. Near upper part of follicle. In i.: *p*, papilla; *c*, epithelium surrounding papilla, with pigment in cells; *hy*, hyaline layer of dermic coat with thin outer root-sheath just within it. In ii., iii., iv.: *o*, outer root-sheath; *i'*, layer of Henle and *i''*, layer of Huxley of the inner root-sheath; *c*, cuticle of root-sheath; *h*, hair.

fibrillated, the fibrils passing from cell to cell across intercellular bridges as in the rete mucosum of the epidermis (fig. 679). At the deeper part these cells form a much thinner stratum and pass continuously into those of the hair-knob. The internal layer, or *inner root-sheath*, which represents part of the stratum corneum of the epidermis, is not continuous with that, for it ceases abruptly a little below the orifices of the sebaceous ducts. Lining the root-sheath internally is a layer of imbricated, downwardly projecting scales, the *cuticle of the root-sheath* (figs. 678, 679, *c*); it is applied to the cuticle of the hair proper, to whose upwardly directed scales it fits like a mould. Its scaly cells, as well as those of the hair-cuticle, pass, at the bottom of the follicle, into a layer of columnar cells which covers the surface of the

hair-papilla (fig. 677). The inner root-sheath itself consists of two layers (figs. 678 to 681), which towards the upper part of the follicle become blended into one. The inner (that next the cuticula) is known as *Huxley's layer*; it consists of flattened polygonal cells, two or three deep, containing granules similar in nature to eleidin. The outer (*Henle's layer*) is composed of oblong, somewhat flattened cells, with clear nuclei flattened against the inner border. The protoplasm of its cells is occupied by well-marked longitudinal keratinised fibrils (fig. 681). Between the cells gaps occur which are filled up by projections from the cells of Huxley's layer, so that the two layers of the inner root-sheath dovetail into one another along their whole extent. Near the bottom of the follicle both pass into a single stratum of large polygonal nucleated cells without openings between them. Near the mouth of the follicle the two layers of the inner root-sheath are also not distinguishable from one another (v. Ebner), and on reaching the mouth the inner root-sheath

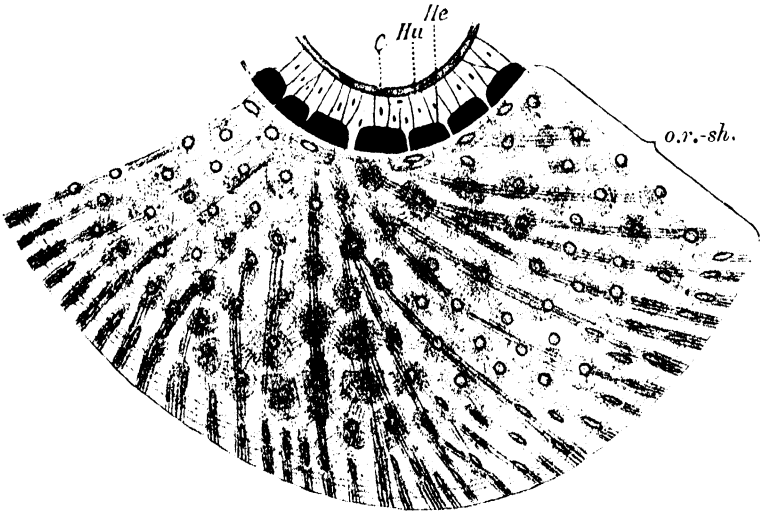


FIG. 679.—TRANSVERSE SECTION OF HAIR-FOLLICLE, HUMAN, SHOWING FIBRILLATION OF CELLS OF OUTER ROOT-SHEATH. (v. Brunn.) Magnified 500 diameters.

o.r.-sh. outer root-sheath; *He*, Henle's layer of inner root-sheath; *Hu*, Huxley's layer of inner root-sheath; *c*, cuticle of root-sheath.

tends to split up into its component cells, which become detached and lost as the hair grows.[1]

The soft bulbous enlargement of the root of the growing hair is formed of cells which are in course of multiplication, and not arranged in definite strata. Laterally they are continued into the cells of the outer root-sheath; superficially they become gradually transformed into the horny cells of the hair and of the inner root-sheath. At the bottom of the follicle they rest upon the hair-papilla (fig. 680). The latter, which is vascular and also receives nerve-fibres, rises up into the bottom of the follicle, fitting into a corresponding excavation of the hair-knob.[2] In the large tactile hairs of animals it is very conspicuous. In short, as the follicle is a recess of the integument, so the hair-papilla represents a greatly enlarged cutaneous papilla.

Muscles of the hairs.—Slender bundles of plain muscular tissue—the arrectores—are connected with the hair-follicle (see Plate). These, which were discovered by Kölliker, arise by a number of fasciculi from the superficial part of

[1] See on the structure of the hair-follicle v. Brunn. in Arch. f. mikr. Anat. xliv. 1895, and *op. cit.*

[2] Giovannini (Anat. Anz. xxxii. 1908) finds that in some of the hairs of the beard the papillæ are divided at the summit into two or three.

the corium, and join to form a somewhat flattened and plexiform muscle which passes down obliquely to be inserted into the outside of the follicle below the sebaceous glands, which they in a measure embrace in their passage. In the dermic coat of the follicle some of the muscular fibres become transverse, and partly encircle the lower part of the follicle. They are placed on the side to which the hair-follicle slants, so that their action in elevating the hair is evident. When the hairs are in groups, as in the scalp, one muscle may divide as it passes to its insertion, and may

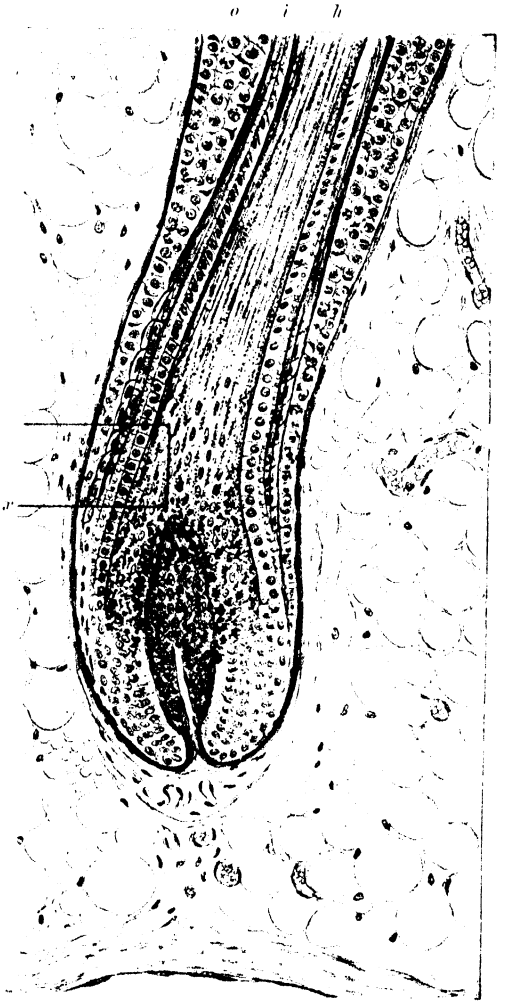


FIG. 680.—LONGITUDINAL SECTION OF A HAIR-FOLLICLE. (Schäfer.) Magnified 200 diameters.
o, outer, *i*, inner root-sheath; *h*, hair; *x*, part shown magnified in fig. 681.

be attached to several follicles (Hesse). In some parts a muscular slip is sent more deeply into the integument and becomes attached to the connective tissue enclosing a sweat-gland.

Nerves of the hairs (figs. 682, 683, 684).—A nerve-fibre passes to each hair follicle, and others, as already remarked, enter the papilla. The one to the follicle arises from the nerves to the adjacent part of the cutis and enters the dermic coat just below the sebaceous glands (fig. 682). Its branches pass in a ring-like manner

round the hair and enter the outer root-sheath, where they terminate as in the rete mucosum of the epidermis. From the ring numerous branches pass for a short

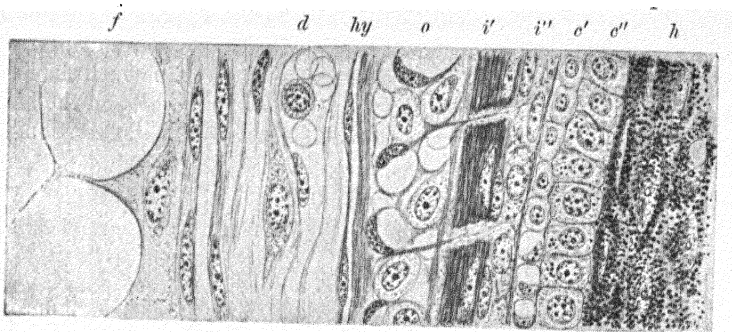


FIG. 681.—A SMALL PORTION OF THE SECTION SHOWN IN FIG. 680 ENLARGED TO EXHIBIT THE STRUCTURE OF THE SEVERAL LAYERS. (Schäfer.)

h, hair; *c''*, its cuticle; *c'*, cuticle of root-sheath; *i''*, Huxley's layer; *i'*, Henle's layer; *o*, outer root-sheath; *hy*, hyaline layer; *d*, dermic coat; *f*, fat-cells.

distance upwards and downwards in the outer root-sheath (fig. 683). In the tactile hairs of animals, the nerves were described by Schöbl [1] as passing over the outer

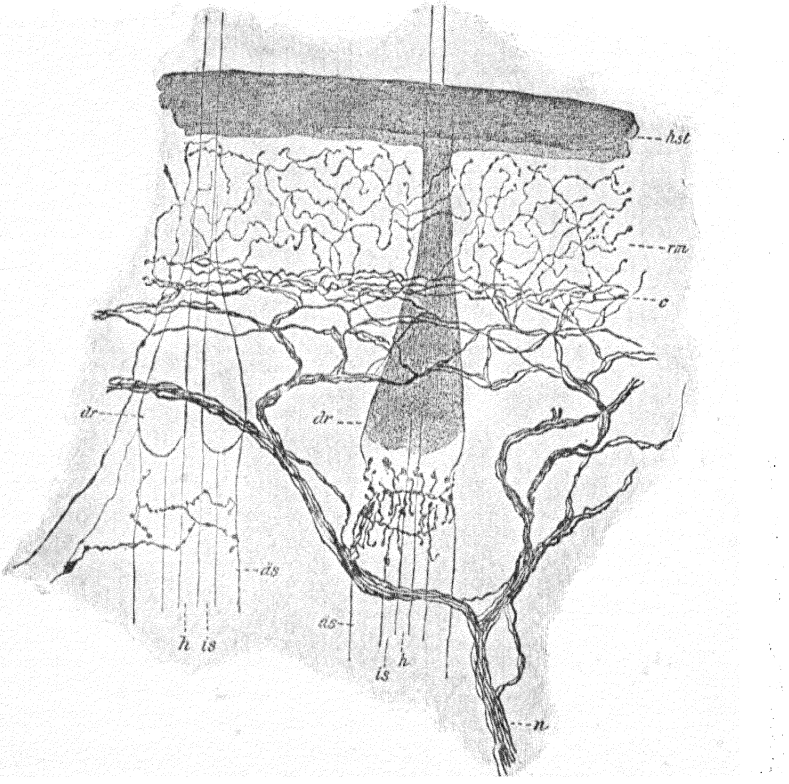


FIG. 682.—NERVES AND NERVE-ENDINGS IN THE SKIN AND HAIR-FOLLICLES. (G. Retzius.)

hst, horny stratum; *rm*, rete mucosum; *c*, superficial nerve-fibre plexus in the cutis; *n*, cutaneous nerve; *is*, inner root sheath of hair; *ds*, outer root-sheath; *h*, hair; *dr*, sebaceous glands.

root-sheath, losing their white substance, and forming a close plexus with vertical meshes; finally ending in an annular expansion, which encircles the hair just below

[1] Arch. f. mikr. Anat. vii. 1871, viii. 1872, and ix. 1873.

the orifices of the sebaceous glands, and is in immediate connexion with the hyaline layer of the follicle. This statement has been generally confirmed, except that the annular expansion of Schöbl has been shown to be an annular ramification of pale

FIG. 683. — FROM A SECTION OF SKIN PREPARED BY THE CHROMATE-OF-SILVER METHOD, SHOWING THE UPPER PART OF TWO HAIRS AND THE TERMINAL ARBORISATIONS OF NERVE-FIBRES IN THEIR ROOT-SHEATHS. (Van Gehuchten.)

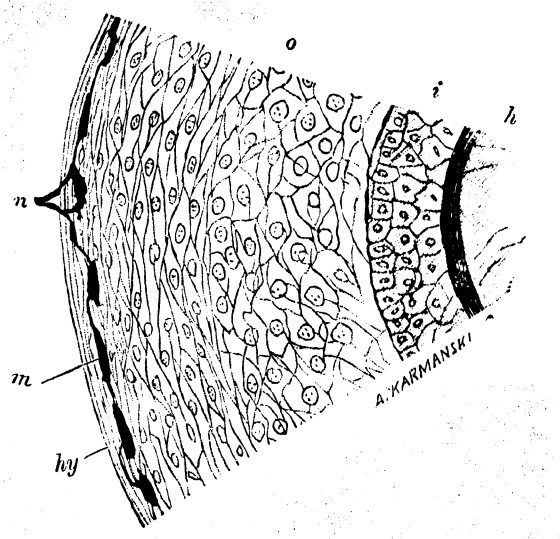


FIG. 684.—NERVE-ENDING IN OUTER ROOT-SHEATH OF TACTILE HAIR OF RABBIT. (Ranvier.)

n, nerve-fibre; *m*, tactile meniscus; *o*, outer root-sheath; *i*, inner root-sheath; *h*, hair; *hy*, hyaline membrane.

fibres amongst the cells of the outer root-sheath, some of the nerve-fibres, which are placed more superficially, terminating in irregular disc-like enlargements (fig. 684)

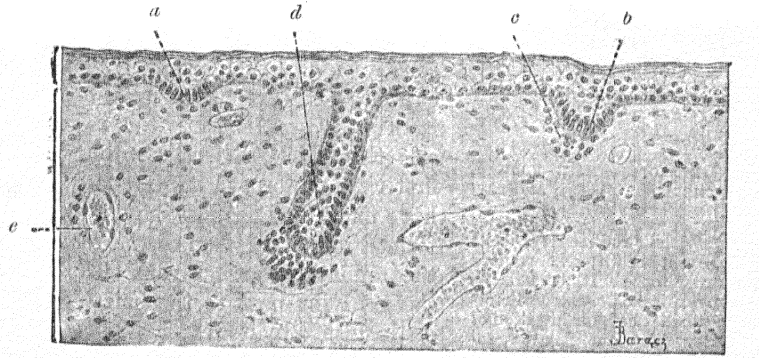


FIG. 685.—HAIR-GERMS IN A SECTION OF THE SCALP OF A HUMAN FŒTUS. (Szymonowicz.) Magnified 230 diameters.

a, commencing down-growth of epidermis; *b*, further stage of down-growth; *c*, connective-tissue cells beginning to accumulate to produce the dermic coat of the follicle; *d*, hair-follicle more advanced in development; *e*, section of a blood-vessel.

between the root-sheath and the hyaline layer.[1] Ordinary hairs receive fewer nerve-fibres, but, as in the tactile hairs, most of these appear to end in the outer

[1] See further on the nerves of hairs, Van Gehuchten, Anat. Anz. vii. 1892; L. Ranvier, Traité technique d'histologie, 1889; G. Retzius, Biol. Unters. iv. 1892, and vi. 1894; E. Botezat, Arch. f. mikr. Anat. l. 1897; Ksjunin, *ibid.* liv. 1899; Szymonowicz, *ibid.* xlv. 1895, and lxxiv. 1909.

root-sheath at about the level of the orifices of the sebaceous glands. In the tactile hairs (*sinus-hairs*) of animals the follicle is partly surrounded by a blood-sinus, which lies between the outer and middle layers of the dermic coat.[1]

The nerve-fibres to the arrector muscles are derived from the sympathetic.

Development of hair in the fœtus.—The rudiments of the hairs may be discerned at the end of the third or beginning of the fourth month of intra-uterine life, as little black specks beneath the cuticle. They are formed of thickenings of the rete mucosum, which soon slant obliquely into the corium (fig. 685). There is no projection of the horny layer at the surface. When these down-growths first occur (fig. 685, *a*), they present an appearance which recalls that of certain small tactile patches, supplied with nerve-fibres, found in the skin of amphibia and some reptiles. Two thickenings early show themselves on the down-growing follicle-rudiment; one of these represents the place where the sebaceous glands will subsequently be developed, the other forms the so-called 'hair-bed' or 'hair-matrix,' and represents the germ of the secondary hair which will replace the first one. It is seen in the fully developed hair-follicle in the neighbourhood of the attachment of the arrector pili. A homogeneous limiting membrane encloses the collection of cells; this is continuous above with a similar simple film which at this time lies between the cuticle and the corium; it becomes the innermost or hyaline layer of the dermic coat of the follicle. The hair-rudiment next lengthens and swells out at the bottom, so as to assume a flask-shape, and becomes fitted over a papilla which has been formed in the subjacent corium. Outside the limiting membrane, the fibres, corpuscles, and other constituents of the dermic coat of the follicle, as well as the arrector muscle, become formed from mesoderm.[2] While this is going on outside the follicle, the cells within it, which at first were uniform in appearance, are found to have undergone changes, having become transformed into the layers of the root-sheath and the miniature conical hair. The inner root-sheath, lying next to the hair (fig. 686, *k*), is distinguished by its translucency from the more opaque outer part that fills up the rest of the cavity. The hair and the inner root-sheath are formed from the cells which cover the top of the papilla. These acquire eleidin-granules, and also, in the case of those which produce the hair, pigment-granules. The eleidin-granules are stated by Ranvier to occur only in the cells that form the medulla of the hair and in those

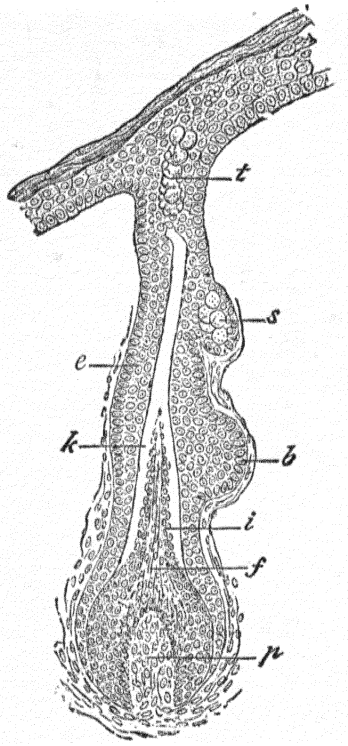


FIG. 686.—DEVELOPING HAIR FROM A HUMAN EMBRYO OF 4½ MONTHS. (Ranvier.)

p, papilla; *f*, hair-rudiment; *i*, cells forming inner root-sheath; *k*, keratinised portion of inner root-sheath, remaining uncoloured by carmine; *e*, external root-sheath; *b*, epithelial bed, for insertion of arrector pili; *s*, sebaceous gland; *t*, sebaceous matter forming independently in the part which will become the neck of the follicle.

[1] See on the structure of sinus-hairs, Tretjakoff, Anat. Anz. xxxvii. 1910.

[2] Stöhr, Anat. Hefte, xxiii. 1903. This paper contains many important details, as well as the history and literature of the subject up to that date. See also Oyama, *ibid.*

that form the inner root-sheath, while the granules which are found in the cells from which the fibrous substance and cuticula of the hair are produced stain brown with picrocarmine and resemble the onychogenic substance of the nail-matrix.

As the young hair reaches in its growth the upper part of the follicle, the central cells which block the neck of the follicle undergo a kind of fatty degeneration, and disintegrate to produce a sebaceous secretion like that of the sebaceous glands (fig. 686, *t*); a channel thus becomes formed between the epidermis-cells, which

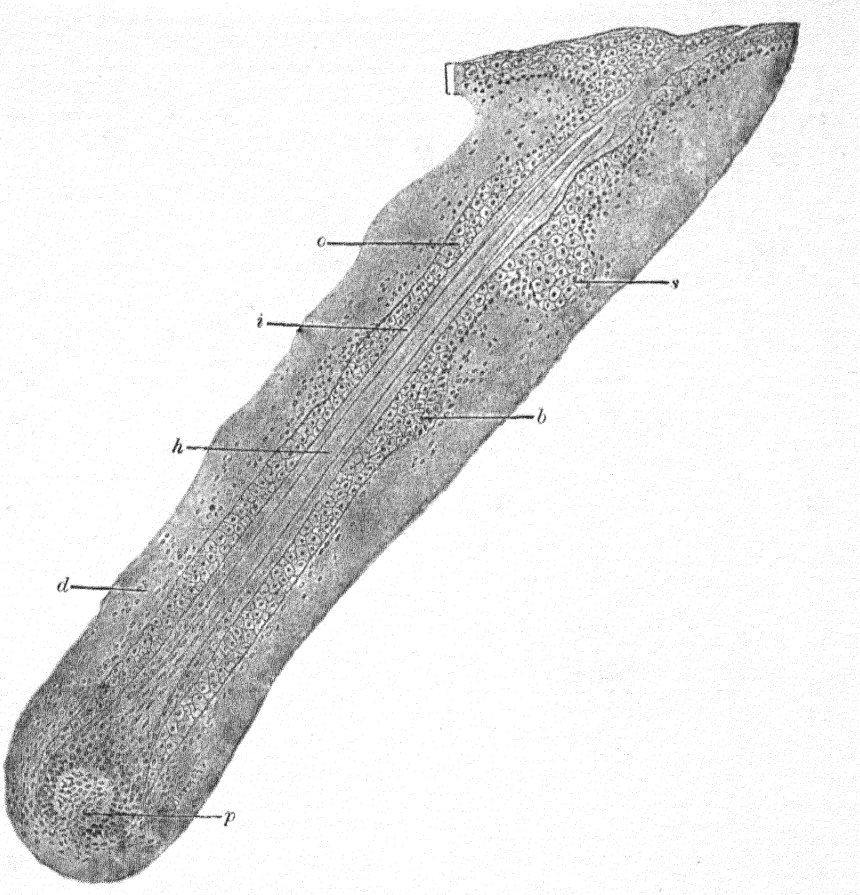


FIG. 687.—LONGITUDINAL SECTION OF A HAIR WITH ITS FOLLICLE FROM A SIX-MONTHS HUMAN EMBRYO. (Szymonowicz.) Magnified about 150 diameters.

p, papilla; *h*, young hair; *i*, inner root-sheath; *d*, dermic coat of follicle; *o*, outer root-sheath; *s*, sebaceous gland-rudiment; *b*, projection for insertion of arrector pili.

usually passes obliquely towards the surface (fig. 687). The young hair continuing to grow, eventually appears through the cuticle; it is often bent like a whip, and the doubled part protrudes. The sebaceous glands are in the meantime becoming formed as lateral buddings of the outer root-sheath into the corium (*s*); they soon open into the mouth of the follicle.

Between the soft cells of the hair-bulb in the growing hair wander-cells containing pigment granules are frequently seen: it has been supposed that the pigment may be carried to the cells of the hair-bulb through their agency (Riehl).

The first hairs produced constitute the *fœtal lanugo*;[1] their eruption takes place about the fifth month of intra-uterine life; some of them are shed before birth, and are found floating in the liquor amnii.

Even after birth new hair-rudiments may for a time continue to be formed either from the rete mucosum of the epidermis or from the outer root-sheath of existing hair-follicles.

Replacement of hairs.[2]—According to Kölliker's observations, the infantile hairs are entirely shed and renewed within a few months after birth; those of the general surface first, and afterwards the hairs of the eyelashes and head, which he finds in process of change in infants about a year old. A formation of new hairs, preceded or accompanied by shedding of the old ones, also goes on during the whole

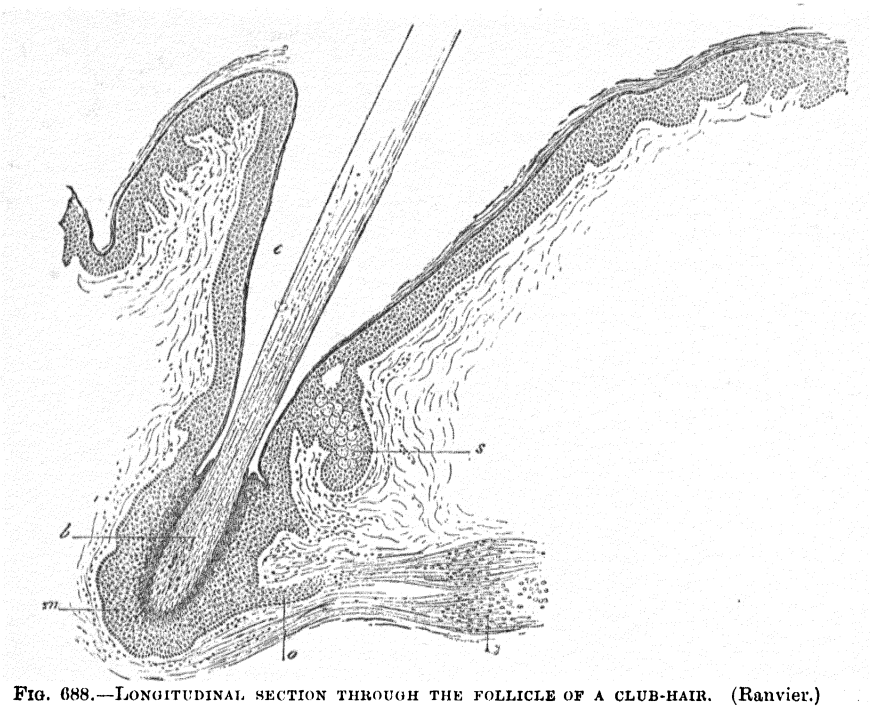


FIG. 688.—LONGITUDINAL SECTION THROUGH THE FOLLICLE OF A CLUB-HAIR. (Ranvier.)

m, epithelium at the bottom of the follicle (which contains no papilla); *b*, modified hair-bulb; *c*, neck of the hair-follicle somewhat opened in preparing the section; *s*, sebaceous gland; *o*, epithelial bud at the level of the insertion of the arrector pili.

of life. The papilla of the old hair diminishes in size and eventually disappears, and the hair-bulb becomes wholly keratinised, so that if the hair be now pulled out it appears solid throughout. As already explained, such hairs have been termed *club-hairs* to distinguish them from the ordinary hollow-bulbed or *papilla-hairs*. The hair-root acquires a closer attachment to the sides of the follicle, within which it gradually becomes shifted towards the surface of the skin (fig. 688), but all active growth ceases, and finally the hair drops out of the follicle. The club-hair is somewhat wider at its lower end, but not bulbous like the papilla-hair. The new hairs are generated in the follicles of the old (figs. 689, 690). An increased growth of cells takes place from the 'hair-matrix,' and a new papilla is produced within the mass of cells thus formed. These cells come to occupy the lower part of the

[1] The term *lanugo* is also used for the small downy covering of hairs which is seen over the general surface of the body after birth and throughout life.

[2] On the mode of replacement of hair see Unna, Arch. f. mikr. Anat. xii. 1876; Ranvier, Traité technique, 1889; Giovannini, Arch. f. mikr. Anat. xxxvi. 1890; G. Aubertin, *ibid.* xlvii. 1896; L. Steida, Anat. Hefte, xl. 1910.

follicle; they multiply and are gradually converted into a new hair with its root-sheath, just as in the primitive process of formation in the embryo. According to some authors the new hair may be developed in connexion with the old papilla; others believe that in all cases a new papilla is formed and that the old one undergoes atrophy, thus resembling the changes which accompany the formation of the permanent teeth. Ultimately the newly formed hair grows towards the mouth of the follicle and protrudes from the surface of the skin, where it may be seen alongside of the club-hair which it is to replace.

When a hair is pulled out the process of regeneration does not, according to Giovannini, begin immediately, but only after an interval of from 6 to 12 weeks. The cells at the bottom of the follicle then exhibit active karyokinesis, migratory cells containing pigment appear amongst them, and changes similar to those which occur in the normal process of formation of the hair are observed.

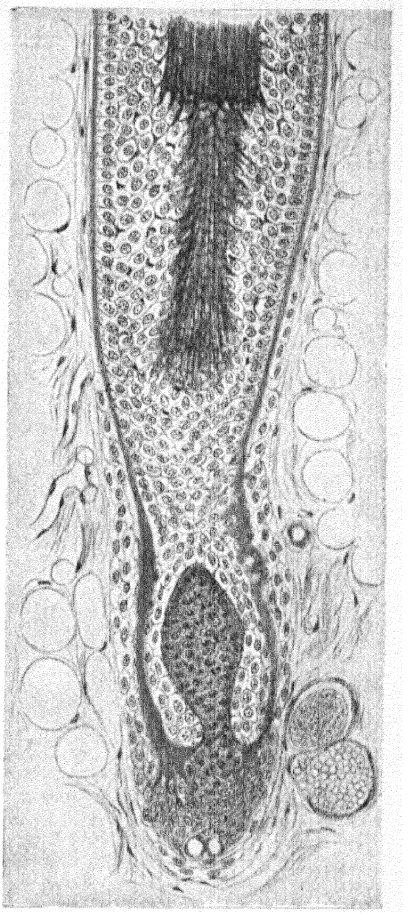


FIG. 689.—LONGITUDINAL SECTION THROUGH THE FOLLICLE OF A CLUB-HAIR, THE ROOT OF WHICH IS UNDERGOING ABSORPTION. (Schäfer.) Magnified 200 diameters.

A new papilla has become formed at the bottom of the follicle.

SEBACEOUS GLANDS.

The **sebaceous glands** (see Plate, p. 463 and fig. 691) are small saccular glands most of which pour out their secretion at the roots of the hairs. For, with very few exceptions (labia minora and eyelids, and, in some individuals, at the red margin of the lips, near the angle of the mouth), they open into hair-follicles, and are found wherever there are hairs. Each has a short wide duct, opening within the mouth of the hair-follicle. Traced backwards the duct leads to a cluster of small rounded secreting saccules, which are almost filled by epithelium-cells (fig. 691) loaded with particles of fatty substance. The saccules possess a basement-membrane, outside which is a covering of connective tissue. The deeper cells multiply constantly and, becoming filled with fatty granules, pass towards the centre of the alveolus. Here they undergo disintegration, and the fatty and other substances with which they are charged form the secretion of the gland, which is discharged by the duct into the mouth of the hair-follicle. The number of saccular recesses connected with the duct varies from four or five to twenty; it may be reduced to two or three, in very small glands, or even to one, but this is rare. The sebaceous glands are lodged in the substance of the corium. They are usually placed on the side to which the hair slopes, in the angle formed by the junction of the arrector pili with the hair, so that when the muscular fibres contract they tend to compress the gland. Several may open into the same hair-follicle. Their size is not regulated by the magnitude of the hair; some of the largest being connected with the fine downy hairs on the alæ of the nose and other parts of the face (fig. 691). There are large sebaceous glands in the skin of the external auditory

meatus; here they are closely associated with the ceruminous glands, which, although secreting a fatty material, are modified sweat-glands (see p. 479). The sebaceous glands here penetrate much more deeply than usual into the cutis vera and may even reach the subcutaneous tissue.

The Meibomian glands of the eyelids are to be regarded as modified sebaceous glands, although they do not open into hair-follicles.

Development of the sebaceous glands.—The rudiments of the sebaceous glands sprout like little buds from the sides of the hair-follicles; they are, in fact, at first excrescences of the external root-sheath (fig. 686, *s*), and are composed

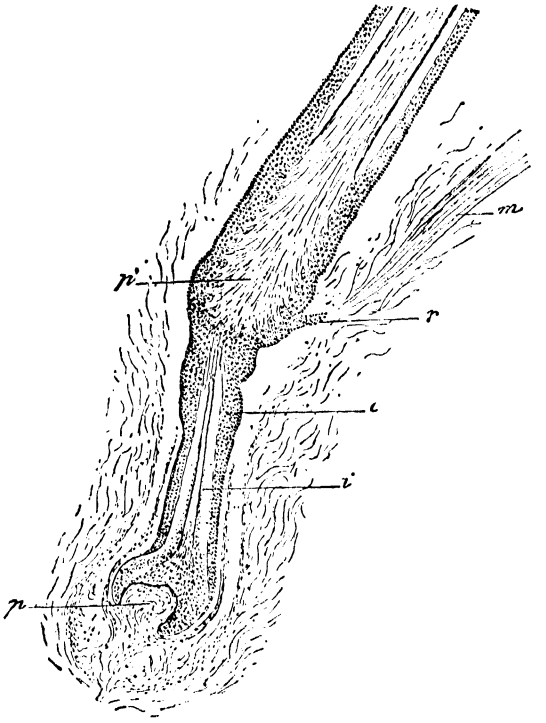


FIG. 690.—REPLACEMENT OF OLD HAIR BY A NEWLY DEVELOPING ONE IN THE HUMAN SCALP. (Ranvier.)

p, papilla of the new hair; *i*, its inner root-sheath; *e*, its outer root-sheath continuous above with that of the old hair, *p'*; *r*, epithelial projection at the level of the insertion of the arrector pili, *m*.

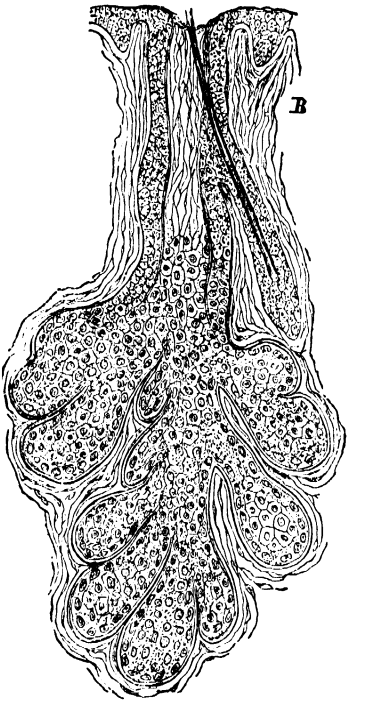


FIG. 691.—LONGITUDINAL SECTION OF A SEBACEOUS GLAND FROM THE CHEEK, WITH A SMALL HAIR GROWING THROUGH ITS DUCT. (Toldt.)

entirely of similar cells. Each little process soon assumes a flask-shape and the central cells become occupied by fat-particles. This fatty transformation of the cells extends along the axis of the pedicle until it penetrates through the root-sheath, and the fat-cells thus escape into the cavity of the hair-follicle, and constitute the first secretion of the sebaceous gland. They are soon succeeded by others of the same kind, and the little gland is established in its office. Additional saccules and recesses, by which the originally simple cavity of the gland is complicated, are formed by budding out of its epithelium, in the same way as the first saccule was produced from the epithelial root-sheath.

The cells of the sebaceous glands form not only granules of fatty material, but also of eleidin (keratohyalin), and part of the cell-substance eventually undergoes keratinisation.[1]

[1] B. Rosenstadt, Internat. Monthly Journ. Anat. and Physiol. ix. 1892.

SWEAT-GLANDS.

The **sudoriferous glands** or **sweat-glands** are for the most part situated below the cutis vera, at variable depths in the subcutaneous adipose tissue (figs. 661 and 662). To the naked eye they have the appearance of small round reddish bodies, each of which, when examined with the microscope, is found to consist of a tube, coiled up into a ball (though sometimes forming an irregular or flattened figure). From the gland proper the tube is continued, as its duct, upwards through the true skin and cuticle, to open on the surface by a slightly widened orifice. The secreting tube (ampulla) is considerably larger than the duct, and also has a wider lumen (fig. 692). The duct, as it passes through the epidermis, is twisted like a corkscrew in parts where the epidermis is sufficiently thick to give room for this (figs. 653, 661); lower down it is straight or but slightly curved. Sometimes the duct is formed of two coiled-up branches which join at a short distance from the gland. The tube, both in the gland and

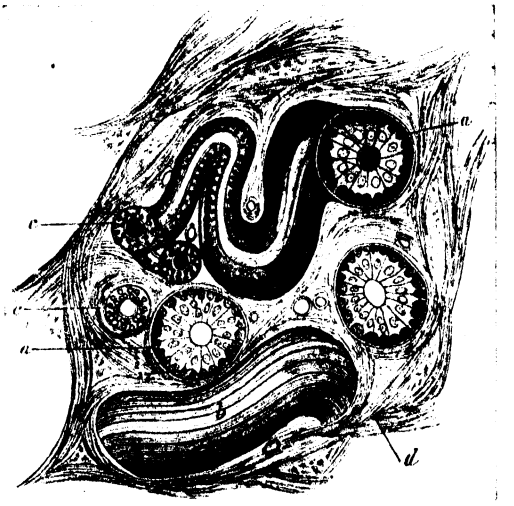


FIG. 692.—SECTION OF A SWEAT-GLAND IN THE SKIN OF MAN. (Schäfer.)

a, *a*, secreting tube in section; *b*, a coil seen from above; *c*, *c*, efferent tube; *d*, intertubular connective tissue with blood-vessels. 1, basement-membrane; 2, muscular fibres cut across; 3, secreting epithelium of tubule.

where it forms the excretory duct, has a vascular investment of connective tissue, reaching no higher than the surface of the true skin; within this investment it consists of a thin membrana propria and an epithelial lining. The epithelium in the gland proper is formed of a single layer of cubical or columnar cells (often containing brownish pigment) and, in the duct, of two or more layers bounded next the lumen by a fine cuticular lining. The epithelium of the duct is continuous with the epidermis; the twisted part of the duct is merely a channel excavated between the epidermis-cells. Between the epithelium and the basement-membrane, in the proper secreting portion of the gland, is a layer of longitudinally and obliquely disposed fibres which are generally described as plain muscular fibres, although the physiological evidence of their muscular nature is not conclusive. They vary in amount. In smaller glands the layer is incomplete, and in the smallest the fibres may be altogether lacking. On the other hand, in the large glands which occur in the axilla, at the root of the penis, on the labia majora, and in the neighbourhood of the anus, the layer of muscular fibre-cells is very well marked. According

to Bonnet the muscular layer is least developed in those parts of the skin which are most subject to the tension produced by contraction of ordinary muscles, and in glands which yield a more fluid secretion. Muscular fibres are absent in the duct. The latter is often coiled two or three times before leaving the gland, but its coils are distinguishable from those of the gland proper by the differences above mentioned. The secreting cells of the sweat-glands show the peculiar striated and granular appearances characteristic of most gland-cells; minute canals or clefts are said to pass from the lumen of the tube between the opposed surfaces of the cells (Ranvier).[1] Secretory changes in the granular cell-contents have been described (Joseph). In the larger axillary glands Tulke[2] finds two kinds of cell, one dark and granular, the other clear; these may represent functional modifications of one and the same kind. The cells of the axillary glands contain yellow pigment in granules and flakes; a similar pigment is seen in their duct-cells. In the larger glands the tube is rarely simple, usually dividing by repeated dichotomous branching into smaller tubules, which before ending give off short cæcal processes; in rare cases the branches anastomose. On detaching the cuticle from the true skin, after its connexion has been loosened by putrefaction, it usually happens that the cuticular linings of the sweat-ducts get separated from their interior to a certain depth, and are drawn out in the form of short threads attached to the under-surface of the epidermis. The coils of the gland tube are held loosely together by connective tissue (fig. 692, *d*), which may form a sort of capsule round the body of the gland. Each sweat-gland is supplied with a dense cluster of capillary blood-vessels and with nerves; the latter have been traced to the gland-cells (Ostroumoff).

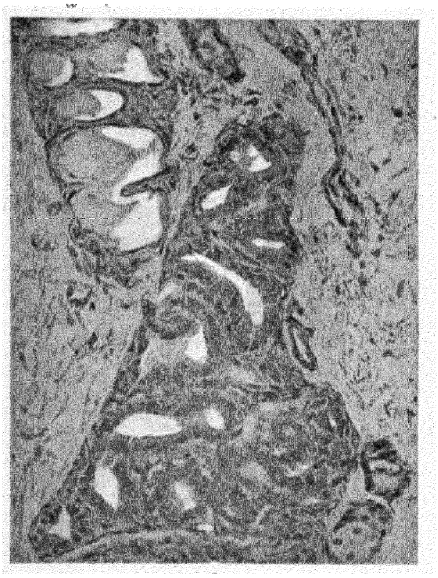


FIG. 693.—SECTION OF CERUMINOUS GLAND OF THE EXTERNAL EAR. (Schäfer.) Photograph.

d, duct of gland, having a spiral course and therefore cut several times; it is partly filled with cerumen; *gl*, secreting tubules of gland; *s*, extremity of a tubule of a sebaceous gland which extended as far as the base of the ceruminous gland.

Sweat-glands exist most numerously in regions devoid of hair, but they occur in all parts of the skin, and may in some cases open into hair-follicles. According to Krause, about 370 occur on a square centimetre of the palm of the hand, and somewhat fewer on an equal extent of the sole of the foot. He found about 200 per square centimetre on the back of the hand, and about 175 on the forehead, and the front and sides of the neck. On the breast, abdomen, and fore-arm there are about 155 to the square centimetre, while on the lower limbs and the back part of the neck and trunk, the number in the same space is not more than from 60 to 80.

As has already been intimated, the size of the sweat-glands also varies. According to Krause, the average diameter of the coil is from 0·17 to 0·35 mm.; but in the axilla he found the greater number to measure from 0·75 to 1·25 mm., and some were nearly 4 mm. in diameter.

[1] Cf. Fananas, Rev. trim. microgr. i. 1896.

[2] Arch. f. mikr. Anat. lxi. 1903.

The *ceruminous glands* in the auditory passage consist of a tube coiled into a ball, like the sweat-glands (fig. 693). Although there is a difference in the nature of the secretion, which is of a fatty nature in the ceruminous glands, the general correspondence between the two in structure and mode of development renders it clear that the ceruminous glands may be regarded as a variety of the sudoriferous; they are, however, considerably larger. As already stated, they are associated with large sebaceous glands (fig. 694). Other modified sweat-glands are the *circumanal glands* and the *glands of Moll* in the eyelids. Both of these show a branching type of tubular glands allied to tubulo-racemose, and both are much larger than the ordinary sweat-glands. There are also found around the anus large and small sweat-glands of the ordinary type, as well as glands with straight ducts and well-marked saccular alveoli.[1]

The **development** of the sweat-glands was first accurately studied by Kölliker. Their rudiments, when discoverable in the embryo (about the fifth month), have much the same appearance as those of the hairs, and consist of processes of the rete mucosum, which grow down into the cutis vera; but they lack the slant which characterises the hair-germs. In hairy parts of the skin they often commence as sprouts from the rete mucosum of each hair-germ, and subsequently become shifted to the adjacent skin-surface.[2] They are formed of cells collected at the growing end into a solid mass of a club shape, continuous by a thinner cell-strand with the rete mucosum. They are surrounded by a homogeneous limiting membrane, prolonged above into that between the derma and cuticle. Their subsequent changes consist in the formation of a canal along the axis of the cell-strand—at first without an outlet—the prolongation of this through the epidermis to open on the surface, the coiling up of the gradually lengthening end-tube into a compact ball, and the twisting of the duct as it proceeds to the orifice. The plain muscular tissue of the sweat-glands is said to be developed from some of the epithelium-cells of the rudimentary gland (Ranvier), and is therefore of ectodermal origin.

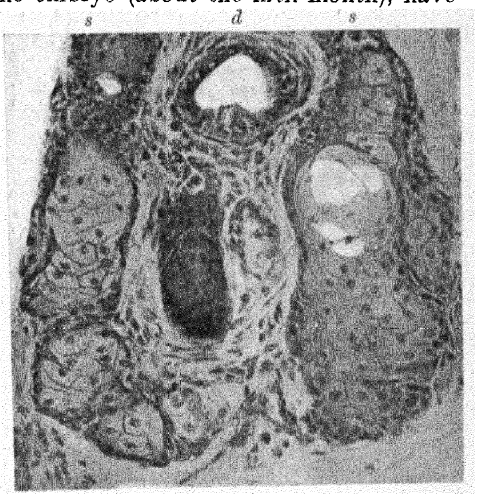


FIG. 694.—SECTION SHOWING THE DUCT OF A CERUMINOUS GLAND ACCOMPANIED BY THE SECRETING TUBULES OF LARGE SEBACEOUS GLANDS. (Schäfer.) Photograph.

d, duct of ceruminous gland; *s*, *s*, sebaceous glands on either side of it.

THE MAMMARY GLANDS.

The mammary glands are to be regarded as modified cutaneous glands; probably they represent sweat-glands, which they resemble in their mode of development. In the human female they form two hemispherical masses on either side of the sternum, covering the pectoral muscles; but in the virgin and nulliparous condition these masses are only in small part glandular, being formed mostly of connective

[1] Huber, Contrib. to med. research, Ann Arbor, 1903 (with Adamson).

[2] Backmund, Anat. Hefte, xxvi. 1904; F. Diem, *ibid.* xxxiv. 1907; C. Wimpfheimer, *ibid.* (all three articles from Stöhr's laboratory).

and adipose tissue, which, with the supervention and progress of pregnancy, gradually disappears and gives place to the growing gland-tissue. Each mammary gland is composed of some fifteen to twenty separate racemose glandules, the ducts of which (*lactiferous ducts*) open separately at the apex of the nipple, each in a small depression. As they pass towards their orifices each duct exhibits a spindle-shaped enlargement known as the *lactiferous sinus* or *ampulla* (fig. 695); at the orifice the duct is again constricted. The aggregation of the glands forms the so-called *corpus mammæ*: the individual parts of this are separated from one another by interglandular connective tissue. This connective tissue may, as already stated, contain a considerable amount of fat, but

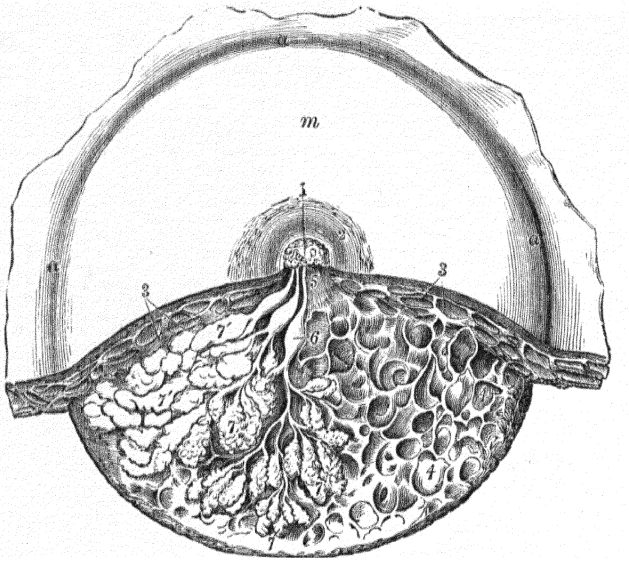


FIG. 695.—DISSECTION OF THE LOWER HALF OF THE FEMALE MAMMA DURING THE PERIOD OF LACTATION. (From Luschka). ⅓.

m, undissected part of the mamma; 1, the mamilla; 2, areola; 3, subcutaneous masses of fat; 4, loculi in the connective tissue which supports the glandular substance; 5, three lactiferous ducts passing towards the mamilla where they open; 6, one of the sinuses or ampullæ; 7, some of the glandular lobules which have been unravelled; 7′, others massed together.

fat is absent in and under the nipple and areola—the pigmented area of skin which immediately surrounds the nipple. In the latter part of pregnancy and during lactation the whole mamma is glandular in appearance, the connective-tissue stroma being greatly reduced in amount. After the cessation of lactation a process of involution succeeds, the mamma becoming again less glandular and the stroma relatively more developed; usually also there is more fatty tissue than before.

Underneath the areola there are a few accessory glandules, constructed on the same principle as the mammary glandules proper, but quite small; they open on the skin of the areola, not at the apex of the nipple. A number of large sebaceous glands also open on the skin of this region; some in conjunction with the accessory glandules and independently of hairs.

The mamma in the male sex has the same parts as in the female, but in an entirely rudimentary condition, the gland being very small; the nipple is usually the only external sign of its existence. Rarely, it has been found to undergo enlargement and to furnish a serous fluid; in very rare cases it has secreted milk.

The nipple and areola contain a large amount of plain muscle in their subcutaneous tissue (fig. 696) : the muscle is arranged in bundles which, in the areola,

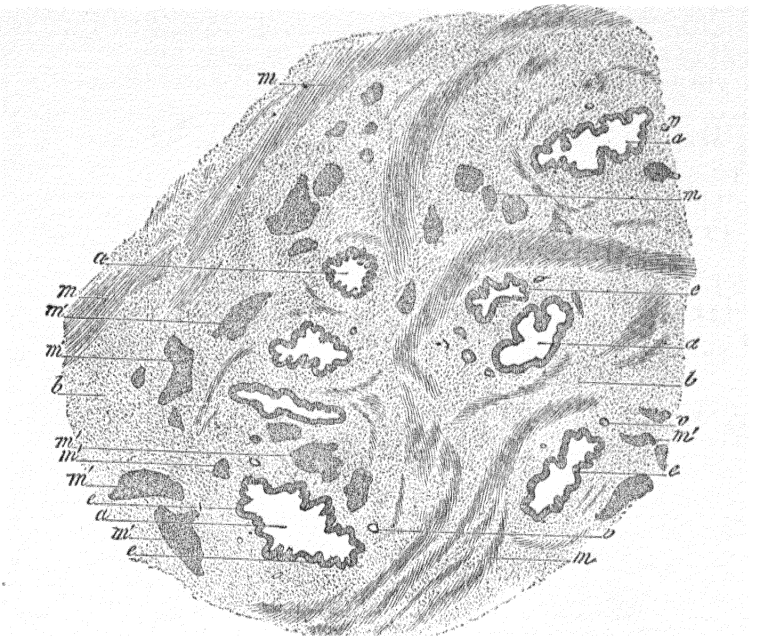


FIG. 696.—TRANSVERSE SECTION OF THE NIPPLE. (Testut, after de Sinéty.)

a, sections of lactiferous ducts, with, *c*, columnar epithelium : *b*, connective tissue ; *m*, *m'*, plain muscular fibres cut longitudinally and transversely respectively ; *v*, blood-vessels.

run partly circularly, partly vertically to the surface ; in the nipple, partly parallel to the milk-ducts, partly encircling them.

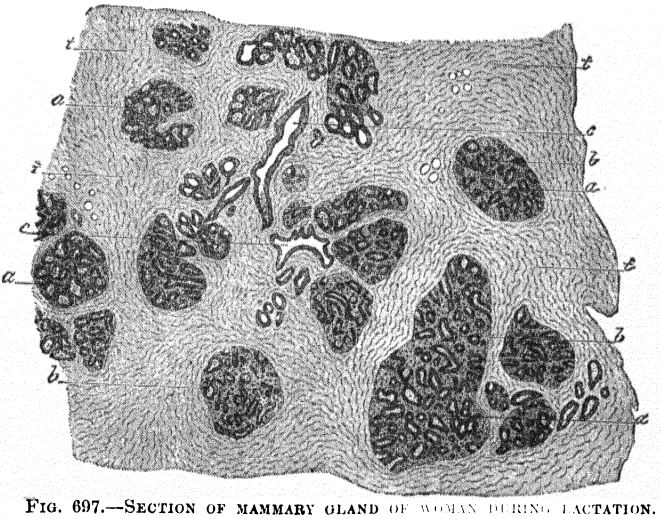


FIG. 697.—SECTION OF MAMMARY GLAND OF WOMAN DURING LACTATION. (Testut, after de Sinéty.)

a, lobule of gland ; *b*, acini lined by cubical epithelium ; *c*, duct ; *t*, connective-tissue stroma.

The **ducts** are lined for a short distance near their mouths by stratified epithelium continuous with that of the skin, but this soon gives place to somewhat

long columnar cells with their nuclei arranged alternately at two levels : the cells, however, form only a single layer. Outside the epithelium is a connective-tissue coat the white fibres of which run for the most part circularly, the elastic fibres longitudinally. The ducts branch again and again, and ultimately end in groups of saccular or tubulo-saccular alveoli (fig. 697).

The **alveoli** in the virgin gland are completely filled with polyhedral epithelium-cells. The wall of the alveolus is formed by a thick basement-membrane (*halo* of C. Langer); outside this is a stratum of stellate intercommunicating connective-tissue cells. In the actively secreting gland the appearance of the alveoli is very different. They now appear as distended saccules with large lumina, separated

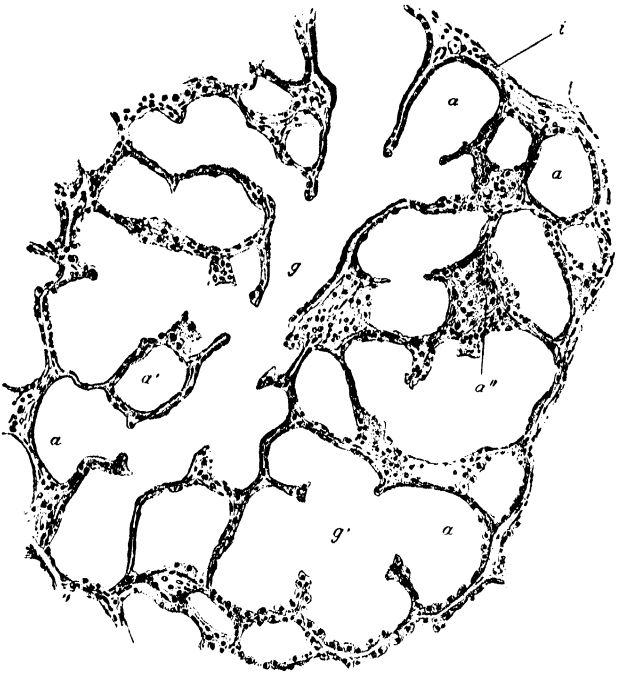


FIG. 698.—SECTION OF MAMMARY GLAND, HUMAN, IN FULL ACTIVITY. (v. Ebner.)
Magnified 110 diameters.

a, *a'*, *a''*, alveoli variously cut, and distended by secretion ; *g*, *g'*, commencing ducts; *i*, connective tissue.

from adjoining acini by relatively thin partitions of connective tissue (fig. 698). The clear basement-membrane of the alveolus is no longer visible, and the lining epithelium, which appears to be in contact with the stellate cells, is flattened or cubical according to the amount of distension of the gland with milk.[1] The cavities of the alveoli and all the ducts are occupied by milk, the fatty globules of which lie free in the fluid filling the alveoli (fig. 699). Similar globules may be seen occupying the inner zone of the epithelium-cells of the alveoli ; these inner zones may indeed in some cells be so filled with fat-globules as to project into the alveolus considerably beyond the general line of the epithelium (fig. 700). There is little doubt that the globules thus formed in the cells are set free by being passed into the lumen of the alveolus—possibly by the dehiscence of the inner zone. The first milk formed (*colostrum*) contains, besides free fat-globules, others which are enclosed within protoplasmic cells ; such cells—known as *colostrum-corpuscles*—are also seen within

[1] Schäfer, article 'Mammary Gland,' in Advanced Text-book of Physiology, 1898.

the secreting alveoli. They are regarded by most authors as detached epithelium-cells, but others consider them to be phagocytic leucocytes which have passed

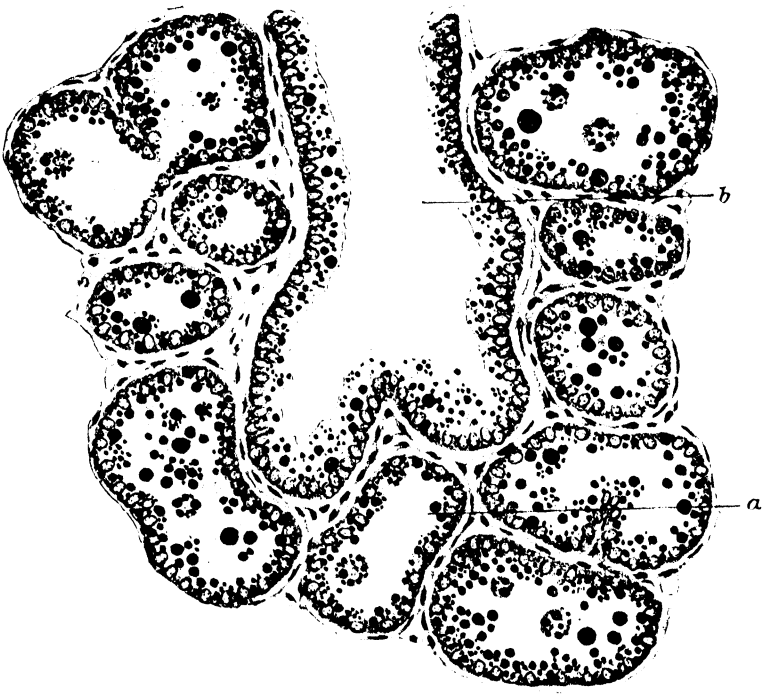


FIG. 699.—SECTION OF HUMAN MAMMARY GLAND DURING LACTATION. (From Marshall's Physiology of Reproduction.) Highly magnified.

a, an alveolus; *b*, a duct. The fat-globules are stained black by osmic acid.

through the epithelium into the milk and taken the fatty globules into their interior.

After lactation is over a general process of involution begins. The alveoli become atrophied and the glandular substance is again reduced to a small amount; but it is never so small as in the virgin condition.

Here and there even in the active gland a certain number of lobules may be seen with their alveoli still in an undeveloped state (fig. 701). It is probable that as lactation progresses, the increasing demand made upon the gland during growth of the offspring will cause these also to undergo evolution.

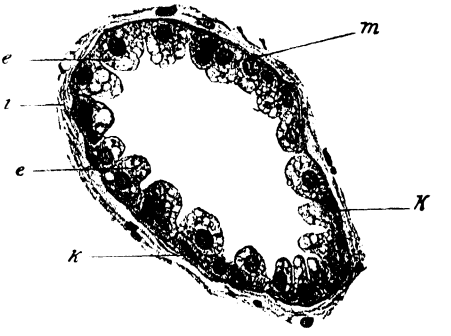


FIG. 700.—AN ALVEOLUS WITH FAT-DROPS IN CELLS. (v. Ebner.) Magnified 360 diameters.

e, cells of alveolus; *k*, cells forming basket-like basement-membrane, *m*; *i*, connective tissue.

The **blood-vessels** form a close network of capillaries investing the alveoli. The glands are supplied with blood by numerous branches of the internal and external mammary arteries which ramify within the connective-tissue septa. The veins are partly deep, accompanying the arteries, partly superficial. The latter form a circular plexus

around the areola; from this plexus venous branches course radially over the surface of the gland.

The **lymphatics** arise from sinus-like spaces surrounding the alveoli (as in other racemose glands). These sinuses anastomose to form an open network. From all parts of the gland the efferent lymphatics converge towards the areola, where they form a subareolar plexus. From this plexus two vessels, which may ultimately unite into one, convey the lymph laterally towards the axillary glands, receiving in their course numerous tributaries. Other lymphatics from the mesial part of the mamma pass to the sternal lymph-glands along the internal mammary artery. Many of the lymphatics are perivascular (Stiles).

FIG. 701.—SECTION FROM THE SAME GLAND AS THAT SHOWN IN FIG. 697. (v. Ebner.) Magnified 110 diameters.

b, connective tissue; *d*, undeveloped alveoli; *d'*, partially developed alveoli; *g*, blood-vessels; *m*, portion of larger duct with two-layered epithelium.

The **nerves** of the mamma pass partly to the skin and the subcutaneous plain muscular tissue, partly to the blood-vessels and glandular tissue. Tactile corpuscles occur in the papillæ of the nipple, and Pacinian corpuscles under the areola. In the glandular tissue nerve-fibre terminations are seen amongst the cells (Dmitrewsky), but the secretion is not under the direct influence of nerves like that of the salivary glands. It appears to be stimulated by "hormones" circulating with the blood. Such hormones can be extracted from the infundibular portion of pituitary body, from corpora lutea, from the involuting mucous membrane of the uterus, and from the lactating gland itself.[1]

Development of the mammary gland.—In embryo-mammals, at an early period, a line of thickening of the epidermis—the *mammary* line—is seen along the lateral wall on each side of the body, extending from the axilla to the groin. This thickening soon disappears except at certain places, where the future mammary glands are to be developed. The first sign of the gland shows itself at the end of the second month in the human embryo (Rein) in the shape of a thickening and downgrowth of the rete mucosum of the epidermis at the site of the future nipple. The thickening spreads laterally so as to correspond with a small area (mammary area), which soon becomes sunk below the general surface. From the thickened rete mucosum of this area special outgrowths of the epithelium into the cutis vera occur, one for each of the lobes of the future gland. These outgrowths, as with other racemose glands, become branched, and their branches end in enlargements. The formation of these sprouts goes on until birth, but the development of glandular alveoli from them does not occur until the approach of puberty in the female, and in the male not at all. The projection of the nipple from the rest of the mammary area does not begin until about the first year after birth; within it a large amount of plain muscular tissue becomes formed. The remainder of the mammary area becomes the areola.

[1] Ott and Scott, Proc. Soc. Exper. Biol. Dec. 1910; Schäfer and Mackenzie, Proc. Roy. Soc. March 1911.

THE ALIMENTARY SYSTEM

The alimentary system comprises the mouth with the tongue and teeth and salivary glands, the pharynx with the tonsils, the gullet, the stomach, the small intestine with the pancreas and liver, and the large intestine. In continuity and in close morphological relation with the alimentary system is the respiratory system, including the nostrils, the larynx, trachea and bronchi, and the lungs; the last are developed much in the same way as the glands which pour their secretions into the alimentary canal, such as the salivary glands and pancreas. The description of the structure of the nasal passages may conveniently precede that of the alimentary canal; the remainder of the respiratory system will be described afterwards.

THE NASAL PASSAGES.

Mucous membrane of the nasal passages.—This membrane, also known as the Schneiderian or pituitary membrane, is very intimately attached to the periosteum and perichondrium of the bones and cartilages of the nose, the connexion being, however, closer in some parts than in others. It is thick and highly

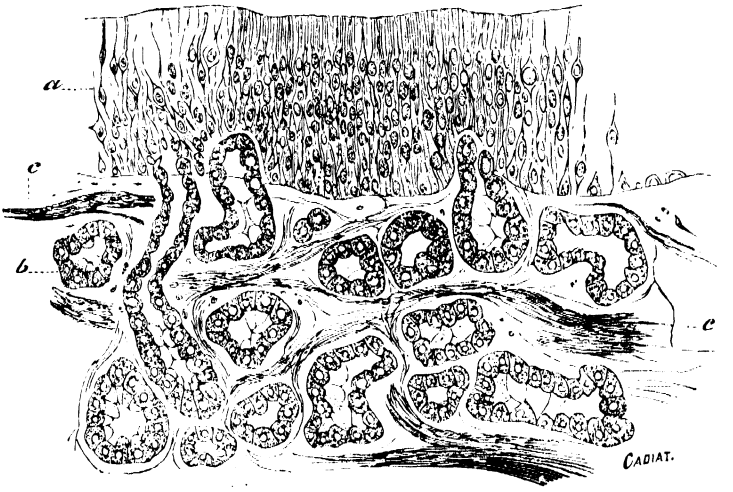


FIG. 702.—SECTION OF THE MUCOUS MEMBRANE OF THE OLFACTORY REGION. (Cadiat.)
a, epithelium; *b*, glands of Bowman; *c*, nerve-bundles.

vascular, especially over the turbinate bones and septum; thinner and less vascular in other parts of the nasal fossæ, and thinnest in the cavities which communicate with the nasal fossæ, where it also has fewest vessels. Except over the uppermost turbinate and the corresponding part of the septum the nasal mucous membrane is covered with *ciliated epithelium*. Between the cells of this are seen the orifices of numerous small racemose mucous glands, which themselves lie in the deeper part of the membrane. These glands are most numerous in the middle and back parts of the fossæ, and largest near the floor. Bundles of plain muscular fibres lie around the gland alveoli in some parts, especially where the membrane is thickest; the muscle-bundles partly encircle the venous plexuses which here lie under the mucous membrane (Klein).

In the uppermost part of the fossæ (olfactory region) the membrane has a yellowish colour and is covered by *non-ciliated columnar cells*, between which lie the *olfactory cells*, which give origin to the olfactory nerve-fibres (see pp. 288, 289). This olfactory part of the membrane contains glands of a different nature from those in the remaining or respiratory part. In place of mucous glands we here find glands with comparatively large alveoli and granular yellowish cells, which yield a

serous secretion (*glands of Bowman*—fig. 702), and open by fine ducts between the epithelium-cells. Amongst the gland-alveoli are seen conspicuous bundles of the olfactory nerve-fibres, which are passing from the olfactory cells in the mucous membrane towards the cribriform plate of the ethmoid bone. Although the gland-

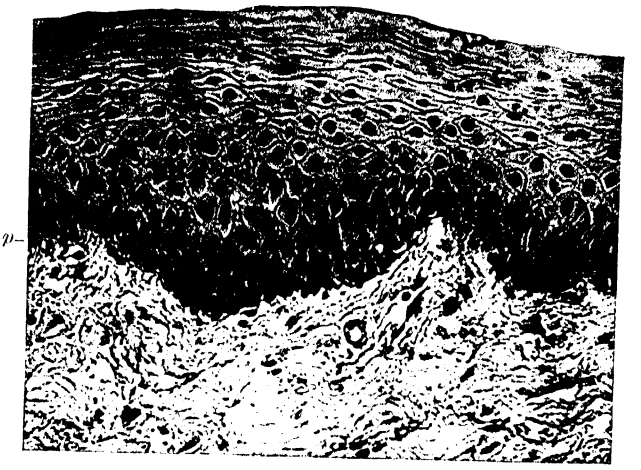


FIG. 703.—SECTION OF MUCOUS MEMBRANE FROM THE BACK OF THE MOUTH (RABBIT). (Schäfer.) Magnified 240 diameters. Photograph.
Two bread papillæ are seen in the section.

cells are mainly serous there are a few mucus-secreting cells amongst them. Here and there patches of ciliated epithelium may be seen in the olfactory region ; the glands which open on to such patches are always mucous glands. Besides the

FIG. 704.—THREE PAPILLÆ FROM THE LIPS, WITH THE BLOOD-VESSELS INJECTED. (Toldt.)

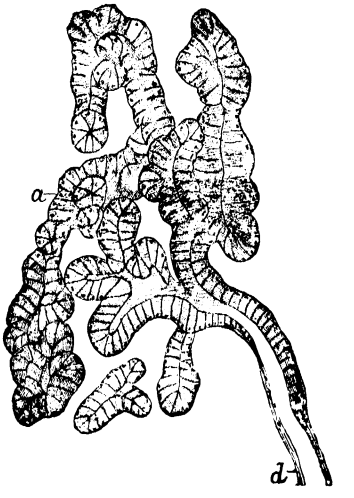


FIG. 705.—PART OF A SMALL MUCOUS GLAND OF THE MOUTH. (Klein.)
a, alveoli ; *d*, duct.

columnar and olfactory cells of the olfactory membrane there are other more deeply lying sustentacular cells, resting on the basement-membrane.[1]

At the most anterior part the nostrils are lined by a prolongation of the skin, covered by *stratified epithelium* (epidermis), and provided with hairs and sebaceous

[1] See Vol. III. Part II. 'The Olfactory Organ.'

glands and other structures special to the skin. In various regions, but especially at the posterior part of the nasal fossæ near their communication with the pharynx, lymphoid tissue occurs in the corium. It may be here and there accumulated into lymphoid nodules, foreshadowing the adenoid tissue found so abundantly in the adjacent upper part of the pharynx.

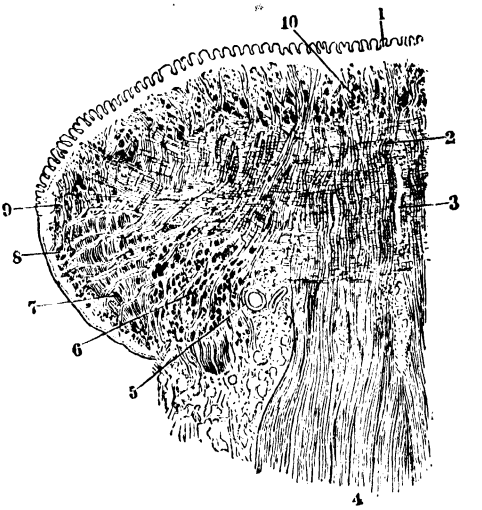


FIG. 706.—CORONAL SECTION OF THE TONGUE ABOUT THE MIDDLE OF ITS LENGTH; LEFT HALF SEEN FROM BEHIND. (W. Krause.)

1, papillæ on the dorsal surface; 2, transverse muscular fibres; 3, septum linguæ; 4, genio-glossus; 5, ranine artery; 6, inferior lingualis; 7, hyo-glossus; 8, vertical muscular fibres; 9, stylo-glossus; 10, superficial lingual muscle.

THE MOUTH.

Mucous membrane of the mouth. — This mucous membrane, which is continuous at the outer margin of the lips with the skin and at the isthmus of the fauces with the mucous membrane of the pharynx, varies considerably in different regions in the closeness of its adhesion to subjacent structures. Thus it is intimately adherent over the hard palate and gums and over the greater part of the tongue; less firmly over the soft palate, and least over the cheeks and lips (except at their free edge) and on the floor of the mouth and under-surface of the tongue. The corium is formed of areolar tissue bounded by an ill-defined basement-membrane, and is covered everywhere by stratified epithelium composed of several layers of cells (fig. 703), but less

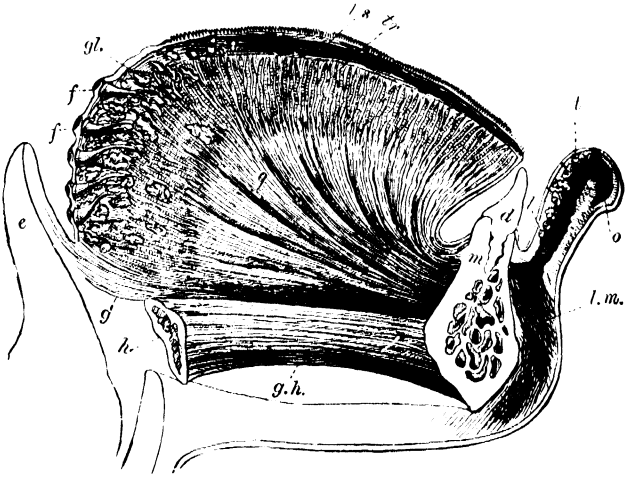


FIG. 707.—LONGITUDINAL VERTICAL SECTION OF THE TONGUE. (Arnold.)

m, symphysis of the lower jaw; *d*, incisor tooth; *h*, hyoid bone; *g.h.*, genio-hyoid muscle; *g*, genio-hyo-glossus spreading along the whole of the tongue; *tr*, transverse muscle; *l s*, superior longitudinal muscle; *gl*, lingual glands; *f*, lymphoid crypts; *e*, epiglottis; *l*, section of the lip and labial glands; *o*, cut fibres of the orbicularis oris; *l.m.*, levator menti.

complex in its composition than the epidermis covering the skin. The superficial scaly cells are constantly being removed, and mingle with the saliva;

their place is taken by other cells which are supplied by mitotic division of the cells of the deeper layers, the newly formed cells pushing those previously formed towards the surface. In many parts, especially at the back of the mouth, leucocytes are found between the epithelium-cells.

The corium projects everywhere into the stratified epithelium in the form of microscopic papillæ (fig. 703), most of which contain vascular loops, while some are provided with end-bulbs. The papillæ are longer and better marked in the mucous membrane at the margins of the lips (fig. 704) than elsewhere. Lymph-vessels are also seen within the papillæ; they pass into a superficial plexus in

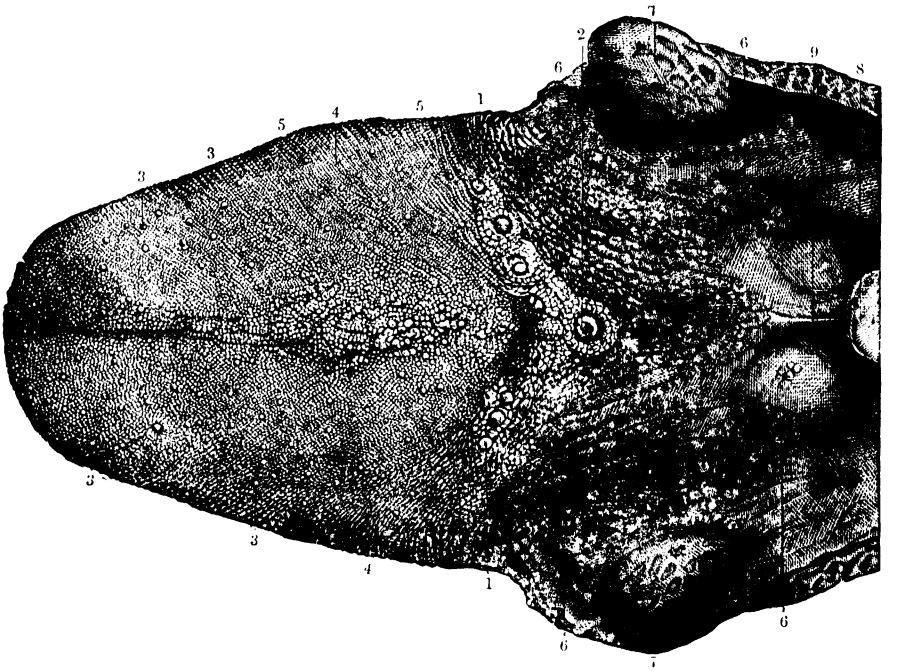


FIG. 708.—PAPILLARY SURFACE OF THE TONGUE, WITH THE FAUCES AND TONSILS. (Sappey.)

1, 2, circumvallate papillæ; behind 2, the foramen cæcum; 3, fungiform papillæ; 4, filiform and conical papillæ; 5, transverse and oblique ranges; 6, mucous glands and lymphoid follicles at the base of the tongue and in the fauces; 7, tonsils; 8, tip of the epiglottis; 9, median glosso-epiglottic fold of the frenum epiglottidis.

the mucous membrane, from which the lymph is conveyed by valved vessels seated in the submucous tissue.

Small racemose mucous glands (fig. 705) are found everywhere under the mucous membrane. They are named *labial*, *buccal*, *molar*, &c., according to their situation, and have the usual structure of such glands (see p. 427).

THE TONGUE.

The substance of the tongue is chiefly composed of muscular fibres running in different directions (figs. 706, 707). Many of them are attached to the mucous membrane, especially of the dorsal surface and tip.

Mucous membrane of the tongue.—The mucous membrane of the tongue resembles that of the mouth generally, and like that is covered by stratified epithelium. It is loosely connected with the muscular substance on the sides and under part, where its surface is smooth; but is closely attached over the upper

surface, which has a roughened aspect, due to the presence of small projections of the membrane, known as the *lingual papillæ*.

The mucous membrane of the tongue is provided with numerous small glands (*lingual glands*), collected principally about the posterior part of its upper surface, near the papillæ vallatæ and foramen cæcum, into which last the ducts of several open. Most of these glands secrete mucus, but some of them, especially those which open in the trenches around the papillæ vallatæ, and at other parts where taste-buds occur, yield a serous secretion (*glands of Ebner*). Other glands are found beneath the mucous membrane of the borders of the tongue. There is, in particular, a group on the under-surface of the tongue on each side near the apex called the *glands of Blandin*. They are there aggregated into a small oblong mass, out of which several ducts proceed and open in a line on the mucous membrane. Most of the glands are tubulo-racemose.

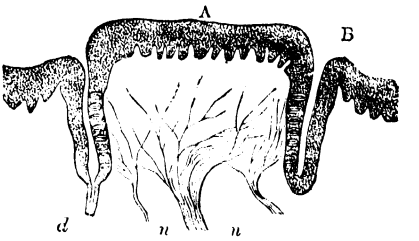


FIG. 709.—VERTICAL SECTION OF CIRCUMVALLATE PAPILLA FROM THE CALF. (Engelmann.) 25 diameters.

A, the papilla: B, the surrounding wall. The figure shows the nerves (*n*) of the papilla spreading towards the surface, and towards the taste-buds imbedded in the epithelium at the sides; in the sulcus on the left the duct of a gland (*d*) is seen to open.

The mucous membrane of the tongue, especially its posterior part, contains a large amount of lymphoid tissue, which is collected at numerous points into the denser nodular masses known as follicular glands, or lymph-follicles. The blood-vessels and lymphatics of this part of the membrane are numerous and large, but the papillæ on its surface are comparatively small, and are completely concealed by the thick superjacent epithelium. The mucous membrane here exhibits recesses or crypts (fig. 707, *f*), either simple or surrounded by smaller ones which open into them, as in the tonsils. The walls of these recesses are studded with lymph-follicles; the recesses receive the ducts of many mucous glands.

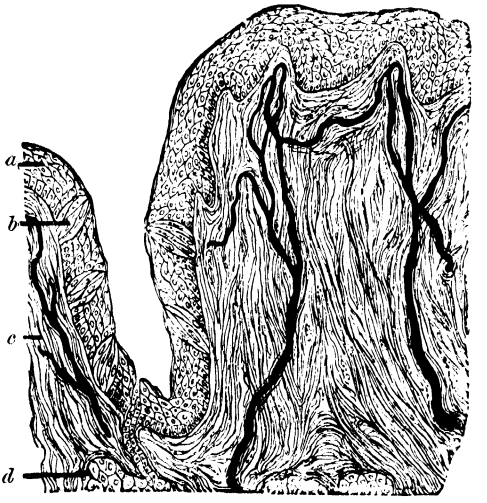


FIG. 710.—SECTION OF CIRCUMVALLATE PAPILLA, HUMAN. THE FIGURE INCLUDES ONE SIDE OF THE PAPILLA AND THE ADJOINING PART OF THE VALLUM. (Heitzmann.) Magnified 150 diameters.

a, epithelium; *b*, taste-bud; *c*, corium with injected blood-vessels; *d*, gland with duct.

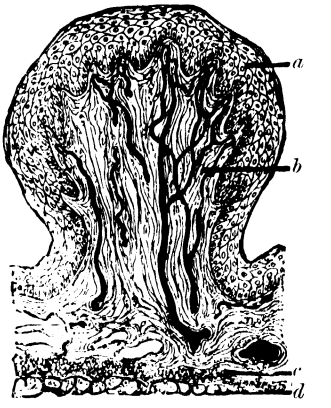


FIG. 711.—SECTION OF FUNGIFORM PAPILLA, HUMAN, WITH THE BLOOD-VESSELS INJECTED. (Heitzmann.)

a, epithelium; *b*, corium; *c*, lymphoid tissue; *d*, muscular fibres of tongue.

Lingual papillæ.—The lingual papillæ found on the anterior two-thirds of the tongue (fig. 708) are of three kinds, *circumvallate*, *fungiform*, and *conical*. They vary both in size and form, but all of them are visible to the naked eye. They themselves, like the rest of the mucous membrane of the tongue and mouth generally, are covered with closely set, microscopic secondary papillæ hidden under the epithelium; these correspond with those of the skin, and each is occupied by a long loop of capillary blood-vessels.

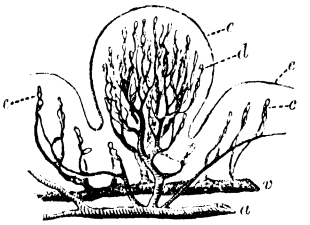


FIG. 712. — A FUNGIFORM PAPILLA WITH THE BLOOD-VESSELS INJECTED. (Todd and Bowman.)

a, artery; *b*, vein; *c*, capillary loops of simple papillæ in the neighbourhood, covered by the epithelium; *d*, capillary loops of the secondary papillæ; *e*, epithelium.

The circumvallate papillæ (fig. 708, *1*, *2*), from 7 to 12 in number, are found at the union of the middle and posterior thirds of the tongue, arranged in two lateral rows, which run obliquely backwards and inwards towards a median papilla, like the limbs of the letter V. Not infrequently there are two papillæ in the middle line. The circumvallate papillæ are situated in cup-like depressions of the mucous membrane; each has the shape of a truncated cone, of which the smaller end is attached to the bottom of the cavity, and the broad flattened base appears on the surface (fig. 709). In some there is a central depression. The papilla is surrounded by a circular trench (fossa), around which again is a slight annular elevation of the mucous membrane (vallum). The ducts of one or more serous glands open into the trench surrounding the papilla (figs. 709, 710, *d*). The stratified epithelium covering the papilla is thick, and completely conceals the secondary papillæ which project into the epithelium.

Taste-buds are found forming a zone around the sides of these papillæ, and in man and some animals upon the opposed wall of the vallum (fig. 710). They are described in the parts of this work dealing with sensory nerve-endings (see p. 283 of this volume, and Vol. III., Part II.).

Taste-buds are not confined to the circumvallate papillæ, but are found here and there on the fungiform papillæ and in the interpapillary epithelium of the organ, even on the under-surface, at least in the fœtus.[1] They have also been found in the hard palate of the fœtus and in the lower part of the pharynx. They have occasionally been seen in the upper part of the gullet and in the part of the larynx which adjoins the pharynx.[2] They have long been recognised on the laryngeal surface of the epiglottis.

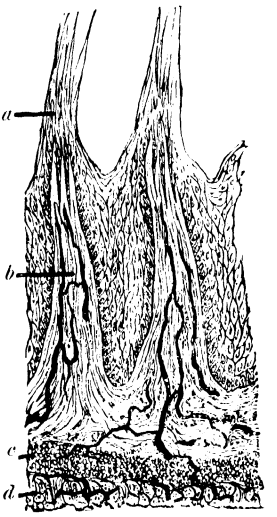


FIG. 713. — SECTION OF TWO FILIFORM PAPILLÆ, HUMAN. (Heitzmann.)

a, epithelium; *b*, corium; *c*, lymphoid tissue; *d*, muscular fibres of tongue.

The *fungiform papillæ*, more numerous than the last, are small rounded eminences scattered over the middle and fore part of the dorsum of the tongue (fig. 708, *3*); and, in even greater number and closer together, at the apex and near the borders. They are easily distinguished in the living tongue owing to their deep red colour. Each papilla is narrow at its attachment; from this point it enlarges in a bulbous manner, the free extremity being rounded (fig. 711). They

[1] Ponzo, Anat. Anz. xxx. 1907.
[2] Idem. See also J. G. Wilson, Brain, xxviii. 1905.

contain numerous blood-vessels which extend into closely set vascular secondary papillæ (fig. 712).

The *conical papillæ* are the most numerous, as well as the smallest. They are minute, tapering, or cylindrical prominences, densely set over the greater part of the dorsum of the tongue (fig. 708, *4*), but gradually disappearing towards its base. They are arranged in lines diverging from the raphe, at first in an oblique direction, parallel with the two ranges of papillæ vallatæ, but gradually becoming transverse towards the tip of the tongue. At the sides they are longer and more slender, and their rows are arranged perpendicular to the border of the tongue.

The microscopic papillæ which occur upon the conical papillæ are peculiar both in containing a number of elastic fibres, and in the character of their epithelial covering; this is always very thick and sometimes forms a separate horny process over each secondary papilla, much greater in length than the papilla which it covers (fig. 713). Over some of the papillæ the horny processes split up into a pencil of fine fibres, (fig. 714); the name 'filiform' has been applied to these.

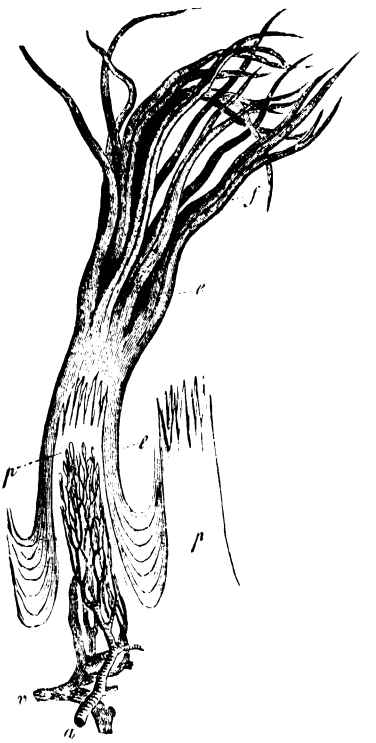


FIG. 714. TWO FILIFORM PAPILLÆ, ONE WITH EPITHELIUM AND WITH THE BLOOD-VESSELS INJECTED, THE OTHER WITHOUT. (Todd and Bowman.) 35 diameters.

p, the substance of the papillæ divided at their upper extremities into secondary papillæ; *a*, artery, and *v*, vein, connected by capillary loops; *e*, epithelial covering, laminated between the papillæ, but extended into hair-like processes, *f*, over the secondary papillæ.

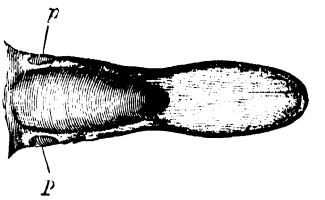


FIG. 715.—TONGUE OF RABBIT, SHOWING THE SITUATION OF THE PAPILLÆ FOLIATÆ, *p*, *p*. (Schäfer.)

The papillary surface of the tongue is abundantly supplied with nerves, some of which terminate in end-bulbs, a few in tactile corpuscles. In the fungiform papillæ the nerves are large and numerous; they are still more abundant, and of greater size, in the circumvallate papillæ, where they are chiefly distributed in the neighbourhood of the taste-buds (fig. 709).

The papillæ, besides being the parts chiefly concerned in the special sense of taste, also possess, in a very acute degree, tactile sensibility; while the conical papillæ, armed with their dense epithelial covering, serve a mechanical purpose, in the action of the tongue upon the food, as is well illustrated by the greater development that these papillæ attain in many carnivorous animals.

In some animals (*e.g.* rabbit) there is present on each side of the tongue, nearly opposite the ends of the V formed by the line of papillæ vallatæ, an oval aggregation of transversely placed ridges or laminæ with intervening furrows, which is termed the *papilla foliata* (fig. 715, *p*, *p*).

The ridges are covered with a thick stratified epithelium, and at their sides numerous taste-buds are imbedded in this epithelium (fig. 716). There is no definite papilla foliata in the human tongue, but in a situation similar to that in which the papilla foliata occurs in animals the mucous membrane often exhibits a number of low ridges, and is beset with taste-buds.[1]

THE TEETH.

A tooth is usually described as consisting of three portions, viz. one which projects above the gums and is named the *body* or *crown*; another fixed in the alveolus or socket, the *root*, consisting of a *fang* or *fangs*; and a third, intermediate between the other two, and, from being usually slightly constricted, named the *neck*. The size and form of each of these parts vary in the different kinds of teeth (see Vol. IV. of this work).

The roots of the teeth are accurately fitted to the alveoli of the jaws, in which they are implanted. Each alveolus is lined by periosteum (*dental periosteum*, fig. 717, *4*), which also invests the contained tooth as high as the neck, and is blended above

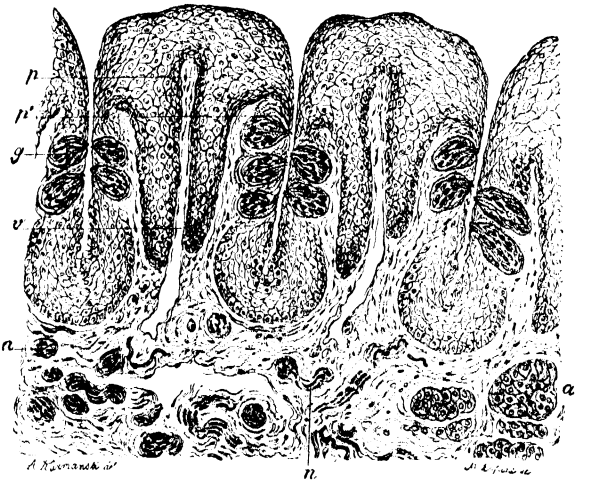


FIG. 716.—VERTICAL SECTION OF PAPILLA FOLIATA OF THE RABBIT, PASSING ACROSS THE FOLIA. (Ranvier.)

p, central lamina of the corium; *v*, section across a sinus-like vein, which traverses the whole length of the folium; *p'* lateral lamina in which the nerve-fibres run; *g*, taste-bud; *n*, sections of nerve-bundles; *a*, serous gland.

with the dense tissue of the gums. The fangs of all the teeth taper from the cervix to the point; this form, together with their accurate adjustment to the alveolus, has the effect of distributing the pressure during use over the whole socket, and of preventing it from bearing on the point of the fang, through which the blood-vessels and nerves enter.

On making a section of a tooth, it is found to be hollow within (figs. 717, 718). The form of the cavity bears a general resemblance to that of the tooth itself; it occupies the interior of the crown, and extends along each fang, at the point of which it opens by a small orifice. In the incisor teeth the cavity is prolonged above into two tapering canals, which proceed one to each corner of the crown; in the bicuspid and molar teeth it advances a short distance into each cusp. In the case of a root formed by the blending of two or more fangs, each division has a separate canal prolonged to its apex.

[1] On the phylogenesis and comparative anatomy of the lingual papillæ see B. Haller, Arch. f. mikr. Anat. lxxiv. 1909.

The central cavity of a tooth is called the *pulp-cavity*, because it is occupied by a soft, highly vascular, and sensitive substance, called the *dental pulp*. This pulp (fig. 719, *P*) consists of a jelly-like connective tissue containing cells, fine fibres, blood-vessels, and nerves. Many of the fibres appear to be continued from processes of the cells: according to Röse they are not collagenous, although a few bundles of ordinary collagenous connective-tissue fibres accompany the blood-vessels and nerves. Near the dentine some of these connective-tissue bundles have a radial arrangement.[1] This is better marked during development of the dentine, when the fibrils extend between the superficial cells, and are continuous with those of the pro-dentine.[2] The cells are partly disseminated in the matrix, and partly form a stratum at the surface of the pulp, where, during the formation of dentine, they are elongated, somewhat like the cells of columnar epithelium (see fig. 740, *c*, p. 508); but after the dentine is completely formed they become flattened, like the osteoblasts under the periosteum of bone. These superficial cells (*odontoblasts*, fig. 719, *Od*, *Od'*) send processes into tubules in the dentine, to be afterwards noticed, of which more than one may come from the same cell. The filaments within the tubules were first noticed by J. Tomes, and are known as *Tomes' fibres*. The arteries and nerves, which are derived from the internal maxillary and fifth pair respectively, enter by the aperture at the point of each fang. The vessels form a capillary network beneath the superficial cells, but some may penetrate between these to the inner surface of the dentine.[3] The nerves end in fine non-medullated fibrils, which are distributed abundantly at the surface of the pulp. Here they form

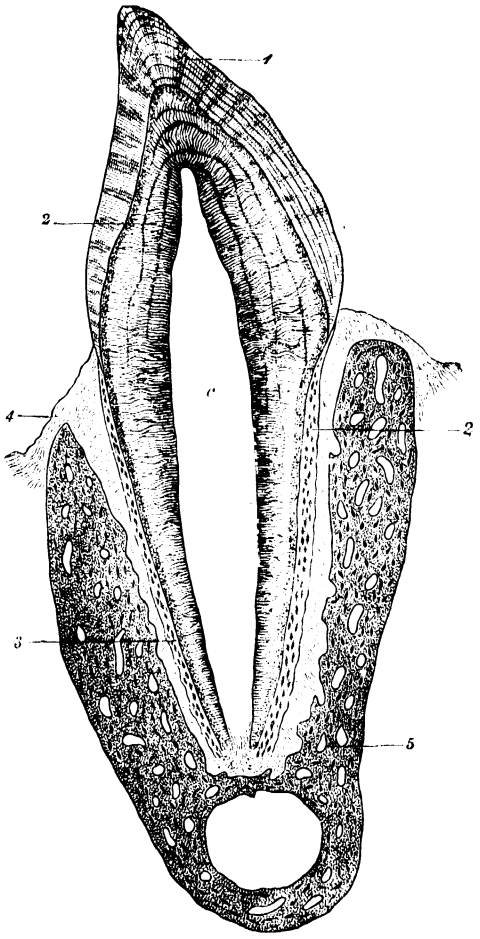


FIG. 717.—VERTICAL SECTION OF PREMOLAR OF CAT. (Waldeyer.) Magnified 15 diameters.

c is placed in the pulp-cavity, opposite the cervix or neck of the tooth; the part above is the crown, that below is the root (fang). 1, enamel with radial and concentric markings; 2, dentine with tubules and incremental lines; 3, cement or crusta petrosa, with bone corpuscles; 4, dental periosteum; 5, bone of lower jaw.

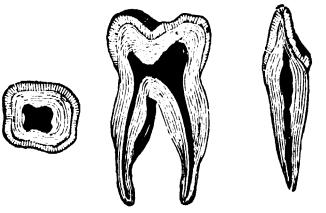


FIG. 718.—SECTIONS OF AN INCISOR AND MOLAR TOOTH.

[1] Studnička, Anat. Anz. xxx. 1907.
[2] Korff, Arch. f. mikr. Anat. lxvii. 1905.
[3] For the distribution of blood-vessels see Lepkowski, Anat. Hefte, viii. 1897 and xvii. 1901.

a dense marginal plexus; from this nerve-fibrils run up between the superficial cells into the dentinal tubules.[1] Lymphatics have been described in the pulp; they also occur in the periodontal membrane.[2]

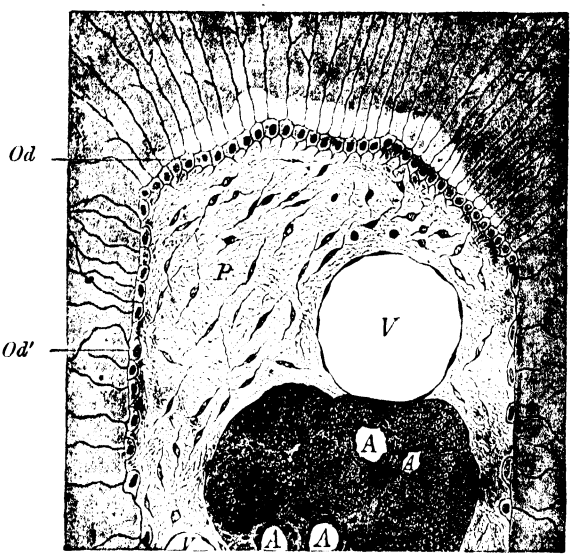


FIG. 719.—SECTION ACROSS THE ROOT OF A YOUNG TOOTH SHOWING THE PULP IN SITU. (Röse.) Magnified about 200 diameters.

P, pulp; *V*, *V*, veins; *A*, *A*, *A*, arterioles; *N*, nerve-bundles; *Od*, columnar odontoblasts still depositing dentine; *Od'*, flattened odontoblasts which have ceased to form dentine.

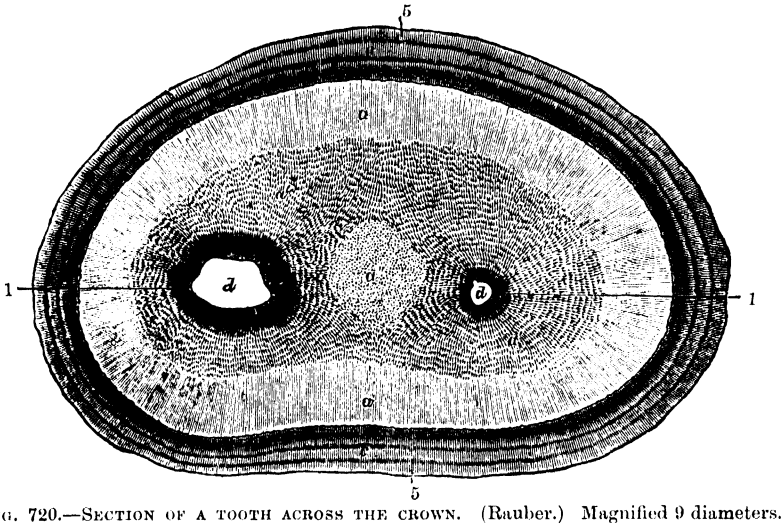


FIG. 720.—SECTION OF A TOOTH ACROSS THE CROWN. (Rauber.) Magnified 9 diameters.

a, dentine, the tubules cut longitudinally; *a'*, the same cut obliquely; *a''*, the same cut across; *c*, enamel, showing contour lines (5); *d*, *d*, portions of the pulp-cavity extending into the cusps, with the dentine tubes converging horizontally (1).

The hard part of a tooth is composed of three distinct substances—viz. the proper dental substance, known as *ivory* or *dentine*, the *enamel*, and the *cement* or

[1] Law (Proc. Roy. Soc. Med. i. 1908) states that he has succeeded in following fibrils into the tubules. Howard Mummery (private communication) has also shown nerve-fibrils passing from the marginal plexus into the tubules and has traced them into all parts of the dentine, even close to the surface. It is difficult to understand the extreme sensitiveness of dentine, especially when inflamed, unless we assume the presence of nerve-fibrils in it.

[2] G. Schweitzer, Arch. f. mikr. Anat. lxix. 1907; lxxiv. 1909.

crusta petrosa (see figs. 717, 720, 721, 722). The dentine constitutes by far the larger portion : the enamel is found only upon the exposed part or crown ; the cement covers with a thin layer the surface of the fang.

Dentine.—This resembles bone in its aspect and general chemical constitution, but is not identical with it in structure.

The dentine of human teeth is composed of 28 parts per cent. of animal and 72 of earthy matter. The former is resolved into gelatin by boiling. The composition of the latter,

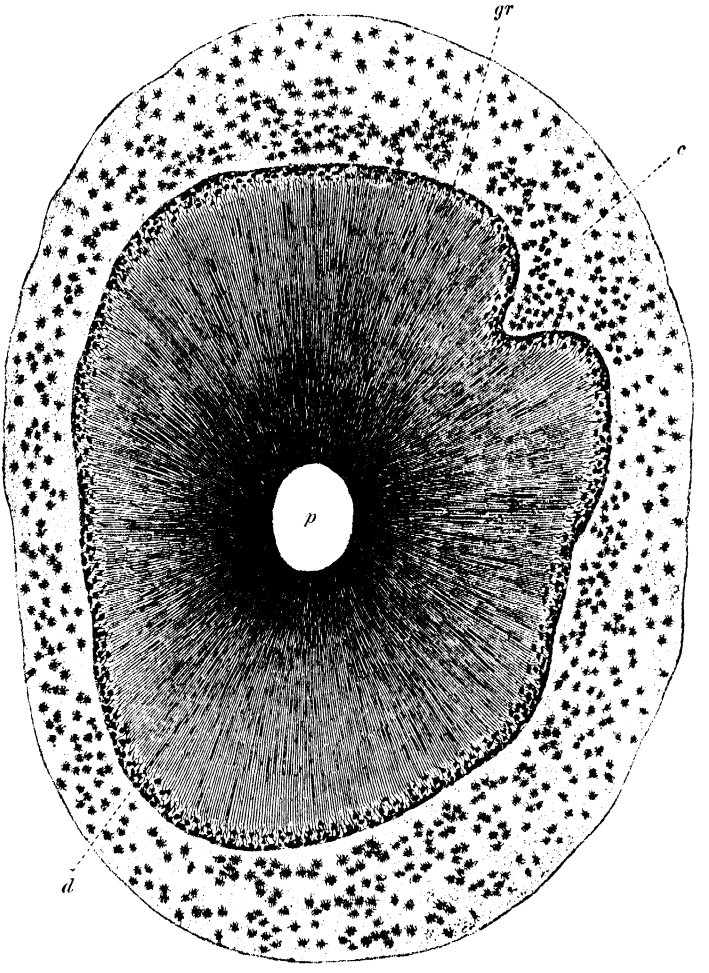


FIG. 721.—SECTION OF A HUMAN CANINE TOOTH, ACROSS THE FANG. (Sobotta.)
Magnified 25 diameters.

p, pulp-cavity ; *d*, dentine ; *gr*, its granular layer ; *c*, cement.

according to Bibra, is as follows: Phosphate of lime 66·7 per cent., carbonate of lime 3·3, phosphate of magnesia and other salts, including a trace of fluoride of calcium, 1·8. Berzelius found 5·3 carbonate of lime.

Dentine is penetrated throughout by fine tubes (*dentine tubules*), which, being nearly parallel, give it a striated aspect (figs. 721, 722). When a thin section of a macerated tooth, prepared by grinding, is viewed under the microscope by transmitted light, the solid substance, or matrix, is transparent and apparently homogeneous, while the tubes, being (in a dried specimen) filled with air, are dark ; but

when seen with reflected light on a dark ground, the latter appear white ; in these respects they resemble lacunæ and canaliculi of bone.

The *dentine tubules* open at their inner ends into the pulp-cavity, which has accordingly very numerous minute orifices over the whole surface. They pass in

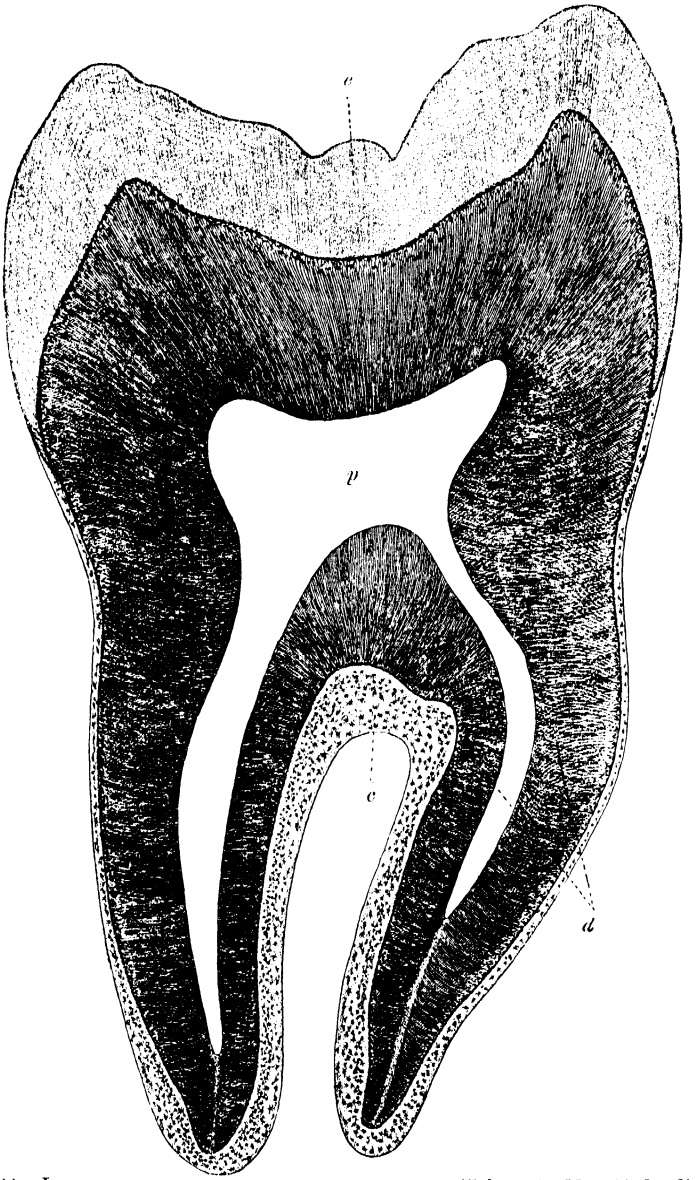


FIG. 722.—LONGITUDINAL SECTION OF A MOLAR TOOTH. (Sobotta.) Magnified 8 diameters.
p, pulp-cavity; *d*, dentine; *c*, cement; *e*, enamel.

a radiating manner through every part of the ivory towards its periphery. In the upper part of the crown they have a vertical direction ; towards the sides, and in the neck and root, they gradually become oblique, then horizontal, and are finally even inclined downwards towards the point of the fang. The tubules describe in their course two or three gentle curves (*primary curvatures*), and in addition each

is twisted throughout its whole length in numerous fine spiral turns, which follow more closely one upon another; these are the *secondary curvatures* (fig. 723). In form a tubule may accordingly be likened to the thread of a corkscrew, stretched so that the turns are drawn far apart and their breadth proportionally diminished (Welcker).

The tubules are only slightly divergent as they pass towards the surface; and, as they occasionally divide dichotomously, at first without being much diminished in size, they continue to occupy the substance of the dentine at almost equal distances. Their nearly parallel primary curvatures produce, by the manner in which they reflect the light, an appearance of concentric undulations in the dentine, which may be well seen with a low magnifying power (*Schreger's lines*). The average

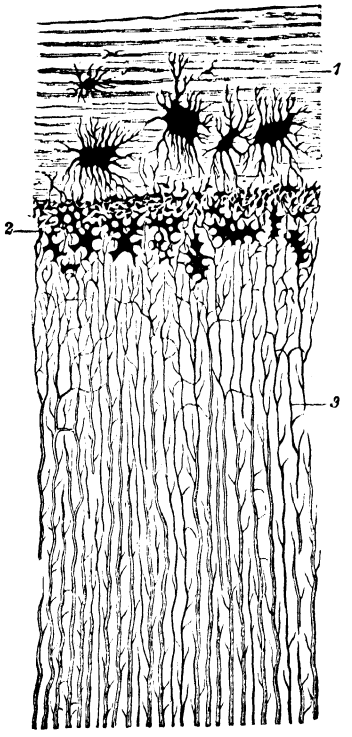


FIG. 723.—SECTION OF FANG, PARALLEL TO THE DENTINE TUBULES (HUMAN CANINE). (Waldeyer.) Magnified 300 diameters.

1, cement, with large bone lacunæ and indications of lamellæ; 2, granular layer of Purkinje (interglobular spaces); 3, dentinal tubules.

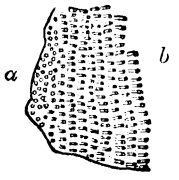


FIG. 724.—SECTIONS OF DENTINE TUBULES. (Fraenckel.)

a, cut across; *b*, cut obliquely. Magnified about 300 diameters.

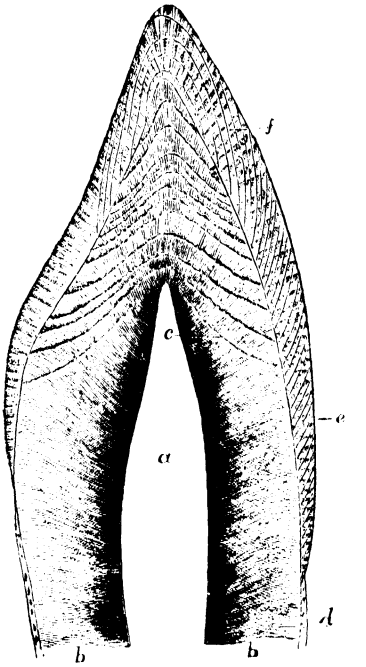


FIG. 725.—VERTICAL SECTION OF THE UPPER PART OF AN INCISOR TOOTH. (Kölliker.) Magnified 7 diameters.

a, the pulp-cavity; *b*, dentine; *c*, arched incremental lines; *d*, cement; *e*, enamel, with bands indicating the direction of the ranges of fibres; *f*, coloured lines of the enamel.

diameter of the tubules at their inner and larger end is 0·0055 mm.; the distance between adjacent tubules is commonly about two or three times their width (fig. 723). From their sides, numerous exceedingly fine branches are given off, which penetrate the hard intertubular substance, where they either anastomose or terminate blindly (fig. 723). These lateral ramuscles are more abundant in the fang. Near

the periphery of the dentine the tubules, which by division and subdivision have become very fine, terminate imperceptibly by free ends.

