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HOW WE CAME BY OUR BODIES

BY

CHARLES B. DAVENPORT

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TO

JOHN CAMPBELL MERRIAM

WHOSE SUGGESTION INITIATED, WHOSE
ENCOURAGEMENT AND SUPPORT HAVE MADE POSSIBLE
THIS BOOK.

INTRODUCTION

In the past few years great advancement has been made in the science of heredity, or genetics. Also, our knowledge of organic chemistry and molecular physics has enlarged immensely. It has seemed desirable to bring the new principles that have been discovered to bear upon the subject of development, and specifically upon the development of the child. In this attempt it is necessary to express much in the form of hypothesis, or in lines of work still to be undertaken. There may be sections which will appear speculative. But hypothesis is necessary to point the way to new research and speculation may help in the formation of hypotheses.

The book has not, however, been written solely or primarily for the biologist. It is hoped that a careful reading of it will create a renewed popular interest in children as the most wonderful of natural creations. That there has been a loss of interest in reproduction is obvious from the rapidly declining birth rate. It is hoped that this book may restore an interest in reproduction of reasonably sized families as the greatest gift that one generation can make to the next. The book is the product of the mature consideration of a geneticist and eugenicist, and it is believed that it will show that the former can throw light upon the problems of the latter.

The author is indebted to many sources and individuals for aid in the preparation of this work. For illustrations he has drawn heavily upon *Developmental Anatomy* of L. B. Arey, published by W. B. Saunders Co.; *Textbook of His-*

tology of Maximow and Bloom, also published by W. B. Saunders Co. of Philadelphia; *Histology* of Ramón y Cajal, published by W. Wood & Co.; Jackson's edition of Morris' *Human Anatomy*, published by P. Blakiston's Son & Co. of Philadelphia; Sharp's *Introduction to Cytology*, published by McGraw-Hill Book Co., New York; J. Kollmann's *Handatlas der Entwickelungsgeschichte des Menschen*, published by G. Fischer, Jena, and *Handbuch der Entwickelungsgeschichte des Menschen* by F. Keibel and F. P. Mall, published at Leipzig by S. Hirzel. Grateful acknowledgment is made to the authors and publishers of these books for permission to use their figures. Precious photographic records, which are reproduced in the illustrations, have been received from the hands of Mrs. Wanda K. Farr, Dr. Charles W. Metz, Dr. H. W. Chalkley, Dr. J. H. Northrop, Dr. Ralph W. G. Wyckoff, Dr. William K. Gregory, Dr. Warren K. Lewis, Dr. B. H. Willier. The author is indebted to Dr. Calvin B. Bridges, Dr. W. E. Castle, Dr. S. Poljak and Dr. George L. Streeter for special data; also to Dr. Myrtle B. McGraw.

The entire manuscript was read by the late Dr. R. G. Harris and Mrs. Gertrude C. Davenport, sections by Dr. Bradley M. Patten and Dr. Robert W. Bates. The author is heavily indebted to these biologists for the assistance they have given. The author feels an especial sense of gratitude to the Carnegie Institution of Washington and especially its president, Dr. John C. Merriam, for the continued support that it has provided, making possible the preparation of this book after the author's retirement from administrative duties in connection with the Department of Genetics.

NOTE ON WEIGHTS AND SIZES

The study of the cell and its structure soon takes us into a realm of measurements where the measuring units in common use, like inches and ounces, do not readily apply. Accordingly, in this book, the reader is asked to keep in mind the more useful metric system of measures. To aid in this the following table will be useful:

Lengths

1 centimeter (cm.) = 2/5 of 1 inch.

1/10 cm. = 1 millimeter (mm.), about 2/3 the breadth of the head of a pin.

1/10,000 cm. = 10^{-4} cm. or 1/1000 mm. = 1 μ, about double the length of a wave of light.

1/100,000,000 cm. = 10^{-8} cm. or 1/10,000 μ = 1 Ångstrom unit, 1/2 the diameter of some atoms.