The tubules have each a proper wall (*sheath of Neumann*) independent of the intertubular matrix, but intimately adhering to it. By steeping sections of decalcified dentine in strong hydrochloric acid, the matrix is destroyed, and these membranous walls, which consist of a more resisting material, remain behind. Röse states that these sheaths, which are formed of a material which calcifies either late or not at all, anastomose freely, and that it is their anastomoses which have been often taken for those of the tubules themselves.

In the temporary, and sometimes even in the permanent teeth, the tubules are constricted at short intervals, so as to present a moniliform character. The terminal branches of tubules are occasionally seen to pass on into the cement covering the fang, and to communicate with canaliculi proceeding from the bone lacunæ characteristic of that layer. Tubules have likewise been observed by Tomes and others penetrating into the enamel. In this case they pass, not into the enamel prisms, but into the interprismatic substance (fig. 727).

The matrix of the dentine (*intertubular substance*) may, after decalcification, be torn into laminæ parallel with the internal surface of the pulp-cavity, and therefore across the direction of the tubules (Sharpey). It has been shown by v. Ebner and Mummery that the matrix contains fine fibrils arranged for the most part parallel to the surface of the pulp, like those of the lamellæ of bone. These fibrils are not themselves calcified, but are enveloped in the calcified interfibrillar substance, and, according to Mummery, are continuous with fibrils of the dental pulp.

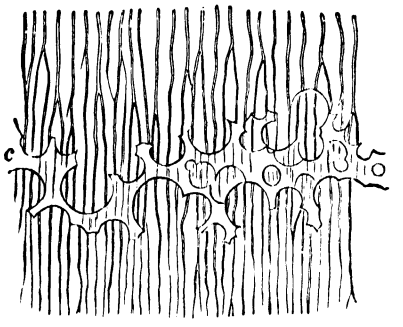


FIG. 726.—A SMALL PORTION OF THE DENTINE WITH INTERGLOBULAR SPACES (Kölliker.) Magnified 350 diameters.

c, portion of incremental line formed by the interglobular spaces, which are here filled up by the transparent material used in mounting the specimen.

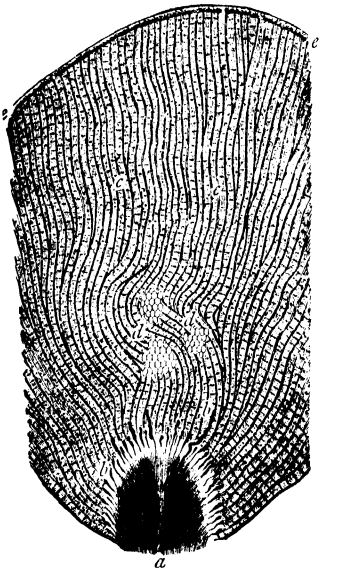


FIG. 727.—SECTION OF PART OF THE CROWN OF A TOOTH, PARALLEL WITH THE GENERAL SET OF THE ENAMEL PRISMS. (Rauber.) Magnified 200 diameters.

a, pointed projection of dentine; *b*, tubules extending from the dentine into the enamel; *c*, enamel-prisms; *d*, prisms cut across; *e*, cuticle of the enamel.

The laminated structure is an indication of the deposition of dentinal substance in successive strata in the process of formation of the tooth—the laminæ corresponding with the shape of the pulp-surface at successive stages of the process. Not infrequently lines, varying in number and breadth, are seen in sections of the dry tooth, conforming in direction with the lamination just spoken of (*incremental lines*, Salter, fig. 725, *c*). They are caused by the drying of imperfectly calcified dentine, which shows little cavities bounded by, and therefore receiving their figure from,

minute nodules or globules of dentine, and hence named *interglobular spaces* (fig. 726, *c*). The interglobular spaces, and the globules surrounding them, vary in size within wide limits. A layer, in which they are very fine—*granular layer* (fig. 721, *gr.*; fig. 723, 2)—is not uncommonly found towards the outer surface of the dentine.

Enamel.—The enamel is the covering which encrusts and protects the exposed portion or crown of a tooth (fig. 722). It is the hardest of all the dental tissues, but is gradually worn down by protracted use. It is thickest on the grinding surface and cutting edge of the teeth, and becomes gradually thinner towards the neck, where it ceases.

Bibra found it to contain 96·5 per cent. of earthy constituents, viz. phosphate of lime with traces of fluoride of calcium 89·8, carbonate of lime 4·4, phosphate of magnesia and other salts 1·3, and of animal matter 3·5 per cent. Berzelius gave the proportion of carbonate of lime as 8, and of animal matter as only 2 per cent. C. Tomes obtained only the merest traces of animal matter from the enamel of adult teeth.

In the deep part of the enamel minute fissures not infrequently exist, which run between clusters of the prisms down to the surface of the dentine (fig. 728); other much larger and more evident fissures are often observed leading down from the depressions or crevices between the cusps of the molar and premolar teeth. The surface of the enamel is marked by fine striations, due to the arrangement of the columns or prisms of which the enamel is composed. Sections of a tooth usually show coloured lines in the enamel parallel with the contour of the surface of the pulp (figs. 717, 720). These probably represent successive layers of deposition of the developing enamel.

The *enamel-columns* (figs. 728, 729) have the form of solid six-sided prisms. Their diameter is ordinarily about 0·005 mm. They are marked by frequent dark transverse shadings, which are usually ascribed to the existence of shallow constrictions along the fibres. Although this may be in part the cause, it is not improbable that the transverse markings are partly the result of the manner in which the prisms are built up in successive stages by the cells which produce them, each marking representing the termination of a stage. The inner ends of the prisms are implanted in minute hexagonal depressions on the surface of the dentine; the outer ends are free, and, like the sections of the prisms, have, under a high magnifying power, a tessellated appearance (fig. 729, B). The prisms are united by a small amount of a substance which appears similar to the intercellular substance of epithelium, but is perhaps calcified. In marsupials and some rodents there are regular canaliculi in this interprismatic substance.[1]

FIG. 728.—THIN SECTION OF THE ENAMEL AND A PART OF THE DENTINE OF AN UNWORN TOOTH. (Kölliker.) Magnified 350 diameters.

a, cuticle of the enamel; *b*, enamel-fibres or columns with cross striæ; *c*, clefts in the enamel communicating with the extremities of some of the dentinal tubules (*d*).

After exposure for a short time to the action of an acid, the enamel of newly formed or still growing teeth may be broken up, and its structural elements more easily distinguished (fig. 729, A). In broken enamel prisms thus treated a longitudinally striated structure has been described (Annell).

[1] For the cement-substance of enamel and the form of the prisms see Smreker, Arch. f. mikr. Anat. lxvi. 1905; on the structure of enamel see also v. Ebner, *ibid.* lxvii. 1905.

It is further found, on treatment with acid, that a very thin membrane (*enamel-cuticle, Nasmyth's membrane*) entirely covers the outer surface of the enamel of unworn teeth (figs. 727, 728). This membrane forms a protective covering to the enamel. Chemically it is of a horny nature, and withstands prolonged boiling as well as the action of strong acids and most other re-agents. It is formed of short flattened prisms, the uncalcified remains of the last formed portions of the enamel prisms. After the action of nitrate of silver, it exhibits markings like those seen in a pavement-epithelium.

Cement.—The crusta petrosa or cement is the third hard substance that enters into the formation of the teeth. It is a layer of true bone, slightly modified in structure, investing that part of the dentine which is not protected by the enamel (figs. 721, 722). It covers the whole fang, towards the lower end of which it becomes gradually thicker; it is specially developed at the apex, and along the grooves of the compound fangs. As life advances, the cement generally increases

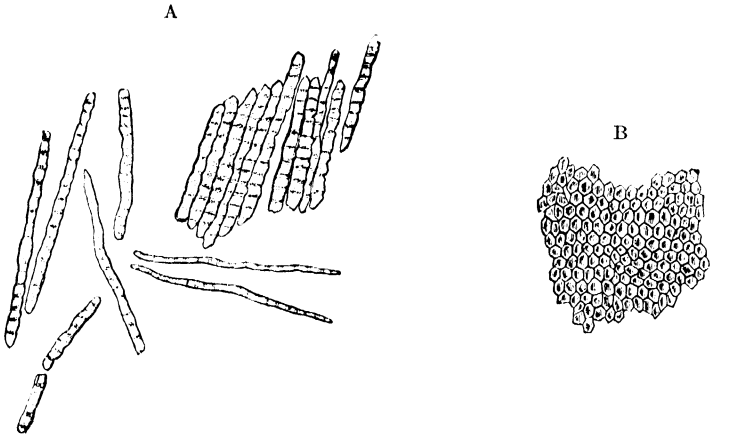


FIG. 729.—ENAMEL-PRISMS. (Kölliker.) Magnified 350 diameters.

A, fragments and single columns of enamel, isolated by the action of hydrochloric acid. B, surface of a small fragment of enamel, showing the hexagonal ends of the prisms.

in thickness, especially near the point of the fang, where it sometimes blocks up the orifice leading to the pulp-cavity.

The crusta petrosa is lamellar in structure; it contains lacunæ and canaliculi resembling those of bone, but larger and more irregular (figs. 723, *1*, 730, *e*). Where the cement is very thick it may contain Haversian canals. On the milk-teeth the cement is thinner, and contains fewer cells. Perforating and decussating fibres, similar to those of ordinary bone, occur in the cement. It is covered externally by the dental periosteum (figs. 717, 730), by means of which it is firmly fixed into its bony socket.

Secondary dentine.—Certain varieties of hard tissue are liable to be formed in the pulp-cavity of a tooth after the regular production of the dentine is completed. The chief kinds hitherto described are the following:

1. **Osteodentine** (Owen).—This is a hard substance somewhat resembling bone in structure, which sometimes becomes deposited within the pulp-cavity. It is traversed by canals, which contain blood-vessels and pulp-tissue, and which may be surrounded by concentric lamellæ like the Haversian canals of bone. From these canals numerous tubules radiate, larger than the canaliculi of bone, resembling, in this respect, and also in their mode of ramification, the tubes of the dentine. The osteodentine may or may not coalesce with the previously formed dentine.

2. **Dentine of repair** (Salter).—Opposite places where the outer surface of the dentine has become denuded, so that the peripheral ends of the tubules are there exposed, as may happen in the crown from injury or wear of the enamel, or at the cervix from continued friction

and abrasion of the cement, a deposition of dentinal matter is liable to be formed on the inner surface of the dentine, exactly corresponding in position and extent with the area occupied by the central ends of the exposed tubules. Many of the affected tubules become subsequently filled up by a deposit of hard matter within them, so that on section both the secondary dentine and the corresponding part of the primary dentine appear clearer and more transparent than the remainder of the dentinal substance (see fig. 731).

When the surface-injury has been considerable, the dentine of repair is largely in excess, and may in such cases completely fill up the pulp-cavity.[1]

Development of the Teeth (figs. 732 to 739).[2]—The first trace of the teeth appears during the sixth week of intra-uterine life (in embryos of 11 mm. to 12 mm. long) in the form of a longitudinal thickening of the epithelium of the mouth along the line of the future jaw. The thickening in question is produced by multiplication of the deeper-lying cells of the epithelium, and in some animals, *e.g.* ruminants, is marked by a prominence raised above the general level of the epithelial surface (fig. 738). The ectodermic thickening grows into the mesoderm as a solid longitudinal strand of cells, at first semi-cylindrical in section, and

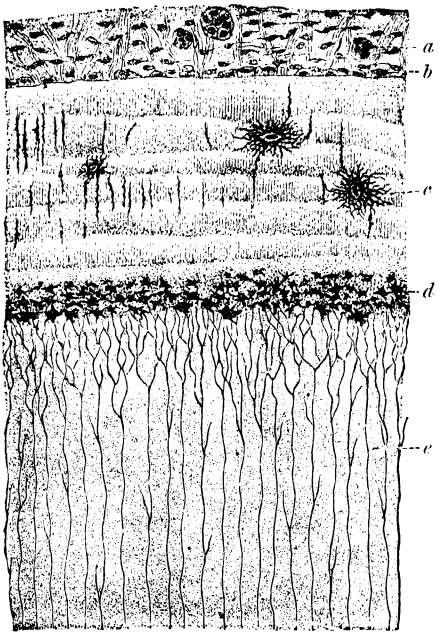


FIG. 730.—SECTION OF THE FANG OF A TOOTH SHOWING DENTINE AND CEMENT TOGETHER WITH THE DENTAL PERIOSTEUM. (Röse.) Magnified 200 diameters.

a, nests of epithelial cells within the dental periosteum which are the remains of the epithelial sheath of Hertwig; *b*, osteoblasts which have formed the cement; *c*, lacuna of the cement; *d*, granular layer of the dentine; *e*, dentine.

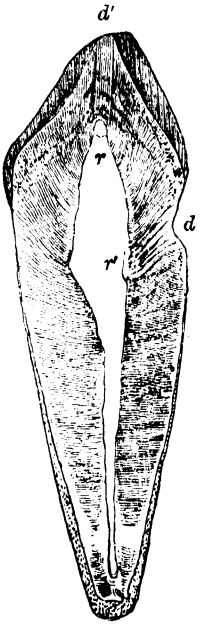


FIG. 731. — LONGITUDINAL SECTION OF INCISOR TOOTH SHOWING DENTINE OF REPAIR. (Salter.) Slightly magnified.

d, *d'*, denuded surfaces of dentine; *r*, *r'*, corresponding deposits of secondary dentine. Two or three incremental lines are observed in the dentine.

lying in a sort of gutter or deep groove formed in the mesoderm to receive it; there is to begin with no indication of the formation of separate teeth. The strand in question is the *primitive dental lamina* (fig. 732, *1*): it is also known as the 'common enamel-germ,' because part of it is concerned in the production of the enamel of the teeth. But the lamina is not merely a dental germ, for before long (embryo of 17 mm., or seventh week) it is found that the originally simple strand of cells separates longitudinally into two. One of these, the outer, or labial, which dips vertically into the embryonic jaw, becomes hollowed out from the surface to form the labio-dental furrow (fig. 733, *d.l.f.*), and may accordingly be termed the *labio-dental*

[1] In animals other kinds of dentine are found; for a description of these, and other details regarding the structure and development of the teeth of vertebrates, the student is referred to special works on the subject, such as the 'Manual of Dental Anatomy,' by C. S. Tomes, and the 'Histology and Patho-histology of the Teeth,' by A. Hopewell-Smith.

[2] The following account of the development of the teeth is largely based upon the description given by Röse in Dental Cosmos.

lamina, whilst the other, lingual or inner part, takes first a vertical and then an inward (lingual) direction, and is the actual tract of cells in connexion with which the teeth of both dentitions subsequently become developed. The name *dental lamina*, or *common dental germ*,[1] should therefore be retained for this portion of the original strand of ectoderm-cells. The separation of the two strands begins in front and extends gradually backwards: it is not complete until

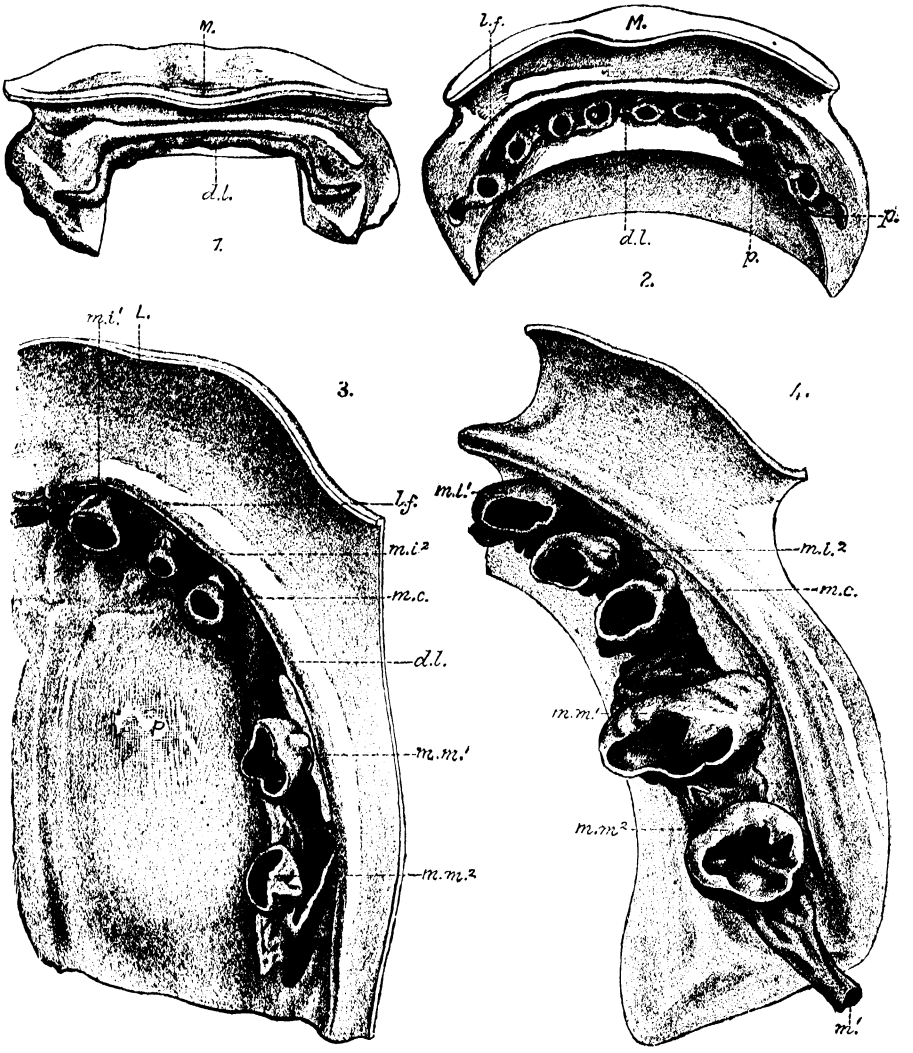


FIG. 732.—FIGURES (FROM RÖSE'S MODELS) SHOWING FOUR SUCCESSIVE STAGES IN THE DEVELOPMENT OF THE DENTAL LAMINA AND TOOTH-GERMS OF THE MILK-TEETH OF THE UPPER JAW. Only the buccal epithelium and the epithelial structures of the tooth-germs are represented, and everything is shown as seen from above, *i.e.* from the attached surface.

1. From an embryo 25 mm. long.—*d.l.*, dental lamina; *M.*, aperture of mouth.

2. From an embryo 40 mm. long.—*M.*, mouth; *l.f.*, reverse of labio-dental furrow; *d.l.*, dental lamina; *p.*, mould for papilla of milk-canine; p^1, mould for papilla of second milk-molar.

3. From an embryo 115 mm. long.—*L.*, epithelial layer of upper lip; *l.f.*, reverse of labio-dental furrow; *d.l.*, dental lamina; $m.i.^1$, epithelial rudiment of first milk-incisor; $m.i.^2$, *m.c.*, $m.m.^1$, $m.m.^2$, epithelial rudiments of second milk-incisor and of milk canine, and first and second molars respectively.

4. From an embryo 180 mm. long.—$m.i.^1$, $m.i.^2$, *m.c.*, $m.m.^1$, $m.m.^2$, as before; $m.^1$, rudiment of first permanent molar.

[1] 'Dental germ' should be used instead of the more common expression 'enamel-germ,' because the cells in question not only form enamel, but also determine the extent of the formation of dentine by the adjacent mesoderm-cells (see p. 511).

the eleventh or twelfth week. The dental lamina, when thus separated from the labio-dental, forms a flat band of cells connected by one edge with the epithelium lining the mouth, whilst the other, or free edge, projects almost horizontally inwards in the substance of the embryonic jaw. Subsequently, however, as the milk-teeth develop, it takes a more vertical direction. Over the line of its attachment to the epithelium of the mouth there is a shallow furrow, the *dental furrow* (fig. 733, *d.f.*), which is at first rather outside (or on the labial side of) the most prominent part of the jaw, but gradually comes to lie further inwards. At about nine weeks (embryo of 25 mm.) the border of the dental lamina in each jaw begins to exhibit ten enlargements corresponding in situation to the ten milk-teeth. At ten weeks (embryo of 32 mm.) these enlargements show a moulding on one of their surfaces (upper in the upper jaw and lower in the lower) (fig. 732, 2, *p.*, *p.*[1]), and the adjacent mesoblast fits against this moulded surface

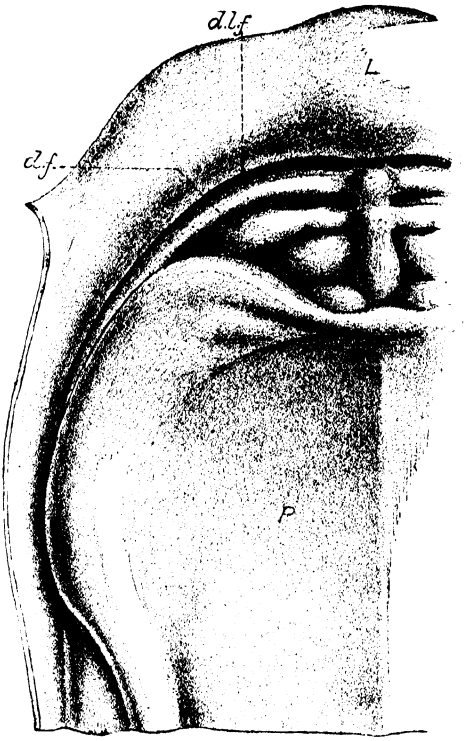


FIG. 733.—PALATINE (GINGIVAL) SURFACE OF THE MODEL WHICH IS SHOWN FROM ABOVE IN FIG. 732, 3.

P, palate; *L*, upper lip; *d.l.f.*, labio-dental furrow; *d.f.*, dental furrow.

and becomes differentiated into the form of a papilla, which very early exhibits the shape of the crown of the future tooth, being simple in the incisors and multiple in the molars.[1] The papillæ have all appeared by eleven and a-half weeks, and the enlargements of the dental lamina, which are now very evident, grow round and gradually invest the papillæ at their sides also. The dentine and pulp of the milk-teeth are formed from these papillæ, whilst the enlargements of the dental lamina form *special dental germs* for the milk-teeth and furnish their enamel.

In the meantime the dental lamina has grown further inwards beyond these prominent special dental germs, which appear now as ten rounded masses of cells attached to the labial side of the flat common dental lamina 'like swallows' nests built against a board' (fig. 732, 3) and the posterior part of the lamina extends backwards in the substance of the jaw a short distance behind the last of the special dental germs for the milk-teeth. This backward extension of the dental lamina is only attached indirectly to the buccal epithelium. At about seventeen weeks (embryo of 18 centimetres long) it shows another enlargement, which is the special germ of the first permanent molar, and, in connexion with this enlargement, the corresponding

[1] In the canines, however, the papilla is at first double, not single. It has been suggested that this is probably an indication of the originally premolar character of these teeth.

papilla soon makes its appearance (fig. 732, *4*, m^1). Behind this again the dental lamina is continued backwards into the gum as a thin flat band of epithelium. About four months after birth an enlargement for the second permanent molar appears, and the corresponding papilla at six months. About the third year the enlargement for the third permanent molar, or wisdom-tooth, begins to be visible in an extension of the dental lamina still further backwards; its papilla is seen about the fifth year. Meanwhile, important changes have been occurring in the dental lamina, in the attachments of the special germs to it, and in the special germs themselves.

The changes in the common dental lamina consist in the formation of numerous excavations of irregular size and form, with the result that from a complete flat band of cells it becomes partly atrophied and changed into a cribriform tract (fig. 732, *3* and *4*; fig. 735, *d.l.*): in transverse sections of the jaw it appears to be broken up into separate portions (fig. 739). This is, however, not really the case, although the lamina is pierced with apertures so as to be almost reticular in

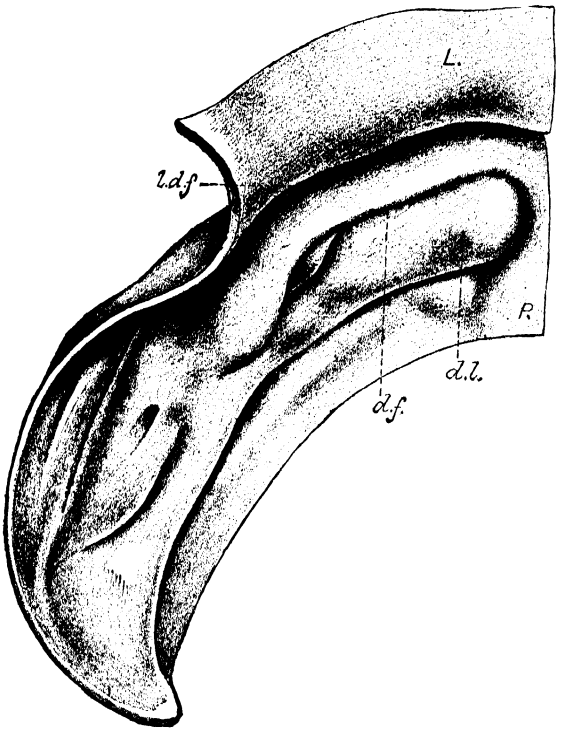


FIG. 734.—GINGIVAL SURFACE OF THE MODEL WHICH IS SHOWN FROM ABOVE IN FIG. 732, 4.

P., palate; *L.*, upper lip; *l.d.f.*, labio-dental furrow; *d.f.*, dental furrow; *d.l.*, prominence caused by dental lamina with its enlargements.

character. The change begins in front about the seventeenth week, and gradually extends backwards, but the most posterior part is still complete (non-cribriform) at the time of birth, and even for some time after. Moreover, at certain points the reticulation is absent, viz. on the lingual side of and slightly lateral to the special germ of each milk-tooth; at these points the dental lamina again undergoes a thickening. These thickenings become the special enamel-germs for the teeth of succession of the second dentition. In connexion with each one a papilla becomes formed in the same way as for the milk-teeth; but by no means simultaneously, for the germs of the permanent incisors and canines are formed, along with their papillæ, at about the twenty-fourth week (embryo of 30 cm.), whereas the enlargements of the dental lamina which are eventually to form the enamel-organs of the first and second premolars are not visible until the twenty-ninth and thirty-third weeks respectively, and the corresponding papillæ are not formed until the tenth and eighteenth months after birth.

The special dental germs are, as already stated, at first simply enlargements of the common germ or lamina which grow out on its inner side. They rapidly increase in size, and are then connected by a broad tract of cells with the common germ. This *connecting strand* gradually

gets thinner and flatter, and, like the common dental lamina itself, becomes cribriform, so that in sections there appear to be breaches of its continuity. Its connexion, however, with the common dental germ, and through this with the buccal epithelium on the one hand and the germ of the corresponding tooth of the secondary dentition on the other hand, long persists. As

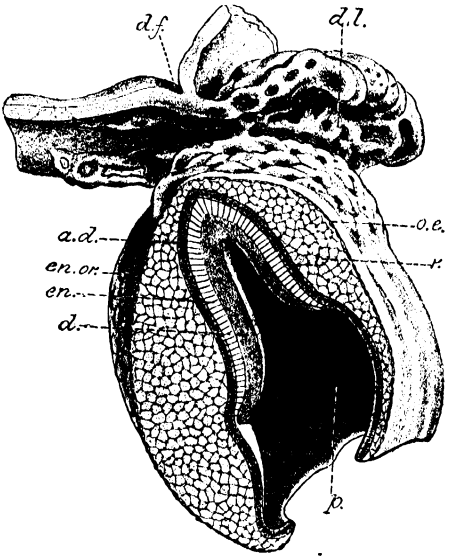


FIG. 735.—SECTION OF SECOND MILK-INCISOR OF AN EMBRYO 30 CENTIMETRES LONG. THE EPITHELIAL STRUCTURES ONLY ARE REPRESENTED. (From a model by C. Röse.)

d.f., dental furrow in the buccal epithelium; *d.l.*, dental lamina now become cribriform; *p.*, space occupied by the papilla; *d*, dentine; *en.*, enamel of the developing tooth; *en.or.*, enamel organ, its surface cribriform; *a.d.*, ameloblasts; *r.*, reticular tissue; and *o.e.*, outer epithelium of the enamel-organ

with the common lamina, the atrophic process begins in connexion with the front teeth, and gradually extends backwards, so that at birth the connecting bands of the milk-incisors are almost completely broken up, whilst that of the second milk-molar is still uninterrupted. The

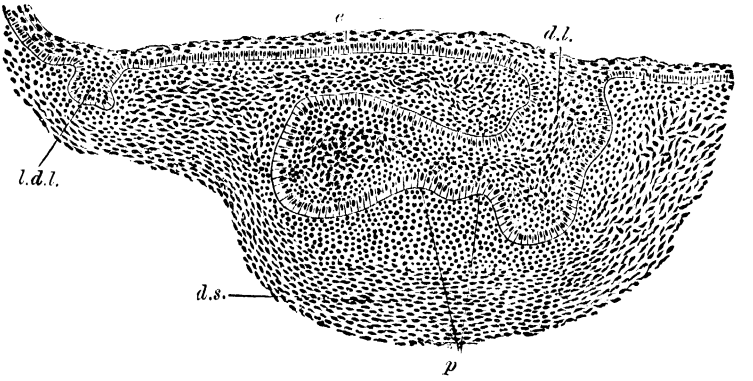


FIG. 736.—SAGITTAL SECTION THROUGH THE FIRST LOWER MILK-MOLAR OF A HUMAN EMBRYO 30 M.M. LONG. (Röse.) Magnified 100 diameters.

l.d.l., labio-dental lamina, here separated from and well in advance of the dental lamina; *d.l.*, placed over the shallow dental furrow, points to the dental lamina, which is spread out below to form the enamel-germ of the future tooth; *p.*, bicuspidate papilla, capped by the enamel-germ; *d.s.*, condensed tissue forming dental sac; *e.*, mouth-epithelium.

common dental lamina and the bands connecting the special dental germs with it thus become ultimately broken up into separate fragments or islands of dental epithelium of varying size and form. Such 'islands' are frequently seen in the infant near the surface of the gum, as pearl-like masses or nests, the so-called 'glands of Serres.' Normally they have no functional

importance, and gradually disappear entirely; but, abnormally, they may give rise to cysts and other new formations, and in some cases fragments of dentine, and even more or less complete teeth, may become developed in connexion with them.

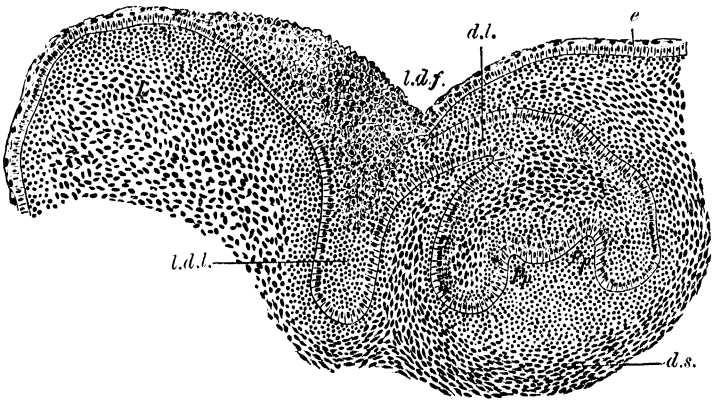


FIG. 737.—SIMILAR SECTION THROUGH THE CANINE TOOTH OF AN EMBRYO 40 MM. LONG. (Röse.) Magnified 100 diameters.

l.d.f., labio-dental furrow. The other lettering as in fig. 786.

Histogenetic changes.—The special dental germs are at first masses of rounded or polyhedral epithelial cells, but the cells of the outermost layer early show a

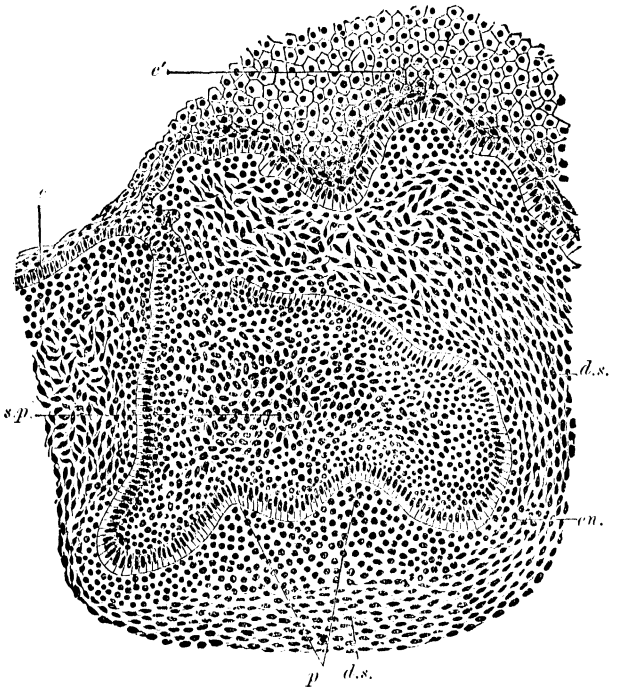


FIG. 738. - SECTION THROUGH THE GERM OF THE FIRST MILK MOLAR OF A COW'S FŒTUS 47 MM. LONG. (Rose.) Magnified 200 diameters.

p., bicuspidate papilla; *d.s.*, dental sac; *e*, mouth-epithelium; *e'*, its thickening over the dental germ, characteristic of Ruminantia; *en.*, enamel epithelium; *s.p.*, enamel-pulp.

tendency to be columnar (figs. 736 to 738). This tendency becomes pronounced as soon as the papilla begins to make its appearance, and now, while the cells immediately resting upon the papilla become long, regular, prismatic columns, the central cells of

the germ develop processes, fluid being at the same time secreted between them. The result is the formation of a reticular tissue, having to the naked eye the appearance of a jelly, to which the name of *enamel-pulp* has been applied (fig. 739, *SP*). The more peripheral cells do not participate in this change, but remain polyhedral or become cubical and flattened (*outer enamel-epithelium*); they pass gradually into the long columnar prisms that invest the papilla. These prisms are the cells which form the enamel-fibres; they also determine by their presence the production of dentine by the superficial cells of the papillæ. They are termed the *enamel-cells* or *ameloblasts*; they form the *membrana adamantinæ* of Purkinje. The whole epithelial dental germ thus transformed is known as the *enamel-organ* (*organon adamantinæ*).

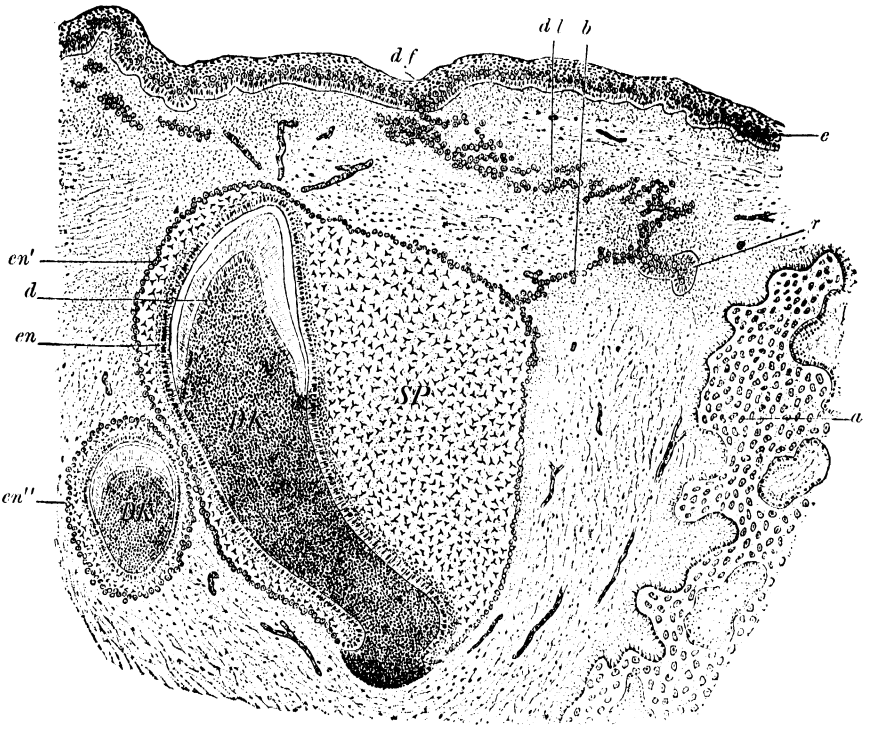


FIG. 739.—SECTION OF THE FIRST MILK INCISOR OF A HUMAN EMBRYO 30 CENTIMETRES LONG. FRONTAL SECTION THROUGH LOWER JAW. (Röse.)

DK, tooth-pulp; *d*, odontoblasts; *a*, bone of the alveolar process of the jaw; *en*, *en'*, inner and outer layers of the enamel-organ; *SP*, enamel-pulp; *d f*, dental furrow; *e*, mouth-epithelium; *d l*, remains of dental lamina; *b*, cell-bridge, connecting this with tooth-germ; *r*, reserve germ for the permanent tooth; *en''*, germ of second milk incisor cut obliquely.

These changes begin in the milk-incisors at about 14 weeks. At about 20 weeks (embryo of 24 cm.) the first traces of calcification are visible in the form of a simultaneous deposit of enamel and of dentine upon the crown of the central incisors. The outer enamel-epithelium now begins to grow into the surrounding connective tissue in the form of epithelial sprouts, and before long there seem to be breaches of continuity between these sprouts; but, according to Röse, the enamel-pulp is never invaded by vascular connective tissue, as has been sometimes described.

In the meantime changes have been occurring in the dental papillæ. These are composed at first of undifferentiated mesoderm; but their more superficial cells—those which are immediately in contact with the columnar epithelium of the special dental germs—early become elongated, and by their distal end abut against that epithelium, whilst the other end is tapered, and may be branched like the other cells

of the embryonic connective tissue. It is from this superficial layer of cells—which in sections has a palisade-like appearance—that the dentine becomes gradually formed; its cells have accordingly received the name of *odontoblasts*. There is nothing of the nature of a membrane—the so-called *membrana preformativa*—between the adamantoblasts and the odontoblasts, but the two layers are in immediate contact. The other cells of the dental papilla become branched connective-tissue cells, and some connective-tissue fibrils form in the intercellular substance; in this way the dental pulp is developed.

Meanwhile the whole tooth-germ—papilla and enamel organ—has become included within a vascular membrane of connective tissue which is known as the *dental sac*.

Formation of dentine.—The odontoblasts, either by secretion or, as some think, by direct transformation of the peripheral end of each cell, form a layer of dentinal matrix (*prodentine*) immediately at the surface of the papilla at its apex, or, if it have more than one cusp, then at the apex of each cusp. This layer is at first uncalcified (fig. 740), and is probably the structure which used to be described as a membrana preformativa. Although, in ordinary preparations, it has a homogeneous appearance, special modes of preparation and staining show it to be composed of collagenous fibrils similar to those which constitute the lamellæ of bone.[1] These fibrils are in fact continuous between the odontoblasts with the fibrils of the dental pulp (fig. 741).[2] The fibrils in the prodentine are at first vertical to the surface of the tooth (v. Korff's fibrils); subsequently others are seen having a course nearly parallel to it and across the direction of the tubules. They represent the permanent fibrils of the dentine.

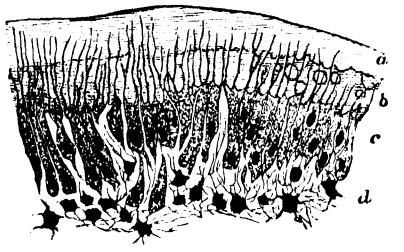


FIG. 740.—SECTION OF DEVELOPING DENTINE FROM THE INCISOR TOOTH OF A YOUNG RAT. (Schäfer.)

a, outer layer of fully formed dentine; *b*, uncalcified matrix, with one or two nodules of calcareous matter near the calcified part; *c*, odontoblasts sending processes into the dentine; *d*, pulp. The section is stained with carmine, which colours the uncalcified matrix, but not the calcified part.

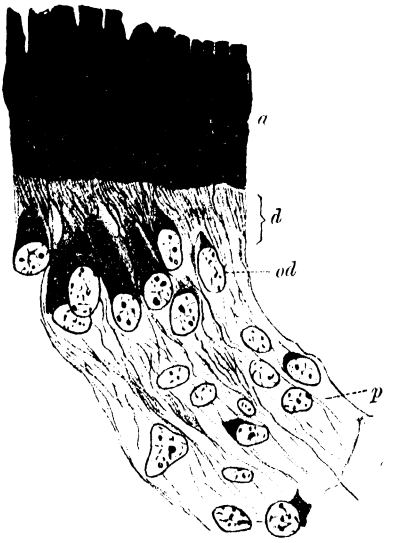


FIG. 741.—PART OF A SECTION OF DEVELOPING TOOTH OF PIG. (v. Korff.)

a, ameloblasts; *d*, fibres of the first formed layer of dentine; *od*, odontoblasts; *p*, pulp. The fibres of the pulp are seen to be in continuity with those which enter into the formation of the dentine.

Globules of calcareous matter soon appear in the prodentine. They are at first isolated, but by further deposition of lime salts they become more or less

[1] v. Ebner, Schaff's Handb. d. Zahnheilk, 1890.

[2] Mummery, Phil. Trans. 182, 1891; v. Korff, Arch. f. mikr. Anat. lxvii. 1905; lxix. 1906; and Ergebn. d. Anat. xvii. 1907; Anat. Anz. xxxv. 1910; v. Ebner, Wiener Sitzungsb. cxv. 1906 and Anat. Anz. xxxiv. 1909; Studnička, Anat. Anz. xxx. 1907; xxxi. 1907; xxxiv. 1909. See also on the development of dentine F. T. Paul, Trans. Odont. Soc. 1899.

blended into a continuous calcification, which thus forms the first cap of dentine. In the meanwhile, the odontoblasts have formed a second layer of uncalcified matrix of a similar fibrous structure within the first one, and calcification proceeds in this as in the first. In like manner a succession of layers becomes formed, each one extending laterally rather farther than its predecessor; thus in teeth where there are at first separate deposits for different cusps these become ultimately blended, and as each successive layer is calcified its calcareous deposits blend with those of the preceding and more superficial layers. In places this blending remains incomplete, portions of the dentinal matrix remaining uncalcified between the successive layers; in a macerated tooth these portions get destroyed, and cleft-like spaces arise. Since these are bounded by calcified deposit which has been originally laid down in globules, they present a knobbed outline, and are known as interglobular spaces (see p. 499 and fig. 726).

As the odontoblasts form the successive layers of dentine in the manner above described, they retire gradually towards the centre. But whilst thus retiring they

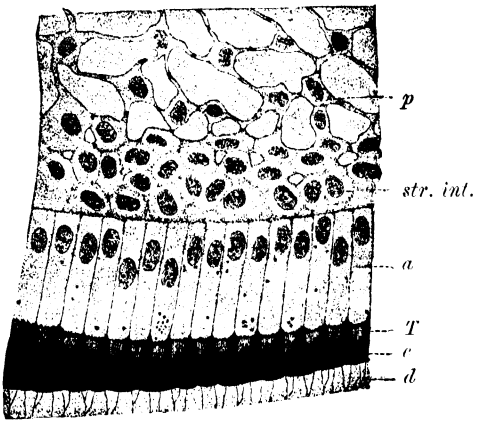


FIG. 742.—SECTION SHOWING THE STRUCTURE OF THE PART OF THE ENAMEL-ORGAN WHICH LIES NEXT TO THE DENTINE. (Röse.)

d, dentine; *e*, newly formed enamel stained black by osmic acid *T*, Tomes' processes from the ameloblasts, *a*; *str. int.*, stratum intermedium of enamel-organ; *p*, branched cells of enamel-pulp.

leave *in situ*, in the layers of forming dentine, filamentous processes of cell-protoplasm, from which finer side-processes grow out. The dentine matrix becomes formed and moulded around these processes, which are thus left within tubes that become the dentine tubules, whilst the processes of the odontoblasts become the fibres of Tomes. The same cell continues to spin out such a filament or filaments as long as the formation of dentine continues, each tubule being thus completed in its whole length from a single odontoblast. In most cases two or more processes are connected at first with each cell, and these coalesce as the cell recedes, the main branchings of the dentinal tubules being thus formed.

As the tooth approaches completion, the other cells of the dental papilla not immediately concerned in the formation of dentine become the cells of the dental pulp.

Formation of enamel.—The prismatic fibres composing the enamel of the teeth are formed by the agency of those ends of the ameloblasts that abut against the dental papilla. On the inner aspect of each of these cells a finely globular deposit occurs (Annell), which stains with osmic acid (figs. 742, 743, *e*) and resembles keratin in its extreme resistance to the action of mineral

acids (*enamel-droplets*, v. Spee). The layer thereby formed, which is not yet calcified, appears altogether external to the cells—although a process from each

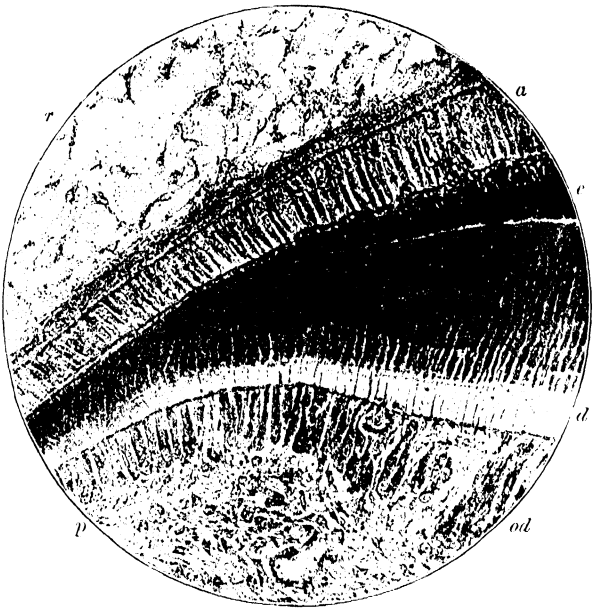


FIG. 743.—SECTION OF DEVELOPING TOOTH. (L. Williams.) Photograph.

r, reticulum or pulp of enamel-organ; *a*, ameloblasts; *e*, uncalcified enamel stained black by osmic acid; *d*, dentine; *od*, odontoblasts; *p*, pulp.

ameloblast extends into it as a tapering fibre (J. Tomes, fig. 742, *T*). The layer is produced simultaneously with or immediately after the first layer of prodentine, against which it is applied. Before long it is converted into a fibrous formation (fig. 744, *f*): a change reminiscent of the process of keratinisation of the epidermis. Presently the fibrous layer thus formed undergoes calcification, and the first cap of enamel is then complete. The ameloblasts next produce a second layer of keratin-like material, which also undergoes fibrillation, and from this, after calcification, another stratum of enamel is formed, and so on.[1] As with the dentine, the formation of enamel appears first at the apex of each cusp, so that there are as many caps as cusps; these eventually become blended. The ameloblasts gradually retire as the successive layers of enamel are being produced by them, and this retiral goes on as long as the formation of enamel continues—that is to say, until the crown of the tooth is completed. In the meantime the enamel-pulp gradually diminishes, and eventually almost disappears. The remainder of the enamel-organ forms a thin epithelial cap over the crown, but this cap soon

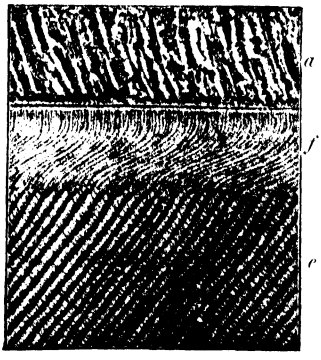


FIG. 744.—DEVELOPING ENAMEL SHOWING AMELOBLASTS AND THE FIBROUS SUBSTANCE PRODUCED BY THESE CELLS, WHICH FORMS THE BASIS OF THE ENAMEL PRISMS. (From a photograph by Leon Williams.)

a, portions of the ameloblasts; *f*, fibrous basis of enamel-prisms; *e*, calcified part of enamel.

[1] J. Leon Williams, Proc. Roy. Soc. lix. 1895.

disappears on the emergence of the tooth beyond the gum. Besides this epithelial cap, and underneath it, there is found a very thin membrane, which is more persistent, and which covers the crown of the tooth for some little while after emergence (fig. 727, *e*). This is *Nasmyth's membrane*, or the *enamel-cuticle* (see p. 500); according to v. Brunn, it is the last formed keratinous layer of enamel, which has remained uncalcified.

It has usually been considered (Tomes, Waldeyer, and others) that the enamel-prisms are formed by direct calcification *in situ* of the inner ends of the ameloblasts, the outer nucleated end growing *pari passu* with the inner, which has been converted into enamel. But the view

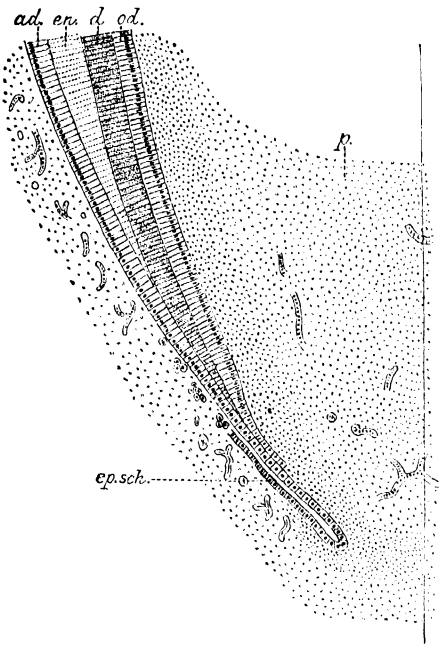


FIG. 745.—LONGITUDINAL SECTION OF THE LOWER PART OF A GROWING TOOTH, THE CROWN OF WHICH IS FORMED, SHOWING THE EXTENSION OF THE LAYER OF AMELOBLASTS BEYOND THE CROWN TO MARK OFF THE LIMIT OF FORMATION OF THE DENTINE OF THE ROOT. (Röse.)

p., pulp; *od.*, odontoblasts; *d.*, dentine; *en.*, enamel; *ad.*, ameloblasts, continuous below with *ep.sch.*, the epithelial sheath of Hertwig.

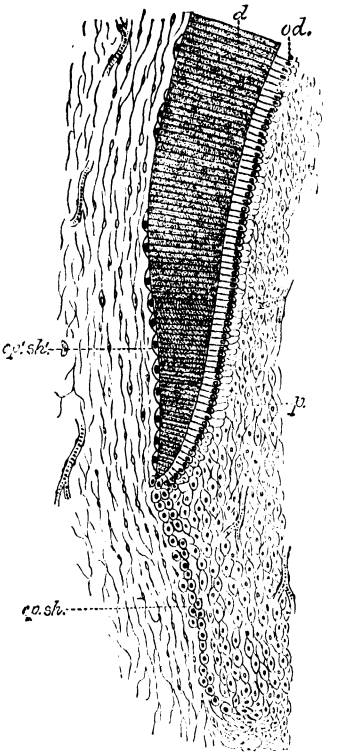


FIG. 746.—SECTION SIMILAR TO THAT SHOWN IN FIG. 745, BUT FROM A TOOTH MORE ADVANCED IN GROWTH. (Röse.)

ep.sh., epithelial sheath; *ep.'sh'.*, remnants of this, overlying dentine of fang; *p.*, pulp; *od.*, odontoblasts; *d.*, dentine.

stated in the text is probably correct, viz. that the layer of ameloblasts sheds out a substance within which calcareous matter is subsequently deposited; the enamel-prisms being formed rather as a secretion from the ameloblasts than by transformation *in situ*.[1]

Formation of cement.—The roots of the teeth begin to be formed shortly before the time for the emergence of the crowns beyond the gum, but they are not completed until long after the crowns have come through. They are determined in their form—moulded, as it were—by a growth of the epithelium of the dental germ, which extends in the form of a fold, the *epithelial sheath* of Hertwig (figs. 745, 746), towards the future apex of each fang (v. Brunn). On the inner surface of this sheath odontoblasts form dentine, as in the crown, and thus the root is gradually produced. The epithelial sheath becomes gradually atrophied and

[1] See on the development of enamel H. Ganzer, Anat. Anz. xxviii. 1906.

ultimately broken up into isolated portions, which may be seen occasionally, even in the adult, as epithelial islands in the connective tissue of the dental periosteum (fig. 730 *a*).[1]

After the formation of the dentine of the root has begun, the vascular tissue of the dental sac begins to break through the epithelial sheath near the crown, and forms a layer of osteogenic tissue at the surface of the newly deposited dentine.[2] The osteoblasts of this tissue produce layers of true bone, with osteogenic fibres, lacunæ, and canaliculi, upon the surface of the dentine of the root; these layers form the cement of the fang. The extreme end of each fang, which is the last part to be produced, is formed wholly of cement, for the epithelial sheath which determines the formation of dentine never extends quite as far as the permanent apex.

The dental sacs, which enclose the developing teeth before their eruption, are conspicuous in the jaws of infants a few months old. They consist of an outer fibrous coat connected with the periosteum, and an inner highly vascular coat, with a little jelly-like connective tissue between the two. The inner coat is lined by the epithelium of the enamel-organ. The blood-vessels are derived partly from the dental arteries which course along the base of the sacs, partly from those of the gums. Their extreme vascularity doubtless has relation to the nutrition of the enamel-organ.

At birth calcification of the crowns of all the milk-incisors and canines is fairly advanced. The separated cusps of the milk-molars have also blended, and the calcification of the first permanent molar is just beginning in the form of separate caps for each cusp, one of which has usually appeared at birth, while the others follow shortly after. These, however, do not run together until six months after birth.

The germs of the permanent incisors and canines are visible to the naked eye at birth, lying behind and slightly lateral to the corresponding milk-teeth; but there is no trace as yet either of the premolars or of the second permanent molar. The last mentioned makes its appearance between four and six months after birth, the papilla of the first premolar about the tenth month, that of the second premolar about the eighteenth month. At two years, when the second milk-molars are just coming through the gum, the crown of the first permanent molar is finished, but there are still only isolated cusps on the second permanent molar of the upper jaw, and none on the second permanent molar of the lower jaw. In the premolars also the (two) cusps are still separate at this time.

The various phases in the formation of the teeth occur almost simultaneously in the corresponding teeth of both jaws.

Formation of the alveoli.—All the tooth-germs are at first included in a common osseous trough or groove, which encloses the whole dental lamina and the adjacent connective tissue. This begins to be formed at about 14 weeks (embryo of 11·5 cm.). Bony septa subsequently become formed and subdivide the trough into loculi, but even at birth these septa are incomplete, and up to this time, and even later, both the milk-tooth and the corresponding permanent tooth-germ are enclosed in the same loculus. As the fangs become developed the loculi deepen and also become subdivided to form separate cavities for the teeth of both first and second dentition. Around the milk-teeth they become narrowed to form alveoli which closely invest the roots; but although the whole of the developing tooth is at one time imbedded in the cavity of the alveolus, the bone never completely closes over it, an aperture being always left over the crown, through which the dental sac is connected by soft tissues with the surface of the gum. In the same way, when the teeth of the second dentition become invested within alveoli, these always have a narrow opening through which the so-called *gubernaculum dentis*, a band of connective tissue containing remains of the common dental lamina, passes (fig. 747).

Development of the permanent teeth.—Ten permanent teeth in each jaw succeed the milk-teeth, and six are superadded further back in the jaw. It will be convenient to treat first of the ten anterior teeth or *teeth of succession*.

The sacs and pulps of these teeth have their foundations laid before birth in the way already described. It will be remembered that behind and lateral to each milk-follicle there is found

[1] C. Tomes has shown that an epithelial sheath is formed in the same manner, even in the teeth of animals (*e.g.* Taturia) in which the dental germ produces no enamel at all.

[2] In some animals the cement of the teeth is preceded by the formation of cartilage, which becomes ossified as in the endochondral formation of bone (Magitot, v. Brunn). According to Magitot, in animals such as ruminants, in which the cement covers the crown, a special cartilaginous 'cement-organ' is developed for its production.

about the sixteenth week a thickening of the common dental lamina (p. 504, and fig. 739, *r*); this forms the enamel-germ of the corresponding permanent tooth. There are ten of these in each jaw, and they are formed successively from before backwards. They soon elongate and recede into the substance of the gum behind the germs of the milk-teeth. In the meantime, a papilla is formed at the bottom of each (that for the central incisor appearing first) and the germ becomes enclosed within a dental sac; the sac of the permanent tooth adhering to the back of that for the temporary tooth. The bone of the jaw not only forms a loculus for the reception of the milk-sac, but ultimately also a small posterior recess or niche for the permanent tooth-sac, with which the recess keeps pace in its growth. In the lower jaw, to which our description may now, for convenience, be confined, the permanent sac is at length found at some distance below and behind the milk-tooth; the sac for the permanent tooth soon acquires a pear-shape, and is then connected with the gum by a solid pedicle of fibrous tissue (fig. 747, I., II., *c*). The recess in the jaw (*a'*) has a similar form, being drawn out into a long canal, which opens on the edge of the jaw by an aperture behind the corresponding milk-tooth. The permanent tooth is thus separated from the socket of the milk-tooth by a bony partition, which, as well as the root of the milk-tooth just above it, becomes absorbed as the crown of the permanent tooth rises through the gum. When this absorption has proceeded far enough, the milk-tooth becomes loosened and falls out or is removed, and the permanent tooth takes its place. The absorption of the dental substance commences at or near the ends of the fangs, and proceeds upwards until nothing but the crown remains. The cement is first attacked, then

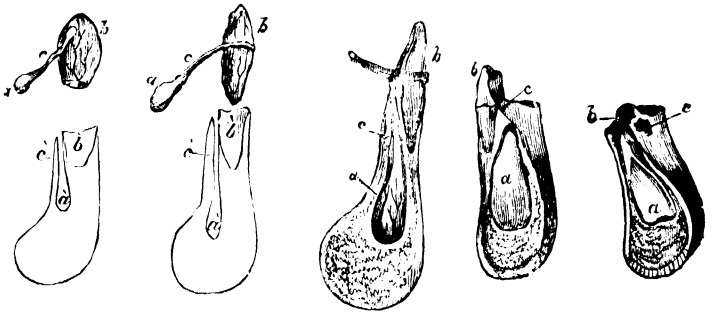


FIG. 747.—SKETCHES SHOWING THE RELATIONS OF THE TEMPORARY AND PERMANENT DENTAL SACS AND TEETH. (After Blake, with some additions.)

The lower parts of the first three figures, which are somewhat enlarged, represent sections of the lower jaw through the alveolus of a temporary incisor tooth: *a*, indicates the sac of the permanent tooth; *c*, its pedicle; *b*, the sac of the milk-tooth or the milk-tooth itself; *a'*, *b'*, indicate the bony recess in which the permanent and temporary teeth are lodged, and *c'*, the canal by which that of the former leads to the surface of the bone behind the alveolus of the temporary tooth. The fourth and fifth figures, which are nearly of the natural size, show the same relations in a more advanced stage—in IV., previous to the change of teeth; in V., when the milk-tooth has fallen out and the permanent tooth begins to rise in the jaw; *c*, the orifice of the bony canal leading to the place of the permanent tooth.

the dentine; but the process is similar in the two tissues. The change is not produced merely by pressure, but, as in the case of the absorption of bone, through the agency of multi-nucleated absorbing cells or osteoclasts, developed at the time, and applied to the surface of the fang.[1] The sockets begin to be formed around the neck of the tooth as soon as the crown projects, and are formed simultaneously with the developing fangs.

The six posterior (or *superadded*) permanent teeth—that is, the three permanent molars on each side—do not come in the place of other teeth. They arise from successive extensions of the common dental lamina carried backwards in the jaw behind the milk-teeth, as follows:

The part of the common lamina posterior to the last temporary molar long continues unobliterated, and from it there is developed at about the seventeenth week of embryonic life a special enamel-germ which forms the rudiment of the first permanent molar (fig. 732, *i*, *m*[1]). After a long interval, viz. about the fourth month after birth, the germ for the second permanent molar appears in the dental lamina, which is now projecting backwards from the neck of that for the first molar. After another long interval, during which the sac of the first permanent molar and its contained tooth have acquired great size, and that of the second molar has also

[1] See on the absorption of the fangs of the milk-teeth G. Fischer, Anat. Hefte, xxxviii. 1909.

advanced considerably in development, the same changes once more occur and give rise to the sac and papilla of the wisdom-tooth (third year). The subsequent development of the permanent molar teeth takes place within their sacs just like that of the other teeth. In exceptional instances, a fourth molar may be formed in like manner in a further backward extension of the dental lamina.

After all the teeth of the second dentition are thus formed, the dental lamina generally ceased to form more special enamel-germs, and gradually atrophies in the manner already described. But in rare instances a third series of germs make their appearance postero-lateral to the teeth of the second dentition, and a third complete series of teeth may result therefrom.

Calcification begins first in the anterior permanent molar teeth. Its order and periods may be thus stated: First molar, one cusp shows calcification at birth, the rest soon after birth; central incisor, lateral incisor, and canine, about six months after birth, the central incisor first, the canine last; bicuspids, two years or more; second molar, two years; third molar or wisdom-tooth, about twelve years.

Historical.—The first consistent account of the development of the teeth was given by Goodsir (*Edin. Med. and Surg. Journal*, 1838), who described the appearance of a groove in the mucous membrane of the jaw, the formation of special depressions in this groove corresponding to the milk-teeth, the appearance of papillæ within these, the enclosure of the papillæ within follicles covered by membrane, and finally the time and mode of eruption of the several teeth.

Goodsir's results, which, so far as they went, were accurate, were obtained from specimens which had been badly preserved, and in which the epithelium, which is now regarded as the important element in tooth-formation, had become detached in consequence of maceration.

The views of Goodsir prevailed until 1863, when Kölliker (*Gewebelehre*) clearly showed the important part taken by the ingrowing of the rete mucosum of the epithelium in the formation both of the common and of the special enamel-germs. This had been already pointed out by Marcusen (*Bull. de l'Acad. de Pétersbourg*, 1849) and by Huxley (in fishes and reptiles, *Quar. Jour. of Micr. Sci.* 1853), but was nevertheless not generally accepted. Kölliker's results were confirmed and extended by the work of Waldeyer, Kollmann, Magitot, C. S. Tomes, and others. Baume first pointed out the independent origin of the teeth of succession from the common dental lamina; previous observers had followed Kölliker (and Goodsir) in ascribing the origin of their germs to the special germs of the milk-teeth. Pouchet and Chabry were the first to describe the common origin of the labio-dental furrow and the common dental lamina. Finally, the most important details regarding the origin of the human teeth are to be met with in the works of Magitot and Legros and of Röse. Röse's account[1] is based upon sections of the jaw of embryos of various ages, from which he has constructed models showing several stages of development in a strikingly objective form; figures of some of these models have here been reproduced.

[1] Arch. f. mikr. Anat. xxxviii. 1891. Other papers by Röse, as well as the literature of the subject up to 1895, are given in the 10th edition of this work.

The salivary glands belong to the class of tubulo-racemose glands, the structure of which, as well as the changes undergone by their cells during secretion, has been already dealt with at some length (see pp. 424 to 440). It will therefore be only necessary here to refer to the special modifications of structure met with in the different glands of man and animals.

The salivary glands proper of man comprise the *parotid*, which is the largest and is entirely serous; the *submaxillary*, which contains both serous and mucous alveoli, as well as serous cells in the form of 'crescents' in the mucous alveoli, and is therefore a mixed gland; and the *sublingual*, much the smallest of the three, which is in man mainly of the mucous type, but contains a certain number of serous cells in the otherwise 'mucous' alveoli.

FIG. 748.—SKETCH OF A SUPERFICIAL DISSECTION OF THE FACE, SHOWING THE POSITION OF THE PAROTID AND SUBMAXILLARY GLANDS. (Allen Thomson.) Two-fifths natural size.

p, parotid gland; *p'*, socia parotidis (a small separate portion of the gland); *d*, the duct of Stensen before it perforates the buccinator muscle; *a*, transverse facial artery; *n*, *n*, branches of the facial nerve emerging from below the gland; *f*, the facial artery passing out of a groove in the submaxillary gland and ascending on the face; *sm*, superficial portion of the submaxillary gland.

In animals many differences are found. Thus, in rodents and insectivora the sublingual is purely mucous and the submaxillary purely serous;[1] in the cat and dog the submaxillary is of mucous type, but with serous cells ('crescent' cells) at the periphery of the alveoli; in the dog there are mucous alveoli amongst the serous (R. Heidenhain); these also occur in the kitten, according to Metzner, but disappear with growth. The orbital gland of the cat and dog, which is closely similar in structure to the submaxillary, is also a mucous gland. This gland is placed, as its name implies, in the orbit, and sends its duct to open into the mouth on the inner surface of the cheek, near the second upper molar. It contains serous cells in the form of crescents.[2] The orbital (infraorbital) of the rabbit is a serous gland. In the guinea-pig Klein[3] described a small mucous gland attached to the parotid and sending its duct into

[1] According to Cohoe these glands in the rabbit are not entirely serous (Amer. Journ. Anat. vi. 1906).
[2] Lavdowsky, Arch. f. mikr. Anat. xiii. 1877. [3] Quart. Journ. Micr. Sci. xxi. 1881.

Stensen's duct. Various authors have noticed that in the parotid of the dog mucous alveoli are frequently found amongst the serous alveoli, and this condition has occasionally been seen in man.[1]

The parotid gland (fig. 748).—The parotid duct (*duct of Stensen*) opens on the inner surface of the cheek opposite the second upper molar-tooth. It is lined by long columnar epithelium-cells in two rows, resting on a basement-membrane; its wall is formed outside this by connective tissue and by plain muscle disposed circularly. Traced back into the gland the duct branches again and again, its epithelium becoming short and simple; the branches finally merge into intraglandular ducts (*salivary ducts*) of uniform diameter, lined by a single layer of wedge-shaped columnar cells, set on a basement-membrane, and almost filling the lumen of the duct. The cells lining these salivary ducts are in the parotid less distinctly striated in their outer zone than those of the submaxillary and sublingual. They stain deeply with hæmatoxylin and stand out prominently in sections of the gland.

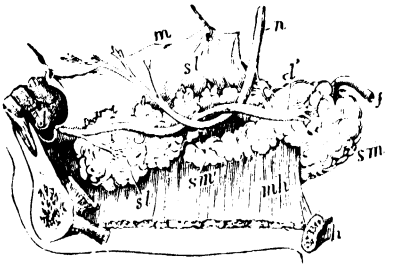


FIG. 749. VIEW OF THE RIGHT SUBMAXILLARY AND SUBLINGUAL GLANDS FROM THE INSIDE. (Allen Thomson.)

Part of the right side of the jaw, divided from the left at the symphysis, remains; the tongue and its muscles have been removed; and the mucous membrane of the right side has been dissected off and hooked upwards so as to expose the sublingual glands; *s m*, the larger superficial part of the submaxillary gland; *f*, facial artery passing through it; *s m'*, deep portion prolonged on the inner side of the mylo-hyoid muscle *m h*; *s l*, *s l'*, sublingual gland; *d*, *d'*, duct of Wharton; *h*, hyoid bone; *n*, lingual nerve; to the left of *d'*, is the submaxillary ganglion and the chorda tympani nerve.

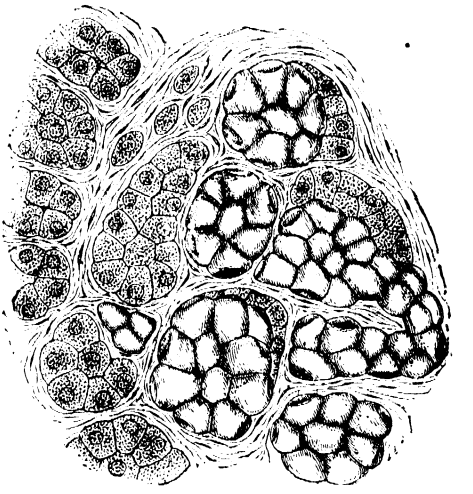


FIG. 750.—HUMAN SUBMAXILLARY GLAND. (R. Heidenhain.)

To the right of the figure is a group of mucous alveoli, to the left a group of serous alveoli.

The salivary ducts lead into or from the lobules of the gland by narrow *intermediary* or *lobular ductules* of moderate length. These branch within the lobule and finally end in the ultimate lobules, which are formed of groups of more or less spherical alveoli.

The alveoli of the parotid possess only serous cells. These in the fresh condition have a granular aspect; but the granules become destroyed under the action of most fixing reagents, so that in stained preparations they are not seen, having apparently been replaced by clear substance. After secretion the granules are few in number, and confined chiefly to the neighbourhood of the lumen. In this condition, in stained preparations, the protoplasm, being comparatively free from granules, is more deeply coloured than in the resting gland.

The submaxillary gland.—This gland in man has both mucous and serous alveoli (fig. 750). The mucous alveoli contain also serous cells, which lie between the mucous cells and the basement-membrane, forming crescentic patches (figs. 750, 751,

[1] For the character of the salivary glands in domestic animals see Illing, Anat. Hefte, xxvi. 1904; in the macaque monkey, *ibid.* xxxiv. 1907.

752, and 753). The duct of the gland (*Wharton's duct*) opens, on the floor of the mouth in front of the attachment of the tongue. Its coats are of the same nature as those of Stensen's duct, but thinner. Like that it divides on reaching the gland, and after branching a few times the ducts become of uniform size and are lined by a distinctly striated wedge-shaped columnar epithelium, set on a basement-membrane (*salivary ducts*) (fig. 751, *d*). The serous alveoli (fig. 750) are precisely similar in disposition and structure to those of the parotid. The mucous alveoli are rather larger and more elongated, the lobular or intermediary duct being proportionately narrower; the parts of the salivary ducts into which the lobular ducts pass are somewhat enlarged.

The mucous cells are during rest filled with mucin (or mucigen) granules, but with most fixing reagents these swell and become indistinct, and the 'loaded' cells when thus altered and stained appear filled by a clear mass pervaded by a fine reticulum of protoplasm. The nucleus is pressed flat into the part of the cell which rests upon

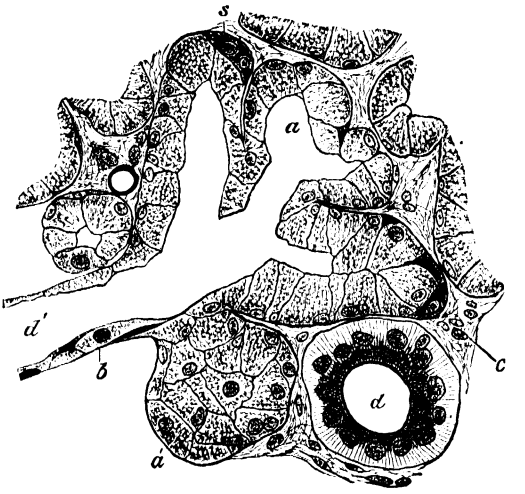


FIG. 751.—SECTION OF SUBMAXILLARY, SHOWING THE COMMENCEMENT OF A DUCT IN THE ALVEOLI. (Schäfer.) Magnified 425 diameters.

a, one of the alveoli, several of which are in the section shown grouped around the commencement of the lobular ductule, *d'*; *a'*, an alveolus, not opened by the section; *b*, basement-membrane in section; *c*, interstitial connective tissue of the gland; *d*, section of a salivary duct lined with characteristically striated columnar cells; *s*, crescentic group of darkly stained cells at the periphery of an alveolus.

the basement-membrane. The serous cells of the mucous alveoli (really 'mixed alveoli') form, as already stated, crescentic patches between the mucous cells and the basement-membrane ('crescents' of Gianuzzi). These 'crescents' communicate with the lumen of the alveolus by secreting canaliculi (figs. 752, 753, *d*) which pass between the mucous cells and ramify amongst the cells forming the crescents and even within the individual cells. In the submaxillary of the cat the crescents may extend almost round the alveolus. After a prolonged period of secretion, and the consequent discharge of mucin from the mucous cells, the latter become smaller and more protoplasmic, and in hardened stained preparations more nearly resemble the serous cells of the crescents, but the distinction between them is still evident.

Although the idea that the cells of the 'crescents' in mixed alveoli are specifically different from the mucous cells is held by most authors, some—*e.g.* Stöhr and Metzner—consider that the crescent-cells represent a phase of activity of the mucous cells. In support of this contention are quoted the following facts, viz. (1) that in the embryo and young animal the distinction into mucous cells and crescent-cells is not seen; (2) that in the exhausted gland the distinction also tends to disappear; and (3) that in mucous glands of some animals there appear to be

transitional forms between the two. But in nearly all cases the difference is so great in the staining of the cells, the appearance of the granules, the position of the cells in the alveoli, and the manner in which the secretion of the 'crescents' is passed (by secretory canaliculi) into the lumen, as to render the view that there is a specific difference between the two kinds of cell by far the most probable.

The sublingual gland.—This gland in man consists of a number of small glands which open by several ducts (*ducts of Rivinus*), from 8 to 20 in number, partly into Wharton's duct, partly independently into the floor of the mouth. Sometimes a longer duct—the *duct of Bartholin*—runs alongside Wharton's duct, to open near its orifice. This conveys the secretion from a part of the gland close to the submaxillary, representing the retrolingual of animals (see below). The human sublingual is a mucous gland without distinct serous alveoli, but serous cells are found in the form of crescents as in the mucous alveoli of the submaxillary (fig. 754). It closely resembles the submaxillary of the dog in structure.

In many animals the sublingual is represented by two glands, one of which, the *glandula sublingualis monostomatica*—termed

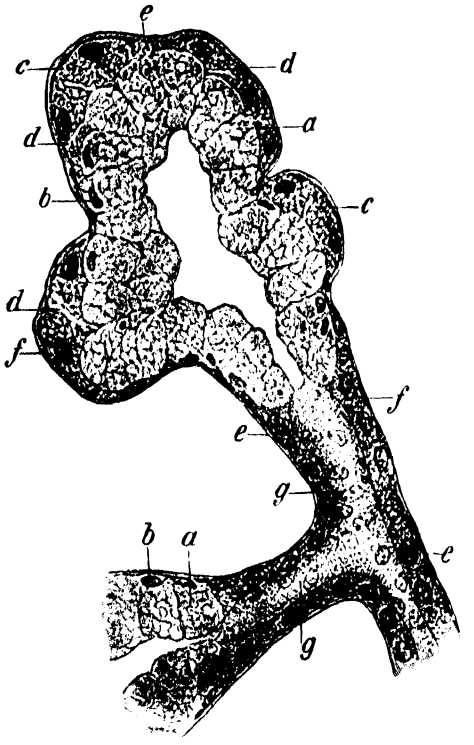


FIG. 752.—FROM A SECTION OF SUBMAXILLARY GLAND OF SHEEP, SHOWING THE PASSAGE OF A LOBULAR DUCTULE INTO THE ALVEOLI. (Illing.)

a, mucous cells of alveoli; *b*, their nuclei; *c*, cells of crescents; *d*, secretory canaliculi; *e*, basement-membrane; *f*, its basket-cells; *g*, lumen of duct.

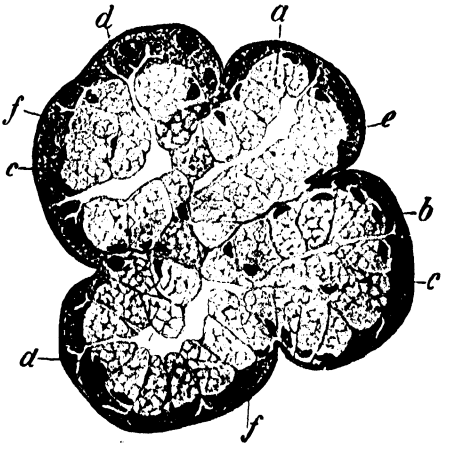


FIG. 753.—A LOBULE OF SUBMAXILLARY OF PIG IN TRANSVERSE SECTION. (Illing.)

The magnification in this figure is greater than in fig. 751; the lettering is the same as in that figure.

by Ranvier the *retrolingual gland*[1]—lies along Wharton's duct, and is especially developed near the hilum of the submaxillary gland; it has its own duct (duct of Bartholin). In the cat the retrolingual is mainly composed of mucous alveoli with a thick layer of serous cells next to the basement-membrane (fig. 755, B). The other, *glandula sublingualis polystomatica*, or *sublingual proper* (very inconspicuous in the dog and cat), communicates with the mouth by a number of ducts (ducts of Rivinus), like the sublingual in man. Its alveoli are mucous with serous cells at the periphery (fig. 755, A). The sublingual proper appears to be present in most animals, while the retrolingual is absent in the rabbit and hare, and in the horse, and is also, as above stated, usually unrepresented in man.

Development of the salivary glands.—The salivary glands, as well as the small glands of the buccal mucous membrane, are developed as buds from the deeper layer of the

[1] Arch. de physiol. xviii. 1886.

stratified epithelium of the mouth. These buds are at first solid, and exhibit an expanded or bulbous growing extremity, which, by its extensions and ramifications, eventually forms all

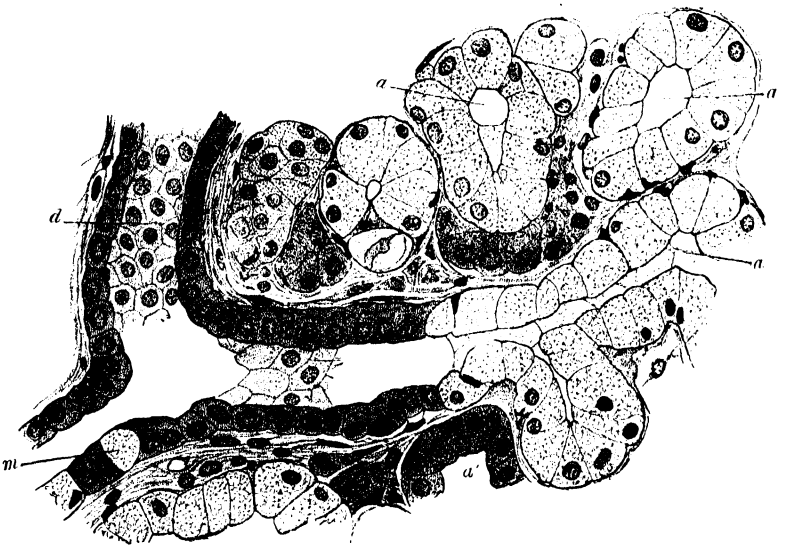


FIG. 754.—FROM A SECTION OF HUMAN SUBLINGUAL. (v. Ebner.) Magnified 500 diameters.

d, lobular ductule dividing below into two branches; *a*, *a*, *a*, alveoli lined by mucus-secreting cells—one of them shows a crescentic mass of serous cells at its periphery; *a'*, an alveolus, from the cells of which the mucus has been discharged; *m*, a mucus-secreting cell amongst the ordinary epithelium-cells of the ductule.

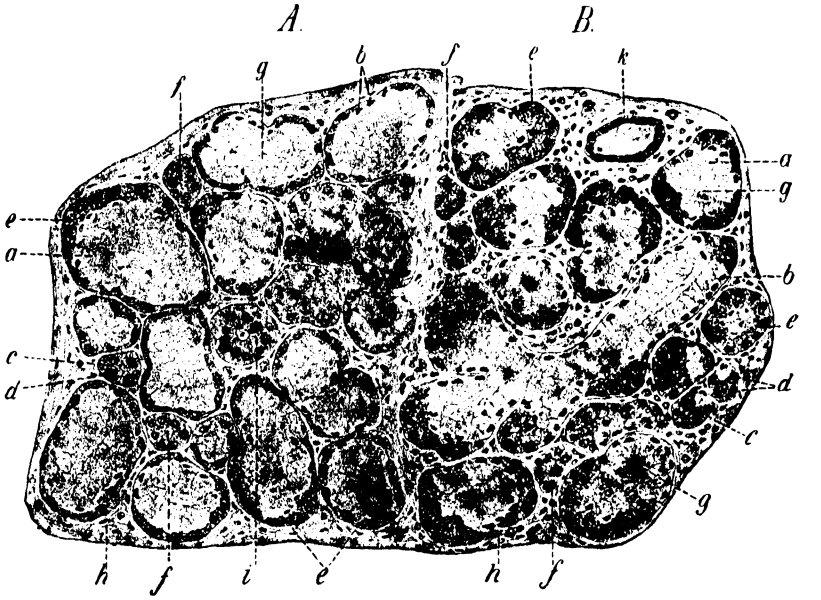


FIG. 755.—SECTION OF SUBMAXILLARY (*A*) AND RETROLINGUAL (*B*) OF CAT. (Illing.)
The glands are in close juxtaposition and the section passes through the junction.

a, mucous cells; *b*, their nuclei; *c*, serous cells; *d*, their nuclei; *e*, serous cells forming a complete ring encircling the mucous cells; *f*, alveoli cut near periphery, showing the serous cells only; *g*, lumen of alveolus; *h*, interstitial connective tissue; *i*, section of a salivary duct; *k*, section of a larger duct.

the ducts and alveoli of the gland. A cavity soon forms within the at first solid excrescence, and this becomes connected with the cavity of the mouth on the one side, and on the other

gradually extends into the ramifications. But as long as the gland-substance continues to be formed, the growing terminations of the ducts remain solid and bulbous.[1]

The order of development of the salivary glands is submaxillary, parotid, sublingual.[2] Even at an early stage of the formation of alveoli secretion-granules are visible in the alveolar cells, and mucus is found in the ducts. The 'crescents' are relatively late in making their appearance as distinct structures.

THE PHARYNX AND TONSILS.

Mucous membrane of the pharynx and fauces.—The mucous membrane of these parts has a smooth, shining, red appearance, and is unprovided with prominent papillæ, although microscopic papillæ of the corium project into the epithelium where this is stratified. It is richly supplied with small racemose mucous glands, and in certain parts, *e.g.* in the isthmus of the fauces and in the upper or respiratory portion of the pharynx, especially near the apertures of the Eustachian tubes and

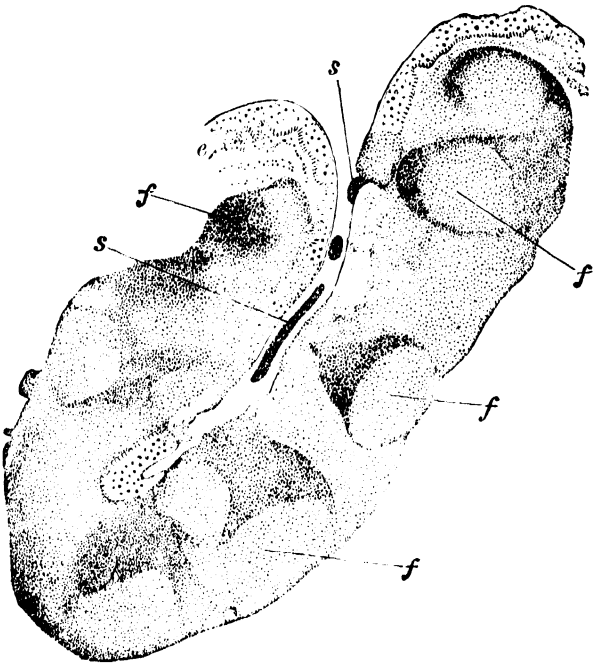


FIG. 756.—SECTION THROUGH ONE OF THE CRYPTS OF THE TONSILS, MAGNIFIED. (Stöhr.)

e, stratified epithelium of general surface, continued into crypt; *f*, *f*, follicles or nodules of lymphoid tissue; opposite each nodule or germ-centre numbers of lymph-cells are passing into and through the epithelium; *s*, *s*, masses of cells which have thus escaped from the tonsil to mix with the saliva as salivary corpuscles.

of the posterior nares, there are large accumulations of lymphoid tissue. In the isthmus of the fauces these form the two masses known as the *tonsils*. The accumulations in the upper part of the pharynx have been in like manner termed the *pharyngeal tonsils* (pharyngeal adenoids), but the adenoid tissue occurs here in a more diffused condition than in the true tonsils.[3] The epithelium is stratified over the whole mucous membrane below the level of the soft palate, but above that level it is for the most part ciliated. The stratified epithelium turns over the edge of the soft palate and extends a short distance upon its upper or posterior surface. Over the pharyngeal tonsil the epithelium is also stratified. The distribution of ciliated

[1] Chievitz, Arch. f. Anat. 1885.
[2] R. Metzner, Ber. d. d. physiol. Gesellsch. in Zentr. f. Physiol. xxiii. 1909.
[3] On the extent of the pharyngeal tonsil in the child see J. Symington, Brit. Med. Journ. October 15, 1910.

epithelium is more extensive in the embryo than after birth. Some of the gland-ducts of the lower part of the pharynx are said by Klein to retain their ciliated lining throughout life.

Outside the mucous membrane the wall of the pharynx is composed of fibrous tissue, which is attached above to the base of the skull. In contact with the fibrous wall and partly inserted into it are the pharyngeal muscles (cross-striated); these are described elsewhere in this work (Myology).

The **tonsils** are composed of masses of lymphoid tissue arranged around crypt-like depressions in the mucous membrane (fig. 756). These crypts open at the surface of the tonsil and there discharge the secretion of mucous glands which open into the crypts. The mucus carries with it a large number of leucocytes which have passed into the crypts from the lymphoid tissue: for, as originally shown by Stöhr, the cells of this tissue penetrate in large numbers between the cells of the stratified epithelium of the tonsils, and become free at the surface. Occasionally this process is accompanied, even in health, but much more in the inflamed

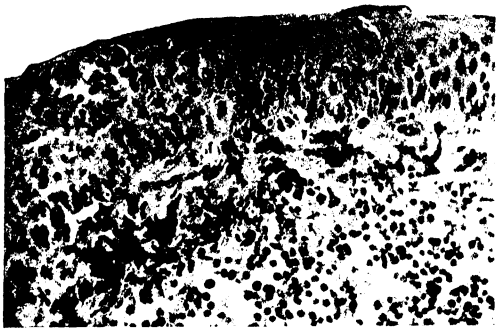


Fig. 757.—Part of a section of rabbit's tonsil showing infiltration of the epithelium by leucocytes. (Schäfer.) Magnified 66 diameters. Photograph.

condition, by a partial disintegration of the epithelium, apparently effected by phagocytic cells (fig. 757). The lymphoid tissue shows many 'germ-centres,' the nodular character of the tissue being in this way produced by local multiplication of the lymphocytes.

The lymphoid tissue of the tonsils and of the pharynx generally is richly provided with blood-vessels. There are also many lymphatics in its deeper layers.[1]

[1] On the blood-vessels of the lymphoid tissue of the pharynx and fauces see Alagna, Anat. Anz. xxxii. 1908.

The alimentary canal from the commencement of the œsophagus to the end of the rectum is constructed on the same principle, viz. in form of a tube (fig. 758) composed of a *mucous coat* inside with a *muscular coat* outside, the two being united by a quantity of loose connective tissue which has received the name of *areolar* or *submucous coat.* The stomach and the greater part of the intestines are also enclosed within an invagination of the peritoneum, which thus furnishes a *serous coat* to those viscera.

The mucous membrane is throughout formed of epithelium and corium, with a layer of plain muscular tissue, termed the *muscularis mucosæ*, next to the submucous coat. The epithelium in the œsophagus is of the stratified scaly variety, in the stomach and intestines it is columnar.

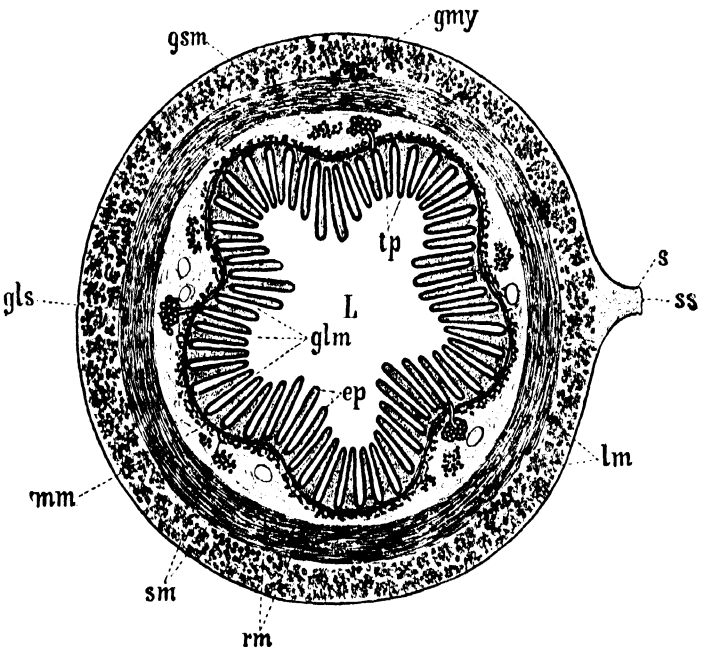
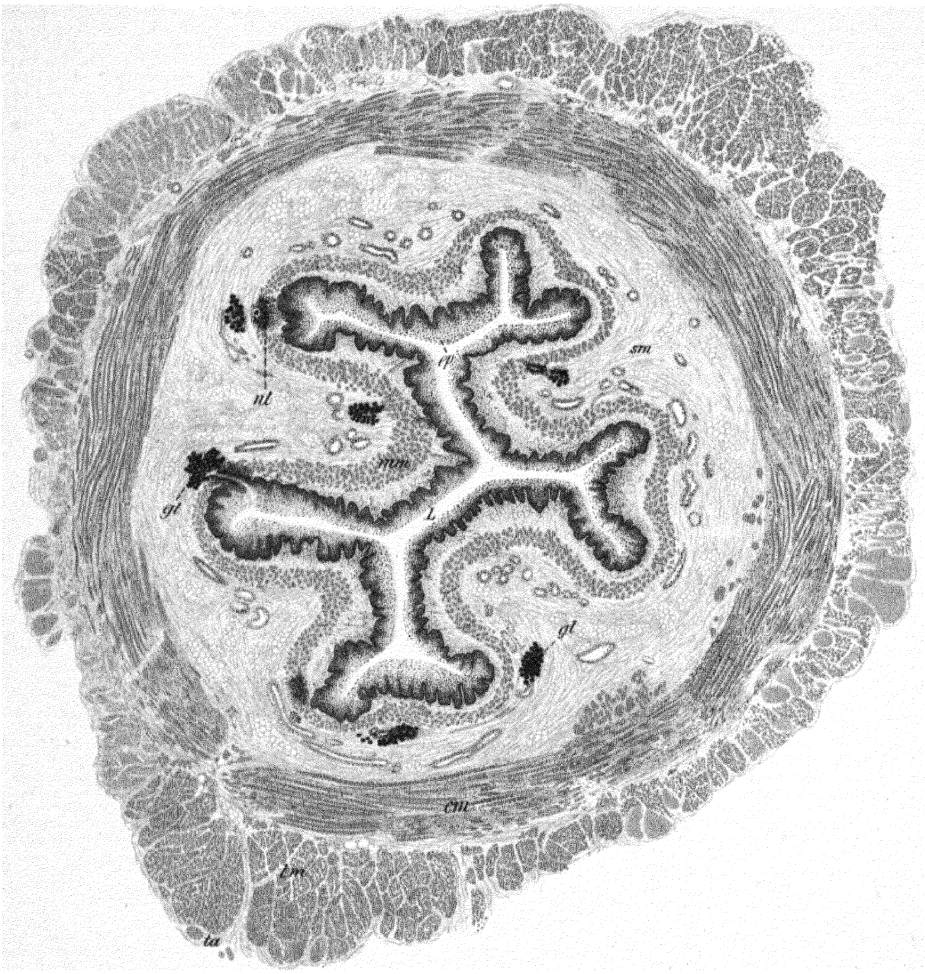


FIG. 758.—DIAGRAM OF SECTION OF ALIMENTARY TUBE. (Sobotta.)

L, lumen; *glm*, glands of mucous membrane; *ep*, epithelium; *gls*, glands in submucosa; *mm*, muscularis mucosæ; *sm*, submucous coat; *rm*, circular muscular layer; *lm*, longitudinal muscular layer; *s*, serous coat; *ss*, mesentery; *gmy*, ganglion of plexus myentericus; *gsm*, ganglion of plexus submucosus.

In the œsophagus, as in the mouth and pharynx, small racemose mucous glands lie in and beneath the mucous membrane and send their ducts to open at its surface. In the stomach and intestines most of the glands are tubules, which open by innumerable mouths on the inner surface and are contained within the thickness of the mucous membrane. But in the commencement of the small intestine there are other glands (*glands of Brunner*) which lie in the submucosa and send their ducts from this through the mucosa to the surface.

The muscular coat in all these parts of the alimentary canal is formed of two layers, an outer, with the bundles of fibres disposed longitudinally, and an inner, somewhat thicker, with the bundles disposed circularly. Between the two layers is a gangliated nervous plexus (*plexus myentericus of Auerbach*). Another, finer, gangliated plexus lies in the submucosa (*plexus submucosus of Meissner*). In the stomach there is a third incomplete layer of muscular fibres, which extends over the enlarged part or fundus, and the fibres of which run obliquely from the œsophageal opening (cardia) downwards and towards the pyloric part. In the stomach and intestines the muscular coat is composed only of plain muscle, but in the upper part of the œsophagus the muscular tissue of this coat is cross-striped; lower down plain muscle-bundles



Transverse section of human oesophagus, middle third (Sobotta). Magnified 10 diameters. Haematoxylin-eosin.

L, lumen; *ep*, epithelium; *gl*, glands; *nl*, lymph-nodule; *mm*, muscularis mucosae; *sm*, submucosa; *cm*, circular muscle; *lm*, longitudinal muscle; *ta*, tunica adventitia.

become mixed with the cross-striped; at the lower end of the tube the tissue is wholly formed of plain muscle.

In a portion of the large intestine (cæcum, colon) the longitudinal muscle-layer is thickened along the course of three bands, which extend from end to end of this portion of the gut and which are somewhat shorter than the rest of the longitudinal fibres. The effect of this is to produce puckerings in the wall, which are of a permanent character and give a sacculated appearance to the part.

In the œsophagus, stomach, and large intestine the surface of the mucous membrane is smooth, and when these parts are distended they exhibit no folds or prominences on the inner surface (other than the puckerings just mentioned as occurring in the colon and its cæcum), although when empty the mucous membrane may display the effaceable folds known as *rugæ*. But in the small intestine the whole of the mucous membrane from the pylorus to the ileocæcal valve is beset with fine tongue- or finger-shaped prominences known as *intestinal villi*, and a large portion of the small intestine also shows on its inner surface prominent ineffaceable transverse folds of the mucous membrane known as *valvulæ conniventes*, themselves covered by villi.

THE ŒSOPHAGUS OR GULLET.

The walls of the gullet are composed of three coats : viz. an external or muscular, a middle or areolar, and an internal or mucous coat (see accompanying Plate). Outside the muscular coat there is a layer of areolar tissue, with well-marked elastic fibres.

The **muscular coat** consists of an *external longitudinal layer* (fig. 759, *b*) and an *internal circular layer* (*c*). This twofold arrangement of the muscular fibres prevails, as just stated, throughout the whole length of the alimentary canal; but the two layers are here much thicker, and more evident than in any other part of the alimentary tube, except quite at the lower end of the intestine. The external or longitudinal fibres are disposed at the commencement of the gullet in three bands, one in front and one on each side. The lateral bands are continuous above with the inferior constrictor of the pharynx; the anterior arises from the back of the cricoid cartilage at the prominent ridge between the posterior crico-arytenoid muscles, and its fibres spread out on each side of the gullet as they descend, soon blending with those of the lateral bundles to form a continuous layer around the tube. The direction of many of the fibres is at first slightly oblique, but towards the lower end it is more directly longitudinal. The internal or circular fibres are separated above by the fibres of the lateral longitudinal bands from those of the inferior constrictor of the pharynx. The rings which they form around the tube have a horizontal direction at its upper and lower part, but in the intervening space are slightly oblique. At the lower end both layers of fibres become continuous with the muscular layers of the stomach.

The muscular coat of the upper end of the œsophagus is of a well-marked red colour, and consists wholly of striped muscular fibres; these, as already mentioned, are gradually replaced by plain muscular fibres, so that plain fibres are almost the only ones found in the lower half of the tube. A few striped fibres may, however, be found even at the lower end, and in some animals they preponderate throughout the whole length of the tube.[1]

The longitudinal fibres of the œsophagus are sometimes joined by a broad band of smooth muscle, passing from the left pleura, and sometimes also by another from the left bronchus. According to Cunningham, the former is almost constantly present, and the latter very frequently.

The **areolar** or **submucous** coat is placed between the muscular and mucous coats, and connects them loosely together. In it are contained the mucous glands (fig. 759, *h*), which open on the mucous membrane.

[1] On the arrangement of the muscular fibres of the œsophagus see Coakley, Researches from the Loomis Laboratory, Univ. of the City of New York, 1892.

The **mucous membrane** is of firm texture, and is paler in colour than that of the pharynx or stomach. From its loose connexions its outer surface is freely movable on the muscular tunic; and under ordinary circumstances the mucous lining is thrown into longitudinal folds or rugæ, which are in mutual contact. These folds disappear on distension of the canal.

Microscopic papillæ (*f*) are seen upon the corium; they project into and are covered by the stratified scaly epithelium. In the embryo for a certain period the œsophagus is lined by columnar ciliated epithelium (Neumann), patches of which may persist even to the time of birth (Klein).

The small compound racemose or tubulo-racemose glands, named *œsophageal glands*, which are for the most part seated in the submucous tissue, are specially numerous at the lower end of the tube. A few of the smallest are situated in the substance of the mucous membrane. The cells of these glands are columnar. Their ducts are usually surrounded by collections of lymphoid tissue as they pass through the mucous membrane.

The mucous membrane is bounded next to the submucous coat by longitudinally disposed plain muscular fibres, which, imperfect above, form a continuous layer towards the lower end of the tube (*muscularis mucosæ*, *e*).

FIG. 759.—SECTION OF THE HUMAN ŒSOPHAGUS. (From a drawing by V. Horsley.) Moderately magnified.

The section is transverse, and from near the middle of the gullet. *a*, fibrous covering; *b*, divided fibres of the longitudinal muscular coat; *c*, transverse muscular fibres; *d*, submucous or areolar layer; *e*, muscularis mucosæ; *f*, mucous membrane, with vessels and part of a lymphoid nodule; *g*, laminated epithelial lining; *h*, mucous gland; *i*, gland duct; *m'*, striated muscular fibres cut across.

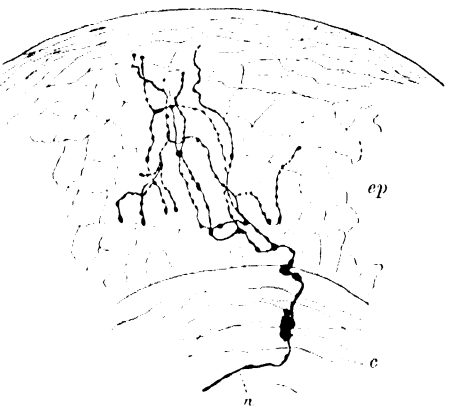


FIG. 760.—ENDING OF NERVE-FIBRILS IN STRATIFIED EPITHELIUM OF ŒSOPHAGUS OF RABBIT. (G. Retzius.)

ep, epithelium; *c*, corium; *n*, a nerve-fibre passing from the corium to the epidermis and there ending in an arborisation of varicose fibrils.

Vessels and nerves.—The *blood-vessels* have for the most part a longitudinal arrangement. There are separate networks for the mucous membrane, muscularis mucosæ and muscular coat, and the glands and fat lobules which are met with in the submucosa have each their capillary plexus. *Lymphatics* are found in both the submucous and mucous coats, those of the latter commencing as in the mouth and pharynx within the papillæ. A small amount of lymphoid tissue is also present, and may be accumulated into lymphoid nodules, especially in the neighbourhood of the ducts of the mucous glands.[1] Both here and in the

[1] M. Flesch, Anat. Anz. iii. 1888; Dobrowolski, Ziegler's Beitr. xvi. 1894.

pharynx the alveoli of the mucous glands are invested by sinus-like lymphatic vessels (Kidd). The nerves form a gangliated plexus between the two layers of the muscular coat, as in other parts of the alimentary canal, but it is here characterised by the comparatively large size of the groups of ganglion-cells and of the cells themselves, and also by the fact that it contains, besides non-medullated fibres, a considerable number of medullated nerve-fibres (derived from the vagi) and distributed in terminal arborisations (motor end-organs) in the striped muscular fibres (Ranvier). The non-medullated fibres are distributed chiefly to the plain muscular tissue. There is also a gangliated plexus in the sub-mucous tissue, from which fibres pass to the glands, and to the muscularis mucosæ, whilst others penetrate between the deeper layers of the stratified epithelium and end in an open arborisation of varicose fibrils between the cells (fig. 760).[1]

THE STOMACH.

The stomach has four coats, named, in order from without inwards, the serous, muscular, areolar or submucous, and mucous tunics (fig. 761).

The **external** or **serous coat** (*s*), derived from the peritoneum, is a thin, smooth, transparent, and elastic membrane, which closely covers the entire viscus, excepting along its two curvatures, and a small area near the cardiac end. Along the line of these curvatures the attachment is looser, leaving an interval occupied by the larger blood-vessels.

The second, or **muscular coat**, is composed of plain muscular tissue, forming three sets of fibres, disposed in layers, and named, from their direction, the longitudinal, the circular, and the oblique fibres.

The first or outermost layer consists of the *longitudinal* fibres (fig. 761, *l.m.*, fig. 762, A), which are in direct continuity with those of the œsophagus. They spread out in a radiating manner from the cardiac orifice, and are found in greatest abundance along the curvatures, especially the lesser one. On the anterior and posterior surfaces they are very thinly scattered, or scarcely to be found, but towards the pylorus are well marked and form a thick uniform layer, which, passing over the pylorus, becomes continuous with the longitudinal fibres of the duodenum.

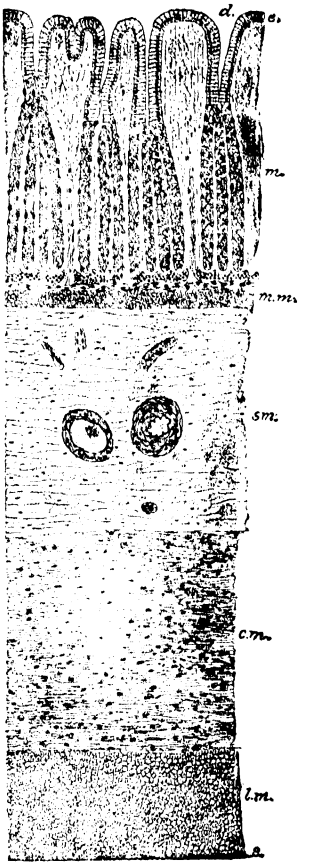


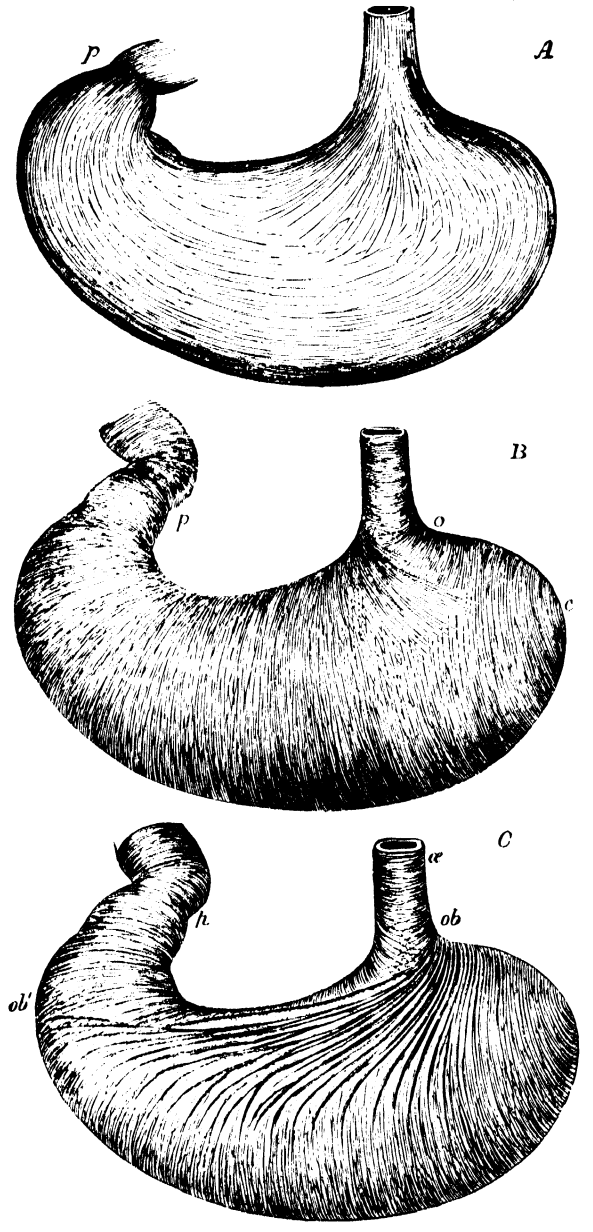
FIG. 761.—SECTION THROUGH THE COATS OF THE STOMACH. Diagrammatic. (Mall.)

m., mucous membrane; *e.*, epithelium; *d*, orifice of gland-duct; *m.m.*, muscularis mucosæ; *sm.*, submucous coat; *c.m.*, circular muscular layer; *l.m.*, longitudinal muscular layer; *s.*, serous coat.

The second set consists of the *circular* fibres (fig. 761, *c.m.*, fig. 762, B), which form a complete layer over the whole extent of the stomach. They commence by small and thinly scattered rings at the extremity of the great cul-de-sac, describe larger and larger circles as they surround the body of the stomach at right-angles to its curved axis, and towards the pyloric end again form smaller rings, and at the same time become much thicker and stronger than at any other point. At the

[1] G. Retzius, Biol. Unters. iv. 1892.

pylorus itself they are gathered into a thick bundle, which forms, within a circular fold of mucous membrane, a well-marked projection—the *pyloric sphincter*. Some of the circular fibres appear to be continued from those of the œsophagus, spreading from its right side.



The innermost muscular layer is incomplete, and consists of the *oblique* fibres (fig. 762, C). These are continuous with the circular fibres of the gullet, on the left of the cardiac orifice, where they form a considerable stratum; from that place they descend obliquely upon the anterior and posterior surfaces of the stomach, where they spread out from one another, and, taking the direction of the circular fibres, gradually disappear amongst these on the greater curvature.

The **submucous coat** connects the muscular and mucous coats (fig. 761, *sm.*). It consists of areolar tissue, in which occasional fat-cells may be found; it is the seat of division and passage of the blood-vessels and contains a plexus of lymph-vessels and a gangliated nervous plexus.

The **internal coat** or **mucous membrane** is a smooth, soft, rather thick and pulpy membrane, which during life and immediately after death has

FIG. 762.—SKETCH OF THE ARRANGEMENT OF THE FIBRES IN THE MUSCULAR COAT OF THE STOMACH. (Allen Thomson.) One-third natural size.

A, external layer of longitudinal fibres, as seen from the outside; B, middle layer of circular fibres as seen on removing the longitudinal layer; C, oblique fibres exposed by removing some of the fibres of the circular layer, the cut edges of which are seen below the small curvature.

c, the cardiac end; *p*, the pyloric end. In A are shown the stronger longitudinal fibres passing along the small and large curvatures, and all round the pyloric end, and radiating from the end of the gullet over the front (and back) of the stomach; in B, the nearly uniform layer of circular fibres, in two sets crossing each other obliquely at *o*, and at the cardiac end becoming concentric to the centre of the great cul-de-sac; in C, the oblique fibres, *ob*, *ob'*, which form a continuation of the circular fibres of the gullet (*œ*), and spread from the left side of the cardia, gradually merging into the deeper circular fibres, with which finally they entirely blend.

generally a somewhat pink hue owing to the blood in its capillary vessels. In infancy the vascular redness is more marked.

The mucous membrane is thickest in the pyloric region, and thinnest in the great cul-de-sac. It always becomes thinner in old age.

It is connected with the muscular coat by means of the intervening submucous layer so loosely as to allow of considerable movement or displacement. In consequence of this, and of the want of elasticity of the mucous membrane, the internal surface of the stomach, when that organ is in an empty or contracted state, is thrown into numerous convoluted ridges, *rugæ*, which are produced by the wrinkling of the mucous together with the areolar coat, and are entirely obliterated by distension of the stomach. These folds are most evident along the greater curvature, and have a general longitudinal direction.

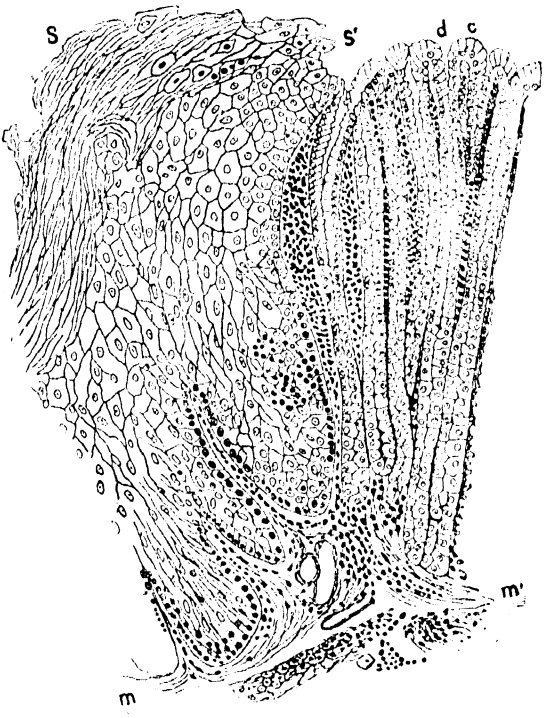


FIG. 763.—SECTION OF THE JUNCTION OF THE ŒSOPHAGEAL AND GASTRIC MUCOUS MEMBRANE OF THE KANGAROO. (Schäfer and Williams.) Magnified 185 diameters.

S, stratified epithelium of œsophagus abruptly discontinued at *S'*; *c*, columnar epithelium of gastric mucous membrane; *d*, orifices or ducts of glands of the cardia; *m*, corium of œsophageal mucous membrane sending papillæ into the epithelium; *m'*, corium of gastric mucous membrane.

On close examination of the gastric mucous membrane with the aid of a simple lens, it is seen to be marked throughout, but more plainly towards the pyloric extremity, with small depressions, which have a polygonal figure, and vary from about 0·12 to 0·25 mm. across, being larger and more oblong near the pylorus. They are the enlarged mouths or ducts of the tubular glands with which the mucous membrane of the stomach is beset (fig. 761). Towards the pyloric region of the stomach these depressions are larger and deeper, and in vertical section their margins appear elevated into pointed processes, which have a resemblance to rudimentary villi, but true villi exist only in the small intestine, and make their appearance in the duodenum, immediately beyond the pylorus.

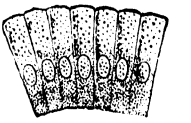


FIG. 764. EPITHELIUM OF THE SURFACE OF THE STOMACH EXAMINED FRESH. (R. Heidenhain.) Highly magnified.

Surface epithelium.—The thick stratified epithelium of the œsophagus passes abruptly at the cardia into a simple layer of columnar epithelium, which completely covers the inner surface of the stomach, and extends to a variable distance into the mouths of the gastric glands. The transition of the stratified into the columnar epithelium occurs quite suddenly, the lowermost columnar cells of the stratified epithelium passing into the single columnar layer of the gastric surface, and all the other layers of the stratified epithelium ceasing abruptly (fig. 763).

The epithelial cells of the surface of the stomach (fig. 764) differ in some respects from the columnar epithelium of the intestine. They are more elongated in form, and in inactive conditions of the organ they exhibit two parts, the attached end of the cell being granular, the free part—that turned towards the cavity of the organ—occupied by a clear, muco-albuminous substance (mucigen). There is no distinct striated border as in the intestinal cells. The clear substance swells and is discharged from the cell during digestion, leaving empty the part of the cell which contained it; a similar change is produced by water and various other re-agents. The cells are in fact all mucus-secreting cells (goblet-cells). According to Carlier they are connected laterally by protoplasmic bridges. Between the smaller ends of these cells, small round or oval cells occur, sometimes in nests (Watney).

Glands.—As was first shown by Sprott Boyd, the surface of the mucous

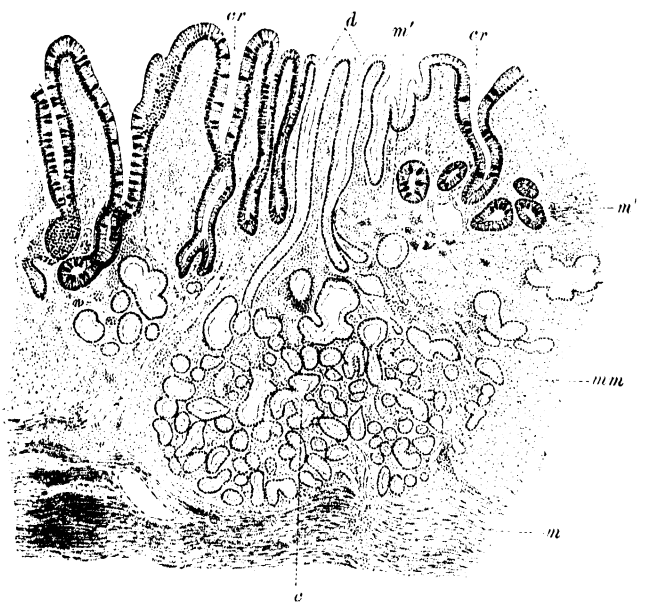


FIG. 765.—SECTION OF HUMAN STOMACH NEAR THE CARDIA. (v. Ebner, after J. Schaffer.) Magnified 45 diameters.

c, cardiac glands; *d*, their ducts; *cr*, glands similar to crypts of Lieberkühn, with goblet-cells; *mm*, mucous membrane; *m*, muscularis mucosæ; *m'*, muscular tissue within mucous membrane.

membrane of the stomach is dotted with small round apertures, which are the openings of minute glandular tubules, placed perpendicularly to the surface. On making a vertical section of the membrane, and submitting it to microscopic examination, it is seen to consist almost entirely of these small tubules, arranged parallel with each other (fig. 761). Each mouth or duct, together with the tubules which open into it, constitutes a *gastric gland*.

Some of the glands may be simple, consisting of a single tubule throughout, but most are cleft into two or three tubules, or even, by the branching of these, into four or six. The glands have externally a basement-membrane, composed of flattened cells joined edge to edge; these cells have processes which on the one side join the retiform tissue of the mucous membrane, and on the other side, more delicate, extend in amongst and support the enclosed epithelium-cells.

Three kinds of glands are distinguishable in the mucous membrane of the stomach: they are, respectively, the *glands of the cardia*, the *glands of the fundus*, and the *glands of the pyloric canal*.

The gastric glands have certain features in common. They are all tubular and confined to the mucous membrane proper, except close to the pylorus, where they pierce the muscularis mucosæ (here imperfect) and extend into the submucous tissue (fig. 798), passing by gradual transition into the glands of Brunner of the duodenum. In man and most animals each gastric gland is formed, as just mentioned, of secreting tubules which commence blindly near the muscularis mucosæ, and, running parallel with one another, open into the enlarged mouth or duct of the gland. In the horse Zimmermann finds that the secreting tubules of the same gland may anastomose.[1] The mouth or duct appears as a wide depression

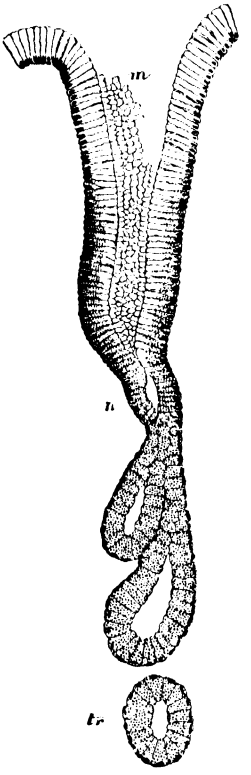


FIG. 766.—A PYLORIC GLAND, FROM A SECTION OF THE DOG'S STOMACH. (Ebstein.)

m, mouth; *n*, neck; *tr*, a deep portion of a tubule cut transversely.

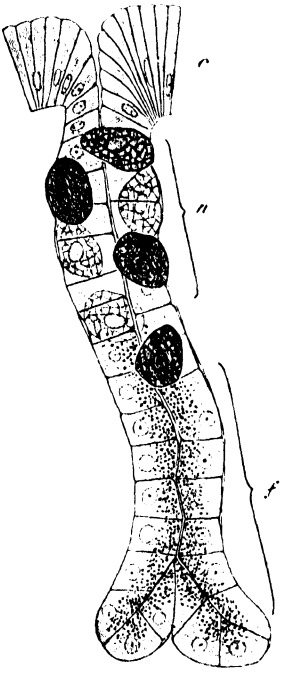


FIG. 767.—A FUNDUS-GLAND OF SIMPLE FORM, FROM THE BAT'S STOMACH. Osmic-acid preparation. (Langley.) Magnified 420 diameters.

c, columnar epithelium of the surface; *n*, neck of the gland with central and parietal cells; *f*, base or fundus occupied only by central cells, which exhibit granules accumulated towards the lumen of the gland.

of the general surface (see p. 527), and is lined by epithelium similar to that of the surface (goblet-cells).

The **glands of the cardia** (fig. 765) are found in man in a zone which may extend to 3 cm., from the cardiac orifice, but is usually very small. They are either simple or compound. Those of simple type have somewhat enlarged blind extremities and short mouths, and the secreting tubules are lined by a moderately high columnar epithelium somewhat like that of the pyloric glands; the cells being filled with fine granules. Those of the compound or tubulo-racemose type are somewhat similar in structure to the glands of Brunner of the duodenum. Their cells are clear and columnar. According to Bensley they are partly mucus-secreting, and partly

[1] Arch. f. mikr. Anat. lii. 1898.

contain zymogen-granules: the zymogen (pepsin) secreting tubules may also show parietal cells. Such glands as Bensley describes belong, however, to the same category as the glands of the fundus (see below). The true cardiac glands have no parietal cells, and according to the observations of Haane and of Ellenberger and Hofmeister (in the pig) these glands do not yield pepsin, but an amylolytic ferment. Schaffer has described similar glands in the lowest part of the œsophagus of man.

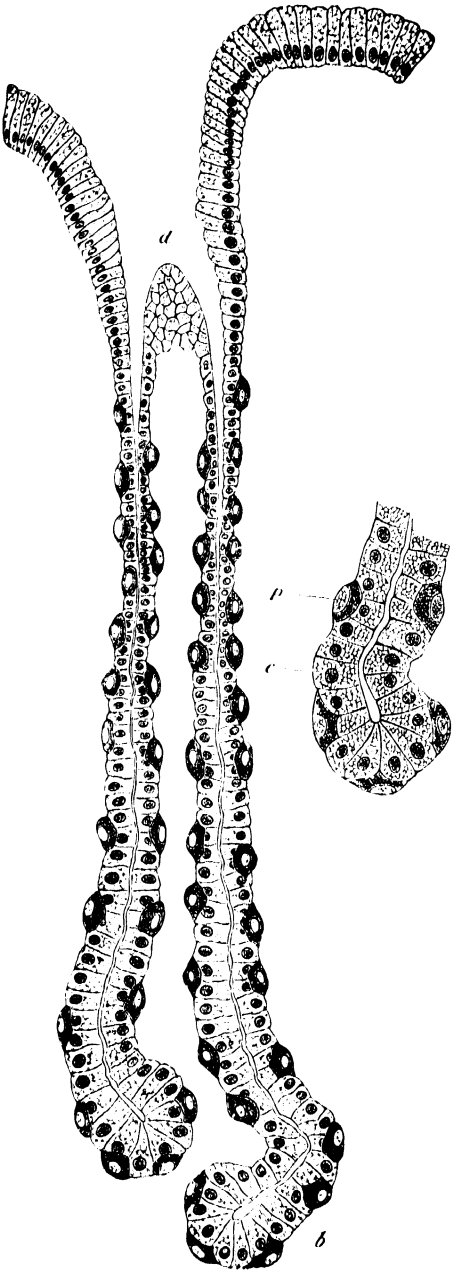


FIG. 768. A FUNDUS GLAND FROM THE DOG'S STOMACH. (Klein and Noble Smith.)

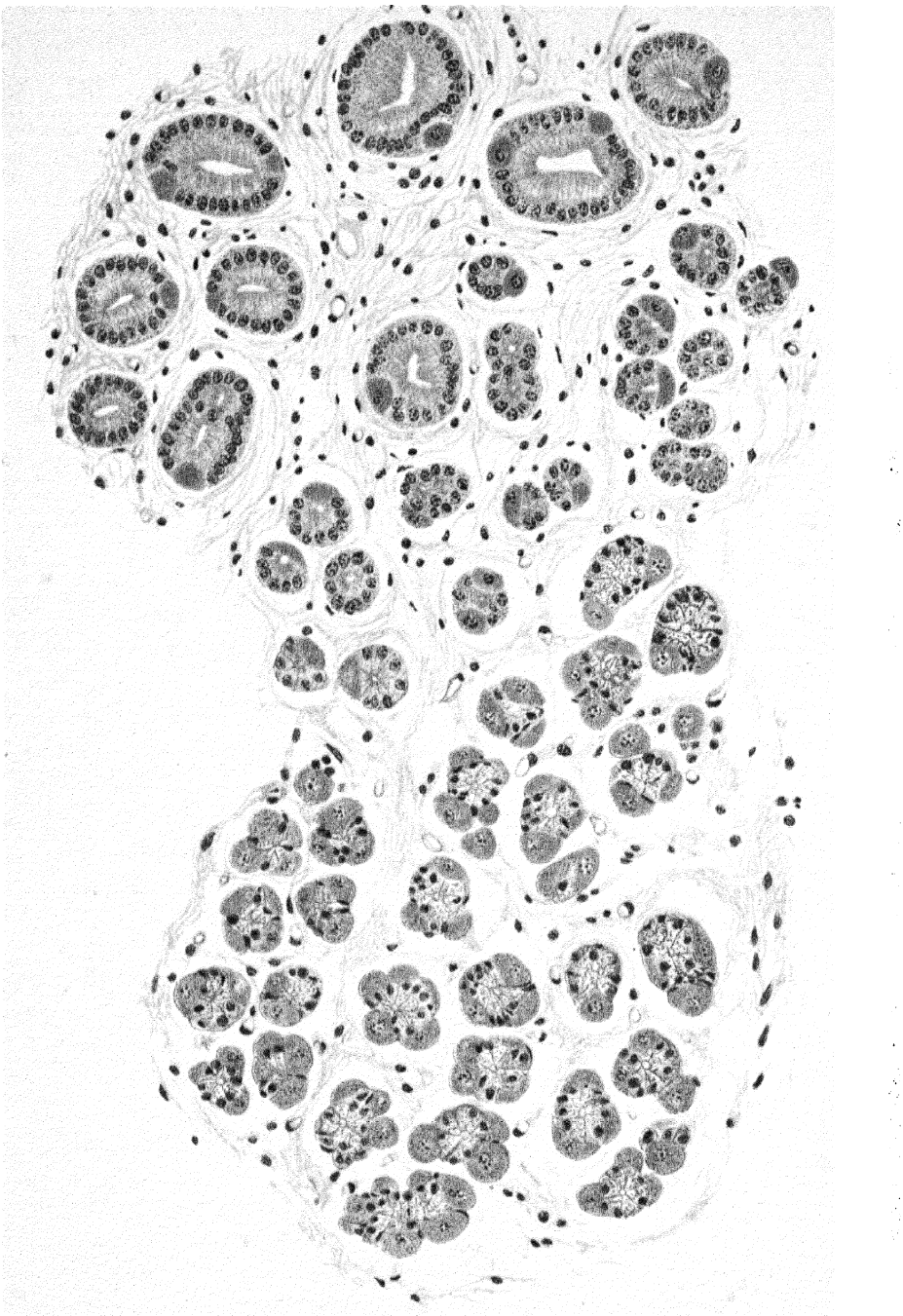
d, duct or mouth of the gland; *b*, base or fundus of one of its tubules. On the right the base of a tubule more highly magnified; *c*, central cell; *p*, parietal cell.

FIG. 769. A GASTRIC GLAND: THE LUMEN SHOWN BY CHROMATE OF SILVER. (E. Müller.)

The cells are not represented, but the extension of the lumen into the network surrounding the parietal cells is well shown.

The glands of the cardia were first described by Schäfer and Williams (Proc. Zool. Soc. 1876) in the kangaroo, where they are simple tubules; subsequently by Ellenberger in a number of animals.

The secreting tubules of the **pyloric glands** (fig. 766) are occupied during rest by finely granular cells; the granules largely disappear during active secretion.



Section of mucous membrane of fundus of dog's stomach, passing across the direction of the oxyntic glands. Haematoxylin-eosin. Magnified 250 diameters. (Schäfer.)

The section is somewhat oblique and shows at the upper part of the figure the ducts or mouths of the glands cut across and at the lower part the secreting tubules with central or chief and parietal or oxyntic cells; the latter coloured by eosin. The tubules are somewhat separated from the interglandular tissue as the result of shrinkage.

These cells yield pepsin, but none of the acid of the gastric juice. Amongst the ordinary cells of these glands some are here and there found which stain with osmic acid much more deeply than the rest. The nature and function of these cells, which were described by Nussbaum, is not known. They are not identical with the parietal cells of the fundus-glands. Occasionally, true parietal cells have been noticed in the pyloric glands and even in Brunner's glands in the duodenum.

The **glands of the fundus** (figs. 767, 768, and accompanying Plate), which are found over the whole extent of the mucous membrane except in the pyloric canal and in a zone quite close to the cardiac orifice, possess in their secreting tubules two kinds of gland-cells. In a cross-section of a tubule, those of the one kind, wedge-shaped and more or less filled with very distinct granules, are seen to lie next to the lumen of the tube; the cells of the other kind, large, oval, and very finely granular, lie between

FIG. 770.—PART OF TUBULE OF A FUNDUS GLAND OF THE STOMACH, WITH THE LUMEN AND SECRETORY CANALICULI STAINED; THE GLAND-CELLS ARE ALSO SHOWN. (Zimmermann.) Highly magnified.

c, chief or central cells; *p*, parietal cells; *l*, lumen of tubule prolonged into arborescent canaliculi which penetrate into the parietal cells.

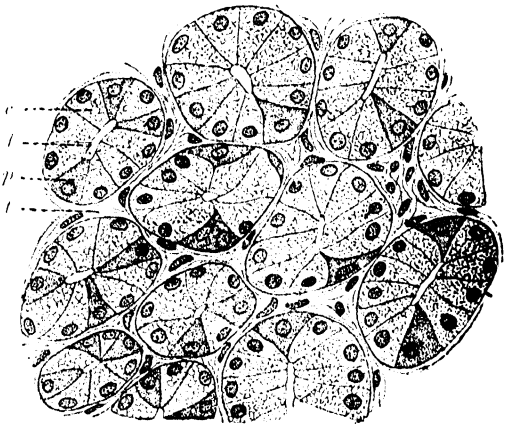


FIG. 771.—CROSS-SECTION OF FUNDUS GLANDS FROM THE HUMAN STOMACH, SHOWING THE CONDITION OF THE CELLS DURING FASTING. (Böhm and v. Davidoff.) Magnified 500 diameters.

c, central cell; *l*, lumen of gland; *p*, parietal cell; *l*, connective tissue between glands.

these and the basement-membrane, which is generally bulged out by them. From this difference of relative position the cells have been termed respectively the *central* and the *parietal cells*. They are also known as the *chief cells* (Hauptzellen) and the *superadded cells* (Belegzellen); or, from their supposed functions, the *pepsin-forming* and the *acid-forming* cells.[1] The secretion of the parietal cells, which are separated from the lumen of the tubule by the central cells, is conveyed away by extensions of the gland-lumen in the form of ramifying secretory canaliculi (figs. 769, 770). The parietal cells are most numerous near the part of the secreting tubule which opens into the duct of the gland. Sometimes they occur in the duct itself (see accompanying Plate), or even under the epithelium of the general surface of the stomach.

[1] Oxyntic cells (Langley), from ὀξύς, acid.

In some animals (porpoise, pig) the parietal cells lie each in a special pit formed by basement-membrane, communicating with the rest of the gland only by a narrow orifice. In the glandular stomach of birds they line secondary tubules which lead out of the main tube, this alone being lined by chief cells. In the frog and other amphibia the fundus glands have only parietal (oxyntic) cells, the chief cells being altogether absent, but glands containing cells similar in appearance and function to the chief cells of the stomach are found in the œsophagus.

Various observers have noted the occasional presence of leucocytes within the cytoplasm of the parietal cells. Harms[1] has described mitoses in some of the cells of the fundus glands (both central and parietal) of the (growing) mouse.

During the functional activity of the stomach the cells of the gastric glands undergo changes which are strictly comparable to those described as occurring in the cells of the serous salivary glands. In the intervals of digestion the principal cells of the cardiac glands are enlarged and almost fill the lumen of the tubule. In this so-called 'resting' or 'loaded' condition they are in some animals granular throughout, while in others there is a small outer zone clear of granules. They become smaller and distinctly differentiated into two zones during activity, some of the granules being dissolved and discharged along with the secretion, the rest tending towards the lumen of the gland so as to leave the outer part of each cell clear of

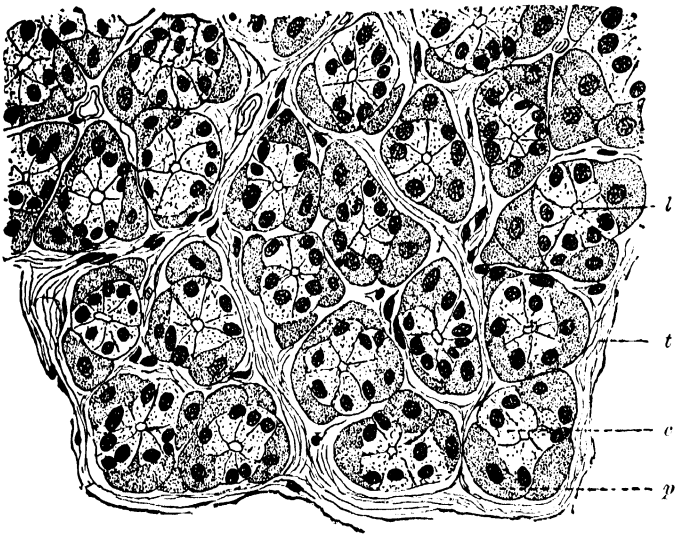


FIG. 772.—CROSS-SECTION OF FUNDUS-GLANDS FROM THE HUMAN STOMACH, SHOWING THE CONDITION OF THE CELLS DURING DIGESTION. (Böhm and v. Davidoff.) Magnified 500 diameters.

(References as in fig. 771.)

granules (fig. 767). After digestion has ceased the outer parts of the cells become again partially or wholly occupied by granules (Langley). Changes of a similar nature have also been seen by Langley and Sewall in the pepsin-forming œsophageal glands of the frog and newt—even in the living condition. On the other hand the parietal cells of the fundus glands are smaller during fasting, when they are angular in form (fig. 771). During digestion they become enlarged and more spheroidal, bulging out the tunica propria of the glands (fig. 772).

R. Heidenhain stated that the central cells and the parietal cells of mammals undergo a similar change during digestion, both becoming at first enlarged and subsequently shrinking to less than their volume during rest. He found these changes to occur later in the parietal than in the central cells. An enlargement of the central cells during the period of activity seems, however, not to take place; according to most recent authorities the parietal cells alone show such enlargement.

The secreting cells of the pyloric glands undergo changes similar to those of the central cells of the fundus glands, becoming smaller with secretion.

[1] Anat. Hefte, xli, 1910.

Besides the three above-described types of gland, in certain parts of the human stomach true crypts of Lieberkühn occur (Schaffer), similar in all respects to those of the small intestine, and like these lined by typical columnar cells with striated border and with occasional goblet-cells between. The deepest cells also exhibit granules similar to those described by Paneth in the intestinal glands (Jouvenal). These crypts of Lieberkühn are most numerous in a zone which lies between the area occupied by fundus glands and that occupied by pyloric glands, especially on the greater curvature. They are, however, found scattered amongst the glands both of the pyloric region and of the fundus, especially near the zone in question: a few occur quite close to the pylorus and to the cardia (fig. 765, *cr*). Where they are present the surface epithelium is also of the intestinal type.

Muscularis mucosæ.—Between the glands and at their base the mucous membrane consists of delicate connective tissue with retiform lymphoid tissue in

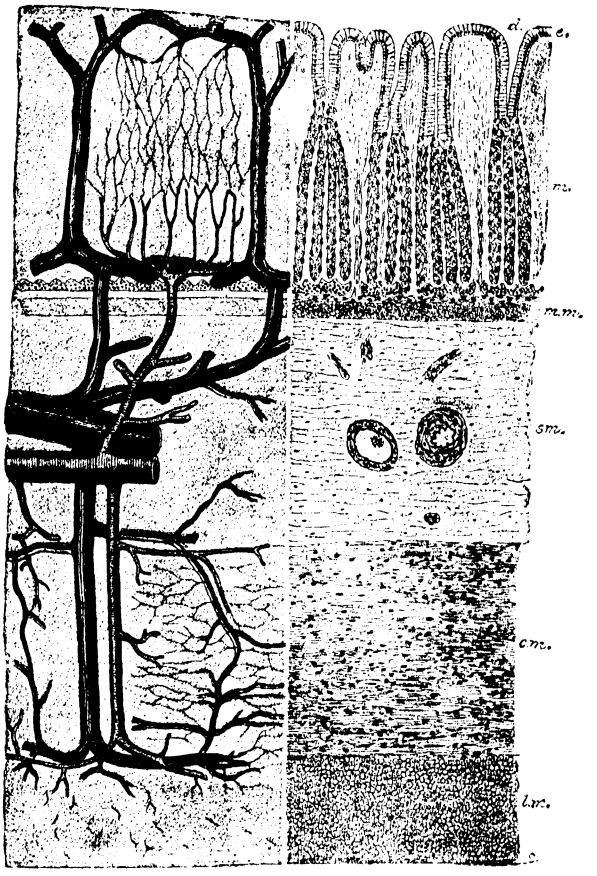


FIG. 773.—SECTION THROUGH THE STOMACH TO SHOW THE ARRANGEMENT OF THE PRINCIPAL BLOOD-VESSELS IN RELATION TO ITS COATS. Diagrammatic. (F. P. Mall.)

On the right side of the figure the glandular and muscular elements are shown; on the left only the blood-vessels. It will be seen that the principal vessels are in the submucous tissue, and that from these, branches are distributed to the mucous membrane and to the muscular coat. For explanation of lettering see fig. 761.

small amount. Externally a thin layer of plain muscular tissue (*muscularis mucosæ*, fig. 773, *m.m.*) bounds the mucous membrane, and separates it from the submucous tissue. It consists of two strata (an outer longitudinal and an inner circular), and is better marked in some animals than in man. Offsets pass from it between the gastric glands towards the surface of the mucous membrane.

Lymphoid tissue of mucous membrane.—The stomachs of young persons sometimes present a mamillated aspect, due to little elevations of the surface, produced by local accumulations of lymphoid tissue, somewhat resembling the solitary follicles of the intestine. These lymphoid accumulations, which are most numerous near the junction of the stomach and small intestine (Watney), are situated amongst the glands, and do not extend into the submucous tissue; they are not so distinctly circumscribed as those of the intestine, but fade off into the surrounding retiform tissue. They vary in development in different individuals, and are sometimes not found.

Vessels and nerves.—The stomach is a highly vascular organ. Its arteries, derived from all three divisions of the cœliac axis, are conveyed to it between the folds of the peritoneum, and form, by anastomosis, two principal arterial arches, which are placed along its two curvatures. The branches of these pass through the muscular coat (to which they give off some arterioles) into the submucous areolar

FIG. 774.—PLAN OF THE BLOOD-VESSELS OF THE MUCOUS MEMBRANE OF THE STOMACH. (Modified from Brinton.)

a, small arteries passing to break up into the fine capillary network, *d*, between the glands; *b*, coarser capillary network around the mouths of the glands; *c*, *c*, veins passing vertically downwards from the superficial network; *e*, larger vessels in the submucosa.

FIG. 775.—LYMPHATICS OF THE HUMAN GASTRIC MUCOUS MEMBRANE, INJECTED. (Lovén.)

The glands are only faintly indicated; *a*, muscularis mucosæ; *b*, plexus of fine vessels at base of glands; *c*, plexus of larger valved lymphatics in submucosa.

tissue, where they freely anastomose, and whence they are distributed to the mucous membrane and to the muscular layers (fig. 773). The terminal arterial branches (fig. 774, *a*) which enter the mucous membrane are spirally coiled in its deeper part. Hence they pass between the tubules, ramifying freely in a radial manner and forming a plexus (*d*) of fine capillaries upon the walls of the tubules; this plexus passes superficially into a coarser capillary network around the mouths of the glands. The veins, fewer in number than the arteries, arise from the latter network, and take an almost straight course (*c*, *c*) through the mucous membrane between the glands; they join to form a plexus of larger vessels near the bases of the glands. From this plexus branches pass off, which, after piercing the muscularis mucosæ and forming a wide venous plexus in the submucous tissue, return the blood into subserous vessels which carry it into the splenic and superior mesenteric veins, and also directly into the vena portæ. The gastric veins, as well

as other tributaries of the vena portæ, have a particularly well-marked muscular coat and contain numerous valves (Hochstetter).

The **lymphatics** are very numerous. As shown by Lovén, they arise in the mucous membrane (fig. 775) as a dense network of lacunar spaces, situated between and amongst the gland-tubuli, which, as well as the blood-vessels, in many parts they enclose in sinus-like dilatations. Near the surface of the membrane the lymph is collected into vessels which form loops or possess dilated extremities: these vessels are less superficial than the blood-capillaries. At the deeper part of the mucous membrane the interglandular lymphatics pass into a plexus of fine vessels (fig. 775, *b*), immediately underlying the tubular glands; then piercing the muscularis mucosæ (*a*), they form a coarser, more deeply seated network (*c*) in the submucous coat, the vessels of this network being provided with valves. Thence efferent lymphatics proceed, and, piercing the muscular coat, between the layers of which is another plexus, they follow the direction of the blood-vessels beneath the peritoneal investment, and traverse lymphatic glands found along the two curvatures of the stomach.

The **nerves**, which are large, consist of the terminal branches of the two vagi, and of offsets from the sympathetic system, derived from the solar plexus. The left pneumogastric nerve descends on the front, and the right upon the back of the stomach; both nerves are here composed almost entirely of non-medullated nerve-fibres. Numerous small ganglia have been described by Remak and others on both the vagal and sympathetic twigs. The nerves form gangliated plexuses, both between the layers of the muscular coat and in the submucous coat. From these plexuses nerve-fibrils proceed to the muscular tissue and to the mucous membrane.

The pylorus.—While there is no special apparatus at the cardiac orifice of the stomach for closing the passage from the œsophagus, the opening at the pyloric end, leading from the stomach into the duodenum, is provided with a sphincter muscle. On looking into the pyloric end of a distended stomach, the mucous membrane is seen projecting in the form of a circular fold, called the *pylorus*, leaving a correspondingly narrow opening. Within this fold are circular muscular fibres, belonging to the general system of circular fibres of the alimentary canal, which are here collected in the form of a strong band, whilst the longitudinal muscular fibres and the peritoneal coat pass over the pyloric fold to the duodenum, and do not enter into the formation of the sphincter (fig. 776). Externally the pylorus may be easily felt, like a thickened ring, at the right end of the stomach, where also a slight external constriction is visible.

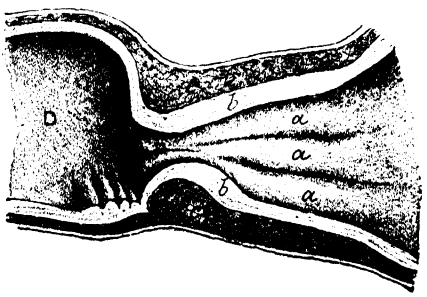


FIG. 776.—SECTION THROUGH PYLORIC PART OF STOMACH AND COMMENCEMENT OF DUODENUM FROM A SPECIMEN HARDENED IN SITU. (J. Symington.) Natural size.

a, *a*, *a*, longitudinal folds of the mucous membrane in pyloric part of stomach; *b*, section of mucous membrane; *c*, circular muscular fibres of stomach, the longitudinal fibres are just visible to the naked eye as a narrow line external to the circular fibres; D, duodenum; P, pyloric orifice.

The following articles on the structure of the stomach and its glands (including the œsophageal glands of amphibia) may be referred to: Aufschnaiter, Wiener Sitzungsb. ciii. 1894 (muscular coat); Bensley, Amer. Journ. Anat. ii. 1902; Disse, Arch. f. mikr. Anat. lxiii. 1903 (blood-vessels), and *ibid.* lxxviii. 1911 (lymphatics); v. Ebner in Kölliker's Handbuch der Gewebelehre, 1902; Edelmann, Deutsche Zeitschr. f. Thiermed. xv. 1889, and Inaug. Diss. Rostock, 1889 (glands of cardia); C. Golgi, Arch. ital. di biol. xix. 1893 (secretory canaliculi); M. Greenwood, Journ. Physiol. v. 1884 (changes in gland-cells); Gubaroff, Arch. f. Anat.

1886 (cardiac orifice); G. Haane, Arch. f. Anat. 1905 (glands of cardia); E. Hamburger, Arch. f. mikr. Anat. xxxiv. 1889 (leucocytes in parietal cells); R. Heidenhain in Hermann's Handbuch der Physiologie, v. 1883; A. Hopffe, Arch. f. Anat. 1910 (glands of cardia); Jouvenal, Journ. de l'anat. et de physiol. 1906 (crypts of Lieberkühn); Marie Kaufmann, Anat. Anz. xxviii. 1906 (parietal cells in pyloric region); Kupffer, Festschr. d. ärztl. Ver. München, 1883 (glands of cardia); J. N. Langley, Phil. Trans. 1881 (changes in gland-cells); Langley and Sewall, Proc. Roy. Soc. 1879, and Journ. Physiol. ii. 1879 (changes in gland-cells); A. Liebert, Anat. Hefte, xxiii. 1904 (fundus glands of monkey); F. P. Mall, Johns Hopkins Hospital Rep. i. 1890 (blood-vessels); R. Metzner in Nagel's Handbuch der Physiologie, 1906; E. Müller, Biol. förens. Förhandl. iv. 1891–2, and Om inter- och intra-cell. Körtelgånger, Stockholm, 1894 (secretory canaliculi); Noll and Sokoloff, Arch. f. Physiol. 1905 (changes in gland-cells); Nussbaum, Arch. f. mikr. Anat. xiii. 1877 (glands of pylorus); Oppel, Vergl. mikr. Anat. d. Wirbelthiere, 1896; Rollett in Stricker's Handbuch der Gewebelehre, 1871; Schaffer, Wiener Sitzungsb. cvi. 1897; Zimmermann, Arch. f. mikr. Anat. lii. 1898 (gland-cells and secretory canaliculi).

THE SMALL INTESTINE.

The small intestine commences at the pylorus, and, after many convolutions, terminates in the large intestine. Its average length in the adult is about 22 feet; it becomes gradually narrower from its upper to its lower end.

The first ten or twelve inches immediately succeeding to the stomach, comprising the widest and most fixed part of the tube, is called the *duodenum*. The remainder, which is arbitrarily divided into an upper two-fifths called the *jejunum*, and a lower three-fifths called the *ileum*, is much convoluted and movable, being connected with the posterior abdominal wall by a long and extensive fold of peritoneum called the mesentery, and by numerous blood-vessels and nerves. Although there is no distinct line of demarcation between the jejunum and the ileum, yet the portion of the small intestine included under these two names gradually undergoes certain changes in structure and appearance from above downwards, so that the upper end of the jejunum can readily be distinguished from the lower part of the ileum.

The small intestine, like the stomach, is composed of four coats, viz. serous or peritoneal, muscular, areolar, and mucous.

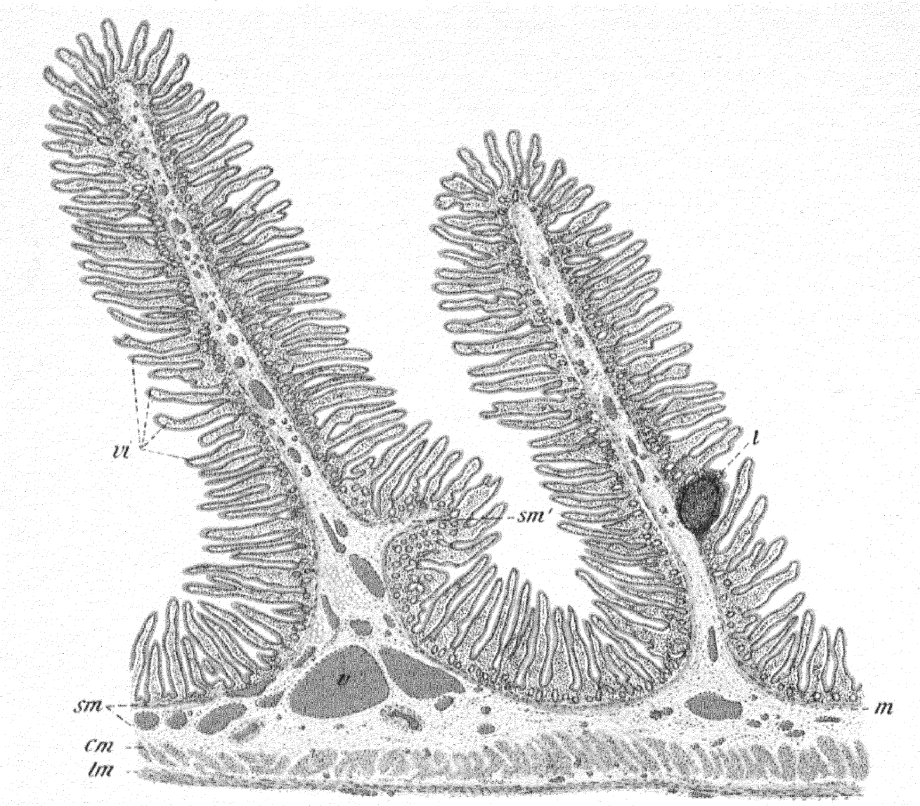
The external or **serous coat** almost entirely surrounds the intestinal tube over the whole extent of the jejunum and ileum, leaving only a narrow interval behind, where it passes off and becomes continuous with the two layers of the mesentery. The line at which this takes place is named the *attached* or *mesenteric border* of the intestine, the opposite border being known as the *free border*. The duodenum is but partially covered by peritoneum.

The **muscular coat** consists of two layers of fibres, an outer longitudinal, and an inner circular set. The fibres are disposed in bundles, with connective tissue between the bundles. The *longitudinal* fibres constitute an entire but comparatively thin layer, and are most obvious along the free border of the intestine. The *circular* layer is thicker and more distinct.

The muscular tunic becomes gradually thinner towards the lower part of the small intestine. It is pale in colour, and is composed of plain muscular tissue, the cells of which are of considerable length. There is a gangliated plexus of nerve-fibres and a network of lymphatic vessels between the two muscular layers.

The **submucous coat** of the small intestine is a layer of areolar tissue of loose texture, which is connected more firmly with the mucous than with the muscular coat. Within it the blood-vessels ramify before passing to the mucous membrane. It also contains a gangliated plexus of nerve-fibres and a network of large lymphatic vessels.

The **mucous membrane** is formed of reticular tissue, containing many lymph-corpuscles, and extended towards the intestinal cavity in the form of villi.



Longitudinal section of human jejunum passing through two valvulae conniventes (Sobotta). Magnified 15 diameters. Haematoxylin-eosin.

vi, villi; *l,* lymphoid nodule; *m,* muscularis mucosae; *sm,* submucosa; *sm',* process of submucosa from valvula connivens; *v,* veins of submucosa; *cm,* circular muscular layer; *lm,* longitudinal muscular layer.

It is bounded at the free surface by columnar epithelium, which also covers the villi and is invaginated into the numerous small tubular glands opening on to the surface (fig. 777). Next to the submucous coat it is terminated by a thin double layer (inner circular and outer longitudinal) of plain muscular fibres—the *muscularis mucosæ*—which sends prolongations towards the surface between the glands and into the villi. The elastic fibres of the mucous membrane form a close reticulation over the muscularis mucosæ (Mall).

The mucous membrane is characterised by the finely flocculent or shaggy appearance of its inner surface, resembling the pile upon velvet. This appearance is due to the surface being thickly covered with the minute processes named *villi*. It is one of the most vascular membranes in the body. In the fresh condition it is of a reddish colour in the upper part of the small intestine, but is paler, and at the same time thinner, towards the lower end.

The mucous membrane, in addition to small effaceable folds or rugæ, possesses also permanent folds, which cannot be obliterated, even when the tube is forcibly distended. These permanent folds are the *valvulæ conniventes* or *valves of Kerkring*. They are crescentic projections of the mucous membrane, placed transversely to the axis of the bowel and following one another closely (fig. 778, and accompanying Plate). The majority do not extend more than about one-half or two-thirds round the interior of the tube, but it has been shown by Brooks and Kazzander that some form complete circles, and others spirals. The spiral forms may occur singly or in groups of two or three. They generally extend a little more than once round the bowel, but in rare cases may

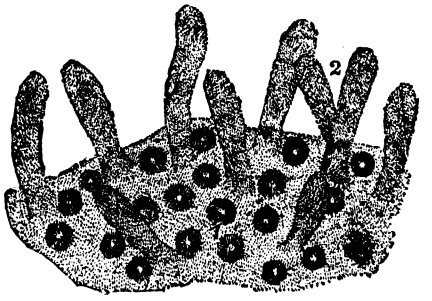


FIG. 777.—SMALL PORTION OF THE SURFACE OF THE MUCOUS MEMBRANE OF THE SMALL INTESTINE. (Rauber.) Magnified 30 diameters.

1, mouths of crypts of Lieberkühn; 2, villi.

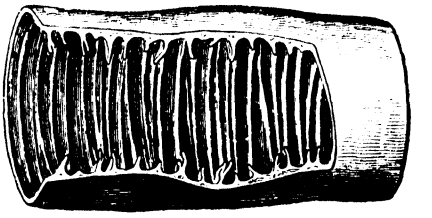


FIG. 778.—PORTION OF SMALL INTESTINE DISTENDED WITH ALCOHOL AND LAID OPEN TO SHOW THE VALVULÆ CONNIVENTES. (Brinton.)

go round two or three times. At their highest point the valves project inwards for about a third of an inch. Some of the valvulæ conniventes are bifurcated at one or both ends; others terminate abruptly. Each consists of a fold of mucous membrane, that is, of two layers placed back to back, united closely by submucous areolar tissue. They contain no part of the circular or longitudinal muscular coats. Being extensions of the mucous membrane, they serve to increase the absorbent surface to which the food is exposed.

The valvulæ conniventes are not uniformly distributed over the various parts of the small intestine. There are none quite at the commencement of the duodenum; a short distance from the pylorus they begin to appear; beyond the point at which the bile and pancreatic juice are poured into the duodenum they are very large, regularly crescentic in form, and placed so near to each other that the intervals between them are not greater than the breadth of one of the valves; they continue thus through the rest of the duodenum and along the upper half of the jejunum; below that point they begin to get smaller and farther apart, and finally, towards the middle or lower end of the ileum, having gradually become more irregular and

indistinct, sometimes even acquiring a very oblique direction, they altogether disappear.

The **villi,** peculiar to the small intestine, and giving to its internal surface the velvety appearance already spoken of, are small processes of the mucous membrane, which are closely set on every part of the inner surface, over the valvulæ conniventes, as well as between them.

Their length varies from 0·5 mm. to 0·7 mm., or sometimes more. They are

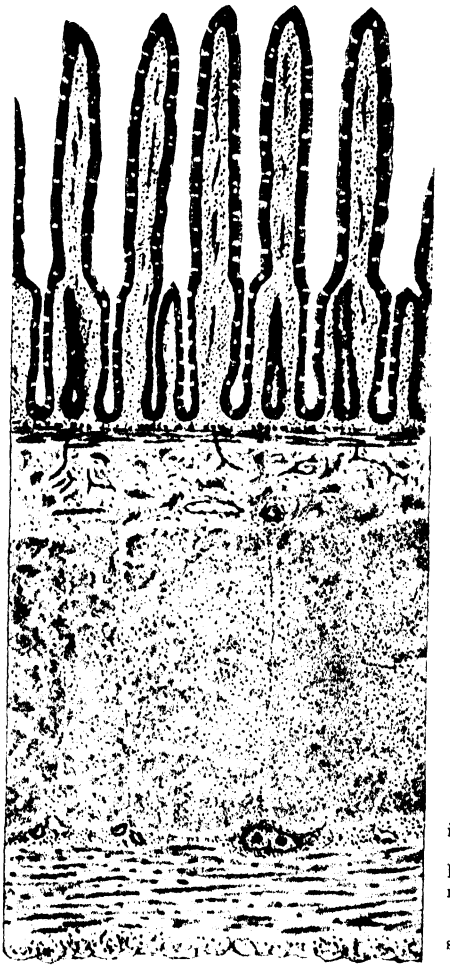


FIG. 779.—SECTION OF JEJUNUM OF CAT PARALLEL WITH THE LONG AXIS OF THE INTESTINE. (Schäfer.) Magnified 40 diameters.

largest and most numerous in the duodenum and jejunum, and become gradually smaller and fewer in number in the ileum. According to Rauber, they are short and leaf-shaped in the duodenum, and as the gut is followed downwards they become gradually longer and thinner, being tongue-shaped in the jejunum, and filiform in the ileum.[1] Occasionally two or three are connected together at their base. In the upper part of the small intestine there are from 10 to 18 villi in a

[1] On modifications of the shape of the villi in animals, and its relation to the food, see Bujard, Verhandl. d. Anat. Ges., Anat. Anz. xxxii. 1908, and Internat. Monthly Journ. of Anat. and Physiol. xxvi. 1909. See also on types of villi, W. A. Hilton in Amer. Journ. Anat. i. 1902.

square millimetre, and in the ileum from 8 to 14 in the same space. It is estimated that there are about four millions altogether (W. Krause).

Chaput describes the villi as being so closely arranged as to be separated merely by narrow clefts into which the crypts of Lieberkühn open. This may be the case in the empty condition of the intestine, but when it is distended they are necessarily more separated from one another, as usually described.

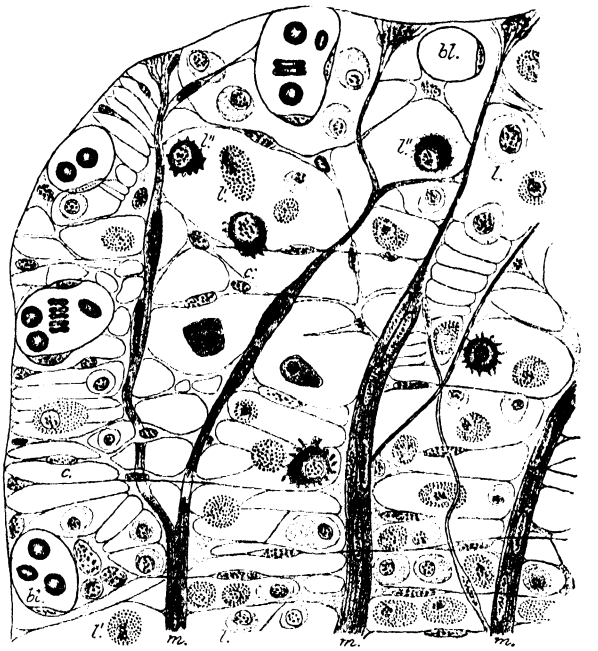


FIG. 780.—PART OF A SECTION THROUGH A VILLUS OF THE DOG. (R. Heidenhain.) Highly magnified.

m., plain muscle; *l.*, *l'.*, *l''.*, leucocytes, which are seen in large numbers in the interstices of the reticular tissue; *bl.*, vessels; *c.*, connective-tissue cells, covering the fibrils of the reticulum. The epithelium of the villus is not represented.

A villus consists of a prolongation of the proper mucous membrane. It is covered by columnar epithelium (fig. 779), and encloses a network of blood-vessels,

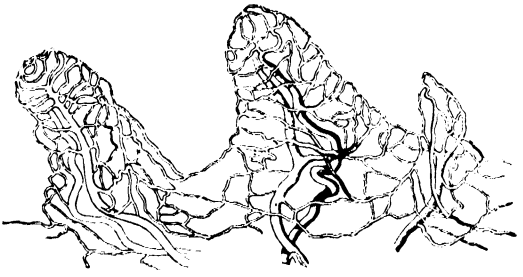


FIG. 781.—MAGNIFIED VIEW OF THE BLOOD-VESSELS OF THE INTESTINAL VILLI. (Sharpey.)

The drawing was taken from a preparation injected by Lieberkühn, and shows, belonging to each villus, a small artery and vein with the intermediate capillary network.

one or more lymphatic vessels (lacteals), and a few longitudinal plain muscular fibres, these being all supported and held together by reticular tissue (fig. 780). Under the epithelium is a basement-membrane composed of a condensation of the reticular tissue covered by flattened cells; these cells are on the one hand connected

with the branched cells of the reticular tissue, and on the other hand send processes between the epithelium-cells. Nerve-fibrils penetrate into the villi from the plexus of Meissner, and form arborisations throughout their whole substance (fig. 806). Each villus receives, as a rule, one small arterial twig, which runs from the submucous coat through the muscularis mucosæ to the base of the villus, and then up the centre to near the middle of the villus, where it begins to break up into a number of capillaries (fig. 781). These form near the surface, beneath the epithelium and limiting membrane, a fine capillary network (fig. 782) from which the blood is returned for the most part by one or two venules, which in man commence near the tip of the villus, and pass down to its base to join the venous plexus of the mucous membrane, whence the blood is conveyed to the large veins of the submucosa. The general arrangement of the vascular supply of the villi varies considerably in different animals.

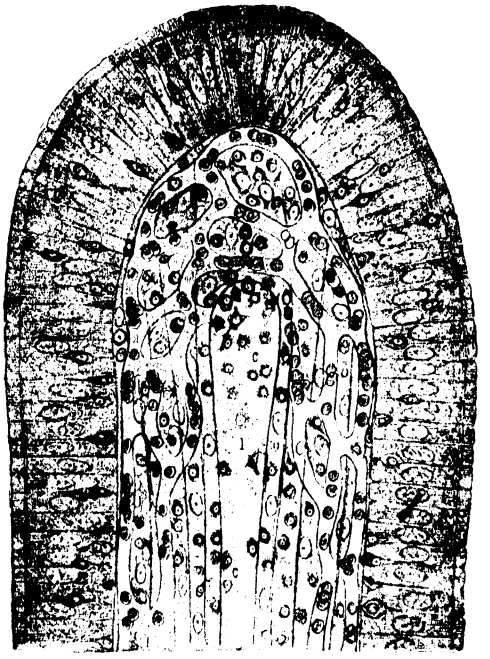


FIG. 782.—LONGITUDINAL SECTION OF VILLUS OF RAT, KILLED DURING ABSORPTION OF FOOD. (Schäfer.)

Numerous leucocytes are seen between the columnar epithelium-cells, within the reticulum of the villus and in the upper part of the lacteal, within which some of them are becoming disintegrated.

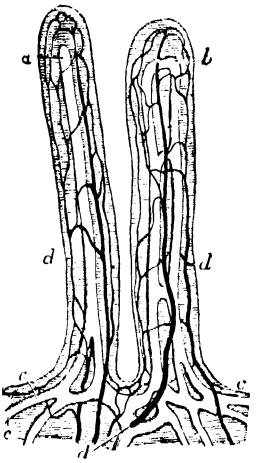


FIG. 783.—INJECTED LACTEAL VESSELS IN TWO VILLI OF THE HUMAN INTESTINE. (Teichmann.) Magnified 100 diameters.

The lacteals are represented as filled with white substance and the blood-vessels with dark. *a*, *b*, the lacteal vessels, single in one villus and double in the other; *c*, the horizontal lacteal vessels with which those of the villi communicate; *d*, the blood-vessels, consisting of small arteries and veins with capillary network between.

A lacteal lies in the centre of each villus (figs. 782, 783, 784, 785, 786), and is in the smaller villi usually a straight vessel, with a closed and somewhat expanded extremity, and of considerably larger diameter than the blood-capillaries of the part. According to the observations of Teichmann, there are sometimes two (never more) intercommunicating lacteals in a single villus in the human subject (fig. 783, *b*); but both he and Frey found a copious network in the villi of the sheep. Like the lymphatics elsewhere, the lacteals in the villi are bounded by a delicate layer of endothelial cells. These are connected with the branched cells of the reticular tissue of the villus, and these again with the flattened cells which help to form the basement-membrane.

The muscular tissue within the villus was discovered by Brücke ; it consists of small bundles of plain fibre-cells disposed longitudinally around the lacteal ; on being stimulated in the living condition it produces an obvious retraction of the villus. This muscular tissue is a prolongation from the muscularis mucosæ. The fibre-cells at the sides and towards the end of the villus pass from the lacteal to be attached to the basement-membrane (fig. 780, *m.m.*) ; usually their attachment to this is forked (Watney). There is considerable variation in different animals in the amount and distribution of muscle-fibres in the villi (see figs. 785, 786).[1]

Columnar epithelium-cells (fig. 782 and figs. 785 to 788) cover not only the villi but also the rest of the surface of the intestine, and extend into the tubular glands. Their general characters have already been described under ' Epithelium ' (pp. 85 to 88).[2] The cells are set upon the surface of the basement-membrane, often by a somewhat flattened extremity. There is never any continuity between their attached extremity and the branched corpuscles of the retiform tissue of the villus, such as has often been supposed to exist ; on the contrary, the epithelium separates with the greatest readiness from the subjacent tissue, and almost always with a simple truncated extremity, sometimes pitted but never much branched. Between the epithelium-cells are leucocytes in variable number, but most numerous in the lower part of the intestine and near the lymphoid nodules. They are often seen in considerable numbers between the columnar cells and the basement-membrane.

Amongst the ordinary epithelium-cells are mucus-secreting cells (fig. 789), the outer half of which is filled with mucigen; in some this has become discharged as mucus from the cell, and the free end is ruptured (*goblet-cells*, figs. 790, 791). The number of cells secreting mucus varies much in different animals, and perhaps under different conditions in the same animal. There are comparatively few in the glands of the small intestine.

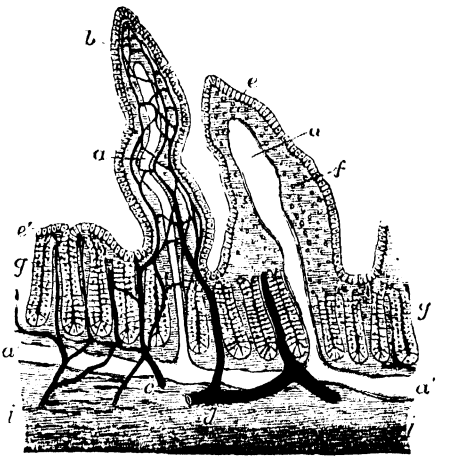


FIG. 784.—VERTICAL SECTION OF THE INTESTINAL MUCOUS MEMBRANE OF THE RABBIT. (Slightly altered from Frey.) Magnified 150 diameters.

Two villi are represented, in one of which the dilated lacteal alone is shown, in the other the blood-vessels and lacteal are both seen injected, the lacteal white, the blood-vessels dark; *a*, the lacteal vessels of the villi; *a'* horizontal lacteal, which they join; *b*, capillary blood-vessels in one of the villi; *c*, small artery; *d*, vein; *e*, the epithelium covering the villi; *g*, tubular glands or crypts of Lieberkühn, some divided down the middle, others cut more irregularly; *i*, the submucous layer.

In addition to their secretory function the epithelial cells are the primary agents in promoting the absorption of digested food-materials from the interior of the gut, and the seat of some of the processes of metabolism which the products of digestion undergo during absorption. Most food-materials cannot be traced in microscopic specimens, but fats, from their insolubility in the watery cell-contents and their property of becoming stained with certain dyes, can be to some extent followed. Fats appear to be absorbed only after having been broken down into fatty acid and

[1] On the muscular tissue of the villi see Trautmann, Anat. Anz. xxxiv. 1909. Other details relating to the structure of the small intestine will be found in the Dissertation of the same author, Zurich, 1907.

[2] On the special structure of the intestinal epithelium see Kulschitzky, Arch. f. mikr. Anat. xlix. 1897, and M. Heidenhain, Plasma und Zelle, 2te Lieferung, 1911.

glycerine and to be built up again within the epithelium-cells. The examination of specimens taken during digestion of a meal containing fat shows this substance within the cells in the form at first of very fine particles mainly near the free end of the cell (fig. 792, A). The fine particles gradually enlarge and run together into droplets (fig. 792, B), and these are passed towards the fixed end of the cell, there again becoming finer. Eventually the fine particles pass out of the epithelium-cells, and the leucocytes within the tissue of the villus may now contain them in

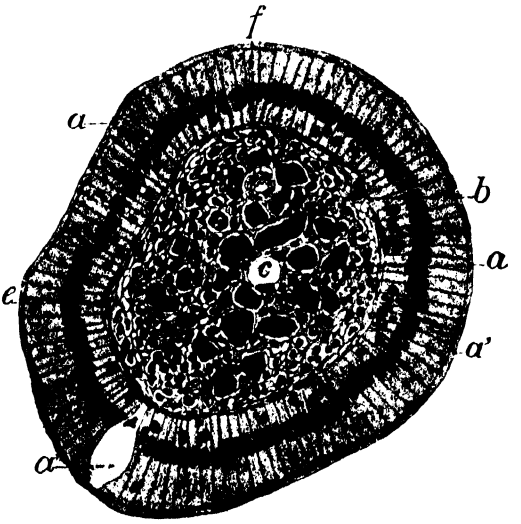


FIG. 785. TRANSVERSE SECTION OF A VILLUS OF PIG. (Trautmann.)

a, epithelium: *a'*, striated border; *a''*, goblet-cell; *b*, lymphoid tissue; *c*, small central lacteal; *e*, plain muscle-fibres cut transversely; *f*, section of arteriole.

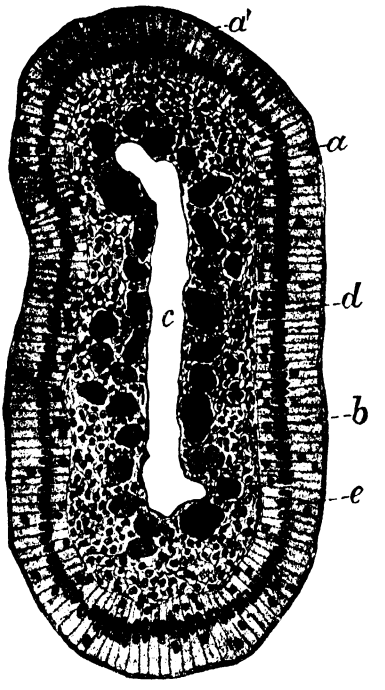


FIG. 786.—TRANSVERSE SECTION OF A VILLUS OF OX. (Trautmann.)

a, epithelium; *a'*, striated border; *b*, lymphoid tissue; *c*, large central lacteal; *e*, plain muscle-fibres cut across.

considerable amount. Still later they are seen within the central lacteal (fig. 793). It is probable that these leucocytes, which are found abundantly within the tissue

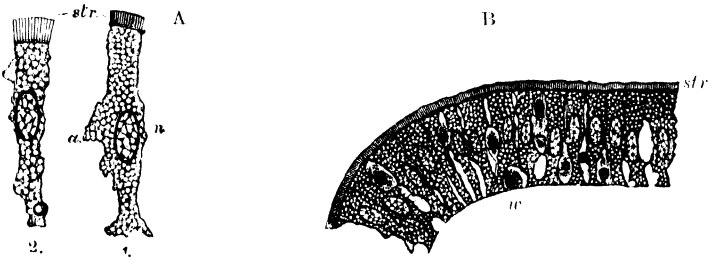


FIG. 787.—COLUMNAR EPITHELIUM-CELLS OF THE RABBIT'S INTESTINE. (Schäfer.)

A. Two cells isolated after maceration in very weak chromic acid. They are much vacuolated, and one of them (2) has a fat-globule attached near its end; the striated border (*str.*) is well seen, and the bright disc separating this from the cell-protoplasm; *n*, nucleus with intranuclear network; *a*, a thinned-out wing-like projection of the cell which probably fitted between two adjacent cells.

B. A row of columnar cells from an intestinal villus of the rabbit. *str*, striated border; *w*, smaller cells of the nature of lymph-corpuscles, between the epithelium-cells.

of the villus, and even amongst the epithelium-cells of the surface, play an important part in the transference of the fat-particles, and perhaps of other

food-substances, from the epithelium-cells to the lacteal. For, as just stated, they contain at certain stages of fat-absorption abundant fatty particles. In the

FIG. 788.—A COLUMNAR EPITHELIUM-CELL, SHOWING MASS OF FIBRILS (CYTOMITOME) WITHIN THE CYTOPLASM. (M. Heidenhain.)

FIG. 789.—A GOBLET OR MUCUS-SECRETING CELL IN COLUMNAR EPITHELIUM. (M. Heidenhain.)

The centrosome is in the mucigen-mass. Part of an ordinary columnar cell is also shown.

transference of carbon particles in the lungs from the interior of the alveoli to the lymphatics, which is due to the activity of amœboid cells, we have an analogous process.

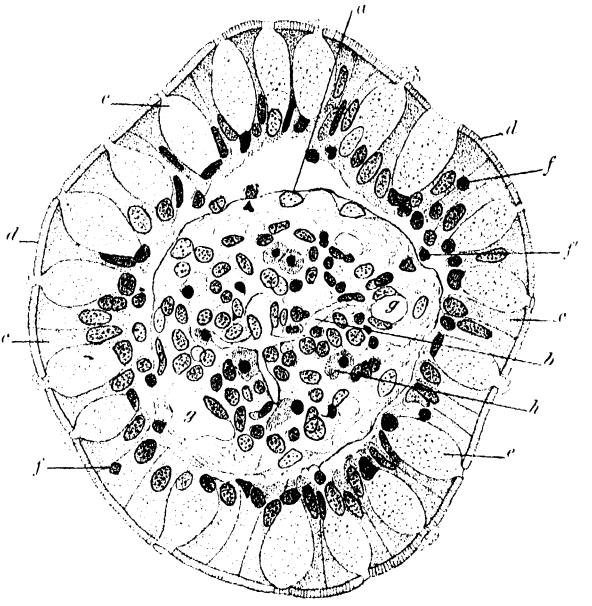


FIG. 790. —TRANSVERSE SECTION OF A VILLUS (MAN), SHOWING NUMEROUS GOBLET-CELLS BETWEEN THE ORDINARY COLUMNAR CELLS. (v. Ebner.) Magnified 530 diameters.

a, basement-membrane, which, along with the reticular tissue of the villus, is somewhat shrunken away from epithelium; *b*, lacteal; *c*, columnar epithelium; *d*, its striated border; *e*, goblet-cells; *f*, leucocytes in epithelium; *f'*, leucocytes below epithelium; *g*, blood-vessels; *h*, muscle-cells, cut across.

In some animals the passage of fat from the epithelium-cells to the lacteals appears to take place in a different manner. For example, in puppies fed on milk

darkly stained streaks may be seen (in osmic preparations) extending from the inter-epithelial spaces to the borders of the central lacteal.

It was denied by R. Heidenhain that the leucocytes of the intestine contain fatty particles during fat-absorption; he stated that the particles within them which are stained black by

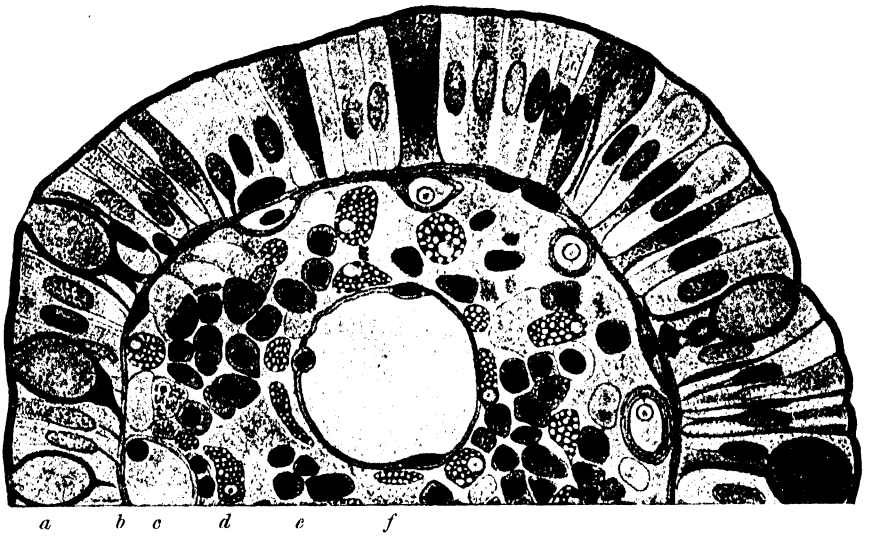


FIG. 791.—PART OF A TRANSVERSE SECTION OF A VILLUS OF GUINEA-PIG. (R. Heidenhain.)

a, columnar epithelium, with goblet-cells between the ordinary cells; *b*, basement-membrane; *c* section of a capillary blood-vessel; *d*, a phagocytic leucocyte; *e*, a group of plain muscle-cells, cut across; *f*, central lacteal.

osmic acid are not fatty, but albuminous, being insoluble in ether. This is not, however, strictly correct. Many of the particles which the lymph-cells contain during fat-absorption unquestionably dissolve in ether and other solvents of fat, although some particles remain undissolved by those reagents. These particles may be of an albuminous nature, or they may still be fatty,

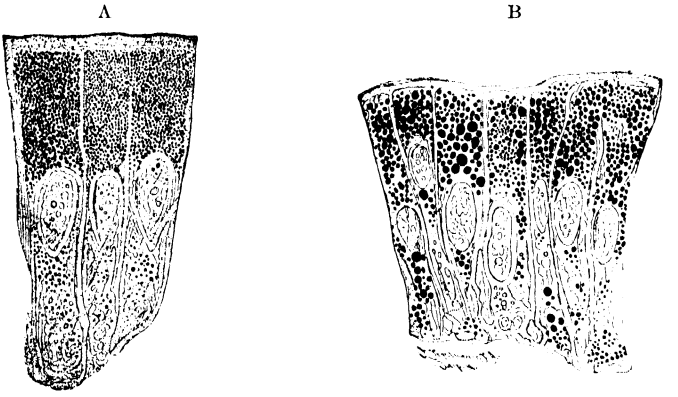


FIG. 792.—TWO STAGES IN THE DEPOSITION OF FAT IN THE INTESTINAL EPITHELIUM OF THE FROG. (Krehl.)

but so modified by the action of the osmic acid as to have been rendered relatively insoluble in ether. In the frog, where absorption proceeds more slowly, and can be more easily traced, no fat is to be seen anywhere but in the epithelium-cells, in the leucocytes, and in the lacteals (fig. 793). In the guinea-pig also, as Heidenhain himself showed, there are many phagocytic leucocytes (fig. 791, *d*), which take up the whole of the absorbed fat after it has traversed

the epithelium.[1] In some animals absorption may take place so rapidly that the absorbed fat, after being finely divided and modified in the epithelium-cells, may be set free between them

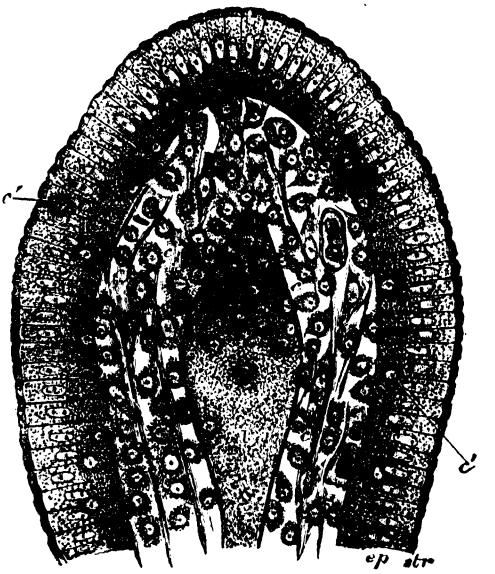


FIG. 793.—SECTION OF PART OF A RAT'S VILLUS DURING ABSORPTION OF FAT. (Schäfer.) Osmic-acid preparation. Highly magnified.

ep, epithelium-cells, containing fatty particles; *str*, striated free border; *c*, lymph-corpuscles in the tissue of the villus, containing fatty particles; *c'*, others between the epithelium-cells; *l*, central lacteal, containing chyle and disintegrating leucocytes.

without all being immediately taken up by leucocytes. Eventually, however, most of it appears to be removed by these cells. The agency of the epithelium-cells in fat-absorption has been

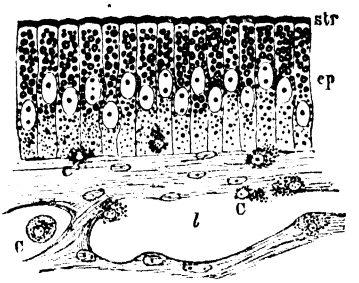


FIG. 794.—SECTION OF FROG'S INTESTINE DURING ABSORPTION OF FAT. (Schäfer.) Osmic-acid preparation. Highly magnified.

ep, epithelium; *str*, its striated border; *l*, lacteal; *c*, *c*, lymph-corpuscles containing fine fatty particles. The fatty particles in the epithelium-cells are coarse in the peripheral and fine in the central zone of each cell.

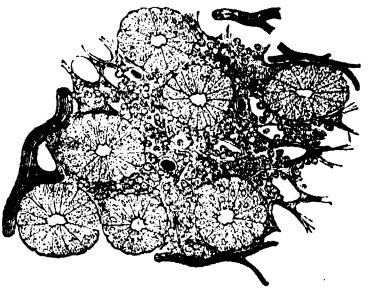


FIG. 795.—SECTION OF THE MUCOUS MEMBRANE OF THE SMALL INTESTINE ACROSS THE CRYPTS OF LIEBERKÜHN. (Rauber.) Magnified 200 diameters.

(The blood-vessels had been injected in this preparation.)

altogether denied (Watney, Zawarykin), but on insufficient grounds, for fat-particles are easily shown within those cells during absorption.

Secreting glands of small intestine.—Two kinds of small secreting glands open on the inner surface of the intestine, viz. the crypts of Lieberkühn and the glands of Brunner, the last being peculiar to the duodenum.

[1] R. Zipkin (Anat. Hefte, xxiii. 1903) also describes the numerous leucocytes in the villi of the monkey (Innuus rhesus) as being phagocytic.

The simple tubular glands of the intestine or **crypts of Lieberkühn** are formed by invagination of the general surface of the mucous membrane, and dip into its thickness. The invagination carries with it the layer of epithelium. Between the glands is the reticular tissue of the mucous membrane, containing many lymph-corpuscles (fig. 795); this tissue is condensed into a basement-membrane for each gland. The epithelium-cells of the glands are

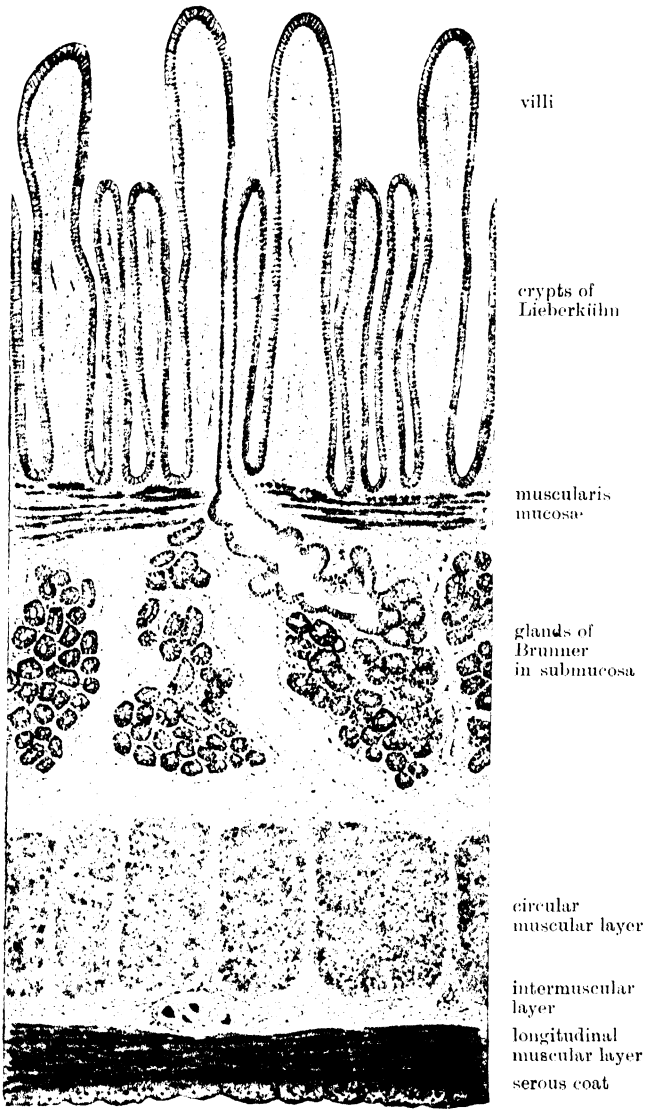


FIG. 796.—SECTION OF DUODENUM OF CAT. (Schäfer.) Magnified about 60 diameters.

of the same character as those covering the general surface of the intestine. The invagination is slightly enlarged at the blind end (fundus), and here, in the small intestine of some animals, including man, occur special cells with distinct secretion-granules, first described by Paneth, and known by his name.[1] Most of

[1] According to S. Klein (Amer. Journ. Anat. v. 1906) the granule-containing cells are not found in carnivora, but are present in insectivora. The granules are not mucinogen, as Bizzozero had supposed to be the case. See also Trautmann, Arch. f. mikr. Anat. lxxvi. 1910.

the epithelium-cells of the glands are columnar, with characteristic striated border: these may perhaps be concerned with absorption, like those which cover the villi. This supposition does not positively exclude their participation in the production of the succus entericus; indeed within the crypts of Lieberkühn absorption would only be possible on the assumption that the fluid products of digestion pass into the crypts. Scattered about amongst the columnar cells are goblet-cells (fig. 797), which are, of course, mucus-secreting: they are far more numerous in the crypts of the large than in those of the small intestine. Outside the epithelium is the basement-membrane, which has been already noticed: it does not exhibit nuclei, although from the appearance of silver-nitrate preparations it has been described as composed of endothelial cells. Between the basement-membrane and the epithelium-cells of the gland and also here and there between these cells,

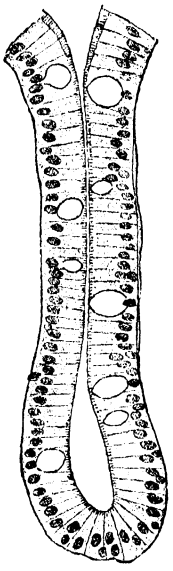


FIG. 797. — A CRYPT OF LIEBERKÜHN FROM THE HUMAN INTESTINE. (Flemming.)

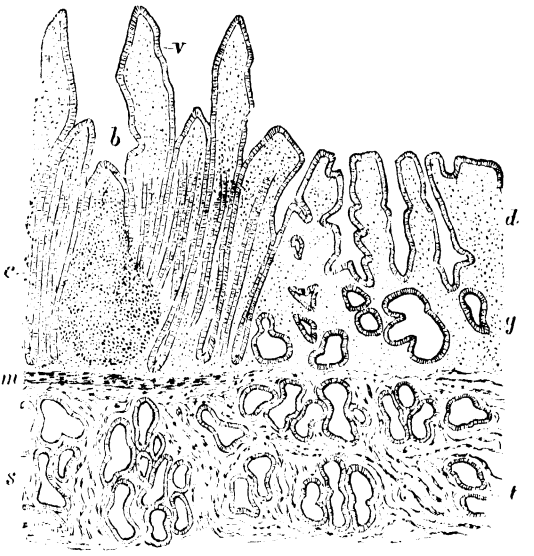


FIG. 798. — SECTION THROUGH THE COMMENCEMENT OF THE DUODENUM AT THE PYLORUS. (Klein.)

v, villi; *b*, apex of a lymphoid nodule; *c*, crypts of Lieberkühn; *m*, muscularis mucosæ; *s*, secreting tubes of Brunner's glands; *d*, ducts of pyloric glands of stomach; *g*, tubes of these glands cut across in mucous membrane; *t*, deeper-lying tubes situated in submucous tissue, and corresponding with Brunner's glands of the intestine.

leucocytes are frequently found, especially in glands of those parts of the mucous membrane which lie over and adjacent to Peyer's patches and solitary lymph-nodules.

It occasionally happens that the intestinal crypts are cleft, thus exhibiting a tendency to become compound. They vary in length from 0·2 to 0·3 mm. in man: they are longest in the duodenum.

Brunner's glands are small compound tubulo-racemose glands, which are found in the duodenum (fig. 796); they are most numerous at the upper end, occupying thickly a space extending from one to two inches beyond the pylorus. A few are said also to be found quite at the commencement of the jejunum. They are imbedded in the submucous coat (sometimes extending partly into the mucous membrane between the crypts of Lieberkühn), and may be exposed by dissecting off the muscular coat from the outside of the intestine. In structure they somewhat resemble the small glands found in various parts of the lining

membrane of the mouth and elsewhere, each consisting of a number of tubular alveoli, connected by the terminal ramifications of the duct; the latter penetrates the muscularis mucosæ, and opens upon the inner surface of the intestine, the opening being situated either between the crypts of Lieberkühn or more rarely at the base of a crypt (Schaffer). In sections through the pylorus the glands of Brunner appear like continuations of the pyloric glands of the stomach (fig. 798), but they are more complicated in structure and more deeply seated; moreover, their cells, which contain fine granules, do not yield the same ferments.[1] These glands are better developed in herbivora than in carnivora. In the latter they are found only close to the pylorus, in the former for a long distance down the gut.[2]

Lymphatic follicles of the small intestine.—The **solitary glands** are soft, white, rounded, and slightly prominent bodies 0·6 mm. to 3 mm. in diameter, which are found thinly scattered over the mucous membrane in all parts of the small intestine. They are found at the mesenteric as well as at the free border, both between and upon the valvulæ conniventes, and are rather more numerous in the lower portion of the bowel. These so-called "glands" are in structure similar to the lymph-follicles of various regions already described, consisting of clumps of dense reticular tissue, the meshes of which are closely packed with lymph-corpuscles and pervaded by fine capillaries. They are here and there united at the sides with the surrounding lymphatic tissue, but are at most points distinctly marked off from it, partly owing to the fact that their supporting reticular tissue becomes closer and finer, partly owing to their being surrounded by a rich plexus of lymphatic vessels; they may even hang, as it were, into a lymph (or lacteal) sinus which entirely surrounds the follicle, except next to the surface of the intestine. The epithelium over the follicle has often a very large number of lymph-corpuscles between the epithelial cells. The base of the follicle is situated in the submucous tissue; but the follicle extends upwards, through the muscularis mucosæ, into the mucous membrane, causing a bulging of the surface towards the interior of the gut (as in fig. 799). The prominent part of the follicle sometimes has villi upon it; placed around very irregularly are seen the mouths of the crypts of Lieberkühn.[3]

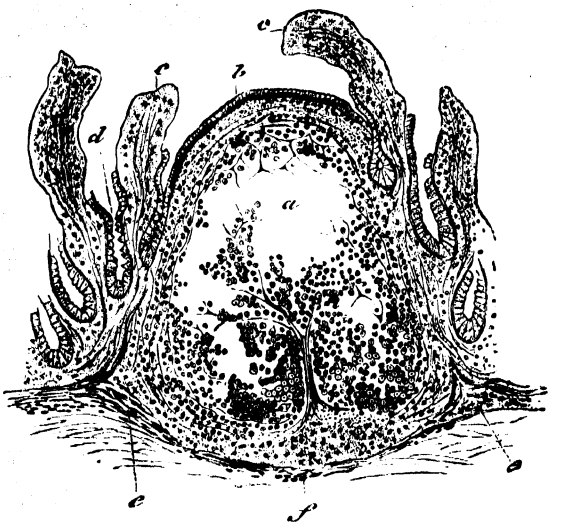


FIG. 799.—SECTION OF A SOLITARY GLAND OF THE SMALL INTESTINE. (Cadiat.)

c, *c*, villi, partially deprived of their epithelium; *d*, crypts of Lieberkühn; *a*, solitary gland composed of retiform lymphoid tissue, which has become partly broken away in preparing the section; *b*, epithelium covering the apex or cupola of the follicle; *e*, *e*, muscularis mucosæ; *f*, submucous coat.

[1] Bogomoletz (Arch. f. mikr. Anat. lxi. 1903) found the granules in the secreting cells increased as the result of protein diet. According to Oppel (Arch. f. mikr. Anat. lxxvi. 1910) some of the cells of Brunner's glands in man contain granules similar to the cells of Paneth of Lieberkühn's crypts. See also M. Kaufmann-Wolf, Anat. Anz. xxxix. 1911.

[2] Scheunert and Grimmer, Int. Monthly Journ. of Anat. and Physiol. 1906.

[3] On the development of the solitary glands see Stöhr, Arch. f. mikr. Anat. li. 1898.

The **agminated glands** or **patches of Peyer** (who described them in 1677) are groups or patches of lymph-follicles. The groups have an oblong figure

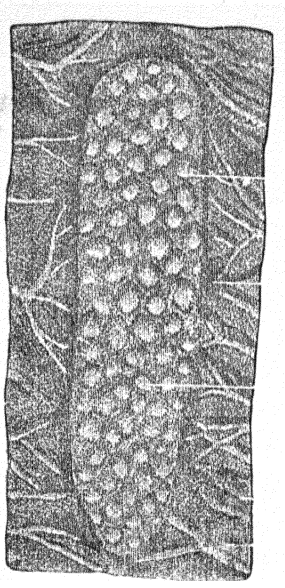


FIG. 800.—A SMALL PATCH OF PEYER'S GLANDS FROM THE ILEUM. (Boehm.) Slightly magnified.

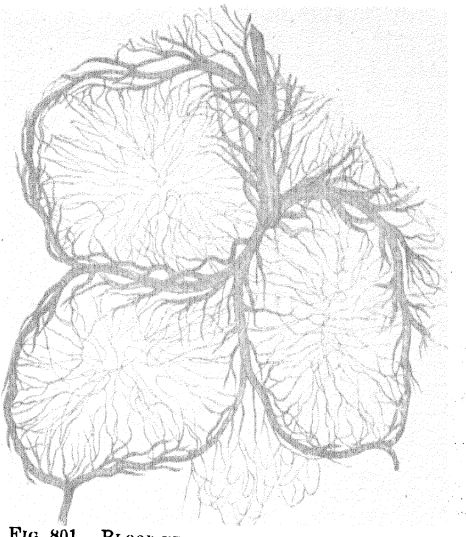


FIG. 801.—BLOOD-VESSELS OF A PEYER'S PATCH. (Kölliker.) Magnified.

The drawing was taken from a preparation made by Frey of the intestine of the rabbit. It represents the fine capillary network spreading from the surrounding blood-vessels into the interior of three lymph-follicles.

(fig. 800), and vary from half an inch to two or even four inches in length and from half an inch to about an inch in width (12 mm. to 100 mm. long and 12 mm. to

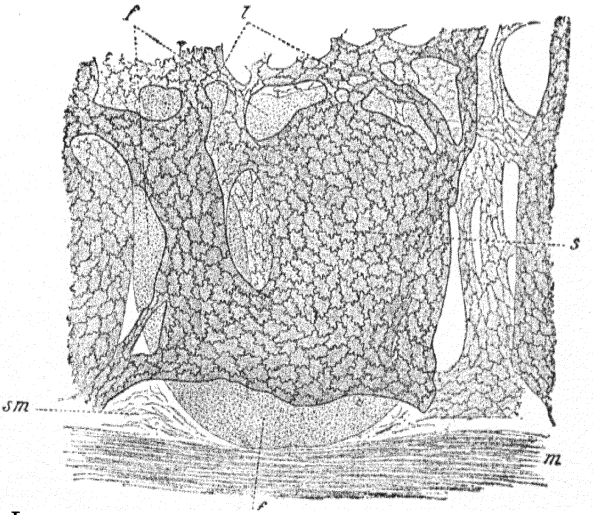


FIG. 802.—LYMPHATICS OF A PEYER'S PATCH. (Kölliker.) Silver-nitrate preparation.

l, lymphatics of mucous membrane; *s*, sinus-like lymphatics surrounding lymph-follicle, *f*; *sm*, submucosa; *m*, muscular coat.

25 mm. broad). They are placed lengthways in the intestine at that part of the tube most distant from the mesentery; hence, to obtain the best view of them, the bowel should be opened by an incision along its attached border.

The lymph-follicles which by their aggregation make up a Peyer's patch are in almost all respects similar to the solitary glands above described. As a rule, their surface is free from villi, and the crypts of Lieberkühn are collected in circles around them. Fine blood-vessels are distributed abundantly on the exterior of the follicles and give off still finer capillary branches, which, supported by the reticular tissue, are disposed principally in lines converging to the centre (fig. 801).

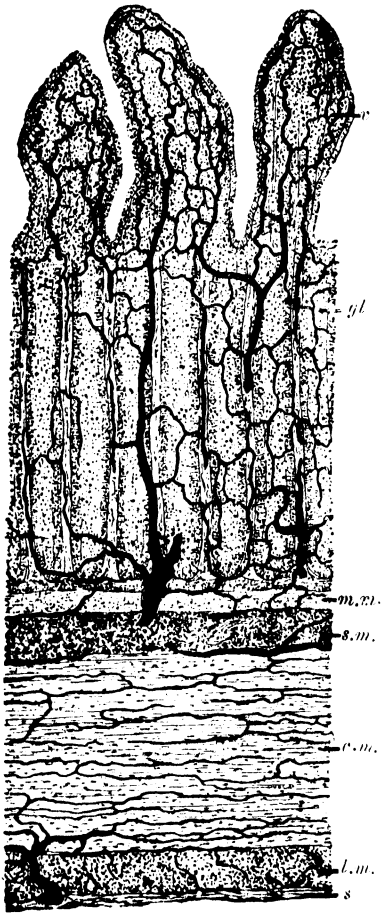


FIG. 803. — SECTION OF SMALL INTESTINE WITH BLOOD-VESSELS, INJECTED. (Heitzmann.)

v, villi; *gl*, glands; *m.m.*, muscularis mucosæ; *s.m.*, submucosa; *c.m.*, circular, and *l.m.*, longitudinal muscular layers; *s*, serous coat.

The lacteal plexuses, which are abundant in the whole extent of the intestine, are especially rich where they surround the follicles of Peyer's glands (fig. 802), often forming sinuses around them, as in the case of the solitary glands.

From twenty to thirty of these oblong patches may in general be found; but in young persons as many as forty-five have been observed. They are larger and placed at shorter distances from each other in the lower part of the ileum; but in its upper portion as well as in the lower end of the jejunum the patches occur less frequently, become smaller, and are of nearly circular form; they may, however, be discovered occasionally in the lower portion of the duodenum. Still smaller irregularly shaped clusters of lymph-follicles are sometimes found scattered throughout the intestine.

Peyer's patches are best marked in the young subject. After middle life they become less obvious, and they disappear almost completely in advanced age, their remains being often indicated by a dark coloration of the mucous membrane.

Blood-vessels of the small intestine.—The branches of the mesenteric artery, having reached the attached border of the intestine, pass round its sides, dividing as they pass into numerous branches, some of which anastomose at the free border. Most of the branches run at first under the serous coat, but they turn in one after the other at successive intervals and pass through the muscular coat into the submucosa, where they ramify abundantly (fig. 803). As they pierce the muscular coat they give off a few vessels to it, but this coat is mainly supplied by recurrent branches which come off the vessels in the submucosa. In the muscular coat the capillaries are arranged with oblong meshes parallel to the muscular bundles in the respective layers.

From the plexus of vessels in the submucosa arteries to the mucosa are given off, and piercing the muscularis mucosæ ramify in the mucous membrane near the base of the glands. From the ramifications arise capillaries which form a close network around the crypts of Lieberkühn, at the surface of the mucous membrane and within each villus, immediately below the basement-membrane. As already stated,

each villus as a rule receives its own small arterial branch. The venules arise near the surface of the mucous membrane and near the tips of the villi, and, gathering up the blood of the capillaries as they pass along, go straight through the muscularis mucosæ to enter a close venous plexus in the submucosa. This plexus also receives most of the venules from the muscular coat, and from it proceed efferent vessels which accompany the entering arterial branches towards the surface, where they run underneath the peritoneal coat towards the mesentery.[1]

Lymph-vessels.—The lymph-vessels of the small intestine—termed *lacteals*, from the milky appearance of their contents (chyle) during the absorption of food containing fat—are arranged in four networks, one in the mucosa, one in the submucosa, one between the two layers of the muscular coat, and the fourth underneath the serous coat. The vessels which form the network of the mucosa are mainly or

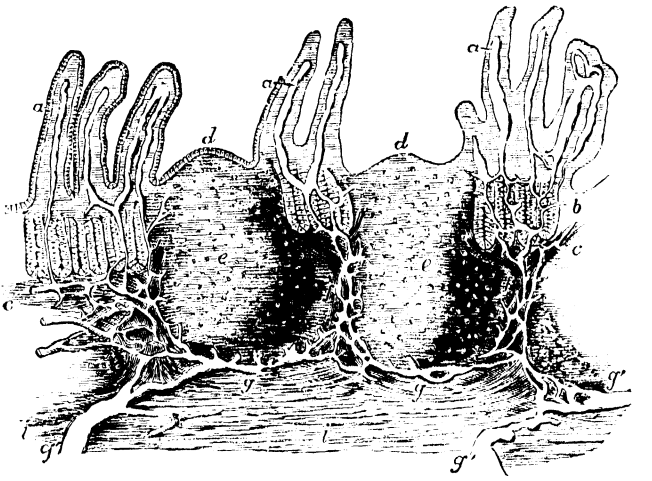


FIG. 804.—VERTICAL SECTION OF A PORTION OF A PATCH OF PEYER'S GLANDS WITH THE LACTEAL VESSELS INJECTED. (After Frey.) Magnified 32 diameters.

The specimen is from the lower part of the ileum; *a*, villi, with their lacteals left white; *b*, some of the tubular glands; *c*, the muscular layer of the mucous membrane interrupted by the lymph-nodules; *d*, cupola or projecting part of the nodule; *e*, central part; *f*, the reticulated lacteal vessels occupying the lymphoid tissue between the nodules, joined above by the lacteals from the villi and mucous surface, and passing below into *g*, the sinus-like lacteals under the follicles, which again pass into the large efferent lacteals, *g'*; *i*, part of the muscular coat.

entirely destitute of valves. They receive the lacteals of the villi (fig. 804), and are in communication with the network of larger valved vessels of the submucosa; the communication being especially free in the neighbourhood of the lymph-nodules which break through the muscularis mucosæ and are almost surrounded by sinus-like lymph-vessels. From the network in the submucosa efferent valved vessels pass through the muscular layers, receiving as they pass the lymph from the intramuscular network, and enter the subserous network. This, which is especially well developed at the attachment of the mesentery, conveys the lymph to the lacteals in the mesentery, which closely accompany the ramifications of the arteries and veins. These lacteals enter the large mesenteric glands near the back of the mesentery, and the efferent vessels from these glands convey the chyle to the receptaculum chyli and thoracic duct.

Besides the main lymphatic network between the two layers of the muscular coat (fig. 805), there are subsidiary networks within the layers, the vessels running in

[1] See on the blood-vessels of the small intestine F. P. Mall, Johns Hopkins Hosp. Bull. xi. 1900.

the connective tissue between the muscular bundles. These vessels of the muscular coat are in complete continuity on the one side with those of the submucosa, and on the other with those of the subserous layer.

Nerves.—The nerves of the small intestine are chiefly derived from the superior mesenteric plexus, which is formed by branches from the lower part of the cœliac plexus and the superior mesenteric ganglion, and also receives fibres from the right vagus nerve at its junction with the cœliac plexus. Most of its sympathetic fibres are originally derived from the great and small splanchnic nerves, which convey both motor and inhibitory impulses to the blood-vessels of the intestine, and others—mainly inhibitory—to the muscular coat, excitatory influences passing to this mainly by the vagi. The branches from the plexus to the intestine at first closely accompany the larger branches of the mesenteric vessels; they ramify along with these and communicate with one another in a plexiform manner. As they approach the intestine they leave the blood-vessels and pass to the gut

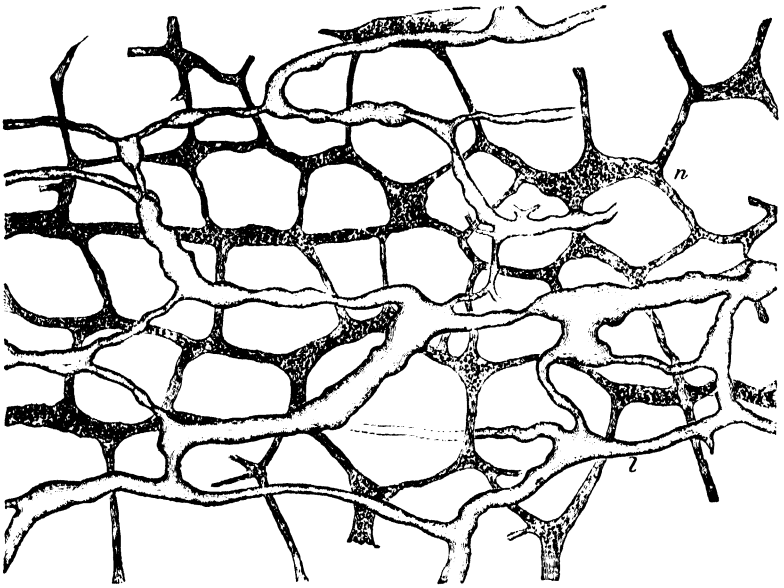
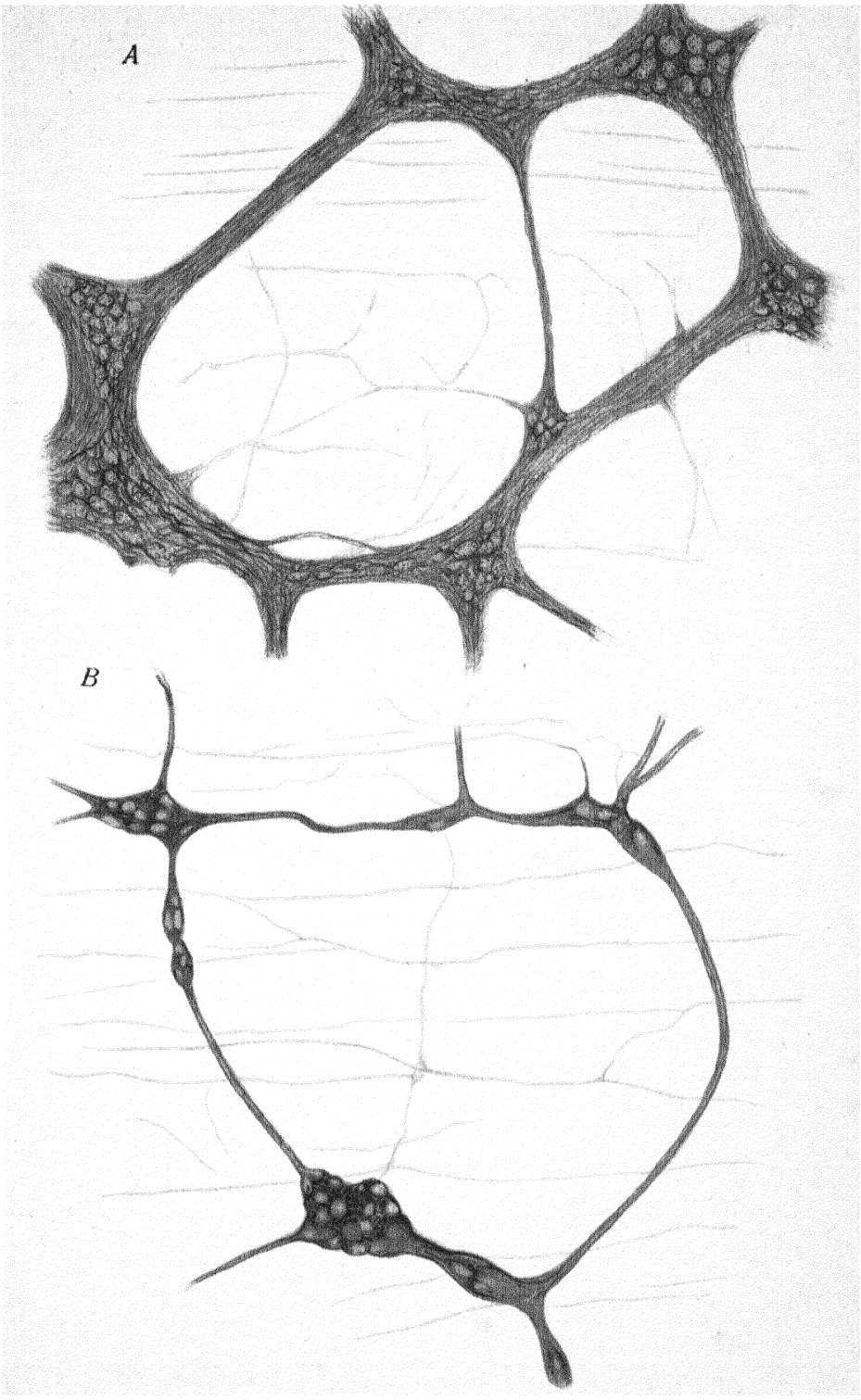


FIG. 805.—LYMPHATIC PLEXUS (*l*) AND NERVOUS PLEXUS (*n*) IN THE MUSCULAR COAT OF THE INTESTINE. (Auerbach.)

in numerous branches. These at first penetrate the longitudinal layer of muscle and enter the gangliated plexus (plexus myentericus of Auerbach) (fig. 805, and A on accompanying Plate) which is there present; from it branches are distributed to the muscular fibres of both layers. Other larger branches pierce the circular layer of muscle, and in the submucosa enter the gangliated plexus of Meissner (see B on accompanying Plate). The minute structure of these gangliated plexuses has already been described (p. 227).

From the plexus of Meissner some fibres are distributed to the muscularis mucosæ; others pierce this and join a fine nerve-plexus throughout the substance of the mucous membrane and within the villi (fig. 806). Some authors state that nerve-fibres can be traced from this plexus amongst the columnar epithelium-cells.

The following papers on the minute anatomy of the intestine may also be mentioned: H. J. Berkley, Anat. Anz. viii. 1893 (nerve-endings); Bizzozero, Anat. Anz. iii. 1888 (glands), Ramón y Cajal, Sistema nerviosa, 1899 (nerve-endings); N. Czermach, Arch. f. mikr. Anat. xlii. 1893 (lymph-nodules); Grünhagen, Arch. f. mikr. Anat. xxix. 1887 (fat-absorption); R. Heidenhain, Pflüger's Arch. xliii. (suppl.), 1888; Krehl, Arch. f. Anat. 1890 (fat-absorption); Kuczynski, Intern. Monatschr. f. Anat. u. Physiol. vii. 1890 (Brunner's glands); F. P. Mall,



Small portions of *(A)* plexus of Auerbach and *(B)* plexus of Meissner. Gold chloride preparations. Magnified 140 diameters. (Schäfer.)

Abh. d. k. Sächs. Gesellsch. d. Wiss. 1887 (blood- and lymph-vessels); E. Müller, Arch. f. mikr. Anat. xl. 1892 (nerve-endings); Nicolas, Bull. d. l. soc. d. sci. de Nancy, 1890 (glands) and Intern. Monatschr. f. Anat. u. Physiol. viii. 1891 (epithelium of large intestine); Paneth, Arch. f. mikr. Anat. xxxi. 1888 (glands); J. E. Schmidt, *ibid.* lxvi. 1905; Stöhr, Arch. f. mikr. Anat. xxxiii. 1889 and *ibid.* li. 1898 (lymph-nodules); Tomarkin, Anat. Anz. viii. 1893 (glands); J. Voigt, Anat. Hefte, xii. 1899 (development of crypts of Lieberkühn).

THE LARGE INTESTINE.

The large intestine extends from the ileocolic valve to the anus; it is divided into the *colon*, with the *cæcum* and *vermiform appendix*, and the *rectum*. It has four coats, like those of the stomach and small intestine, viz.—serous, muscular, submucous, and mucous (see accompanying Plate).

The **serous coat** is for the most part similar to that of the small intestine, except that, along the colon and upper part of the rectum, it is prolonged into numerous little projections, which enclose a certain amount of fat, and are termed

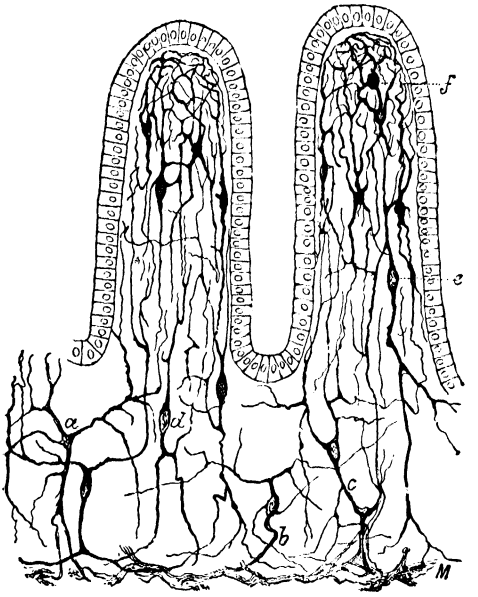


FIG. 806.—NERVE-ENDINGS IN THE SMALL INTESTINE OF THE GUINEA-PIG. (Cajal.) Silver-chromate preparation.

a, *b*, *c*, *d*, small nerve-cells belonging to the interglandular plexus of the mucous membrane; *e*, *f*, corresponding cells belonging to the nerve-plexus of the villi; *M*, nerve-fibres belonging to the plexus of Meissner, distributed to the muscularis mucosæ.

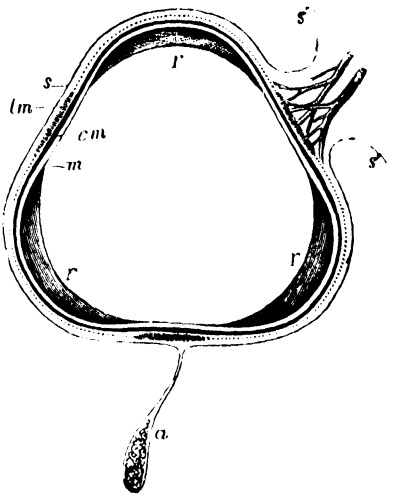


FIG. 807.—OUTLINE SKETCH OF A SECTION OF THE ASCENDING COLON. (Allen Thomson.) Three-fourths natural size.

s, serous covering; *s'*, *s'*, reflection of this at the attached border forming a short wide mesocolon between the folds of which the blood-vessels are seen passing to the colon; *a*, one of the appendices epiploicæ hanging from the inner border; *l m*, one of the three bands formed by the thickening of the longitudinal muscular coat; the dotted line represents the remainder of the longitudinal muscular coat, and the thick line within it, marked *c m*, represents the circular muscular layer; *m*, mucous membrane; *r*, the crescentic bands or indentations which divide the sacculi.

appendices epiploicæ. It is usually incomplete on the posterior and mesial surfaces of the ascending and of the descending colon and of the first part of the sigmoid flexure; also on the posterior surface (and eventually on the lateral surfaces) of the second part of the rectum. The lowest part of the rectum is altogether extra-peritoneal.

The **muscular coat,** like that of the other parts of the intestinal canal, consists of external longitudinal and internal circular fibres.