Weights

1 gram = 15.5 grains or 1/30 of an ounce.

1 milligram = 1/65 of a grain, weight of a hair about 4 inches long.

CONTENTS

PART I

THE COURSE OF DEVELOPMENT

Chapter		Page
1	THE BEGINNINGS	3
	The Egg Cell	3
	Making Room for the Sperm Cell and Receiving It	6
	Development Is Launched; the Egg Divides	8
	The Egg Enlarges; Becomes a Traveler; Develops a Great Thirst; Becomes a Parasite	11
2	OUTLINING THE GENERAL BODY FORM	19
	Plotting Out the Child	19
	The Food Sac and the Food Tube	25
	Head and Tail	26
	The History of the Neck	30
	The Machinery for Walking and Working	34
3	GETTING READY TO LEARN ITS WORLD	47
	The Central Exchange	47
	Eyes but No Light	58
	Ears but Nothing to Hear	66
	"The Very Image of His Father"	74
	Other Organs of External Relations	78
4	PROVISION FOR NUTRITION, SANITATION AND REPRODUCTION	86
	Lungs, before Air	86
	Digestive Organs, with Nothing to Digest	87
	Building the Pump and Laying Pipes for the Central Heating Plant and Community Food Distribution	93
	Plans for the Sewage System and Their Revision	95
	Boy or Girl?	101

CHAPTER PAGE

5 PUTTING ON THE FINISHING TOUCHES . . . 109
THE SKELETON IS REBUILT 109
THE EMERGENCY DEPARTMENT 115
PUTTING ON SIZE 120
THE CHILD IS BORN, HALF MADE 123
THE LONG, LONG ROAD OF CHILDHOOD 125
THE ADOLESCENT EXPLOSION 127
GROWN UP AND READY FOR HIS WORK IN THE WORLD . 130
SUMMARY 130

PART II

THE MACHINERY OF DEVELOPMENT

6 THE CELL AS A CHEMICAL FACTORY 137
SPECULATIONS BEFORE KNOWLEDGE 137
HISTORY OF THE CELL THEORY 146
THE CELL, A WONDERFUL MECHANISM 148
THE CELL WALL 150
THE SOIL AND ITS SEEDS 155
THE FERTILIZING MATERIAL—THE NUCLEUS . . . 158
SHARING THE FERTILIZERS—NUCLEAR DIVISION . . . 161
THE CHEMISTRY AND ARCHITECTURE OF THE CYTOPLASM; ESSENTIAL TO DEVELOPMENT BUT TOO SLOW . . . 165

7 THE GENES AND HOW THEY DO THEIR WORK 185
THE ACCELERATORS: THE GENES, EARLY GUESSES ABOUT GENES 185
MENDEL'S DISCOVERY 188
OUTGROWTHS OF MENDELISM 194
HOW GENES DOUBLE THEMSELVES 205
CONFLICT BETWEEN THE GENISTS AND CYTOPLASMISTS . 211
EVIDENCE FOR THE ROLE OF CYTOPLASM IN DEVELOPMENT 212
WHERE THE GENES DO THEIR WORK 218
HOW THE GENES SPEED UP THE ACTIVITY OF THE CYTOPLASM 227
DEGREE AND VELOCITY OF SPEEDING UP 237
BEGINNINGS IN THE DEVELOPMENT OF A TRAIT . . . 239

CHAPTER PAGE

8 THE MASTER BUILDERS 243
CELL DIVISION 243
IMBIBITION OF WATER 243
DIFFERENTIATION 244
THREADS AND TUBES 253
TRAMP CELLS AND THEIR MIGRATIONS 259

9 HOW THE SEVERAL TISSUES ARE MADE . . 264
BRAIN 264
MUSCLE 266
CONNECTIVE TISSUE 267
BONE 269
SKIN 278
BLOOD 281

10 MEETING STRESSES AND ACCIDENTS 285
MAKING EMBRYOS DEVELOP ABNORMALLY 285
HOW PART ACTS ON PART 286
NATURE'S PLASTIC SURGERY 292
INTRAMURAL MESSAGES: ENDOCRINE GLANDS . . . 297
MISTAKES OF THE BUILDERS 298
TWINS 300
SUMMARY 307