The *longitudinal* fibres, although present to a certain extent all round the large intestine, are, in the cæcum and colon, more thickly collected into three

remarkable flat longitudinal bands (fig. 807, *lm*). These bands commence upon the cæcum, at the attachment of the vermiform appendix, and may be traced along

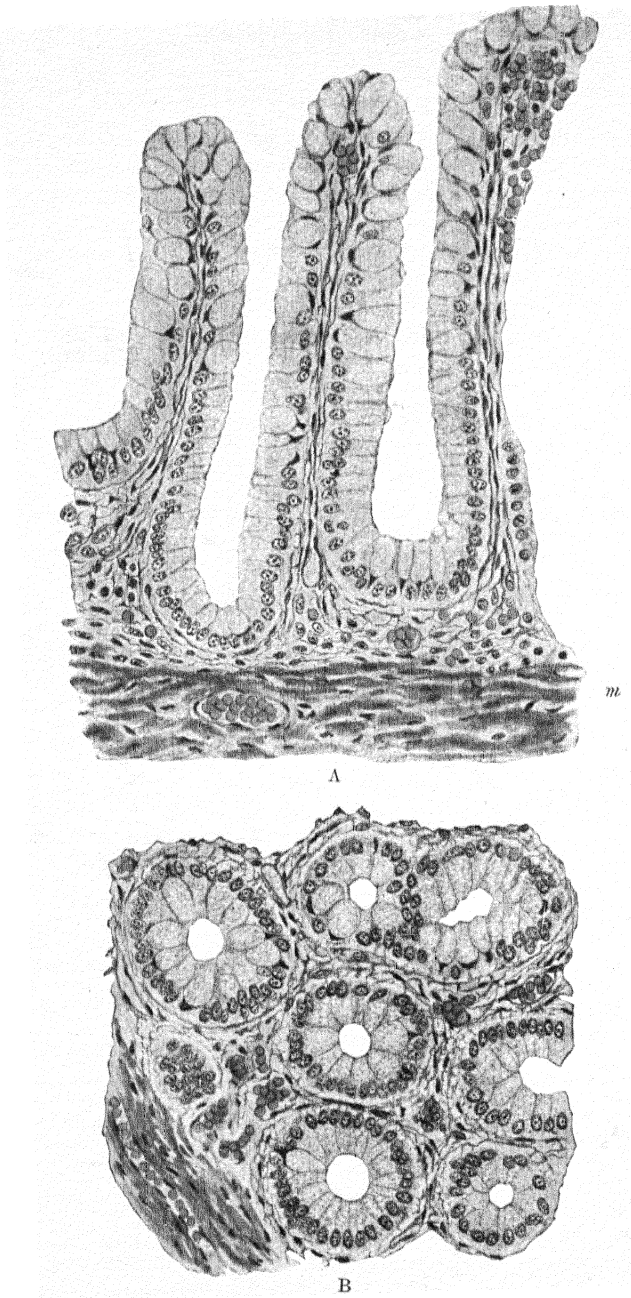
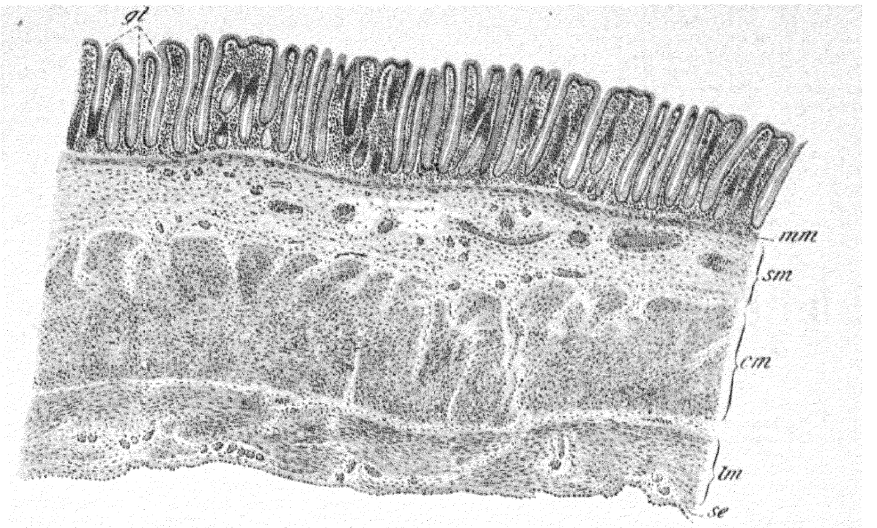


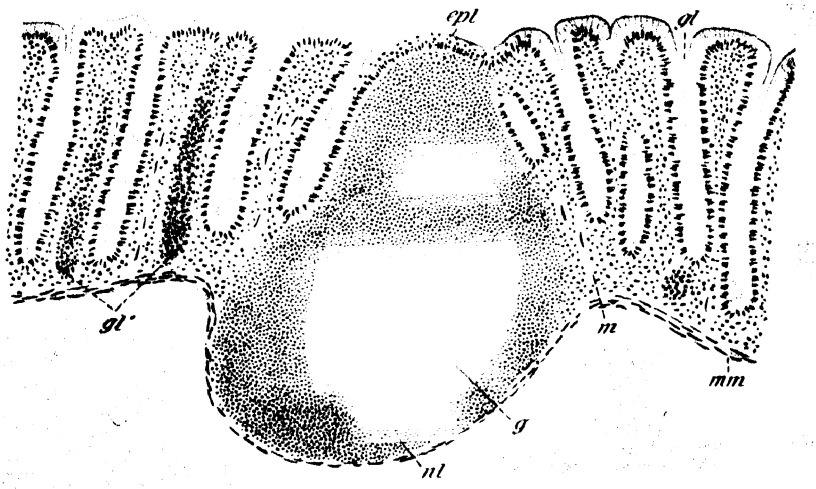
FIG. 808.—GLANDS OF LARGE INTESTINE OF CHILD. (Schäfer.) Magnified 300 diameters.
A, in longitudinal section; B, in transverse section.
m, muscularis mucosæ. The epithelium shows numerous goblet-cells.

the whole length of the colon as far as the commencement of the rectum, where they blend to form two bundles, which pass down, one on its anterior and the other



Section of descending colon, human (Sobotta). Magnified 30 diameters. Haematoxylin-eosin.

gl. **glands;** ***mm,*** **muscularis mucosae;** ***sm,*** **submucosa;** ***cm, lm,*** **circular and longitudinal fibres of muscularis;** ***se,*** **serosa.**



Section of mucous membrane of human rectum (Sobotta). Magnified 60 diameters. Haematoxylin-eosin.

gl, **gland;** ***epl,*** **leucocytes in epithelium;** ***mm,*** **muscularis mucosae;** ***m,*** **muscular fibres in mucous membrane;** ***nl,*** **lymph-nodule;** ***g,*** **its germinal centre;** ***gl'*****, glands cut tangentially.**

on its posterior surface. One of the three bands is placed along the attached border of the colon ; another runs along the border which, in the transverse colon, corresponds with the attachment of the great omentum ; whilst the third band is equidistant from the other two. Near the course of this third band most of the appendices epiploicæ are attached (fig. 807, *a*). Measured from end to end, these three bands are shorter than the intervening parts of the tube, so that the latter are thrown into sacculations; when the bands are removed by dissection the sacculi are entirely effaced on distending the colon, which becomes longer and assumes a cylindrical form. The transverse constrictions seen on the exterior of the intestine, between the sacculi, appear on the inside as sharp ridges separating the cells, and are composed of all the coats. In the vermiform appendix the longitudinal muscular fibres are disposed in a uniform layer.

The *circular* muscular fibres form only a thin layer over the general surface of the cæcum and colon, but are accumulated in large numbers between the sacculi. In the rectum, especially towards its lower part, the circular fibres form a thicker layer, and around the anal canal they become developed into a sphincter muscle, some 4 mm. thick, which is termed the *internal sphincter of the anus.*

The **submucous** or **areolar coat** resembles in all respects that of the small intestine.

The **mucous membrane** differs from that of the small intestine in being smooth and destitute of villi. Viewed with a lens, its surface is seen to be marked all over by the orifices of numerous tubular glands (*crypts of Lieberkühn*) (fig. 808 and Plate), resembling those of the small intestine, but longer and more numerous, and further distinguished from them by the large number of mucus-secreting cells which they contain. In some animals all the cells of these glands may be found to be mucus-secreting ; in others every alternate cell presents this character, the cells between being of the ordinary columnar kind. The glands occur in all parts of the large intestine except in a narrow zone at the lowest end of the rectum near the continuation of the columnar epithelium of the gut into the stratified epithelium of the anus.

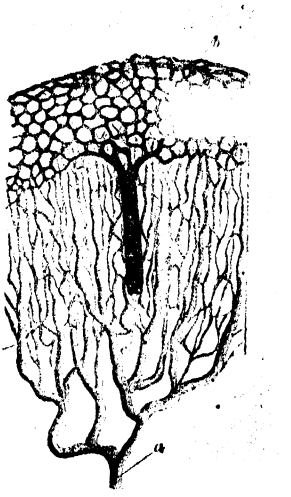


FIG. 809.—BLOOD-VESSELS OF LARGE INTESTINE AS SEEN IN VERTICAL SECTION. (Kölliker.)

a, artery passing up from submucosa; *c*, vein arising from capillary plexus, *b*, which surrounds the mouths of the glands.

The epithelium covering the general surface of the mucous membrane is of the columnar kind, in every respect similar to that of the small intestine, except that there are many more goblet-cells. As in the stomach the mucous membrane consists of areolar connective tissue with a certain amount of reticular tissue, and is bounded next the submucous coat by a layer of plain muscular fibres (*muscularis mucosæ*), which sends prolongations up between the glands to be attached to the basement-membrane near the surface, in the same way as in the small intestine.

Vessels and Nerves.—In the large intestine an arrangement of capillary plexuses and venous radicles obtains, similar to that which has been described in the stomach (fig. 809). At the lower end of the rectum the blood-vessels have a general longitudinal arrangement in the submucous coat. In the anal canal they lie in longitudinal folds of the mucous membrane and freely anastomose laterally. The veins here are large. Beginning in small dilatations at the lower end, they pass upwards for about three inches in the submucosa, and, freely communicating

with one another, form the hæmorrhoidal plexus. The arrangement of the lymphatics is nearly the same as in the small intestine.

Scattered over the whole of the large intestine are found lymph-follicles, similar to the solitary glands of the small intestine. They are most numerous in the cæcum and its vermiform appendix, being placed closely all over the latter; their abundance constituting the chief characteristic of this diverticulum (fig. 810).

The richness in lymph-vessels varies in different parts. They are most numerous in the cæcum and become less abundant in the lower parts. The efferent lymph-vessels pass partly to the cœliac, partly to the lumbar glands; those from the appendix enter the ileo-cæcal and ileo-colic glands. A connexion is observed

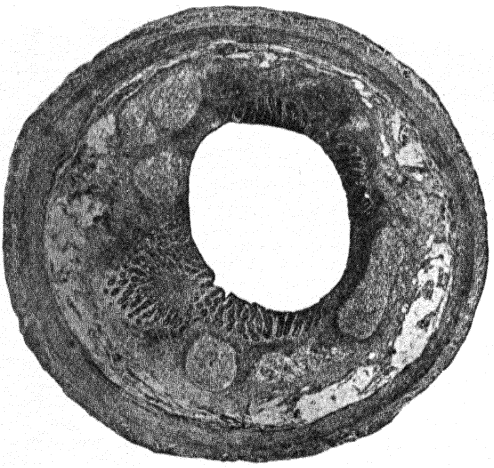


FIG. 810.—TRANSVERSE SECTION OF VERMIFORM APPENDIX. (G. Mann.)

between the lymph-vessels of the cæcum and ascending colon (and sometimes of the appendix) and the superficial lymphatics of the right kidney.[1]

Nervous plexuses similar to those of the small intestine are found in the muscular and submucous coats of the large intestine. They receive nerve-fibres from the superior and inferior mesenteric and hypogastric plexuses of the sympathetic and also, in the lower part, from the anterior roots of the second and third sacral nerves. These last differ from those derived from the sympathetic by passing into the coats of the gut without having previously lost the medullary sheath.

[1] K. Franke, Arch. f. Anat. 1910. According to Lockwood (Journ. Anat. and Physiol. xxxiv. 1900) some lymph-vessels pass from the appendix to glands in the iliac fossa and to others which adjoin the external and internal iliac arteries.

The pancreas is a long gland of a reddish cream colour and irregularly prismatic shape, which lies across the posterior wall of the abdomen, behind the stomach. Its right end is the larger, and is termed the *head*; from this arises a short and slightly constricted *neck*, which connects the head with the *body*. The body passes to the left, its left extremity or *tail* touching the spleen, whilst the head is in close relationship and partly encircled by the duodenum, into which the duct of the gland opens.

The principal excretory duct, called the *pancreatic duct* or *canal of Wirsung*, runs through the entire length of the gland from left to right, buried entirely in its substance. Commencing by the union of the small ducts derived from the groups of lobules composing the tail of the pancreas, and receiving in succession at various angles and from all sides the ducts from the body of the gland, the canal of Wirsung pursues a nearly straight course in the axis of the gland until it reaches the neck. Here it turns obliquely downwards, backwards, and to the right through the neck and head, gradually approaching the posterior surface of the latter. Near its termination it comes in contact with the left side of the common bile-duct, which it accompanies to the second part of the duodenum. As it traverses the head of the pancreas it is joined by numerous branches, one of which coming from the lower part of the head is larger than the others. The bile and pancreatic ducts, placed side by side, pass very obliquely through the muscular and areolar coats of the intestine, and terminate, on its internal surface, by a common orifice, situated near the junction of the second and third portions of the duodenum, between three and four inches below the pylorus. The pancreatic duct, with its branches, is readily distinguished within the glandular substance by the very white appearance of its thin fibrous walls. Its widest part, near the duodenum, is from 2 mm. to 2·5 mm. in diameter. It is lined by a remarkably thin and smooth membrane, which near the termination of the duct may show a few scattered crypt-like recesses.

Occasionally the main duct gives off at the neck an accessory duct, which passes to the right and opens into the duodenum about an inch above the common opening of the bile and main pancreatic ducts. This accessory duct or duct of Santorini is occasionally found of large size, evidently serving as the principal channel for the passage of the pancreatic secretion into the duodenum, the lower part of the duct of Wirsung being then small.[1]

The variations of the pancreatic ducts are of interest in connexion with the mode of development of the pancreas. From the observations of Zimmermann [2] and O. Hamburger [3] it appears that in the human subject the pancreas is formed from two distinct outgrowths from the wall of the duodenum. One of these, the smaller, is in close relation with the duodenal end of the common bile-duct; the other, situated nearer the pylorus, is much larger, and forms the greater part of the pancreas. About the sixth week of embryonic life the two processes join, and their contained ducts subsequently communicate with one another. The portion of the upper duct on the duodenal side of the point of union grows less rapidly than the lower duct. It becomes the duct of Santorini, while the lower duct, with the peripheral portion of the upper one, forms the main channel for the pancreatic secretion, and is known as the main pancreatic duct, or canal of Wirsung.

Structure.—The pancreas belongs to the class of tubulo-racemose glands. In its general characters it closely resembles the salivary glands, but it is somewhat softer in its texture than those organs, the lobes and lobules being less compactly arranged, and the connective tissue looser.[4]

[1] See on the disposition of the ducts W. M. Baldwin, Anat. Record, v. 1911.
[2] Verhandl. d. Anat. Gesel. in Anat. Anz. iv. 1889. [3] Anat. Anz. vii. 1892.
[4] On the connective tissue of the pancreas see Piazza, Anat. Anz. xxxvi. 1910. On the general structure Höcke, Inaug. Diss. Zürich, 1907.

The ducts are lined with a simple layer of long columnar epithelium, the cells becoming shorter and more cubical in the smaller ducts. They do not exhibit the well-marked longitudinal striation met with in the duct-cells of some of the salivary glands. The ultimate branches of the ducts connected with the alveoli are much narrowed, and are lined with flattened cells; in optical section these cells appear spindle-shaped.

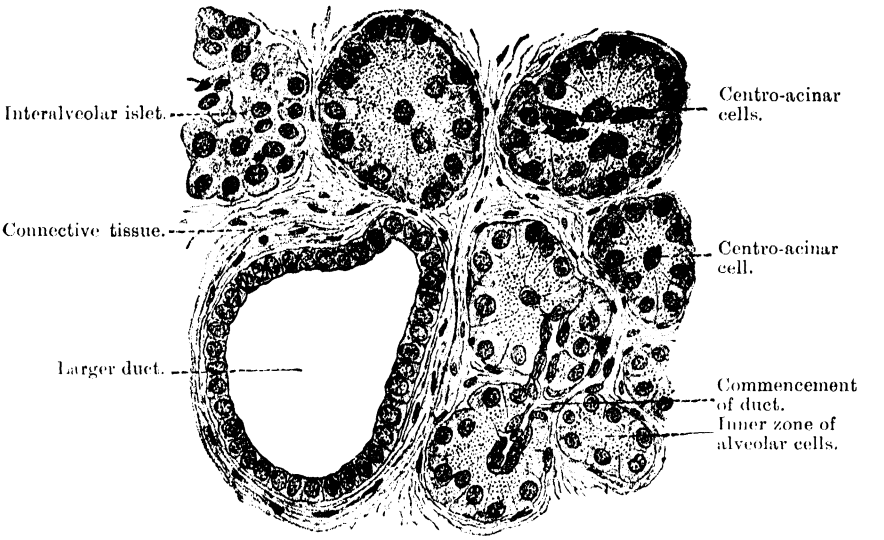


FIG. 811.—SECTION OF HUMAN PANCREAS. (Böhm and Davidoff.) Magnified 450 diameters.

The pancreas, although in general structure similar to the salivary glands, shows important differences of detail. It secretes no mucus, but an albuminous fluid, and is therefore reckoned amongst serous glands. In certain respects it resembles the parotid gland. Thus in shape its alveoli are in man very similar to those of the parotid, *i.e.* they are nearly spherical, although in both cases from

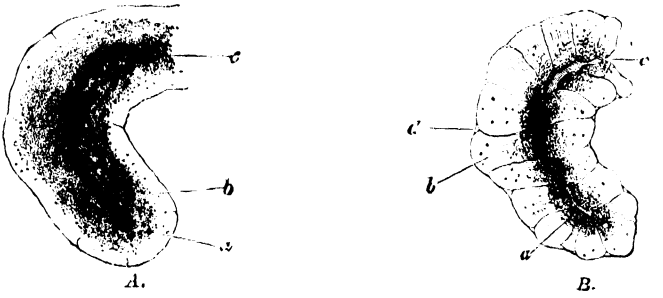


FIG. 812.—AN ALVEOLUS OF THE RABBIT'S PANCREAS AT REST AND IN ACTIVITY. (Kühne and Lea.)

A., during rest, the cells loaded with granules, and the inner zone, *a*, large, and the outer zone, *b*, narrow.

B., after activity, the inner zone small, and the outer zone large and distinctly striated. The cell outlines are also now visible. *c*, lumen of alveolus; *d*, basement-membrane.

mutual compression the spherical shape may be converted into a rounded angular form; moreover, during rest they are almost completely filled by the secreting cells. The general appearance of the cells is also similar to those of the parotid, except that there is always in each secreting cell of the pancreas, even

after a period of prolonged inactivity, a well-marked outer zone which is free from granules (figs. 811, 812), and in fixed and hardened specimens stains like protoplasm. There are no ducts in the pancreas corresponding in structure to the so-called 'salivary ducts' of the salivary glands, *i.e.* tubules of nearly uniform diameter, ramifying throughout the gland and lined by striated columnar epithelium-cells which nearly fill the lumen. In the pancreas, on the other hand, the ducts diminish regularly in size as they branch through the gland, and the branch which passes to a lobule gives off to each alveolus a *junctional* or *intercalary duct*, always small in diameter and lined by flattened cells; this duct opens abruptly into the alveolus. It is also a frequent feature in the pancreas to see the cells of the junctional ducts prolonged into the lumen of the alveolus, where they are known as the *centro-acinar cells* (Langerhans) (fig. 811), an appearance seen occasionally, but to a much less extent, in the parotid and other salivary glands.[1] Lastly, the existence amongst its lobules of the *islets of Langerhans*, to be presently described, serves at once to distinguish the pancreas from all other acinous glands.

FIG. 813.—ALVEOLI OF DOG'S PANCREAS, CELLS LOADED. Osmic preparation. (Babkin, Rubasckin and Ssawitsch.)

The secretion-granules in the alveolar cells of the pancreas are readily observed in osmic preparations (figs. 813 to 815) and also in the fresh gland,[2] and may be seen during life in those parts of the gland which in the rabbit and other animals lie between the layers of the mesentery; where the changes which take place during secretion can also be followed. This was first done by Kühne and Lea,[3] who found the granules gradually to disappear during secretion, so that if the gland be stimulated, *e.g.* by pilocarpin, the clear outer zone of the cell becomes relatively increased in size and the granular zone becomes confined to the free border of each cell (fig. 812). Accompanying these changes the cells become altogether smaller and their outlines more distinct; the outer zone of each cell appears now also indistinctly striated. Similar changes occur as the result of more natural methods of provoking secretion, such as the injection of secretin into the blood-vessels or of acid into the duodenum (fig. 814), and the stimulation of the vagus nerve (fig. 815).[4] The influence of the nucleus in the production of the secretion, as well as the formation of a paranucleus from which the secretion-granules are believed to be formed has already been alluded to (p. 59).[5] As first described by Nussbaum, the paranucleus may be invisible during the resting condition of the

FIG. 814. — ALVEOLI OF DOG'S PANCREAS AFTER A PERIOD OF ACTIVITY PRODUCED BY APPLICATION OF ACID TO MUCOUS MEMBRANE OF DUODENUM. (Babkin, Rubasckin and Ssawitsch.)

[1] R. Krause, Arch. f. mikr. Anat. xlv. 1895.
[2] Cl. Bernard, Mémoire sur le pancréas, 1856.
[3] Heidelberg Unters. 1882.
[4] Babkin, Rubasckin and Ssawitsch, Arch. f. mikr. Anat. lxxiv. 1909.
[5] For the literature see Garnier, Journ. de l'Anat. et de la physiol. xxxvi. 1900.

cell, but becomes conspicuous, in stained preparations, during activity. Its development from extruded nuclear matter and the formation from it of the zymogen-granules have been described by some authors, but have been denied by others. In any case the secretion-granules, in the pancreas as in other glands, are probably formed from the particles known as *chondrosomes* or *mitochondria* [1] (see p. 24), which are present in the protoplasm of most cells, and are thought to be the chief agents in the formation of all structures connected with the active functions of cells. An enlargement of the nucleus of the pancreatic cell during activity and its transference towards the base of the cell was observed during life by Kühne and Lea.

FIG. 815.—ALVEOLI OF DOG'S PANCREAS AFTER A PERIOD OF ACTIVITY PRODUCED BY VAGUS STIMULATION. (Babkin, Rubaschkin and Ssawitsch.)

Various observers, after forcing injections from the duct backwards into the alveoli of the pancreas, have seen fine intercellular canaliculi, comparable to those of the liver, passing from the lumen of an alveolus between the secreting cells. These can be shown much more easily, however, by the

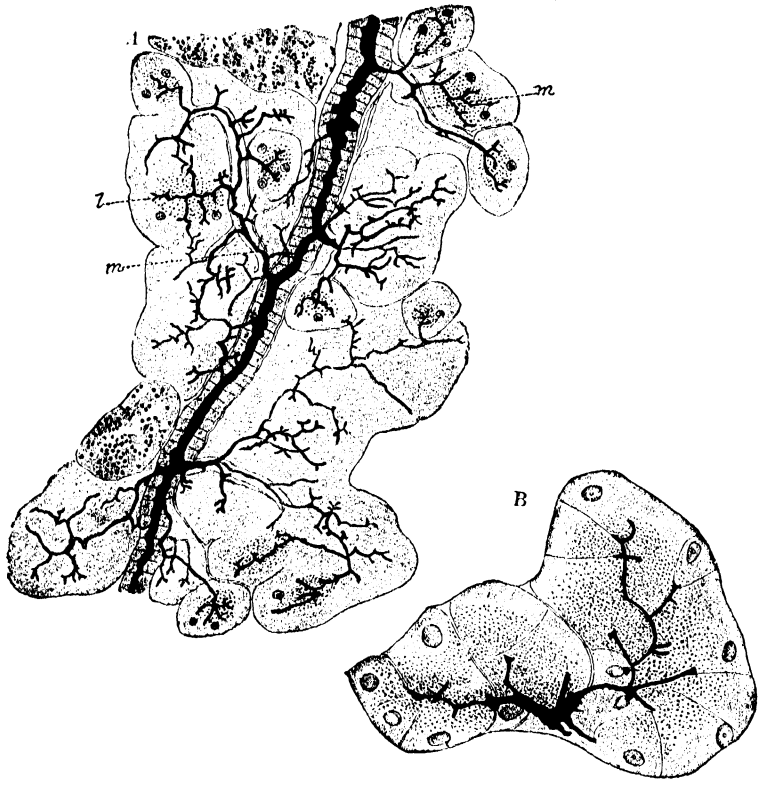


FIG. 816.—ORIGIN OF THE DUCTS OF THE PANCREAS, AS SHOWN BY THE CHROMATE-OF-SILVER METHOD. (E. Müller.)

A, duct cut longitudinally, lined by columnar epithelium, and giving off laterally the intercalary or lobular ductules, *m*, to the alveoli, *l*. The manner in which the ducts commence within the alveoli is shown under a higher power in B.

[1] Regaud, C. r. soc. biol. 1909; H. Hoven, Anat. Anz. xxxvii. 1910; O. Schultze, Anat. Anz. xxxviii. 1911.

use of the Golgi silver-chromate method (fig. 816, A), and with a high magnifying power the canaliculi can be seen penetrating not only between the cells of the alveoli, but, according to some authors, even into the interior of the cells (B).[1]

Blood-vessels, lymphatics, and nerves.—The *arteries* of the pancreas are derived from the splenic and hepatic divisions of the cœliac axis, and from the inferior pancreatico-duodenal branch of the superior mesenteric. Its *veins* are tributaries of the splenic and superior mesenteric, and therefore belong to the portal system. The *lymphatics* pass to some of the neighbouring cœliac glands. Their arrangement within the pancreas is similar to that found in the salivary glands.

The *nerves* are derived from the solar plexus, and accompany the arteries to the organ. They are almost exclusively non-medullated and have minute ganglia on them as they traverse the gland. Besides these ganglia, small stellate cells, said to be of nervous nature, are found upon the nerves near their distribution to the epithelium-cells of the alveoli, over and between which the nerve-fibrils ultimately ramify, as in the salivary glands.[2]

Islets.—The *islets of Langerhans*, which, as above mentioned, are peculiar to the pancreas, consist of a variable number of irregular clumps of epithelium-like protoplasmic cells lying in the interalveolar tissue of the pancreas; they are generally most numerous in the part of the organ which is near the spleen (Opie). In hæmatoxylin preparations of the gland they are less stained than the alveoli. In injected preparations they are distinguishable by the large size, irregular shape, and convoluted arrangement of their sinus-like capillaries (fig. 817), which penetrate between the epithelium-cells of the islet, so that the walls of the capillaries come into actual contact with these cells.[3] The nerves of the islets also have a different arrangement from those of the acini,[4] while the epithelium-cells are clearer than those of the alveoli, and the granules they contain are finer. According to Lane,[5] there are two kinds of cells in the islets, having granules of different chemical nature.

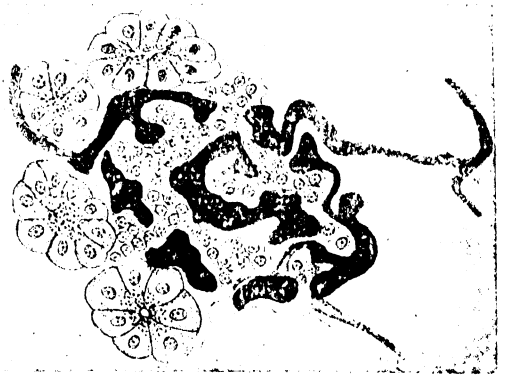


FIG. 817.—INJECTION OF BLOOD-VESSELS OF AN 'ISLET' OF THE PANCREAS. (Kühne and Lea.)

The relationship between the islets and the glandular substance of the pancreas is not fully cleared up. According to most authors, the islet tissue is directly continuous with the alveolar tissue, and the islets may during life become formed at the expense of the alveoli or *vice versâ*. Thus H. Dale[6] found that when the pancreas is stimulated to activity by means of *secretin* the islets become greatly increased in size and number, whereas in the resting pancreas they are small and relatively few. Dale also found the islet tissue similarly increased after a period of hunger,[7] from which it would seem that activity of the gland is not alone a sufficient explanation

[1] Cajal and Sala, Trab. d. lab. d. hist. d. Barcelona, 1891; E. Müller, Arch. f. mikr. Anat. xl. 1892; S. Dogiel, Arch. f. Anat. 1893. On the structure of the ducts of the pancreas see K. K. Helly, Arch. f. mikr. Anat. lii. 1898.

[2] Cajal and Sala, *op. cit.*

[3] de Witt, Journ. Exp. Med. viii. 1906 (reconstruction-study).

[4] Pensa, Internat. Monatsch. f. Anat. u. Physiol. xxii. 1905.

[5] Amer. Journ. Anat. vii. 1907.

[6] Phil. Trans. B. excvii. 1904. Lewaschew (Arch. f. mikr. Anat. xxvi. 1886) and Statkewitsch (Arch. f. exp. Pathol. xxxiii. 1893) had previously arrived at similar conclusions.

[7] Rennie, however, could determine no such increase in a snake which had fasted for many months. Intern. Monatschr. f. Anat. u. Physiol. xxvi. 1909.

of the increase. Nerlich [1] states that in the dog canaliculi can be injected in the islets from the ducts of the gland. Macallum [2] found in a case of diabetes in man that there was apparent continuity between the islets and the secreting tubules. Vincent and Thompson describe a close histological relationship between the secreting alveoli and the islets.[3] In confirmation of Dale they state that the islets increase in number and size during inanition, and they further find (in birds) that on re-nourishing the animal the number and size of the islets again diminishes to normal. Laguesse [4] confirms the observations of Dale and of Vincent and Thompson, and holds that the islets increase and decrease at the expense of the alveoli. On the other hand, both Heiberg [5] and Kuster [6] state that in number and in size the relation of the glandular tissue to the islets remains constant, and Diamare [7] and others have failed to find in the adult condition any connexion between islets and glandular tissue. De Witt [8] found the individual variations under normal conditions fully as great as under varied conditions of digestion, hunger, and diet.

Although the view (based mainly on the histological evidence above given) which regards the islets as merely a part of the general secretory apparatus of the pancreas, altering in amount vicariously with the alveoli, is to some extent supported by the consideration of the mode in which they are originally developed, viz. as solid lateral outgrowths from the developing ducts of the embryonic pancreas,[9] yet it must be confessed that the dissimilarity in the appearance and staining reactions of their cells, the sharp differentiation which they generally show against the secreting alveoli,[10] and especially the peculiar nature of their blood-supply, renders it difficult of acceptance. For the alterations which the alveoli must undergo to become converted into islet-tissue are of such a profound nature that it seems impossible for such changes to be brought about as the result of the mere injection of secretin, the action of which is rapid and lasts but for a short time.[11]

The fact that the islet-tissue does not undergo atrophy and retrogression along with the secreting alveoli when the ducts of the gland are obstructed,[12] points to its independence of function. There are indeed strong grounds for considering that the islets are concerned with that function of the pancreas which deals with the regulation of the metabolism of carbohydrates,[13] interference with which in consequence of removal or disease of the organ produces diabetes. On this account it is generally held that the islet-tissue forms in its entirety an organ of internal secretion, yielding either an enzyme or a hormone which, after passing into the blood, is destined to play an essential part in the carbohydrate metabolism of the body.

[1] Inaug. Diss. Breslau, 1906.

[2] Amer. Journ. Med. Sci. cxxxiii. 1907.

[3] Intern. Monatschr. f. Anat. u. Physiol. xxiv. 1907 and Trans. R. S. Canada, 1908. These authors describe a lumen as being sometimes present between the cells of the islets in reptiles and fishes.

[4] C. r. soc. biol. 1905, 1908, and 1909; Arch. d'anat. micr. xi. 1909; and Journ. de physiol. et path. xiii. 1911. See also Sauerbeck, Virch. Arch. clxxvii. 1904; J. S. Goodall and H. G. Earle, Brit. Med. Journ. Sept. 1909.

[5] Anat. Anz. xxix. 1906.

[6] Arch. f. mikr. Anat. lxiv. 1904.

[7] Diamare, Intern. Monatschr. f. Anat. u. Physiol. xvi. 1899 and xxii. 1905 (observations on fishes). Cf. also Helly, Arch. f. mikr. Anat. lxvii. 1905; Heiberg, Anat. Anz. xxix. 1906 and xxxiii. 1910, and Kyrle, Arch. f. mikr. Anat. lxxii. 1908. See also the article by Heiberg in Ergebn. d. Anat. xix. 1909, where the subject is discussed at length

[8] *Op. cit.*

[9] Weichselbaum and Kyrle (Arch. f. mikr. Anat. lxxiv. 1909) found them appearing in this way in the human embryo of 8 cm.; they affirm that no new islets are formed in the adult. R. M. Pearce (Amer. Journ. Anat. ii. 1903) found them growing out from the developing ducts in an embryo of 73 days. See also Mironescu, Arch. f. mikr. Anat. lxxvi. 1910, and Bensley (footnote 11).

[10] In fishes the islets are unconnected with the glandular tissue. One islet-mass is usually much larger than the rest (Rennie, Quart. Journ. Micr. Sc. xlviii. 1904).

[11] This view is strongly supported by the observations of Bensley (Amer. Journ. Anat. xii. 1911), who has conclusively shown that the variations described by Dale and by Vincent and Thompson as the result of secretin and of inanition are well within normal individual variation. The islets are most numerous in new-born animals. Many disappear as growth advances, but others may grow from the ducts, with which for the most part they remain connected by small irregular ductules

[12] W. Schultze, Arch. f. mikr. Anat. lvi. 1900; Tschassownikow, *ibid.* lxvii. 1905; de Witt, Amer. Journ. Anat. iv. 1905; Visentini, Arch. f. Physiol. Suppl. 1908.

[13] Thus when atrophy of the alveolar structure results from ligature of the ducts, the islet-tissue remains unatrophied, and no change occurs in the carbohydrate metabolism, but if the shrunken remains of the gland be now removed—including of course the islet-tissue diabetes immediately results, just as after extirpation of the whole pancreas. Further, it has been found *post mortem* in some cases of pancreatic diabetes that there has been degenerative change in the islets alone. Cf. Opie, Johns Hopkins Hosp. Bull. 1900 and 1904; M. B. Schmidt, Münch. Med. Wochenschr. xlix. 1902, and Weichselbaum, Wiener Sitzungsb. cxix. 1910.

The liver, by far the largest gland in the body, forms a solid mass of a brownish-yellow colour, but of a dark-red and somewhat mottled appearance when its vessels are filled with blood. It occupies the uppermost part of the abdominal cavity, and is closely invested by a layer of peritoneum, which is reflected from it in the form of the so-called *ligaments of the liver*. Besides this serous covering the liver has a thin *capsule* composed of connective tissue.

Structure and distribution of blood-vessels.—The liver is composed of a very large number of minute portions, each about one millimetre in diameter, known as the *hepatic lobules* (fig. 818). It differs from all other externally secreting glands in the body in the fact that these lobules are solid masses of cells, and the

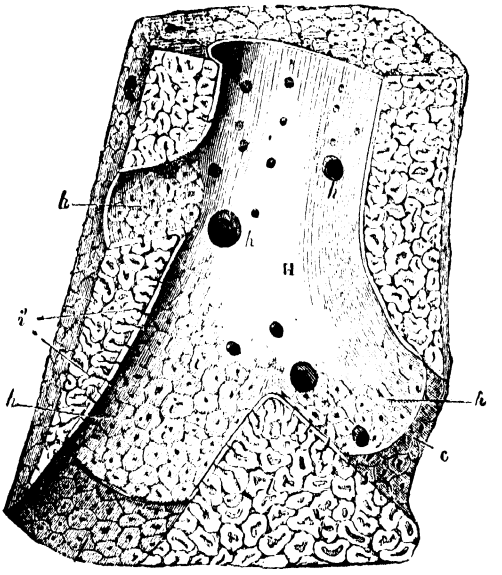


FIG. 818.—SECTION OF A PORTION OF LIVER PASSING LONGITUDINALLY THROUGH A CONSIDERABLE HEPATIC VEIN, FROM THE PIG. (After Kiernan.) About 5 diameters.

H, hepatic venous trunk, against which the sides of the lobules are applied; *h*, *h*, sublobular hepatic veins, on which the bases of the lobules rest, and through the coats of which they are seen as polygonal figures; *i*, mouth of the intralobular veins, opening into the sublobular veins; *i'*, intralobular veins shown passing up the centre of some divided lobules; *c*, *c*, walls of the hepatic venous canal, with the polygonal bases of the lobules.

FIG. 819.—LONGITUDINAL SECTION OF A PORTAL CANAL, CONTAINING A PORTAL VEIN, HEPATIC ARTERY, AND HEPATIC DUCT, FROM THE PIG. (After Kiernan.) About 5 diameters.

P, branch of vena portæ, situated in a portal canal, formed amongst the lobules of the liver; *p*, *p*, larger branches of portal vein, giving off smaller ones named interlobular veins; there are also seen within the large portal vein numerous orifices of interlobular veins arising directly from it; *a*, hepatic artery; *d*, biliary duct; at *c*, the venous wall has been partially removed.

ducts proper remain at their periphery, communicating with the interior of the lobule only by secretory canaliculi, the *bile-canaliculi*. A further difference is to be found in the character of the blood supplied to the organ, which is mainly venous, collected into the portal vein from the stomach, intestines, spleen, and pancreas. The liver receives also a certain amount of arterial blood brought to it by the hepatic artery. Both portal vein and hepatic artery enter the portal fissure on the under-surface of the organ along with the hepatic duct, and the branches of all three are conducted to every part of the liver, ensheathed by a loose connective tissue termed the *capsule of Glisson*, which passes in at the portal fissure and lies everywhere

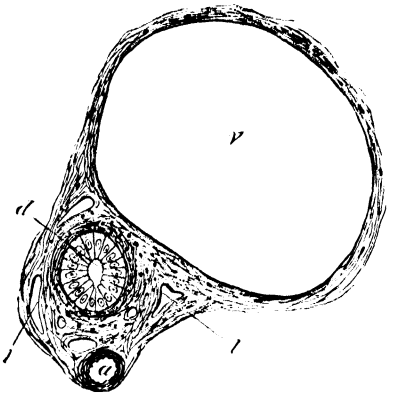


FIG. 820.—SECTION OF A PORTAL CANAL. (Schäfer.) Magnified.

a, branch of hepatic artery; *v*, branch of portal vein; *d*, bile-duct; *l*, *l*, lymphatics in the areolar tissue of Glisson's capsule which encloses the vessels.

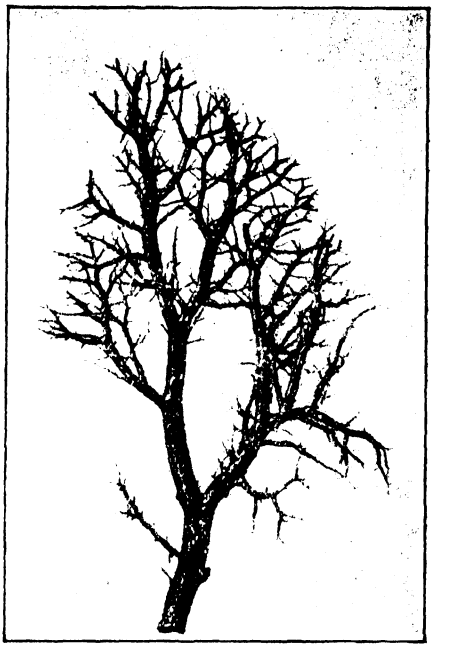


FIG. 821.—TERMINAL BRANCHINGS OF PART OF THE PORTAL VEIN WITHIN THE LIVER. (Mall.) Twice the natural size.

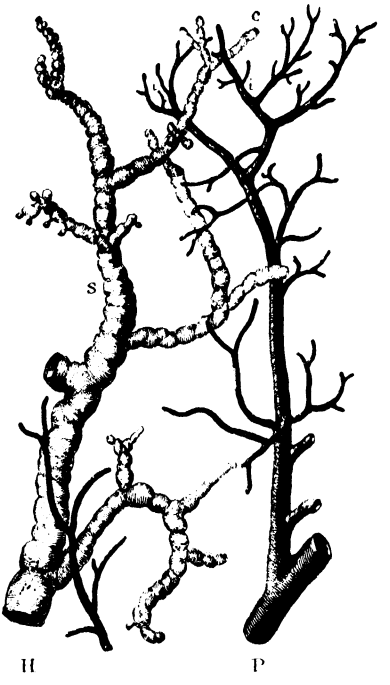


FIG. 822.—TERMINAL BRANCHES OF HEPATIC VEIN (H) AND PORTAL VEIN (P). (Mall.) Magnified 20 diameters. The vessels were injected with celloidin and isolated by the corrosion method. The hepatic vein is characterised by spiral constrictions which extend to the smallest tributaries.

S, Sublobular branch of hepatic vein; *c*, central vein of a lobule; *i*, interlobular branch of portal.

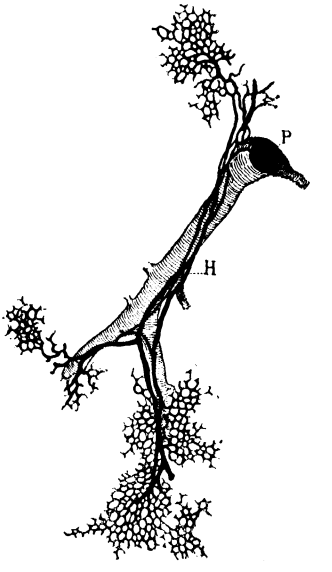


FIG. 823.—ENDING OF BRANCHES OF HEPATIC ARTERY IN CAPILLARY NETWORK OF LIVER-LOBULES. (Mall.) Magnified 40 diameters.

P, Branch of portal vein; H, branches of hepatic artery accompanying the portal vessel and ending in the capillary network of the lobules.

between the lobules, separating them more or less from one another.[1] The blood is conveyed in this way to branches of the portal vein, which run everywhere between the lobules—hence termed *interlobular veins*; these deliver it into a net-

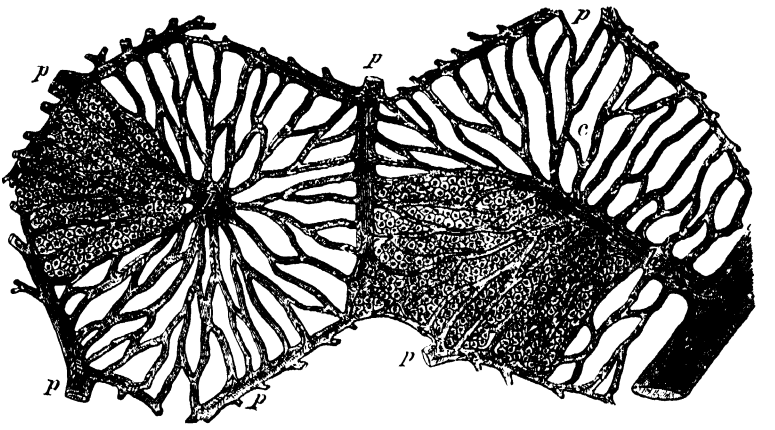
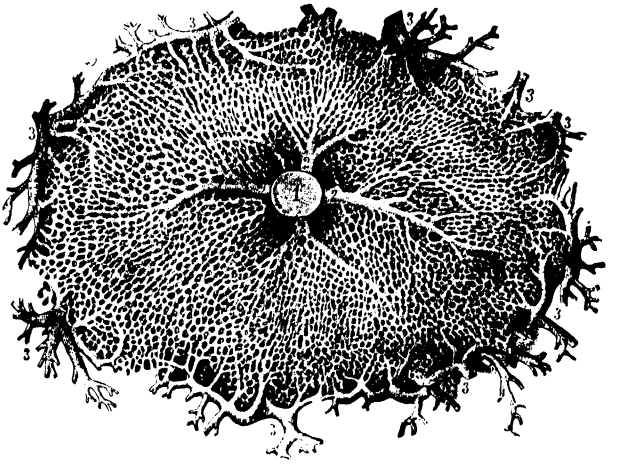


FIG. 824.—DIAGRAMMATIC REPRESENTATION OF TWO HEPATIC LOBULES. (Schäfer.)

The left-hand lobule is represented with the intralobular vein cut across; in the right-hand one the section takes the course of the intralobular vein. *p*, interlobular branches of the portal vein; *h*, intralobular branches of the hepatic veins; *s*, sublobular vein; *c*, capillaries of the lobules. The arrows indicate the direction of the course of the blood. The liver-cells are only represented in one part of each lobule.

work of capillary blood-spaces which pervade the lobules and converge towards the centre of each lobule to form a *central* or *intralobular vein* (fig. 824). This carries the blood out of the lobule into *sublobular veins*, which course through the liver in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posterior part of the organ as the *hepatic veins*, opening into the vena cava inferior. The central and sublobular veins are therefore tributaries of the hepatic veins : they

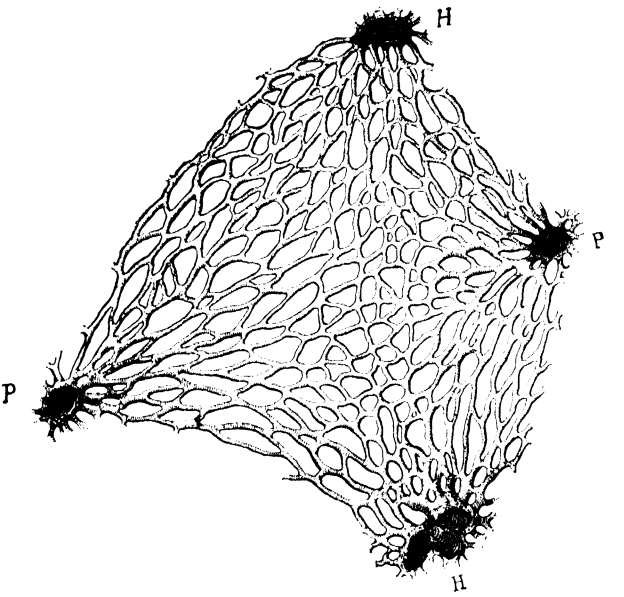


FIG. 826.—PART OF CAPILLARY NETWORK OF LIVER AT THE JUNCTION BETWEEN TWO OR MORE LOBULES. (Mall.) Magnified 85 diameters.

P, interlobular branches of portal vein; H, intralobular branches of hepatic vein. In the middle is an area the capillaries of which are not elongated in any special direction and in which the blood passing from P to H must move very slowly. Such an area is termed by Mall a 'nodal point.' It marks the interconnexion between the capillary networks of adjacent lobules.

are only connected with the branches of the portal vein and hepatic artery through the capillary channels of the lobules.

The *hepatic artery* sends branches which furnish capillaries to the capsule of the

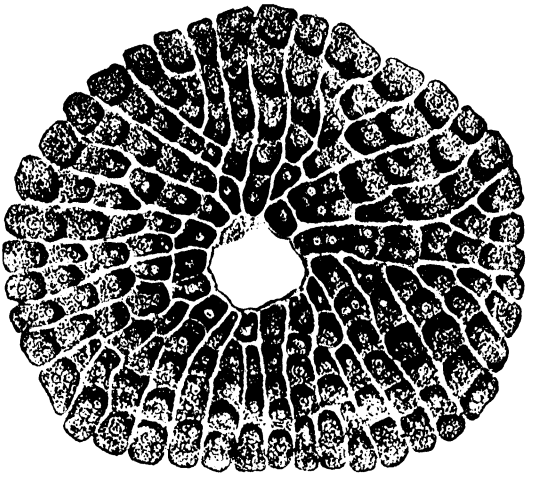


FIG. 827.—LIVER-CELLS CONTAINING GLYCOGEN. (Barfurth.)

organ, to the walls of the gall-bladder and bile-ducts, outside and within the organ, and to the connective tissue of Glisson's capsule. The blood which has traversed these

capillaries enters portal vessels and ultimately goes to the lobules. But most of the blood carried by the hepatic artery is distributed directly by its interlobular

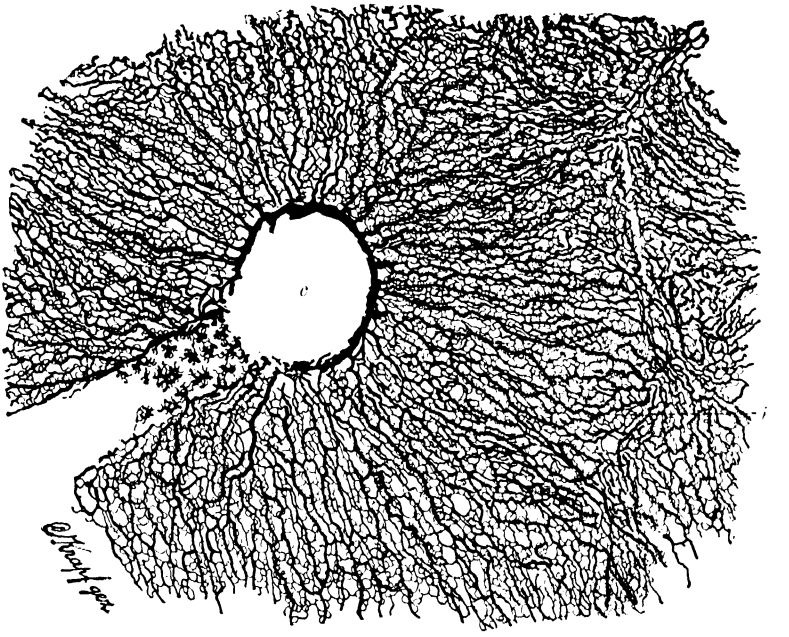


FIG. 828.—RETICULUM OF A LIVER-LOBULE. (Oppel.)
c, central vein; *i*, interlobular interval.

branches to the capillary channels of the lobules (fig. 823), which are thus supplied with a certain proportion of arterial blood.

The canals in the liver-substance in which run the branches of the portal vein, hepatic artery, and bile-duct, surrounded by the loose connective tissue of the capsule of Glisson, are known as *portal canals* (figs. 819, 820).

Each *lobule* represents a liver in miniature. It is composed of a mass of cells (fig. 827) supported by reticular connective tissue (fig. 828),[1] and is pierced everywhere by converging capillary blood-channels through which the blood courses but slowly. These blood-channels are not true capillaries, but sinusoids. They are not surrounded by connective tissue containing lymph-spaces, as are the capillaries of other glands, but are in direct contact with the liver-cells—from which they are separated at most by their lining endothelium. This is, however, in many places incomplete, and its cells are irregularly branched and more or less isolated from their fellows (*stellate cells of Kupffer*)[2]; the result is that the blood flowing through the sinusoids comes into direct contact with the liver-cells. In other words,

FIG. 829.—SECTION OF LIVER OF RABBIT INJECTED FROM THE PORTAL VEIN SHOWING INTRACELLULAR CANALICULI INJECTED FROM THE INTERCELLULAR SINUSOIDS. (Schäfer.)
Most of the cells contain two nuclei.

[1] F. Mall, Abhandl. d. k. Sächs. Gesellsch. f. Wiss. xvii. 1891; A. Oppel, Anat. Anz. vi. 1891.
[2] Arch. f. mikr. Anat. xii. 1876. Also *ibid.* liv. 1899. See also Herring and Simpson, Proc. Roy Soc. B. lxxviii. 1906.

the materials for secretion are derived directly from the blood itself, and do not pass to the cells through the medium of the lymph. As evidence that there is this free contact of the blood with the cells it is found that red blood-corpuscles occur occasionally (even in the normal liver) within the liver-cells, and that injection material driven even at a low pressure into the portal vein or into the aorta finds its way with great ease from the blood-channels of the lobule into the substance of the liver-cells (fig. 829 and accompanying Plate). This is rendered possible by the fact that the cells are permeated by fine branching canaliculi which communicate with the surface of the cells abutting on the sinusoids. This communication of intracellular channels with blood-vessels is, so far as is known, peculiar to the liver, although an intimate relationship between blood-capillaries and tissue-cells is common to nearly all internally secreting glands; of which the liver, on account of its glycogenic and urea-forming functions, must be reckoned amongst the most important. Such relationship not only enables the cells of the organ to be directly nourished from the blood-plasma, but also adapts them for readily passing the products of their internal secretion into the blood-stream.

The close relationship which subsists between the blood in the capillaries (sinusoids) of the liver and the hepatic cells is well shown in the figures of the accompanying Plate, which is reproduced from the paper by Herring and Simpson in the 'Proceedings of the Royal Society,' B. vol. lxxviii. In this plate figs. 1 and 2 are taken from the normal dog's liver and show hæmoglobin within some of the liver-cells: in most cases in the form of a crystal within the nucleus (which is elongated by the crystal). Fig. 3 represents a small portion of a section of cat's liver, with sinusoid blood-channels between the cells. The endothelium of the sinusoid is defective, and is represented by partially detached cells, two of which, spindle-shaped in section, are seen projecting into the channel. These cells are phagocytic and contain granules of coloured matter which is probably derived from disintegrated blood-corpuscles. About a dozen erythrocytes are shown within the blood-channels. Figs. 4 to 9 are all from specimens of liver injected with carmine-gelatine. The irregular nature of the sinusoid blood-channels, so different from the regular tubular character of ordinary blood-capillaries, is accurately portrayed in these figures, as is the presence of the injecting material in the interior of the cells, extending in several into actual contact with the nucleus. Of these figures, 4 and 5 are from the rat, and were injected from the aorta at a pressure of 80-100 mm. of mercury; 6 from the monkey, injected from the portal vein at a pressure of 60 mm.; 7 from the dog; 8 from the cat; and 9 from the fowl. The last three were injected from the aorta at a pressure of 100 mm. In no case was this pressure exceeded; in some instances the inferior vena cava was cut and left unobstructed throughout. The presence of the injection-material in the cells is therefore not due to extravasation caused by high pressure, but must have followed a natural channel. It is seen within the liver-cells in all well-injected specimens, provided the sections are sufficiently thin for the cell-contents to be clearly shown. Fig. 10, which is from a case of chloroform-poisoning in a child, shows a liver-cell containing globules of fat (stained by osmic acid); these are in direct communication with fat in the interior of a blood-channel.

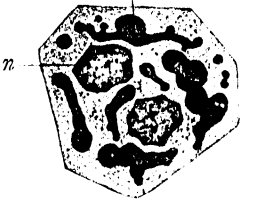
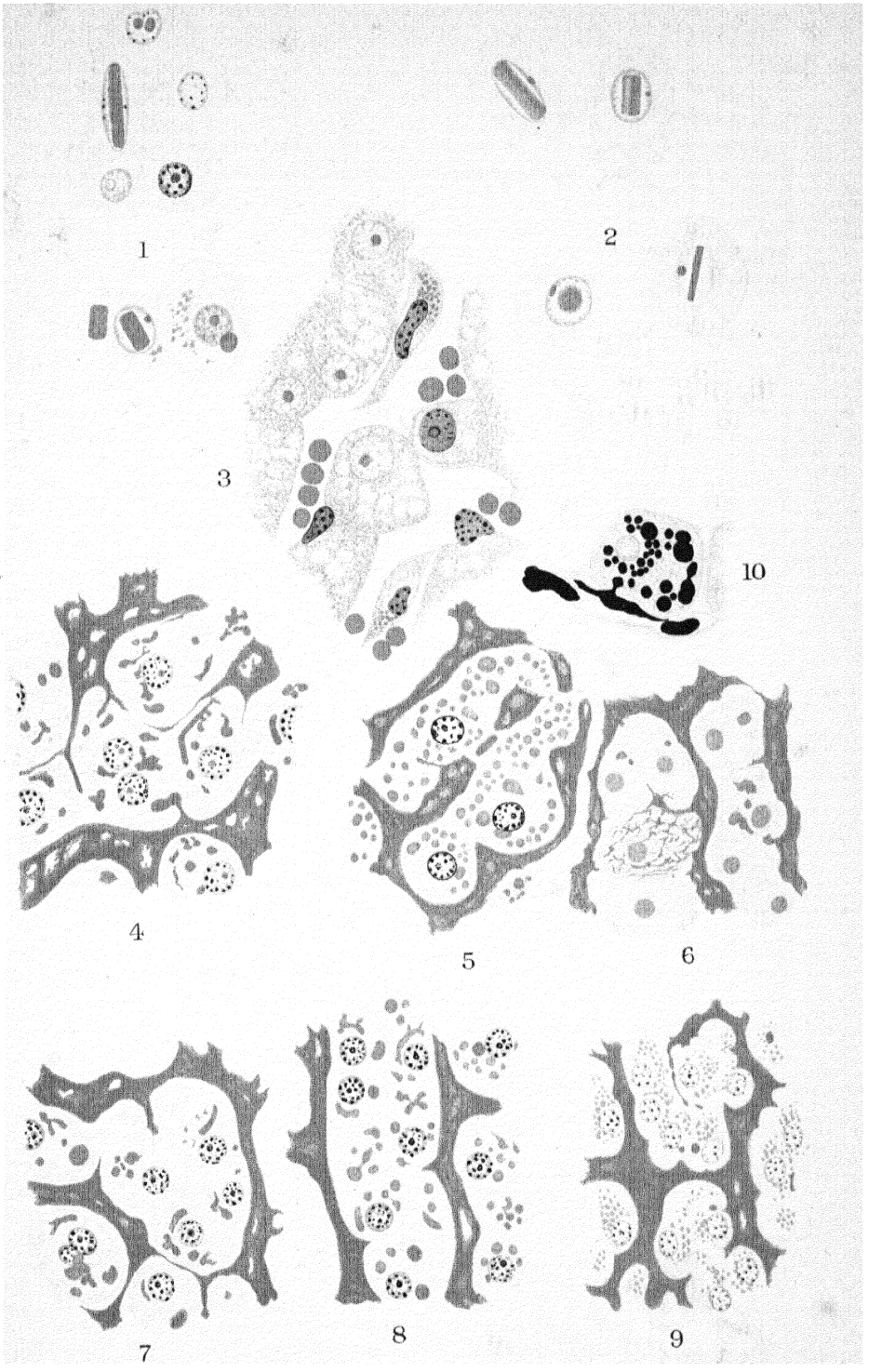


FIG. 830.—A CELL FROM THE HUMAN LIVER IN A CASE OF JAUNDICE, SHOWING ENLARGED INTRACELLULAR CANALICULI. (Browicz.)

n, one of the two nuclei; *c*, part of the network of canaliculi within the cytoplasm.

The question of the relation of the hepatic cells to the blood-channels of the liver is dealt with in a complete fashion in the paper by Herring and Simpson, above referred to. The intracellular canaliculi in question were first described in sections of rabbit-liver by Schäfer, in 1902, but the necessity of assuming a close relationship between the blood and liver-cells had been previously insisted on by Browicz, who appears to have been the first to describe blood-corpuscles and hæmoglobin crystals within the liver-cells.[1] Browicz also described canaliculi within the liver-cells (fig. 830), but failed to notice their relation to the blood-sinusoids. In icterus neonatorum he found crystals of bilirubin within the nuclei of cells. The passage of

[1] Anz. d. Akad. d. Wiss. in Krakau, 1897, 1898, 1899, and 1905; Arch. f. mikr. Anat. lv. 1900.



Preparations showing the close relations subsisting between the blood and the hepatic cells (Herring and Simpson).

(For description see text.)

injection-material from the blood-vessels into the cells was noticed in the frog by J. H. and E. H. Fraser in 1895.[1]

Bile-canaliculi.—The external secretion—the bile—issues from the cells by a special path. Everywhere between the cells, on the sides which are not in contact with the blood-channels, fine canals—the bile-canaliculi—penetrate, enclosing the cells within the meshes of a network of minute tubules which penetrate to all parts of the lobule (figs. 831, 832).

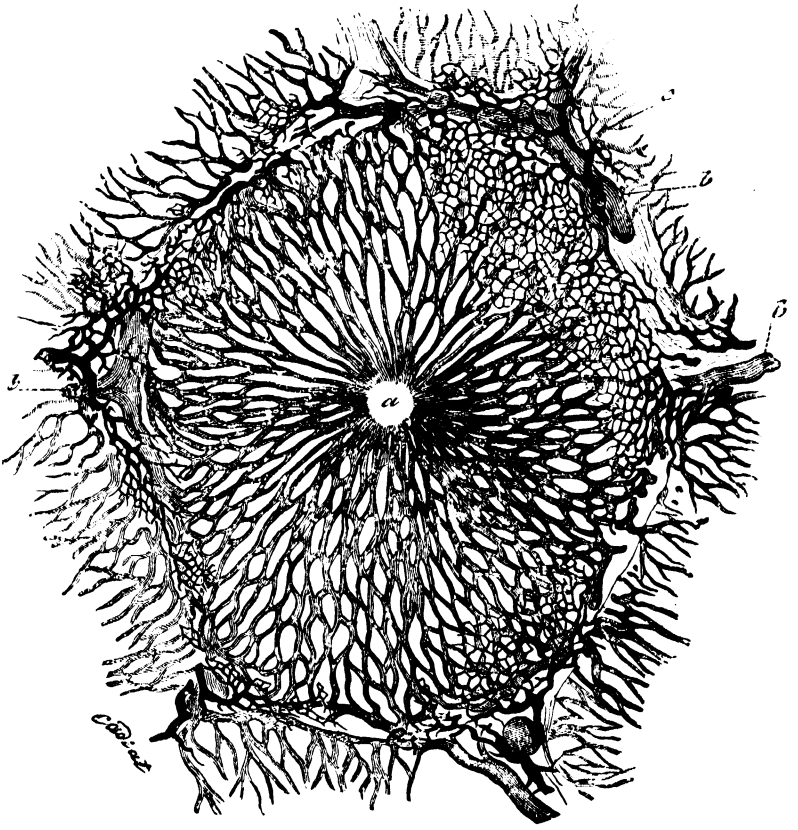


FIG. 831.—SECTION OF A LIVER-LOBULE WITH THE BLOOD-VESSELS AND DUCTS INJECTED. (Cadiat.)

b, *b*, interlobular veins; *a*, intralobular vein; *c*, interlobular bile-ducts, with which the bile canaliculi from the lobule are connected. The canaliculi have only become injected in the peripheral parts of the lobule.

The canaliculi may be shown by injecting the bile-ducts, and also by introducing sulph-indigotate of soda into the blood and after a certain lapse of time killing the animal and examining the liver, since this colouring-matter is secreted with the bile. But the most ready way to exhibit the canaliculi is by treating small portions of liver by the Golgi chromate-of-silver method.[2]

At the surface of the lobules the bile-canals are larger and are surrounded by cubical epithelium-cells, which on the one hand merge into the columnar cells lining the interlobular bile-ducts, and on the other are continuous with the cells of the liver-lobule. In this way the bile is conducted from all parts of the lobule to its periphery and passes there into the interlobular ducts; these convey it towards the

[1] Journ. Anat. and Physiol. xxix. 1895.
[2] See on the biliary canaliculi in animals G. Retzius, Biol. Unters. iii. 1891 and iv. 1892.

portal fissure and so away by the hepatic duct. This last joins with the duct of the gall-bladder to form the common bile-duct, which opens into the duodenum along with the duct of the pancreas.

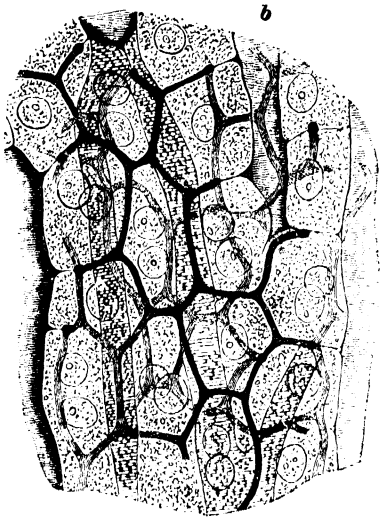


FIG. 832.—SECTION OF RABBIT'S LIVER WITH THE INTERCELLULAR NETWORK OF BILE-CANALICULI INJECTED. (E. Hering.) Highly magnified.

Two or three layers of cells are represented; *b*, *b*, blood-capillaries.

F. B. Mall[1] has pointed out that although the hepatic lobules appear to represent units of liver-substance—especially in such animals as the pig and camel, in which they are entirely surrounded and separated from one another by connective tissue continuous with that of Glisson's capsule—nevertheless it is logical to regard as the true gland-unit the area of liver-substance drained by the ultimate branch of one of the interlobular bile-ducts, and supplied with blood by the ultimate branch of one of the interlobular portal veins and by the accompanying branch of the hepatic artery. Such an area would include portions of several of the units usually described as liver-lobules, and would more accurately represent the lobule of an ordinary gland, which is always the part connected with the expansion—simple or branched—of the end of a gland-duct, and always receives the terminal branch of an artery.

The **hepatic cells** are protoplasmic bodies, polyhedral in shape; many of them have two nuclei. They contain granules and globules of various kinds, such as pigment, fat, and glycogen (fig. 827), but true secretion-granules have not been demonstrated within them. They are probably united with one another throughout the lobule into a syncytium by protoplasmic bridges; the intracellular canaliculi are continuous across these bridges. The secretion which the liver-cells form passes into the intercellular bile-canals by fine channels in the protoplasm of the cells (fig. 833), but it is uncertain if these intracellular channels are preformed or not.

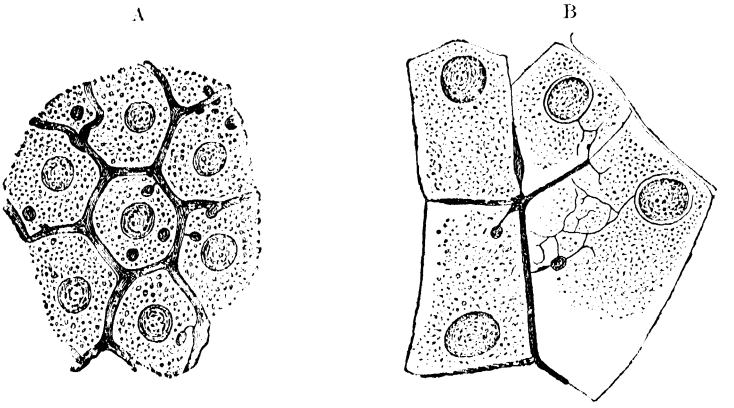


FIG. 833.—SKETCHES ILLUSTRATING THE MODE OF COMMENCEMENT OF THE BILE-CANALICULI WITHIN THE LIVER-CELLS. (Heidenhain, after Kupffer.)

A. Canaliculi of the rabbit's liver artificially injected from the hepatic duct with Berlin-blue solution. The intercellular canaliculi are seen to give off minute twigs, which penetrate into the liver-cells, and there terminate in vacuole-like enlargements.

B. From a frog's liver naturally injected with sulph-indigotate of soda. A similar appearance is obtained, but the communicating twigs are ramified.

[1] American Journal of Anatomy v. 1905. A similar view of liver-structure has been put forward by Sabourin (see Prenant and Bouin, Histologie, t. ii. 1911).

Nerve-fibrils have been seen passing to the cells and terminating amongst them (fig. 834) and even within them.[1]

Lymphatics.—Although the lymph of the liver has not the same relationship to its cells as obtains with other glands, there is no lack of lymphatics either in the connective tissue of the capsule of Glisson, or in that which accompanies the tributaries of the hepatic veins, and a large amount of lymph is formed in the liver and passes out from it by both sets of vessels. It can, however, only enter these vessels at the periphery of the lobules (where they communicate with one another), for, contrary to what is generally believed and taught, no lymph-vessels penetrate into the lobule. The descriptions given of lymph-spaces surrounding capil-

FIG. 834.—PLEXUS OF NERVE-FIBRILS WITHIN A HEPATIC LOBULE OF THE PIGEON. (Korolkow.) Methylene-blue method.

a a, axis-cylinders of nerve-fibres, passing between the cell-trabeculæ of the lobule, *c*; *b b*, fibrils ramifying over the cells of the trabeculæ.

laries within the lobule are due to a misinterpretation of injected preparations; as a matter of fact there is no interval between the blood-channels and hepatic cells.[2]

The lymphatics which pass out by the portal fissure are joined by a considerable lymph-vessel from the gall-bladder. The connective-tissue capsule of the liver appears to be devoid of lymphatics, but an efferent vessel passes round from the portal fissure into the suspensory ligament and conveys part of the lymph of the organ towards the diaphragm.

Bile-ducts and gall-bladder.—The branches of the bile-duct within the capsule of Glisson are formed of a basement-membrane lined with clear columnar cells. The hepatic duct has in addition a coat composed of fibrous and plain muscular tissue running circularly, and this is also the structure of the cystic duct and of the common bile-duct. The larger branches of the bile-ducts within the

[1] Korolkow, Anat. Anz. viii. 1893. See also A. B. Macallum, Quart. Journ. Micr. Sci. xxvii. 1887; H. J. Berkley, Anat. Anz. viii. 1893; Allegra, Anat. Anz. xxv. 1904.

[2] See on the lymphatics of the liver Herring and Simpson (*op. cit.*). Full reference to the literature of the subject will be found in their paper.

liver, as well as the main hepatic, cystic, and common bile-ducts, have small compound tubulo-racemose glands opening on their inner surface (fig. 835). In most parts the glands are numerous, but they become rarer in the cystic duct, near the

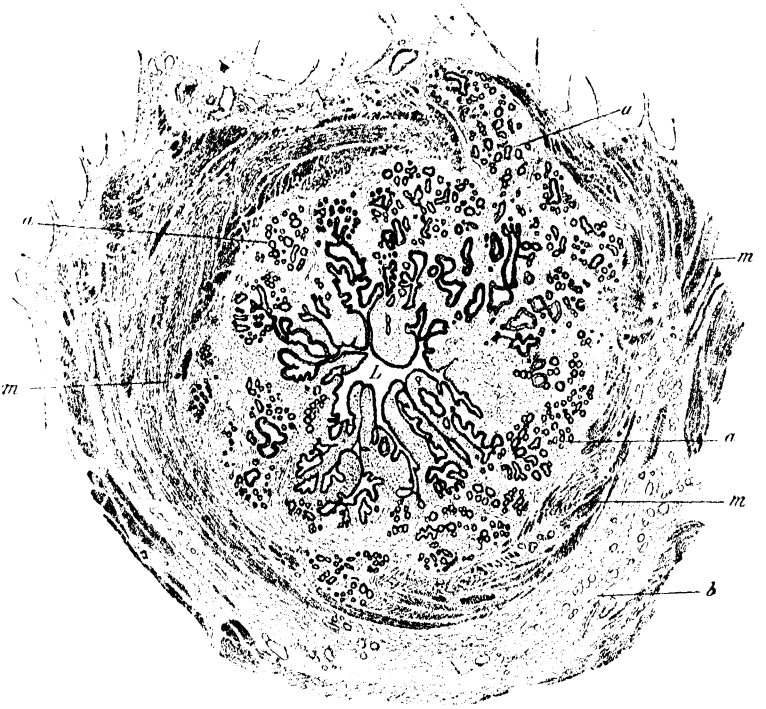


FIG. 835.—SECTION ACROSS HEPATIC DUCT. (v. Ebner.) Magnified 16 diameters.

L, lumen of duct rendered irregular by folds and by the orifices of numerous small glands which open into it; *a*, alveoli of glands; *b*, loose connective tissue with blood-vessels and a few fat-cells; *m*, plain muscle-fibres, for the most part taking a circular direction.

gall-bladder, and in the latter are generally altogether absent: if present they are found near the neck. In the neighbourhood of the portal fissure they are very ex-

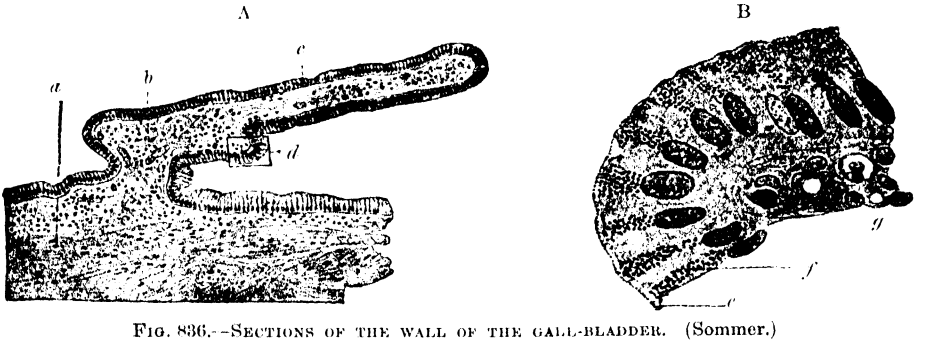


FIG. 836.—SECTIONS OF THE WALL OF THE GALL-BLADDER. (Sommer.)

A, Under a low magnifying power. *a*, muscular coat; *b*, a fold of mucous membrane; *c*, columnar epithelium; *d*, portion represented in B more highly magnified.

B, magnified portion of epithelium and subjacent corium. *e*, striated border; *f*, mucigen-granules in cells; *g*, blood-capillaries.

tensively developed in connexion with the hepatic duct. Besides these true glands there occur diverticula of varying size and length leading off from the hepatic duct and its larger branches, which ramify in the connective tissue of the capsule of

Glisson, in which they form a network of anastomosing tubules. All these glands and diverticula are lined by columnar epithelium, amongst which are found a varying number of goblet-cells.

The **gall-bladder** has a mucous membrane internally, lined with columnar cells (fig. 836) : this membrane is commonly thrown into folds (rugæ), some of which near the neck are permanent. Externally to the mucous membrane are a fibrous and a muscular coat, with a considerable amount of elastic tissue. The liver is the only gland of the alimentary canal provided with a reservoir in which secretion can be stored in the intervals of its discharge. Some animals are destitute of a gall-bladder.

The epithelium of the gall-bladder resembles on the whole that which lines the small intestine (fig. 836, B), and is usually stated to have a similar striated border. The cells secrete mucus. According to Sobotta and Sommer[1] the appearance of a border is produced by mucin-droplets, which are also seen in the greater part of the cell-body. The nuclei lie near the base of the cells.

Agata[2] has described a net-like structure within the cells lining the gall-bladder similar to that which has been noticed in other columnar epithelium-cells (see p. 25).

[1] Verhandl. d. Anat. Gesellsch. in Anat. Anz. 1909.
[2] Arch. f. mikr. Anat. lxxvii. Abt. I. 1911.

Both in general structure and in mode of development the lungs resemble secreting glands, the chief difference being that the comparatively thick protoplasmic cells of the alveoli of secreting glands become represented after birth in the pulmonary alveoli by a very thin flattened epithelium, which can only be brought clearly to view by the use of the silver-nitrate method. The ducts of a secreting gland are represented in the lungs by the trachea and bronchi with all their ramifications in the substance of these organs. A section of developing lung is in fact by no means unlike a section of a developing tubulo-racemose gland, as may be seen by referring to fig. 854. The function of the lungs in respiration necessitates rhythmic changes in their volume, and this is permitted by their enclosure within the thorax, all the changes of volume of which they readily and uniformly follow. The outer surface of the lung glides over the inner surface of the thoracic cage by virtue of the fact that the cavity in which the lung lies is lined by a serous membrane (pleura) which is reflected over its surface. Each lung is therefore free to move except at the part on its inner surface, the hilum or root, where this reflection occurs, and there the bronchi and the blood- and lymph-vessels and nerves enter or leave the organ.

The upper end of the trachea at its opening into the pharynx is modified to form the larynx or organ of voice. The structure of this will be first considered.

THE LARYNX.

The larynx is formed of a number of separate cartilages held together by fibrous tissue and capable of being moved by muscles, some of which (extrinsic muscles) pass to them from outside and others (intrinsic muscles) either extend from one cartilage to the other or are so disposed as to produce constriction of the orifice. Of the several cartilages which make up the framework of the larynx the two largest, viz. the *thyroid* and *cricoid*, are of the hyaline variety; the *arytenoids* are mainly hyaline, but acquire elastic fibres at their apices and in their vocal processes, whilst the *cartilage of the epiglottis*, the *cartilages of Santorini*, and the *cartilages of Wrisberg* (when present) are elastic cartilage. Those which are hyaline show a tendency to ossify: this process may begin as early as the twentieth year in the thyroid and cricoid, and a few years later in the arytenoids.

The cavity of the larynx is divided into an upper and a lower compartment by the comparatively narrow aperture of the glottis, or *rima glottidis*, the margins of which, in their anterior two-thirds, are formed by the lower or *true vocal cords*; the whole laryngeal cavity, viewed in transverse vertical section (fig. 837), thus presents the appearance of an hour-glass. The upper compartment, often called the *vestibule*, communicates with the pharynx by the *superior aperture* of the larynx, and contains immediately above the rima glottidis the *ventricles* (*s*), with their pouches or *saccules* (*s'*), and the upper or *false vocal cords*. The lower compartment passes inferiorly into the tube of the windpipe without any marked constriction or delimitation between them. The whole of the interior of the larynx is lined by mucous membrane.

The **superior vocal cords** or ventricular bands, also called *false vocal cords*, because they are not immediately concerned in the production of the voice, are prominent rounded folds of mucous membrane enclosing very numerous glands. They form somewhat arched projections, immediately above the corresponding ventricle (fig. 838, *b*).

The **inferior** or **true vocal cords,** the structures by the vibration of which the sounds of the voice are produced, bound the anterior two-thirds of the aperture of the glottis, corresponding with the thyro-arytenoid ligaments, the projecting edge of which forms the vocal cord on each side. The cords are situated at the inner and free edge of a mass of tissue triangular on coronal section (fig. 838). One surface of this mass looks upwards, and forms the floor of the ventricle, another looks downwards and inwards, and bounds the lower division of the laryngeal cavity, while the third is external and is in contact with the antero-posterior bundles of the thyro-arytenoid muscle. The cords themselves are composed of closely arranged fine elastic fibres which extend from the angle of the thyroid cartilage in front to the vocal process of each arytenoid cartilage behind. The vocal cords are continuous above and below with the adjacent elastic tissue and elastic ligaments of the larynx. The mucous membrane covering them is so thin and closely adherent as to show the yellowish colour of the ligaments through it.

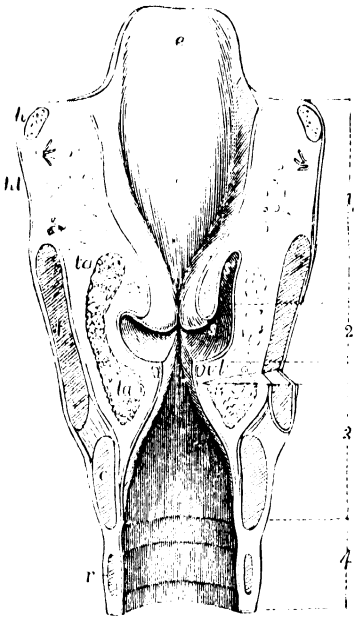


FIG. 837.—ANTERIOR HALF OF A CORONAL SECTION THROUGH THE LARYNX NEAR ITS MIDDLE. (Allen Thomson.)

1, upper division of the laryngeal cavity; 2, central portion; 3, lower division, continued into 4, trachea; *e*, the free part of the epiglottis; *e'*, its cushion; *h*, great cornu of the hyoid bone; *ht*, thyro-hyoid membrane; *t*, thyroid cartilage; *c*, cricoid cartilage; *r*, first ring of the trachea; *ta*, thyro-arytenoid muscle; *vl*, inferior thyro-arytenoid ligament in the membrane of the true vocal cord at the rima glottidis; *s*, the ventricle; above this, the superior or false cords; *s'*, the sacculus or pouch opened on the right side by carrying the section further forward.

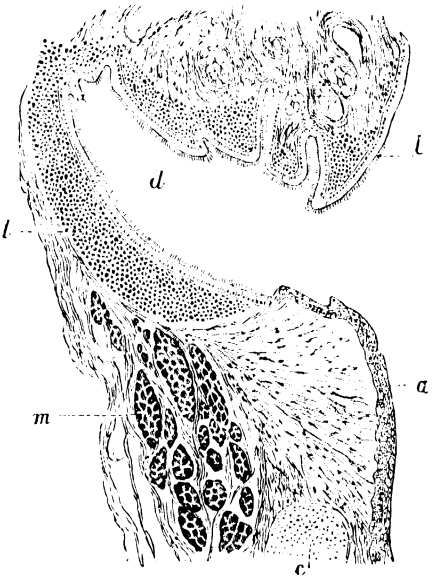


FIG. 838. VERTICAL SECTION THROUGH THE VENTRICLE OF THE LARYNX OF A CHILD. (Klein.)

a, stratified epithelium over true vocal cord; *b*, ciliated epithelium over false vocal cord; *c*, nodule of elastic cartilage (cartilage of Luschka); *d*, ventricle; *l*, lymphoid tissue; *m*, bundles of thyro-arytenoid muscle, cut across.

A small nodule of elastic cartilage (*cartilage of Luschka*) is found in the anterior and inferior part of the vocal cord (fig. 838, *c*).

The **ventricles** or **sinuses** of the larynx (fig. 837) lie between the false and true vocal cords (fig. 838, *d*). They are lined by ciliated epithelium; their mucous membrane contains a large amount of lymphoid tissue.

The small recess named the *laryngeal pouch* leads from the anterior part of the ventricle upwards, for the space of half an inch. Numerous small mucous glands, sixty or seventy in number, open into its interior, and it is surrounded by a quantity of fat.

The **mucous membrane of the larynx.**—The laryngeal mucous membrane is thin and of a pale colour. In some situations it adheres closely to the subjacent parts, especially on the epiglottis, and still more so in passing over the true vocal cords, on which it is very thin. In and near the aryteno-epiglottic folds it covers a quantity of loose areolar tissue, which is liable in disease to infiltration, constituting œdema of the glottis. Like the mucous membrane in the rest of the air-passages, that of the larynx is covered in the greater part of its extent with a columnar epithelium provided with cilia (fig. 839) by the action of which the mucus is urged upwards; but at the edges of the superior orifice and over the upper part of the back of the epiglottis the epithelium assumes a stratified form, as in the pharynx and mouth. Upon the true vocal cords also the epithelium is stratified, although both above and below them it is columnar and ciliated. Patches of stratified epithelium are likewise found here and there in the ciliated tract above the glottis. The anterior surface of the epiglottis is covered by stratified epithelium, which is thicker than that on the posterior surface where no microscopic papillæ project into it from the corium. Taste-buds are here and there found imbedded in the stratified epithelium of the larynx (but not over the vocal cords). The ciliated epithelium-cells, between which numerous goblet-cells occur, rest on a thick basement-membrane, and the corium of the mucous membrane below this contains much lymphoid tissue and many elastic fibres (fig. 839), as in the trachea.

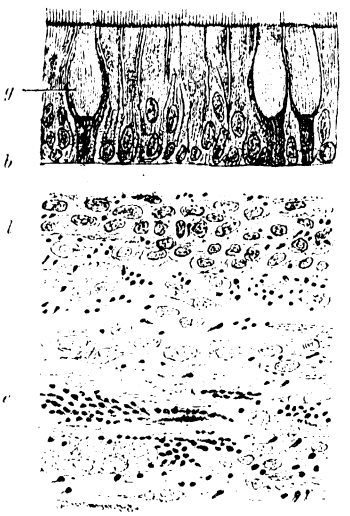
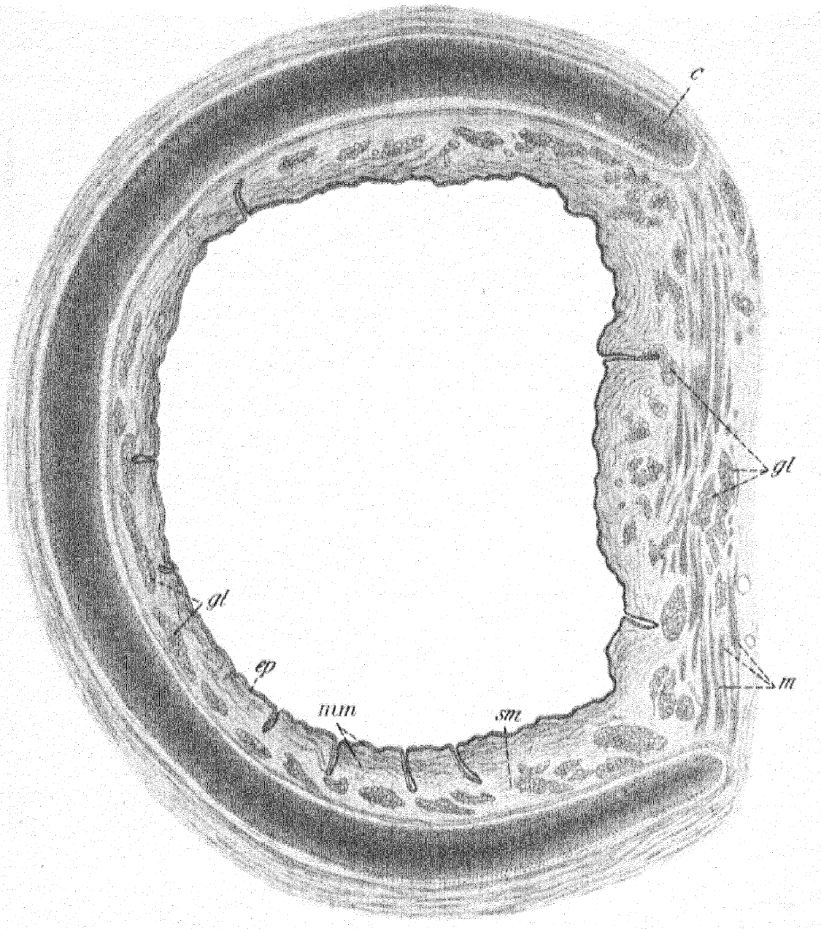


FIG. 839.—SECTION OF MUCOUS MEMBRANE OF LARYNX. (Merkel.)

g, a goblet-cell amongst the ciliated epithelium-cells; *b*, basement-membrane; *l*, lymphoid tissue; *e*, elastic fibres, cut across.

The lining membrane of the larynx is provided with *tubulo-racemose glands*, which secrete an abundant mucus. Their orifices may be seen almost everywhere excepting upon and near the true vocal cords. They abound particularly upon the epiglottis, in the substance of which are found upwards of fifty small compound glands, some of them perforating the cartilage. Between the anterior surface of the epiglottis, the hyoid bone, and the root of the tongue is a mass of yellowish fat, erroneously named the epiglottic gland, in or upon which some small glands may exist. Another collection of glands is placed within the fold of mucous membrane in front of each arytenoid cartilage, from which a series may be traced forwards, along the corresponding superior vocal cord. The glands of the laryngeal pouches have already been noticed.

Vessels and nerves of the larynx.—The *arteries* of the larynx are derived from the superior thyroid, a branch of the external carotid, and from the inferior thyroid, a branch of the subclavian. The *veins* join the superior, middle, and inferior thyroid veins. The *lymphatics* are divisible into two sets, upper and lower. The upper pierce the thyro-hyoid membrane and join glands near the bifurcation of the common carotid artery; the lower pass through the crico-thyroid membrane, and end either in one or two small glands often found in front of that membrane, or in some inferior laryngeal glands at the side of the lower part of the larynx. Their mode of distribution resembles that in the trachea. The *nerves* are supplied



Section across the trachea of an eight-year old child (Sobotta). Magnified 6½ diameters. Haematoxylin-eosin.

ep, epithelium; *gl*, glands; *c*, cartilage; *m*, muscular layer; *sm*, submucosa; *mm*, mucous membrane.

from the superior laryngeal and inferior or recurrent laryngeal branches of the pneumogastric nerves, joined by branches of the sympathetic. The superior laryngeal nerves supply the mucous membrane and the crico-thyroid muscles, and also, in part, the arytenoid muscle. The inferior laryngeal nerves supply, in part, the arytenoid muscle, and all the other muscles, excepting the crico-thyroid.

The superior and inferior laryngeal nerves of each side communicate with each other in two places, viz. at the back of the larynx beneath the pharyngeal mucous membrane, and on the side of the larynx under the ala of the thyroid cartilage. Numerous ganglion-cells are found on the branches, both on those which enter the muscles, and on those under the mucous membrane. End-bulbs are also found in the mucous membrane which covers the posterior surface of the epiglottis (Lindemann). Other nerve-bundles enter the epithelium, within which they end in arborisations of fine fibrils (fig. 840).

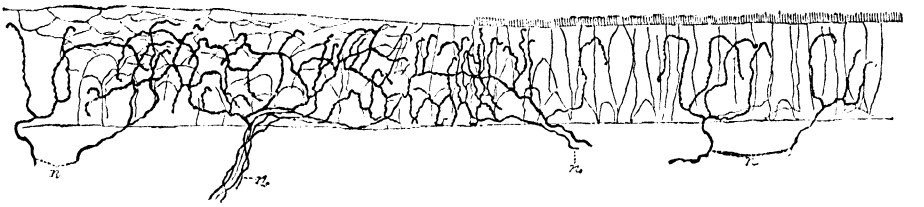


FIG. 840.—INTRA-EPITHELIAL NERVE-TERMINATIONS IN THE LARYNX. (G. Retzius.)
Silver-chromate preparation.

The section is taken at a place where the ciliated epithelium passes into stratified.

The following papers relate to the minute structure of the larynx; Benda, Arch. f. Physiol. 1895 (vocal cords); Boldyrew, Arch. f. mikr. Anat. vii. 1871 (nerves and vessels); Chievitz, Arch. f. Anat. 1882 (ossif.); Dion, Arch. f. mikr. Anat. xi. 1875; H. Eichler, Arch. f. Anat. 1911 (larynx of domestic animals); S. Exner, Sitz. d. Wiener Akad. 1884, Virch. Arch. cxxxi. 1893 and Arch. f. Physiol. 1893 (nerves); Fränkel, Arch. f. Laryngol. vii. 1893 (vocal cords); Friedrich, Arch. f. Laryngol. iv. 1896; Sophie Fuchs-Holfring, Arch. f. mikr. Anat. lii. 1898 and liv. 1899 (glands); Heymann, Virch. Arch. cxviii. 1889 (epithelium and glands); Kanthack, Virch. Arch. cxvii. 1889 (vocal cords); Luschka, Arch. f. mikr. Anat. v. 1869 (ventricle); F. Merkel, article 'Kehlkopf,' in v. Bardeleben's Handbuch der Anatomie, 1902; Reinke, Anat. Hefte, ix. 1897 (vocal cords); G. Retzius, Biol. Unters. iv. 1892 (nerves); W. Stirling, Journ. Anat. and Physiol. xvii. 1883 (nerves of epiglottis); Verson in Stricker's Handbook, 1871.

THE TRACHEA AND BRONCHI.

TRACHEA.—The trachea consists of a framework of incomplete cartilaginous rings or hoops united by fibrous and elastic connective tissue, and behind, where the tube is flattened, by plain muscular tissue also. It is lined throughout by a mucous membrane, and provided with glands.

The **cartilages** are from sixteen to twenty in number. Each forms a curve of rather more than two-thirds of a circle, resembling the letter C (see accompanying Plate). The depth of each cartilage from above downwards is three or four millimetres, and the thickness 1 mm. The outer surface of each is flat, but the inner is convex from above downwards, so as to give greater thickness in the middle than at the upper and lower edge. The cartilages are held together by strong connective tissue, which is elastic and yielding to a certain extent, and not only occupies the intervals between the cartilages, but is prolonged over their outer and inner surfaces, so that they are, as it were, imbedded in the tissue.

The cartilages terminate abruptly behind by rounded ends, but the connective tissue is continued across between them, and completes the tube; in this situation it is looser in its texture.

The first or highest cartilage, connected by the general sheet of connective tissue with the cricoid cartilage of the larynx, is broader than the rest, and often divided

at one end. Sometimes it coalesces to a greater or less extent with the cricoid or with the next hoop below. The lowest cartilage, placed at the bifurcation of the trachea, is peculiar in shape, its lower border being prolonged downwards in the middle line, and at the same time bent backwards so as to form a curved projection between the two bronchi. The cartilage next above this is slightly deepened in the middle line. Sometimes the extremities of two adjacent cartilages are united, and not infrequently a cartilage is divided at one end into two short branches, the opposite end of that next it being likewise bifurcated so as to maintain the parallelism of the entire series. The use of these cartilaginous hoops is to keep the windpipe open, a condition essential for the free passage of air into the lungs.

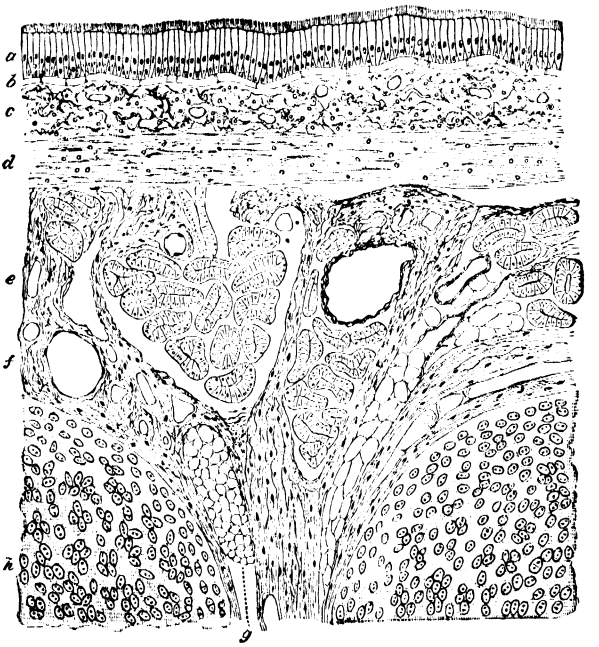


FIG. 841.—LONGITUDINAL SECTION OF THE HUMAN TRACHEA, INCLUDING PORTIONS OF TWO CARTILAGINOUS RINGS. (Klein and Noble Smith.) Moderately magnified.

a, ciliated epithelium; *b*, basement-membrane; *c*, superficial part of the mucous membrane, containing the sections of numerous capillary blood-vessels and much lymphoid tissue; *d*, deeper part of the mucous membrane, consisting mainly of elastic fibres; *e*, submucous areolar tissue, containing the larger blood-vessels, small mucous glands (their ducts and alveoli are seen in section), fat, &c.; *f*, connective tissue investing and uniting the cartilages; *g*, a small mass of adipose tissue in this layer; *h*, cartilage.

Within the sheet of connective tissue at the posterior flattened part of the trachea is a continuous pale reddish layer of *unstriped muscular fibres* (*m* in Plate), which pass across, not only between the ends of the cartilages, but also opposite the intervals; they doubtless serve to narrow the tube by approximating the ends of the cartilages. Those opposite the hoops are attached to the extremities of the latter, and encroach also for a short distance upon their inner surface. Outside the transverse fibres are a few fasciculi having a longitudinal direction.

The submucous tissue consists of loose areolar tissue which serves to connect the mucous membrane with the fibrous layer and the cartilaginous rings. It contains mucous glands, and a quantity of adipose tissue is often found in it.

The mucous membrane is smooth and of a pale pinkish white colour in health, although, when congested or inflamed, it becomes intensely purple or crimson. It contains a considerable amount of lymphoid tissue. Underneath the epithelium

is a basement-membrane (figs. 841, 842, *b*), well marked in the human trachea, through which nerves and processes from the subjacent connective-tissue cells here and there pass into the epithelium. Throughout the mucous membrane a number of fine elastic fibres are found, but in the deeper parts the elastic fibres are very large and numerous (*d*). Along the posterior membranous part they are more abundant than elsewhere, and are there collected into distinct longitudinal bundles, which produce visible elevations or flutings of the mucous membrane. These bundles are particularly strong and numerous opposite the bifurcation of the trachea.

The epithelium consists of a layer of long columnar ciliated cells, often very irregular at their fixed end, where they are impressed by smaller cells, between which they penetrate to reach the basement-membrane. The cilia serve to drive the mucous secretion upwards towards the larynx. Between these ciliated cells are found others, also

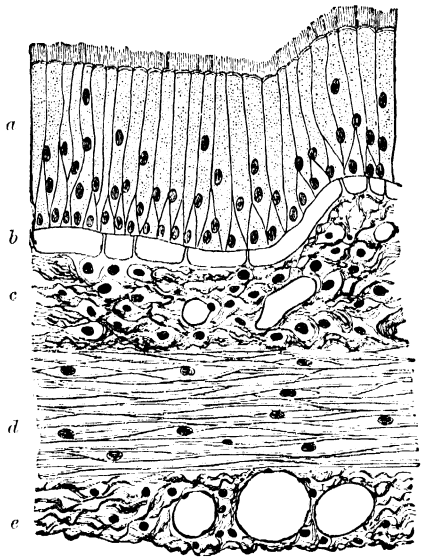


FIG. 842.—A PART OF THE SECTION REPRESENTED IN THE PRECEDING FIGURE MORE HIGHLY MAGNIFIED. (Klein and Noble Smith.)

The letters represent the same parts as in that figure.

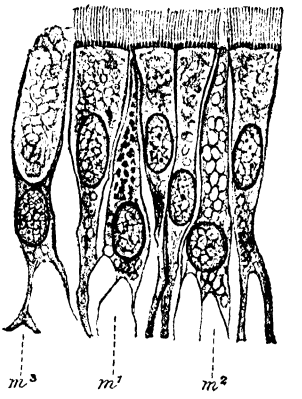


FIG. 843.—CILIATED EPITHELIUM-CELLS FROM THE TRACHEA OF THE RABBIT. (Schäfer.) Highly magnified.

m^1, m^2, m^3, mucus-secreting cells, lying between the ciliated cells, and seen in various stages of mucin-formation.

elongated; they are prolonged at one end towards the surface, whilst the other end, which is not infrequently forked, reaches to the subjacent membrane. These intermediate cells secrete mucus, the globules of which are to be seen in them in various stages of formation; some are seen to have become converted into goblet-cells by the extrusion of their mucinoid contents (fig. 843). A few lymph-corpuscles are also found amongst the epithelial cells, as in other epithelia.

The trachea is provided with numerous small *mucous glands*. The largest are situated at the back part of the tube, either close upon the outer surface of the fibrous layer, or occupying little recesses formed between its meshes. Smaller glands are found between the cartilaginous rings upon and within the fibrous membrane, and still smaller ones close beneath the mucous membrane. They are racemose glands, and their alveoli are lined by columnar epithelium: the excretory ducts pass through the muscular layer and the mucous membrane, on the surface of which their orifices are perceptible.

Vessels and nerves.—The *arteries* of the trachea are principally derived from the inferior thyroid. The larger branches run for some distance longitudinally and then join a superficial capillary plexus with polyhedral meshes. The *veins*

enter the adjacent plexuses of the thyroid veins. A rich plexus of *lymphatics* may readily be injected in the mucous membrane and submucous tissue, where they form separate networks, but the lymphoid follicles, so common in the alimentary mucous membrane, and also in the walls of the smaller bronchi, are rarely present. When they occur they usually surround the ducts of the glands as they pass through the mucous membrane. The nerves come from the trunk and recurrent branches of the pneumogastric, and from the sympathetic system. There are numerous ganglia upon them, especially outside the muscular layer at the back of the tube. Nerve-fibrils penetrate between the epithelium-cells.

In the dog, cat, sheep, and rabbit, the upper half of the trachea is supplied chiefly by the superior laryngeal nerve, through the anastomosis between the superior and inferior nerves in the larynx (Kandarazi).

Bronchi.—The general structure of the undivided portions of the bronchi corresponds with that of the trachea in every particular. Their cartilaginous rings, which resemble those of the trachea in being imperfect behind, are, however, shorter and narrower. The number of these rings on the right side varies from six to eight, whilst on the left the number is from nine to twelve.

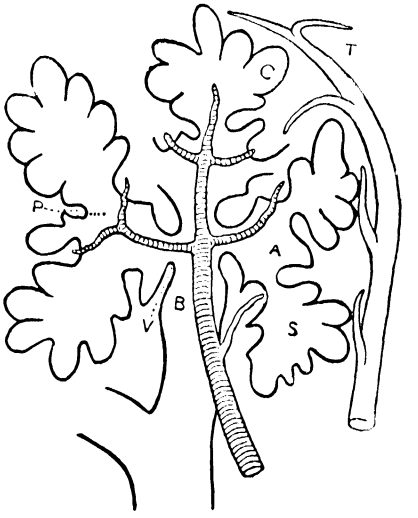


Fig. 844.—Diagram of the ending of a bronchial tube. (W. S. Miller.)

B, termination of lobular bronchiole in V, vestibule, by means of which it communicates with the atria, A; S, air-sac, opening out of atrium, and beset with air-cells, C; P, lobular arteriole; T, one of the lobular venules.

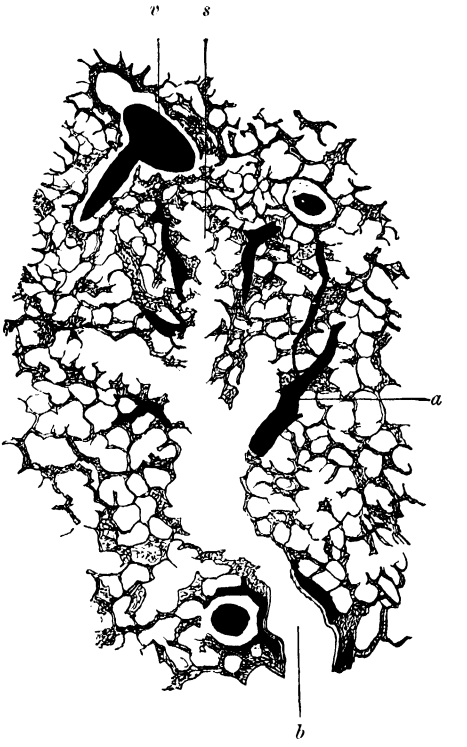


Fig. 845.—Section of lung (human). (F. Merkel.) Low power.

a, artery; *v*, vein; *b*, small bronchial tube opening into terminal or lobular bronchiole, which communicates with the groups of alveoli (air-sacs, *s*).

The bronchi are supplied by the bronchial arteries and veins, and the nerves are from the same source as those of the trachea.

THE LUNGS.

Termination of the bronchi; structure of the bronchial tubes.—The principal divisions of the bronchi, as they pass into the lungs, divide into tubes of less calibre, and these again subdivide in succession into smaller and smaller tubes, often distinguished as *bronchia, bronchioles,* or *bronchial tubes,* which, diverging in all directions, never anastomose, but terminate separately. The larger

branches pass off at acute angles, but the more remote and smaller ramifications spring less acutely. After a certain stage of subdivision each bronchial tube, reduced to a small size (about 0·2 mm.), is termed a *lobular* or *terminal bronchiole*, and its walls become beset here and there with small hemispherical saccules, termed

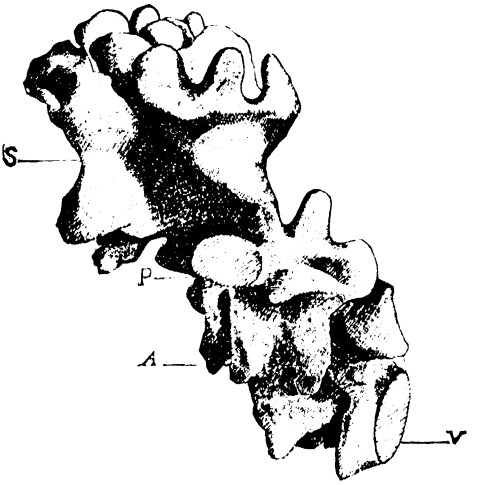


FIG. 846.—CAST OF LOBULE OF DOG'S LUNG, SHOWING A SINGLE INFUNDIBULUM OR AIR-SAC. (W. S. Miller.)

A, atrium; *V*, vestibule; *S*, air-sac (infundibulum); *P*, section of the neck of a second air-sac (cut away). The irregular projections on the atrium and air-sac are the alveoli.

air-cells, or *alveoli*. Each lobular bronchiole ends in a so-called *vestibule*, out of which open dilatations, which have been termed *atria* by W. S. Miller. Each atrium is continued into two or more blind and sacculated diverticula, the *infundibula*, or *air-sacs* (Miller): their walls are completely covered with alveoli, which are also found on the walls of the vestibule and atrium (figs. 844 to 846).

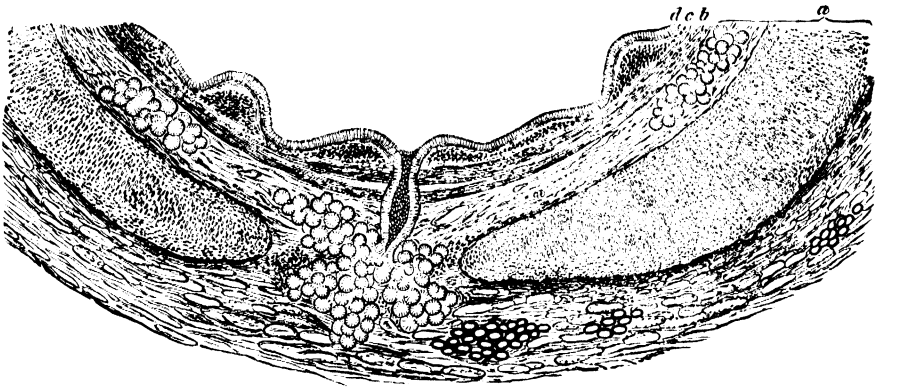


FIG. 847.—PORTION OF A TRANSVERSE SECTION OF A BRONCHIAL TUBE, HUMAN (6 MM. IN DIAMETER). (F. E. Schultze.) Magnified 30 diameters.

a, cartilage and fibrous layer with mucous glands, and, in the outer part, a little fat; in the middle, the duct of a gland opens on the inner surface of the tube; *b*, annular layer of involuntary muscular fibres; *c*, elastic layer, the elastic fibres in bundles which are seen cut across; *d*, columnar ciliated epithelium.

Within the lungs the air-tubes are not flattened on one aspect like the bronchi and trachea, but form completely cylindrical tubes. Although they contain the same elements as the larger air-passages, they are reduced gradually to a state of greater tenuity, possessing throughout certain peculiarities of structure. Thus, the *cartilages*

no longer appear as imperfect rings running only upon the front and lateral surfaces of the air-tube, but are disposed over all sides of the tubes in the form of irregularly shaped plates and incomplete rings of various sizes (fig. 845). These are most

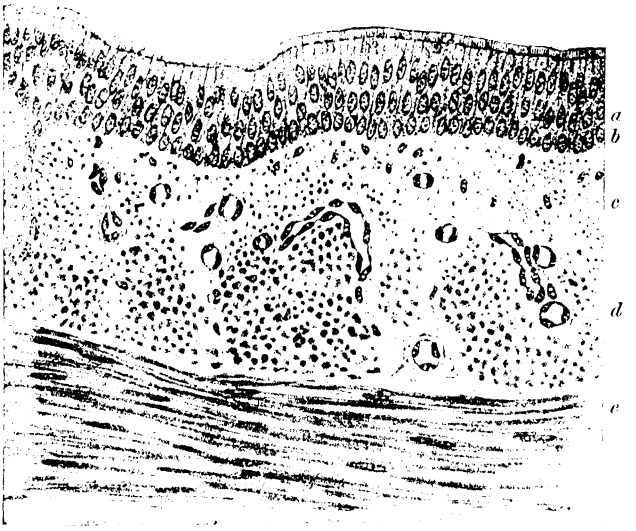


FIG. 848.—SECTION OF MUCOUS MEMBRANE AND MUSCULAR COAT OF A BRONCHIAL TUBE. (Schäfer.) Magnified 200 diameters.

a, ciliated epithelium; *b*, basement-membrane; *c*, superficial part of mucous membrane, with fine elastic fibres; *d*, deeper part with numerous coarser fibres; *e*, plain muscle of bronchus; *f*, duct of a gland passing through mucous membrane.

developed at the points of division of the bronchia, where they form a sharp concave ridge projecting inwards into the tube. They may be traced, becoming rarer and rarer and more reduced in size, as far as bronchia one millimetre in diameter,

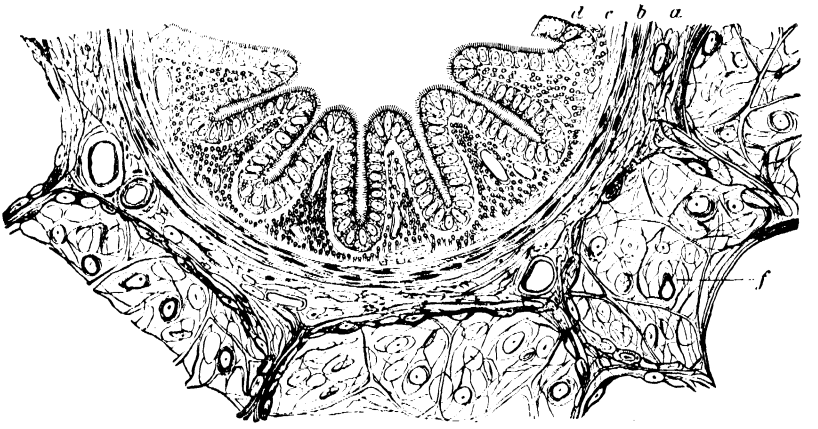


FIG. 849.—SECTION OF A SMALL BRONCHIAL TUBE (4 MM. IN DIAMETER) FROM THE PIG'S LUNG. (F. E. Schultze.) Magnified 240 diameters.

a, fibrous layer; *b*, muscular layer; *c*, mucous membrane in longitudinal folds, with numerous longitudinally running elastic fibres cut across; *d*, ciliated epithelium; *f*, surrounding alveoli.

The folding of the mucous membrane is probably the result of strong post-mortem contraction of the muscular layer.

after which they disappear. The general sheet of connective tissue extends to the smallest tubes, becoming thinner by degrees, and degenerating into areolar tissue. In it are mucous and muco-serous glands which send their ducts to open on

the mucous membrane. These occur most numerously in the larger tubes ; in those which measure less than 1 mm. they are rarely if ever found. The *mucous membrane*, which extends throughout the whole system of air-passages, is also thinner than in the trachea and bronchus, but it retains its ciliated columnar epithelium (figs. 847 to 850). The longitudinal bundles of *elastic fibres*, which chiefly lie in the deeper part of the mucous membrane, are very distinct in both the large and small bronchia, and may be followed by dissection as far as the tube can be laid open, and by the microscope into the smallest tubes (fig. 850). The *muscular fibres*, which in the trachea and bronchi are confined to the back part of the tube, surround the bronchial tubes as a continuous layer of annular fibres, lying inside the cartilaginous plates ; they are found, however, beyond the place where the cartilages cease to exist, and appear as irregular annular fasciculi even in the smallest tubes.

Pulmonary alveoli.—At the point where the small bronchial tubes lose their cylindrical character, and begin to be beset with air-cells, their structure also gradually undergoes a change. The muscular layer almost disappears, the longitudinal

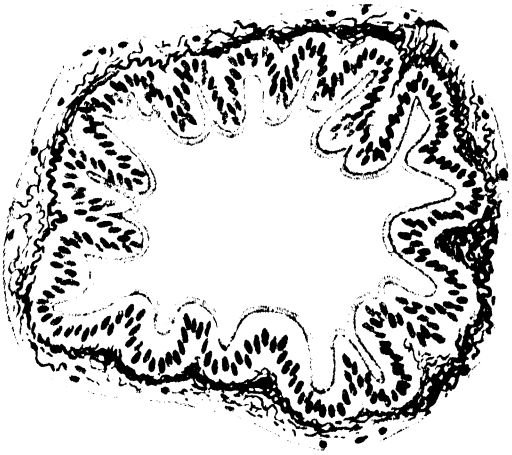


FIG. 850. SECTION OF A SMALL BRONCHIAL TUBE, HUMAN. (Sobotta.) Magnified 280 diameters. The elastic fibres of the mucous membrane are stained.

elastic bundles are broken up into an interlacement of elastic tissue, which surrounds the mouths of the air-cells and the walls of the infundibula (fig. 851), and the columnar ciliated epithelium gives place to a stratum of non-ciliated cells. The change in the character of the epithelium first occurs in the lobular bronchioles, where patches of small pavement-epithelium cells begin to appear amongst the ciliated cells, especially in the neighbourhood of the air-cells upon the walls of these tubes. At the end of the lobular bronchiole, near the atrium, all the cells which line the wall of the tube are of the non-ciliated pavement variety. But the air-cells themselves, both those which are scattered over the respiratory bronchioles and those which cover the infundibula, as well as intermediate portions of the infundibula which occur here and there between the air-cells, possess an epithelium of a peculiar character (fig. 852). The cells of this epithelium are of two kinds, viz. : 1, large, thin, very delicate cells, irregular in size and shape, lying over the blood-vessels, but also in many cases extending over the interstices between them ; and, 2, small, flat, polygonal, nucleated cells, which lie singly or in small groups of two or three, between the others, and always in the interstices of the capillary network. These are similar to the cells found in patches in the lobular bronchioles. If the lung is greatly distended they also become flattened out.

In the fœtus the alveoli are entirely lined with small granular pavement-cells, but with the distension which follows upon the first respiratory efforts most of the cells become transformed into the large thin epithelial scales above described.

The walls of the alveoli, which mainly consist of delicate fibrillated connective tissue (fig. 851), with corpuscles scattered here and there, are supported and

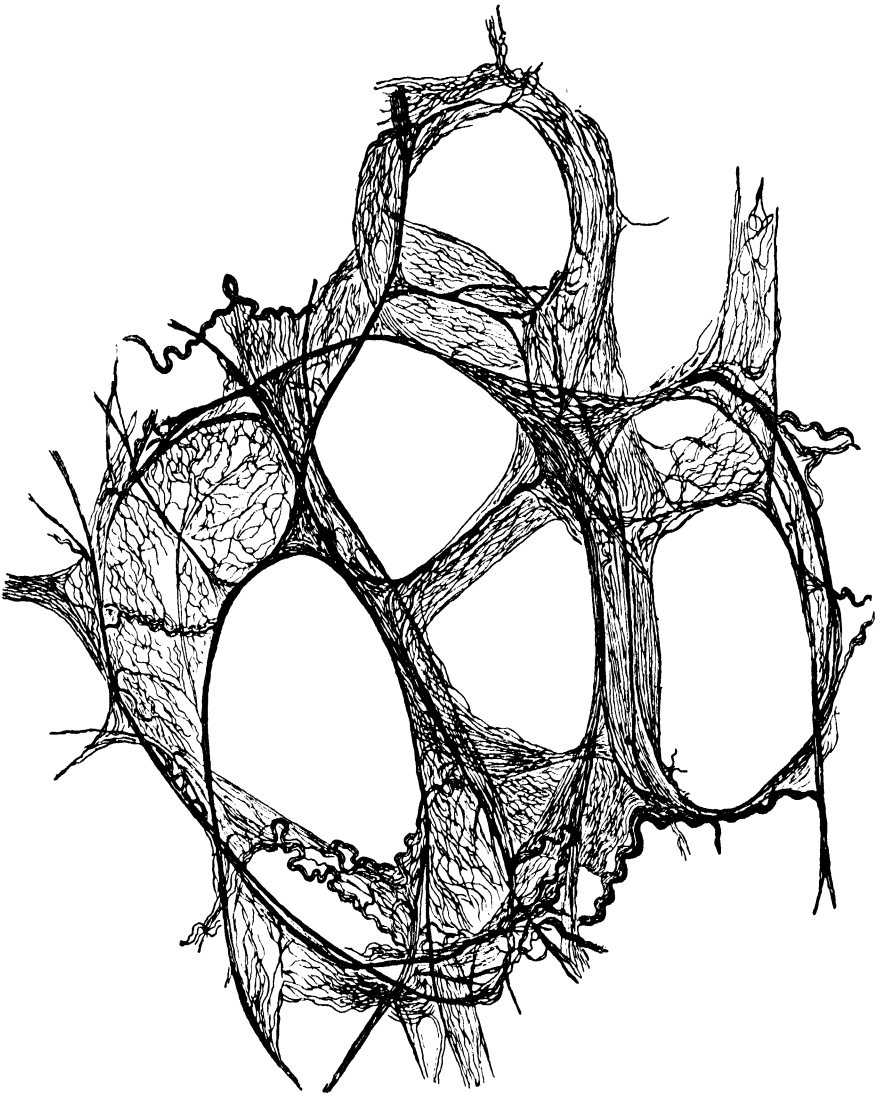


Fig. 851.—Reticular tissue of pulmonary alveoli. (F. P. Mall.) Highly magnified.

strengthened by scattered coiled elastic fibres. These fibres are especially numerous near the orifices of the alveoli, in addition to which, according to some authorities, there is likewise an intermixture of muscular fibre-cells.

The alveoli vary greatly in appearance in sections of the lung, according to the state of distension of the organ, and although they are usually described as hemispherical, their shape is generally irregularly angular, with rounded angles.

They are readily seen in a lung which has been inflated with air, although under these conditions they are usually distorted; also upon portions of lung injected with mercury or wax or collodion. In the lungs of some animals,

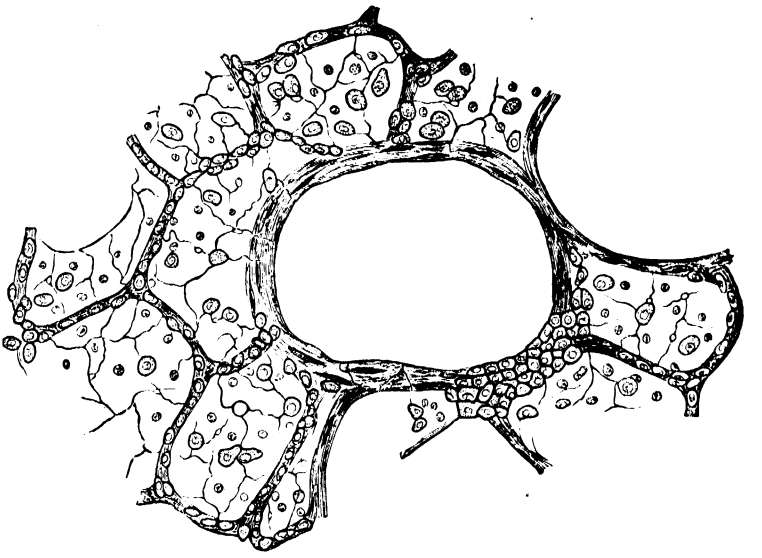


FIG. 852.—SECTION OF PART OF CAT'S LUNG, STAINED WITH NITRATE OF SILVER. (Klein and Noble Smith.) Highly magnified.

The small granular and the large flattened cells of the alveoli are shown. In the middle is a section of a terminal bronchial tube, with a patch of the granular epithelium-cells on one side.

as the lion, cat, and dog, they are large enough to be distinctly visible on the surface of the organ. In the adult human lung their diameter in a condition of moderate distension is usually about 0·25 mm. ($\frac{1}{100}$ inch), but varies from 0·1 mm. to 0·4 mm.; they are larger on the surface than in the interior, and largest towards the thin edges of the organ; they are also large at the apex of the lung. Their dimensions go on increasing from birth to old age, and they are larger in men than in women. In the infant the diameter is usually under 0·12 mm. It is calculated by Aeby that there are from 300 million to 400 million alveoli in the human lung.

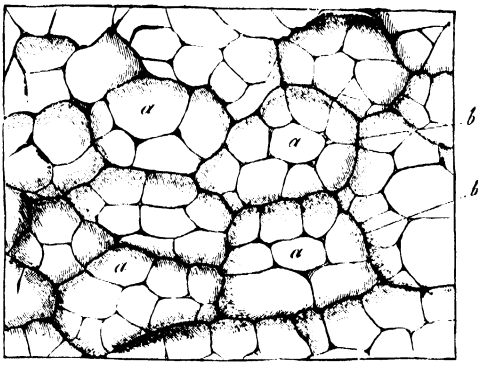


FIG. 853.—PORTION OF THE OUTER SURFACE OF THE COW'S LUNG. (From Kölliker, after Harting.) Magnified 30 diameters.

a, pulmonary alveoli filled artificially with wax; *b*, the margins of the smallest lobules.

The whole lung has therefore a lobulated structure, like that of a compound racemose gland. In the fœtus the lungs present at one time very much the appearance of a racemose gland in process of development (fig. 854). The infundibula may be regarded as corresponding to the smallest or ultimate lobules of such a gland. They are represented by polygonal areas enclosing groups of six or eight air-cells which are seen at the surface of the lung (fig. 853). They are grouped into larger or secondary lobules, and these again into yet larger divisions. The various lobules are united and separated by connective

tissue in variable amount, more between the larger and less between the smaller groups. From the mutual compression to which they are subjected the lobules and alveoli are bounded by flattened sides, and they are compactly fitted both to one another and between the larger air-tubes and vessels of the lungs.[1]

Blood-vessels, lymphatics, and nerves of the lungs. Pulmonary vessels.—The branches of the *pulmonary artery* accompany the bronchial tubes, but in their remote ramifications they subdivide further, a branch passing to each atrium, and being distributed to the capillary network of all the infundibula which open out of it (fig. 844, P). The venules commence on the outer border of the air-sacs, and course independently of the arterioles. The main arterial

FIG. 854.—FROM A SECTION OF LUNG OF PIG-EMBRYO, 13 CM. LONG, SHOWING THE GLANDULAR CHARACTER OF THE DEVELOPING ALVEOLI. (J. M. Flint.) Magnified 70 diameters.

a, interstitial connective tissue; *b*, a bronchial tube; *c*, an alveolus; *l*, lymphatic clefts *p*, pleura.

trunk runs immediately behind the main bronchial trunk, giving off corresponding branches as it proceeds. The arteries ramify without anastomoses, and the arterioles which pass to the atria send small branches, about 0·025 mm. ($\frac{1}{1000}$ inch) in diameter, between the air-cells, partially encircling their mouths (fig. 855). From these vessels the capillary network arises, and covers each alveolus, passing in the interalveolar septa between the adjacent air-cells. As was pointed out by Rainey, the capillary network in these partitions is single in the lungs of man and mammalia, the capillaries winding through the septa from one alveolus to the other, although in the lungs of amphibia and reptiles the capillary network of each alveolus is distinct.

[1] Some authors have described intercommunicating foramina between adjacent lobules or infundibula, but such intercommunication is denied by most authorities. For a discussion of the subject see F. Merkel, article 'Athmungsorgane' in von Bardeleben's Handbuch der Anatomie, 1902, pp. 108–110.

The capillaries are fine, and the network they form so close that the meshes are scarcely as wide as the vessels themselves. They are very superficial, being covered only by the thin layer of tesselated epithelium above described, while, as just mentioned, in the partitions between contiguous alveoli the vessels of the network project on either side in an arched or loop-like manner into the cavities of the alveoli. The mucous membrane of the bronchial tubes, especially near the air-cells, is partly supplied with blood from branches of the pulmonary artery.

The radicles of the *pulmonary veins* arise from the capillary network of the alveoli and from that of the smaller bronchial tubes; several venules arise from each lobule. They are collected in the septa between and outside the infundibula, apart from the terminations of the arteries and bronchioles. The branches of those veins which arise from the infundibula near the surface of the lung run alone for a certain distance through the substance of the organ. Some of them join deeper veins; others as they pass towards the hilum remain superficial, forming a wide-meshed plexus near the surface of the lung, finally tending towards the hilum to join the larger veins near the root of the lung. The veins from the more deeply lying infundibula form frequent communications, and finally coalesce into large branches, which ultimately accompany the bronchial tubes and arteries, coursing as a rule in front of the bronchial tubes, and thus proceed to the root of the lung. In their course together through the lung the artery is usually found above and behind a bronchial tube, and the vein below and in front.

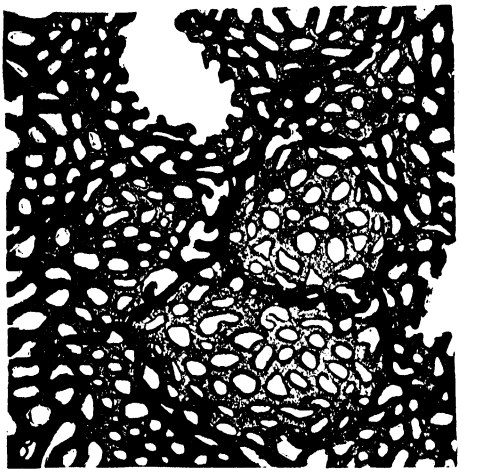


Fig. 855. Section of injected lung of rabbit, including several contiguous alveoli. (Szymonowicz.) Magnified 300 diameters.

The pulmonary vessels differ from the systemic in regard to their contents, inasmuch as the arteries convey dark blood, whilst the veins carry red blood. The pulmonary veins, unlike the other veins of the body, are not more capacious than their corresponding arteries; indeed, according to Winslow, Santorini, Haller, and others, they are somewhat less so. There is less difference in structure between these arteries and veins than between those of the systemic circulation. The pulmonary veins have no valves. The arteries of different secondary lobules are usually independent, the veins freely anastomose

Bronchial vessels.—The bronchial arteries and veins, which are much smaller than the pulmonary vessels, carry blood for the nutrition of the lung. The *bronchial arteries*, from one to three in number for each lung, arise from the aorta, or from intercostal arteries, and follow the divisions of the air-tubes through the lung. They are ultimately distributed in three ways: (1) many of their branches ramify in the bronchial lymphatic glands, in the coats of the large blood-vessels, and in the walls of the bronchial tubes, supplying an outer capillary plexus with transverse meshes to the muscular coat, and an inner plexus with close longitudinal meshes to the mucous membrane: this plexus, in the lobular bronchioles, is continuous with that supplied by the pulmonary artery; (2) others form plexuses in the interlobular areolar tissue; (3) branches pass to the surface of the lung beneath the pleura and join the network of pulmonary venous capillaries found there.

The *bronchial veins* have not quite so extensive a distribution in the lung as the bronchial arteries, since part of the blood carried by the bronchial arteries is returned by the pulmonary veins. The superficial and deep bronchial veins unite at the root of the lung, opening on the right side into the large azygos, and on the left usually into the left upper azygos vein.

According to Zuckerkandl it is not only at the extremities of the bronchial tubes that the blood brought by the bronchial arteries is returned by the pulmonary veins, but in other parts small bronchial veins open into pulmonary branches; and even veins which receive branches from the larger bronchia, from the bronchial glands, and from the posterior surface of the pericardium, empty their contents partly into the great trunks of the pulmonary veins.

A few small branches of the intercostal arteries pass to the pulmonary pleura and surface of the lung through the ligamentum latum pulmonis (Turner).

Lymphatics.—The veins are accompanied by lymphatics, which commence both in the interalveolar tissue and under the pleura, and pass to lymphatic glands at the root of the lung. Others, which eventually join these, accompany the arteries, and others are found in the walls of the bronchial tubes. In the larger bronchial tubes there may be two plexuses, one in the mucous membrane, the other outside the cartilages; the plexus in the mucous membrane lies deeper than the blood-capillaries. There are no lymph-vessels distal to the lobular bronchioles. The lymph-vessels of the bronchia send branches to join those of the pulmonary arteries and veins: these communicating branches come from the end of the lobular bronchioles and from the places where the bronchial tubes branch. The mucous membrane of the bronchi is not infrequently the seat of an accumulation of lymph-corpuscles, which may take the form of distinct nodules; the accumulations are especially well marked at the branchings of the tubes. Other accumulations of lymphoid tissue occur in the adventitia of the pulmonary arteries and veins, and under the pleura, but not as a rule in the form of nodules in the normal lung (Miller). The atria and infundibula (air-sacs) have no lymph-vessels in their walls.

The lymphatics of the lung often contain large mononuclear leucocytes (phagocytes) with carbon particles in their interior. These particles are conveyed to and deposited in the connective tissue of the lung in various parts, especially in those parts which contain lymphoid tissue; some of them are carried to the bronchial glands at the root of the lung. Such particles scattered about in the interlobular connective tissue give a slaty-grey appearance to the organ. The carbon particles are introduced with the air of respiration and appear to be conveyed from the interior of the alveoli into the pulmonary tissues by the agency of leucocytes, which are often seen, in sections of lung, within the air-cells.

Nerves of the lung.—Nerves pass to the lung through the pulmonary plexuses both from the vagi and from the sympathetic system, the fibres of the former being medullated, of the latter chiefly non-medullated. They have ganglia upon their course, around the cells of which many of the medullated fibres end, but some—probably of afferent nature—pass without interruption to be distributed to the mucous membrane of the bronchial tubes and also over the walls of the alveoli. Most of the efferent fibres are destined for the musculature of the bronchial tubes and blood-vessels.

THE PLEURA.

The pleura has the usual structure of serous membranes. The costal part is the thicker, and may be easily raised from the ribs and intercostal spaces. It is strengthened here by a layer of subserous areolar tissue of considerable thickness. On the pericardium and diaphragm the pleura is thinner and more firmly adherent; it is thinnest and least easily detached upon the surface of the lungs. A difference is also noticeable in the character of the superficial epithelial layer, for while on the *pleura costalis* this consists of the ordinary flattened cells, on the *pleura pulmonalis* the cells are less distinctly flattened and more granular and polyhedral,

but they become more flattened when the lung is distended (Klein). Lymphatic vessels are abundant in and beneath the pleura as in other serous membranes; they communicate in many parts, by means of stomata, with the cavity of the membrane. In the *pleura costalis* the stomata are only found over the intercostal spaces, not over the ribs (Dybkowsky); lymph-vessels are also more numerous over the spaces.

Beneath the serous covering of the lung is a thin layer of *subserous* areolar tissue mixed with a large number of elastic fibres. It is continuous with the areolar tissue in the interior of the lung, and has been described as a distinct coat under the name of the second or deeper layer of the pleura. In the lungs of some animals, such as the lion, seal, and leopard, this subserous layer forms a very strong membrane, composed principally of elastic tissue; in others, as the guinea-pig, a network of plain muscular fibres is found within it, the fibres tending to radiate from the apex (Klein). A close plexus of lymph-vessels is also met with in this sub-pleural tissue of the lung. The vessels communicate on the one side by means of stomata with the pleural cavity, and on the other with similar vessels in the inter-alveolar septa. Various authorities have described lymphoid nodules and even minute lymph-glands in or beneath the visceral pleura. A uniform network of venous capillaries covers the surface of the lung underneath the pleura. The network is supplied with blood from the venules of the superficial pulmonary lobules, but also receives blood from the bronchial arteries (see p. 587). Its vessels are less closely arranged than the blood-vessels of the pulmonary alveoli, and are thus, as well as by their position, easily distinguishable from them in specimens of injected lung. The nerves of the pleura visceralis are derived, like those of the lung itself, through the pulmonary plexuses, from the vagus and sympathetic: the latter have ganglion-cells on their course. Those of the pleura parietalis come from various sources, but mostly from the intercostal nerves.

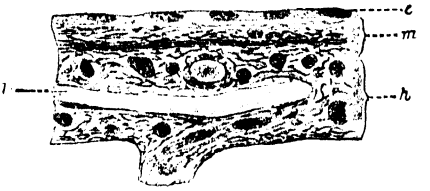


FIG. 856.—SECTION OF PLEURA; OX. (Favaro.) Magnified 270 diameters.

e, endothelium; *m*, substance of membrane with numerous elastic fibres; *h*, hypo-pleura; *l*, lymph-vessel.

The following papers deal with the minute structure of the trachea and lungs and the distribution of their vessels and nerves: Arnstein, Anat. Anz. xiii. 1897 (nerves); Benedicenti, Arch. ital. de biol. xvii. 1892 (nerves of trachea); Berkley, Journ. Comp. Neurol. 1893, and Johns Hopkins Hosp. Rep. iv. 1894 (nerves); Councilman, Journ. Boston Soc. Med. Sci. iv. 1900 (lymphatics); Dybkowski, Ber. d. k. Sächs. Gesel. d. Wiss. 1866 (lymph-vessels of pleura); Drasch, Wiener Sitzungsb. xciii. 1886 (epithelium of trachea); Egdahl, Anat. Anz. xxvii. 1905 (cartilage-plates of bronchial tubes); J. M. Flint, Amer. Journ. Anat. vi. 1906 (later stages of development of lungs); Favaro, Internat. Monthly Journ. Anat. and Physiol. xxvi. 1909 (structure of pleura); Haycraft and Carlier, Quart. Journ. Micr. Sci. xxx. 1890 (epithelium of trachea); W. His, Arch. f. Anat. 1887 (development of lung); E. Klein, The Anatomy of the Lymphatic System, vol. ii. 1875; A. Kölliker, Würzburg Sitzungsb. 1880 (epithelium of alveoli and bronchioles), also Handbuch der Gewebelehre, vol. iii. (edited by v. Ebner); Küttner, C., Virch. Arch. f. path. Anat. lxiii. 1878 (blood-vessels of pleura); F. P. Mall, Johns Hopkins Hosp. Rep. i. 1896 (reticular tissue of lung); F. Merkel, article 'Athmungsorgane' in v. Bardeleben's Handbuch der Anatomie, 1902; W. S. Miller, Anat. Anz. vii. 1892, Journ. Morph. viii. 1893 (general structure), Anat. Anz. xii. 1896 (lymphatics), Arch. f. Anat. 1900, Ref. Handb. of Med. Sciences, Art. 'Lungs,' 1902, Anat. Anz. xxviii. 1906 (bronchial vessels), Amer. Journ. Anat. vii. 1907 (vessels of pleura), Anat. Record, v. 1911 (lymphoid tissue of lung); J. Müller, Arch. f. mikr. Anat. lxix. 1907; Ploschko, Anat. Anz. xiii. 1897 (nerves); Ponzio, Anat. Anz. xxviii. 1906 (nerves); G. Retzius, Biol. Unters. v. 1893 (nerves); F. E. Schultze in Stricker's Handbook, 1870; W. Stirling, Journ. Anat. and Physiol. xvi. 1881 (nerves); *ibid.* xvii. 1883 (attachments of trachealis muscle); W. Turner, Brit. and For. Med.-Chir. Review, 1865 (vessels of pleura); Waters, The Anatomy of the Lung, 1860; Zuckerkandl, Wiener Sitzungsb. lxxiv. 1882 (blood-vessels).

The urinary organs comprise the *kidneys*, *ureters*, *bladder*, and *urethra*. Of these the first are typical examples of compound tubular glands, the ureters represent their ducts, whilst the urinary bladder, into which the ureters open, serves as a receptacle for the collection of the urine. The urethra in the male sex furnishes a common passage for the urine and the secretion of the generative glands. Its structure will be described after that of the generative organs.

THE KIDNEYS.

The kidneys are formed of a mass of tubules—the uriniferous tubules—which in sections through the organ are seen to be so disposed as to mark off two parts—a *cortical part*, nearer the surface, and a *medullary part* (fig. 857). The whole organ is covered by a fibrous *capsule* which dips in at the hilum and penetrates along with the blood-vessels and the duct (ureter) into a large cavity (*sinus*) around which the medulla is arranged. In many animals the medulla forms a single pyramidal mass (fig. 858), fan-shaped in section, the apex of the pyramid projecting as a broad papilla into the enlarged commencement of the ureter (*pelvis*). In other animals, including man, the medulla is formed of a number of separate pyramidal portions, the *pyramids of Malpighi*—about twelve in number in man—the bases of which abut against and are imbedded in the cortical part, which in man is continuous throughout and not separated up into parts like the medulla. The cortex is continued between and distal to the bases of the pyramids, appearing in sections of the organ as if formed by columnar masses, which are known as the *columns of Bertini*. These are not real columns, but portions of cortex which enclose the bundles of tubules known as the medullary rays (see next page). Each of the pyramids ends by a nipple-shaped *papilla* within a corresponding division (*calix*) of the pelvis. In some parts of the kidney two or more pyramids are united towards their apices to form a single papilla; such coalescence is especially marked near the ends of the kidney.

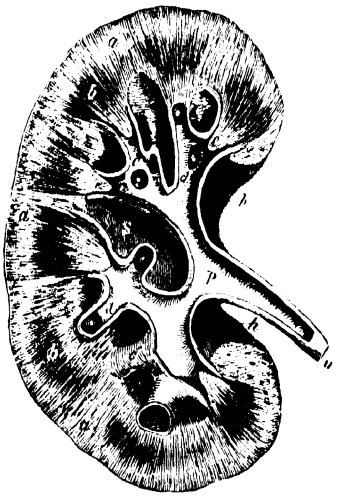


FIG. 857. — PLAN OF A LONGITUDINAL SECTION THROUGH THE PELVIS AND SUBSTANCE OF THE RIGHT KIDNEY. One-half the natural size.

a, cortical substance; *b*, *b*, base of two of the pyramids of Malpighi; *c*, *c*, divisions of the pelvis named calices, or infundibula, laid open; *c'*, one of these unopened; *d*, *d*, points of papillæ projecting into calices; *e*, *e*, longitudinal section of two papillæ near the calices; *p*, pelvis or enlarged portion of the ureter within the kidney; *u*, ureter; *s*, sinus; *h*, hilum.

In the fœtus and new-born infant each pyramid or group of pyramids of the medulla has a separate portion of the cortex continuous with it, the kidney being divided up into a dozen or so distinct parts (*reniculi*) each with its branch of the ureter and artery. The coalescence of these is not completed until some time after birth. In some animals (*e.g.* bear) the reniculi remain distinct throughout life, being separated from one another by connective tissue. If the papilla is examined with a lens it is seen to be beset at its apex, which is dimpled (*foveola*), by minute apertures; these are the openings of the largest uriniferous tubules (*ducts of Bellini*).

The course of the blood in the kidney is peculiar in the fact that that which passes to the Malpighian corpuscles passes from them through a second set of capillaries, to supply the tubules.

Course of the uriniferous tubules, and their relation to the blood-vessels.—These tubules can be traced from the papillæ into the pyramids proper: they divide dichotomously and thus become multiplied to form a very large number of *collecting tubules* which course straight and nearly parallel with one another, but slightly diverging, towards the base of each pyramid. Between the collecting tubules are other straight tubules smaller in size—the *looped tubules of Henle*—as well as a large number of blood-vessels which run parallel with the tubules. All these give the medulla an appearance of being streaked along the length of the pyramid from papilla to cortex, and the streaking is still more marked at the base of the pyramid (*boundary zone*) because the straight tubules of the medulla here become collected into bundles, and between them run many small blood-vessels also collected

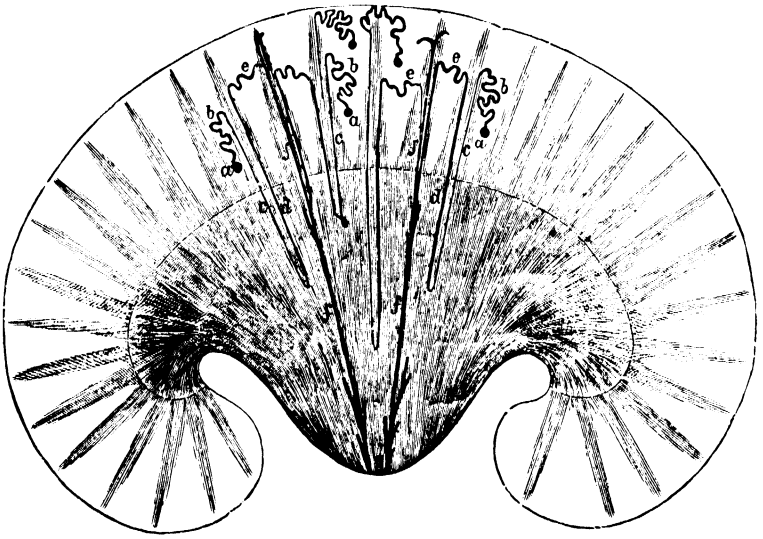


FIG. 858.—DIAGRAM OF THE COURSE OF THE TUBULES IN A UNI-PYRAMIDAL KIDNEY, SUCH AS THAT OF THE RABBIT. (Toldt.)

a, Malpighian bodies; *b*, first convoluted tubule; *c*, *d*, looped tubule of Henle; *e*, second convoluted tubule; *f*, collecting tube; *g*, ducts of Bellini.

into bundles or pencils. The bundles of medullary tubules are continued into the cortex, and reach nearly to the surface of the kidney, appearing in the cortex as rays, diverging from the base of each pyramid (*medullary rays*, fig. 858.) These bundles or rays comprise a continuation of the collecting tubes and also of the looped tubes above mentioned, and, gradually tapering off, lose themselves in the cortex.

The cortex is distinguished from the medulla by the fact that its tubules—except those of the medullary rays—are closely convoluted, forming what is known as the *labyrinth* (fig. 860). Through this convoluted mass of tubules there pass, besides the medullary rays, certain radially arranged vessels—arterioles and venules—which run between the medullary rays through the thickness of the cortex. These are the *interlobular arteries and veins* (figs. 859, 861). The interlobular arteries have relatively thick walls and, at least in the dog, a very complete fenestrated membrane (Mann) (see fig. 525). They carry blood to the cortex from somewhat curved or arched divisions of the renal artery, which lie between cortex and medulla and are usually stated to give off straight arterioles (*arteriæ rectæ*) to the

medulla. The veins have a similar course and arrangement to the arteries, proceeding towards venous vessels which are more distinctly arched than the arteries. The interlobular veins begin near the capsule by a convergence of capillaries and venules from the cortex, forming the so-called stellate veins (*venæ stellulæ*). Besides these interlobular veins, which receive most of the capillaries of the cortex, there are a certain number of small veins which receive blood from the capillaries of the deepest part of the cortex and open direct into the arched veins. The veins of the medulla arise by plexuses near the apices of the papillæ, around the ducts of Bellini. They pass between the radiating tubules, and enter the concave side of the venous arches as the straight venules (*venæ rectæ*). As already stated, the vasa recta are collected into bundles as they pass towards the arching vessels between cortex and medulla, and by this arrangement they give the appearance in the fresh kidney of red streaks alternating with paler medullary substance (*boundary zone*, fig. 859). But the most striking peculiarity of the blood-supply of the kidney consists in the presence within the cortex of globular tufts of ramified capillaries which in the fresh kidney appear to the naked eye as minute red spots—the *glomeruli*—lying with a fairly regular arrangement within the labyrinth alongside of the medullary rays. Each glomerulus is supplied by a short branch of an interlobular artery (figs. 861, 862), which on entering the glomerulus, divides into five or six branches, one for each of its lobules, to the periphery of which they are distributed; each of these lobules consists of a closely reticular mass of capillaries (figs. 863, 864). From these capillaries the blood is collected by venules, which usually begin near the middle of the lobule and unite to form the issuing vessel, which usually leaves the glomerulus close to the entering arteriole. The issuing venule almost immediately proceeds to break up into a second set of capillaries, ramifying in a close network around the tubules. The vessels which pass to and from the glomeruli are termed respectively the *afferent* and *efferent vessels*. Of the two, the afferent has the structure of a small artery; the efferent, although breaking up into capillaries, resembles a small vein in structure. The efferent vessels of the glomeruli nearest the pyramids break up into long meshed capillaries which pass amongst the venæ rectæ into the medulla: they are sometimes termed *false* arteriæ rectæ, but according to Huber, who is confirmed by Gérard, all the arteriæ rectæ are of this nature, none come off direct from the arterial arches. This opinion was held by Bowman, but Virchow

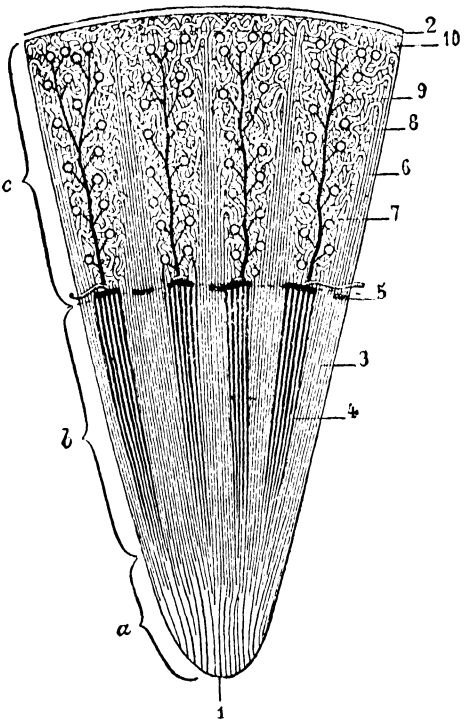


FIG. 859.—DIAGRAM OF A SECTION THROUGH PART OF THE KIDNEY PARALLEL TO THE MEDULLARY TUBULES. (Testut.)

a, papillary zone; *b*, boundary zone; *c*, cortical zone. 1, apex of papilla; 2, capsule; 3, clear striæ of boundary zone, formed by tubules of medulla; 4, dark striæ of boundary zone formed by vasa recta; 5, vascular arches; 6, medullary rays; 7, labyrinth (columns of Bertini); 8, interlobular vessels; 9, Malpighian corpuscles; 10, subcapsular layer of labyrinth.

stated that some of the arteriæ rectæ come direct from the arches, and this view has generally been followed.[1] The efferent vessels are slightly smaller than the afferent; the two are united within the glomerulus by a convoluted mass of branching capillaries (*rete mirabile*), which is, as already noted, itself lobulated. The capillaries of the glomeruli do not show the usual differentiation into endothelium-cells on treatment with silver nitrate (Drasch). The glomerulus is contained within a terminal dilatation of each uriniferous tubule (Bowman).

The basement-membrane, which invests the whole tubule, forms the external

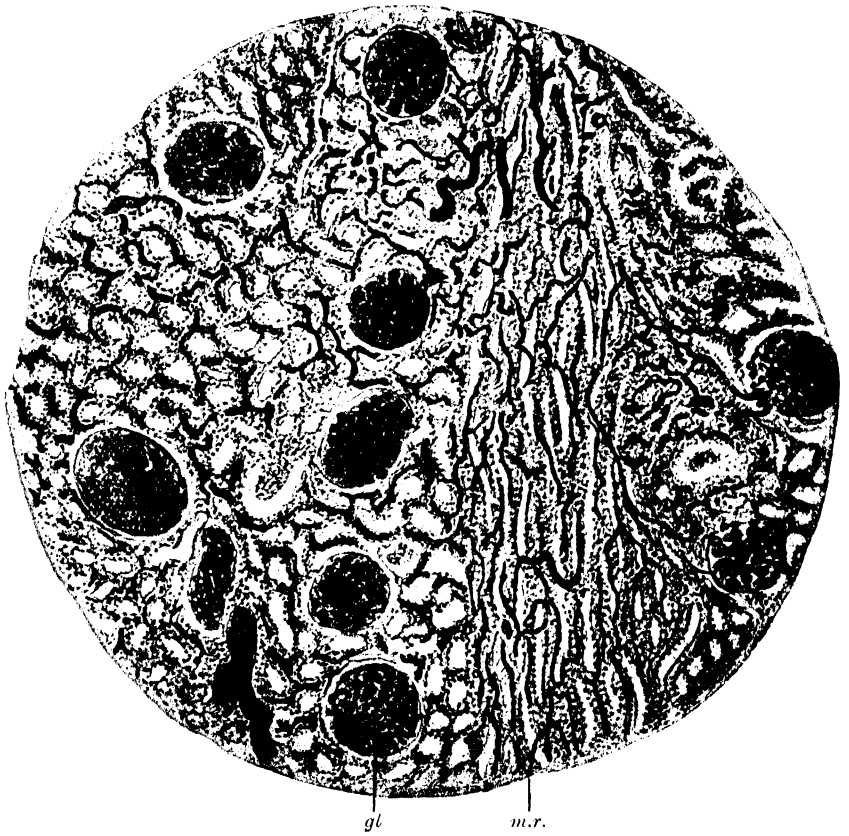


FIG. 860.—PART OF A SECTION THROUGH THE CORTEX OF A HUMAN KIDNEY, THE BLOOD-VESSELS OF WHICH HAVE BEEN INJECTED. (Disse.)

gl, a glomerulus; *m.r.*, section of a medullary ray.

wall of the dilatation; it is here known as the *capsule*. The glomerulus projects freely into the dilatation, covered only by a reflexion of the capsule and of the flattened epithelium which lines it (fig. 865, in fœtus). Both this covering epithelium and the basement-membrane which invests the glomerulus and dips in between its lobes, are, in the adult, much thinner and more delicate than the corresponding structures which form the external wall of the dilatation. The whole structure, including the dilated termination of the tubule and the glomerulus which it encloses, is known as a *Malpighian corpuscle*.

[1] Ludwig, article, 'Kidney,' in Stricker's Handbook, 1891; Golubew, Intern. Monthly Journ. of Anat. and Physiol. x. 1893. Golubew states that they are also given off from the afferent vessels to some of the most deeply lying glomeruli.

The number of Malpighian corpuscles in the kidney is very large. It was estimated by Huecke at about two millions for the human kidney, but this number is probably too high. Schweigger-Seidel reckoned that in the pig's kidney there are about half a million. Miller and Carlton found in actual counts from the kidney of the cat, cut into serial sections, about 16,000 for each kidney.

FIG. 862.—DIAGRAM SHOWING THE RELATION OF THE URINIFEROUS TUBULES TO THE BLOOD-VESSELS. (After Bowman.)

a, one of the interlobular arteries; *a'*, afferent artery passing into the glomerulus, *g*; *c*, capsule of the glomerulus; *t*, convoluted tube; *e'*, *e'*, efferent vessels which subdivide in the plexus of capillaries, *p*, surrounding the tube, and finally terminate in the interlobular vein, *v*.

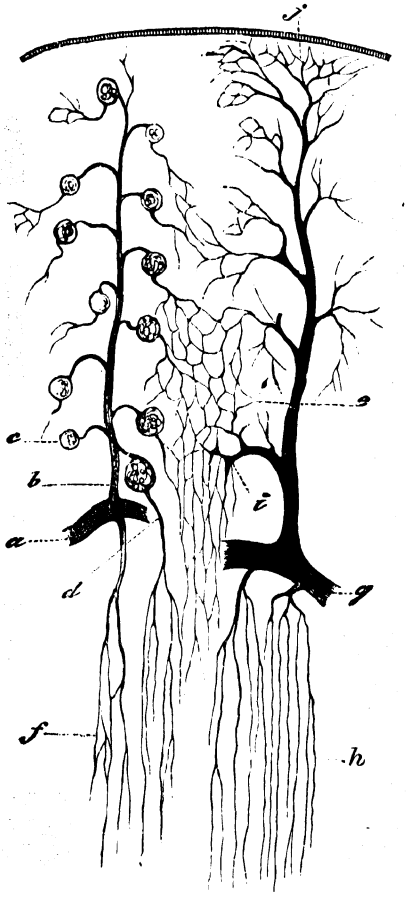


FIG. 861.—VASCULAR SUPPLY OF KIDNEY. (Cadiat.

a, part of arterial arch; *b*, interlobular artery; *c*, glomerulus; *d*, efferent vessel passing to medulla as false arteria recta; *e*, capillaries of cortex; *f*, capillaries of medulla; *g*, venous arch; *h*, straight veins of medulla; *i*, interlobular vein; *j*, vena stellula.

FIG. 863.—INJECTED GLOMERULUS FROM THE INNER PART OF THE CORTICAL SUBSTANCE OF THE HORSE'S KIDNEY. (After Bowman.) Magnified 70 diameters.

a, interlobular artery; *af*, afferent vessel; *m*, *m*, convoluted vessels of the glomerulus; *ef*, efferent vessel; *b*, its subdivision in the medullary substance.

We have already traced the course of the tubules from their openings into the dilated termination of the ureter backwards to the Malpighian corpuscles, but before considering their structure it will be useful to follow their course in the other direction, which is that taken by the urine they secrete (fig. 867.)

On leaving the *Malpighian corpuscle*, to which in man and some other animals it is joined by a narrowed *neck*, the tubule, still not much smaller than the dilated

end which encloses the glomerulus, becomes convoluted (*first* or *distal convoluted tube*), and makes several turns in the neighbourhood of its Malpighian corpuscle, at the same time gradually approaching the nearest medullary ray. On reaching this it turns towards the medulla, being at first spiral (Schachowa), but afterwards quite straight; it now becomes much attenuated as it passes towards the papilla. In this form it is known as the *first* or *descending part of the looped tube of Henle.* Near the papilla it loops round, still of small diameter; but it soon enlarges some-

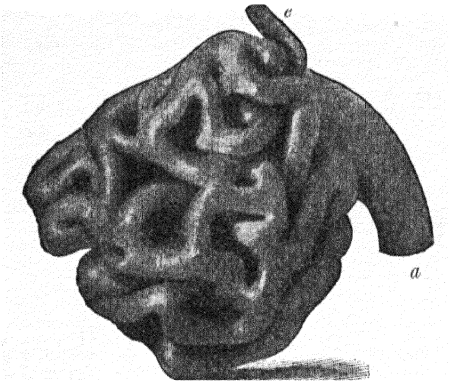


FIG. 864.—MODEL OF A GLOMERULUS. (Johnston.)
a, afferent; *e*, efferent blood-vessel.

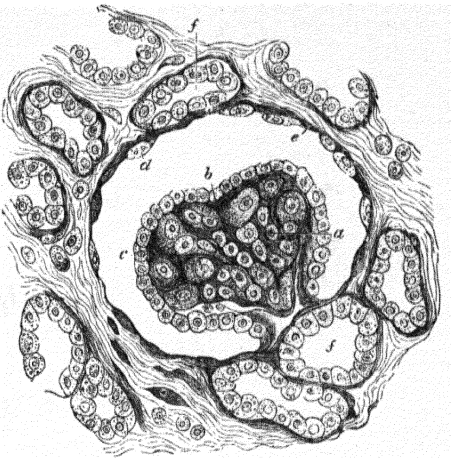


FIG. 865. — SECTION OF CORTICAL SUBSTANCE OF KIDNEY; HUMAN FŒTUS. (E. Klein.) Highly magnified.

a, glomerulus with blood-vessels, not fully developed; *b*, connective tissue between the blood-vessels; *c*, epithelium covering glomerulus, continuous with *d*, epithelium lining Bowman's capsule; *f*, *f*, convoluted tubes.

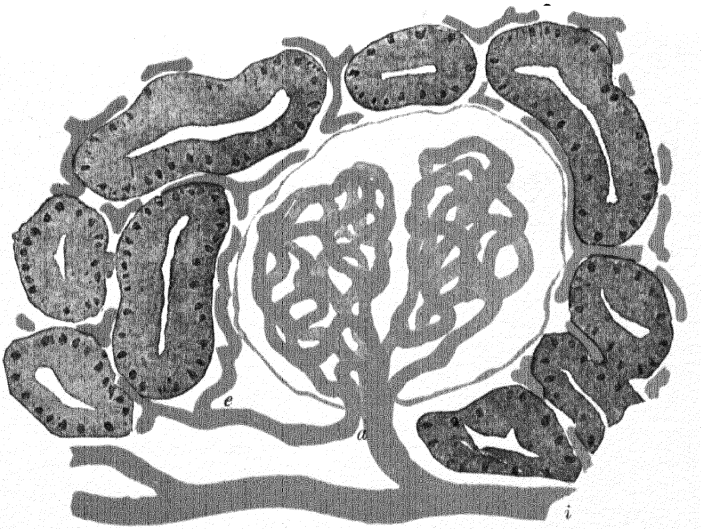
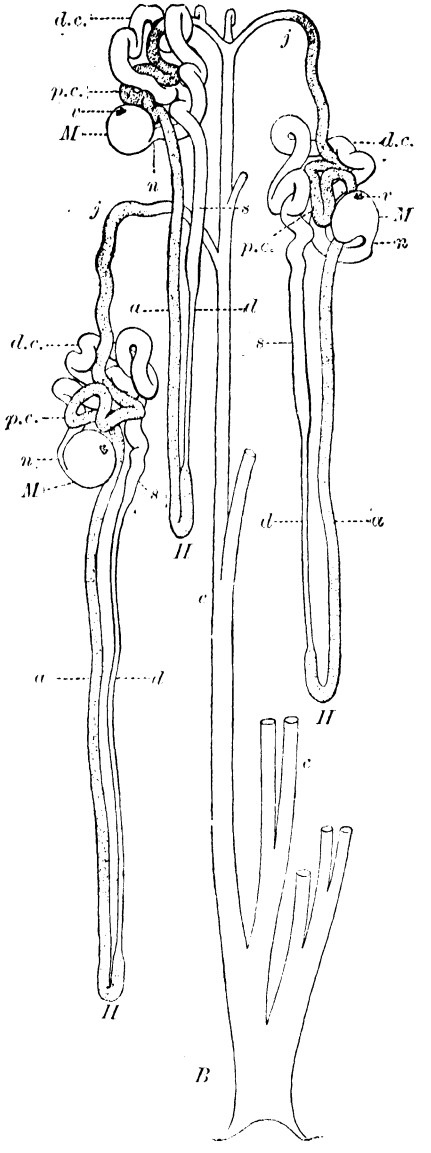


FIG. 866.—PART OF SECTION OF AN INJECTED KIDNEY. (Prenant and Bouin.)
i, interlobular artery; *a*, afferent vessel of glomerulus; *e*, efferent vessel, breaking up into capillaries around the convoluted tubules.

what, and then runs back towards the cortex parallel to its former direction: this part is known as the *second* or *ascending part of the looped tube of Henle.*[1] In this

[1] According to Stoerck the ascending limb of the looped tubule is the smaller; the descending the larger (directly contrary to what has usually been accepted). According to Huber, who adopts the usual view regarding the ascending and descending limbs, the loop in man is always formed by the larger tubule (see fig. 867).

condition it again reaches the medullary ray; but it presently leaves this as a curiously irregular tubule (*zigzag tubule*) which takes a course towards the original



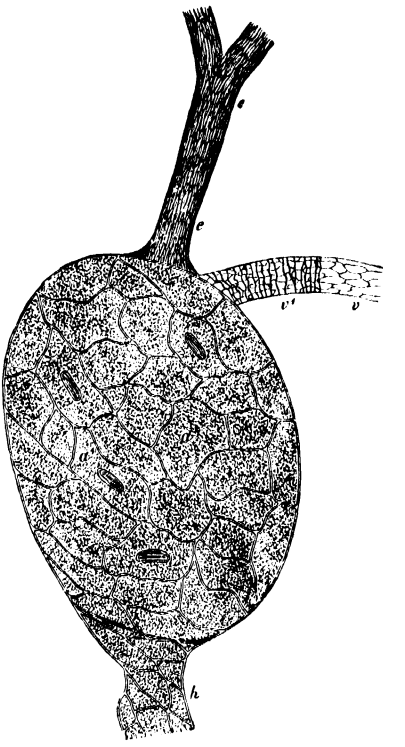


FIG. 868.—MALPIGHIAN CORPUSCLE FROM THE RABBIT'S KIDNEY: NITRATE OF SILVER PREPARATION. (Ludwig.) Highly magnified.

v, vas afferens, showing its endothelial lining; at *v'*, the transverse muscular fibres are also seen; *e*, vas efferens; *a*, *a'*, basement-membrane of capsule with its lining epithelium passing at *h* into that of the commencing uriniferous tubule.

Malpighian corpuscle from which the first convoluted tube emerged.[1] After two or three contortions, which form the *second* or *distal convoluted tubule*,[2] it once more becomes narrowed into the so-called *junctional*

FIG. 867.—PLAN OF THE COURSE OF THE URINIFEROUS TUBULES. (Huber.) This plan, which is based upon reconstructed models of the tubules, exhibits the relation of the convoluted tubules to the Malpighian corpuscles.

M, Malpighian corpuscles; *v*, point of entrance of vessels of glomerulus; *n*, neck; *d.c.*, distal convoluted tubule, which arises from the Malpighian corpuscle; *s*, spiral tubule into which it is continued; *d*, narrow descending limb of loop of Henle; *H*, loop of Henle (this is sometimes formed by the narrow part of the looped tubule, but is here represented as formed by the wider part); *a*, wider ascending limb of loop of Henle; this passes back to the neighbourhood of the same Malpighian corpuscle, often becoming irregular and zigzag at its upper end. Here it becomes continuous with the proximal convoluted tubule, *p.c.*, which eventually passes into the junctional tubule, *j*, by which it is connected with a collecting tubule, *c*. *B*, duct of Bellini, receiving a number of conjoined collecting tubules and opening at a papilla.

[1] Golgi, Rendi d. acc. d. Lincei, v. 1889.

[2] The second convoluted tubule was termed by Schweigger-Seidel 'Schaltstück.' This term also includes the zigzag tubule and the junctional tubule.

tubule, and taking a transverse course towards the medullary ray, it finally enters one of the *straight* or *collecting tubules*, which leads to the medulla; these collecting tubules eventually join to form the *ducts of Bellini*.

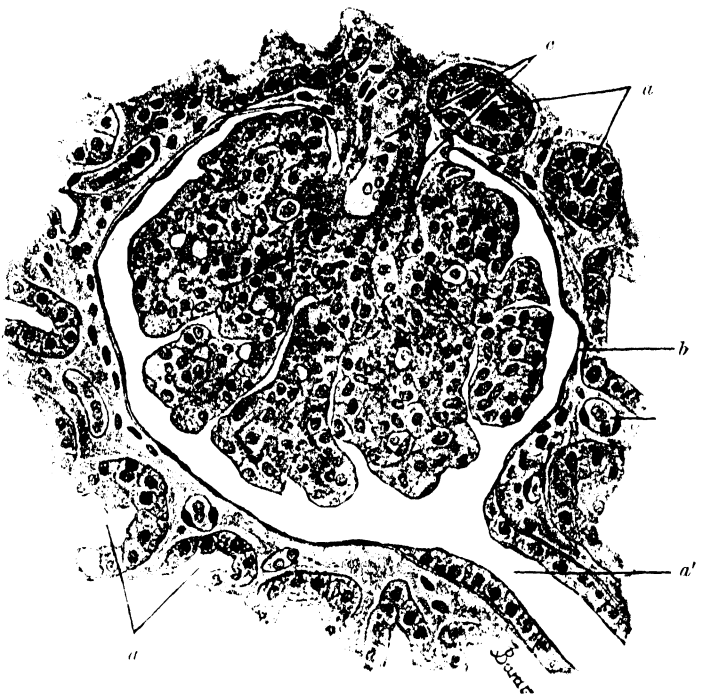


FIG. 869.—A MALPIGHIAN CORPUSCLE FROM THE KIDNEY OF THE MONKEY. (Szymonowicz.) Magnified 350 diameters.

a, *a*, sections of convoluted tubules; *a'*, commencement of convoluted tube from capsule; *b*, capsule; *c*, afferent and efferent vessels. Note the lobulated structure of the glomerulus.

Structure of the tubules.—The *basement-membrane* enclosing the tubules appears in the fresh condition homogeneous; nor does it in ordinary sections exhibit any structure. But, as was shown by Mall, it contains fine longitudinally and circularly disposed fibrils of reticular tissue, these fibrils being continuous with those of the intertubular tissue of the organ (see fig. 875).

In addition to the fibrils the basement-membrane of the tubules is composed of a homogeneous material of a different nature, which resists the action of strong mineral acids. These are accordingly used for macerating portions of the kidney when it is desired to isolate the tubules.

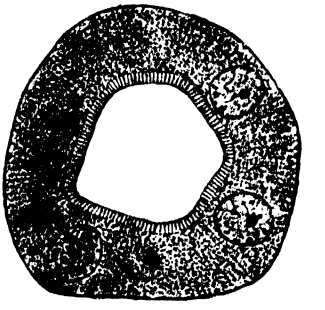


FIG. 870.—SECTION OF A CONVOLUTED TUBULE OF THE RABBIT'S KIDNEY, SHOWING THE STRUCTURE OF THE EPITHELIUM. (Szymonowicz.) Magnified 1100 diameters.

The *epithelium* of the renal tubules varies in the different parts above described. It presents three distinct types. The cells of the first type are clear and columnar, without distinct granules or striæ in the cytoplasm. Those of the second type are also clear, but flattened like the cells of an endothelium. Those of the third type are granular and striated from without inwards, the striations being most marked in the outer zone near the base of the cell, and the granular appearance most distinct in the inner zone; next to the

lumen of the tubule these cells are bounded by a striated border, something like that of the intestinal epithelium.[1]

The clear flattened cells occur in the Malpighian corpuscles, both lining their capsules (fig. 868) and covering their glomeruli (fig. 869). They are also found

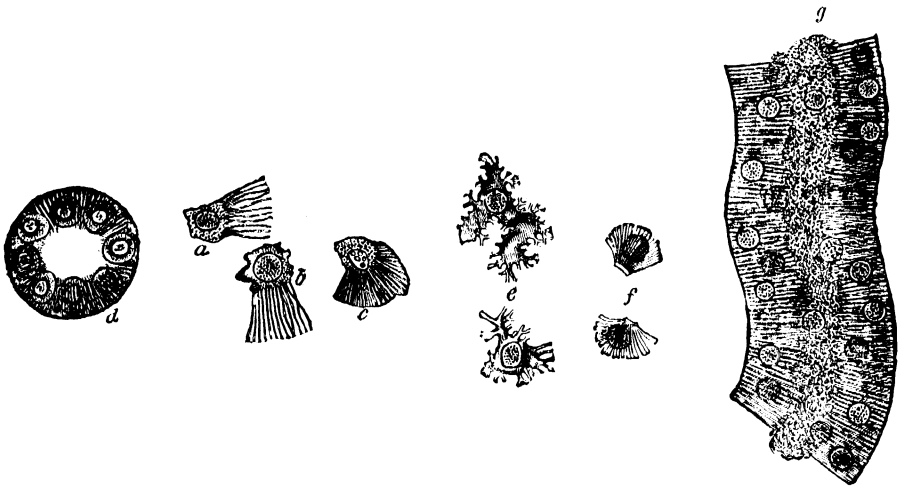


FIG. 871.—TO ILLUSTRATE THE STRUCTURE OF THE EPITHELIUM OF THE CONVOLUTED TUBULES (R. Heidenhain.)

d, section of a convoluted tubule from the rat, showing granular protoplasm occupying a circular area around the nucleus of each cell; *a*, *b*, *c*, isolated cells from the convoluted tubules of the rat; *e*, isolated cells from the dog's kidney, viewed from the inner surface, and showing the irregular contour of the protoplasm; *f*, isolated cells from the newt, showing the rods and the homogeneous cuticular layer; *g*, longitudinal optical section of part of a convoluted tubule from the dog's kidney.

in the narrower portions of the looped tubules (fig. 873), *i.e.* in the descending tubule and usually in the loop itself. The clear columnar cells (which are

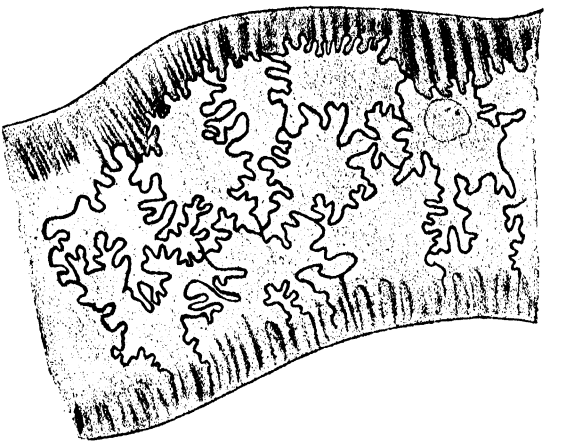


FIG. 872.—PORTION OF A CONVOLUTED TUBE FROM THE KIDNEY, SHOWING THE IRREGULARLY FLUTED OUTLINES OF THE CELLS. (Landauer.) Silver-nitrate preparation.

shortened to a cubical form in certain places) are found in the collecting tubules and in the ducts of Bellini (fig. 874), and also in the parts of the junctional adjacent to the collecting tubules. Cells of the granular striated type (*rodded cells*) are

[1] Nussbaum, Pflüger's Arch. xvii. 1878.

found in both sets of convoluted tubules (figs. 870, 871),[1] in the ascending or larger limb of the looped tubule, in the zigzag tubule and in the first part of the junctional tubule. The granules are derived from mitochondria[2] and appear

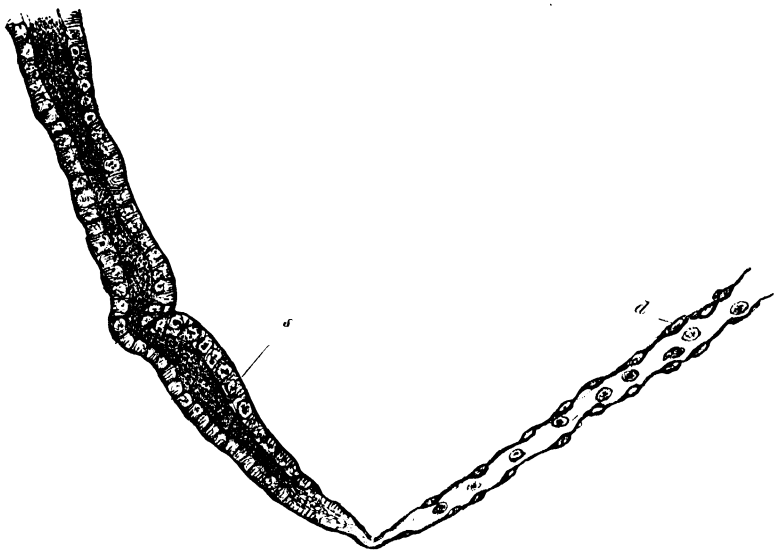


FIG. 873.—PASSAGE OF THE SPIRAL CONTINUATION OF A DISTAL CONVOLUTED TUBULE INTO THE DESCENDING LIMB OF A LOOPED TUBULE OF HENLE. (Disse.) The bend is accidental.
s, end of spiral tubule; *d*, narrow descending limb of looped tubule of Henle.

to be related to the production of secretion. The nuclei of the rodded cells are spherical, and the cells are closely united by a kind of dove-tailing (fig. 872);

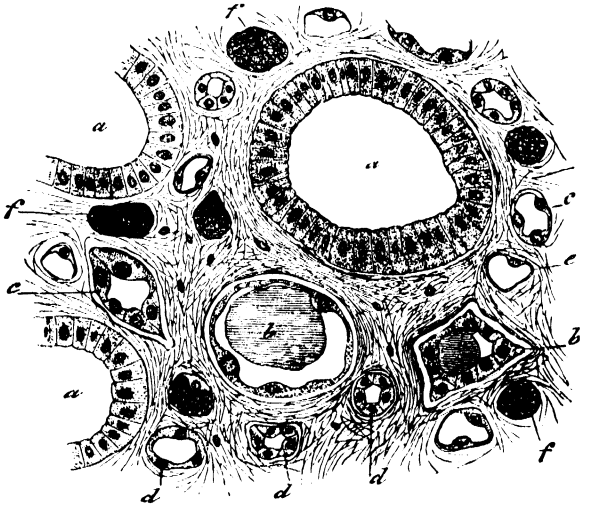


FIG. 874.—SECTION ACROSS A PAPILLA OF THE KIDNEY. (Cadiat.)
a, ducts of Bellini; *b*, *c*, *d*, tubes of Henle, ascending and descending; *e*, *f*, blood-capillaries.

possibly they form a syncytium, but this is not certain. In some animals (*e.g.* mouse) the granular rodded epithelium is continued for a certain distance into the Malpighian corpuscle.

[1] The cells in the second convoluted tubules have a clearer appearance than those in the first.
[2] Kolster, Ziegler's Beitr. li. 1911.

The first convoluted tubule is about 50 μ in outside diameter, the second convoluted tubule somewhat smaller; the descending limb of Henle's looped tubule about 15 μ, the ascending limb nearly twice this size. The straight or collecting tubules are from 18 μ to 50 μ, the larger being nearest the papilla; the ducts of Bellini may measure as much as 300 μ. The Malpighian corpuscles vary in size; in man corpuscles from 150 μ to 200 μ occur in the same kidney. The lumen of the tubules varies not only with their outside diameter but also inversely as the thickness of their epithelial lining. Thus the relatively fine descending parts of the looped tubules of Henle have nearly as large a lumen as the far thicker ascending parts. The zigzag

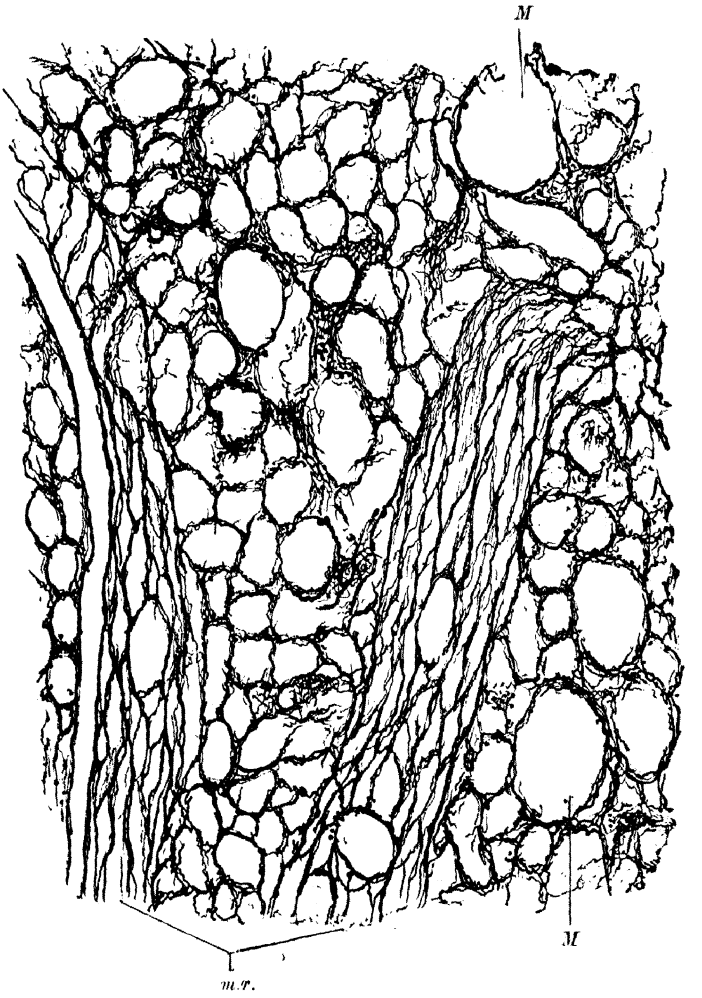


FIG. 875.—INTERTUBULAR CONNECTIVE TISSUE OF CORTEX OF CAT'S KIDNEY, DISPLAYED AFTER PANCREATIC DIGESTION BY SPALTEHOLTZ' METHOD. (Disse.)

m.r., medullary rays; *M*, *M*, Malpighian corpuscles.

tubules have no distinct membrana propria. The lumen of the convoluted tubules varies in different kidneys and in different parts of the same kidney; the secreting epithelium-cells which line them being sometimes shorter, sometimes longer. These differences may represent variations in secretory activity; it is found that in the kidneys of animals which are hibernating—and which are therefore inactive—the cells of the convoluted tubules are usually long and the lumen is almost obliterated. This condition probably represents the resting state of the epithelium.[1]

On the other hand, the state of activity is probably represented by a dome-like swelling of the inner zone of the epithelium-cell; this swelling contains a centrosome or diplosome, and from this

[1] Disse, article 'Harnorgane' in v. Bardeleben's Handbuch der Anatomie, 1902.

a cilium-like filament may extend in some animals (see fig. 59, p. 32; from the salamander larva). In the lower vertebrates, such as the frog, the epithelium-cells at the commencement of the convoluted tubule bear true cilia.

In the ascending parts of the looped tubules the cells sometimes show an arrangement of imbrication from below upwards; in man they have been found to contain brown pigment-granules. The rodded character of the epithelium is very distinct in the zigzag tubules.

The *intertubular tissue* of the kidney (fig. 875) is a form of reticular tissue, which occupies the intervals between the tubules and conveys the blood-vessels, lymphatics, and nerves. Both this tissue and the connective-tissue capsule of the organ receive small branches of the renal arteries; in the capsule these anastomose with branches of the lumbar arteries.

Lymphatics and nerves.—The lymphatics of the interior of the organ pass to the hilum, and also communicate with a set of plexiform lymph-vessels in the capsule.

The lymphatics of the cortex form a network of sinuses which partially enclose the tubules and Malpighian corpuscles: those of the medulla form a long-meshed plexus accompanying the straight and looped tubules. The efferent lymph-vessels follow the course of the arteries. According to Kumita, lymph-vessels issue from the glomeruli along with the blood-vessels.

The nerves are chiefly distributed to the blood-vessels (G. Retzius), but some have been traced to the Malpighian corpuscles and others to the cells of the convoluted tubules (fig. 876) (Berkley, Smirnow).

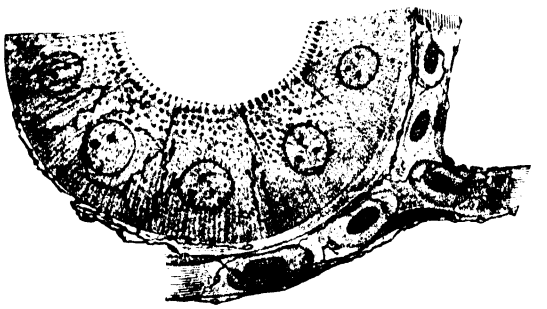


FIG. 876.—NERVE-FIBRILS ENDING OVER CAPILLARY BLOOD-VESSELS AND AMONGST THE EPITHELIUM-CELLS OF A CONVOLUTED TUBE OF THE FROG'S KIDNEY. (Smirnow.)

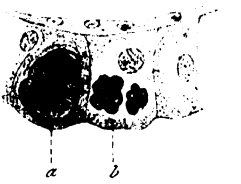


FIG. 877.—URATE DEPOSITS WITHIN THE KIDNEY-CELLS OF A MOLLUSC (Schoppe.)

Urinary concretions (probably uric acid or urates) can be seen in the cells of the convoluted tubules of birds and reptiles (v. Wittich); they have also been described in the rabbit. In the urinary organ of some molluscs they take the form of conspicuous masses (fig. 877, *a*, *b*) (Schoppe). The granules in the cells of the convoluted tubules are said to show changes under the influence of diuretics, becoming fewer, larger, and more irregularly distributed. They are also affected by diet, being more conspicuous and abundant as the result of a purely meat diet (Chalmers Watson). They appear to be formed by breaking up of the rod-like fibres, which are themselves composed of rows of granules (Takaki); probably these granules originate from mitochondria.

The following papers on the structure of the kidney may be referred to: Altmann, Arch. f. mikr. Anat. xvi. 1879 (blood-vessels); Cesar-Bianchi, Intern. Monatschr. Anat. u. Physiol. xxvii. 1910 (cells of tubules); Cresci, Arch. f. Anat. 1909 (vessels of glomerulus); M. Gérard, Journ. de l'anat. 1911 (blood-vessels); C. Hirsch, Anat. Hefte, xli. 1910 (granules in cells). C. Huber, Amer. Journ. Anat. iv. 1905 (Suppl.) (course of tubules); *ibid.* vi. 1907 (efferent vessels of glomeruli and blood-supply of medulla) (see also Brit. Med. Journ. Dec. 15, 1906); Johnston, Anat. Anz. xvi. 1899 (reconstruction of glomeruli); Kumita, Arch. f. Anat. 1909 (lymphatics); F. P. Mall, Abhandl. d. k. Sächs. Akad. d. Wiss. 1891; Johns Hopkins Hosp. Reports, i. 1891; Johns Hopkins Hosp. Bull. xx. 1901 (basement-membranes, fibrillar structure); Maresch, Anat. Anz. xii. 1896 (constitution of pyramids); Meves, Kupffer Festschr. (secretion-changes in cells); Meyer and Rathery, Arch. d'anat. micr. xi. 1909 (granules in cells); W. S. Miller and E. P. Carlton, Trans. Wisconsin Acad. Sci. 1895 (relation of cortex to medulla and number of glomeruli in cat); Peter, Anat. Anz. xxx. Ergänzungsheft, 1907 (course and structure of tubules); Pizzini, Intern. Monthly Journ. Anat. and Physiol. xxv. 1908 (granules of convoluted tubules);

G. Retzius, Biol. Unters. iii. 1892 (nerves); G. Rühle, Arch. f. Anat. 1897 (structure of basement-membranes, effects of diet on granules in cells); H. Sauer, Arch. f. mikr. Anat. liii. 1899 (uric acid in cells of convoluted tubules); Schoppe, Anat. Hefte, vii. 1897 (urinary concretions in cells); R. Standfuss, Arch. f. mikr. Anat. lxxi. 1907 (Malpighian corpuscles); O. Stoerck, Anat. Hefte, xxiii. 1904 (course and structure of tubules); Takaki, Arch. f. mikr. Anat. lxx. 1907 (rodded structure and granules of cells); Van der Stricht, Comptes Rendus, 1891 (secretion changes in cells); Chalmers Watson, Intern. Monatschr. f. Anat. u. Physiol. xxiv. 1907 (granules in cells); Disse, Anat. Hefte, v. 1893 (secretory changes in cells), also in v. Bardeleben's Handbuch der Anatomie (article 'Niere'), vol. vii. 1902; K. M. Zimmermann, Arch. f. mikr. Anat. lxxviii. 1911 (form of epithelium-cells); Zondek, Arch. f. mikr. Anat. lvii. 1900 (origin of arteriæ rectæ).

The development of the tubules is dealt with in vol. i. of this work. The following papers on this subject may be mentioned: J. B. Haycraft, Intern. Monatschr. f. Anat. u. Physiol. xii. 1895; P. T. Herring, Journ. Path. and Bact. vi. 1900; C. Huber, Amer. Journ. Anat. iv. 1905 (Suppl.); Janošik, Arch. f. Anat. 1907; O. Stoerck, *op. cit.*

PELVIS OF KIDNEY AND URETERS.

Pelvis.—On squeezing a fresh kidney which has been split open, a little urine will be seen to drain from the papillæ by fine orifices on their surface. The secretion is carried away and conveyed into the bladder by the ureter. This long tube on being traced up to the kidney is seen to be somewhat enlarged, expanding as it enters the hilum into a dilatation named the *pelvis* (figs. 857, 878). This, within the sinus, divides usually into three, but sometimes only two primary tubular divisions, and these finally end in a larger number of short, truncated, but comparatively wide branches named *calices* or *infundibula*, which receive the papillæ into their wide mouths (fig. 857) and are attached around the bases of those prominences, from which, of course, they catch the issuing urine.

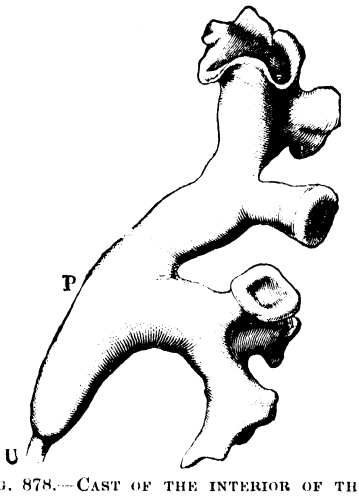


FIG. 878.—CAST OF THE INTERIOR OF THE UPPER END OF THE URETER. (Henle.)
P, pelvis; U, ureter.

A single calix often surrounds two, sometimes even three papillæ, which are in that case united together; hence, the calices are in general not so numerous as the papillæ. The spaces between the calices are occupied by a considerable amount of fat, imbedded in which are seen the main branches of the renal vessels.

Like the rest of the ureter, the pelvis and calices consist of three coats, viz. a strong external fibrous and elastic tunic, which becomes continuous around the bases of the renal papillæ with that part of the external capsule of the kidney which is continued into the sinus; a thin internal or mucous coat, which, at least its epithelium, is reflected over the summits of the papillæ; and between these two a muscular coat, with fibres running both longitudinally and circularly. The longitudinal fibres lie innermost and, according to Henle, are lost near the extremity of the calix, but the circular fibres form a continuous circular muscle round the papilla where the wall of the calix is attached to it. According to Disse there are longitudinal fibres outside the circular, extending over the calices as far as the circular. The muscular coat cannot in man be separated as a distinct stratum from the fibrous coat, for the muscular bundles run to a certain extent in the fibrous tissue of the outer coat. Between the muscular bundles the fibrous coat is continuous with the connective tissue of the mucous membrane. The pelvis is lined by an epithelium like that of the ureter, but in the calices its layers become reduced in number, and near and over the papillæ it is represented by a single layer

of columnar cells (fig. 879). Throughout the greater part of the pelvis there are both longitudinal and circular ridges or projections of the vascular corium into the epithelium, which is thinner opposite the ridges and thicker between them. In tangential sections the ridges produce an appearance of reticulations. Besides these strongly marked ridges of the corium, fine strands of connective tissue extend between the epithelium-cells almost to the surface. The ridges are highly vascular, and within them and the strands of connective tissue just mentioned capillary

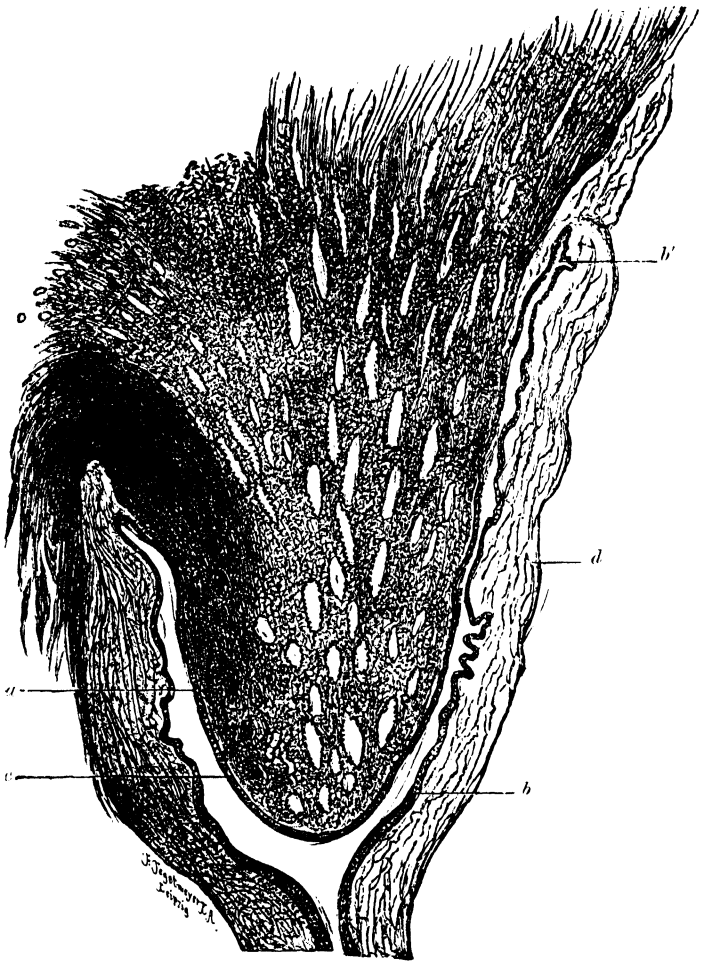


FIG. 879.—LONGITUDINAL SECTION THROUGH A PAPILLA OF THE KIDNEY SHOWING ITS PROJECTION INTO ONE OF THE CALICES OF THE PELVIS. (Disse.)

The ducts of Bellini are seen cut obliquely; the smaller tubules are looped tubules of Henle. *a*, epithelium covering papilla; *b*, epithelium lining calix; *c*, cavity of calix; *d*, connective tissue.

vessels project into the deeper layers of the epithelium, with the cells of which they appear to come in contact (fig. 880).[1] The pelvis contains no true glands, although at places solid buds of epithelium may grow down for a certain distance into the corium.

Near its exit from the sinus of the kidney the pelvis becomes contracted, and opposite the lower end of the gland it assumes a cylindrical form and becomes continuous with the ureter.

[1] Disse, *op. cit.* 1902.

Ureter.—The walls of the ureter consist of an external fibrous coat or adventitia, three strata of plain muscular tissue, and a mucous membrane (fig. 880).

The *adventitia* is a thin layer of connective tissue, which contains ramifications of the larger blood-vessels and nerves, with ganglia here and there, and in some subjects groups of fat-cells. Its connective tissue is freely continuous with that which lies between the muscular bundles of the muscular coat.

The *mucous membrane*, thin and smooth, shows a few longitudinal folds when the ureter is laid open or cut across in the upper part (fig. 881), but lower down in the pelvic part these folds disappear, and the section of the lumen is generally Y-shaped. The mucous membrane is composed of areolar tissue, which becomes gradually looser towards the muscular coat, but there is no distinction into mucous and submucous layers. It is prolonged above to the pelvis of the kidney, and below becomes continuous with the lining membrane of the bladder. The epithelium, which is

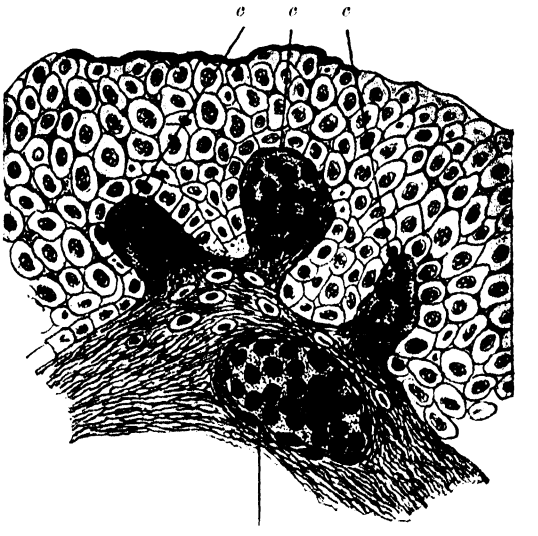


FIG. 880.—FROM A SECTION OF THE WALL OF THE PELVIS OF KIDNEY; HUMAN. (Disse.)

v, a vein within the corium; *c*, *c*, *c*, capillary blood-vessels with ridge-like projections into the epithelium.

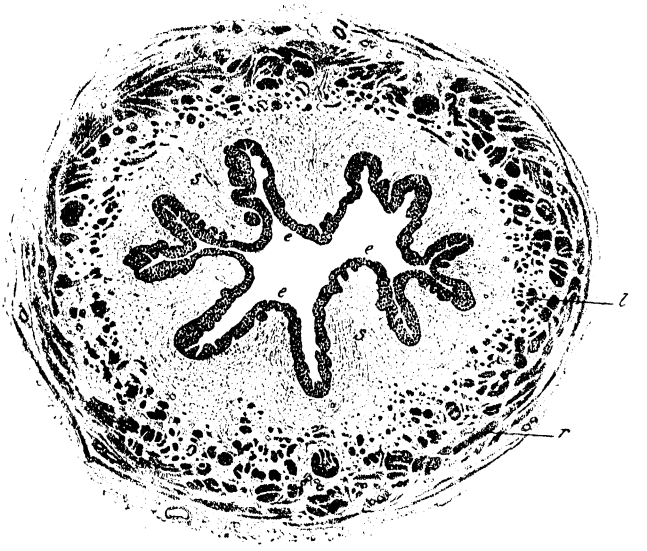


FIG. 881.—SECTION ACROSS THE UPPER PART OF THE URETER. (v. Ebner.)
Magnified 14 diameters.

e, epithelium; *s*, mucous membrane; *l*, longitudinal muscle; *r*, circular muscle.

similar to that of the pelvis and bladder (figs. 880, 883), is transitional, consisting of about four strata, in the uppermost of which the cells are somewhat

cubical, with depressions on their under surface; these fit upon the rounded ends of a second layer of pear-shaped cells; then follow two layers of rounded or oval cells, with processes extending down to the mucous membrane. This description of the shape of the epithelium-cells only applies to them as they occur in the empty condition of the duct; in the distended state the superficial cells are flattened out, and the pear-shaped and oval cells are much shorter. All the cells are connected with one another by 'cell-bridges' as in a stratified epithelium. The superficial cells are covered by a cuticular border on the free surface. They usually have two nuclei, and are believed to divide by amitosis. The deeper cells multiply by karyokinesis.

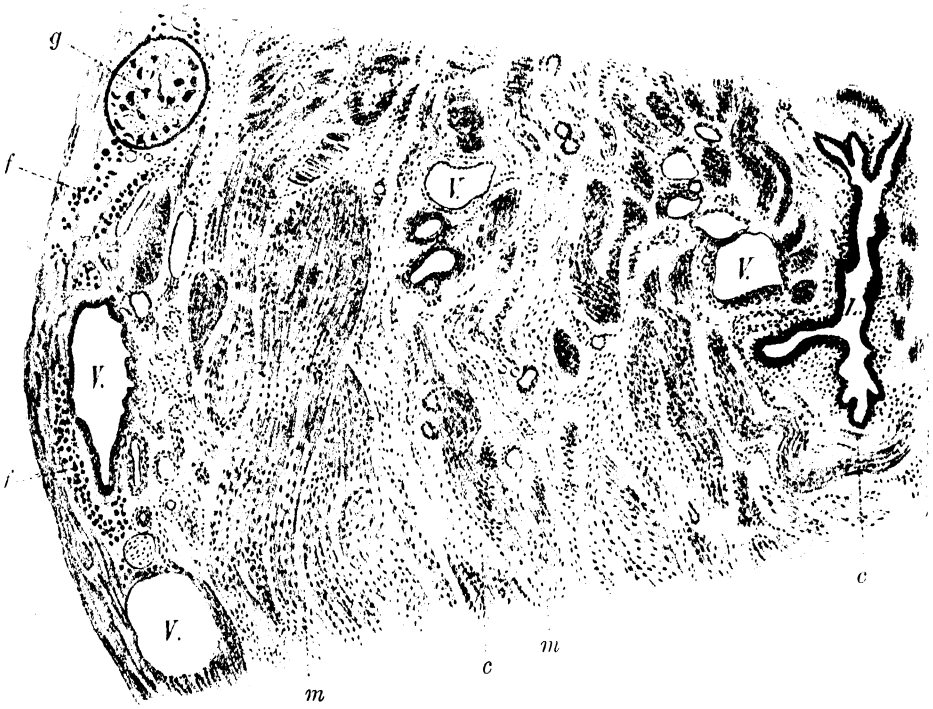


FIG. 882.—SECTION OF URETER, LOWER PART. (Disselhorst.)

L, lumen; *V*, *V*, veins; *g*, a small ganglion; *f*, *f*, fat-cells in adventitia; *m*, muscular bundles, variously cut; *c*, *c*, connective tissue.

As in the pelvis of the kidney, fine connective-tissue prolongations and capillary loops extend into the deeper part of the epithelium, but they are less numerous in the ureter.

A few small mucous glands have occasionally been described at the upper end of the ureter and in the renal pelvis, but they appear not to be present in man. Mucus is however secreted by the lining epithelium.

The *muscular tissue* of the ureter can generally be made out to be arranged in circular and longitudinal bundles, which are usually described as forming three layers, viz. inner and outer longitudinal and intermediate circular. But many of the bundles have an oblique course and the layers are not sharply differentiated from one another. Moreover, there is everywhere a large amount of connective tissue between the muscular bundles, so that the coat is by no means so purely muscular as is that of most of the hollow viscera (fig. 882).

The degree of development of the individual muscular layers differs considerably in different parts of the ureter. At the uppermost end near the pelvis there are chiefly longitudinal bundles

near the epithelium and circular fibres outside these, with a few longitudinal bundles in the adventitia: in the middle part of the ureter the circular fibres are most developed; the longitudinal bundles inside these are, however, still well marked, but those outside are scattered; in the lower or pelvic part the whole wall becomes more muscular, and circularly and obliquely disposed bundles are intermixed with the bundles of the longitudinal layers, and extend almost to the epithelium. Quite near the lower end, close to its passage into the wall of the bladder, the ureter is ensheathed by a mass of longitudinal muscular tissue which appears to be continued from the bladder wall, but is in reality a development of the outer longitudinal muscular layer of the ureter itself. It is termed the *ureter-sheath* (Waldeyer). As it passes obliquely through the bladder wall the ureter retains its independence, traversing a sort of canal in the vesical wall. At the end of this canal, *i.e.* at the vesical orifice of the ureter, its mucous membrane and epithelium are continuous with those of the bladder: at the upper edge of the orifice the mucous membrane projects somewhat beyond that which forms the lower edge, in the form of a valve-like fold—the *valve of the ureter*. Within the ureter-sheath the rest of the muscular tissue of the ureter is wholly in the form of longitudinal bundles which occupy almost the whole thickness of its coats. They are separated from the bladder musculature by a layer of connective tissue, and are easily distinguishable from the muscle-bundles of the bladder: they ultimately end in the mucous membrane of the bladder around the orifice of the ureter.

The muscular bundles of the ureter-sheath are somewhat coarser than those of the rest of this part of the ureter. They are separated from the other muscular tissue by a cleft in the connective tissue; there is another cleft outside them separating them from the adventitia.

Blood-vessels, lymphatics, and nerves.—The ureter is supplied with *arteries* from small branches of the renal, the spermatic, the internal iliac, and the inferior vesical. The *veins* end in various neighbouring vessels. The larger vessels ramify in the adventitia and send branches through the muscularis into the corium of the mucous membrane. From these branches capillaries pass into the muscular bundles and others form a plexus in the mucous membrane under the epithelium. *Lymphatics* are found forming a network in the mucous membrane and communicating with other vessels in the muscular coat and adventitia. The *nerves* come from the renal, spermatic, and hypogastric plexuses. They form plexuses in the adventitia and muscular coats containing small ganglia and scattered ganglion-cells. The nerves are chiefly for the supply of the muscular fibres, but afferent fibres have also been traced into the mucous membrane and epithelium, where they form terminal arborisations.

URINARY BLADDER.

Structure.—The bladder is composed of an *adventitia*, a *muscular* coat, a *submucous* coat, and a *mucous membrane*. There is also a *serous coat* which forms a partial covering, investing only the posterior and upper half of the bladder, and reflected from it upon the surrounding parts.

The *adventitia* is composed of fibrous tissue continuous with that between the muscular bundles; over the greater part of the bladder it is but little developed.

The *muscular coat* consists of unstriped muscular fibres, which are often described as forming layers, the outer consisting of bundles of fibres more or less longitudinal, and the next of fibres more circular in disposition; beneath this, in the submucous coat, is another imperfect longitudinal stratum.

The *longitudinal layer* is most distinctly marked on the dorsal and ventral surfaces of the bladder. Commencing in front (at the neck of the organ) from the pubes in both sexes (*musculi pubo-vesicales*), and, in the male, from the adjoining part of the prostate gland, its fibres may be traced upwards along the anterior surface to the summit of the bladder; and thence may be followed down over the posterior surface and base to the under part of the neck of the viscus, where they become attached to the prostate in the male, and to the front of the vagina in the female. Upon the sides the superficial fasciculi run more or less

obliquely, and often intersect; in the male they also reach the prostate. At the summit a few are continued along the urachus. The longitudinal fibres taken together constitute what has been named the *detrusor urinæ* muscle, but the circular fibres undoubtedly also play a part in the evacuation of the urine.

The *circular* fibres form a somewhat irregular reticulated layer distributed over the body of the bladder, varying in appearance in different individuals. The stratum they form is usually thicker than that formed by the longitudinal fibres. Their course may in general be looked upon as transverse, but throughout the upper two-thirds of the bladder they for the most part cross one another in very oblique bands: towards the lower part of the organ they assume a more circular course; at the base of the bladder they disappear, being here replaced by the submucous muscular layer (see below).

The muscular coat of the bladder forms so irregular a covering that, when the organ is much distended, intervals arise in which the walls are very thin; and, should the internal or mucous lining protrude in any spot through the muscular bundles, a sort of hernia is produced, which may go on increasing, so as to form a vesical sacculus, or *appendix vesicæ*, the bladder thus affected being then termed *sacculated*. Hypertrophy of the muscular fasciculi, which is liable to occur in stricture of the urethra or other affections impeding the issue of the urine, gives rise to that condition named the *fasciculated bladder*, in which the interior of the organ is marked by strong reticulated ridges or columns, with intervening depressions.

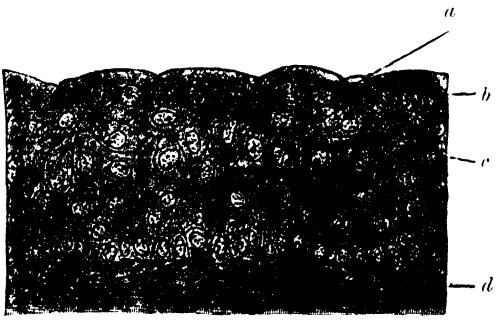


FIG. 883.—SECTION OF THE MUCOUS MEMBRANE OF THE BLADDER TO SHOW ITS EPITHELIUM. (Szymonowicz.)

a, *b*, superficial epithelium-cells; *c*, leucocyte; *d*, connective tissue of mucous membrane.

Next to the muscular coat, between it and the mucous membrane, but much more intimately connected with the latter, is a well-marked layer of areolar tissue, the *submucous coat*. The submucous areolar layer contains a large number of fine fibres of elastic tissue and also numerous muscular bundles which are scattered with no great regularity over the body of the bladder, but at the fundus produce a distinct stratum known as the *submucous muscular layer* (Ellis) especially developed in the neighbourhood of the trigone, where it forms the *sphincter vesicæ internus*.[1] The muscular bundles of the submucous layer are much finer than those of the muscular coat, and are easily distinguished from them in sections.

The *mucous membrane* of the bladder is soft, smooth, and of a pale rose colour. It is continuous above with the lining membrane of the ureters and kidneys, and below with that of the urethra. Neither here nor in the ureters is the mucous membrane provided with a muscularis mucosæ. It adheres loosely to the muscular tissue, and is thus liable to be thrown into wrinkles, except at the trigone, where it is always more even. It is covered with a transitional epithelium (fig. 883), exactly similar to that of the ureters (see pp. 604, 605). The cells vary much in

[1] For further details regarding this structure and its relation to the other muscular fibres of the bladder and ureters, see Disse, 'Die Harnblase,' in v. Bardeleben's Handbuch der Anatomie, 1902.

form according to the condition of distension of the bladder; in the distended organ they are flattened out so as to cover a larger surface, while in the empty condition of the bladder they are of less diameter and proportionately higher (see figs. 160, 161, p. 97). Many of the superficial cells contain two nuclei (fig. 884,'a). They are believed to multiply by amitosis (see fig. 74, p. 40). The deeper cells divide by mitosis; the newly formed cells take the place of others which are thrust

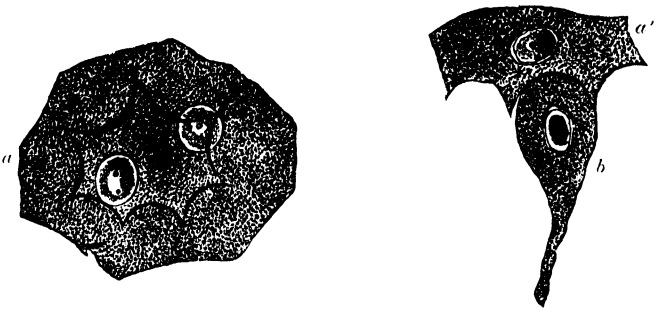


FIG. 884.—EPITHELIAL CELLS FROM THE BLADDER OF THE RABBIT. (Klein.) Highly magnified.

a, large flattened cell from the superficial layer, with two nuclei, and with strongly marked ridges and intervening depressions on its under surface; *a'*, one of the same cells shown in profile; *b*, pear-shaped cell of the second layer showing the manner in which it is adapted to a depression on the superficial cell.

towards the surface. There are no definite glands in the bladder, but in some places downgrowths of the deeper epithelium-cells into the mucous membrane occur, which may be either solid or hollow (fig. 885). These have sometimes been described as true glands. There appears to be no basement-membrane separating the corium of the mucous membrane from the epithelium. As in the pelvis of the kidney and ureter, projections of the corium into the epithelium in the form of vascular ridges are also seen here and there.

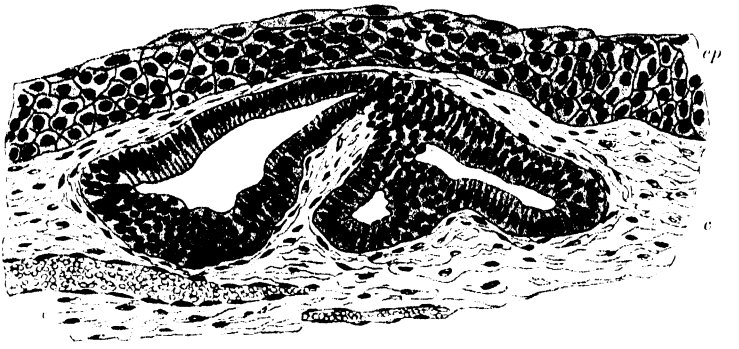


FIG. 885.—SECTION OF PART OF WALL OF BASE OF BLADDER; HUMAN. (Lendorf.) Magnified 230 diameters.

The section passes through a glandular invagination of the epithelium. *ep*, epithelium; *c*, corium.

Blood-vessels, lymphatics, and nerves.—*Arteries.*—The superior vesical arteries proceed from the remaining pervious portions of the hypogastric arteries; in the adult they appear as direct branches of the internal iliac. The inferior vesical arteries are usually derived from the anterior division of the internal iliac. In the female the uterine arteries also send branches to the bladder. These arteries anastomose with one another on the outer surface to form a network; branches from the middle hæmorrhoidal artery join this network. From it offsets pass into

the muscular coat, where they form a capillary network; others traverse the muscular coat and form an arterial plexus in the submucosa from which the capillary network of the mucous membrane is derived. The *veins* form large plexuses around the neck, sides, and base of the bladder; they eventually pass into the internal iliac veins. They do not accompany the arteries. The plexuses are situated in the submucous coat, in the muscular coat, and underneath the serous coat, but in the region of the trigone there is no distinct plexus in the submucosa. The *lymphatics* are confined to the muscular coat and adventitia, except in the region of the trigone, where there is a plexus in the muscular layer of the submucosa. Some lymph-capillaries are continued into the mucous membrane from those of the ureter. The nervous supply of the bladder is bilateral, each half having its own nerves. On each side the *nerves* are derived from two sources, viz.:—(*a*) from the third, the fourth, and sometimes the second sacral nerves: these fibres, which are known as the pelvic splanchnics (Gaskell), consist almost entirely of fine medullated nerves, and pass from the sacral spinal nerves (sacral plexus) directly to the pelvic plexus without going through the gangliated cord of the sympathetic; (*b*) from the hypogastric plexus of the sympathetic: these fibres are nearly all non-medullated. They arise from the upper lumbar nerves, and reach the hypogastric plexus through the aortic plexus and the inferior mesenteric ganglion. Both sets unite in the pelvic plexus, which contains numerous ganglia, and the fibres which go from the plexus to the bladder, where they form the plexus vesicalis, are mainly, if not entirely, non-medullated. According to v. Zeissl, the pelvic splanchnics supply only the longitudinal fibres of the bladder, but Griffiths found that stimulation of the peripheral cut ends of these nerves produces an effect upon the entire muscular coat on the same side. Stimulation of the peripheral cut ends of the hypogastric fibres causes feeble contraction of the corresponding half of the bladder (Langley); but if the bladder be previously contracted their stimulation causes rapid relaxation (Griffiths). There appears, however, to be some variation in different species of animals in the effects produced by stimulation of the different nerve-fibres according to the predominance of excitatory or inhibitory fibres.

The hypogastric plexus also contains sensory fibres, which probably reach the spinal cord through the twelfth dorsal and first and second lumbar nerves.

The nerve-fibres of the bladder pass to ganglia in the adventitia: these ganglia are most numerous near the base. From the ganglia non-medullated nerve-fibres are distributed to the muscular bundles, amongst which a finer gangliated plexus is formed. There is also a fine gangliated plexus in the submucosa: from this nerve-fibres pass to the muscle-bundles and to the corium. Some make their way into the epithelium, where, after penetrating between the cells for a certain distance, they give off branches which run parallel with the surface; from these offsets terminal filaments pass backwards between the deeper cells (G. Retzius).

The following articles on the ureters and bladder may be referred to:—L. Aschoff, Virch. Arch. cxxxviii. 1894 (mucous membrane); A. v. Brunn, Arch. f. mikr. Anat. xli. 1893 (gland-like structures); Cuccati, Mem. d. r. accad. d. sci. d. Bologna, ix. 1888 (nerve-distribution); Disselhorst, Anat. Hefte, iv. 1894 (str. of ureter); A. S. Dogiel, Arch. f. mikr. Anat. xxxv. 1890 (epithelium); Egli, Arch. f. mikr. Anat. ix. 1873 (glands of pelvis); Fenwick, Journ. Anat. and Physiol. xix. 1885 (venous plexuses); Gerota, Anat. Anz. xii. 1896 (lymphatics); Griffiths, Journ. Anat. and Physiol. xxv. 1891 and xxix. 1895; Grünstein, Arch. f. mikr. Anat. lv. 1900 (nerves); Berry Hart, Atlas of Female Pelvic Anatomy, 1884; O. Hamburger, Arch. f. mikr. Anat. xvii. 1880 (pelvis and ureter); London, Arch. f. Physiol. 1881 (epithelium); A. Lendorf, Anat. Hefte, xvii. 1901 (glands, lymphatics and nerves); Lubarsch, Arch. f. mikr. Anat. xli. 1893 (gland-like structures); Paneth, Wiener Sitzungsb. lxxiv. 1876 (epithelium); G. Retzius, Biol. Unters. iv. 1892 (nerves); Waldeyer, Verhandl. d. Anat. Gesellsch., Anat. Anz. vii. 1892 (ureter-sheath); Zeissl, Pflüger's Archiv., liii. 1893 (nerves of bladder).

The generative glands consist in the male sex of the *testicles*, which produce the spermatozoa; in the female sex of the *ovaries*, which produce the ova. The accessory generative organs in the male sex comprise the *penis* or organ of intromission, and various expansions and modifications of the ducts of the testicles, viz.: the *epididymis*, the *vas deferens* with its *ampulla*, the *seminal vesicles*, the *ejaculatory ducts*, the *prostate*, the *urethra* with *Cowper's glands*, besides certain rudimentary organs, such as the *organ of Giraldès*, the *hydatids of Morgagni*, and the *prostatic vesicle*. The accessory organs in the female sex are the oviduct or

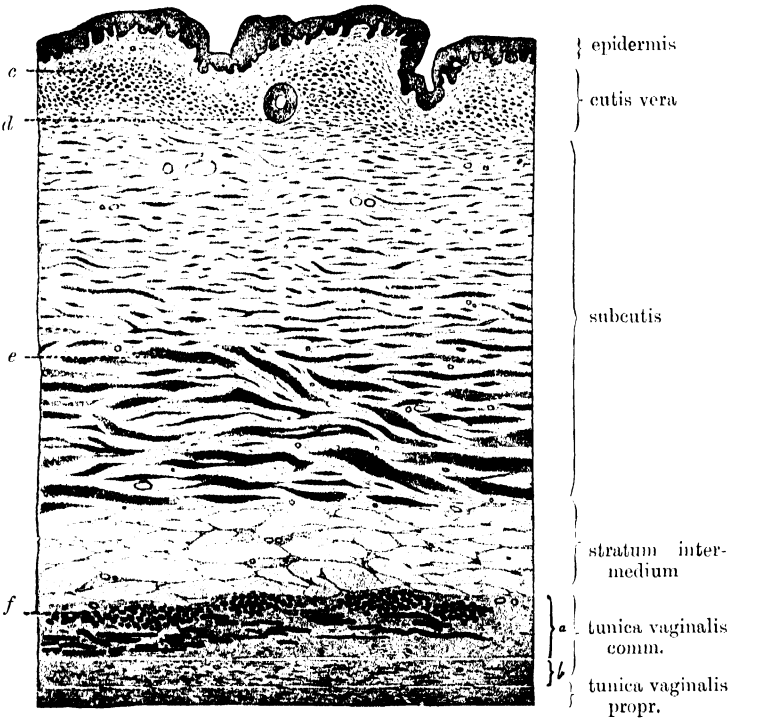


FIG. 886.—LONGITUDINAL SECTION THROUGH THE ANTERIOR WALL OF THE SCROTUM OF AN ADULT. (Eberth.) Magnified 17 diameters.

a, outer; *b*, inner layer of tunica vaginalis communis; *c*, fine muscle-bundles in cutis, cut across; *d*, hair-follicle; *e*, longitudinal muscle-bundles of dartos; *f*, external cremaster muscle.

Fallopian tubes, with their fimbriated extremities opening into the peritoneal cavity, the *uterus*, the *vagina*, and the *vulva*, with the *clitoris*, *labiæ* and *glands of Bartolin*, which last represent the glands of Cowper of the male sex. The urethra opens in the female at the upper part of the vulva, and although it does not, as in the male sex, transmit the secretion of the generative as well as that of the urinary glands, it may nevertheless be described most conveniently with the organs of generation.

MALE GENERATIVE ORGANS.

THE TESTICLES.

The testicles are contained within a purse-like sac of integument, known as the *scrotum*. The skin of this (fig. 886) is very thin and of a dark colour; it is commonly thrown into rugæ or folds, which are more or less marked according to the extent of contraction of the plain muscular tissue, fine bundles of which are present in it in

considerable amount (fig. 886, *c*), in addition to the muscle of the *dartos* (*e*). The last-named is a vascular layer containing many strongly marked bundles of involuntary muscular tissue, and lying immediately beneath the skin of the scrotum; it also forms a septum between the two testicles. The contraction of the scrotum is especially provoked by cold, and is better marked in robust than in weak conditions of the body; under contrary conditions the scrotum becomes relaxed.

The skin of the scrotum is thinly beset with curled hairs slightly flattened in section; their bulbs are large and may be seen or felt through the skin when this is stretched. The skin also allows the superficial veins to be seen through it.

Besides the skin and dartos the testicles are covered within the scrotum by the *spermatic fascia*, the *cremaster muscle*, the *infundibuliform fascia*, and the *tunica vaginalis* or serous membrane. These, as well as the *spermatic cord* which conveys

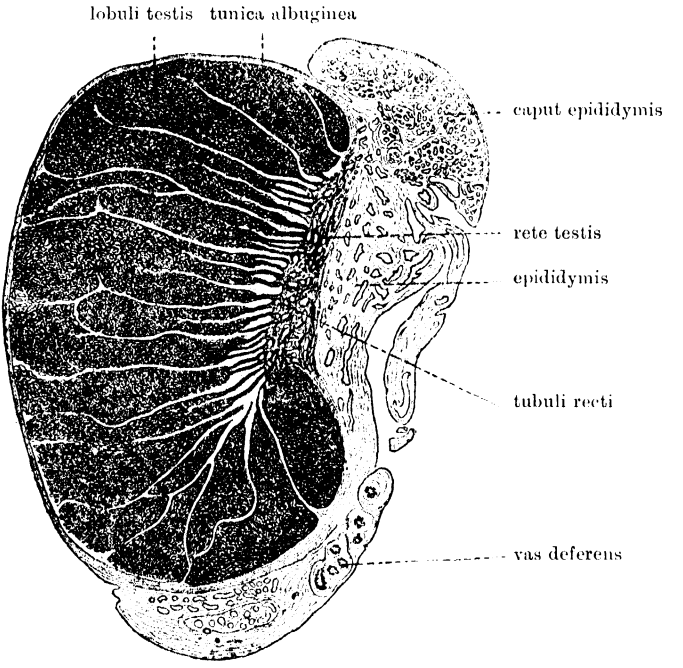


FIG. 887.—SECTION THROUGH THE TESTIS AND EPIDIDYMIS. (Böhm and v. Davidoff.)

the duct of the testicle and the vessels, nerves and lymphatics to or from the scrotum, will be described in detail in the part of this work which deals with the anatomy of the viscera (Vol. II. Part II.).

The testicle is an example of a compound tubular gland. Its tubules—the *seminiferous tubules*—considerably larger than the tubules of the kidney, are bounded by a comparatively thick and tough membrane, formed of several layers of a homogeneous connective tissue, containing many elastic fibres (fig. 910); between the layers and covering it externally are flattened epithelioid cells. The tubules are held together by loose connective tissue, which has peculiar interstitial cells containing yellowish pigment-granules, much more developed in some species of animal (cat, boar) than in man.

The *seminiferous tubules*, which are highly convoluted—*tubuli contorti*—are arranged in groups or lobules (*lobuli testis*, figs. 887, 888), incompletely separated by strong fibrous septa (*septula testis*) which extend inwards from the thick fibrous capsule of the organ, intercommunicating at intervals with one another. The

capsule is known as the *tunica albuginea*; it is covered by a layer of flattened epithelium-cells—cubical or columnar in the fœtus—the remains of the germinal epithelium. Outside this is a serous cavity originally continuous with the peritoneal cavity and bounded externally by a serous layer, the *tunica vaginalis*. The tunica albuginea is mainly formed of a fibrous layer containing many elastic fibres and some plain muscle-fibres. It has relatively few blood-vessels in its substance, but on its inner surface is a layer of loose, highly vascular connective tissue, sometimes known as the *tunica vasculosa testis* (Astley Cooper), which extends over the septula and serves to distribute the blood-vessels to the lobules. Outside the fibrous layer and immediately under the epithelium is a looser connective-tissue layer, thinner than the main substance and containing but few elastic fibres; the two strata are only imperfectly separated in the adult.

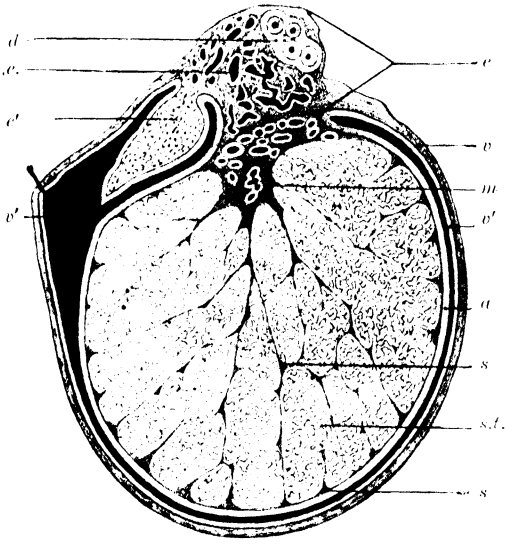


FIG. 888.—TRANSVERSE SECTION OF TESTICLE AND EPIDIDYMIS, MAN. (Eberth.)

a, tunica albuginea; *s.t.*, seminiferous tubules; *s*, trabeculæ dividing the gland into lobules; *c*, tunica vaginalis; *c'*, cavity of tunica vaginalis; *m*, mediastinum testis; *e*, epididymis; *e'*, caput epididymis; *v*, vas deferens (its convolutions have been cut four times); *r.e.*, vasa efferentia.

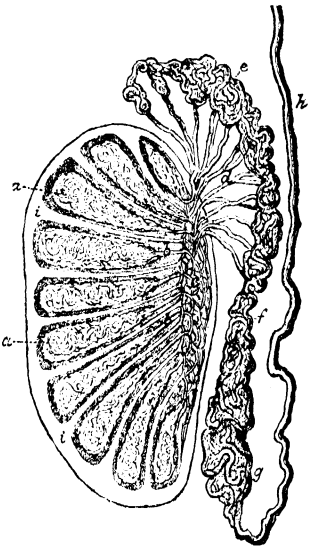


FIG. 889.—PLAN OF A VERTICAL SECTION OF THE TESTICLE, SHOWING THE ARRANGEMENT OF THE DUCTS.

The true length and diameter of the ducts have been disregarded. *a*, *a*, tubuli seminiferi coiled up in the separate lobes; *b*, vasa recta; *c*, rete; *d*, vasa efferentia ending in the coni vasculosi; *e*, *f*, *g*, convoluted canal of the epididymis; *h*, vas deferens; *i*, *i*, section of the back part of the tunica albuginea with fibrous processes running between the lobes.

At the posterior border for about a third of its extent the capsule is continuous with a mass of fibrous tissue which extends into the interior of the organ, and is known as the *mediastinum testis* or *corpus Highmori*. This is joined by the septa above mentioned, which converge to it from the capsule. Sections of the mediastinum testis display a network of small tubules—*rete testis*—into which open the straightened out and narrowed continuations of the seminiferous tubules, known as the *straight tubules* (fig. 898). From the opposite side of the rete testis, at its upper and posterior aspect, there emerge a certain number (12 to 20) of efferent tubules about ·5 mm. in diameter, which are at first less and afterwards more and more convoluted, and also increase somewhat in diameter as they proceed. These tubules thus form masses of gradually increasing size, the so-called *coni vasculosi*. These unite to form the beginning of a very long and extremely convoluted duct of considerable size—*the duct or tube of the epididymis* (figs. 889, 890, 891).

The convolutions of this tube, together with those of the coni vasculosi, are held together by connective tissue and blood-vessels, and form a mass—the *epididymis*—on the posterior aspect of the testicle proper: it is included within the serous sac which encloses the main organ, and has a special fibrous investment thinner and looser than that of the testicle. From the lower end of the epididymis its tube is continued into the large, thick-walled muscular tube known as the *vas deferens* (figs. 889, 890, 891, *h*), which passes up along the spermatic cord to reach the cavity of the pelvis, and there curves round the side and base of the urinary bladder to enter the urethra in its prostatic portion. The vas deferens is dilated near its termination into a reservoir of about double the diameter of the vas, known as the *ampulla*, and also receives the duct of the *seminal vesicle* (fig. 894; see also

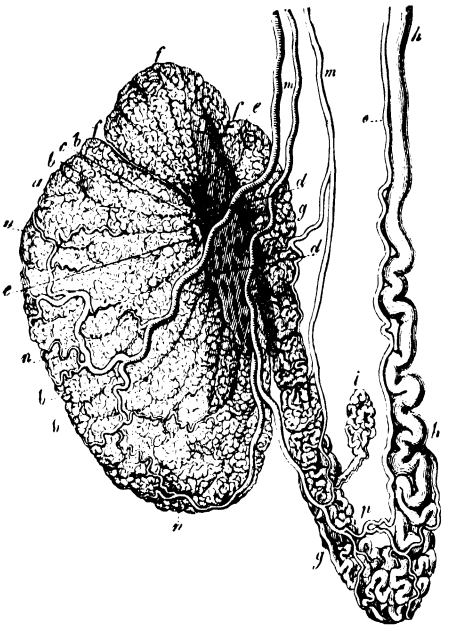


FIG. 890.—TESTIS, EPIDIDYMIS, AND VAS DEFERENS. (From Kolliker, after Arnold.)

a, body of the testicle; *b*, lobules; *c*, vasa recta; *d*, rete vasculosum; *e*, vasa efferentia; *f*, coni vasculosi; *g*, epididymis; *h*, vas deferens; *i*, vas aberrans; *m*, branches of the spermatic artery passing to the testicle and epididymis; *n*, ramification in the testis; *o*, artery of the vas deferens; *p*, its union with a twig of the spermatic artery.

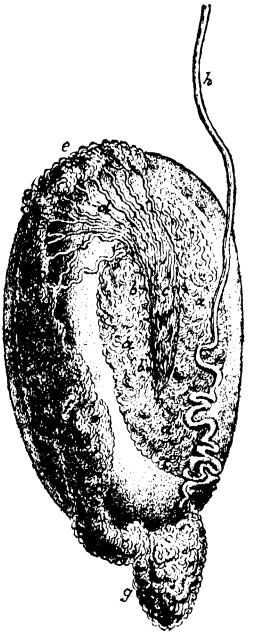


FIG. 891.—DUCTS OF THE TESTICLE INJECTED WITH MERCURY. (From Haller.)

a, body of the testicle; *b*, tubuli in the interior of the gland; *c*, rete vasculosum; *d*, vasa efferentia terminating in the coni vasculosi; *e*, *f*, *g*, convoluted canal of the epididymis; *h*, vas deferens ascending from the globus minor of the epididymis.

fig. 929, p. 639), just before its entrance into the urethra. The seminal vesicle is formed of a main portion and, usually, five accessory portions, which open into it; each part consists of a convoluted tube, the main part being, when unravelled, about 12 cm. long. The vas deferens is at first convoluted, but within the spermatic cord in its passage through the inguinal canal and pelvis it is simple in arrangement. The vas is a long, thick-walled tube, some 40–45 cm. in length when straightened out, and 2–3 mm. in diameter. It is lined by a two-layered columnar epithelium, which rests on a basement-membrane. Outside this is a connective-tissue corium, which with the epithelium is usually in longitudinal folds. Outside the mucous membrane and separated from it by a submucosa is the muscular coat, and outside this a connective-tissue adventitia. The muscular coat consists of three layers of plain muscular tissue, viz. inner and

outer longitudinal layers, and a very well-marked middle circular layer (fig. 893). The *ampullæ* and the *seminal vesicles* are enclosed in a common fibrous and muscular capsule. They have the same general structure as the vas deferens, but their walls are thinner, less muscular, and deeply corrugated (fig. 894, and lower figure of Plate opposite p. 635). The mucous membrane is beset with irregular gland-like diverticula which are often branched ; their epithelium shows two layers of cells, the inner columnar, the outer cubical. The columnar cells exhibit secretion appearances in the form of drop-like exudations from the free border like those seen in the epididymis and vasa efferentia (fig. 897). The epithelium of all these tubes contains yellowish-brown pigment-granules of varying

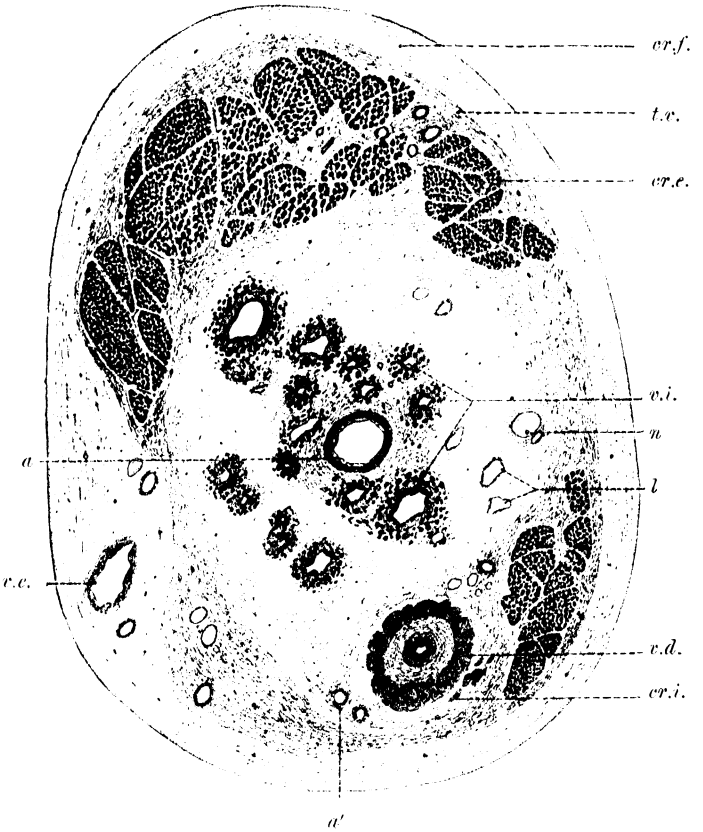


FIG. 892.—SECTION OF THE RIGHT SPERMATIC CORD OF AN ADULT AS SEEN FROM ABOVE. The section is taken somewhat above the middle of its length. (Eberth.) Magnified 11 diameters.

cr.f., cremasteric fascia ; *t.v.*, tunica vaginalis ; *cr.e.*, external cremaster muscle ; *v.i.* internal spermatic veins ; *v.e.*, external spermatic vein ; *n.*, internal spermatic nerve : *l*, lymph-vessels ; *a*, internal spermatic artery ; *cr.i.*, internal cremaster muscle ; *v.d.*, vas deferens.

size and of fatty nature. They are not confined to the epithelium, however, but are also seen in the connective-tissue cells, and even in the plain muscle-cells. They are best marked in the vesiculæ seminales.

G. Walker finds in connexion with the seminal vesicles of the guinea-pig and rat an accessory gland, which he terms the *coagulating gland* from the fact that its secretion acts like a ferment upon the secretion of the seminal vesicles, causing it to coagulate (Johns Hopkins Hosp. Bull. xxi. 1910).

The part of the vas deferens which intervenes between the vesicula seminalis and the orifice of the duct into the urethra, is termed the *ejaculatory duct*. In the structure of its walls, which are deeply corrugated longitudinally, it resembles generally the ampullæ and vesiculæ seminales.

The dorsal portion of the ejaculatory duct is provided with irregular large diverticula, some five in all. Its mucous membrane is beset with simple and branched gland-like invaginations lined with long columnar epithelium-cells with other cells at their base—thickened in some parts so as to be several cells thick—similar to that found in the ampullæ, and beset with yellowish pigment-granules. The uppermost part of the ejaculatory duct is dilated into a sinus; this is the only part of the main duct with muscular tissue in its walls, but the large diverticula have a distinct muscular layer (Felix).

The *tube of the epididymis*, some 6 to 8 metres long and about 0·4 mm. in diameter, has a comparatively thin wall (fig. 895) composed of a basement-membrane, a circular muscular layer, and a connective-tissue adventitia, and is lined by very long columnar cells which show a marked canalisation of their protoplasm (trophospongium, fig. 896). Each cell has a bunch of what appear to be cilia, but the filaments are matted together and are not vibratile. The bunch of filaments is

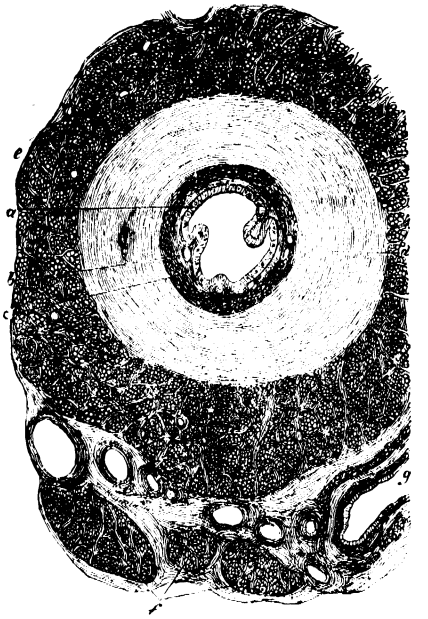


FIG. 893.—SECTION ACROSS THE COMMENCEMENT OF THE VAS DEFERENS. (Klein.)

a, epithelium; *b*, mucous membrane; *c*, *d*, *e*, inner, middle, and outer layers of the muscular coat; *f*, bundles of the internal cremaster muscles; *g*, section of a blood-vessel.

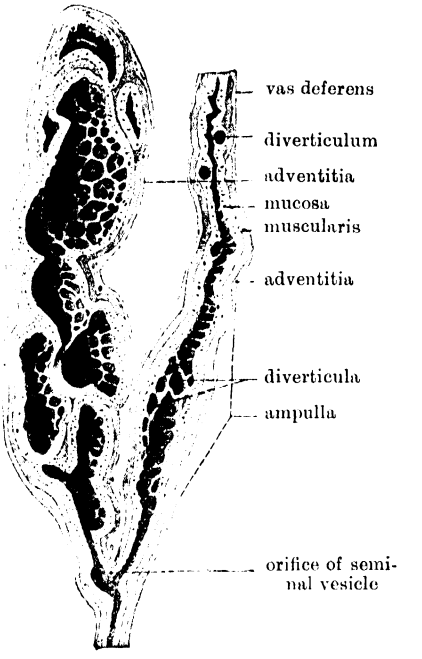


FIG. 894.—LEFT SEMINAL VESICLE WITH THE CORRESPONDING VAS DEFERENS AND ITS AMPULLA. (Eberth.)

Frontal section. The interior looked at from behind.

prolonged into the cell protoplasm as far as the nucleus. They appear to be concerned with the extrusion of secretion from the cells. A double centrosome is always found at the side of the bunch, near the free surface of the cell. There is a second layer of smaller cubical or rounded, sometimes conical, cells next to the basement-membrane. The epithelium of the tube of the epididymis has true cilia near its upper end. A similar epithelium is found in the coni vasculosi. Between the ciliated cells are others which are non-ciliated (fig. 60, p. 32), and, from the free ends of these, drops of secretion may in many instances be seen projecting; similar drops may be observed free within the lumen of the tube (fig. 897). The ciliated cells disappear gradually as the ducts are traced backwards to the rete, at least in man; the epithelium near the rete is beset with irregular thickenings with depressions between them simulating glands. The tubules of the rete testis,

like the straight tubules which open into them, are lined with cubical or flattened cells.

The *seminiferous tubules* (*tubuli contorti*) are of fairly large diameter (0·2 mm.) and very long in proportion, a single tubule isolated after maceration in

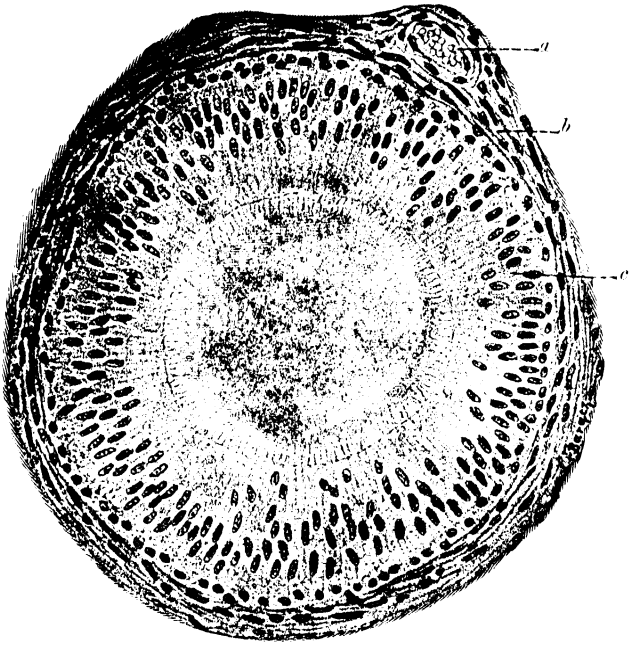


Fig. 895.—Section of the tube of the epididymis. (Szymonowicz.) Magnified 300 diameters.

a, blood-vessel; *b*, circular muscular fibres; *c*, epithelium.

acid, measuring as much as 70–80 cm. (Sappey). There are altogether between 800 and 900 tubules in the testis (Lauth). In spite of the comparative facility with which they may be unravelled it has not been definitely determined whether they anastomose at their peripheral ends, or whether they begin with blind

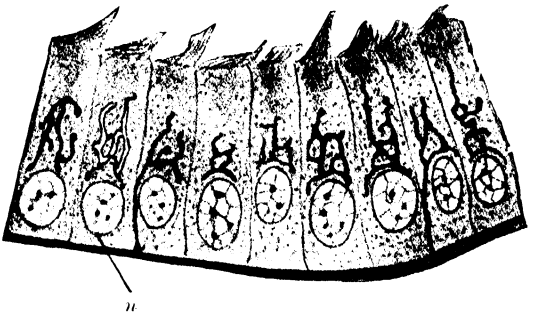


Fig. 896.—Cells of epididymis, showing canalisation of the cytoplasm. (E. Holmgren.)

n, nucleus. In two cells the canals extend to the basement-membrane.

extremities. Some authorities describe numerous anastomoses, others deny their existence. Eberth [1] was not able to find a single anastomosis, but was equally unsuccessful in finding any blind endings to the tubules. Their total combined length has been estimated at from 650 to 800 metres. Some of them show bulgings

[1] 'Die männlichen Geschlechtsorgane' in v. Bardeleben's Handbuch, 1904.

and even lateral branches, but these are rare ; on the whole they have a uniform diameter and smooth contour.

Each tubule is bounded by a relatively thick membranous wall (7–10 μ) com-

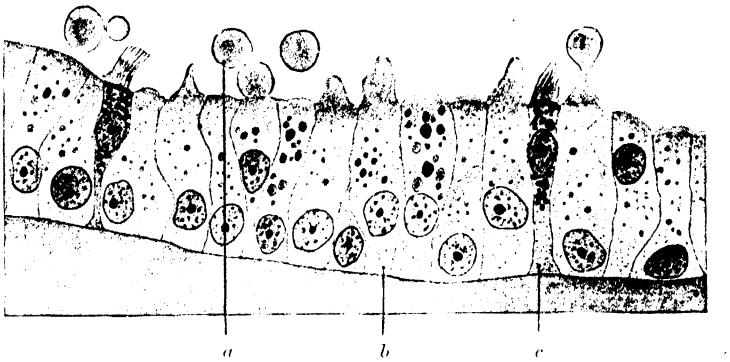


FIG. 897.—SECTION OF EPITHELIUM OF VAS EFFERENS NEAR ITS JUNCTION WITH THE EPIDIDYMIS. (Eberth.) Magnified 600 diameters.

a, a drop of secretion, free in the lumen of the duct; *b*, a secreting cell; *c*, a ciliated cell containing pigment-granules.

posed of a number of lamellæ. The lamellæ are formed partly of flattened cells, partly of connective-tissue ground-substance with numerous elastic fibres, arranged

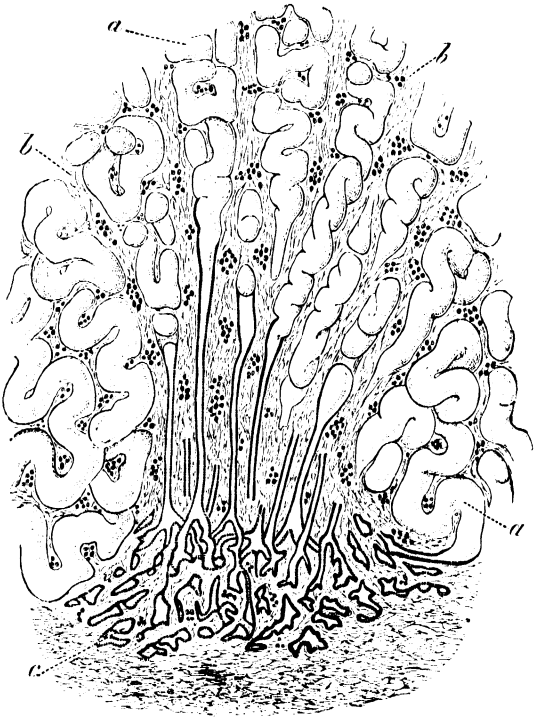


FIG. 898.—PASSAGE OF CONVOLUTED SEMINIFEROUS TUBULES INTO STRAIGHT TUBULES, AND OF THESE INTO THE RETE TESTIS. (Mihalkovics.)

a, seminiferous tubules; *b*, fibrous stroma continued from the mediastinum testis; *c*, rete testis.

in a close network, with for the most part a circular course around the tubule (fig. 910). The lamellæ become more pronounced and their fibres more distinct as development proceeds. The innermost lamellæ are very closely arranged, and

give the appearance of a basement-membrane; but there may be a delicate basement-membrane next to the epithelium.

Towards the mediastinum testis several tubuli contorti join to form the tubuli recti (fig. 898); before their junction they become considerably smaller, and the tubuli recti preserve the smaller diameter. These tubules possess only a single layer of epithelium, so that their lumen is larger than that of the tubuli contorti. As they approach the mediastinum the connective-tissue wall of the tubuli contorti becomes loosened out and blends with the connective tissues of the mediastinum testis, so that the tubules of the rete testis have no membrana propria distinct from the general connective tissue between them. A basement-membrane similar to that of the tubuli contorti reappears, however, in the efferent ducts of the testis and the coni vasculosi, and circular muscular fibres are added in the coni vasculosi and in the duct of the epididymis.

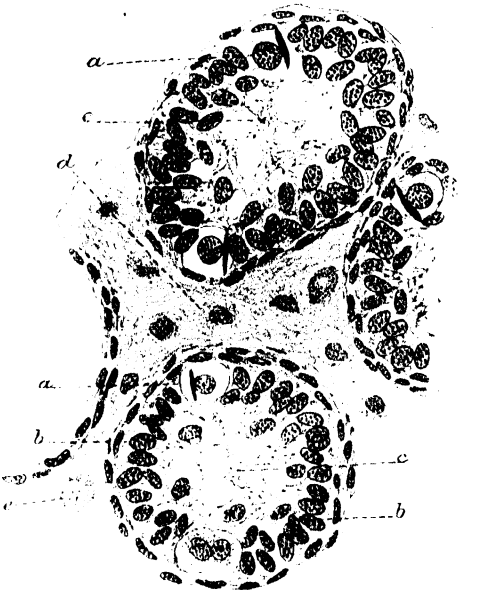


FIG. 899.—SECTION OF A TESTICLE OF A 9-YEAR-OLD CHILD. (Spangaro.)

a, enlarged cells (spermatogonia), some of them dividing; several contain crystals (Lubar's crystals); *b*, cells lining the tubule; *c*, coagulated contents of tubule; *d*, interstitial tissue; *e*, mast-cells.

Spermatogenesis.—The seminiferous tubules are lined with several layers of epithelium-cells which vary in appearance according to the condition of development of the spermatozoa. In the young subject before puberty the epithelium is formed of two or three layers of cells (fig. 899), which show no well-marked distinction, except that those of the outer layer next to the membrane of the tubule are rather more regularly arranged than the rest; the cells at first almost fill the tubule, leaving little or no lumen. Amongst them a certain number of large, clear cells begin quite early to be differentiated: these become the spermatogonia (see below). After puberty some tubules are to be seen containing fully developed spermatozoa, and others at various stages of formation (fig. 900), and, as just mentioned, the appearance of the tubules differs accordingly (figs. 901, 902). In tubules in which the spermatozoa are fully developed and ready to be discharged there appear to be three layers of cells, viz.: 1, the lining epithelium, formed of cubical cells, some of which enlarge to form the *spermatogonia*; 2, large spherical cells derived from these and themselves in process of

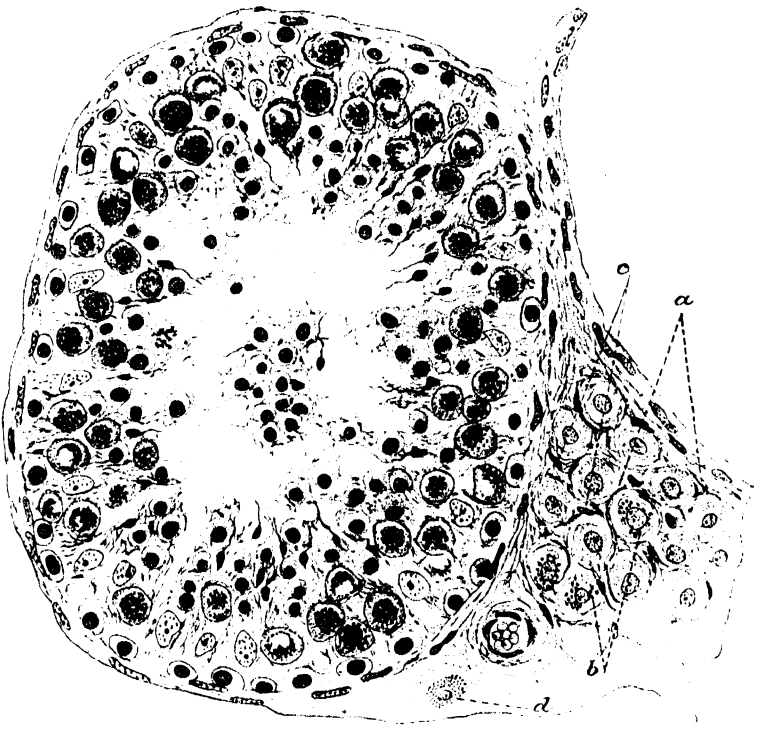


FIG. 900.—SECTION FROM THE TESTICLE OF A 42-YEAR-OLD MAN. (Spangaro.)

a, interstitial cells; *b*, some containing pigment; *c*, nuclei of ordinary connective-tissue cells; *d*, mast-cell. In the section of the tubule may be seen in succession from without inwards, spermatogonia, spermatocytes, spermatids, and spermatozoa. A few spermatids and spermatozoa are detached and occupy the middle of the tubule.

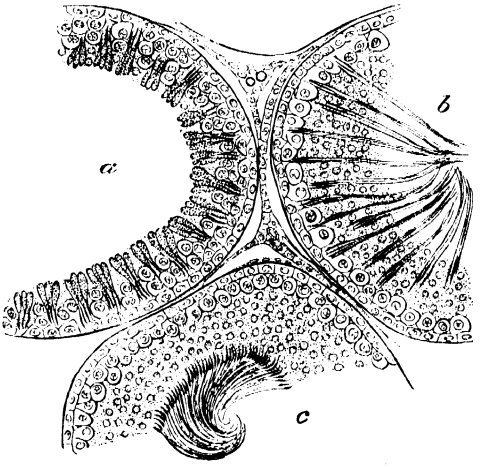


FIG. 901.—SECTION OF PARTS OF THREE SEMINIFEROUS TUBULES OF THE RAT. (Schäfer, from a preparation by A. Fraser.) Moderately magnified.

a, with the spermatozoa least advanced in development; *b*, more advanced; *c*, containing fully developed spermatozoa. Between the tubules are seen strands of interstitial cells with blood-vessels and lymph-spaces.

mitotic division, the *spermatocytes*; and 3, a large number of small cells with resting nuclei, the *spermatids*.[1] These last are ready for transformation into spermatozoa

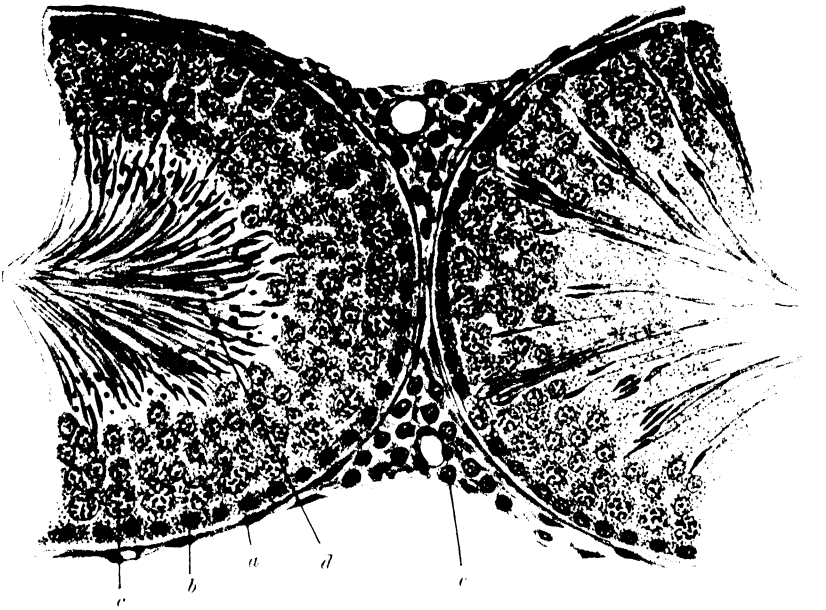


FIG. 902.—PORTIONS OF TWO TUBULES FROM THE RAT CORRESPONDING TO THE TUBULES *b* AND *c* OF FIG. 901, BUT MORE HIGHLY MAGNIFIED. (F. H. A. Marshall.)
a, basement-membrane; *b*, spermatogonium; *c*, spermatocyte; *d*, spermatozoa within lumen of tube; *e*, interstitial cells.

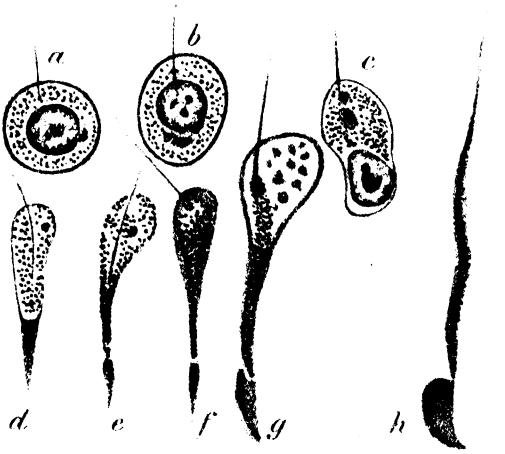


FIG. 903.—TRANSFORMATION OF A SPERMATID INTO A SPERMATOZOON: MOUSE. (Benda.)
a, spermatid with a filament extending from its centrosome beyond the cytoplasm. The archoplasm lies on one side of the nucleus; *b*, extension of the filament; the archoplasm is now at the opposite pole of the nucleus; *c*, elongation of the cell and passage of the nucleus towards the end opposite the "tail" filament to form the head of the future spermatozoon; *d* to *h*, transformation of nucleus into head of spermatozoon, and formation of middle piece from part of cytoplasm. The spiral fibre of the middle piece is produced from the mitochondria of the cytoplasm.

[1] 'Young spermatozoa' of H. H. Brown (Quart. Journ. Micr. Sci. xxv. 1885), who was the first to give a clear description of the changes which occur in the seminal epithelium in the production of spermatozoa.

as soon as those which are fully formed (and which usually occupy the lumen of the tubule) are discharged.

The spermatocytes are formed from the spermatogonia by ordinary mitosis, but in the formation of spermatids from spermatocytes there are at least two successive divisions, neither of which are of the ordinary type of mitosis, but are respectively hetero- and homotypical (see pp. 51 and 52). At the final division the number of chromosomes in each cell is reduced to one-half.

The process of transformation of spermatids into spermatozoa (figs. 903, 904) consists in the accumulation of the chromatin of the nucleus at one pole of the cell to form the head of the spermatozoon, and the outgrowth of a filament from the (double) centrosome to form the tail filament of the spermatozoon, the rest of the cell becoming partially atrophied [1] and transformed into the middle piece of the spermatozoon. These changes are known collectively as *spermatogenesis*. In their course the developing spermatozoa become grouped together into bundles with the head end of each directed towards the membrane of the tubule ; these ends become imbedded in an enlarged lining cell known as a *cell of Sertoli*. Through this the

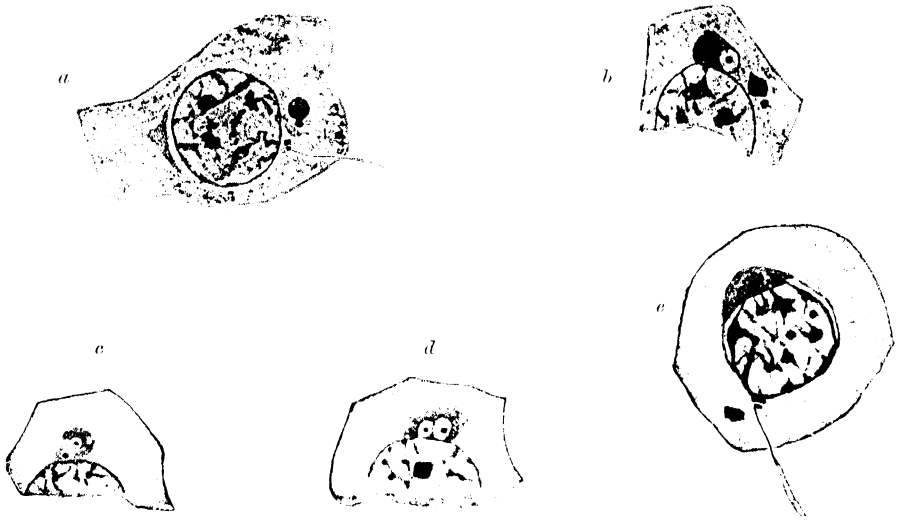


FIG. 904.—THE EARLIER CHANGES IN THE SPERMATIDS IN THE COURSE OF FORMATION OF THE SPERMATOZOA. (Niessing.)

The tail-filament is seen (in *a* and *e*) to extend from the centrosome, which lies close to the nucleus. The head-cap (shown in *e*) is produced by a transformation of part of the archoplasm which becomes vacuolated (*b*, *c*, *d*).

developing spermatozoa appear to derive nutriment (fig. 905). But as the transformation into fully formed spermatozoa proceeds the heads of the spermatozoa become gradually shifted further from the membrane of the tubule, this being apparently effected by a growth in length of the cells of Sertoli. Eventually the spermatozoa become set free from these cells and then lie wholly within the lumen of the tubule. These changes in the form and arrangement of the developing spermatozoa give a streaked appearance to the epithelium of the tubule when seen in section. While these changes in the spermatids are proceeding, the spermatocytes are at the same time undergoing mitotic division to form a new crop of spermatids, so that a constant series of changes is being produced in the

[1] Some of it may be thrown off and the granules within the cells set free as the 'seminal granules.'

FIG. 905. A CELL OF SERTOLI WITH WHICH THE SPERMATIDS (THREE OF WHICH ARE SHOWN) ARE BEGINNING TO BE CONNECTED: HUMAN. (Bramman.)

The cell contains globules (of nutritive substance) staining with osmic acid, and similar but smaller globules are also seen in the spermatids. A 'ring' is usually formed around the tail filament by one of the particles of the (double) centrosome; this is shown in each of these spermatids close to the 'head.'

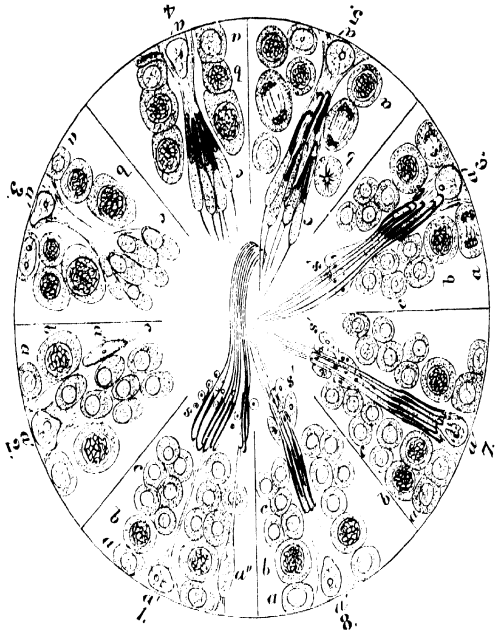


FIG. 906.—DIAGRAM EXHIBITING THE CYCLE OF PHASES OF SPERMATOGENESIS IN THE RAT. (Schäfer.) (This diagram is founded upon the drawings of H. H. Brown.)

a, spermatogonia, seen dividing in 6; *a'*, cells of Sertoli; *b*, spermatocytes, with skein-like nuclear filaments: these cells are seen actively dividing in 5; *c*, spermatids forming an irregular column or clump in 6, 7, 8, and 1, and connected to Sertoli cell, *a'*, in 2, 3, 4, and 5. In 6, 7, and 8, advanced spermatozoa of one crop are seen between columns of spermatids of the next crop. *s'*, parts of the spermatids which disappear when the spermatozoa are fully formed; *s*, seminal granules, probably resulting from the disintegration of *s'*; *a''*, in 1 and 2, are Sertoli cells which are probably becoming atrophied.

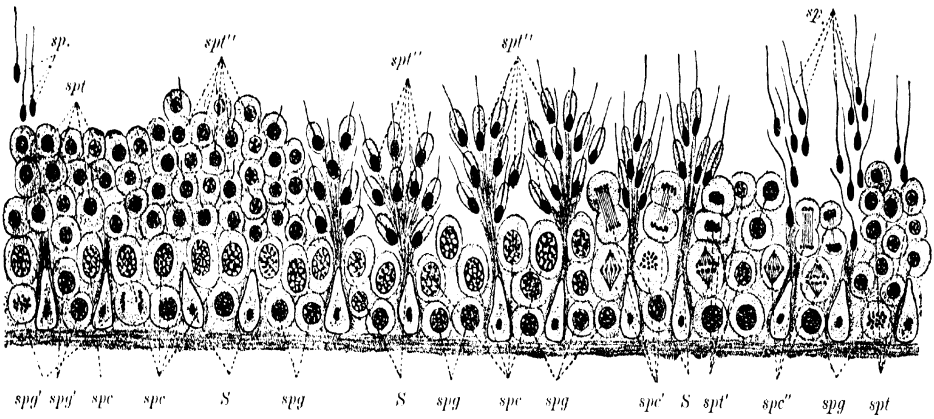


FIG. 907.—DIAGRAM SHOWING THE PHASES OF SPERMATOGENESIS IN A LONGITUDINAL SECTION OF A TUBULE. (Sobotta.)

spg, spermatogonia; *spg'*, dividing spermatogonia; *spc*, spermatocytes; *spc'*, dividing spermatocytes; *spt*, spermatids; *spt'*, dividing spermatids; *spt''*, spermatids in process of transformation into spermatozoa; *sp*, spermatozoa; *S*, cells of Sertoli.

appearance of different parts of the tubules or even in longitudinal sections of the same tubule. Such differences of appearance are represented diagrammatically in figs. 906 and 907.

Since the spermatozoa represent the product of the seminiferous tubules and are themselves complete cells the testicle is not a true secreting gland in the same sense as the salivary gland or the kidney, but its cells are bodily passed into the duct after having undergone certain morphological changes.

The spermatozoa.—A spermatozoon is composed of a head, middle piece, and tail (fig. 908). The *head* is formed from the nucleus of the spermatid: it stains intensely with basic dyes. In man it has a flattened oval shape, narrowing in a wedge-like manner towards the free extremity. This extremity is covered by a clear *head-cap*, derived from the archoplasm of the spermatid by a process of vacuolation (fig. 904); the head-cap is not distinguishable in the fully formed spermatozoon of man. The *middle piece* is formed from the cytoplasm of the spermatid or at least from a part of the cytoplasm; the greater portion either breaks away or becomes atrophied. In some animals it is encircled by a spiral fibre developed from mitochondria (Benda, fig. 903); this fibre is not distinct in the human spermatozoon. The middle piece contains a centrosome from which a fine cilium-like filament extends into the tail. The *tail* in the human spermatozoon is a fine tapering filament; the terminal part is somewhat suddenly narrowed (*end piece*). The fibril from the centrosome extends throughout the tail. Sometimes there are two or more fibrils, and in some animals there is a membranous fringe along the tail.

The average length of the human spermatozoon is from 50 μ to 60 μ; the head being about 4·5 μ and the middle piece about the same or a little more. In breadth the head measures about 2·5 μ and in thickness 1·5 μ; the middle piece is less than 1 μ in diameter. The tail is about ten times the length of the head (45 μ).

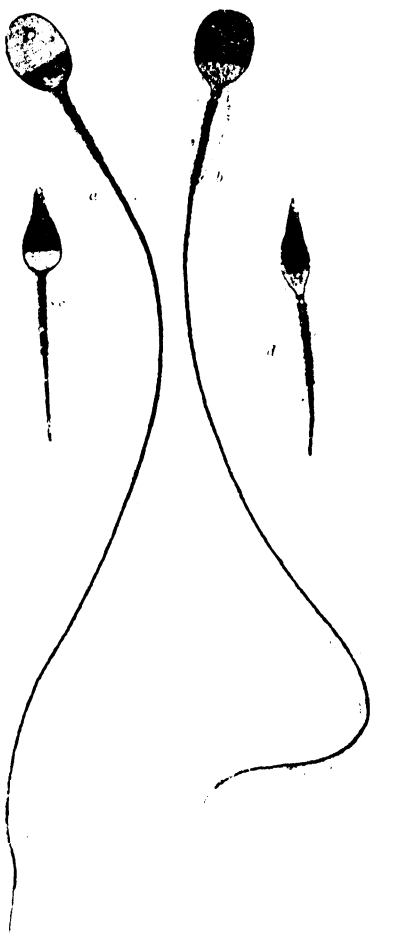


FIG. 908.—HUMAN SPERMATOZOA. (Broman.) Highly magnified.

a and *b* represent spermatozoa in face, in different foci of the microscope; *c* and *d*, in profile view.

Great variations in size, in the shape of the head and in the details of structure of the spermatozoa are found in different species of animals (see fig. 909). Even in the same animal it is common to find more than one kind of spermatozoon; some, much the fewer in number, being far larger than the rest (*giant spermatozoa*). This holds true for man as well as for most animals investigated. The larger spermatozoa in man are as much as 75 μ in length, and

3·5 μ in the breadth of the head. Duplication of head or tail, occasionally met with, is probably due to abnormality of development.

Blood-vessels, lymphatics, and nerves.—Blood-vessels pass into the organ by the mediastinum, and ramify over the septula and inner surface of the tunica albuginea; these vessels pass amongst the seminiferous tubules. In the intertubular tissue are large sinus-like lymphatics, which pass out to the spermatic cord alongside the blood-vessels. There is also a lymphatic plexus under the albuginea and a subserous plexus under the tunica vaginalis.

The arteries and veins of the testis and epididymis are thin-walled and have relatively little muscular tissue. The internal spermatic artery, which passes to the testicle in the spermatic cord, resembles in structure ordinary arteries of the same size; but the corresponding veins in the cord have very thick walls, with a circular muscular coat even thicker than that of the arteries, and with longitudinal muscular fibres both in the intima, and in the form of strong bundles also in the adventitia.

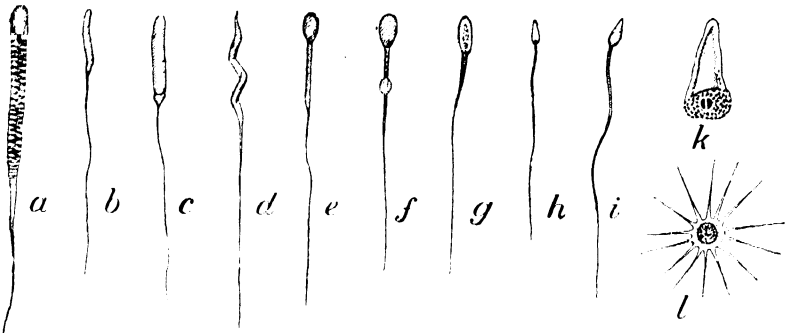


Fig. 909.—Different forms of spermatozoa. (From Verworn.)

a, of bat; *b*, *c*, of frog; *d*, of finch; *e*, of ram; *f*, *g*, of boar; *h*, of a jelly-fish; *i*, of a monkey; *k*, of round-worm; *l*, of crab.

The nerves are derived from the sympathetic; they accompany the blood-vessels and are mainly distributed to these (Retzius). They do not penetrate into the tubules.[1] Those of the epididymis have occasional ganglia in their course, but there are no ganglia on the nerves to the vas deferens (Timofeew).

Intertubular substance.—The tissue between the tubules is composed of loose areolar tissue with numerous elastic fibres, many of which encircle the tubules and help to constitute their walls (fig. 910). The tissue contains a few ordinary flattened connective-tissue cells and mast-cells, and a variable amount of cells and cell-groups of peculiar character, known as the *interstitial cells* (Leydig) (figs. 900, 901, 902). According to the testimony of most observers, these cells have a mesenchymic origin, and should therefore be regarded as modified connective-tissue cells. But in animals in which they are abundant, as the cat and the boar, they have the appearance of masses of epithelium-like cells, either isolated or joined together into strands which may form a network between the tubules. When present in abundance they confer a firm character upon the testicular substance. In man they are fairly numerous, and are composed of polygonal or somewhat flattened cells with well marked excentric nuclei, each showing a distinct nuclear network and nucleolus. The cell-protoplasm contains a double centrosome (Eberth) close to the nucleus (fig. 911, *a*). The cytoplasm frequently is found to

[1] According to Sclavunos nerve-fibrils penetrate to the epithelium both in the seminiferous tubes and in the ducts (Anat. Anz. ix. 1894).

enclose granules or globules of a fatty or lipoid nature, sometimes of a yellow colour; they are blackened by osmic acid. There may also be crystals

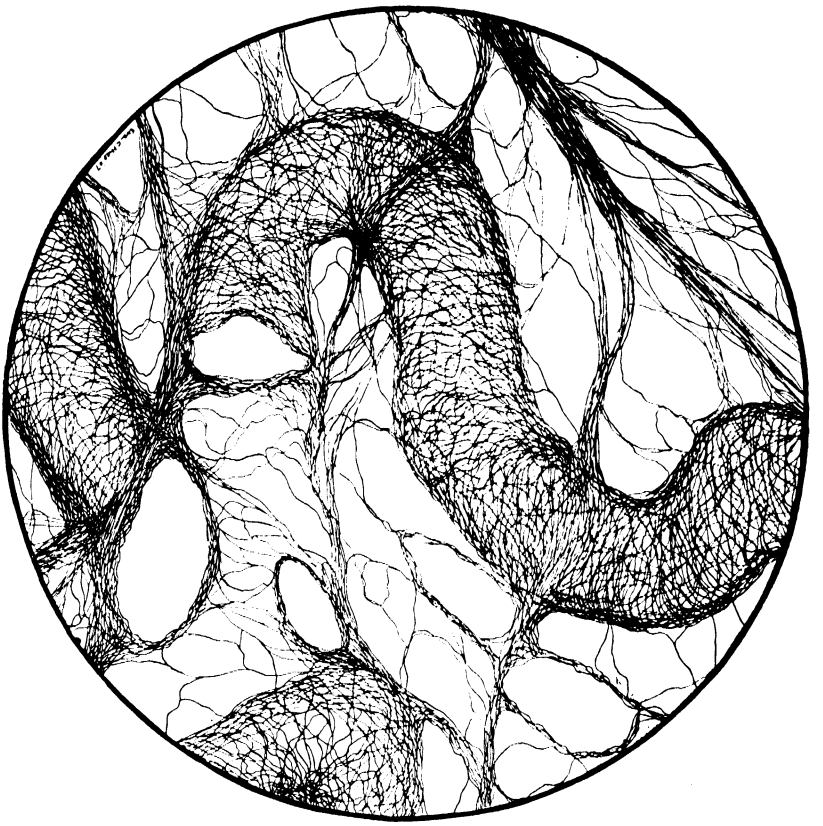


FIG. 910.—ELASTIC FIBRES OF INTERTUBULAR CONNECTIVE TISSUE OF TESTICLE, SEEN ENCIRCLING THE TUBULES. (E. C. Hill.)

(fig. 911) of an indeterminate nature, varying in size and number, but generally of an elongated prismatic shape.

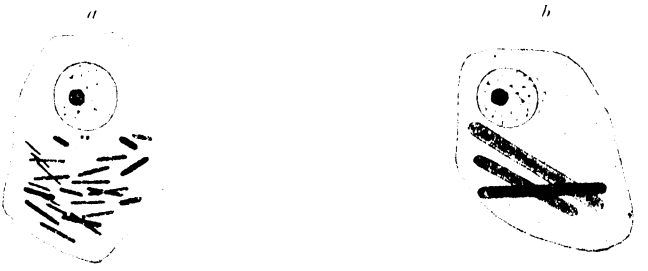


FIG. 911.—TWO INTERSTITIAL CELLS OF THE HUMAN TESTICLE, CONTAINING REINKE'S CRYSTALS. (Eberth.) Magnified 1000 diameters.

In *a* the crystals are smaller and more numerous than in *b*. A double centrosome is seen in *a*.

These crystals were first described by Reinke. The interstitial cells are not the only cells in the testicle where crystalline bodies are met with, for crystals which appear to be similar in character are found in some of the spermatogenic cells of the seminiferous tubules (Lubarsch) and other much smaller bacillus-like crystals occur in the cells of Sertoli (Spangaro). Crystalline

masses are also found in the ejaculated semen after evaporation (Böttcher): these, which contain a base named *spermin*, are probably derived from the secretion of the prostatic glands.

The interstitial cells are found in the fœtus in considerable number, but their amount diminishes relatively during childhood, to become increased again at puberty. In animals which are subject to seasonal changes they are most developed during the periods of sexual activity.

Rudimentary structures found in connexion with the testis and epididymis.—The *appendix of the testicle* (hydatid of Morgagni) is a small pedunculated body which lies over the upper part of the organ (fig. 912, *h*), its peduncle being attached at the angle between the testicle and epididymis. It is convex externally and concave where it rests on the testicle, and is surrounded by an extension of the serous coat of the gland. The surface, which is often smooth but may be deeply corrugated, is covered with ciliated epithelium. The appendix is composed of a vascular connective tissue, which contains some plain muscle. Within it is a closed tube with narrow lumen, lined either by ciliated or by simple columnar epithelium. The lumen of the tube may be dilated; it is found sometimes to open into the serous cavity of the tunica vaginalis testis. The appendix of the testicle is developed from the free or upper extremity of the Müllerian duct.

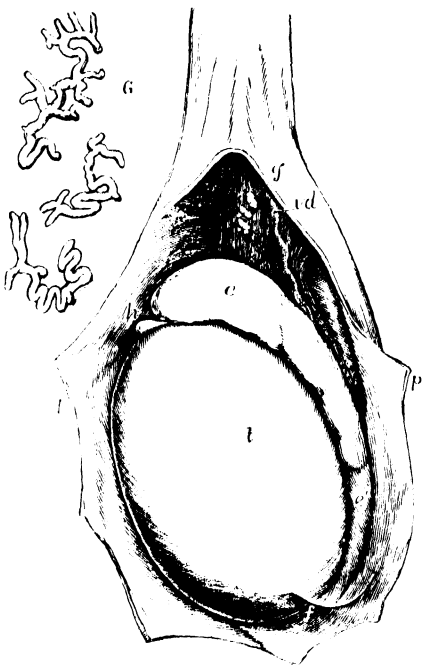


FIG. 912.—THE LEFT TUNICA VAGINALIS OPENED, SHOWING THE TESTIS, EPIDIDYMIS, &c., FROM THE OUTER SIDE. (Allen Thomson.)

p, *p*, cut edges of the parietal layer of the tunica vaginalis drawn aside; *t*, body of the testis; *e*, *e'*, epididymis; *f*, a fold of the tunica vaginalis passing from the body of the testis to the side. In the upper part of the figure the tunica vaginalis has been dissected off at the place of its reflexion on the cord to show *c d*, the vas deferens, and *g*, the organ of Giraldès; G, the three small nodules of this organ enlarged about ten times, and showing the remains of tubular structure within them; *h*, hydatid of Morgagni, or appendix of the testicle.

Another somewhat similar structure, of pyriform shape, the *appendix of the epididymis*, which is also sometimes referred to as a hydatid of Morgagni, is often found attached to the upper or lateral surface of the head of the epididymis by a distinct stalk. It is composed, like the appendix testis, of a vascular connective tissue; it, however, contains an elongated closed cavity of relatively considerable lumen, filled with fluid and lined by columnar or ciliated epithelium. The cavity is sometimes subdivided into smaller parts, and both these and the single cavity may be considerably dilated. The surface is covered by serous endothelium. In the child the cavity or cavities may communicate with that of the tunica vaginalis. The stalk contains bundles of plain muscular tissue.

According to Kobelt this hydatid is developed from the remains of some of the tubules of the Wolffian body, but it seems more probable that it owes its origin, as suggested by Toldt, to a portion of the Müllerian duct.

What appears to be remains of a part of the Wolffian duct is met with in connexion with the rete testis, and consists of a tubule, somewhat like a vas efferens, which may be dilated into one or more small cysts. This is termed the *appendix of the rete*.

Vas aberrans.—This name was applied by Haller to a long narrow tube, or diverticulum (fig. 890, *i*), discovered by him, and almost invariably met with, which leads off from the lower part of the canal of the epididymis, or from the commencement of the vas deferens, and, becoming tortuous and convoluted, is rolled up into an elongated mass which extends upwards for an inch or more amongst the vessels of the spermatic cord; here the tube ends by a closed extremity. Its length, when unravelled, ranges from about 5 to 30 centimetres; its width increases towards its blind extremity. Sometimes this diverticulum is branched; occasionally there are two or more such aberrant ducts. Its structure appears to be similar to that of the vas deferens. Its origin is probably connected with the Wolffian duct of the fœtus. Luschka states that occasionally it does not communicate with the canal of the epididymis.

Roth has described other small blind vasa aberrantia lying along the epididymis and connected with the rete testis.

Organ of Giraldès.—The small body thus named is situated in the front of the cord immediately above the head of the epididymis (see fig. 912, *g*). It consists usually of several small irregular masses containing convoluted tubules lined with columnar ciliated epithelium, and is scarcely to be recognised until the surrounding connective tissue has been rendered transparent by re-agents. It has also received the name of *paradidymis* (Waldeyer). Its tubules appear to be vestiges of part of the Wolffian body.

In connexion with the paradidymis, there are often met with small masses of chromaphil cells resembling those of the medulla of the suprarenal capsules (*paraganglia* of Kohn). Portions of tissue which resemble the cortex of the suprarenal are also present occasionally, if not constantly, in the mediastinum testis between the vessels of the pampiniform plexus of the spermatic cord; and also adjacent to the vas deferens, especially near its commencement in the tail of the epididymis. This tissue is not, however, usually associated with the chromaphil substance.

Changes in the structure of the testicle with age.—These changes have been studied by Spangaro, who finds that, normally, as age progresses—although spermatozoa may still be formed at a very advanced age—certain changes tending towards atrophy manifest themselves. Thus the tubules become smaller in diameter, and their walls relatively thicker, whilst the spermatogonia are relatively less numerous. On the other hand the spermatocytes and spermatids may be relatively more abundant than in the young subject. Abnormally the testicle may undergo marked atrophy with the advance of age, the tubules being much diminished in size and the spermatocytes and spermatids becoming few in number or disappearing altogether, the spermatogonia and the cells of Sertoli being the only elements which are left. Ultimately the atrophy may proceed to loss of all the contents of the tubules, which become completely collapsed and empty, the whole organ being greatly shrunken.

THE PENIS.

The penis is composed principally of erectile tissue, arranged in three long somewhat cylindrical masses, which are enclosed in fibrous sheaths (figs. 913 to 916). Of these masses, two, named *corpora cavernosa penis*, placed side by side, form the principal part of the organ, whilst the other, situated beneath the two preceding,

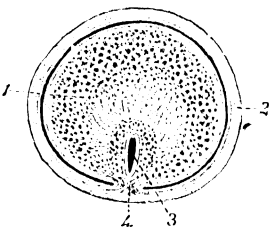


FIG. 913.—TRANSVERSE SECTION OF THE GLANS PENIS IN THE DISTENDED STATE, HALF AN INCH BEHIND THE MEATUS. (Symington.)

1, glans penis; 2, prepuce; 3, urethra; 4, frænum of the prepuce.

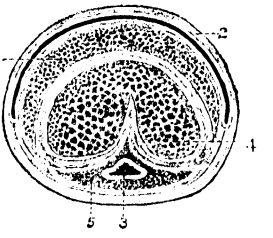


FIG. 914.—TRANSVERSE SECTION OF THE GLANS PENIS IN THE DISTENDED STATE, SEVEN-EIGHTHS OF AN INCH BEHIND THE MEATUS. (Symington.)

1, glans penis; 2, prepuce; 3, urethra; 4, corpus cavernosum; 5, corpus spongiosum.

surrounds the canal of the urethra, and is named *corpus cavernosum urethræ* or *corpus spongiosum*; it is enlarged distally to form the *glans*.

Integument.—The skin which is continued from that of the pubes and scrotum forms a simple investment as far as the neck of the glans. Here it is doubled up in a loose fold, the *prepuce* or *fore-skin*. At the meatus urinarius the skin is continuous with the mucous membrane of the urethra.

Upon the body of the penis the skin is thin, free from fat, and, in the anterior two-thirds of its length, from hairs also; when present the hairs are short and thinly scattered, especially on the dorsal surface. In these respects the skin differs remarkably from that on the pubes, which is thick, covers a large cushion of fat, and, after puberty, is beset with hairs. The skin of the penis is very movable and distensible, and is of a darker colour than the skin generally. It contains both

sebaceous and sweat glands, the latter smaller than ordinary. On the inner side of the prepuce the integument changes its character, and approaches that of a mucous membrane, being red, thin, and moist. In man it contains no glands, although Tyson described in the orang glands round the corona glandis (*glandulæ odoriferæ*), and in some other animals racemose glands yielding a sebaceous secretion occur within the prepuce.

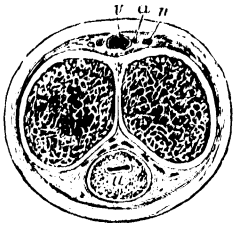


FIG. 915. TRANSVERSE SECTION OF THE BODY OF THE PENIS IN THE DISTENDED STATE. (Altered from Henle.)

The outer outline indicates the integument surrounding the deeper parts; the erectile tissues of the corpora cavernosa and the septum pectiniforme are shown in section; *n*, placed on the section of the spongy body below the urethra; *v*, the single dorsal vein; *a*, the dorsal artery, and *n*, the nerve of one side.

The skin which covers the surface of the glans contains no glands. It is beset under the epithelium with large vascular and nervous papillæ. It adheres intimately and immovably to the spongy tissue of the glans. In some individuals the skin of the glans is roughened by papillary projections, especially at the corona; in others the surface is smooth.

Beneath the skin on the body of the penis is a layer continuous with the dartos scroti. Like that it contains plain muscle-fibres; these diminish in number distally, but occur even as far as the extremity of the prepuce. The fibres have for the most part a circular direction. Under the tunica dartos the ordinary superficial

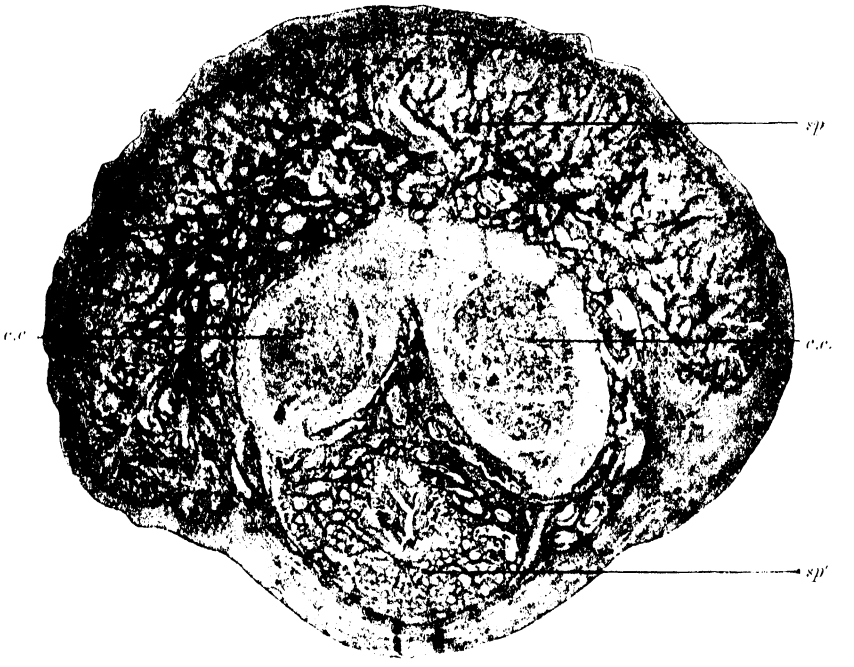


FIG. 916.—TRANSVERSE SECTION OF GLANS PENIS OF CHILD. (Rothfeld.)

c.c., corpora cavernosa; *sp*, corpus spongiosum; *sp'*, corpus spongiosum urethræ, with the lumen of the urethra in the centre appearing as an irregular slit with folded walls.

fascia is very distinct, and richly supplied with elastic tissue; it is continuous with that of the groin and perineum. Near the root of the organ there is a dense

band of fibro-elastic tissue, named the *suspensory ligament,* lying amongst the fibres of the superficial fascia ; it is triangular in form ; its anterior border is free, its upper border is connected with the fore part of the pubic symphysis, and below it runs down upon the dorsum of the penis.

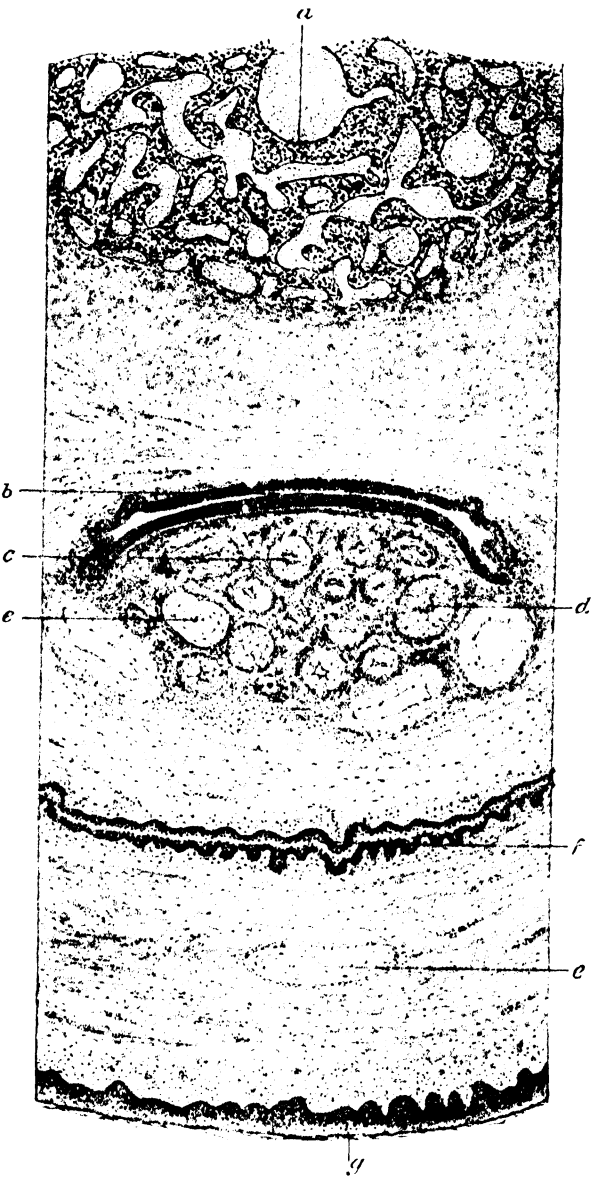


FIG. 917.—FROM A TRANSVERSE SECTION OF THE PENIS OF A MONKEY. (F. H. A. Marshall.)

a, part of corpus spongiosum glandis; *b*, urethra; *c*, corpus spongiosum urethræ; *d*, nerve; *e*, *e*, Pacinian corpuscles; *f*, fold of preputial epithelium.

The **corpora cavernosa** form the principal part of the body of the penis. They are two cylindrical bodies placed side by side, flattened on the median aspect, and closely united and in part blended together along the middle line in the anterior three-fourths of their length ; whilst at the back part, in contact with the symphysis

pubis, they separate from each other in the form of two bulging and then tapering processes named *crura* (fig. 929, cc), which, extending backwards, are attached to the pubic and ischial rami, and are invested by the erectores penis or ischio-cavernosi muscles. The enlarged portions at the root, named by Kobelt the *bulbs of the corpora cavernosa*, attain a much greater proportionate development in some quadrupeds than in man. In front, the corpora cavernosa are closely bound

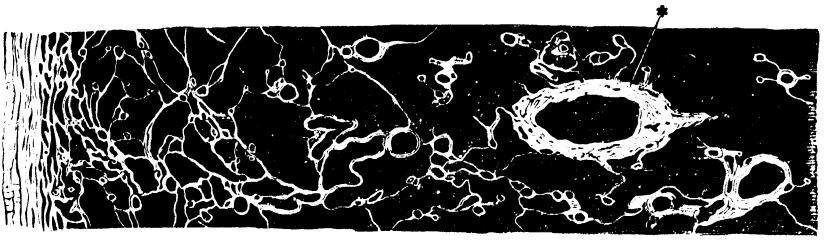


Fig. 918.—Part of a section of one of the corpora cavernosa, injected from the deep artery of the penis. (Henle.)

On the left is seen the fibrous tissue; at *, a section of the arteria profunda penis.

together into a blunt conical extremity, which is covered by the glans penis and firmly connected to its base by fibrous tissue.

The under-surface of the united cavernous bodies is marked by a longitudinal groove, in which is lodged the corpus spongiosum. The upper or anterior surface is also marked with a slight median groove in which the dorsal vein of the penis is situated near the root; this surface is attached to the pubes by the suspensory ligament.

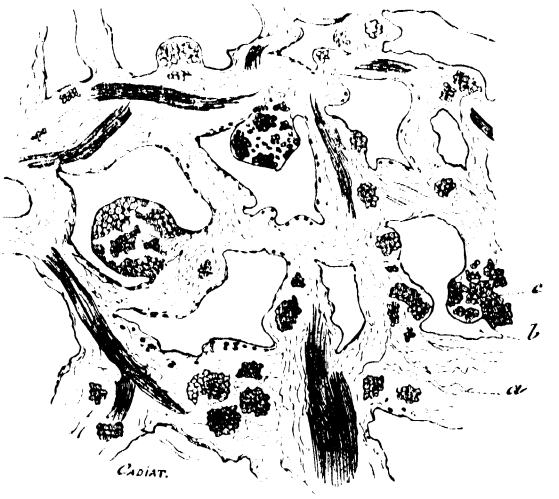


Fig. 919.—Section of erectile tissue of penis in a non-distended condition. (Cadiat.)

a, trabeculæ of connective tissue with many elastic fibres and bundles of plain muscular tissue, some of which are cut across (*c*); *b*, blood-sinuses.

The median septum between the two corpora cavernosa is thick and complete near the root of the penis; but further forward it becomes thinner, and only imperfectly separates their cavities, for it exhibits, particularly towards the anterior extremity, numerous clefts, extending from the dorsal to the urethral edge, and admitting of a free communication between the erectile tissue of the two sides. From the arrangement of these slits, the intermediate white portions of the

septum resemble somewhat the teeth of a comb; hence the partition has received the name of *septum pectiniforme*.

The external fibrous investment of the cavernous structure (tunica albuginea) is white and dense, from one to two millimetres thick, and very strong and elastic. It is composed for the most part of longitudinal bundles of shining white fibres, with a moderate number of elastic fibres, enclosing the two corpora cavernosa in a common covering; internal to this, each corpus cavernosum is surrounded by a layer of circular fibres, which enter into the formation of the septum.

From the inside of the fibrous envelope, and from the sides of the septum, numerous lamellæ pass into the interior of the corpus cavernosum, and there join the bands and cords composed of fibrous elastic and plain muscular tissue, named *trabeculæ*, which run through and across the cavity in all directions, thus subdividing it into a multitude of intercommunicating spaces, and giving the entire structure a spongy character (fig. 918).

The trabeculæ, whether lamelliform or cord-like, are larger and stronger near the circumference than along the centre of each cavernous body; they also become gradually thicker towards the crura. The interspaces, conversely, are larger in the middle than near the surface; their long diameter is, in the latter situation, placed transversely to that of the penis; they become larger towards the fore part of the penis. At many places there are projections from the trabeculæ into the spaces; these are mainly formed of muscular tissue (fig. 919). The spaces are occupied by venous blood, being in reality large cavernous veins, and are lined by a layer of endothelium similar to that lining other veins.

FIG. 920.—PORTION OF THE ERECTILE TISSUE OF THE CORPUS CAVERNOSUM MAGNIFIED, SHOWING THE AREOLATED STRUCTURE AND THE DISTRIBUTION OF AN ARTERIOLE. (J. Müller.)

a, a small artery supported by the larger trabeculæ, and branching out on all sides; *c*, the tendril-like arterial tufts or helicine arteries of Müller; *d*, the areolated structure formed by the finer trabeculæ.

FIG. 921.—HELICINE ARTERIES WITH THEIR SHEATHS, AS SEEN WITH A LOW POWER. (Henle.)

A and B, from the corpus cavernosum penis; D, from the corpus spongiosum urethræ; C, transverse section of one of the helicine arteries; in this and the other figures the smaller lateral prolongations of the arterial vessels into the sheath are shown: * *, fasciculi of connective tissue passing off from the summit of two of the sheaths.

The intertrabecular spaces thus form a labyrinth of intercommunicating venous areolæ divided by the trabecular tissue, and opening freely from one corpus cavernosum to the other through the septum, especially in front. The blood is

carried away from these spaces by two sets of veins, the one set joining the prostatic plexus and pudendal veins; the others passing into the dorsal vein. Of these last some issue from between the corpus cavernosum and the spongy body of the urethra, encircling the penis nearly at right angles, while others pass more directly into the dorsal vein from the upper surface.

The principal arteries of the corpora cavernosa are the cavernous branches of the pudic arteries (profundæ penis) of the right and left sides, which run through the middle of each corpus cavernosum; but the dorsal artery of the penis also sends small twigs through the fibrous sheath of the corpora cavernosa, along the upper surface, especially in the fore part of the penis. Within the cavernous tissue, the numerous arteries (*arteries of the trabeculæ*) are supported by the trabeculæ in the middle of which they run, and terminate in branches of capillary minuteness which open into the intertrabecular spaces; some of the arterial twigs project into the spaces, and there form peculiar curling and somewhat dilated vessels, which

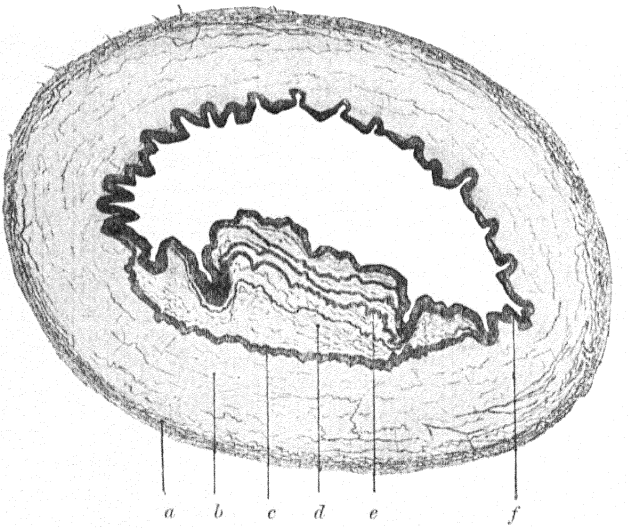


FIG. 922.—SECTION OF AN ARTERY OF THE BULBUS URETHRÆ OF AN ADULT. (Eberth.) Magnified 300 diameters. The elastic tissue is stained by Weigert's method.

a, adventitia; *b*, muscularis; *c*, elastica externa; *d*, pad of intima with, *e*, elastic lamellæ; *f*, elastica interna.

were named by J. Müller, *helicine arteries*. These are usually bound down by small fibrous bands (figs. 920, 921).

The helicine arteries are most abundant in the posterior part of the corpora cavernosa, and are found in the corresponding part of the corpus spongiosum urethræ; but they have not been seen in the glans penis. They are more distinct in the human subject than in animals, where they are often missed. Small capillary branches pass from them to supply the tissue of the enclosing sheath; at their extremities the helicine arteries open into the cavernous spaces.

In addition, blood passes into the venous spaces from the capillary network of the tunica albuginea and trabeculæ; some of the small arteries of the trabeculæ open directly into the venous spaces at the periphery of the corpora cavernosa (and also in the bulb of the corpus spongiosum) without the intervention of capillaries.

The arteries of the corpora cavernosa have a very well marked muscular coat composed entirely of circular fibres; here and there some of the muscle-fibres of the trabeculæ run longitudinally in contact with them, but there is no longitudinal muscular coat. In many of the arteries, both large and small, the intima shows

localised thickenings; at the place of thickening the elastic layer may be split up into several strata (fig. 922). At certain places, especially where branches are given off, these thickenings are so marked as to be able, when the muscular coat contracts, to close the lumen and thus act as valves.

In the veins leading from the cavernous tissue the circular muscular fibres are relatively little developed, but the intima contains a large number of longitudinal muscular fibres, which form pad-like prominences projecting into the lumen (fig. 923).[1]

The **corpus spongiosum** commences below the triangular ligament of the perineum, where it is placed between the diverging crura of the corpora cavernosa, and somewhat behind their point of junction. The enlarged and rounded posterior extremity is named the *bulb*, and projects backwards somewhat

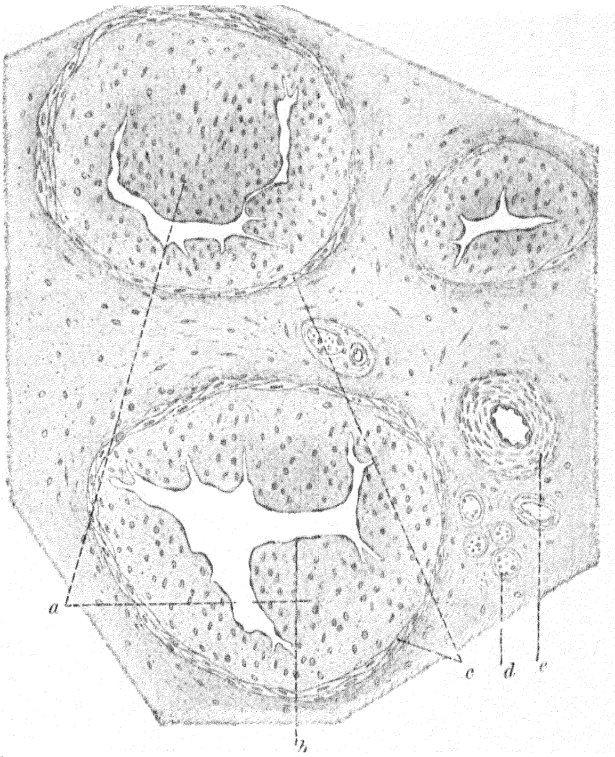


FIG. 923.—TRANSVERSE SECTION OF BRANCHES OF THE VENA PROFUNDA PENIS OF AN ADULT. (Eberth.) Magnified 100 diameters.
a, pads of intima; *b*, endothelium; *c*, circular muscle-fibres; *d*, nerves; *e*, small artery.

beyond the urethra (fig. 929, B). It extends forwards as a cylindrical or slightly tapering body, lodged in the groove on the under side of the united cavernous bodies, as far as their blunt conical anterior extremity, over which it expands so as to form the glans penis. In the whole of this extent it encloses the urethra.

The posterior bulbous part (*bulb of the urethra*), varies in size in different subjects. It receives an investment from the triangular ligament on which it rests, and is embraced by the ejaculator urinæ, or bulbo-cavernosus muscle. The posterior extremity of the bulb exhibits, more or less distinctly, a subdivision into two lateral portions or lobes, separated by a slight furrow on the lower surface, and by a slender fibrous partition within, which extends for a short distance forwards; in early infancy this is more marked. It is above this part that the urethra, having pierced

[1] According to Golowinski these pad-like projections occur also in the arteries and veins of the corresponding organs of the female (Anat. Hefte, xxx. 1906).

the triangular ligament, enters the bulb, surrounded obliquely by a portion of the spongy tissue, named by Kobelt the *colliculus bulbi*; from this a layer of venous erectile tissue passes back upon the membranous and prostatic portions of the urethra to the neck of the bladder, lying closely beneath the mucous membrane. At first the urethra is nearer the upper than the lower part of the corpus spongiosum, but it soon gains and continues to occupy the middle of that body.

According to the observations of Retterer, who investigated the development of the organ, the glans penis is formed only by true corpus spongiosum as to the part immediately encircling the urethra, the greater portion being developed from integumental tissue, which has become very vascular and cavernous, and which has united with the anterior ends both of the corpora cavernosa and of the corpus spongiosum; the vascular connexion with the latter is however by far the most complete (Journ. de l'anat., 1892).

The structure of the corpus spongiosum is essentially the same as that of the corpora cavernosa, but with a much less developed fibrous framework. Like the corpora cavernosa, it is distended with blood during erection, but it does not acquire the same rigidity. The fibrous tunic (fig. 924, 1) is much thinner, is less white in colour, and contains more elastic tissue; the trabeculæ are finer and more equal in size; the areolæ are smaller, more uniform, and directed for the most part with their long diameter in the line of that of the penis; in the glans, the meshes are smallest and most uniform. As they approach the urethra the lacunæ acquire more the character and structure of a network of veins. There is more muscular tissue in the trabeculæ of the corpus spongiosum of the urethra than in that of the corpora cavernosa, but less in the corpus spongiosum of the glans. Plain muscular fibres immediately surround the canal of the urethra, and also form part of the external coat of the spongy substance.

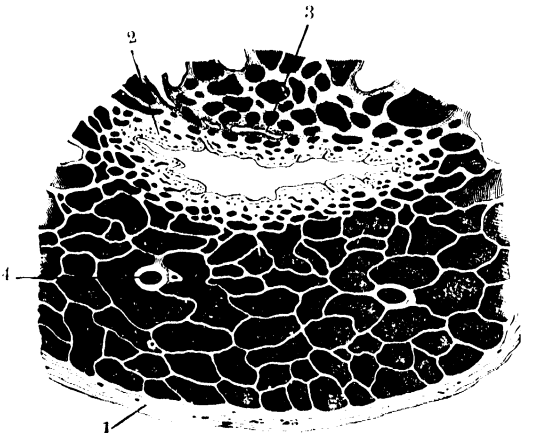


Fig. 924. Section of the corpus spongiosum injected from its artery. (Henle.)

1, fibrous tunic of the corpus spongiosum; 2, mucous membrane of the urethra; 3, section of a lacuna of the mucous membrane; 4, section of an artery.

A considerable artery derived from the internal pudic enters the bulb on each side, and supplies the greater part of the spongy body, sending branches as far as the glans penis, but this part is chiefly supplied by branches from the arteria dorsalis. Besides these, another but much smaller branch of the pudic artery enters the bulb on the upper surface, about an inch from its posterior extremity, and runs forwards in the corpus spongiosum to the glans (Kobelt). The arteries open into the venous spaces chiefly if not entirely by the intervention of capillaries. Veins issue from the glans and adjoining part of the spongy body, to end in the vena dorsalis penis; those of the rest of the spongy body for the most part pass backwards through the bulb, and end in the prostatic and pudic venous plexuses; some emerge from beneath the corpora cavernosa, anastomose with the veins of those bodies, and end partly in the cutaneous veins of the penis and scrotum, and partly in the pudic and obturator veins.

The **lymphatics** of the penis form a dense network on the skin of the glans

and prepuce, and also underneath the mucous lining of the urethra. They pass chiefly into the inguinal glands. Deeper, subfascial lymphatics are also described as arising in the skin of the glans penis and from two well-marked plexuses in the lateral fossa of the frenulum; they pass backwards on the dorsum of the organ with the subfascial vein to enter the inguinal glands.

The **nerves** of the penis are derived from the dorsal and superficial perineal branches of the pudic nerve and from the hypogastric plexus of the sympathetic. The former are distributed to the skin and mucous membrane, the latter entirely to the cavernous and spongy bodies. Some of the fibres end in the epidermis, others in the epithelium and mucous membrane of the urethra. Simple and compound end-bulbs (genital corpuscles) and Pacinian bodies are also found. Many of the nerve-fibres pass to the muscular tissue of the blood-vessels and trabeculæ.

URETHRA OF THE MALE.

The male urethra extends from the neck of the bladder to the extremity of the penis. Its total length when moderately stretched is 18 to 20 cm. In sections across the penis the walls of the canal are in close apposition, the outline of the urethral cleft being vertical or ⊥-shaped in the glans (figs. 913, 914), transverse in the body of the penis (fig. 915), stellate in the membranous part, and crescentic about the middle of the prostatic part (fig. 925). Its diameter when moderately distended differs at different parts. The wall of the tube consists of a mucous membrane, supported by an outer layer of submucous tissue connecting it with the several parts through which it passes. In the submucous tissue plain muscle occurs throughout the whole extent of the urethra (Zuckerkandl), the inner fibres disposed longitudinally, the outer in a circular direction. But the muscular coat completely encircles the tube only as far as the openings of the glands of Cowper, and is mainly longitudinal. In front of that situation the muscular fibres are confined to the upper and lateral walls. Herzog failed to find muscular fibres in the part within the glans.

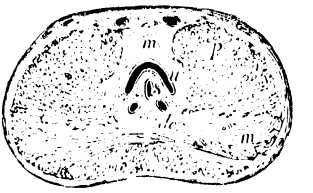


FIG. 925.—TRANSVERSE SECTION OF THE URETHRA THROUGH THE PROSTATE GLAND. (Allen Thomson.)

u, the urethra into which the eminence of the caput gallinaginis rises from below; *s*, the utricle cut through; *d c*, the ejaculatory ducts; *m*, superiorly, the deep sphincter muscular fibres; *m*, lower down, intersecting muscular bands in the lateral lobes of the prostate; *p*, glandular substance of prostate.

The lining membrane of the *prostatic portion of the urethra* is thrown into longitudinal folds, when not distended by fluid. Towards the neck of the bladder a slight elevation on the posterior surface passes back into the uvula vesicæ. Somewhat in advance of this, and continued from it along the floor (posterior wall) of the passage, projects a narrow median ridge which gradually rises into a peak, and sinks down again at its anterior or lower end; it is formed by an elevation of the mucous membrane and subjacent tissue. This is the *crista urethræ* or *colliculus seminalis*. On each side of this ridge the surface is slightly depressed, so as to form a longitudinal groove, named the *prostatic sinus*, the floor of which is pierced by numerous foramina, the orifices of the prostatic ducts. Through these a viscid fluid oozes out on pressure. The ducts of the middle lobe open some above the urethral crest, and some below it. The mucous membrane of the prostatic urethra is covered by an epithelium like that of the bladder.

At the fore part of the most elevated portion of the crest, and exactly in the middle line, is the orifice of a blind recess, upon or within the lateral margins of which are placed the slit-like openings of the common seminal or ejaculatory ducts,

one at each side. This median opening leads into the *prostatic utricle* (prostatic vesicle, uterus masculinus).

The utricle is a cul-de-sac running upwards and backwards, for a distance of from 6 to 12 mm. Its orifice forms a longitudinal cleft about 2 or 3 mm. in length, but the utricle increases somewhat in diameter towards its farther end or fundus. The narrow portion runs in the urethral crest; its fundus lies behind and beneath the middle lobe, and in some cases reaches to the posterior surface of the prostate gland. Its parietes, which are distinct and of some thickness, are composed of fibrous tissue and mucous membrane, together with a few muscular fibres. They enclose on each side the ejaculatory duct. Numerous small ramified and convoluted glands open on the inner surface of the utricle. The epithelium is columnar and by some authors is stated to be ciliated. Small glands open into its cavity near the entrance into the urethra. The colliculus contains well-marked erectile and plain muscular tissue. It has been supposed that this eminence, when distended with blood, may offer an obstacle to the passage of the semen backwards into the bladder.[1]

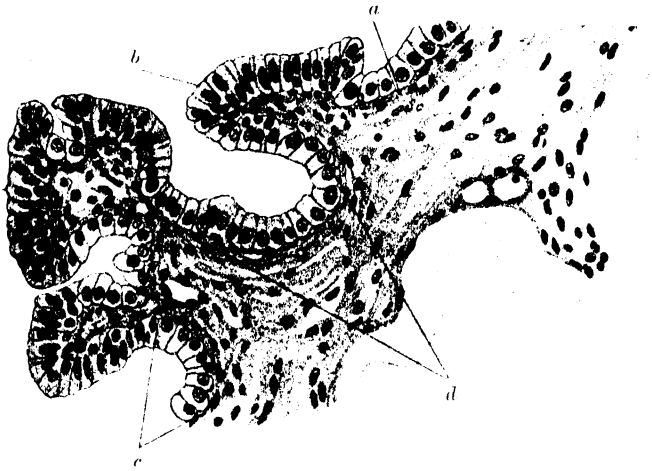


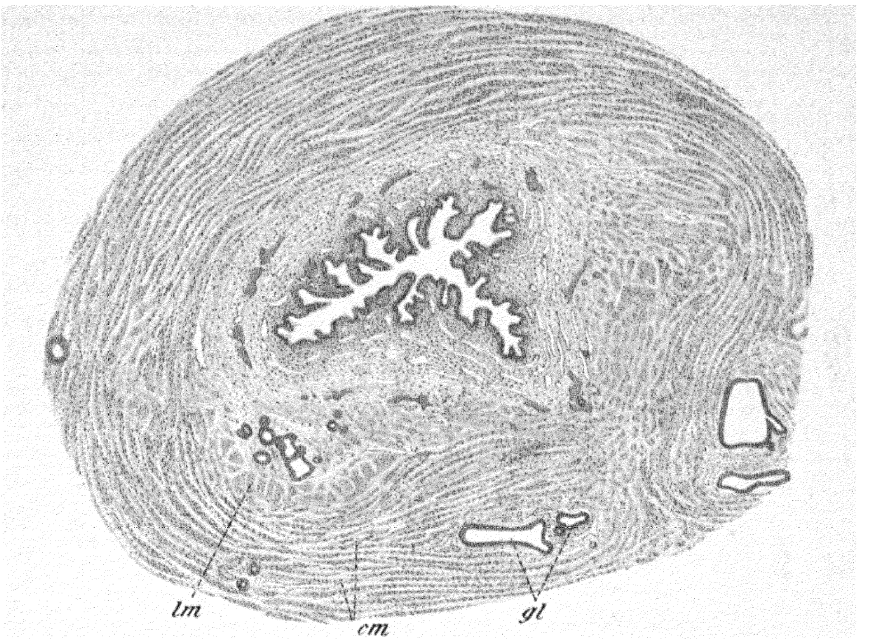
FIG. 926.—SECTION OF THE MUCOUS MEMBRANE OF THE URETHRA, PROXIMAL TO THE ORIFICES OF COWPER'S GLANDS. (Lichtenberg.) Magnified 200 diameters.

d, corium of mucous membrane, with numerous blood-vessels; *b*, epithelium; *c*, *d*, crypt-like invaginations of the epithelium. The cells of these crypts are shorter than those of the general surface; they secrete mucin.

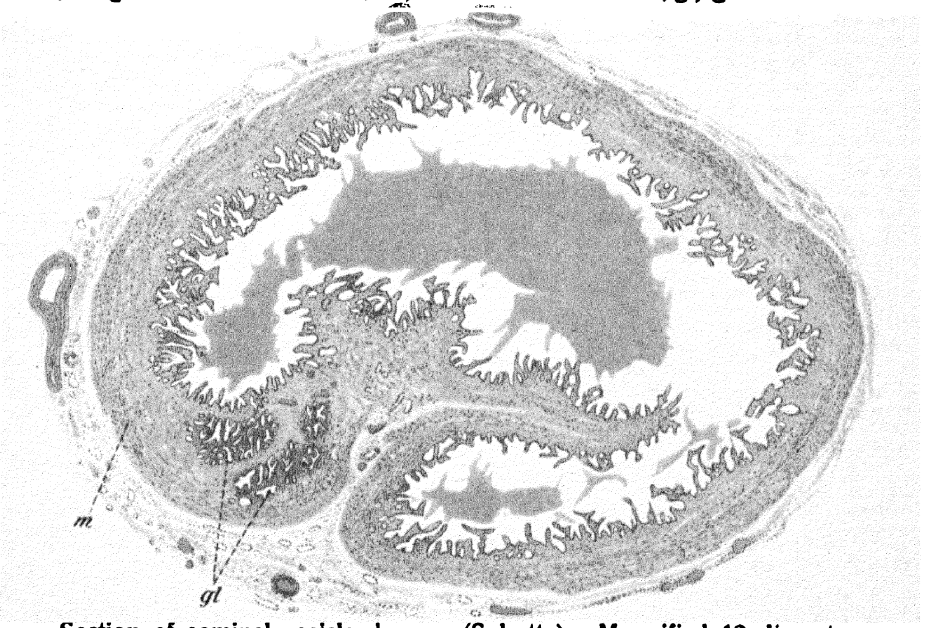
The *membranous portion of the urethra* comprises the part between the apex of the prostate and the bulb of the corpus spongiosum. It is 18 mm. long; but about two-thirds of its posterior surface is covered by the bulb of the corpus cavernosum, which projects backwards over it. This membranous portion is the narrowest part of the urethra. It lies between the two layers of the triangular ligament, and both these fibrous membranes are prolonged upon it, the one backwards and the other forwards. Between these layers the urethra is surrounded by erectile tissue, by some veins, and also by plain muscular tissue, and by the fibres of the compressor urethræ muscle. On each side are Cowper's glands. The plain muscular fibres of this portion of the urethra are continued over the outer and inner surfaces of the prostate into the muscular fibres of the bladder posteriorly, and into those of the spongy portion of the urethra anteriorly (Hancock).

The *spongy portion of the urethra*, by far the longest and most variable in length and direction, includes the remainder of the canal, the part surrounded by the erectile tissue of the corpus spongiosum. Its length is about 15 cm.

[1] But cf. G. Walker, Arch. f. Anat. 1899.



Section across membranous part of male urethra (Sobotta). Magnified 18 diameters.
lm, longitudinal muscle fibres; *cm*, circular muscle fibres; *gl*, glands of Littré.



Section of seminal vesicle, human (Sobotta). Magnified 12 diameters.
m, muscular coat; *gl*, gland-like invaginations of mucous membrane.

The **mucous membrane** of the urethra is lined by epithelium, of which the superficial cells are long and columnar (figs. 926, 927), except for a short distance (5 to 8 mm.) from the orifice, where the epithelium is squamous and stratified, and where the subjacent membrane is beset with papillæ. A stratified squamous epithelium has also been described in places in the membranous and prostatic portions; indeed there appear to be considerable individual differences in the character of the epithelium of these parts.[1] The epithelium rests on a basement-membrane. Outside the mucous membrane, which is rich in elastic fibres, there is a layer of convoluted vascular structure, composed of anastomosing veins which communicate with the adjacent cavernous tissue of the corpus spongiosum. Between the ordinary columnar epithelium-cells may in parts be seen mucus-secreting (goblet) cells, either singly or in groups; they are most numerous in the depressions of the mucous membrane (simple glands of Littré, fig. 926). Within the submucous tissue is the layer of plain muscular fibres, already mentioned, incompletely separating it from the proper substance of the spongy body.

The whole lining membrane of the urethra, except near the orifice, is beset with

FIG. 927. PART OF A SECTION OF THE URETHRA DISTAL TO THE ORIFICES OF COWPER'S GLANDS. (Lichtenberg.) Magnified 155 diameters.

a, *b*, orifices of crypts; *c*, blind end of a crypt; the nuclei of its cells shown.

the orifices of small glands, commonly named the *glands of Littré*, the ducts of which pass obliquely forwards through the membrane. They vary much in size and in the extent to which their cavities are ramified and sacculated, some being quite simple. These are confined to the mucous membrane, while the larger and more complex glands extend into the submucosa. Their ducts are lined by the same kind of columnar epithelium as lines the urethral tube itself, but the fundus of each gland and all its lateral recesses have clear columnar mucus-secreting cells (fig. 928). Besides these glands there are large recesses or *lacunæ*, opening by oblique orifices turned forwards, or down the canal. These are most abundant along the floor of the urethra, especially in its bulbous part. Some of the recesses are of considerable length and run back parallel with the urethra. One large and conspicuous recess, opening on the upper surface near the orifice of the urethra, is named the *lacuna magna*. A median fold of the membrane rising from the inferior surface of this part of the urethra has been named the *valve of the fossa navicularis*. Stratified concrements like those met with in the prostate (see below) are found in old subjects in the glandular recesses of the urethra (Robin and Cadiat).

[1] See Herzog, Arch. f. mikr. Anat. lxiii. 1904.

Cowper's glands.—In the bulbous portion of the urethra, near its anterior end, are the paired openings of the ducts of *Cowper's* or the *bulbo-urethral glands*. These (fig. 929, C.G.) are situated above the bulb, behind the membranous portion of the urethra and between the two layers of the triangular ligament, the inferior layer supporting them against the urethra. The arteries of the bulb pass above, and the transverse fibres of the compressor urethræ beneath these glands. They form two

FIG. 928.—SECTION THROUGH THE OPENING OF THE DUCT OF A GLAND OF LITTRÉ OF THE MALE URETHRA. (Lichtenberg.) Magnified 200 diameters.

g, gland; *m*, its mouth; *u*, epithelium of urethra. The gland is similar in structure to Cowper's glands, but simpler in conformation. Its cells are mucus-secreting.

small firm rounded masses, about the size of peas. They are compound racemose glands, composed of several small lobules held together by a firm investment. This latter, as well as the walls of the ducts, contains muscular tissue. The epithelium of the acini consists of clear columnar cells, with a basal nucleus and reticular cytoplasm, staining like the cells of mucous glands. Secretion-capillaries penetrate between the cells. 'Crescents' and 'serous' cells appear to be absent. After secretion the gland-cells are found to be smaller and more cubical and to have

lost their clear appearance. The ducts are lined with cubical epithelium. The ducts unite outside each gland to form a single excretory duct. These ducts run forward near each other for about 3 or 4 cm., first in the spongy substance and then beneath the mucous membrane, and terminate in the floor of the bulbous

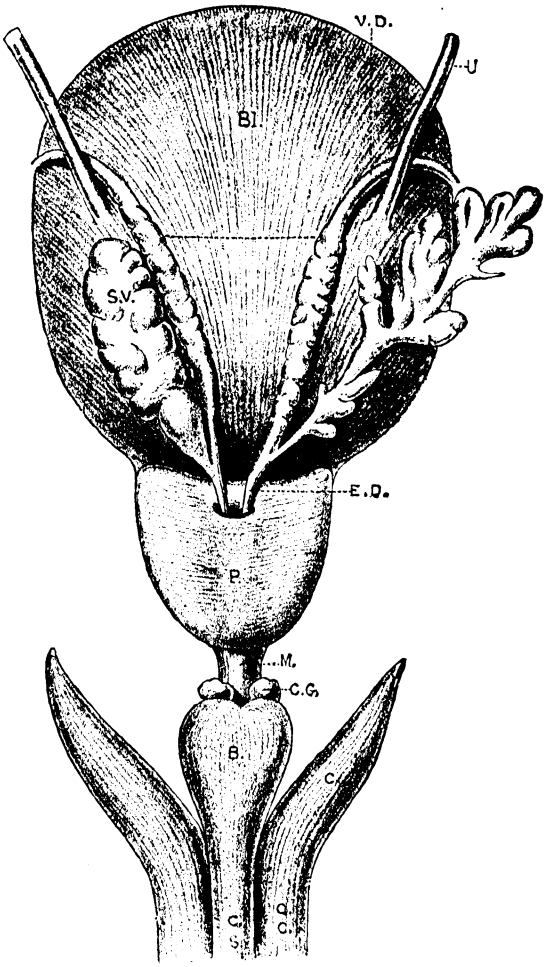


FIG. 929.—BASE OF THE MALE BLADDER, PROSTATE, &c. (Symington.)

Bl, part of base covered by peritoneum, separated by a dotted line from a triangular space left uncovered by that membrane; U, ureter; S. V., seminal vesicle; E. D., ejaculatory duct; P, prostate; M., membranous part of urethra; B, bulb; C.S., corpus spongiosum; C.G., Cowper's gland.

part of the urethra by two minute orifices opening obliquely. The glands secrete a viscid fluid, the use of which is not known. They appear to diminish in size in old age. Sometimes there is only one present, and it is said that both may be absent. According to Braus, the acini of these glands may sometimes anastomose to form a network.

PROSTATE GLAND.

The prostate gland (figs. 925, 929) is one of the accessory male organs of generation. It atrophies in the adult after the testicles are excised, and when these organs are removed in infancy it remains undeveloped. In animals it enlarges, with the testicles, during the breeding season.

It is a firm, glandular, and muscular body, comparable in size and shape to a chestnut, traversed by the first part of the urethra and by the common ejaculatory ducts. It also encloses the prostatic utricle.

Structure.—The gland is covered by a dense fibrous coat, which is continuous with the recto-vesical fascia, and with the superior layer of the triangular ligament. This fibrous capsule, which includes much plain muscular tissue, is divisible into two layers, between which the prostatic plexus of veins is enclosed (Adams). From the capsule trabeculæ extend through the gland towards the colliculus seminalis. The glandular substance is associated with a large quantity of plain muscular tissue, which forms the principal part of the stroma of the organ (fig. 930). This muscular tissue forms an external layer below the fibrous capsule, and extends everywhere through the glandular substance: there is also a strong layer of circular fibres

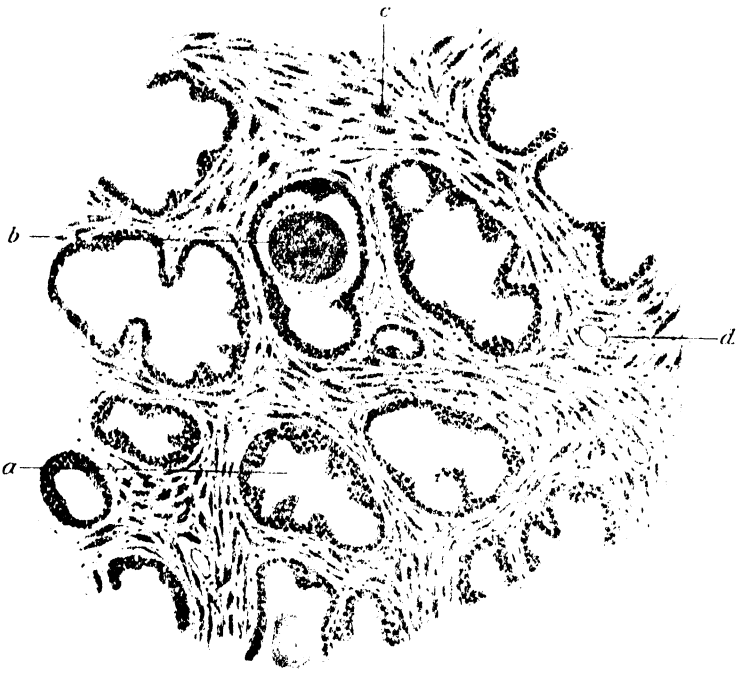


Fig. 930.—Section of prostate of monkey. (F. H. A. Marshall.)

a, alveolus; *b*, concretion within an alveolus; *c*, muscular fibres in stroma; *d*, a blood-vessel.

continuous posteriorly with those of the bladder, and in front with the thin layer surrounding the membranous part of the urethra. The part of the prostate above or in front of the urethra is almost entirely muscular; in the hinder part the muscular substance is in greatest quantity near the bladder. Small nodules of lymphoid tissue are found in certain parts of the gland.

The glandular substance is spongy and yielding; its colour is reddish-grey, or sometimes brownish. It consists of numerous tubular alveoli, which unite into a smaller number of excretory ducts (15 to 30). The tubular alveoli are beset everywhere with irregular evaginations, many of which are branched; their branches may anastomose with one another to form networks. The epithelium is short-columnar or cubical throughout; there is a second layer of small cells next to the basement-membrane. In the fœtus and child the epithelium forms several layers and may nearly fill the tubules. In the adult there are frequent papillary elevations of the gland-wall, covered by thickened epithelium (fig. 930). There is a thin

connective-tissue wall, with fine elastic fibres, appearing like a basement-membrane. In the upper part of the gland the acini are smaller and more saccular; in the middle and lower parts the tubes are longer and convoluted at their ends. The capillary blood-vessels form a close network over the ducts and acini, as in most other glands. The different portions of the gland are united by areolar tissue, and supported by processes of the deep layer of the fibrous capsule and by the muscular stroma. The ducts open upon the floor of the urethra, chiefly in the hollow on each side of the colliculus seminalis. The acini are often found distended so as to form cyst-like enlargements. They frequently contain concrements of laminated appearance resembling starch-grains, and known as 'amyloid' bodies (fig. 930, *b*); these are formed of a colloid substance giving protein reactions.

Blood-vessels, lymphatics, and nerves.—The *arteries* are derived from the vesical, hæmorrhoidal, and pudic. The *veins* form a plexus imbedded in the fibrous covering round the sides and front of the gland; this plexus is highly developed in old subjects. The veins communicate in front with the dorsal vein of the penis, and behind with branches of the internal iliac vein. *Lymphatics* are numerous. They commence in the glandular part and, accompanying the veins, pass to a plexus at the periphery of the organ, between the two layers of the fibrous capsule. They go to lymph-glands in the pelvis. The *nerves*, which are derived from the hypogastric plexus, consist of both medullated and non-medullated fibres, and are interspersed with ganglion-cells. They end in the muscular tissue of the gland and of its blood-vessels; some have been traced to the gland-epithelium. End-bulbs and Pacinian bodies have also been observed on the superficial nerves.

Examined after death, the prostatic fluid has a milky aspect, due to the admixture of a large number of epithelial cells; probably, during life, it is more transparent. It is not a mucous secretion, but according to Adams the fluid has an acid reaction, and exhibits under the microscope numerous granules, epithelial cells and nuclei. Some of the granules are composed of lecithin (Fürbringer, Jena Sitzungsb., 1881).

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FEMALE GENERATIVE ORGANS.

The generative organs in the female (fig. 931) consist of the *ovaries*, the *oviducts* or *Fallopian tubes*, the *uterus*, the *vagina* with the *glands of Bartholin*, and the external organs of generation, including the *labia majora* and *minora* and the *clitoris*. In addition there are certain rudimentary structures near the ovary, known respectively as the *parovarium* or *epoophoron* and the *paroophoron*.

Along with the external organs of generation the structure of the urethra may be described, although it does not, as in the male sex, furnish a path for the sexual secretions.

THE OVARIES.

The ovaries are two small, somewhat flattened, solid-looking ovoid bodies lying one on each side of the pelvis, and projecting into the peritoneal cavity at the posterior part of the broad ligament, which is itself formed of a fold of peritoneum. During active sexual life a number of clear vesicles are seen near the surface of the ovary, sometimes projecting slightly beyond the surface (fig. 932). These are the ripe or ripening *Graafian follicles*, each of which contains an ovum surrounded by epithelium, the follicle itself being lined by similar epithelium. On cutting into the ovary (figs. 933, 934) other smaller immature follicles may be seen within its substance, many being microscopic. Frequently one or more solid-looking yellowish masses of varying size are seen in the ovary: these are the *corpora lutea* (figs. 933, 2; 934, 10; 935); they have been developed from Graafian follicles from which the ovum has been discharged. If such an ovum becomes impregnated and undergoes development the corpus luteum becomes greatly hypertrophied and may then occupy a considerable part of the ovary: in some animals there may be several such enlarged corpora lutea within each ovary. Ultimately the corpora lutea

undergo atrophy, and each is replaced by a shrunken whitish body to which the name *corpus albicans* has been applied (fig. 933, *3*).

In the unimpregnated female the corpus luteum begins to retrograde within ten or twelve days after rupture of the follicle, and, becoming shrunken to form a corpus albicans, ultimately disappears.

Whilst the testicles resemble secreting glands in general structure, although

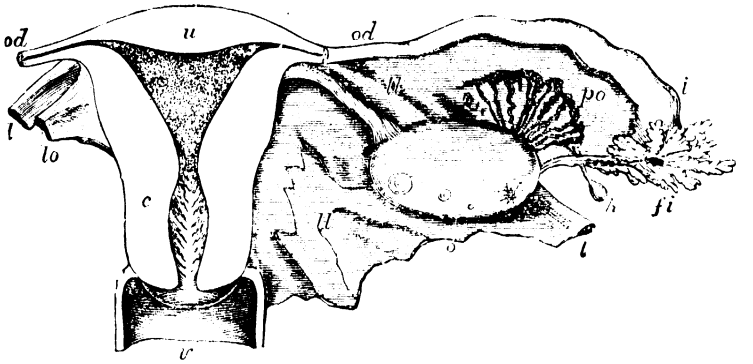


FIG. 931.—DIAGRAM OF THE OVARY AND UTERUS AND THEIR APPENDAGES, AS SEEN FROM BEHIND. (Allen Thomson.) Two-thirds natural size.

The uterus and upper part of the vagina have been laid open by removing the posterior wall; on the left side the Fallopian tube, round ligament, and ovarian ligament have been cut short, and the broad ligament removed; *u*, the fundus of the uterus; *c*, the cervix opposite the os internum; the triangular shape of the uterine cavity is shown, and the dilatation of the cervical cavity with the rugæ termed arbor vitæ: *v*, upper part of the vagina; *od*, Fallopian tube or oviduct; *l*, round ligament; *lo*, ligament of the ovary; *o*, ovary (here represented with its long axis horizontal, although in the natural position within the body it is oblique or nearly vertical); *i*, wide outer part of the right Fallopian tube; *f i*, its fimbriated extremity; *po*, parovarium; *h*, one of the hydatids frequently found connected with the broad ligament.

not in the character of their products, the ovaries bear little or no resemblance to those organs. Each ovary is formed of a solid mass of fibrous-looking tissue (*stroma*), which contains between its fibres very many elongated cells, like those of embryonic fibrous tissue. The stroma is rather more condensed near the surface (*tunica*

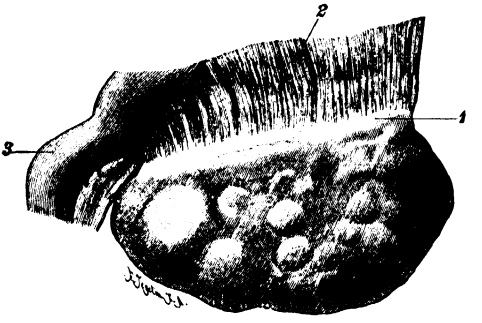


FIG. 932.—HUMAN OVARY. (W. Nagel.)

1, Line of separation between peritoneum and tunica albuginea of ovary; 2, mesovarium; 3, Fallopian tube with ovarian fimbria.

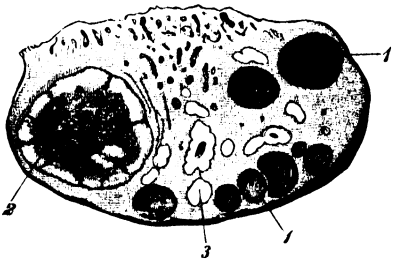


FIG. 933.—SECTION OF A HUMAN OVARY. (W. Nagel.)

1, 1, Graafian follicles; 2, corpus luteum; 3, corpus albicans.

albuginea). The ovary projects into the peritoneal cavity but is not actually covered by serous membrane; the peritoneum ceasing abruptly at the attachment of the ovary to the broad ligament (fig. 932, 1, and fig. 938, *z*). Along the line of attachment (*hilum*) blood-vessels and nerves enter and leave the ovary, and accompanying these is a strand of fibrous tissue which contains plain muscle amongst its fibres. There are also sometimes to be seen in this situation a number of *interstitial cells*

recalling the interstitial cells of the testis. Similar cells may occur scattered in groups about the stroma ; they are numerous in some animals.

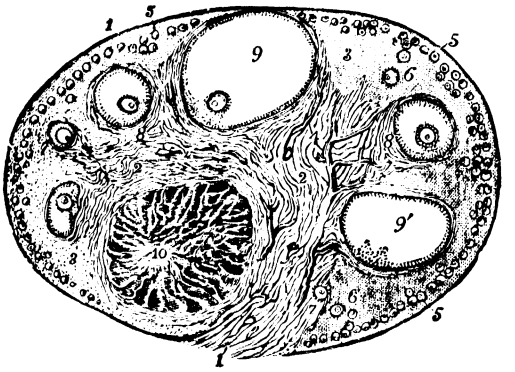


FIG. 934.—SECTION OF THE OVARY OF THE CAT. (Schrön.) Magnified 6 diameters.

1, outer covering and free border of the ovary; 1', attached border; 2, the central ovarian stroma, presenting a fibrous and vascular structure; 3, peripheral stroma; 4, blood-vessels; 5, Graafian follicles in their earliest stages lying near the surface; 6, 7, 8, more advanced follicles which are imbedded more deeply in the stroma; 9, an almost mature follicle containing the ovum in its deepest part; 9', a follicle from which the ovum has accidentally escaped; 10, corpus luteum.

Covering the whole free surface of the ovary, which is smooth in the young subject but may be uneven or pitted in later life, is a layer of short clear columnar or pyriform epithelium-cells (*germinal epithelium*) (fig. 936). There are small cells; but rather larger spheroidal cells (*primitive ova*) occasionally occur between them. Here and there, especially in children and young animals, this epithelium is thickened, and dips for a short distance into the fibrous substance or stroma of the ovary (fig. 937). In fœtal animals these ingrowths of germinal epithelium take the form of long solid strands of germinal cells, which were first described by Pflüger under the name egg-tubes: near the surface of the ovary the strands may be hollow and duct-like, recalling somewhat the appearance of gland-tubules. But as development pro-

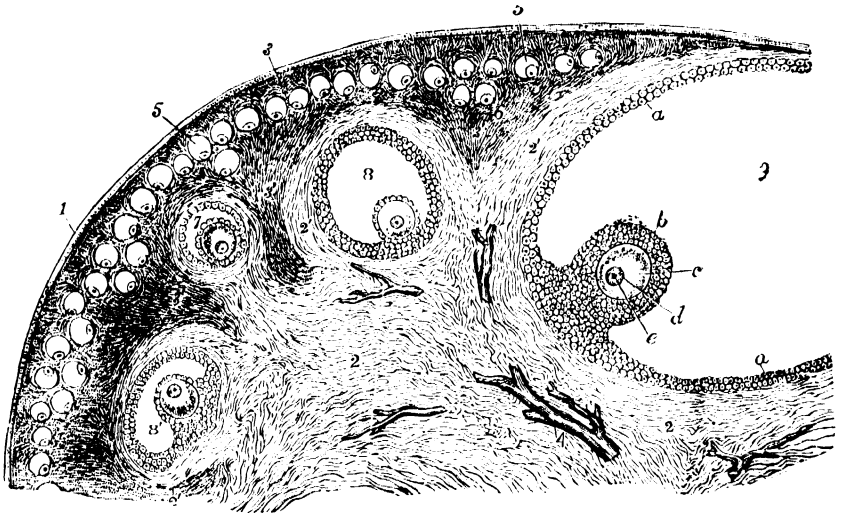


FIG. 935.—A PORTION OF THE SECTION OF CAT'S OVARY REPRESENTED IN THE PRECEDING FIGURE; MORE HIGHLY MAGNIFIED. (Schrön.)

1, epithelium and outer covering of the ovary; 2, fibrous stroma; 3, 3', less fibrous, more superficial stroma; 4, blood-vessels; 5, small Graafian follicles near the surface; 6, one or two more deeply placed; 7, one farther developed, enclosed by a prolongation of the fibrous stroma; 8, a follicle farther advanced; 8', another of an elliptical shape; 9, part of a ripe follicle; *a*, tunica granulosa; *b*, discus proligerus; *c*, ovum; *d*, germinal vesicle; *e*, germinal spot.

ceeds the egg-tubes become divided up by ingrowths of stroma into islets of germinal cells; it is from these that the Graafian follicles, next to be described,

are formed. Remains of the egg-tubes are sometimes seen in the ovaries of adult animals (fig. 938, *b*). Imbedded in all parts of the stroma except near the hilum are a large number of spherical or ovoid vesicles, each containing an ovum together with a number of other cells. These vesicles are the *Graafian follicles*: they are found of all sizes from a diameter little larger than the contained ovum and entirely microscopic (fig. 939), to a rounded sac as large as a pea, often forming a pellucid projection at the surface of the ovary. The smallest Graafian follicles contain only a small immature ovum and a single layer of epithelium-cells surrounding it; the largest contain an ovum of mature size (about 0·2 mm.)

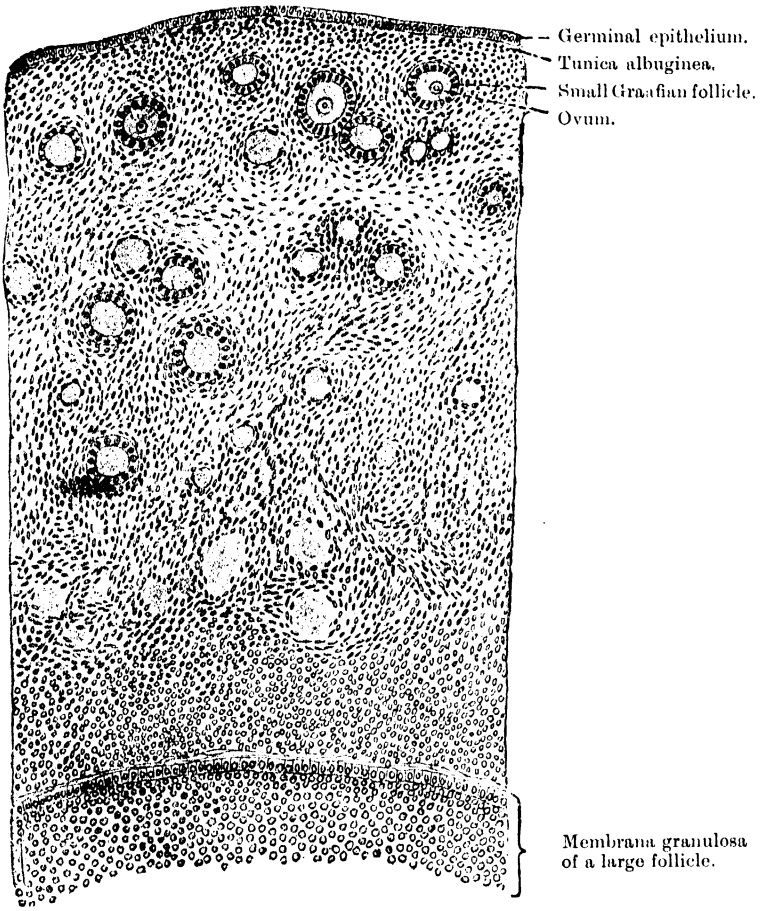


FIG. 936.—SECTION OF PART OF THE OVARY OF A YOUNG GIRL. (v. Böhm and Davidoff.) Magnified 190 diameters.

surrounded by a considerable mass of follicular epithelium-cells (*discus proligerus* or *cumulus*), by which it is attached to the wall of the follicle, while layers of the same cells line the follicular wall (*theca*) and form the so-called *membrana granulosa*. These larger follicles (fig. 940) are distended by fluid (*liquor folliculi*), and as this fluid accumulates they come to occupy a considerable cavity in the stroma, eventually, as we have seen, even projecting from its surface. It is at the projecting part that the follicle ultimately bursts, liberating the ovum surrounded by its discus proligerus; but the epithelium which lines the follicle remains *in situ* and undergoes proliferation, becoming developed into the epithelial tissue of a corpus luteum.

The smallest Graafian follicles are usually found near the surface of the ovary in the so-called cortical layer. They form in some animals an almost continuous series immediately within the subepithelial layer of the ovarian stroma (fig. 935); but in the human ovary they are relatively few in number, and are separated from one another by considerable intervals of stroma. In the new-born child they are much more numerous, but many atrophy as growth progresses.[1] As the Graafian follicles enlarge they sink into the stroma; the largest are found in the deeper parts. It is only their distension by the liquor folliculi which again brings one part of the enlarging follicle to the surface. Every Graafian follicle does not develop to the point of discharging its contents—many undergo atrophy after developing to a certain size, and their contents, including the ovum, become shrunken (fig. 938, *k*) and eventually absorbed. The theca of the larger follicles is double, having a specially differentiated part of the stroma as its outer layer and a stratum containing large granular cells as its inner layer; both layers contain blood-vessels, the inner being provided with

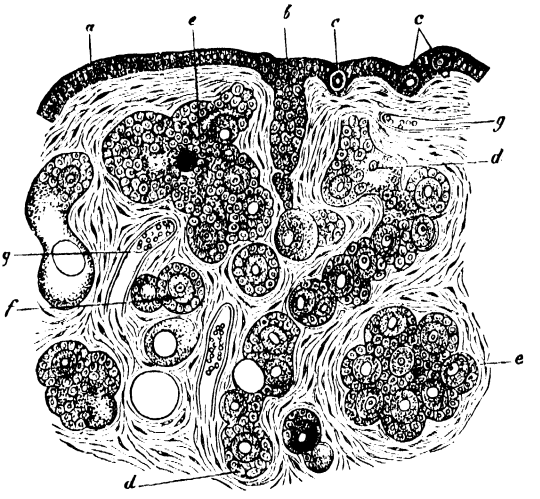


FIG. 937.—SECTION OF THE OVARY OF A NEWLY-BORN CHILD. (Waldeyer.) Highly magnified.

a, Ovarian or germinal epithelium; *b*, formation of an ovarian tube; *c*, *c*, primordial ova lying in the germ epithelium; *d*, *d*, longer tube becoming constricted to form nests of cells; *e*, *e*, larger nests; *f*, distinct follicle with ovum and epithelium; *g*, *g*, blood-vessels.

a capillary network, the outer having the ramifications of the arterioles and venules. The blood-vessels enter the wall at its deepest part, and converge towards a point near the middle of its most projecting portion (*stigma*), where the rupture of the mature follicle occurs.

The ova within the smaller follicles are of small size, but contain a larger spherical clear nucleus and large nucleolus: they have no very distinct membrane. As the Graafian follicles enlarge the ovum enlarges within it, and the follicular epithelium-cells arrange themselves like a columnar epithelium around the ovum. The membrane of the ovum now begins to appear, and as the enlargement of the follicle proceeds it attains a considerable thickness. It is probably formed by the columnar cells of the discus proligerus—but it does not wholly shut them off from the ovum, for they retain a connection with its cytoplasm by fine processes which pass through pores in the membrane (G. Retzius). These pores give the

[1] It is stated that there are as many as 100,000 ova in the ovaries at birth and about 20,000 at puberty. Of these not more than 400 attain maturity (see F. H. A. Marshall, The Physiology of Reproduction, 1910).

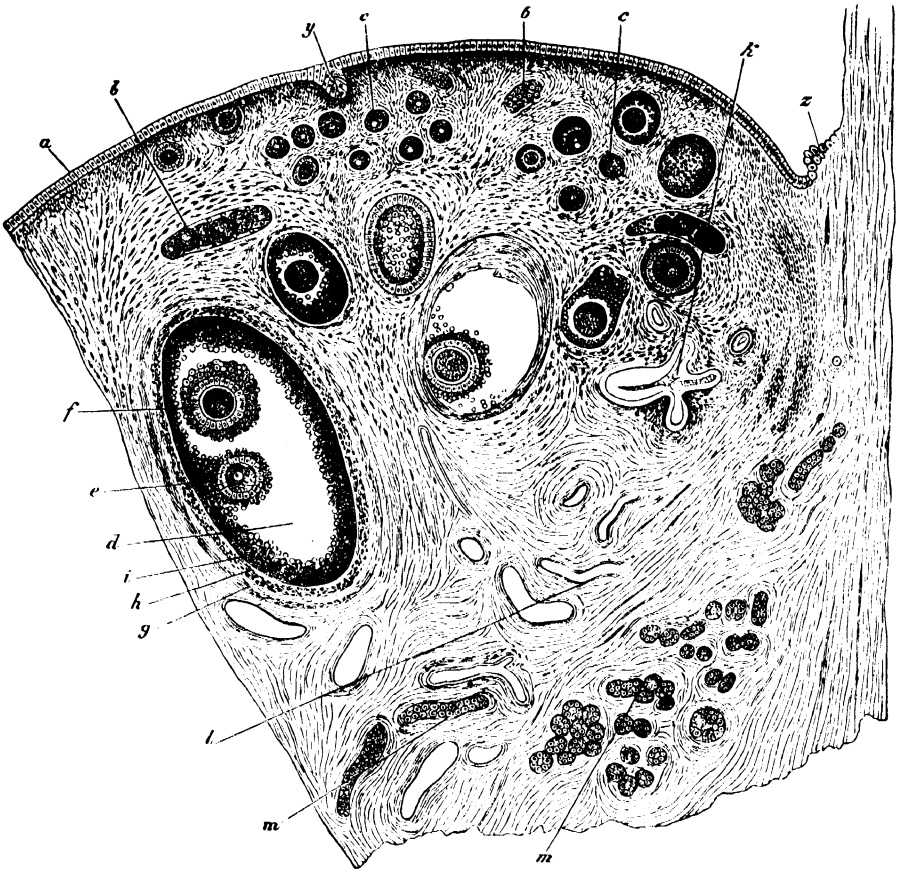


FIG. 938.—SECTION OF THE OVARY OF AN ADULT BITCH. (Waldeyer.) Magnified 15 diameters.

a, germ-epithelium; *b*, egg-tubes; *c*, *c*, small follicles; *d*, more advanced follicle; *e*, discus proligerus and ovum; *f*, second ovum in the same follicle (this occurs but rarely); *g*, outer tunic of the follicle; *h*, inner tunic; *i*, membrana granulosa; *k*, collapsed retrograded follicle; *l*, blood-vessels; *m*, *m*, longitudinal and transverse sections of tubes of the parovarium; *y*, involuted portion of the germ-epithelium of the surface; *z*, place of the transition from peritoneal to germinal or ovarian epithelium.

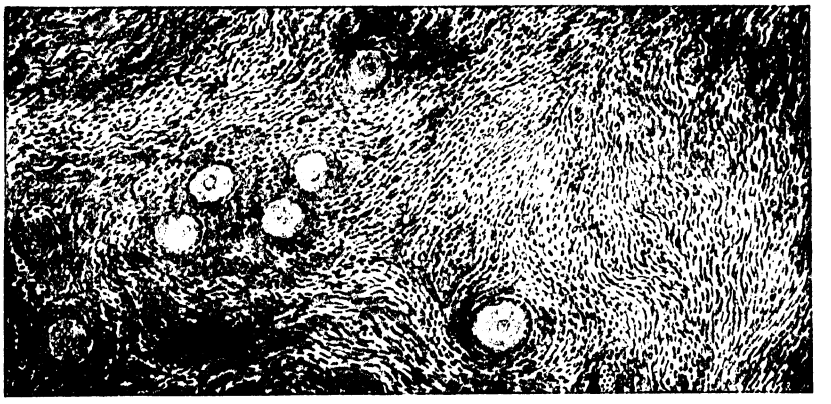


FIG. 939.—SECTION OF PART OF HUMAN OVARY SHOWING SMALL GRAAFIAN FOLLICLES IMBEDDED IN THE FIBRO-CELLULAR STROMA. (Sellheim.)

membrane an appearance of radial striation. It is known as the *zona radiata* or *zona pellucida* (v. Baer), the latter term being derived from its appearance in the fresh condition (fig. 941). It is possessed of considerable toughness and requires a considerable amount of pressure to rupture it.

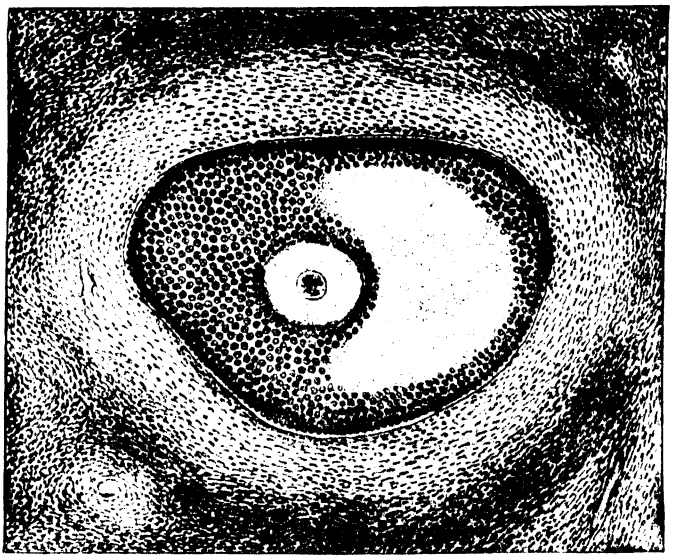


FIG. 940.—A MODERATELY LARGE GRAAFIAN FOLLICLE FROM THE HUMAN OVARY, SHOWING OVUM SURROUNDED BY 'DISCUS PROLIGERUS' AND WALL OF FOLLICLE LINED BY 'MEMBRANA GRANULOSA.' BETWEEN THEM IS AN ACCUMULATION OF LIQUOR FOLLICULI. (Sellheim.)

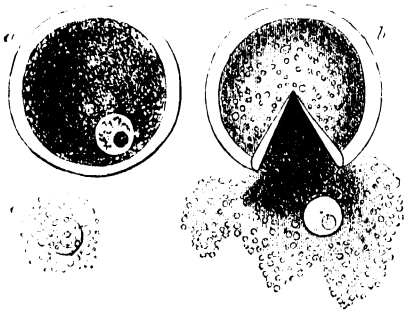


FIG. 941.—OVARIAN OVUM OF A MAMMAL. (Allen Thomson.)

a, an entire ovum, viewed under pressure; the granular cells have been removed from the outer surface, the germinal vesicle is seen within the yolk-substance; *b*, the external coat or zona burst by increased pressure, the yolk-protoplasm and the germinal vesicle having escaped; *c*, germinal vesicle more freed from the yolk-substance. In all the three figures macula is shown.

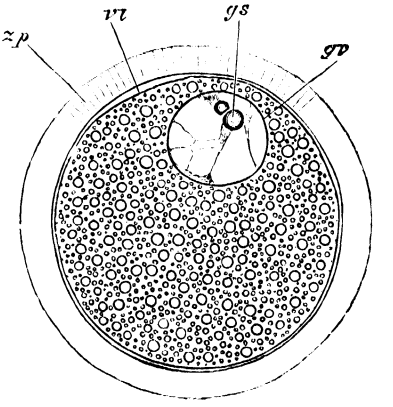


FIG. 942.—OVUM OF A MAMMAL, HIGHLY MAGNIFIED. SEMI-DIAGRAMMATIC. (Schäfer.)

zp, zona pellucida, showing radiated structure; *vi*, vitellus, round which a delicate membrane is seen; *gv*, germinal vesicle; *gs*, germinal spot.

Within the zona the ovum consists of cytoplasm (*vitellus* or *yolk*) containing numerous yolk-granules (fig. 942), which are especially abundant in the central parts: the superficial layer may be clear of them. Amongst them lies the nucleus (*germinal vesicle* of Purkinje), which measures about 0·05 mm. in diameter; it has a prominent

nucleolus (*germinal spot, macula germinativa* of Wagner). While still within the Graafian follicle, the nucleus may approach the surface of the ovum and exhibit mitotic division changes (formation of polar globules) (fig. 943), but this change occurs more commonly after discharge of the ovum and while it is within the Fallopian tube.

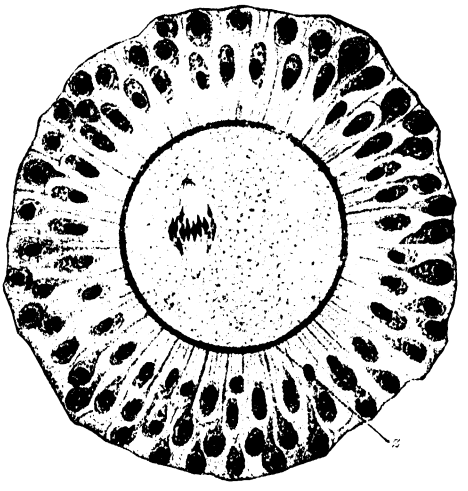


FIG. 943.—OVARIAN OVUM OF MOUSE, SURROUNDED BY CELLS OF DISCUS PROLIGERUS. (Sobotta.)

z, zona. The nucleus is in process of division by heterotypical mitosis (first polar spindle).

FIG. 944.—OVARY OF 28-DAY RABBIT, SHOWING STROMA INTERGROWING WITH THICKENED GERMINAL EPITHELIUM. (Felix and Bühler.)

a, germinal epithelium; *b*, a thickened downgrowth of this epithelium; *c*, stroma.

Immediately surrounding the zona radiata, as the ovum lies within the mature Graafian follicle, is a thin stratum of granular substance, probably deposited upon the exterior of the ovum by the innermost cells of the discus proligerus, which immediately encircle the ovum

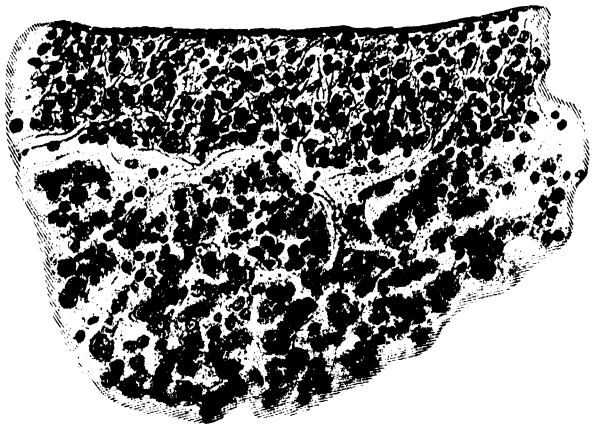


FIG. 945.—OVARY OF HUMAN FŒTUS, SHOWING THE THICKENED GERMINAL EPITHELIUM, TOGETHER WITH ELONGATED GROUPS OF GERMINAL EPITHELIUM-CELLS AND PRIMITIVE OVA WITHIN THE STROMA. (Felix and Bühler.)

within the follicle (fig. 943) and often cling to it for a time after its discharge. When the Graafian follicle bursts and the ovum is set free, this granular material appears to imbibe water, and, as is specially noticeable in the ovum of the rabbit, swells up into a clear gelatinous envelope, which has been termed, from a possible homology with the white of

the bird's egg, the *albumen*. But in the mammal this structure has not the nutritive importance to the embryo which is possessed by the corresponding formation in the bird, and it disappears during the passage of the ovum down the Fallopian tube.

Formation of the Graafian follicles.—The ovary is formed, as already stated (see also Vol. I.), by a proliferation and ingrowth of the germinal epithelium, whilst at the same time the vascular stroma grows out between the epithelial strands (fig. 944) so as to isolate these in the form of the egg-tubes of Pflüger already mentioned. These egg-tubes consist of cylindrical or irregular columns of germinal epithelium-cells (fig. 945) which communicate with one another, and at first also with the surface, but ultimately become broken up by growths of stroma tissue into smaller and smaller portions, which now appear in the form of islands or nests of epithelium in the substance of the stroma.[1] Both the egg-tubes and the islands produced from them contain amongst the ordinary small germinal epithelium-cells a much smaller number of larger spherical cells each with a large nucleus and distinct nucleolus: these are the

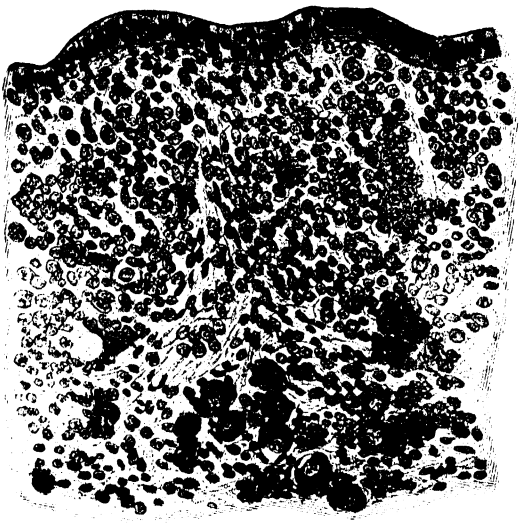


FIG. 946.—LATER STAGE IN THE FORMATION OF GRAAFIAN FOLLICLES. (Felix and Bühler.)
Some of the primitive ova are considerably enlarged and surrounded by other germinal epithelium-cells, forming primitive Graafian follicles.

primitive ova (fig. 946). Ultimately the subdivision of the islets and cell-columns proceeds to such an extent that each is reduced to one or two, occasionally more, primitive ova surrounded by a simple layer of germinal epithelium, the cells of which are cubical (fig. 947) or flattened (fig. 948) in shape. These small islets form the *primitive Graafian follicles*, which are accumulated in great numbers in the more superficial parts of the ovary of the child and young animals, and are in some animals found in this situation throughout the greater part of life (figs. 934 and 935, from the cat). Ultimately only a single primitive ovum remains as a rule in each primitive follicle, having developed, it is believed, at the expense of the rest.

As the development of the ovary proceeds some of these primitive follicles become enlarged. The enlargement is accompanied and indeed caused by increase in size of the primitive ovum and growth and proliferation of the germinal

[1] According to Miss Lane-Claypon some of the germinal epithelium-cells also become diffused throughout the stroma, and give origin to the epithelium-like interstitial cells. This author believes that these cells, as well as those within the cell-nests, are capable of producing ova. Most authorities have looked upon the interstitial cells of the ovary as of connective tissue origin.

epithelium-cells which surround it. Along with the enlargement of the primitive ovum its nuclear chromatin undergoes a succession of remarkable changes (Winiwarter, Lane-Claypon), already alluded to (p. 54) as the *synaptic changes*, and common both to these cells of the ovary and to the spermatocytes of the testis. At the termination of these changes, the meaning of which is not fully understood, the chromatin resumes the reticular form of the ordinary resting nucleus, although its amount is small relatively to the size of the nucleus (fig. 948). On the other hand the nucleolus, which may disappear in the synaptic stage, is now very large and distinct, and is not uncommonly formed of a number of masses of nucleolar substance of varying size. The ovum, although still small, has the general structure of the mature egg-cell before it undergoes the mitotic changes which result in the formation of the polar globules (see p. 51); it may now be regarded as a fully formed ovarian ovum. It is surrounded by only a single layer of follicular epithelial cells, but these are beginning to become columnar. They presently undergo proliferation and give rise to a second layer, so that there is now a double stratum of epithelium-cells within the follicle (fig. 949, D, E), one immediately surrounding the ovum and the other lining the wall of the follicle, which by this time is beginning to be differentiated from the general ovarian stroma. The two strata form the beginnings respectively of the discus proligerus and the membrana granulosa; but they are at first everywhere in contact with one another. By this time also a distinct membrane—the commencing *zona radiata*—has begun to appear around the ovum, and a basement-membrane (hyaline layer) may be seen lining the theca interna.

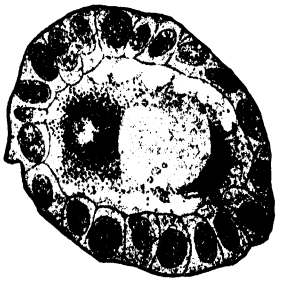


FIG. 947.—PRIMITIVE OVUM SURROUNDED BY A SINGLE LAYER OF CUBICAL FOLLICULAR CELLS. (Van der Stricht.)

The cytoplasm of the ovum shows a centrosome and numerous mitochondria.

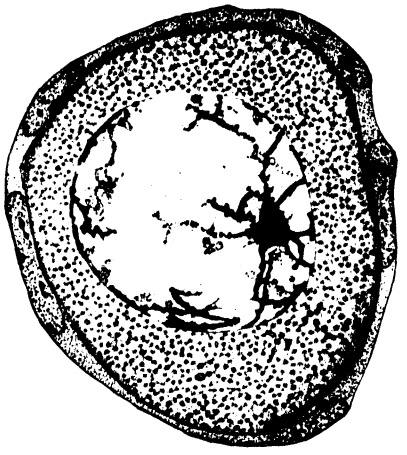


FIG. 948.—PRIMITIVE GRAAFIAN FOLLICLE OF RABBIT SUBSEQUENT TO THE SYNAPTIC CHANGES OF THE OVUM NUCLEUS. (Winiwarter.) Magnified 1700 diameters.

The ovum, which contains a nucleus with reticular chromatin and the cytoplasm of which is filled with granules, is surrounded by a single layer of flattened follicular epithelium.

Both discus proligerus and membrana granulosa become thickened by further proliferation, and the ovum and Graafian follicle grow *pari passu* with such proliferation. Presently fluid begins to make its appearance at one place between the two strata, and gradually increases in amount. This is the liquor folliculi, which, without doubt, is secreted by the cells of the membrana granulosa, and upon the accumulation of which chiefly depend the subsequent growth of the follicle, and in all probability its eventual distension and bursting.

Occasionally two and very rarely three ova are developed in one Graafian follicle in the human subject.

In the largest follicles both discus proligerus and membrana granulosa are many layers thick, and are composed mainly of spherical or polyhedral cells somewhat loosely connected together near the liquor folliculi, within which many of them undergo disintegration; they are more closely packed nearer the ovum and the wall of the follicle respectively. The cells which cover the ovum and those

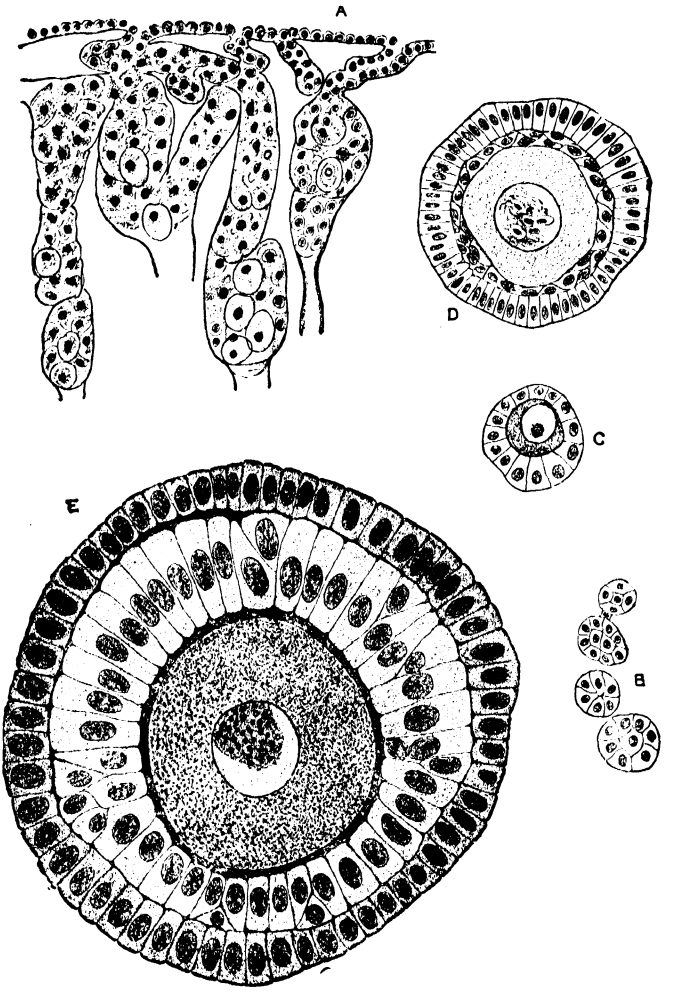


FIG. 949.—FIGURES SHOWING VARIOUS STAGES IN THE DEVELOPMENT OF THE GRAAFIAN FOLLICLES IN THE RABBIT. (Schäfer.) Highly magnified.

A, From a section of the ovary of a young rabbit, showing the 'egg-tubes' of Pflüger continuous with the germinal epithelium of the surface. Some of the egg-tubes contain primitive ova. B, primitive Graafian follicles derived from the breaking up of an egg-tube. C, a Graafian follicle within which the permanent ovum has now become distinct. The follicle has only a single layer of epithelium. D, a larger follicle in which there are two distinct layers of epithelium, but the inner layer is formed of flattened cells. E, a larger but still quite young follicle in which the inner layer of cells as well as the outer is composed of columnar epithelium. Figs. B, C, D, and E are taken from sections of ovaries more advanced in development than A.

which actually line the follicular wall are columnar in shape, and, as already noticed, those which immediately surround the ovum send fine prolongations of their protoplasm through the pores of the zona radiata.

Those Graafian follicles that attain maturity and burst become developed into corpora lutea, a description of the formation of which will immediately be given. But a very large

number of follicles, after attaining a certain amount of growth and development, undergo degeneration (atresia), the ovum becoming shrivelled and eventually disappearing, the follicular epithelium degenerating—a process which is shared by the theca interna—and the cavity remaining for some time as an irregular cyst, which shrivels and eventually disappears, being perhaps absorbed.

After the cessation of sexual activity the Graafian follicles cease to enlarge and as age advances an increasing number become atrophied. Changes also occur in the interstitial tissue of the ovary leading to sclerosis of its stroma and a general shrinking in size. Some of these changes are illustrated in fig. 952.

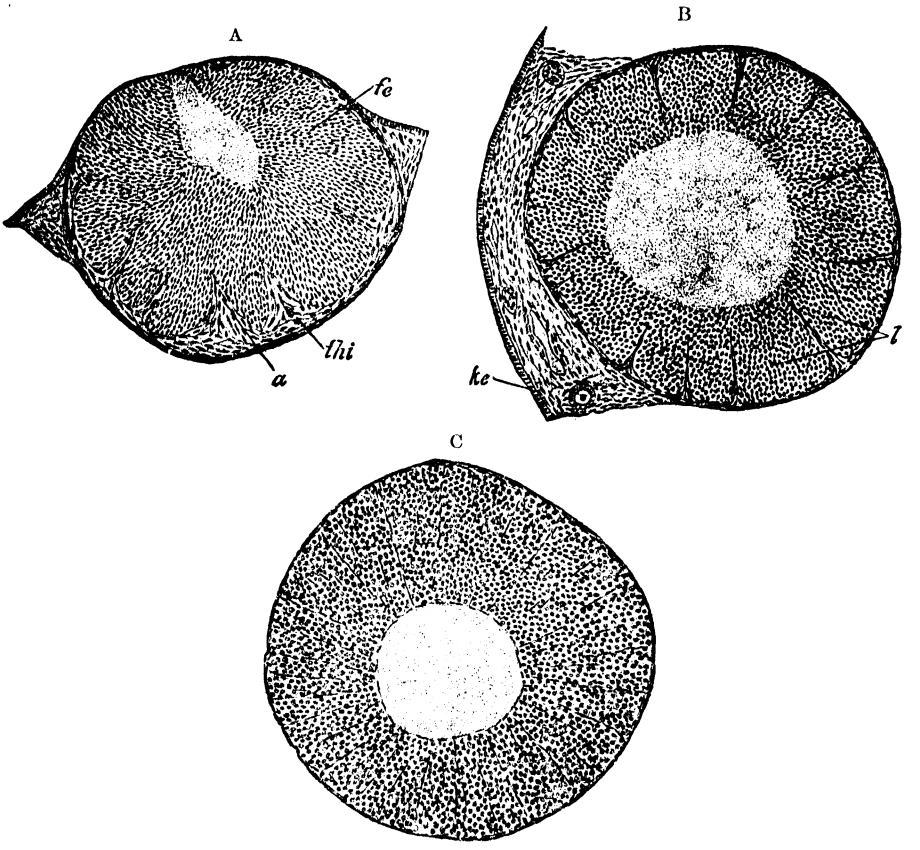


FIG. 950.—THREE STAGES IN THE FORMATION OF THE CORPUS LUTEUM IN THE MOUSE. (Sobotta.)

A, commencing ingrowth of the vascular tissue of the theca folliculi into the hypertrophied follicular epithelium; *a*, vascular ingrowth; *thi*, theca or wall of follicle; *fe*, follicular epithelium.

B, a further stage in which the vascular ingrowths of the theca converge towards a central cavity. Between the ingrowths or trabeculæ the follicular epithelial cells, which are undergoing rapid multiplication, appear as if disposed in columns; *l*, leucocytes amongst the follicular cells; *ke*, surface epithelium of the ovary.

C, a further stage, the columns being now narrower and the trabeculæ more numerous.

Development and structure of the corpus luteum.—The corpora lutea are produced after the rupture of the Graafian follicles and the escape of their contents by what may perhaps be most correctly described as a process of hypertrophy of the walls of the empty follicles. The hypertrophied follicular wall becomes thrown into plaits or folds, which as they increase in extent occupy more and more of the cavity of the empty follicle, until this has become entirely filled. The hypertrophy has usually been described as the result of the proliferation of the polyhedral interstitial stroma-cells, which, as already stated, occur in

abundance in the wall of the follicle; and there is in addition a considerable development of blood-vessels, which run, accompanied by fibrous tissue, into the folds into which the wall of the follicle is thrown, and give off capillaries that ramify abundantly in the folded wall. But according to the observations of J. Sobotta upon various animals, confirmed by Stratz, Van der Stricht, F. H. A. Marshall and other investigators, the main part of the thickening is due to a simple hypertrophy of the epithelium-cells of the membrana granulosa, into which grow vascular processes of the wall of the follicle (chiefly from the theca interna) (fig. 950); amongst them a certain number of leucocytes penetrate. Meanwhile the irregular cleft-like space which now alone represents the cavity of the follicle, as well as the opening resulting from the rupture of the follicle and by which its cavity communicated with the surface, become occupied by a sort of jelly-like connective tissue, constituting a kind of hilum for the follicle. To this central fibrous band converge the strands of fibrous tissue which accompany the blood-vessels in the folds of the

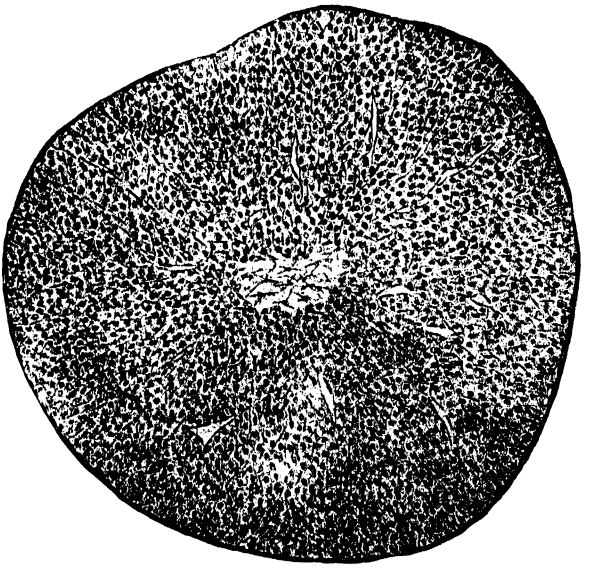


FIG. 951.—MORE ADVANCED CORPUS LUTEUM OF THE MOUSE, SHOWING ITS FORMATION COMPLETED. (Sobotta.)

The central cavity is now occupied by jelly-like connective tissue and the converging trabeculæ anastomose with one another so as somewhat to break up the columnar arrangement of the luteal cells.

hypertrophied wall of the corpus luteum. At the same time the plaited disposition of the wall becomes in great measure obscured, so that a section of a corpus luteum, when advanced in development (fig. 951), exhibits a fibrous framework having a radial disposition, with the intervals between the radiating trabeculæ occupied by a tissue almost wholly composed of large yellowish cells. Amongst these cells are numerous cleft-like spaces (lymphatic), and except for the fact that the columnar disposition is less distinct and that the capillary blood-vessels come more closely into relationship with the cells of the tissue, the structural appearances are not unlike those which are met with in the cortical part of the suprarenal capsule.

The view that the corpus luteum mainly owes its origin to the membrana granulosa of the Graafian follicle was that originally taken by Bischoff. On the other hand, von Baer considered that it was wholly due to a hypertrophy of the connective-tissue wall of the follicle; many modern authorities have taken this view.[1]

[1] For a full account of the subject see Marshall, *op. cit.* 1910.

The corpus luteum is at first sharply marked off by the theca folliculi from the surrounding ovarian stroma, but after a time it is less sharply marked off from the neighbouring parts of the stroma, into which it may be said gradually to merge and in this way to disappear. The result is that, as age advances, the stroma of the ovaries, at least in some animals, becomes gradually pervaded with cells which have been derived from corpora lutea.

The corpus luteum is an organ of internal secretion. It appears to be related to the proper fixation of the ovum in the uterus, for if the corpus luteum be destroyed or the ovary removed at an early period of pregnancy, abortion occurs. At later stages it is related to the functions of the mammary gland, extracts of corpus luteum having a markedly galactagogue action.

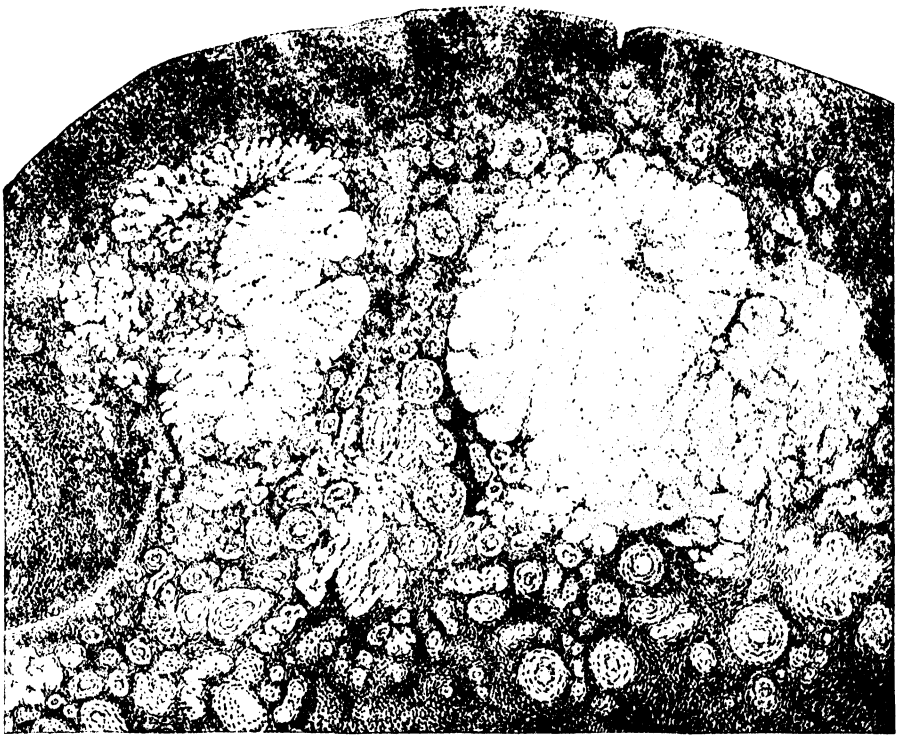


FIG. 952.—SECTION OF OVARY OF WOMAN OF FIFTY-SIX, SHOWING DEGENERATION OF FOLLICLES AND SCLEROSIS OF STROMA. (Sellheim.)

Vessels and nerves of the ovaries.—*Arteries.* The ovary is supplied directly by the ovarian artery, analogous to the spermatic in the male, which anastomoses freely by an internal branch with the termination of the uterine artery. Sometimes this anastomotic branch is so large that the ovary seems to be supplied almost entirely by the uterine artery. The ovarian artery always sends numerous branches to the Fallopian tube. The smaller arteries penetrate the ovary along its attached border, pierce the proper coat, and run in flexuous parallel lines through its substance. The internal part of the stroma through which the larger vessels run is known as the *zona vasculosa.* Both arteries and veins are extraordinarily numerous and convoluted, and the whole organ is exceptionally vascular. The *veins* correspond in general with the arteries; they form a plexus near the ovary named the *pampiniform plexus.* The general arrangement of the vessels within the organ and the manner in which the Graafian follicles and corpora lutea are supplied with blood is indicated in the accompanying illustration (fig. 953) from J. G. Clark (Johns Hopkins Hosp. Rep. ix. 1900). For details regarding the

vascular arrangements and the changes which they undergo in the course of development and growth of the ovary the reader is referred to this paper.

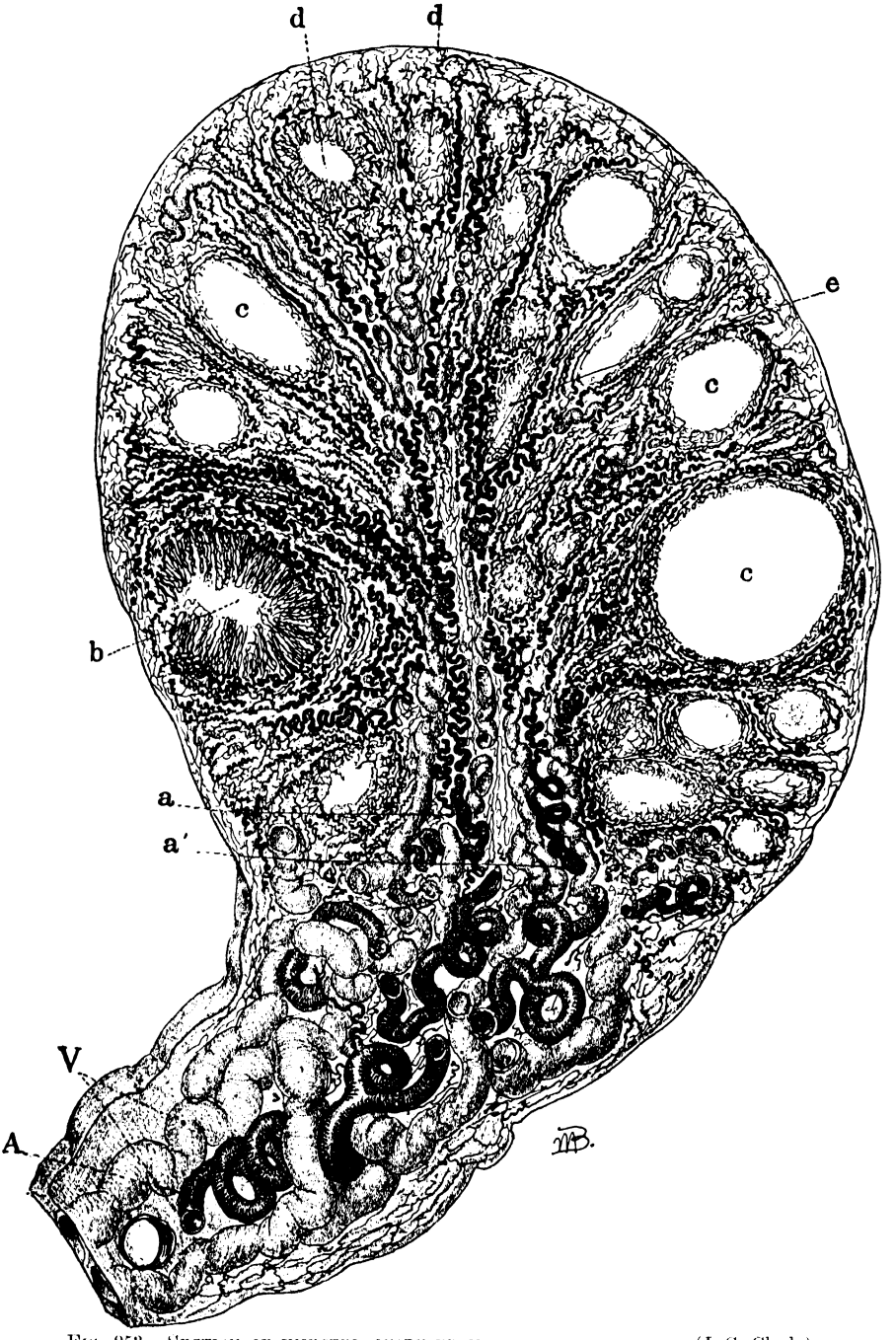


FIG. 953.—SECTION OF INJECTED OVARY FROM A GIRL OF SIXTEEN. (J. G. Clark.)
Magnified about 8 diameters.

A, ovarian artery; *a*, *a'*, its deeply lying parallel branches, which are seen giving off arterioles towards the superficial parts; *V*, ovarian veins; *b*, a corpus luteum; *c*, *c*, Graafian follicles; *d*, *d*, unruptured follicles which are in process of atresia; *e*, a more complete phase of atresia (corpus albicans).

The *lymph-vessels* form networks around the larger Graafian follicles which communicate with cleft-like lymphatics accompanying the blood-vessels in their course through the stroma. They leave the ovary at the hilum by several efferent vessels which join those issuing from the body of the uterus. Exner and Buckel could find no lymph-vessels in the corpora lutea, although His had described their existence within these structures. The *nerves* are derived from the ovarian plexus, and from the uterine nerves, and send offsets to the Fallopian tubes. They course along the ovary as three trunks, one of which goes mainly to the tube; the others communicate freely with one another and are furnished with microscopic ganglia and with groups of specialised cells (*phœochrome cells* of Winiwarter). The fibres are chiefly non-medullated and are distributed to the muscular tissue of the blood-vessels of the ovary, of the broad ligament, and of the Fallopian tube: some pass to the cortical zone, and ramify around the Graafian follicles. Fibrils have even been traced amongst the epithelium-cells of the membrana granulosa. Some fibres are said to end in Pacinian corpuscles (Winiwarter).

The following papers on the ovary may be mentioned: B. M. Allen, Amer. Journ. Anat. ii. 1904 (interstitial cells); Ancel and Bouin, Compt. rend. d. l. soc. de Biol. lxvi. 1909; Journ. de Physiol. 1911 (functions of corpus luteum); M. Athias, Anat. Anz. xxxix. 1911 (origin and structure of interstitial cells); F. M. Balfour, Quart. Journ. Micr. Sci. xviii. 1878 (oögenesis); Buckel and Exner, Wiener Sitzungsb. lxx. 1874 (lymph-vessels); J. G. Clark, Arch. f. Anat. 1898 (corpus luteum); Johns Hopkins Hosp. Rep. ix. 1900 (vessels of ovary); Cohn, Arch. f. mikr. Anat. lxii. 1903 (corpus luteum and interstitial cells); Felix and Bühler, in Hertwig's Handbuch d. Entwickelungslehre; O. Fellner, Arch. f. mikr. Anat. lxxiii. 1909 (changes in Graafian follicles during pregnancy); Fraenkel, Arch. f. Gynäk. lxviii. 1903 (corpus luteum), lxxv. 1905 (interstitial cells); Fraenkel and Cohn, Anat. Anz. xx. 1901 (corpus luteum and pregnancy); Heape, Quart. Journ. Micr. Sci. xxvi. 1886, and Proc. Roy. Soc. B. lxxvi. 1905 (changes in Graafian follicles); Honogré, Arch. de biol. xvi. 1900 (Graafian follicles); Jankowski, Arch. f. mikr. Anat. lxiv. 1904 (corpus luteum); Joseph, Arb. d. Zool. Instit. Wien, xviii. 1909 (Graafian follicles); Kölliker, Verhandl. d. anat. Gesellsch. in Anat. Anz. xiv. 1898 (atresic follicles); Lane-Claypon, Proc. Roy. Soc. B. lxxvii. 1905, and Journ. Obst. and Gyn. xi. 1907 (interstitial cells); L. Loeb, Anat. Anz. xxviii. 1906 (corpus luteum); A. L. McIlroy, Proc. Roy. Soc. Edin. xxxi. 1910 (development of ova and follicles); K. Mackenzie, Quart. Journ. Exper. Physiol. iv. 1911 (relation of corpus luteum to mammary secretion); F. H. A. Marshall, Phil. Trans. B. cxevi. 1904 (corpus luteum); J. W. Miller, Arch. f. Gyn. xci. 1911 (involution of corpus luteum); Minot, 'Human Embryology,' 1892; W. Nagel, 'Die weibliche Geschlechtsorgane,' in v. Bardeleben's Handb. d. Anatomie, 1896; Ott and Scott, Proc. Soc. Exp. Biol. Dec. 1910 (relation of corpus luteum to mammary secretion); Pflüger, 'Ueber die Eierstöcke, &c.,' Leipzig, 1863; A. Robinson, Journ. Anat. and Physiol. xxi. 1887 (position and peritoneal relations of ovary); G. Retzius, Hygiea Festband, 1889 (Graafian follicles) and Biol. Unters. v. 1893 (nerves); Riquier, Arch. f. mikr. Anat. lxxv. 1910 (cells of corpus luteum); A. Russo, Anat. Anz. xxxiii. 1908 (formation of zona pellucida and of liquor folliculi); Schäfer, Proc. Roy. Soc. xxx. 1880 (development of Graafian follicles); Schäfer and Mackenzie Proc. Roy. Soc. B. lxxxiv. 1911 (relation of corpus luteum to mammary secretion); Seitz, Arch. f. Gynäk. lxxvii. 1906 (atresic follicles); Sobotta, Anat. Anz. x. 1895, Arch. f. mikr. Anat. xlvii. 1896, Anat. Hefte, viii. 1897, Ergebn. der Anat. u. Entwickl. viii. 1898, Anat. Hefte, xxxii. 1907 (formation of corpus luteum), Würzburg Sitzungsb. 1906 (atrophy of follicles); T. G. Stevens, Journ. Obst. and Gyn. Jan. 1904 (atrophy of follicles); Stratz, 'Der geschlechtsreife Säugethiereierstock,' 1898; Van der Stricht, Compt. rend. de l'assoc. d. anat. 1908 (corpus luteum); Van der Stricht, Verhandl. d. Anat. Gesellsch. in Anat. Anz. 1901 (atresic follicles); Timofeew, Anat. Anz. ix. 1894; Van Winiwarter, Arch. de biol. xvii. 1901 (oögenesis), Anat. Anz. xxxiii. 1908 (interstitial tissue of human ovary), Arch. de biol. xxv. 1910 (nerves and muscular tissue of ovary); Van Winiwarter and Sainmont, Arch. de biol. xxiv. 1909, Anat. Anz. xxxii. 1908 (oögenesis); Waldeyer, 'Eierstock und Ei,' 1870, 'Die Geschlectszellen' in Hertwig's 'Handb. der Entwicklungslehre,' 1903.

Parovarium or **Epoophoron.**—The organ so named by Kobelt, or the *organ of Rosenmüller*, who first described it (1802), is a structure which can usually be brought plainly into view by holding against the light the fold of peritoneum between the ovary and Fallopian tube (see fig. 931, *po*). It consists of a group of scattered tubules lying between the Fallopian tube and ovary, lined with columnar and in places with ciliated epithelium, but having no external openings. Their walls are formed of connective tissue with some plain muscle-fibres. The tubules converge towards their ovarian end, but remain separate there, while at the other they are more or less distinctly united by a longitudinal

tube, sometimes of considerable size, and prolonged for some distance downwards in the broad ligament. According to Ballantyne the tubules are thicker and better developed in women who have borne children than in others. The structure undergoes partial atrophy after the menopause. Its more developed form in some animals, as the cow and pig, constitutes the *duct of Gärtner*.[1] The origin of this vestige of a fœtal structure is referred to under Development (Vol. I.). Here it is sufficient to state that it corresponds essentially to the epididymis of the male. Vestiges corresponding to the organ of Giraldès of the male are also sometimes to be detected in the adult female, in the shape of tubular remnants, situated in the broad ligament nearer to the uterus than the parovarium. These constitute the *paroophoron* of Waldeyer.

Cyst-like rudiments are also frequently found between the epoophoron and the opening of the Fallopian tube : they are sometimes attached to the broad ligament by a stalk (fig. 954, *i*). They have been compared to the hydatids of Morgagni

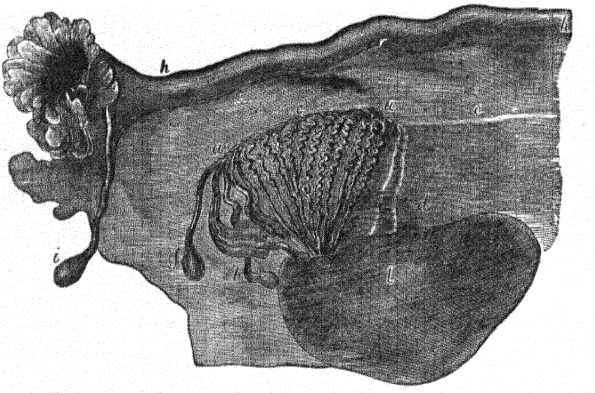


FIG. 954.—ADULT OVARY, PAROVARIUM AND FALLOPIAN TUBE. (Kobelt.)

a, *a*, Epoophoron (parovarium) formed from the upper part of the Wolffian body; *b*, remains of the uppermost tubes, sometimes forming hydatids; *c*, middle set of tubes; *d*, some lower atrophied tubes; *e*, atrophied remains of the Wolffian duct; *f*, the terminal bulb or hydatid; *h*, the Fallopian tube, originally the duct of Müller; *i*, hydatid attached to the extremity; *l*, the ovary.

of the male, but are probably not developed from the Müllerian duct (which forms the Fallopian tube) but from portions either of the tubules or of the main tube of the epoophoron.

See on the epoophoron and paroophoron Ballantyne and Williams, 'The structures in the Mesosalpinx,' 1893; Waldeyer, 'Eierstock u. Ei,' Leipzig, 1870; 'Eierstock u. Nebeneierstock,' in Stricker's Handbook, 1871; Janošik, Wiener Sitzungsb. xci. 1885.

THE FALLOPIAN TUBES

The ovary being regarded as a gland for the production of ova the Fallopian tube represents its duct. It is, however, very different from other gland-ducts, since it does not immediately start from the ovary but opens into the peritoneal cavity near that organ by a minute orifice seen in the middle of its fimbriated or fringed ovarian extremity. The fimbriæ come into close relation with the surface of the ovary, to the upper end of which one of them is attached; when the ovum is discharged it generally lodges either upon this or one of the other fimbriæ. The fimbriæ are covered on the surface opposite the ovum with cilia, which produce a current in the direction of the orifice of the tube; the ovum is carried into this and is then gradually propelled towards the uterus by the cilia lining the tube. The uterine end of the tube communicates with the cavity of

[1] See on the duct of Gärtner in man, R. Meyer, Arch. f. mikr. Anat. lxxiii. 1909.

the uterus by a very small aperture, but in most of its extent the lumen of the tube is larger, varying in different parts from 2 mm. to 8 mm.

Each tube has a strong muscular wall with both longitudinal and circular fibres of plain muscle and a thick mucous membrane, which is thrown into permanent longitudinal folds (fig. 955). There are no glands in its mucous membrane and very few elastic fibres. The tube is lined throughout by ciliated epithelium. The cilia cause a current towards the uterus. The two tubes may be regarded as fused at their lower ends to form the (median) uterus. In many animals each tube is directly continued into one half of a double uterus (uterus bicornis). Externally the tube is covered by peritoneum except along its attachment to the broad ligament; at its open fimbriated end the serous endothelium comes into direct relation and continuity with the ciliated epithelium of the tube and its fimbriæ. Between the peritoneal coat and the muscular layer is loose connective tissue; in this the blood-vessels and nerves are conducted to the wall of the tube.

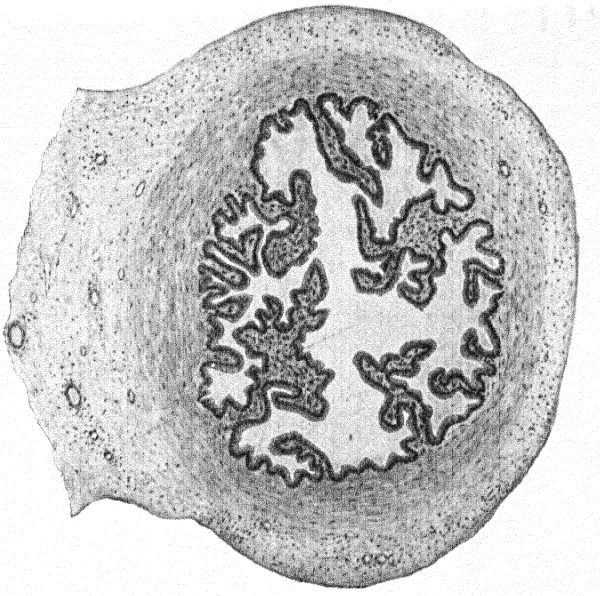


FIG. 955.—TRANSVERSE SECTION OF FALLOPIAN TUBE, SHOWING FOLDED MUCOUS MEMBRANE AND WELL-DEVELOPED INTERNAL CIRCULAR AND LESS WELL-MARKED EXTERNAL LONGITUDINAL MUSCULAR LAYERS. (F. H. A. Marshall.)

The muscular coat is strongest at the uterine end, the mucous membrane thickest near the fimbriated end. Ballantyne and Williams[1] have described a second thin layer of longitudinal fibres within the circular layer. As in the uterus, there is no sharp limitation between the muscular layer and the mucous membrane, and the larger part of the muscular layer must probably be regarded as a much thickened muscularis mucosæ.

The folds or plicæ of the mucous membrane have secondary folds upon them in the ampullary part of the tube: the deep furrows between these have sometimes been described as glands, but although true glands appear to be absent, the increase of surface which the folds represent is probably connected with the secreting function of the mucous membrane. Although the lining membrane of the tube is termed a mucous membrane, it is stated that its secretion contains no mucus [2] and even little or no protein.[3]

[1] Brit. Med. Journ. 1891. [2] Bond, Lancet, ii. 1899 (in rabbit).
[3] J. Thomson Sherlaw, Brit. Med. Journ. ii. 1908.

Blood-vessels, lymphatics and nerves.—The *arteries* are derived from the upper terminal branch of the uterine artery; there are also anastomotic branches from the internal ovarian artery. The *veins* are in communication with the uterine and ovarian veins, and form a close plexus along the line of attachment of the tube to the broad ligament. Here also the efferent *lymph-vessels* are found accompanying the blood-vessels: they pass towards lymph-glands in front of the aorta and vena cava.[1] Both blood- and lymph-vessels are distributed abundantly to the mucous membrane; the layers of the muscular coat have each a special capillary plexus.

The *nerves* are furnished from the branches which pass to the uterus and ovaries: they are distributed in large measure to the muscular coat, but also to the mucous membrane, and filaments have been traced even into the epithelium.[2]

THE UTERUS.

The uterus is composed of the *fundus*, which is the name given to the part above the entrance of the Fallopian tubes, the *body* or main part, and the *cervix* or neck, which opens at the *os uteri* into the vagina.

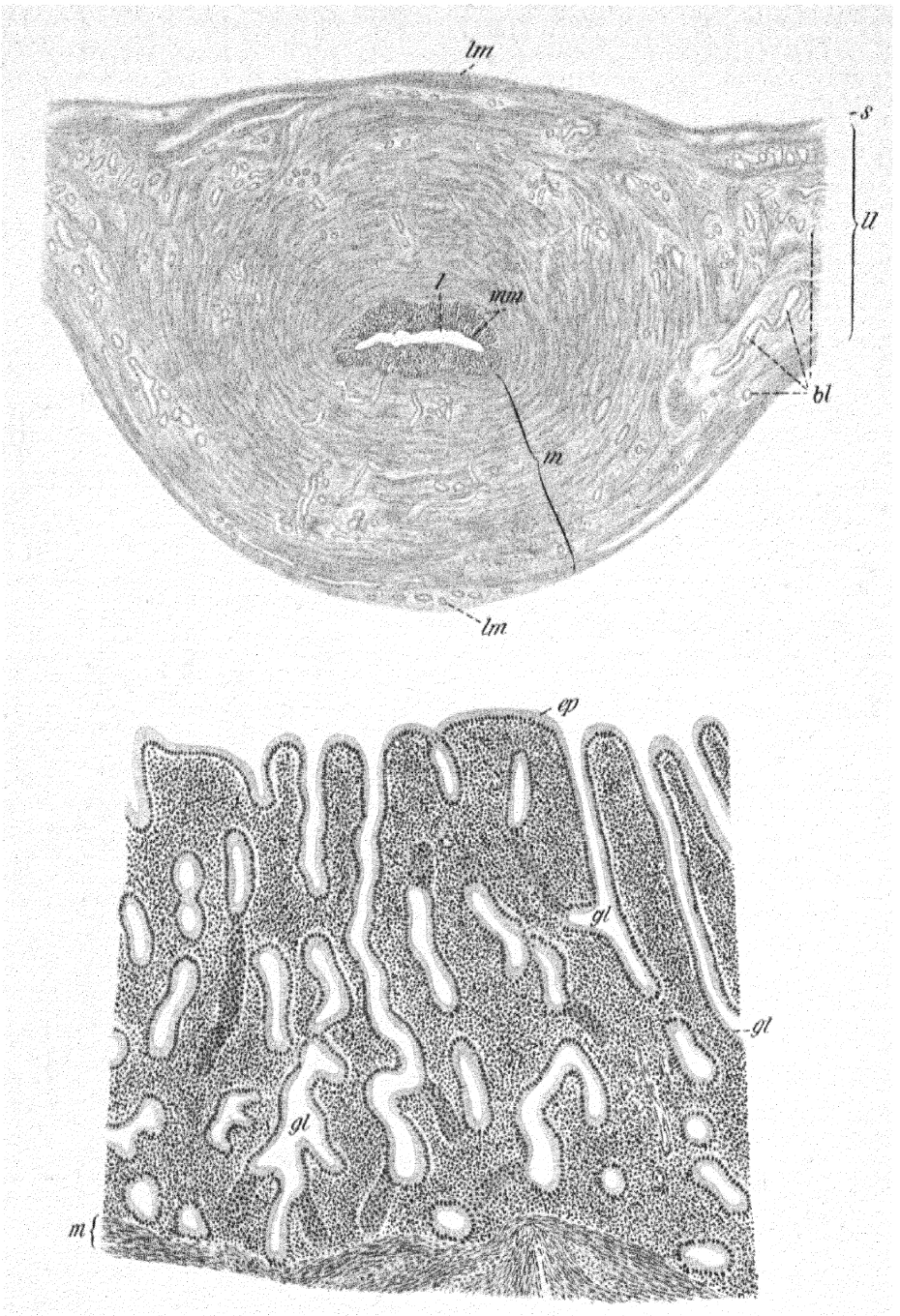
The walls of the uterus consist of an outer serous covering derived from the peritoneum, an inner mucous membrane, and an intermediate muscular layer (see upper figure of accompanying Plate).

Muscular layer.—The thick middle part of the wall of the uterus is mainly composed of plain muscular fibres of small size, 0.23 mm. in length in the unimpregnated uterus, but much longer in the gravid state (fig. 958). These fibres interlace closely; they are disposed in bundles and layers, and are intermixed with areolar tissue, containing a large number of blood-vessels and lymphatics, and some nerves. The areolar tissue is more abundant near the outer surface. The arrangement of the muscular fibres is best studied in the uterus at the full period of gestation, in which the bundles become augmented in size. They may be referred to three sets, of which the two more external correspond with the muscular coat of other hollow viscera, whereas the internal is an immensely hypertrophied *muscularis mucosæ*.

The *external layer* of the muscular coat forms a thin superficial sheet immediately beneath the peritoneum, and incomplete strata situated more deeply. A large proportion of these fibres, beginning as longitudinal bands at the cervix, arch transversely and obliquely over the fundus and adjoining part of the body of the organ, and pass on each side into the broad ligament. Some of them converge at either side towards the commencement of the round ligaments, along which they are in part prolonged to the groin; others pass off to the Fallopian tubes, while strong transverse bands from the anterior and posterior surfaces are extended into the ovarian ligaments. Other fibres run back from the cervix uteri beneath the utero-sacral folds of the peritoneum. The *inner layer* of the muscular coat, which is also thin, is composed of fibres found chiefly on the back of the uterus; these stretch over the fundus and towards the sides, running somewhat irregularly between the ramifications of the blood-vessels. The muscular coat proper seldom exceeds 6 mm. in total thickness, but it is not easy to assign its limits exactly, for there is little or no submucous areolar tissue forming a distinct coat, as in most of the hollow viscera. But the place of ramification of the blood-vessels before they pass into the mucous membrane serves to determine the boundary between the muscular layer of the mucous membrane and the muscular coat proper (J. Williams).

The *mucous membrane* of the uterus is characterised by the enormous hypertrophy of the muscular layer proper to it—the muscularis mucosæ just described; indeed this forms the greater part of the thickness of the uterine wall. The

[1] Poirier in Traité d'anatomie, 1895. [2] v. Gawronsky, Arch. f. Gynäk. xlvii. 1894.



Human uterus (Sobotta). 1. Section across the body, represented twice the natural size. 2. Section of mucous membrane, magnified 150 diameters. Haematoxylin-eosin.

s, serosa; *lm*, longitudinal muscular fibres; *m*, circular muscular fibres; *mm*, nucous membrane; *l*, lumen; *ll*, broad ligament; *bl*, blood-vessels; *ep*. epithelium; *gl*, glands.

presence of this mass of plain muscular tissue in it confers a distinct character on the outer part of the membrane, so that in sections it is differentiated from the inner part or corium. It consists of bands of fibres disposed with comparative regularity near the fundus, being arranged there in numerous concentric rings round the openings of the two Fallopian tubes, the widest circles of the two series meeting from opposite sides in the middle of the uterus. In the lower part of the body, and in the cervix, the internal fibres run more transversely. They form the so-called sphincters of the os internum and os externum. At the neck, however, there are also longitudinal fibres within the transverse.

The arrangement of the muscular fibres both of the muscular coat proper and of the muscularis mucosæ is more regular and more easily made out in the uterus of the lower mammals (below Primates), most of which possess a bi-cornuate uterus consisting of two long tubular portions uniting below before opening into the vagina. A section across one of the horns of such a uterus is represented in fig. 956, from which it will be seen that the fibres of the muscularis mucosæ (*m.m.*) run almost entirely in a transverse or circular direction, and are imperfectly separated by an areolar layer (*a.*), containing the large blood-vessels of the organ, from the inner thin layer of circular fibres of the muscular tunic proper (*c.m.*). Outside these are seen the stout bundles of the outer or longitudinal muscular layer (*l.m.*), and most externally the peritoneal or serous coat (*s.*).[1]

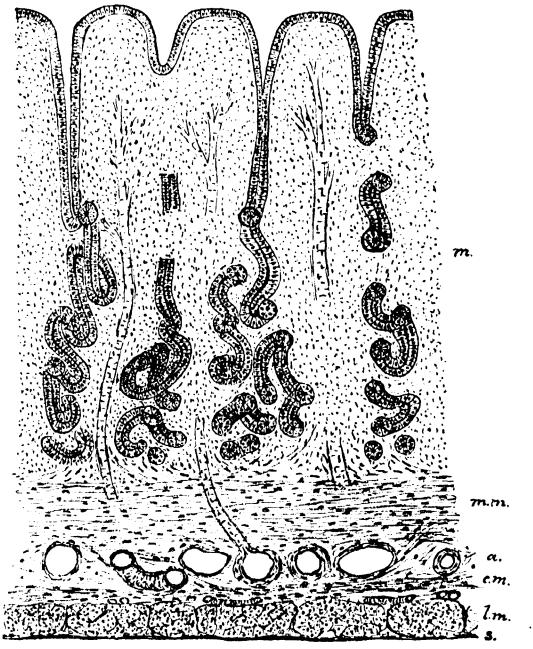


FIG. 956.—TRANSVERSE VERTICAL SECTION OF THE WALL OF ONE OF THE CORNUA UTERI OF THE RABBIT. (Schäfer.)

s, serous layer; *l.m.*, longitudinal fibres of the muscular coat; *c.m.*, circular fibres of the same; *a*, areolar tissue with large blood-vessels; *m.m.*, muscularis mucosæ; *m.*, mucosa, with coiled glands.

As regards its inner part or corium, the mucous membrane lining the cavity of the body differs greatly from that of the cervix, a distinct line of demarcation separating the two portions.

The *mucous membrane of the body* of the uterus is smooth, except during the menstrual period, and in the unimpregnated state is entirely devoid of ridges; it is of a peculiar soft spongy consistence, of a dull reddish colour, and very vascular.

Under the microscope it appears composed in great measure of small, rounded, spindle-shaped, or irregular cells imbedded in a homogeneous ground-substance, and with but few connective-tissue fibres apparent (fig. 2 of Plate). According to Leopold, however, there are numerous fibres, and they form a spongework with lymphatic spaces in the meshes. The superficial part of the corium has a rich capillary network, but blood-vessels are abundant in all parts of the thickness of the mucous membrane. The inner surface is everywhere covered by columnar ciliated epithelium, and is beset, but somewhat sparingly, with the orifices of the *uterine glands* (fig. 2 of Plate). These, which were discovered by Sharpey, are simple

[1] See on the musculature of the uterus, Sobotta, Arch. f. mikr. Anat. xxxviii. 1891. For other references W. Nagel, 'Die weibliche Geschlechtsorgane,' 1896.

tubes bounded by a basement-membrane and lined with ciliated columnar cells like those covering the inner surface. They pass usually obliquely and often with an irregular or convoluted course into the deeper part of the mucous membrane, and there terminate by blind, sometimes forked extremities, situated amongst the bundles of the muscularis mucosæ. Towards their extremities the uterine glands are often filled with cells, but in the greater part of their extent they have a distinct lumen.

The epithelium-cells are sometimes short and cubical rather than columnar.[1] Cilia are not always to be found on them. Nerve-fibres have been traced into the epithelium.

The *mucous membrane of the cervix* is much firmer and more fibrous than that of the body. Between the rugæ of the *arbor vitæ* there are numerous saccular and tubular glandular invaginations, much wider than the glands of the body of the uterus. In the lower part of the cervix (vaginal portion) the mucous membrane is beset with vascular papillæ, and the epithelium is stratified, but in the upper half or more the epithelium is columnar and ciliated like that of the body. The glands,

FIG. 957.—SECTION OF MUCOUS MEMBRANE OF HUMAN UTERUS DURING MENSTRUATION, SHOWING MASSES OF BLOOD WHICH HAS ESCAPED FROM RUPTURED CAPILLARIES INTO THE INTERGLANDULAR TISSUE, AND HAS AT ONE PLACE (*) BROKEN THROUGH THE SURFACE EPITHELIUM. (Sellheim.)

of the cervix uteri are short, with a large lumen; they are lined throughout with columnar ciliated epithelium, even where the epithelium of the surface is stratified. Besides the ordinary glands there are almost constantly to be seen the so-called *ovula Nabothi*; clear yellowish vesicles of variable size, but visible to the naked eye, embedded in the membrane. These probably arise from closed and distended gland-tubes, but their exact nature is doubtful. During pregnancy the mucous glands of the cervix secrete a considerable quantity of tenacious mucus, which effectually closes the passage into the vagina from the uterine cavity. The blood-vessels of the cervix have comparatively thick walls.

The internal surface of the os uteri is covered, like the vaginal portion, with stratified epithelium, which conceals vascular papillæ. It is destitute of glands.

Periodic structural changes in the uterus.—At each successive recurrence of *menstruation* a complete removal of the superficial part of the mucous membrane takes place by a process of softening and molecular disintegration. This

[1] Björkenheim, Anat. Hefte, xxxv. 1907.

is preceded by an extravasation of blood from the superficial vessels, and commences, along with the menstrual discharge, close to the cervix, or at the os, advancing progressively towards the fundus during the remaining days of the flow of blood (J. Williams). Previous to this change, there is a great increase in the general vascularity of the parts, and the mucous membrane becomes very much thicker (*premenstrual phase*). This begins to be evident six or seven days before the menstrual flow commences, the vessels become dilated and the glands both enlarged and elongated, as well as more coiled: they also show increased secretion. The superficial part of the mucous membrane is now marked off from the deeper part, which acquires a spongy appearance (Brouha).[1]

Stage of menstruation or destructive phase.—There are found at first small blood extravasations in the superficial layer, which increase in amount and produce subepithelial accumulations of blood (hæmatomata) (fig. 957). The epithelium of the surface becomes disintegrated and cast off; and this process of disintegration proceeds to involve the interglandular tissue and even the glands themselves. The blood which has become extravasated by rupture of the capillary vessels finds its way into the cavity of the uterus, where it becomes mixed with mucus and eventually appears at the vulva.

Some authorities hold that the destruction may be confined to the superficial layer and even to the epithelium, but there is a considerable amount of evidence in favour of a more extensive change. Probably there is a good deal of individual variation. The process of disintegration in some instances certainly reaches as far as the inner fibres of the muscularis mucosæ.

Post-menstrual phase: stage of repair.—The process of restoration of the uterine membrane, which begins even before the cessation of the menstrual flow, proceeds in the same order, from the lower end upwards to the fundus, and consists in a very rapid proliferation of the cells of the mucous membrane and of the epithelium of the glands. The whole of the destroyed epithelial structure both of the glands and of the general surface is renewed from the epithelium of those parts of the glands that have escaped disintegration. The epithelial regeneration is very rapid, and the inner surface is already covered again with epithelium very shortly after the menstrual flow has ceased, but the original thickness of the mucous membrane is not at once attained, the growth in thickness progressing gradually up to the time of the next menstruation, and with it the growth in length and the intricacy of the uterine glands. The lining membrane of the cervix does not participate in the changes referred to.

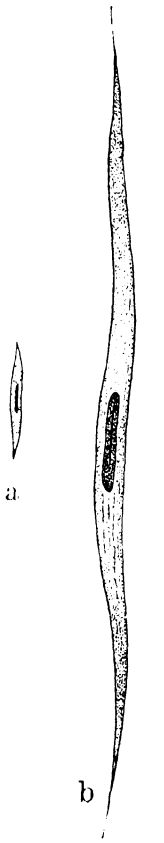


FIG. 958. — MUSCULAR FIBRES (*a*) FROM NON-PREGNANT, (*b*) FROM PREGNANT UTERUS, DRAWN TO THE SAME SCALE. (Sellheim.)

In *gestation* more extensive alterations ensue. The weight of the organ increases enormously. Its colour becomes darker, its tissue less dense and its muscular bundles more evident. A very great increase takes place in the muscular tissue, this increase being mainly the result of the enlargement of the already existing elements, the cells becoming enlarged to the extent of from seven to eleven times

[1] Liége méd. 1911 (quoted from abstract in Zentralbl. f. Anat. viii. 1911). The subject of the periodic changes which the uterus undergoes is dealt with in considerable detail by Marshall, Physiology of Reproduction, 1910, where also references to most of the literature will be found.

in length,[1] and from two to five times in breadth (Kölliker) (fig. 958). A formation of new cells is also said to occur, mainly in the innermost layers (but whether by proliferation of pre-existing cells or otherwise is not stated), and to continue until the sixth month of pregnancy, when it ceases. The round ligaments become enlarged, and their muscular structure more marked; the broad ligaments are encroached upon by the intrusion of the growing uterus between their layers. The mucous membrane and the glands of the body of the uterus at first undergo an enlargement very similar to that which precedes menstruation; they subsequently become the seat of peculiar changes, more particularly described under Development (Vol. I.). The blood-vessels and lymphatics are greatly enlarged, and the arteries become very tortuous as they ramify upon the organ. The nerves also undergo considerable increase in size.

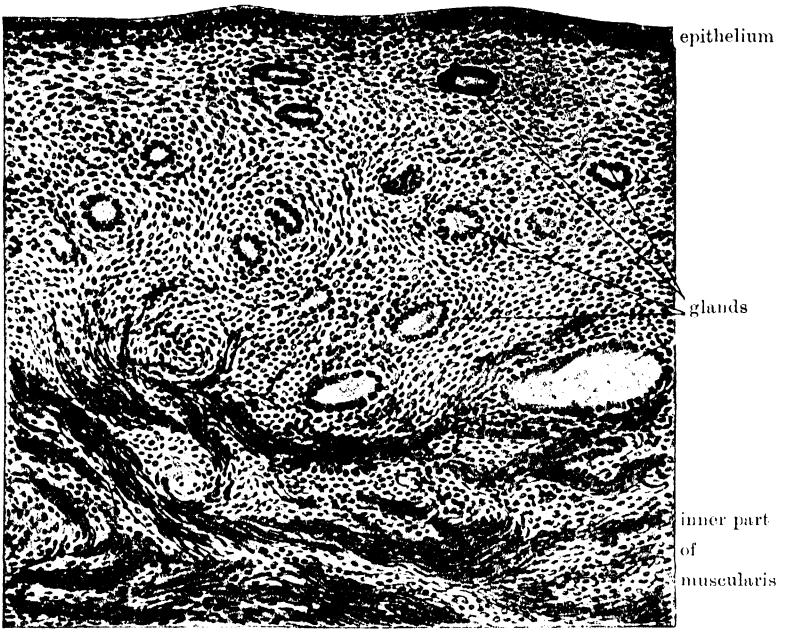


FIG. 959.—SECTION OF UTERINE MUCOUS MEMBRANE FROM A WOMAN OF SIXTY. (Sellheim.)

After parturition the uterus gradually but rapidly diminishes till it nearly regains the size and structure of the unimpregnated organ. During this change the enlarged muscular fibres undergo fatty degeneration, and are said to be subsequently absorbed, while a new set of fibre-cells is developed. After the first pregnancy, however, the organ never regains its original virginal character.

After the menopause the uterus undergoes a gradual process of atrophy (fig. 959). The mucous membrane becomes more fibrous and thinner, the glands diminish in size and tend to become obliterated and the muscular coat becomes shrunken and thinner. Sometimes there is a cystic enlargement of some of the glands.

Vessels and nerves.—The *arteries* which supply the uterus are the right and left ovarian (corresponding to the spermatic of the male) and the uterine. They are remarkable for their frequent anastomoses, and for their singularly tortuous course. After passing a short distance into the thickness of the

[1] The increase is from 40 μ – 60 μ in the virgin uterus up to 300 μ – 600 μ at the end of gestation (W. Nagel). Cf C. S. Minot, Human Embryology, 1892.

uterine wall they divide into branches which penetrate the muscular tissue of the mucous membrane, supplying it with capillaries. They then pass towards the inner portion of the membrane and open into a network of large capillaries which pervades the tissue in that situation, being especially developed near the surface and around the glands. In the cervix, however, and especially in the vaginal portion, the arteries, which in this situation possess walls of considerable thickness, after entering the mucous membrane, divide into a number of small branches which pass directly towards the surface and open into the capillary network there present; from this network loops pass into the papillæ. The *veins* correspond with the arteries; they are very large, and form plexuses of sinus-like vessels with thin walls in immediate contact with the stroma of the mucous membrane. The *lymphatics* commence, according to Leopold,[1] as cleft-like spaces in the mucous membrane; there are also well-marked lymphatic vessels extending as a plexus through the whole thickness of the membrane (Hoggan).[2] These open into plexuses of vessels in the muscularis mucosæ and muscular coat proper; and these again are in communication with valved vessels beneath and in the serous covering.

The *nerves* are derived from the inferior hypogastric plexus, the spermatic plexuses, and the third and fourth sacral nerves. They consist of both medullated and non-medullated fibres; in the lower animals small ganglia connected with the non-medullated fibres have been observed in the submucous tissue (De la Torre).

THE VAGINA.

The wall of the vagina is composed from within outwards of a mucous membrane, a muscular and a fibrous coat (fig. 960). It is thickest in front, in the vicinity of the urethra, which indeed may be said to be imbedded in it. The vagina is firmly connected by areolar tissue to the neck of the bladder, and loosely to the rectum and levatores ani muscles; at the upper end, for about a fourth part of its length, its posterior surface receives a covering from the peritoneum, which descends thus far in the form of a cul-de-sac between the vagina and the rectum. Round the tube is found a layer of loose erectile tissue most marked towards the vulva.

Externally the vagina is formed by a coat of dense areolar tissue. Beneath this its walls are composed of unstriped muscle, not distinctly separable into strata, but composed chiefly of fibres having a longitudinal direction. They are continuous above with those of the uterus.

At its lower end the vagina is embraced by striated muscular fibres, which constitute the *sphincter vaginæ*.

On the *inner surface* of the vagina, anteriorly and posteriorly, a slightly elevated ridge extends from the lower end upwards in the middle line; the two form the *columns of the vagina*, or *columnæ rugarum*. Numerous dentated transverse ridges (*rugæ*) are also observed, particularly in persons who have not borne children, running at right angles from the columns. These columns and rugæ are most evident near the entrance of the vagina and on the anterior surface; they gradually become less marked, and disappear towards the upper end.

The mucous membrane, besides the columns and rugæ, has vascular microscopic papillæ, projecting into a stratified scaly epithelium, but the papillæ are relatively low and few in number. The vagina is stated to be unprovided with mucous glands, the mucus met with in it being derived from the uterus.

Vessels and nerves.—The vagina is richly supplied with vessels and nerves. The *arteries* are derived from branches of the internal iliac, viz. the vaginal, internal, pudic, vesical, and uterine. The *veins* correspond, but they first surround the

[1] Arch. f. Gynäk. vi. 1874. [2] Journ. Anat. and Physiol. xvi. 1881.

vagina with numerous branches, and form at each side a plexus named the vaginal plexus. There is a close network of *lymphatics* in the mucous membrane, which also contains a considerable amount of lymphoid tissue, often collected into lymphoid nodules.[1] The *nerves* are derived from the hypogastric plexus of the sympathetic, and from the fourth sacral and pudic nerves of the spinal system; they are traceable to the erectile tissue, to the muscular fibres, and to the epithelium.

The **hymen** is formed by a fold of mucous membrane; it has the same structure as the mucous membrane of the vagina.

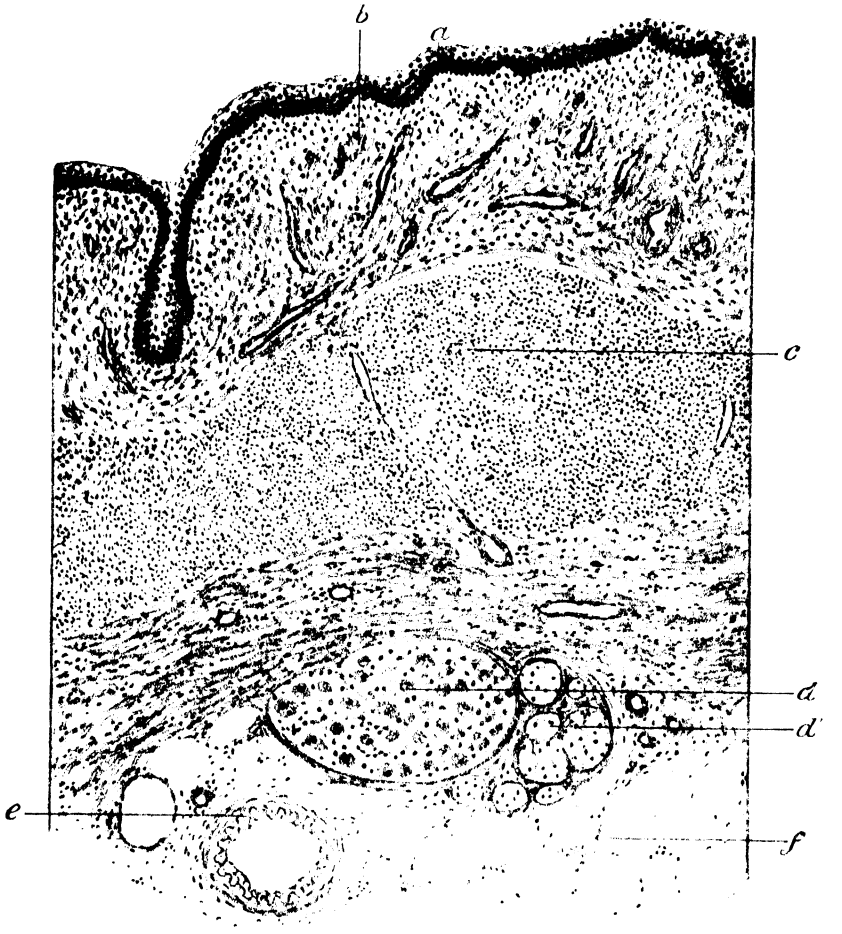


FIG. 960.—TRANSVERSE SECTION OF VAGINA OF MONKEY, LOWER PART. (F. H. A. Marshall.)

a, stratified epithelium; *b*, mucous membrane; *c*, muscular coat, the fibres cut across; *d*, a nerve-ganglion; *d'*, nerves; *e*, an artery; *f*, fat-cells.

On either side of the entrance of the vagina between the hymen and the labia minora are the orifices of the ducts of **Bartholin's glands**, which correspond to Cowper's glands in the male. The glands themselves lie on each side of the vagina near its commencement. They are reddish yellow, round or oval bodies, about half an inch long. They have the structure of tubulo-racemose mucous glands, the alveoli being lined by very long mucus-secreting cells with their nuclei near the basement-membrane of the alveolus. The duct of each gland is itself

[1] W. Krause, Handbuch der menschl. Anat. 1879.

beset with small mucous tubules, and is lined by columnar epithelium, except near its orifice, where the epithelium is stratified. The wall of the duct contains plain muscular fibres.[1]

Other much smaller glands yielding a similar mucous secretion send their ducts to open at the vestibule near the orifice of the vagina (glandulæ vestibulares minores).

The **clitoris** corresponds to the penis in the male, but is not penetrated by the urethra, and is far less developed. It has structures corresponding with the corpora cavernosa and the corpus spongiosum glandis. Its integument, provided with vascular papillæ, is likewise richly furnished with nerves, ending in end-bulbs, and in tactile and Pacinian corpuscles.

The bulb of the urethra of the male is represented in the female by two oval masses of erectile tissue, the *bulbi vestibuli*, which lie in the lateral walls of the vestibule; each is continued in front into a venous plexus which joins the erectile tissue of the glans clitoridis.

The scrotum of the male is represented in the female by the *labia majora*, which are folds of integument containing much fat and a tissue resembling the dartos in the male. Their outer surfaces are covered with hair, the inner being smooth and hairless: they contain numerous sebaceous and sweat glands. Within and between the labia majora are two much thinner integumental folds, the *labia minora*; these have the characters of mucous membrane, being moist, red and destitute of hairs.

THE URETHRA IN THE FEMALE.

The female urethra compared with that of the male is a short and wide tube. Its wall is composed of two layers, the muscular and mucous coats respectively.

The *mucous membrane* is whitish, except near the orifice; it is raised into longitudinal folds, which are not entirely obliterated by distension, especially one which is particularly marked on the lower or posterior surface of the urethra. Near the bladder the membrane is soft, with many tubular mucous glands, which may contain concrements like those of the prostate in the male. Lower down these increase in size and lie in groups between the longitudinal folds. Immediately within and around the urethral orifice are several larger and wider crypts (para-urethral ducts).

The lining membrane is covered with a stratified scaly epithelium, but near the bladder it becomes transitional. The submucous tissue contains plain muscle-fibres, arranged longitudinally near the inner and circularly near the outer part; amongst the muscle-bundles are numerous white and elastic fibres. Between the meshes of this tissue is a highly vascular structure, in which are many large veins; this is sometimes spoken of as a *corpus spongiosum urethræ*. Outside this layer are striated fibres, which do not, however, form a complete stratum; they are best developed, as a circular layer, near the bladder and near the external urethral orifice, while longitudinal fibres occur most numerously in the upper part of the posterior urethral wall. Between the layers of the triangular ligament the female urethra is embraced by the fibres of the compressor urethræ muscle.

The *blood-vessels* and *nerves* of the female urethra are very numerous, and are derived from the same sources as those of the vagina. The *lymphatics* pass into those of the bladder.

[1] See on the structure of Bartholin's glands, V. Müller, Arch. f. mikr. Anat. xxxix. 1892; Rautmann Arch. f. mikr. Anat. lxiii. 1904.

THE INTERNALLY SECRETING GLANDS.[1]

The organs which will be described under this head are the *thyroid gland* and the *parathyroids*, the *pituitary body* or *hypophysis*, the *suprarenal capsules* or *adrenals*, the *thymus*, *carotid* and *coccygeal glands*, and certain small accumulations of cells resembling in some particulars of structure the suprarenal capsules, which, from their close relationship in development with the sympathetic ganglia—in this respect resembling the medulla of the suprarenal capsules—have been termed *paraganglia* (Kohn). All these organs resemble one another in being formed of epithelial cells which have a special relationship to blood-vessels or lymphatics: none possess a duct in adult life, although the thyroid, at an early stage of development, had such a structure connecting it with the mouth, and the anterior part of the pituitary is developed in connexion with a tubular growth from the buccal ectoderm in a manner somewhat similar to the development of the externally secreting glands.

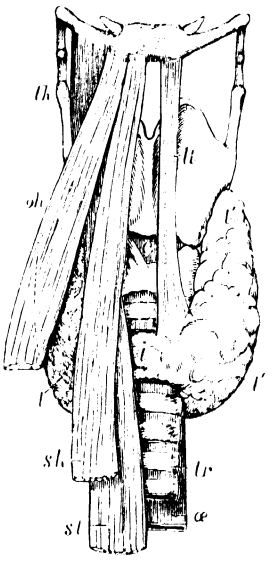


FIG. 961. SKETCH SHOWING THE FORM AND POSITION OF THE THYROID BODY. (Allen Thomson.) One half the natural size.

The larynx and surrounding parts are viewed from before; on the right side the muscles covering the thyroid body are retained, on the left side they are removed; *th*, right thyro-hyoid muscle; *oh*, omo-hyoid; *sh*, sterno-hyoid; *st*, sterno-thyroid; *c*, crico-thyroid membrane; *tr*, trachea; *œ*, œsophagus; *t*, right lobe of the thyroid body; *t'*, the left lobe; *i*, the isthmus; *li*, the fibrous or muscular band termed levator thyroideæ, which is more rarely found in the middle line or to the right side.

Although these organs are for the sake of convenience grouped together under the head of internally secreting glands, it is not certainly known with regard to the thymus, the carotid gland, and the coccygeal gland that these organs yield an active internal secretion, and indeed the same may be said regarding the cortex of the suprarenal capsules and the anterior part of the pituitary. But the thymus is so intimately related in development to the thyroid and parathyroids, and the cortex of the suprarenals so closely bound up into one organ with the medulla of these glands that it is difficult not to believe that there is some functional interrelationship between them. We are probably justified in considering them all as belonging to the group of internally secreting organs, although, with regard to some, the actual experimental proof is still lacking.

THE THYROID.

The thyroid gland lies in the neck on both sides of the larynx and upper end of the trachea (fig. 961). It consists of a right and left half or lobe, the two lobes being generally united in man by a narrow part or isthmus which crosses the front of the trachea. The gland is very abundantly supplied with blood, probably more so than any other organ in the body in proportion to its size, and is of a deep brownish-red colour during life: it is encapsuled by connective tissue, which also forms a framework of areolar and reticular tissue throughout the substance of the gland, binding together the proper glandular substance and imperfectly separating it into small lobules of irregular form and size.[2]

The thyroid takes origin partly from a median diverticulum of the pharyngeal entoderm, partly from lateral diverticula of the fourth visceral pouches (fig. 980).

[1] An extensive bibliography dealing with both structure and functions of these organs will be found in the articles 'Innere Sekretion und Drüsen ohne Ausführsgang' by Swale Vincent, in the Ergebnisse der Physiologie, 1910–11, and also in Biedl, 'Innere Secretion, ihre physiol. Grundlage, u.s.w.,' 1910.

[2] See on the reticular tissue of the gland, J. M. Flint, Amer. Journ. Anat. iv. 1904.

The gland substance consists of a large number of closed vesicles spherical or oval in shape[1] and of varying size (from ·045 mm. to 1 mm.) (fig. 962); they are lined by cubical epithelium and occupied by glairy fluid, which exudes from the

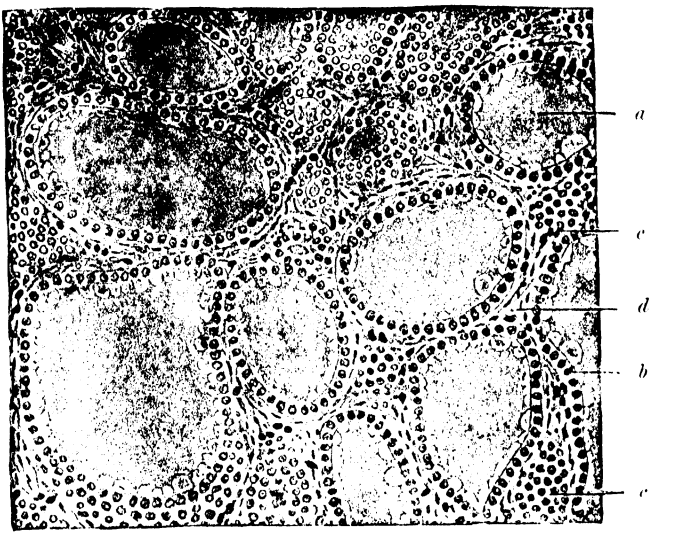


FIG. 962.—SECTION OF HUMAN THYROID. (Szymonowicz.) Magnified about 180 diameters.

a, vesicle occupied by colloid, which has partly shrunk away from the epithelium; *b*, epithelium of a large vesicle; *c*, *c*, epithelium of vesicles which are cut tangentially; *d*, interstitial connective tissue.

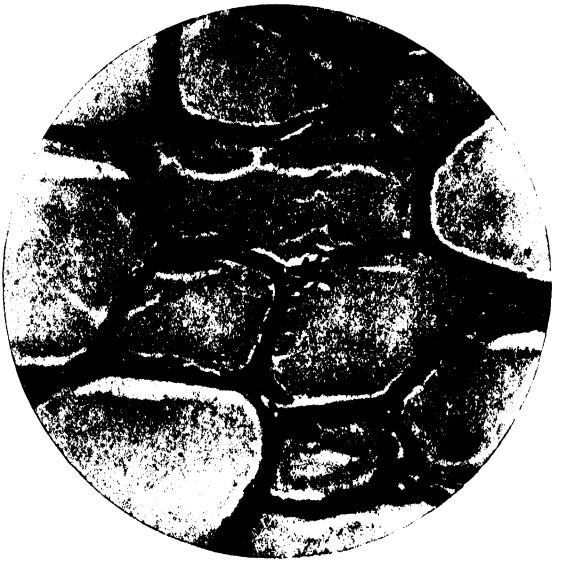


FIG. 963.—PHOTOGRAPH OF A SECTION OF THE THYROID GLAND OF A WILD RAT. (Chalmers Watson.) Magnified 250 diameters.

cut surface and is known as 'colloid.' The most important organic constituent of this appears to be combined with iodine, forming a substance known as *iodo-*

[1] Streiff (Arch. f. mikr. Anat. xlviii. 1897) found the vesicles sometimes branched, even in the adult condition.

thyrin.[1] The colloid is coagulated by most fixing reagents, and may then be stained with hæmatoxylin and other basic dyes. Under some circumstances it is not coagulated into a gelatinoid mass, but shows a precipitate after fixation. The vesicles appear to have no basement-membrane (Baber)[2]; the cells, therefore, are in close relationship with the reticular connective tissue of the gland, and the capillary blood-vessels, which are extremely numerous, and the lymphatics come in almost direct contact with the cells. The colloid may sometimes be detected in the spaces of the reticular tissue and in the lymph-vessels: it appears to pass into them from the vesicles by exuding between the lining epithelium-cells.[3]

Both the cells and the contents of the vesicles vary considerably in appearance in glands from different individuals, the variation depending in part upon the general state of nutrition of the animal, and thus indirectly upon the diet,[4] in part upon topographical and climatic conditions, the effects of which require further investigation.[5] This is well illustrated in the photographs of thyroid of rat

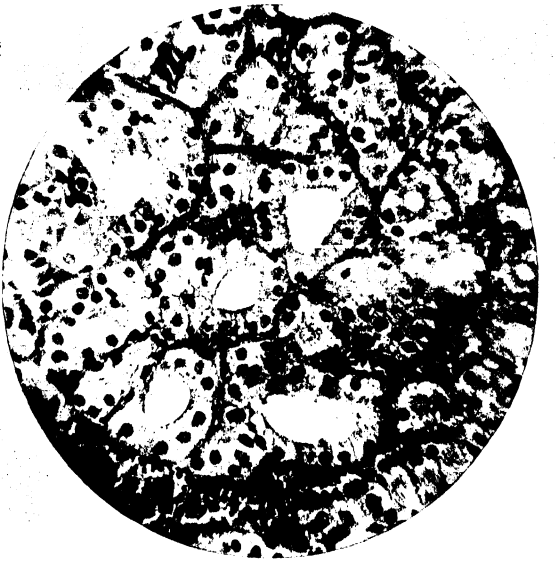


FIG. 964.—PHOTOGRAPH OF A SECTION OF THE THYROID GLAND OF A WILD RAT. (Chalmers Watson.) Magnified 250 diameters

shown in fig. 963 and fig. 964. In fig. 963 the gland-vesicles are shown distended with abundance of colloid material and the cells are relatively flattened. In fig. 964 the cells are more cubical or even columnar, the vesicles are less distended, and there is little stainable matter in their contents. In both these cases the animals appeared perfectly healthy, so that it is not easy to say which appearance is to be accepted as normal. Between these extremes all intermediate conditions are met with in different specimens. Besides such variations, which are common to all the vesicles of a gland, the cells may show individual differences in their staining capacity, and in the number and nature of the granules in their protoplasm.[6] That the granules often

[1] See on the iodine-containing material of the thyroid and its relation to the structure and functions of the gland, Marine and Williams and Marine and Lenhart, Arch. f. Int. Med. 1908 and 1909; Reid Hunt, Journ. Amer. Med. Assoc. xlix. 1907; Reid Hunt and Seidell, Bull. No. 47 of U.S. Public Health, Marine Hospital Service, Hygiene Laboratory, 1908.

[2] Phil. Trans. 1881.

[3] E. Schmid, Arch. f. mikr. Anat. xlvii. 1896.

[4] Chalmers Watson, Quarterly Journal of Experimental Physiology, ii. 1909.

[5] Cf. D. Marine, Cleveland Med. Journ. 1907.

[6] G. Galeotti, Arch. f. mikr. Anat. xlviii. 1897. Cf. also Langendorff, Arch. f. Physiol. 1889, and Hürthle, Pflüger's Archiv, lvi. 1894. The changes in the cells as the result of increased activity are also dealt with by W. S. Halstead, Johns Hopkins Hosp. Rep. i. 1891

seen in them are connected with the secretory activity of the cell is probable, but observations are still lacking regarding the exact nature of the secretory appearances.

The secretion of the thyroid is essential to health. If, in man, the gland be removed by the knife or destroyed by disease, or if it be congenitally absent or atrophied, a condition of myxœdema or of cretinism may result,[1] which can only be ameliorated by administering thyroid substance or extract.[2]

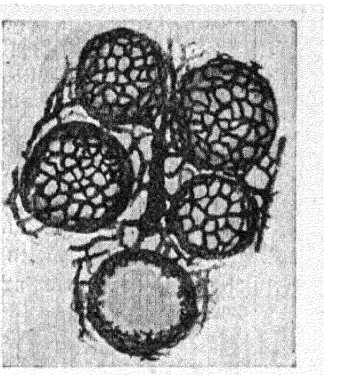


FIG. 965.—THYROID OF DOG, INJECTED. (Schäfer.) Photograph.

Besides the characteristic yellow glairy fluid, the vesicles may also contain detached epithelium-cells, white blood-corpuscles, which seem to have migrated into the cavities, and red blood-corpuscles in various stages of disintegration and decolorisation; but whether these last are accidental or normal constituents is uncertain.

In the interstitial connective tissue of the gland occur a number of cells similar to the plasma-cells of Waldeyer ('parenchyma-cells,' Baber).

Occasionally small bodies detached from the main mass of the thyroid are found, having all the structure of the normal thyroid (*accessory thyroids*).

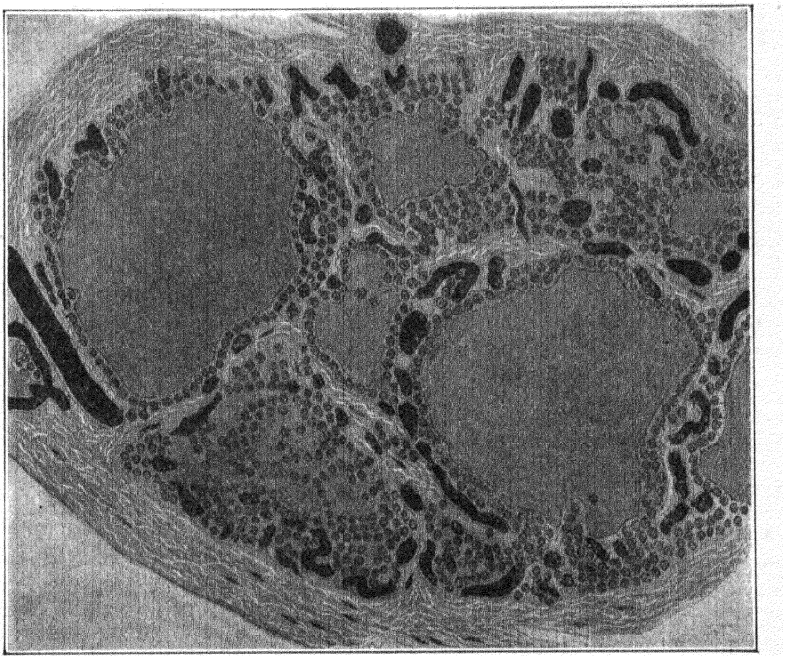


FIG. 966.—SECTION OF HUMAN THYROID, INJECTED. (Major.) Highly magnified. The close relationship of the capillaries to the epithelium of the vesicle is well shown.

One of the most frequent pathological changes to which the thyroid body is subject consists in a great accumulation of colloid substance within its vesicles: in certain forms of goitre it distends them to an enormous degree. Goître is especially common in certain regions, *e.g.* Derbyshire,

[1] V. Horsley, Proc. Roy. Soc. xxxviii. 1884, xl. 1886; Murray, Diseases of the Thyroid Gland, 1900; Edmunds, Journ. Pathol. iii. v. vi. vii., and The Pathology and Diseases of the Thyroid Gland, 1901.

[2] Myxœdema does not necessarily occur as a result of thyroid removal in animals, although it seems to be a constant feature of thyroid atrophy in man. See Munk, Virch. Arch. cl. 1897; Kishi, *ibid.* clxxvi. 1904; Vincent and Jolly, Journ. Physiol. xxxii. 1905 and xxxiv. 1906; Halpenny and Gunn, Quart. Journ. Exp. Physiol. iv. 1911

some of the Swiss valleys and the region of the great lakes of North America. The affection in these districts is not confined to man, but extends to many of the lower animals.

In the fœtus, and during early infancy, the thyroid is relatively larger than in after-life; its proportion to the weight of the body in the new-born infant being that of 1 to 240 or 400, whilst at the end of three weeks it becomes only 1 to 1160, and in the adult is 1 to 1800 (Krause). In advanced life the thyroid body is liable to become indurated; it also frequently contains earthy deposit and its vesicles may attain a large size.

Vessels and nerves.—The *arteries* of the thyroid body are the superior and inferior thyroids of each side, to which is sometimes added a fifth vessel, the thyroidea ima. The arteries are remarkable for their large relative size, and for their frequent and large anastomoses; they terminate in a capillary network upon the outside of the vesicles (figs. 965, 966), each of which has an arteriole and venule.[1] The capillaries are in close contact with the epithelium and may even project between the epithelium-cells. The *veins*, which are also large, ultimately form plexuses on the surface, from which a superior, middle, and inferior thyroid vein are formed on each side. The superior and middle thyroid veins open into the internal jugular; the inferior veins issue from a plexus formed in front of the trachea, and open into the innominate veins. The *lymphatics* of the thyroid body form numerous and large anastomosing trunks, both at the surface of the organ and throughout its substance; they originate, according to the observations of Frey, in the connective tissue which unites the gland-vesicles, with the cavity of which they appear not to be in communication. According to Matsunaga[2] they originate between the epithelium-cells. By using intermittent pressure, Hürthle succeeded in causing injection-material to pass into the vesicles from the lymph-paths.

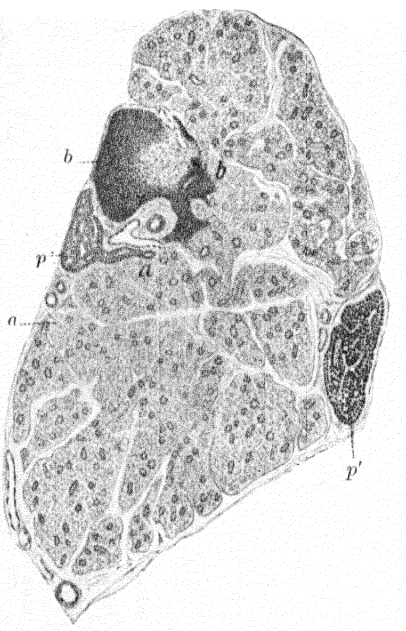


FIG. 967.—TRANSVERSE SECTION OF THE LEFT LOBE OF THE THYROID OF A TWO-MONTHS KITTEN. (Kohn.) Magnified 20 diameters.

a, thyroid tissue; *b*, *b*, thymus tissue; *p*, *p'*, inner and outer parathyroids.

The *nerves* are derived from the middle and inferior cervical ganglia of the sympathetic. They accompany the blood-vessels. According to Andersson there are no ganglion-cells in their course. Their terminal branches extend close to the base of the epithelium-cells, between which they, in all probability, penetrate.[3]

PARATHYROIDS.

Under the name of parathyroid glandules Sandström[4] described (in 1880) a pair of small glandular masses on each side, usually lying in close proximity to the lateral lobes of the thyroid body (fig. 967, *p*, *p'*), sometimes deeply imbedded in the substance of the thyroid, and constant in occurrence in man and other mammals. They vary in size from 3 mm. to 15 mm. in diameter, being on the average about 6 mm. long and 3 to 4 mm. broad. Their weight varies from ·01 gramme to ·1 gramme.[5]

[1] R. H. Major, Amer. Journ. Anat. ix. 1909. [2] Arch. f. Anat. 1909.
[3] O. Andersson, Biol. Föreningens Förhandl. iv. 1891–2; H. J. Berkley, Johns Hopkins Hosp. Rep. v. 1894; Sacerdotti, Atti d. r. accad. d. sci. d. Torino, xxix. 1893.
[4] Läkaref. Förhandl. xv. 1880. [5] Welsh, Journ. Anat. and Physiol. xxxii. 1898.

They are usually flattened, and their colour is brown, somewhat like that of the thyroid itself, but rather more yellow. In structure, however, they differ from the thyroid proper, being composed not of hollow vesicles, but of solid masses of epithelium-like cells (which sometimes appear in sections as if arranged in anastomosing columns) with numerous convoluted blood-vessels between them (fig. 968). Connected with the cell-masses there are frequently lymph-follicles. They differ completely in structure from the normal thyroid and are not therefore to be confounded with the accessory thyroids previously mentioned. These bodies were undoubtedly noticed by some of the older authors (Remak, Virchow, and others), but their importance was not recognised nor were they systematically treated of. Soon after the appearance of Sandström's account, their structure was indepen-

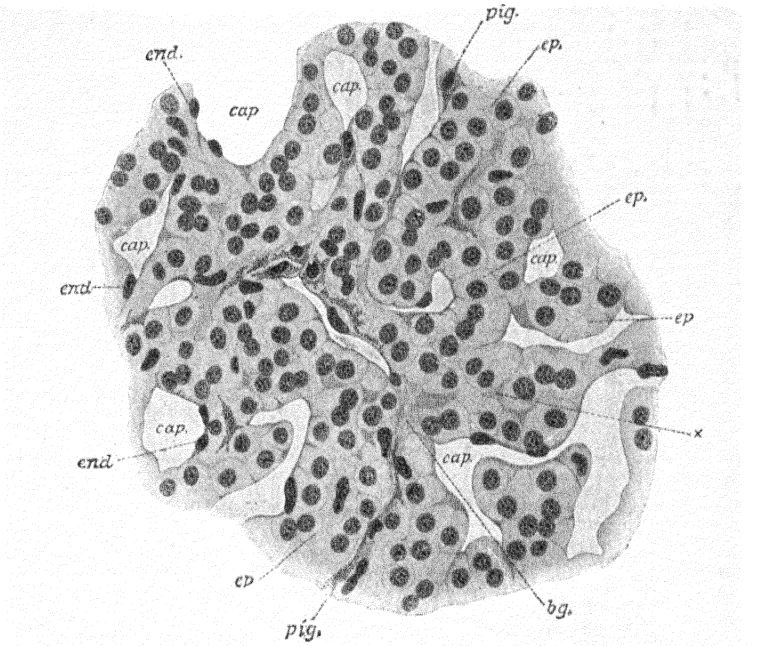


FIG. 968.—SECTION OF PARATHYROID. (Kohn.)
ep, secreting epithelium; *pig.*, cells containing pigment; *cap.*, sinus-like capillaries; *end.*, endothelium-cells.

dently described by Baber (1881); of late years many observers have directed their attention to these bodies.[1]

Kohn,[2] who has made a careful investigation of their structure and their relations to the main part of the thyroid, states that in mammals one parathyroid ('outer epithelial body') is constantly met with on the outer surface of each lateral lobe of the thyroid and another ('inner epithelial body') on the inner surface of each lateral lobe (see fig. 967, *p*, *p'*). Associated in position with these bodies, at least in some animals, is a small mass of 'adenoid' tissue, which has a structure characteristic of thymus-tissue, including the well-known epithelial nests (concentric corpuscles); this tends to blend insensibly with the neighbouring interstitial tissue of the thyroid (fig. 967, *b*). According to Prenant,[3] the tissue of the parathyroids is similar in general structure and appearance to that of the carotid

[1] Welsh, *op. cit.*; Schaper, Arch. f. mikr. Anat. xlvi. 1895; Schreiber, Arch. f. mikr. Anat. lii. 1898; Kürsteiner, Anat. Hefte, xi. 1899; Zuckerkandl, *ibid.* xix. 1902; Rulison, Anat. Record, iii. 1909; Bérard and Alamartine, C. r. soc. biol. 1909.
[2] Arch. f. mikr. Anat. xliv. 1895, and xlviii. 1897.
[3] La Cellule, x. 1894.

glands, and does not represent undeveloped thyroid-tissue. The parathyroids take origin from the third and fourth visceral pouches of the embryo (fig. 979), from which also the thymus and the lateral rudiments of the thyroid are derived. When first developed they resemble embryonic thymus rather than thyroid tissue (see Vol. I., p. 172, and fig. 216).

FIG. 969.—NORMAL THYROID TISSUE OF CAT. (Vincent and Jolly.)

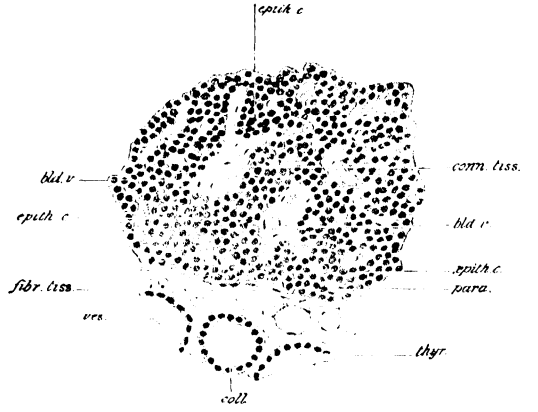


FIG. 970.—NORMAL PARATHYROID TISSUE OF CAT. (Vincent and Jolly.)

A small portion of thyroid, showing one complete vesicle and portions of two others, is included in the figure.

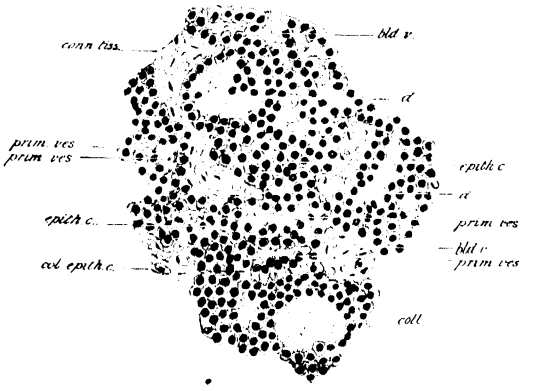


FIG. 971.—PARATHYROID OF CAT AFTER PREVIOUS REMOVAL OF THYROID. (Vincent and Jolly.)

A tendency to formation of vesicles containing colloid is observable.

Structure.—The parathyroids are composed of small masses of epithelium-like cells, not very unlike the epithelium-cells of the thyroid, arranged in intercommunicating trabeculæ with strands of highly vascular connective tissue between the trabeculæ. According to Welsh[1] the cells are of two kinds; but these may represent two functional conditions of the same kind of cell. Rulison[2] also describes two kinds of cells in the human parathyroid: the one kind clear, the other kind less numerous, somewhat larger and having oxyphil granules in their cytoplasm.[3] According to Rulison the capillaries of the parathyroids have the character of sinusoids. Sometimes, but rarely, the cells seem to be set around a spherical space, and thus to simulate thyroid vesicles, but normally the structural appearances are quite different from those of the thyroid; nor is there in the parathyroids a tendency to the accumulation of colloid. But Gley,[4] and Vincent and Jolly[5] found in the cat that the parathyroid tissue may develop vesicles indistinguishable from those of the thyroid if the whole of the thyroid have been removed, and only parathyroids left (figs. 969 to 972).

This result has been also obtained in the dog by Halpenny

[1] *Op. cit.* [2] *Op. cit.*

[3] See also on secretion-granules in parathyroid-cells, D. Forsyth, Brit. Med. Journ. 1907; Engel, Intern. Monatschr. f. Anat. u. Physiol. xxvi. 1909; Weber, C. r. soc. biol. 1909. [4] C. r. soc. de biol. 1893.

[5] Journ. Physiol. xxxii. 1904. See also D. Forsyth, Brit. Med. Journ. ii. 1907; and Journ. Anat. and Physiol. xlii. 1908; Getzowa, Virch. Arch. clxxxviii. 1907; and Alagna, Anat. Anz. xxxiii. 1908.

and Thompson.[1] Edmunds,[2] on the other hand, was unable to find such development into thyroid tissue, and regards the parathyroids as entirely independent in structure, as they appear to be in function. Schreiber found that in man, although they usually appear to have a structure unlike that of the thyroid, they may with advancing age develop vesicles containing a colloid-like material. Schaper has also described such vesicles in the parathyroids.

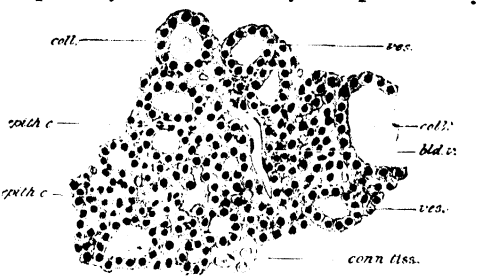


FIG. 972.—PARATHYROID OF CAT, SOME TIME AFTER REMOVAL OF THYROID. (Vincent and Jolly.)

Characteristic colloid-containing vesicles are now evident in the parathyroid.

The parathyroids are even more essential to life in most animals than the thyroid itself. If they are removed, severe nervous symptoms, known as 'tetany,' result; these generally have a speedily fatal termination. This 'tetany' is most common in carnivora and in the young of herbivora[3]: that it is not obtained always has been

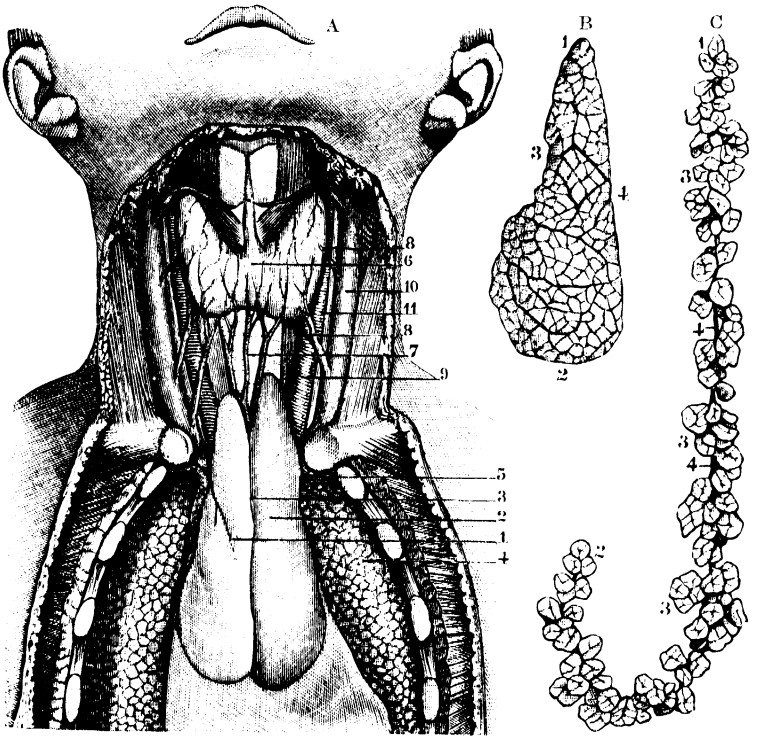


FIG. 973.—THE THYROID AND THYMUS IN A CHILD OF SIX MONTHS. (Sappey.)

A. Situation, form and relations of the glands. 1, right lobe, 2, left lobe, 3, median furrow of thymus; 4, lung, somewhat everted; 5, internal mammary vein; 6, thyroid; 7, inferior, 8, middle thyroid veins; 9, common carotid artery; 10, internal jugular vein; 11, vagus nerve. B. Right lobe of thymus after removal of its envelope; 1, its apex; 2, its base; 3, thin outer border; 4, thick inner border. C. The gland unravelled, showing the lobules, 3, grouped around a central cord; 4, the central cord or strand of connective tissue, connecting the lobules.

ascribed to one or more of the parathyroids being sometimes less closely associated with the thyroid, and only with difficulty found and removed: such dislocated parathyroids are

[1] Anat. Anz. xxxiv. 1909. For a detailed account of the anatomical relations of the thyroid and parathyroid throughout the vertebrate series see F. D. Thompson, Phil. Trans. B. cci. 1910.

[2] Journ. Path. and Bact. v. 1898, and xiv. 1910.

[3] S. Simpson, Proc. Soc. Exp. Biol. ix. 1911 (in young lambs).

apt to be left behind, even when the thyroid itself and all the tissue that surrounds it have been cut away.[1] Tetany has been observed in man as the result of parathyroidectomy: the implantation of (human) parathyroid appears to be the only permanently efficacious remedy,[2] although the symptoms may be temporarily relieved by extract of pituitary or of parathyroid and by certain salts.[3]

THE THYMUS GLAND.

The thymus is composed of two lateral lobes; sometimes united by a median isthmus (fig. 973). It is invested by a thin capsule of areolar tissue, which sends partitions into the gland: on its outer surface the capsule is covered by a layer of flattened cells. Each lobe consists of numerous polyhedral *primary lobules*, connected by a more delicate intervening areolar tissue. These primary lobules are made up of a number of *secondary* or *ultimate lobules* (also termed *follicles*) (fig. 974), one to two millimetres in diameter. Each of these ultimate lobules is composed of a central part or *medulla*, and an external part or *cortex*. The cortex is in many respects similar in structure to that of a lymph-gland, being subdivided by inward prolongations of the connective tissue investing the secondary lobule, but in man these partitions do not extend beyond the cortex. The cortex contains a fine

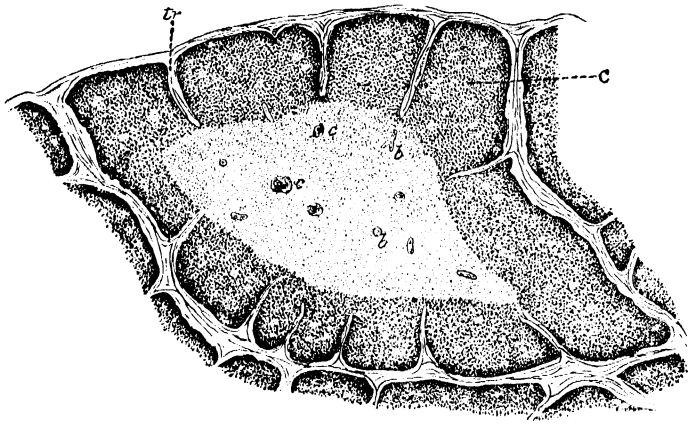


FIG. 974.—SECTION OF A SECONDARY LOBULE OF THE THYMUS OF A CHILD. (Schäfer.)
c, cortex of the lobule partly separated into nodules by the trabeculæ, *tr*; *b b*, blood-vessels; and *c*, *c*, concentric corpuscles in the medulla.

reticulum, the meshes being filled with lymphoid cells (*lymphocytes*, *thymus corpuscles*). In some animals the subdivision of the cortex is complete and extends to the medulla.

The medulla is surrounded by cortex, but comes to the exterior of the lobule here and there, where it is joined to the medulla of adjacent lobules (fig. 982): it is usually at these points that the blood-vessels enter the medulla. The reticulum of the medulla is coarser than that of the cortex; it contains here and there nests of cells which have a concentric structure, and are known as the *concentric corpuscles of Hassall*. They vary in size from 0.025 mm. to three times that diameter, or more; the larger ones (compound corpuscles) often contain smaller ones in their interior (figs. 975, 976).

[1] In some animals (*e.g.* rat, rabbit) parathyroids may be found imbedded in the thymus (Erdheim, Mitth. a. d. Grenzgebieten d. Med. u. Chir. xvi. 1906; Pipere, Arch. ital. de biol. xlix. 1908).
[2] For a case of this kind see W. H. Brown, Annals of Surgery, liii. 1911.
[3] Macallum and Voegtlin, Journ. Exp. Med. xi. 1909 (calcium, strontium); Ott, 'The Parathyroid Glandules,' Phila. 1909; Joseph and Meltzer, Journ. Pharm. and Exp. Ther. ii. 1911 (sodium chloride). See further on the effect of parathyroid extirpation Halsted, Amer. Journ. Med. Sci. cxxxiv. 1907; Thompson, Leighton, and Swarts, Journ. Med. Research, xxi. 1909; Glaserfeld, Berlin klin. Wochenschr. Jan. 1909; Carlson and Jacobson, Amer. Journ. Physiol. xxviii. 1911.

Each nest is composed of an envelope of keratinised epithelium-like cells enclosing a central mass, formed of one or more granular cells, which may have undergone degeneration. Cells like those in the centre of the nest are also found, unenclosed, in the retiform tissue of the follicle, and occasionally attain a large size. The amount

FIG. 975.—PART OF THE MEDULLA OF A THYMUS GLAND SHOWING THE RETICULUM, THE LYMPHOID CELLS OR THYMUS CORPUSCLES AND TWO CONCENTRIC CORPUSCLES. (Cadiat.)

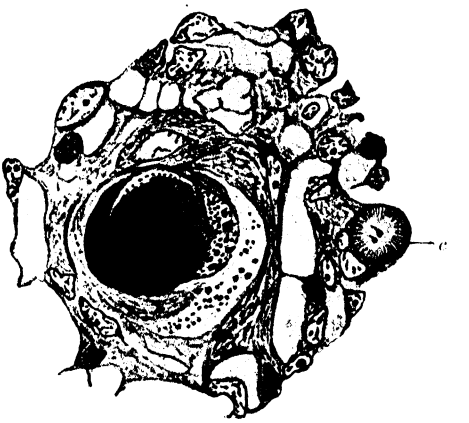


FIG. 976.—A CONCENTRIC CORPUSCLE OF THYMUS OF ADULT DOG, WITH PART OF THE ADJOINING RETICULUM. (Hammar.)
c, a small ciliated cyst.

of the Hassall corpuscles does not necessarily remain constant in the same thymus. Wallis found the total volume of Hassall corpuscles to increase after birth.[1]

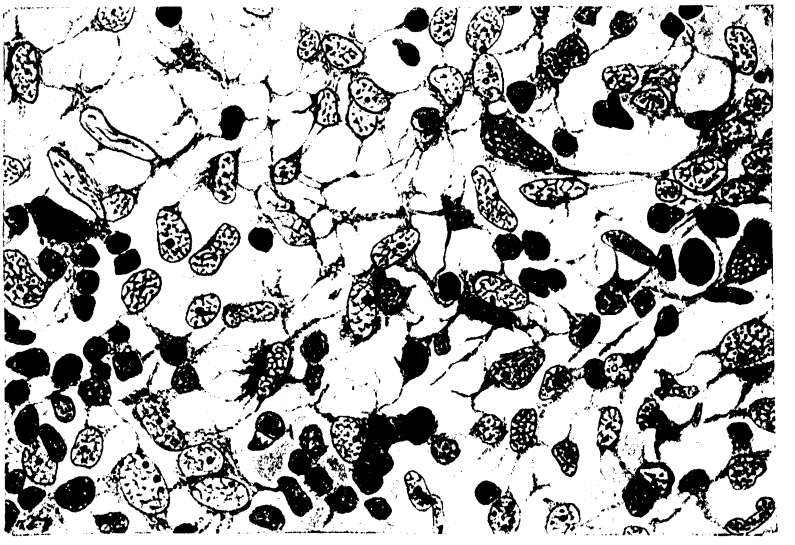


FIG. 977.—SECTION OF MEDULLA OF THYMUS OF HUMAN FŒTUS, 70 MM. IN LENGTH, SHOWING BRANCHED CELLS OF RETICULUM, WITH A FEW LYMPHOCYTES IN ITS MESHES. (Hammar.)

There is evidence of mitotic division of the thymus leucocytes, but there are no distinct *germ-centres* in the lymphoid tissue such as occur in the lymph-glands and spleen.

The reticulum of the thymus (figs. 977 to 979) differs from that of the lymph-glands in being essentially formed of a syncytium of branched cells. These are not mesodermic but entodermic, being formed from proliferated cells of the epithelial

[1] Arch. f. mikr. Anat. lxiii. 1904.

tube (fig. 981), which grows on each side from the third visceral pouches of the embryo (fig. 980, *th*) and furnishes the first rudiments of the gland.[1] They therefore have a common origin with the Hassall corpuscles. The cells of the reticulum are large and clear in the medulla, and in places are arranged in close contact

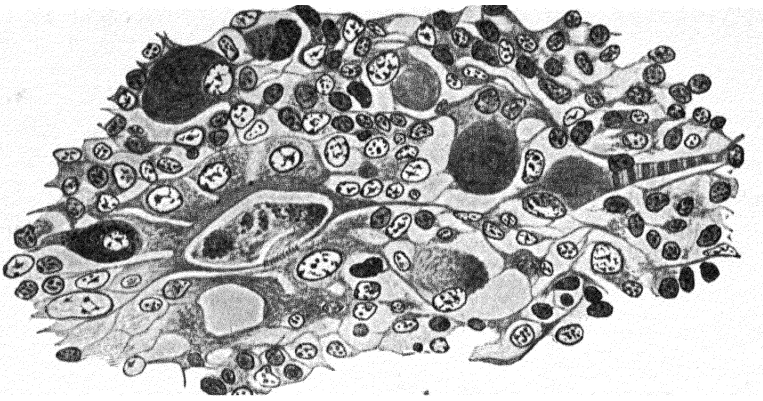


FIG. 978.—MEDULLA OF THYMUS OF FOWL. (Hammar.)

On the right is a cell which is partly transformed into striated muscle. Towards the left is a vesicle containing débris; one of the cells bounding it is ciliated. Degenerated epithelium-cells like those of the Hassall corpuscles are scattered about.

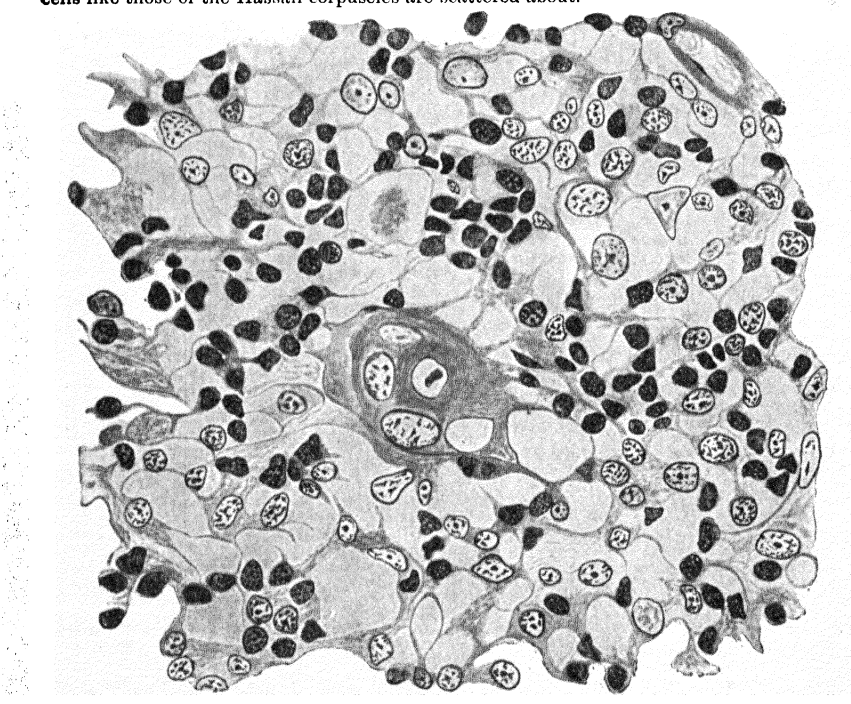


FIG. 979.—MEDULLA OF THYMUS OF RABBIT. (Hammar.)

A multinucleated giant-cell is seen in the reticulum. The small darkly stained bodies are the nuclei of lymphocytes.

[1] The portions of thymus-tissue which occur in connexion with the thyroid (see p. 673) are also developed from the third pouch. It is possible that a part of the thymus may be derived from the fourth pouch. According to A. Zottermann the source of the thymus is different in different animals, in some being purely entodermic (man), in others purely ectodermic (mole), and in others of mixed origin (pig) (Anat. Anz. xxxviii. 1911).

with one another, like epithelium-cells. Lymphocytes are much less numerous in the medulla than in the cortex.

In some animals isolated portions of striated muscle are developed in the medulla[1] (fig. 978) and[1] occasionally vesicles lined by ciliated cells occur (fig. 976, *c*; fig. 978). The presence of giant-cells like those in bone-marrow has also been noted (fig. 979).[2] These are all said to be formed from reticulum-cells (Hammar).

The concentric corpuscles are also derived from the original epithelial tube which forms the basis of the developing thymus (see Vol. I., Pt. I., pp. 169 to 172). According to some authorities[3] the lymphoid cells are also of epithelial (*i.e.* entodermic) origin, and are not derived, as has usually been believed, from the surrounding mesodermic tissue. But this is not corroborated by the researches of Hammar, who finds that the first lymphocytes are brought to the developing gland, and are not originally formed there.[4]

Besides lymphocytes, the lobules contain a certain number of granular oxyphil leucocytes and polymorph leucocytes.

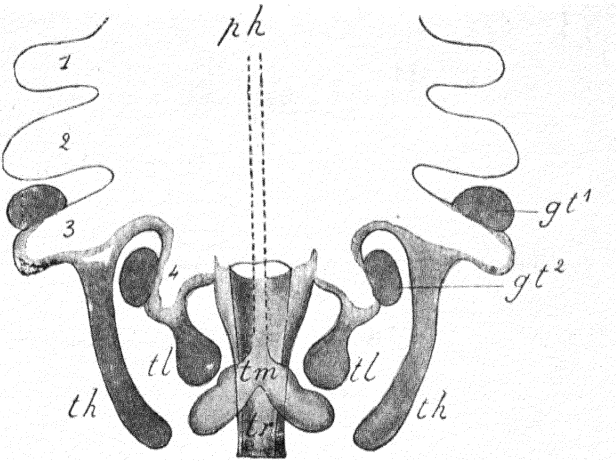


FIG. 980.—ORIGIN OF THYMUS AND THYROID FROM THE VISCERAL POUCHES OF THE EMBRYO. (From Prenant, Bouin, and Maillard.)

1, 2, 3, 4, visceral pouches; *ph*, pharynx; *tr*, trachea; *tm*, median thyroid sprout; *tl*, *tl*, lateral thyroid sprouts; *th*, *th*, thymus; gt^1, gt^2, parathyroids.

Small portions of thymus tissue are constantly found in association with the thyroid and parathyroids (Kohn). These may consist of both cortical tissue and medulla, and exhibit concentric corpuscles. They are developed from the fourth branchial cleft. Nucleated red blood-corpuscles (erythroblasts) like those met with in bone-marrow may occur in the thymus (Schaffer).

The retrogressive development of the thymus gland is accompanied by an increase in the interstitial connective tissue, which also invades the lobules. In this

[1] Pensa, Boll. Soc. Med. Chir. d. Pavia, 1902–4; Hammar, Anat. Anz. xxvii. 1905; R. Weissenberg, Arch. f. mikr. Anat. lxx. 1907.

[2] Watney, Phil. Trans. clxxiii. 1883.

[3] Stöhr, Würzburg Sitzungsb. 1905; Anat. Hefte, xxxi. 1906; *ibid.* xli. 1910; Pappenheimer, Journ. Med. Research, xxii. 1910. E. T. Bell (Amer. Journ. Anat. v. 1906), who studied the development in the pig-embryo, also concludes that the lymphocytes are of epithelial origin. He finds that the Hassall corpuscles develop from parts of the syncytium of branching entoderm cells which form the reticulum. At an early stage colloidal matter may be found in the cells of the Hassall corpuscles.

[4] Hammar, Anat. Anz. xxvii. 1905; Arch. f. Anat. xxix. 1907. See also T. H. Bryce, Journ. Anat. and Physiol. xl. 1906, and Stöhr, Anat. Hefte, xxxi. 1906. Compare Gulland, Lab. Rep. Roy. Coll. Phys Edin. iii. 1891; and Maximow, Arch. f. mikr. Anat. lxxiv. 1909. Hammar has shown that like lymphocytes the thymus corpuscles are easily destroyed by *x*-rays (Arch. f. Anat. 1907. See also H. Rudberg, *ibid.* (Supplement volume)).

tissue plasma-cells become accumulated, and these, at least in the interstitial tissue, appear to be eventually transformed into fat-cells, the normal structure of the thymus becoming gradually, but never completely, obliterated. For it has been shown by Waldeyer, and more recently by Hammar,[1] and by Söderlund and Backman,[2] that even in advanced age not only can the original shape of the thymus be distinctly made out, but that in addition there are constantly to be found traces of its original structure in the form of small masses of thymus-corpuscles and a reticulum of branched cells and even concentric corpuscles. No definite age can be given for the occurrence of involution of the thymus, although it usually begins to atrophy at puberty. It may, however, persist long past middle age and show normal structure. Its involution is much delayed by castration. Conversely its

FIG. 981. — DEVELOPING THYMUS OF LATER EMBRYO. (From Prenant, Bouin, and Maillard.)

The organ is now in the form of a branched epithelial tube, the distal end being solid.

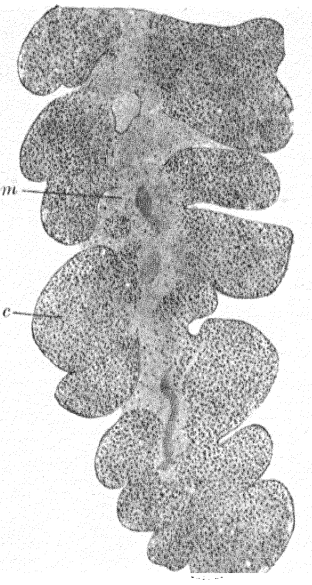


FIG. 982.—MORE ADVANCED STAGE OF DEVELOPMENT OF THYMUS. (From Prenant, Bouin, and Maillard.)

The epithelial tube has become enlarged and thickened and its cavity is obliterated. The distinction into cortex (*c*) and medulla (*m*) is apparent. The medulla comes to the surface here and there.

removal in young animals accelerates sexual maturation at any rate in the male sex, although the general growth of the body is not influenced.[3]

The thymus is an organ the size of which is easily influenced by the nutritive conditions of the body, wasting rapidly in inanition and increasing in size with abundance of nourishment.[4]

Vessels and nerves.—The *arteries* of the thymus are derived from various sources. Their branches penetrate to the ultimate lobules, where they form a

[1] Arch. f. Anat. 1906, Supplement volume. The changes which the thymus undergoes in weight and in structure at different ages are very fully dealt with in this paper.

[2] Arch. f. mikr. Anat. lxxiii. 1909 (in the rabbit).

[3] Paton and Goodall, Journ. Physiol. xxxi. 1904; J. Henderson, *ibid.*; A. Goodall, Journ. Physiol. xxxii. 1905; Soli, Arch. ital. de biol. lii. 1909. The effect of removing the thymus has recently been investigated in dogs by Klose and Vogt (Beitr. z. klin. Chir. lxix. 1910), who state that, after a prolonged period without adverse symptoms, a condition of cachexia, ultimately proving fatal, results. The literature of the subject is given in this paper.

[4] Hammar, *op. cit.* 1906; A. Jonson, Arch. f. mikr. Anat. lxxiii. 1909. Hammar found that the amount of leucocytes and even of Hassall's corpuscles is markedly affected by general conditions of nutrition.

plexus surrounding the cortex; from this capillaries converge towards the medulla. In some animals these vessels loop back towards the cortex, but in others they open into an inner vascular circle which lies just within the boundary of the medulla. The *veins*, for the most part, open into the left innominate vein.

The *lymphatics* are large. According to the observations of His on the calf, the larger blood-vessels passing to the centre are each accompanied by two or more lymphatic trunks. These arise from an interlobular plexus, which again is in connexion with vessels that surround and enclose the individual follicles without penetrating them. One or two collecting vessels pass from each lobe to lymph-glands close to the organ.[1]

The *nerves* are minute. Haller thought that they were partly derived from the phrenics, but according to Cooper no filaments from these nerves go into the gland, although they reach the investing capsule; as does also a branch from the descendens hypoglossi. Small filaments, derived from the vagus and sympathetic nerves, descend, on the thyroid body, to the upper part of the thymus. Sympathetic nerves also reach the gland along its various arteries.

The functions of the thymus, as a whole, are obscure: its structure would lead to the supposition that, like the lymph-glands, it may be a source of supply of lymphocytes, but the appearances are also compatible with its serving as a storage-place for those cells. In certain individuals it is found to persist in a well-developed form until comparatively late in life; this persistence is associated with the condition known to clinicians as the *status lymphaticus*.[2]

THE SUPRARENAL CAPSULES.

The **suprarenal capsules** or **adrenals** are important internally secreting glands which lie in close anatomical relation to the kidneys in man and many animals (fig. 983), but have no corresponding functional relation to them. They consist

FIG. 983.—FRONT VIEW OF THE RIGHT KIDNEY AND SUPRARENAL BODY OF A FULL-GROWN FŒTUS. (Allen Thomson.)

This figure shows the lobulated form of the fœtal kidney, *r*; *v*, the renal vein and artery; *u*, the ureter; *s*, the suprarenal capsule; the letter is placed near the sulcus in which the large veins (*v'*) are seen emerging from the interior of the organ.

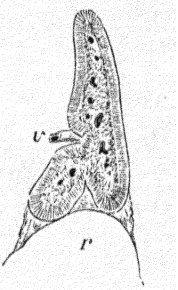


FIG. 984.—SECTION OF THE SUPRARENAL BODY. (Allen Thomson.)

A vertical section of the suprarenal body of a fœtus, twice the natural size, showing the lower notch by which it rests on the summit of the kidney (*r*), and the anterior notch by which the suprarenal vein (*v*) issues, together with the distinction between the medullary and cortical substance.

of a mass of epithelium-like glandular substance enclosed by a connective-tissue capsule, in the deeper layers of which, at least in some animals, are plain-muscle-cells. The capsule sends septa or trabeculæ into the organ. Near the surface

[1] Severeanu, Arch. f. Anat. 1909. See further on the lymphatics of the thymus Matsunga, Arch. f. Anat. 1910.

[2] The literature of the thymus will be found in Hammar, 'Fünfzig Jahre Thymusforschung,' Merkel and Bonnet's Ergebn. d. Anat. xix. 1909.

these trabeculæ are well marked and anastomose, leaving rounded loculi between them (*zona glomerulosa*); in the succeeding and largest zone of the cortex (*zona fasciculata*) the trabeculæ take a parallel course through the cortex running vertically to the surface, but they become broken up as they approach the more central part of the gland, and here they have a reticulated arrangement (*zona reticulata*).

The glandular substance follows the general arrangement of this connective-tissue framework. When the adrenal is cut across in the fresh condition it is readily seen to be composed of two parts (figs. 984 to 986 and accompanying Plate): a cortical part of a yellowish appearance which forms the main mass of the organ

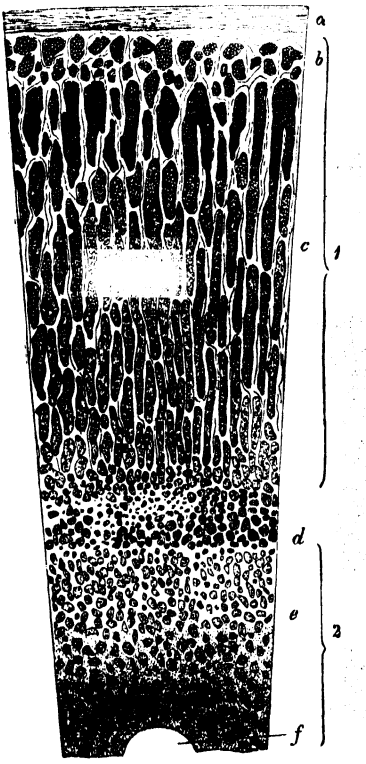


FIG. 985.—VERTICAL SECTION OF SUPRARENAL BODY; HUMAN. (Eberth.) Magnified.

1, cortical substance; 2, medullary substance: *a*, capsule; *b*, zona glomerulosa; *c*, zona fasciculata; *d*, zona reticularis; *e*, groups of medullary cells; *f*, section of a large vein.

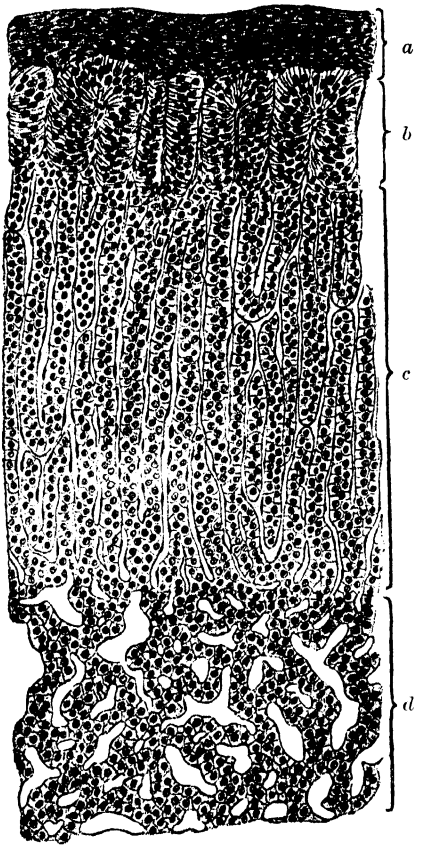
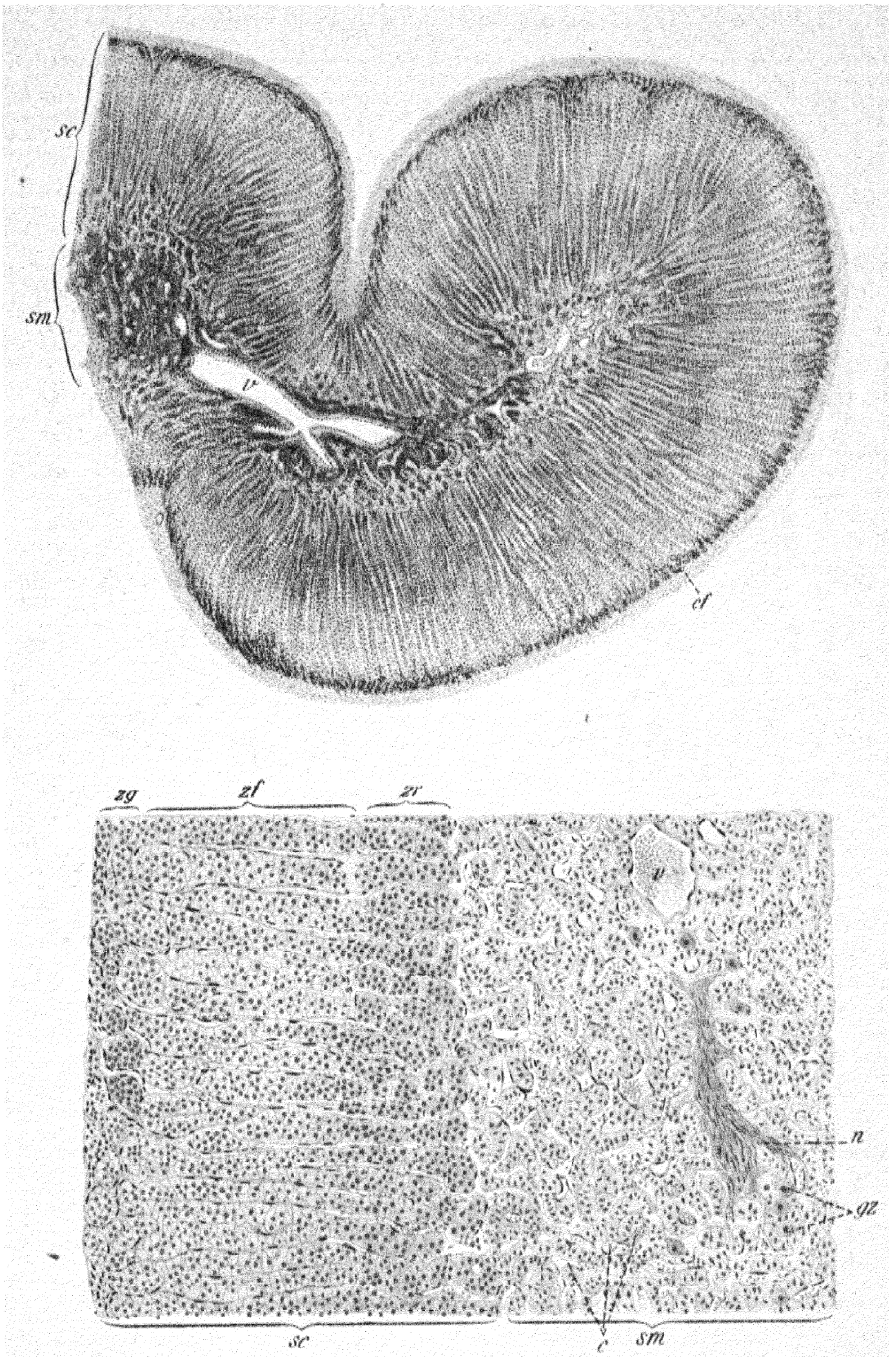


FIG. 986.—SECTION OF THE CORTEX OF THE DOG'S SUPRARENAL. (Böhm and v. Davidoff.)

a, fibrous covering; *b*, zona glomerulosa *c*, zona fasciculata; *d*, zona reticularis.

and exhibits the three zones above enumerated, and a *medulla* of a dark red colour (due to the blood in its venous sinuses) occupying the centre of the gland. If the section is made from a gland hardened by a salt of chromic acid the medulla is of a yellowish-brown colour (see the upper figure of the accompanying Plate); in either case it contrasts with the much paler tint of the cortex. The brown coloration is due to the action of chromic acid upon the secreting cells of the medulla, and has given rise to the term *chromaffin* or *chromaphil* to characterise these cells.[1] Chromaphil cells are not confined to this situation, but are found in a more scattered form in certain other bodies which occur in various places in the abdomen and pelvis, and resemble the medulla of the adrenals in being developed

[1] Also termed *phæochromocytes*.



Suprarenal, human (Sobotta). Haematoxylin-eosin stain. Magnified 15 and 80 diameters respectively.

cf, fibrous capsule; *sc*, cortical substance; *zg*, *zf*, *zr*, its three zones; *sm*, medullary substance; *c*, its capillaries; *v*, veins; *n*, nonmedullated nerves; *g*, sympathetic ganglion cells.

from cells derived from sympathetic ganglion rudiments (see Vol. I., pp. 135, 205); these have been classified together by Kohn under the designation *paraganglia* and will be afterwards noticed.[1]

Removal of the suprarenal bodies is in most animals speedily followed by symptoms of extreme muscular prostration and, within a very few days, by death (Brown-Séquard, 1856). Disease of the organs is usually accompanied by the appearance of bronzed patches on various parts of the skin and mucous membranes (Addison, 1855); the symptoms in advanced disease are similar to those resulting from removal. The watery extract of the medulla of the capsules contains a (non-proteid) substance which produces, when injected even in minute quantities into the blood-vessels of an animal, a great augmentation of the contraction of the muscular tissue of the heart and arteries (Oliver and Schäfer, 1894) and of most structures which receive their nerve-supply through the sympathetic (Langley).

The **cortex** of the suprarenals is formed of polyhedral epithelium-cells varying in diameter from 0.0125 to 0.02 mm., massed together into columns incompletely separated from one another by the connective-tissue trabeculæ which run between them and serve as a supporting framework (see Plate). The protoplasm of the cells is finely granular, and contains also small globules of a lipoid material, giving the cortex the yellowish colour which it exhibits in sections of the fresh organ. In some animals (*e.g.* guinea-pig) the cells of the zona reticularis contain brown pigment-granules. The cells are two or three deep in the glandular columns. Secretion-granules have been described within the cortical cells.[2] No blood-vessels penetrate between them, the blood-supply of the cortex being confined to the connective-tissue septa: these septa also contain lymphatics, which are said to communicate with fine canals between the epithelium-cells (Klein). The arteries of the cortex pass into it from the capsule, breaking up into capillary-like channels in the septa. The capillaries form a network surrounding the cell-columns of the zona glomerulosa and zona fasciculata; these vessels open into a venous plexus situated in the zona reticularis. This plexus communicates with that of the medulla and also, on the inner side of the organ, with the central vein which emerges from the medulla. A few arterioles pass from the capsule through the cortex directly to the medulla.[3]

The zona glomerulosa is in man occupied by cells which are similar to those of the rest of the cortex. But in some animals, such as the dog and horse, the cells of this zone are long and columnar, and arranged so as to enclose a kind of lumen (fig. 986). The zona reticularis is characterised by its more open arrangement, due to the plexus of sinus-like veins it contains; which receive, as just noted, the blood that has traversed the capillaries of the rest of the cortex.

Félicine[4] states that fine particles of China ink can pass between the cortical cells from the vessels, showing that the capillaries of the cortex have incomplete walls, as in the liver: if so, they are probably of a sinusoid nature like those of the medulla. This is certainly the case in the embryo (Luna). The lymphatics of the cortex enter it from the fibrous capsule, where they form a network; this communicates with vessels which run in the septa between the cell-columns of the cortex to join the lymph-vessels in the walls of the medullary veins.

The suprarenal capsules of the human fœtus are of unusually large size. This is almost entirely due, according to Elliott and Armour,[5] to hypertrophy of an inner part of the cortex.

[1] See on the structure of the suprarenal capsules Colson, Arch. de biol. xxv. 1910; Disse, article 'Nebenniere' in v. Bardeleben's Handb. d. Anat. 1902; A. S. Dogiel, Arch. f. Anat. 1894 (nerve-endings); G. Dostoiewsky, Arch. f. mikr. Anat. xxvii. 1886; Elliott and Tuckett, Journ. Physiol. xxxiv. 1906; J. M. Flint, Johns Hopkins Hosp. Rep. ix. 1900, and Anat. Anz. xvi. 1899 (framework); Romeo Fusari, Arch. ital. de biol. xvi. 1891 (nerve-endings); Guarneri and Magini, *ibid.* x. 1888; E. Luna, Anat. Anz. xxxiii. 1908; Marchand, Virchow Festschrift, i. 1891; C. Martinotti, Ann. di freniatr. iii. 1891-1892; Mattei, Giornale della R. Accad. di Med. di Torino, xlix. 1887 (plain muscle); C. S. Minot, Proc. Amer. Assoc. for the Adv. of Science, vol. xxxiv. (morphology); Pfaundler, Sitzungsb. der Wiener Akad. cl. 1892 (vessels); Hans Rabl, Arch. f. mikr. Anat. xxxviii. 1891 (suprarenal of bird); H. D. Rolleston, Journ. of Anat. and Physiol. xxvi. 1892, Brit. Med. Journ. i. 1895; Swale Vincent, Intern. Monatschr. f. Anat. u. Physiol. xv. 1898, and Ergebn. der Physiol. 1910; H. Stilling, Virch. Arch. cix. 1887.

[2] Da Costa, Anat. Anz. xxxi. 1907. [3] Srdinko, Abstr. in Zentralbl. f. Anat. iv. 1907.

[4] Anat. Anz. xxii. 1902, and Arch. f. mikr. Anat. lxiii. 1903. [5] Journ. Path. and Bact. xv. 1911

This hypertrophied part is very vascular and is further distinguished from the ordinary cortex by the absence of lipoids within its cells. It undergoes a fatty change immediately after birth, and by the end of the first year has entirely disappeared. The cortex of the adult gland is formed of cells which at first appear only as a thin marginal layer : these contain lipoids. They undergo development *pari passu* with the atrophy of the fœtal cortex. In the anencephalous fœtus the ' fœtal cortex ' fails to develop, and the suprarenal resembles that of other fœtal animals.[1]

The **medulla** of the suprarenals is formed of a network or spongework of cell-columns, which bound anastomosing venous sinuses (sinusoids),[2] both trabeculæ and sinuses being larger than those of the zona reticularis of the cortex with which

FIG. 987.—SECTION SHOWING ZONA RETICULARIS OF CORTEX, *r*, AND MEDULLA, *m*, OF SUPRARENAL OF DOG. (Szymonowicz.) Magnified 384 diameters.

they are in continuity (fig. 987 and lower figure of Plate). The cells of the medulla are in close relationship to the endothelium lining the blood-sinuses, and in many parts form the only separation between the epithelium-cells and the blood. Some authors have, indeed, described the endothelium as being absent in parts, so that here the epithelium-cells would be directly bathed by the blood-plasma.[3] Irregular lacuna-like diverticula from the sinusoids have also been described as penetrating into the cell-columns[4] : it is thought that these may be for the purpose of facilitating the passage of the secretion of the cells into the blood

[1] See also on the ' fœtal cortex,' E. Thomas, Ziegler's Beitr. l. 1911.

[2] Minot, Proc. Boston Soc. Nat. Hist. xxix. 1900. See on the structure of the blood-vessels of the suprarenals J. S. Ferguson. Amer. Journ. Anat. v. 1905.

[3] Carlier, Anat. Anz. viii. 1893.

[4] Félicine, *op. cit.*

traversing the sinusoids. The cells of the medulla are large; they have a finely granular protoplasm: by certain methods of staining much more distinct granules, which are believed to be connected with their secretion, can be demonstrated within them.[1] In man the cells are mostly of an irregularly polyhedral shape, but in many animals they are distinctly columnar and are arranged along the blood-sinuses like the cells of a secreting gland around the lumen of its alveoli and ducts. As already stated, they possess the specific property of becoming coloured brown by chromic acid and its salts.

The blood of the medullary sinusoids is collected into veins near the centre and ultimately into a single vessel which emerges from the hilum of the gland, and receiving branches from the veins of the cortex and capsule becomes the suprarenal vein.

The medulla and cortex of the suprarenal have not in all vertebrata the same relationship as is found in man, although this relationship obtains in mammals, in birds, and in reptiles. In amphibia both kinds of cell exist, but they are imbedded in the cortex of the kidneys. In teleostean fishes no structure is found representing a medulla. In elasmobranch fishes the cortex is represented by a median gland known as the *inter-renal body*, and the medulla by a series of '*paired bodies*' which lie in close relationship to the ganglia of the sympathetic chain.

The cortex and medulla of the suprarenals are developed from entirely different embryonic rudiments, the cortex being derived from the mesothelium covering the Wolffian body, the medulla from the same cells as form the sympathetic ganglia, these cells becoming in certain parts ganglion-cells, in others chromaphil-cells. (See Vol. I., p. 205.)

Vessels and nerves.—The suprarenals receive *arteries* directly from the aorta as well as from the phrenic and renal arteries. All these vessels break up into small branches before entering the fibrous capsule. The *veins* of each organ are usually united into one, which emerges on the anterior surface at the hilum. That on the right side enters the inferior cava, and that on the left the renal vein. The veins contain longitudinal bundles of plain muscular tissue in their walls. Veins in the capsule communicate with those in the capsule of the adjacent kidney and also with the phrenic veins.[2] *Lymph-vessels* in the gland are numerous. They form a network of large vessels on the inner surface of the fibrous capsule and a second network in the medulla,[3] these two networks being united by lymphatics which traverse the cortex. Efferent vessels pass both from the capsule and from the medulla (at the hilum) and enter lymph-glands near the organ.

The *nerves* are derived from the greater splanchnic, through the solar and renal plexuses. According to Bergmann some fibres come from the phrenic and vagus nerves.[4] They are chiefly medullated, and are destined both for cortex and medulla, some passing direct to the medulla, others after supplying the cortex. They lose their medullary sheath in small peripheral ganglia, some before entering, others within the organ. Besides a nerve-plexus in the capsule there are fine plexuses in the medulla; from the latter fibres pass into the cell-columns. Ganglion-cells of sympathetic type are sometimes seen in the medulla (see *gz* in lower figure of Plate).

[1] Carlier, *op. cit.*; Hultgreen and Andersson, Skandin. Arch. f. Physiol. ix. 1899. See also Stoerck and Harberer, Arch. f. mikr. Anat. lxxii. 1908.

[2] See on the development of the vessels of the suprarenal capsules E. Luna, Internat. Monatschr. f. Anat. u. Physiol. xxvii. 1910.

[3] According to Kumita (Arch. f. Anat. 1909) these run in the walls of the larger veins.

[4] Biedl (Die Nebenniere, 1910) got increased flow of blood through the suprarenals on stimulating the greater splanchnic. Tscheboksaroff (Pflüger's Arch. cxxxvii. 1910) got an increase of adrenin both in the gland and in the blood generally on stimulating this nerve, whereas its section led to a marked diminution of adrenin. Stimulation of the vagus produced no effect. The physiology of the chromaphil substance of the suprarenals is dealt with at considerable length by G. Bayer (Ergebn. d. path. Anat. Jahrg. xiv. 1910), who also gives an extended bibliography of the subject.

THE PARAGANGLIA.

Under this designation are included by Kohn[1] the *carotid glands*, the *coccygeal gland*, and a number of other small glandular bodies, of structure somewhat similar to these or to the suprarenal capsules, found in the neighbourhood of the kidneys and of

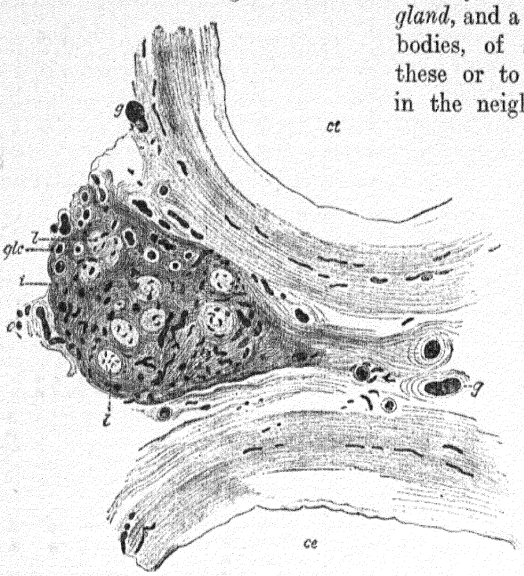


FIG. 988.—SECTION NEAR THE BIFURCATION OF THE COMMON CAROTID ARTERY, PASSING THROUGH THE CAROTID GLAND. (Marchand.) Somewhat magnified.

ci, *ce*, internal and external carotid arteries cut across; *glc*, carotid gland; *g*, blood-vessels; *i*, interstitial connective tissue of gland; *l*, glandular lobules or nodules.

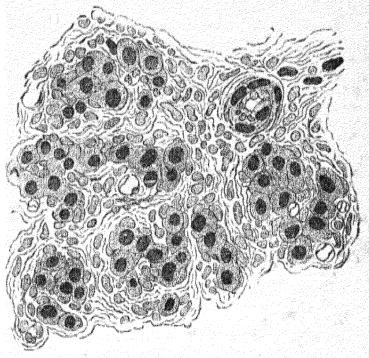


FIG. 989.—SECTION OF PART OF THE CAROTID GLAND (HUMAN), SHOWING THE EPITHELIUM-LIKE CELLS OF WHICH THE GLANDULAR NODULES ARE COMPOSED. (Schaper.) Highly magnified.

Numerous blood-vessels are seen in section among the gland-cells.

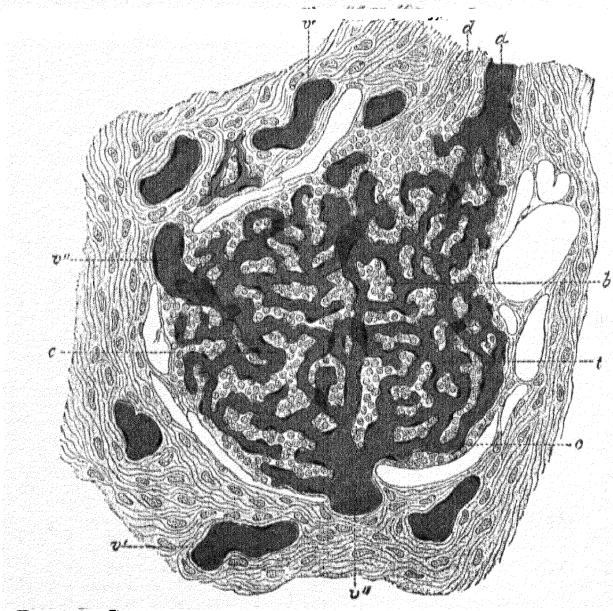


FIG. 990.—DIAGRAMMATIC VIEW OF THE DISPOSITION OF THE BLOOD-VESSELS IN A NODULE OF THE CAROTID GLAND. (Schaper.)

a, arteriole entering nodule; *v''*, veins leaving nodule; *v'*, veins in connective tissue around nodule; *t*, enlarged capillary within nodule; *b*, epithelium-like cells of the gland; *c*, *c*, boundary of nodule abutting upon lymph-spaces; *d*, interstitial connective tissue of gland.

[1] Arch. f. mikr. Anat. lvi. 1900; Ergebn der Anat. xii. 1902; Arch. f. mikr. Anat. lxii. 1903. See also W. Kose, *ibid.* lxix. 1907.

the abdominal aorta. So far as is known, all are associated in development with the cells which form the blastema of the sympathetic ganglia, and are probably related in function to the suprarenal capsules.[1]

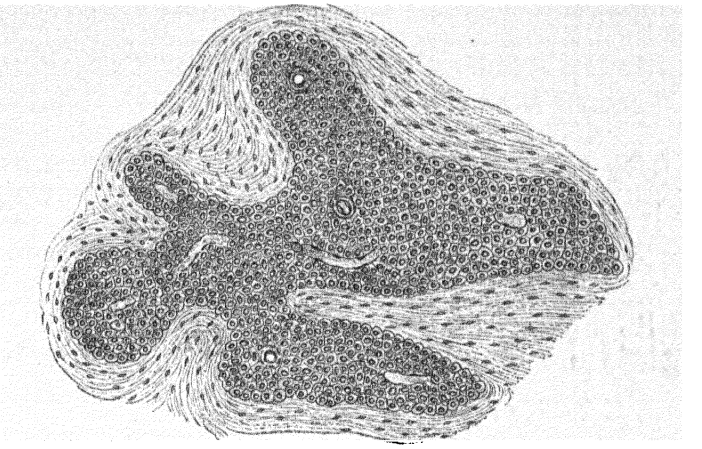


FIG. 991.—SECTION OF AN IRREGULAR NODULE OF THE COCCYGEAL GLAND. (Sertoli.)
Magnified 85 diameters.
The section shows the fibrous covering of the nodule, the blood-vessels within it, and the epithelial cells of which it is constituted.

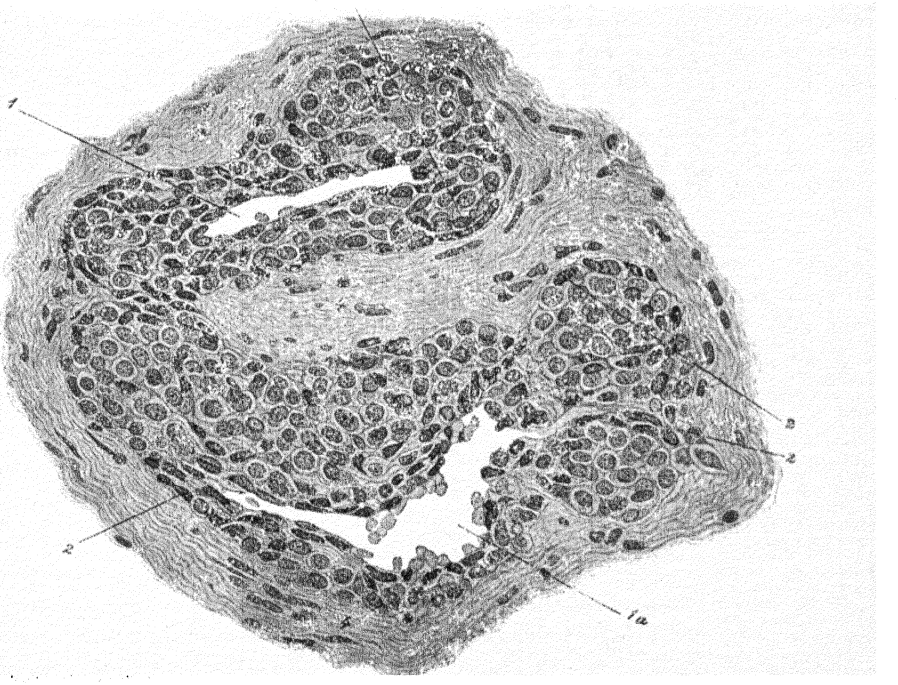


FIG. 992.—SECTION OF COCCYGEAL GLAND. (Walker.)
1, blood-spaces; 2, gland-epithelium; 3, connective tissue.

The **carotid glands** are placed one on each side at the bifurcation of the common carotid (fig. 988). Each consists of a mass of fibrous tissue in which are imbedded small nodules of epithelium-like cells (fig. 989), some of which may show

[1] The paraganglia which contain cells similar to those of the medulla of the suprarenal capsules are termed by Swale Vincent 'chromaphil bodies.'

brown staining with chromic acid and yield a substance having the physiological effects of adrenin.[1] The nodules are pervaded by a dense network of sinus-like blood-capillaries (fig. 990), and large lymphatic vessels surround the outside of the nodules. In mode of origin and to some extent in structure they resemble the parathyroids ; they are developed from the entoderm of the third branchial pouch.[2]

The **coccygeal gland** (Luschka) lies just in front of the apex of the coccyx. It is about 2½ mm. in diameter, but is sometimes broken up into smaller parts. Like the carotid glands, it is formed of masses of epithelial cells imbedded in a fibrous stroma (figs. 991, 992). The masses are irregular in shape and size, and are very vascular, the vessels having a sinusoidal character. The blood is derived from

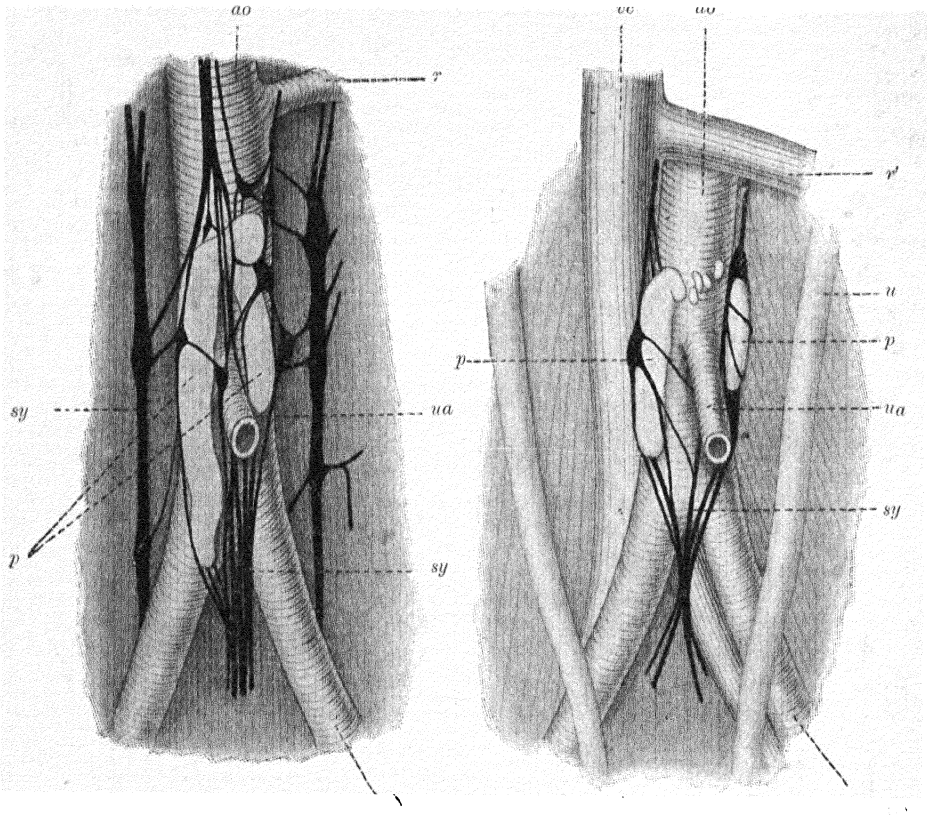


FIG. 993.—DISSECTIONS OF TWO SPECIMENS OF THE LOWER END OF THE AORTA AND ADJACENT STRUCTURES IN THE HUMAN FŒTUS, TO SHOW THE PARAGANGLIA USUALLY PRESENT IN THAT SITUATION (Zuckerkandl.)

ao, aorta; *vc*, vena cava; *r*, *r'*, left renal artery and vein respectively; *u*, uretor; *ua*, umbilical artery; *sy*, sympathetic plexus; *p*, *p*, paraganglia.

the median sacral artery. The cells of the gland come into close relationship to the sinuses, with only a layer of endothelium between ; indeed, the presence of this layer is not always easy of detection. It is usually stated that some of the cells are chromaphil in character, but this is denied by Stoerck.[3]

Numerous nerves pass to the coccygeal gland, and Luschka described ganglion-cells within it, but this description has not been confirmed by modern investigations. The mode of development and the function of the coccygeal gland has not been

[1] Mulon, Arch. gén. de méd. lxxxi. 1903.
[2] H. Fox, Proc. Assoc. Amer. Anat., Amer. Journ. Anat. iv. 1905.
[3] Arch. f. mikr. Anat. lxix. 1906.

definitely ascertained, but it is probably connected with that of the sympathetic (Jakobsson).[1]

Other papers on the carotid and coccygeal are: J. Arnold, Virch. Arch. xxxii. 1865, xxxiii. 1865, xxxv. 1866, xxxviii. 1867; Eberth, in Stricker's Handbuch der Gewebelehre, i. 1871; Heppner, Virch. Arch. xlvi. 1869; W. Luschka, Virch. Arch. xviii. 1860, 'Der Hirnanhang u. die Steissdrüse des Menschen,' Berlin, 1860, Arch. f. Anat. 1862, 'Anatomie d. menschl. Beckens,' 1864; Marchand, in Festschr. z. R. Virchow, i. 1891; Pförtner, Zeitschr. f. ration. Med. xxxiv. 1869; A. Prenant, La Cellule, x. 1894; Schaper, Arch. f. mikr. Anat. xl. 1892; Schumacher, Arch. f. mikr. Anat. lxxi. 1907; Sertoli, Arch. f. Anat. 1862, Virch. Arch. xlii. 1868; Stieda, 'Unters. ü. d. Entwickl. d. Glandula thymus, Glandula thyroïdea u. Glandula carotica,' Leipzig, 1881; Stilling, Du ganglion intercarotidien, Rec. inaug., Lausanne, 1892; Swale Vincent, Anat. Anz. xviii. 1900; Walker, Arch. f. mikr. Anat. lxiv. 1904.

The rest of the **paraganglia** of Kohn are scattered, as already stated, irregularly along the course of the abdominal aorta and between and near the kidneys (fig. 993). They vary a good deal in size and in situation. In structure they resemble the medulla of the suprarenal; some also have cells like those of the cortex of that organ. Many of their cells are chromaphil (fig. 994), and there is every reason to look upon them as accessory in function to the suprarenals.

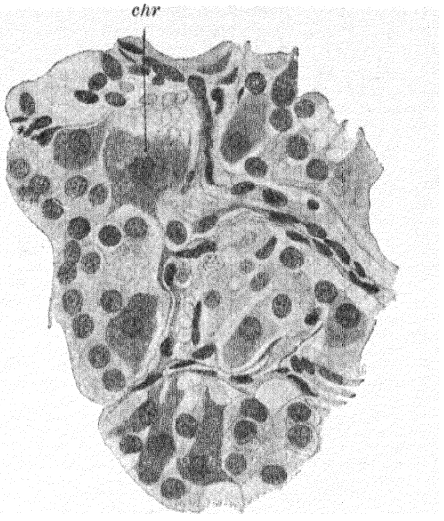


FIG. 994.—SECTION OF PART OF AN ACCESSORY SUPRARENAL (CHROMAPHIL) BODY: NEW-BORN CHILD. (Zuckerkandl.)
chr, a chromaphil cell.

Aichel[2] describes bodies of this nature as occurring occasionally in the following situations: (1) in the kidney or underneath its capsule; (2) in the liver; (3) attached to the renal and solar plexuses; (4) retroperitoneal, below kidney; (5) in the broad ligament of the uterus; (6) in the spermatic cord; (7) between the testicle and epididymis; (8) in the corpus Highmori. According to Kohn[3] the largest of the paraganglia in man lie just above the division of the aorta (fig. 993), others just internal to and below the suprarenal capsules, others in the angle formed by the common iliacs, and yet others at the sides of the rectum. Smaller ones are scattered in the neighbourhood of the kidneys, ureters, aorta, and vena cava, and in the broad ligament. Swale Vincent[4] describes a chromaphil body, noticed previously by Kohn, as constantly present at the back of the abdomen in the dog, cat, and rabbit, and occasionally in the rat. In the male of the last-named animal an accessory body having a structure like that of the suprarenal but without chromaphil-cells[5] is constantly found, attached to the head of the epididymis.

THE PITUITARY BODY OR HYPOPHYSIS CEREBRI.

The **pituitary body** is a small glandular organ about the size of a cob-nut, situated in the pituitary fossa of the sphenoid bone. It is connected by a funnel-shaped projection of the base of the brain (infundibulum) with the third cerebral ventricle, the cavity of which extends into the infundibulum; in some animals, but not in man, the cavity is prolonged into the interior of the gland (fig. 995). The pituitary body is surrounded and encapsuled by a prolongation of the dura mater.

A sagittal section through the organ shows it to be composed of two distinct portions (fig. 995), which in most animals are almost separated from one another by a cleft (fig. 996, *g*) containing a clear, colourless, glairy fluid. On examination with the microscope it is seen that the portion in front of the cleft (*pars*

[1] Arch. f. mikr. Anat. liii. 1899.
[2] *Ibid.* lvi. 1900.
[3] *Op. cit.* 1903.
[4] Proc. Roy. Soc. B. lxxxii. 1910
[5] O. Schwarz, Wien. klin. Woch. 1909.

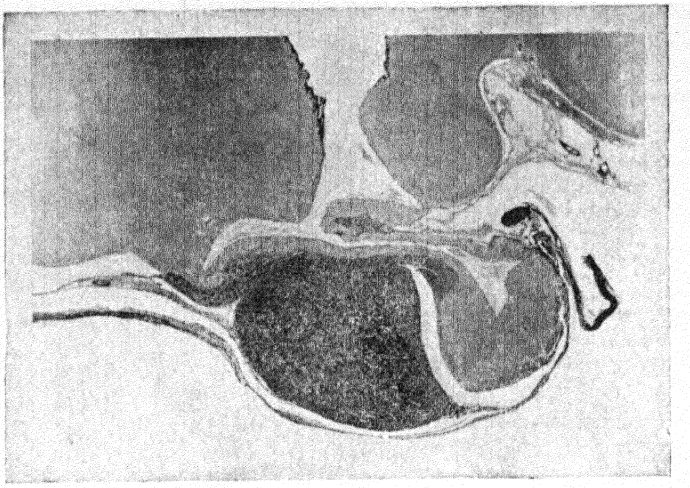


FIG. 995.—MESIAL SAGITTAL SECTION THROUGH PITUITARY BODY AND BASE OF BRAIN OF CAT. (Herring.) Photograph.

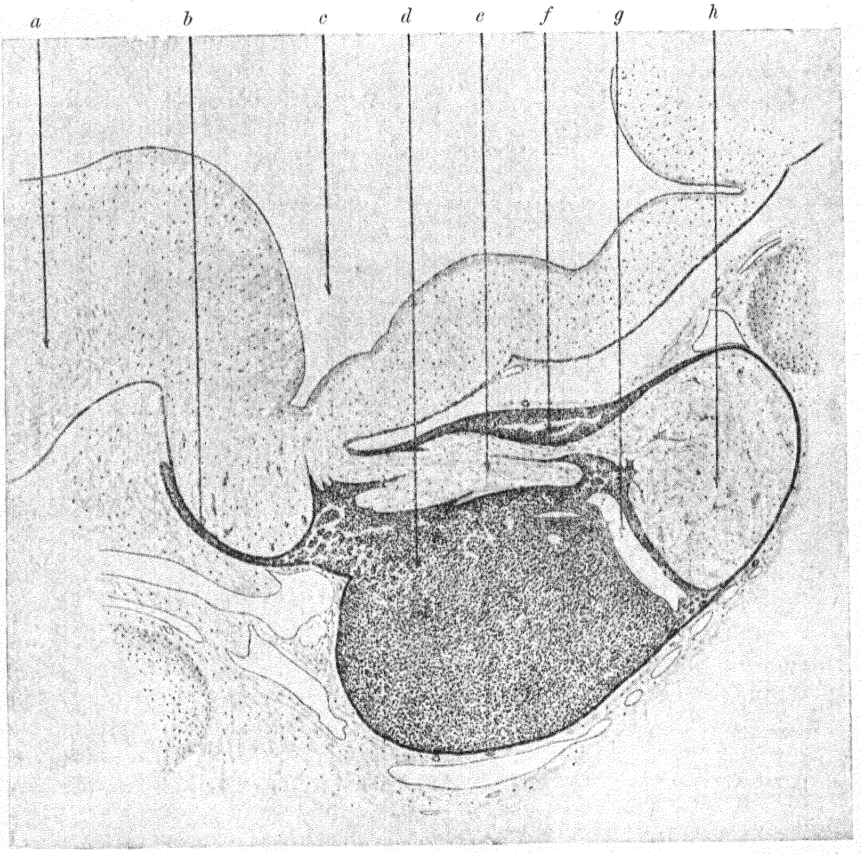


FIG. 996.—MESIAL SAGITTAL SECTION THROUGH PITUITARY BODY OF A HUMAN FŒTUS OF THE FIFTH MONTH. (Herring.)

a, optic chiasma; *b*, tongue-like process of pituitary extending anteriorly; *c*, third ventricle (infundibulum); *d*, pars anterior of pituitary; *e*, neck or isthmus of pars nervosa, connecting it with the bottom of the infundibulum; *f*, epithelium continuous with pars intermedia surrounding neck; *g*, intraglandular cleft; *h*, pars nervosa.

anterior)—which forms by far the larger part of the gland—is composed of trabecular masses of epithelial cells with numerous large sinus-like blood-capillaries between them; while the portion behind the cleft consists of two parts of distinct structure, viz. an intermediate portion (*pars intermedia*), formed mainly of epithelial cells, less distinctly granular than those of the pars anterior and provided with far fewer blood-vessels, and a posterior part (*pars nervosa seu posterior*), which is continuous with the nervous tissue of the infundibulum, not always sharply marked off from the pars intermedia. Shortly stated, the pituitary body

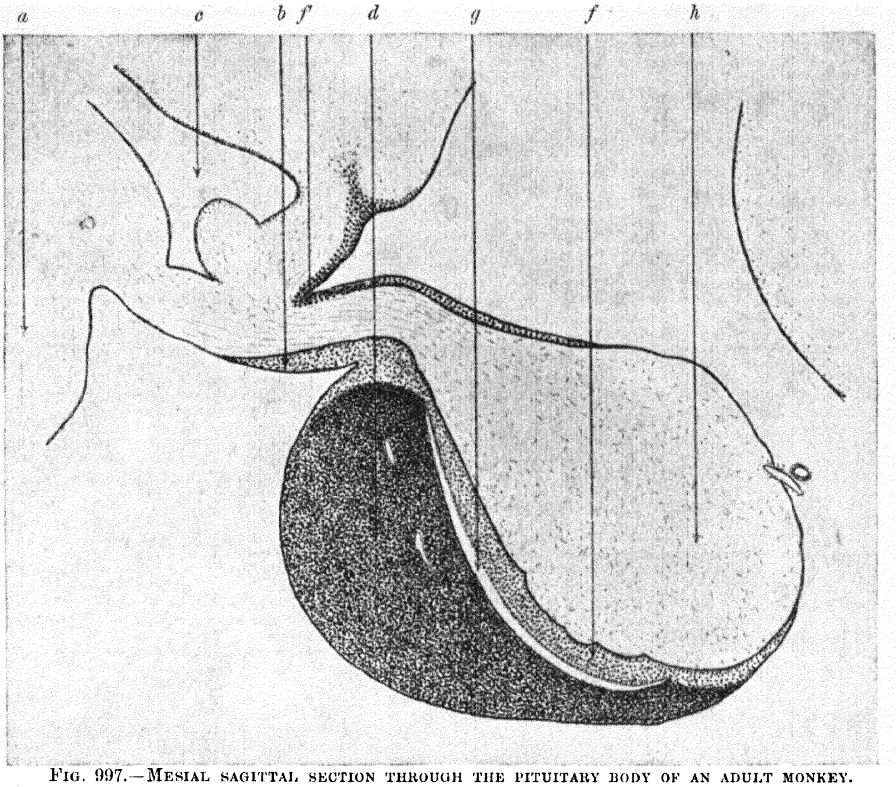


FIG. 997.—MESIAL SAGITTAL SECTION THROUGH THE PITUITARY BODY OF AN ADULT MONKEY. Semi-diagrammatic. (Herring.)

a, optic chiasma; *b*, tongue-like process of pars intermedia; *c*, third ventricle; *d*, anterior lobe; *f*, epithelial investment of posterior lobe (pars intermedia); *f'*, extension of pars intermedia over and into adjacent brain-substance; *g*, intraglandular cleft; *h*, nervous substance of posterior lobe. The dark shading indicates the anterior lobe proper; the lighter shading shows the position of the epithelium of the pars intermedia. The arrangement is similar to that found in man, but the posterior lobe is relatively rather larger in the monkey. It must, however, be remembered that the anterior lobe and the pars intermedia almost surround the posterior lobe, and do not merely lie ventral to it as they appear to do in a median section. In the cat and many other animals the infundibular recess is prolonged well into the posterior lobe.

consists anteriorly of epithelium and posteriorly of nervous tissue, but the epithelial portion shows a distinction into two parts of different character, partially separated from one another by the intraglandular cleft.

Pars anterior.—The epithelium-cells of the pars anterior are arranged in irregular clumps and trabeculæ, separated by a small amount of reticular connective tissue, which contains a network of numerous and large blood-capillaries, apparently sinusoidal in nature (fig. 998). The capillaries come into very close relation with the cells, which in many places appear in section as if set round the capillaries. The cells are of two kinds, clear and granular; which may, however, represent different

conditions of a single kind of cell, since intermediate appearances are also observed; the relative amount of the two kinds varies in different specimens.[1] The one kind of cell has a clear or only very finely granular protoplasm, whereas the protoplasm of the other kind is full of distinct granules, staining with basic dyes and giving a dark appearance in stained sections to this part of the gland. Cells with oxyphil (eosinophil) granules also occur in the pars anterior. Some observers have described a vesicular arrangement of the epithelium-cells, enclosing 'colloid' substance as in the thyroid; but although such an appearance is common in the pars intermedia, it does not, according to Herring, occur in the pars anterior. The appearances of the pars anterior are strongly suggestive of a gland that is adapted to discharge the secretion of its cells directly into the blood.

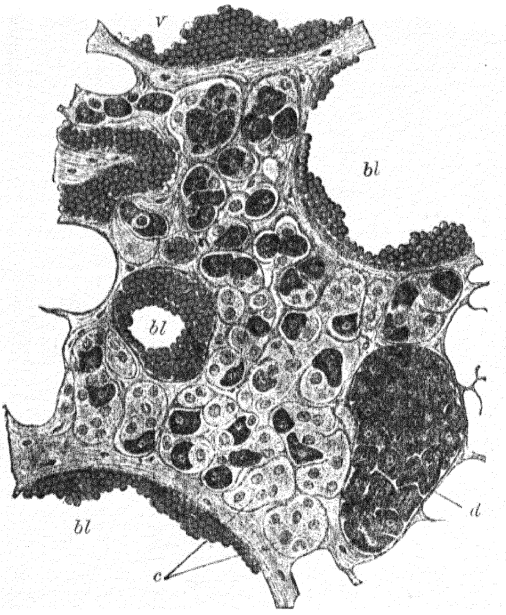


FIG. 998.—SECTION OF PARS ANTERIOR OF PITUITARY (OX). (Dostoiewsky.)
bl, blood-sinuses; *c*, strands of clear cells; *d*, strands of cells containing dark granules. Other strands contain both kinds of cell.

Pars intermedia.—In the pars intermedia the cells are smaller and less distinctly granular—at least the granules are finer—and blood-vessels are far fewer. The cells are massed against the posterior boundary of the intra-glandular cleft (fig. 997); the layer next to the cleft is arranged somewhat like a columnar epithelium. The opposite or anterior wall of the cleft is bounded by flattened cells. The most characteristic feature in the structure of the pars intermedia is the presence of globules of a hyaline material (fig. 999), to which the designation of 'colloid' has been given, although it is not of the same chemical nature as the colloid found within the vesicles of the thyroid. This 'colloid' or 'hyaline' substance appears to be produced by a transformation of the protoplasm of some of the cells of the pars intermedia, for the globules not infrequently contain a nucleus. They vary in size, some being smaller than the epithelium-cells, others many times larger; they are most numerous in the part of the pars intermedia

[1] According to Scaffidi, there are certainly two specifically different types of cell (Arch. f. mikr. Anat. lxiv. 1904). Gemelli (Arch. p. l. sci. méd. xxx. 1906) describes three kinds of cell in the pars anterior, viz. oxyphil, basiphil, and others intermediate in character. Erdheim and Stumme (Ziegler's Beitr. xlvi. 1909) also describe three types of cell, one clear and two granular (oxyphil and basiphil). The clear cells are said to become hypertrophied during pregnancy

which merges into the pars nervosa. In some animals, especially those in which the cavity of the infundibulum is prolonged as a canal into the pars nervosa, the pars intermedia extends around this canal so as almost to reach the base of the third ventricle. Occasionally, where the hyaline matter has accumulated between the cells of the pars intermedia, these seem as if set around it, and simulate the appearance of epithelial vesicles; but true closed vesicles like those of the thyroid are not present. According to Neubert,[1] the cells of the pars intermedia contain glycogen, which is also present in the hyaline substance. After injury of the pituitary the cells of the pars intermedia tend to invade the pars nervosa:[2] this is probably merely an exaggeration of the process of cell-migration which occurs normally.

Pars nervosa.—The pars nervosa is formed almost entirely of neuroglia: it contains no nerve-cells and but a few nerve-fibres; these pass through it

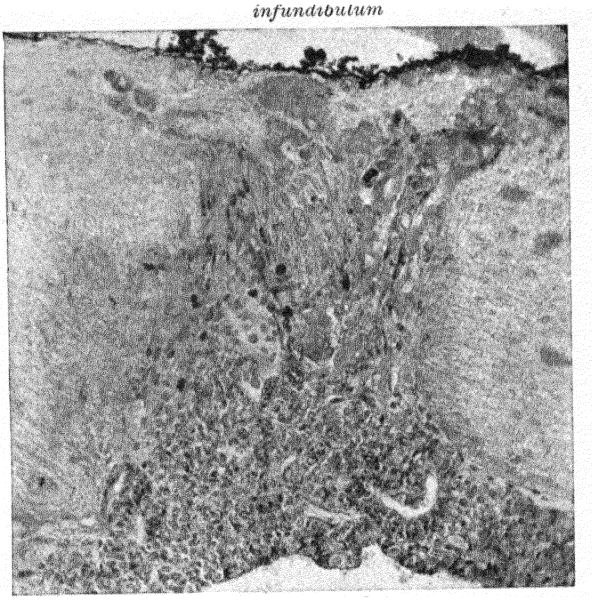


FIG. 999.—SECTION OF PART OF THE POSTERIOR LOBE OF THE PITUITARY OF A DOG, SHOWING MASSES OF COLLOID MATTER PASSING TOWARDS AND INTO THE CAVITY OF THE INFUNDIBULUM. Photographed from a preparation by Herring. Magnified 160 diameters.

The animal had undergone thyroidectomy nineteen days before being killed for examination of the pituitary, and the hyaline secretion is present in unusual amount. Some of this appears to be present in nucleated cells, but for the most part it forms irregular clumps which appear to be streaming from the pars intermedia (below in the figure) to the cavity of the infundibulum (above).

towards the epithelial part of the gland, in which they terminate.[3] The pars nervosa contains many neuroglia-cells and a great number of fibres (fig. 1000) prolonged from the ependyma-cells which line the infundibulum and its prolongation, when this is present. Both the neuroglia-cells and the ependyma-cells of man contain pigment; this appears to be of a lipoid nature.[4] Globules of hyaline matter are also observed in the pars nervosa, lying in spaces within its tissue, most numerously near the pars intermedia, but extending all through its substance as far as the infundibular cavity and its prolongation (fig. 1000, *b*, *d*, *e*). Here they are seen to be discharged into this cavity and to mingle with the ventricular fluid within it. That the hyaline substance is produced

[1] Ziegler's Beitr. xlv. 1909. [2] Cushing and Goetsch, Amer. Journ. Physiol. xxvii. 1910.

[3] Savagnone (Riv. ital. d. neuropat. ii. 1909) finds numerous nerves proceeding to the gland from a group of nerve-cells, situated just behind the optic chiasma. He states that they pass to both anterior and posterior lobes. [4] Kohn, Arch. f. mikr. Anat. lxxv. 1910.

by the cells of the pars intermedia there can be no doubt: it represents in fact the secretion of this part of the gland. But in place of being passed into the blood or lymph, as is the case with the secretion of other internally secreting organs, it is delivered into the third ventricle and mingles with the cerebro-spinal fluid. Its existence in this fluid has been proved experimentally by Cushing and Goetsch. Its amount is greatly increased in animals from which the thyroid body has been removed (fig. 999): from this it has been inferred that the pituitary can act vicariously for the thyroid. But extracts of pituitary have an entirely different physiological effect from thyroid extracts, and the chemical nature of the 'colloid' formed by the pars intermedia is different from that of the thyroid, *e.g.* it contains no iodine, even after thyroidectomy:[1] it is therefore doubtful if the two glands are really functionally complementary to one another.

That the colloid, or hyaline substance, has been occasionally observed amongst

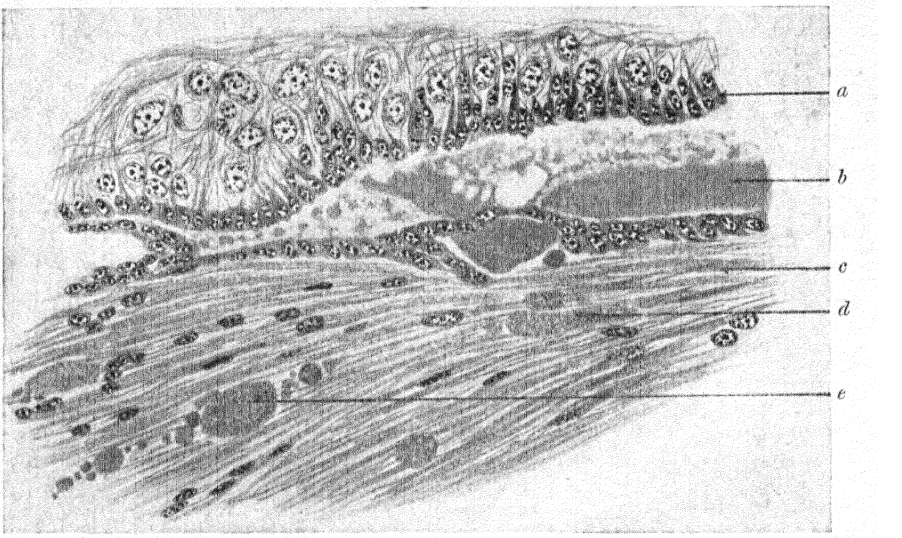


FIG. 1000.—SECTION OF PART OF NECK OF PARS NERVOSA OF THE PITUITARY OF A CAT, SHOWING HYALINE MATTER LYING AMONG THE EPENDYMA FIBRES OF THE PARS NERVOSA AND ALSO PASSING INTO THE CAVITY WHICH IS PROLONGED INTO THE GLAND FROM THE INFUNDIBULUM. (Herring.)

a, ependyma-cells lining the cavity; *b*, hyaline substance (colloid) within the cavity; *c*, ependyma-fibres; *d*, hyaline material between the fibres; *e*, a more granular mass of colloid lying between the fibres.

the cells of the pars anterior—not a place where it occurs normally—may be due to the occasional presence in the pars anterior of cells belonging to the pars intermedia.[2]

In development the epithelial part of the pituitary is derived from the epithelium of a hollow median upgrowth from the buccal ectoderm, which grows towards the third ventricle to reach nearly to the base of the brain, its connexion with the mouth being then cut off. It is met by a downgrowth from the infundibulum; this forms the pars nervosa. The intra-glandular cleft represents a remainder of the cavity of the buccal outgrowth.

[1] Sutherland Simpson and Andrew Hunter, Quart. Journ. Exp. Physiol. iii. and iv. 1910, 1911.

[2] The above account of the structure of the pituitary is founded mainly on the work of P. T. Herring (Quarterly Journ. of Exper. Physiol. vol. i. 1908), who also in the same Journal gives an account of the development of the gland and a general history of the subject, with literature up to that date. A very full bibliography is also given by Masay (Thèse, Bruxelles, 1903) and by Gentès (Soc. Sci. d'Arcachon, 1907). Later observations than these will be found referred to in the Croonian Lecture on the Functions of the Pituitary Body, by E. A. Schäfer (Proc. Roy. Soc. B. lxxxi. 1909).

Remains of the primitive duct from the buccal cavity are not infrequently found. Civeralli[1] has described an accessory gland having the same structure as the pars anterior, lying in the periosteum on the under surface of the basi-sphenoid.[2] Another accessory body is described by Dandy and Goetsch[3] as occurring under the centre of the gland, between the two layers of the dura, and is termed by them the *parahypophysis*. It is an epithelial structure, but differs from the pars anterior of the hypophysis in having no eosinophil cells.

The study of the structure of the pituitary has acquired considerable interest since it has been shown that extracts made from it produce important influences upon the contraction of the heart and blood-vessels and upon the secretion of the kidneys and mammary gland.[4] These effects are obtained only from the posterior portion of the gland, *i.e.* the pars intermedia and pars nervosa, and are probably due to the 'colloid' secretion.

Most authorities agree that the gland is essential to life: if removed death results usually within two or three days.[5] According to Cushing, death also occurs if the anterior part alone

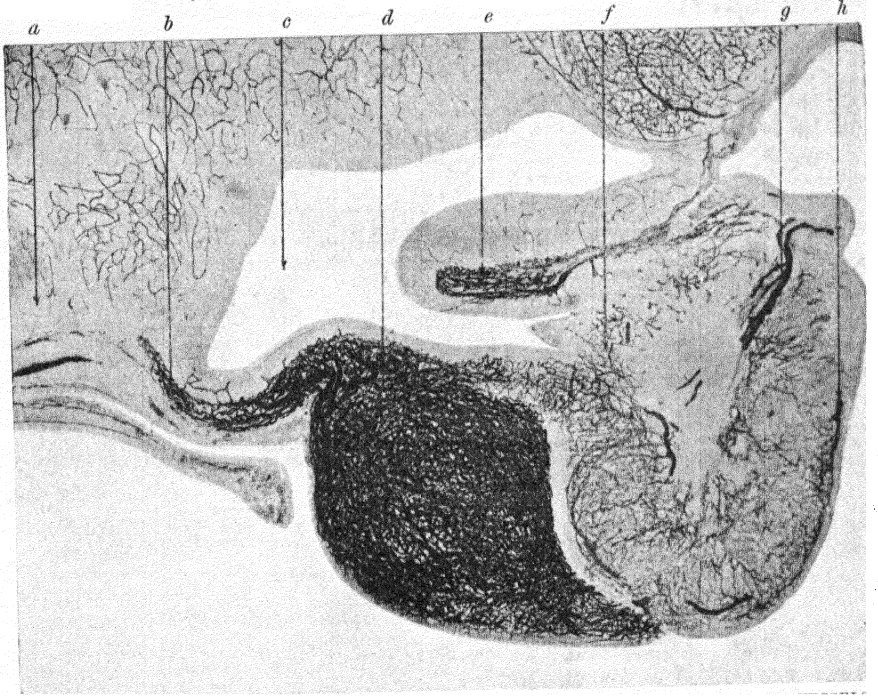


FIG. 1001.—MESIAL SAGITTAL SECTION OF PITUITARY BODY OF ADULT CAT; BLOOD-VESSELS INJECTED WITH CARMINE GELATINE. (Herring.) Photograph.

a, optic chiasma; *b*, tongue-like process of pars intermedia; *c*, third ventricle; *d*, anterior lobe; *e*, pars intermedia lying above neck of posterior lobe; *f*, posterior lobe; *g*, central artery entering posterior lobe at its postero-superior angle; *h*, large vein lying between nervous substance and epithelial investment of posterior lobe.

is removed; in young animals the fatal result is sometimes longer deferred. But Horsley and Handelsmann state that the whole organ may be removed in animals (dogs, cats, monkeys) without the supervention of any adverse symptoms.[6]

[1] Int. Monatschr. f. Anat. u. Physiol. xxvi. 1909.

[2] See also Halberfeld, Ziegler's Beitr. xlvi. 1909, and Citelli, Anat. Anz. xxxviii. 1911.

[3] Amer. Journ. Anat. xi. 1911.

[4] Oliver and Schäfer, Journ. Physiol. xviii. 1895 (action on blood-vessels); W. H. Howell, Journ. Exper. Med. iii. 1898 (action on heart and blood-vessels); Schäfer and Vincent, Journ. Physiol. xxv. 1899 (action on heart and blood-vessels); Schäfer and Herring, Phil. Trans. B. excix. 1906 (action on kidney); Ott and Scott, Proc. Soc. Exper. Biol. viii. Dec. 1910 (action on mammary secretion); Schäfer and Mackenzie, Proc. Roy. Soc. B. lxxxiv. 1911, and K. Mackenzie, Quart. Journ. Exp. Physiol. iv. 1911 (action on mammary secretion).

[5] Paulesco, Journ. de Physiol. 1907, and 'L'hypophyse du cerveau,' 1907; Harvey Cushing, 'The Hypophysis Cerebri,' Journ. Amer. Med. Assoc. liii. 1909; Reford and Harvey Cushing, Johns Hopkins Hosp. Bull. xx. 1909; Crowe, Cushing, and Homans, Quart. Journ. Exp. Physiol. ii. 1909, and Johns Hopkins Hosp. Bull. xxi. 1910; Schäfer, *op. cit*

[6] Brit. Med. Journ. Nov. 4, 1911.

Considerable clinical interest has been aroused in the pituitary since it was shown by Marie [1] that the pathological condition known as acromegaly, which is characterised by hypertrophy of connective tissue and of certain parts of the skeleton, is associated with tumours of the gland, which generally commence as hyperplastic growths of the anterior lobe. The enlargement which the gland undergoes during pregnancy and after ovariotomy points to a connexion between its function and those of the generative organs.[2] As already stated, the hyaline secretion of the posterior lobe is increased in amount and the whole gland is enlarged as the result of thyroidectomy.[3] A great increase of the hyaline substance has also been noticed as the result of extirpation of the pancreas.[4]

Blood-vessels and lymphatics.—The pituitary body is extraordinarily vascular. This statement applies particularly to the pars anterior (fig. 1001), the pars intermedia receiving fewer blood-vessels, and the pars nervosa still fewer.

The source of the blood-supply is dealt with at considerable length by Dandy and Goetsch,[5] who find that the *pars anterior* receives eighteen to twenty small arteries which converge to it from the circle of Willis. They open into numerous large sinusoidal channels, in close proximity to the cells of the gland. No arteries or veins, properly so designated, occur in this lobe. The blood from the sinusoids passes towards veins in the stalk, which enter a venous circle overlying the circle of Willis and draining into the venæ magnæ Galeni. The *pars intermedia* derives its blood-supply from vessels in the stalk and from the adjacent posterior lobe and brain. Its vessels form collateral connexions between those of the pars anterior and pars posterior. The *pars posterior* obtains its arterial supply from a median vessel formed by the junction of two lateral vessels, one from each internal carotid. Its blood is returned by one large vein and other small veins which enter the venous circle above mentioned.

According to Thom,[6] there are numerous interfollicular lymphatics between the strands of cells of the pars anterior, and these, on the one hand, receive the secretion of the cells, and on the other pass it out with the lymph into the subarachnoid space. Creutzfeld also described lymphatic clefts in the organ, which communicate with wide fissures near the dorsal surface, and through these with the subarachnoid space. On the other hand, Edinger,[7] using an injection method, describes pericellular clefts throughout the pars anterior which freely intercommunicate and join other clefts passing along the stalk into the brain-substance, where they enter the perivascular spaces. Edinger believes this to be the path whereby the secretion of the cells of the pars anterior leaves the gland.[8]

[1] Revue de Méd. vi. 1886; Brain, 1889. See also Woods-Hutchinson, New York Medical Journ. lxvii. 1898, and lxxii. 1900.

[2] E. Mayer, Arch. f. Gyn. xc. 1910; Tandler and Gross, Arch. f. Entwickl.-mech. xxx. 1910.

[3] Sutherland Simpson and Andrew Hunter, *op. cit.*

[4] Cushing and Goetsch, *op. cit.*

[5] *Op. cit.*

[6] Arch. f. mikr. Anat. lvii. 1901.

[7] *Ibid.* lxxviii. 1911.

[8] Other papers dealing with the structure of the pituitary are, Bevacqua, Anat. Anz. xxxviii. 1911; A. S. and H. G. Grünbaum, Proc. Physiol. Soc. May, 1911 (Journ. Physiol.); Perna, Anat. Anz. xxxviii. 1911.

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