PART III

HISTORY OF THE ORIGIN OF THE MACHINERY OF DEVELOPMENT

11 THE HISTORY OF OUR GENES AND THE MECHANISM BY WHICH THEY HAVE BEEN HANDED ON TO US 313
BACTERIOPHAGE 315
VIRUSES 316
COCCI AND BACTERIA 316
YEAST 319
PROTOZOA 321
HOW WE CAME BY OUR GENES 324
HOW WE CAME BY OUR CYTOPLASM 326
HOW DID THE CELL ORIGINATE? 327

CHAPTER PAGE

12 THE CHANGING WORLD OF ORGANISMS; MUTATIONS AND HOW THEY ARE HANDED ON 330

ORGANIC CHANGE 330
STATURE 335
BODY BUILD 340
CEPHALIC INDEX 340
SKIN COLOR 342
HAIR COLOR 343
EYE COLOR 344
ALBINISM 346
HAIR FORM 346
HAIR LENGTH 348
BLOOD GROUPS 350
MUTATIONS IN METABOLISM 353
DEFECTS OF HANDS AND FEET 357
EYE DEFECTS 359
MUTATIONS IN THE MENTAL SPHERE 363
DISEASE RESISTANCE 365

13 THE PAST AND THE FUTURE 369

ANCIENT DEVELOPMENTAL PATHS 369
WHAT OF THE FUTURE? 382
SUMMARY 384

INDEX AND GLOSSARY 387

PART I

THE COURSE OF DEVELOPMENT

CHAPTER 1

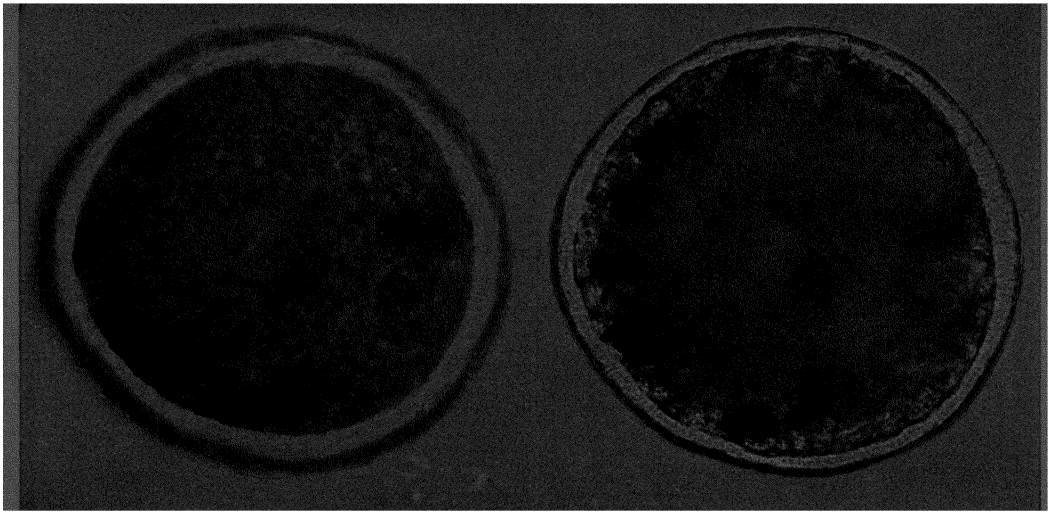
THE BEGINNINGS

THE EGG CELL

Each one of us was once only an egg, so we have a pardonable interest in what we looked like at that time. The human egg is pictured, much magnified, in Fig. 1. It is just visible to good eyes without the use of a lens.* We can roll it around in water and it is circular from every aspect, so it must be a sphere. The reason why it is a sphere is the same as the reason why a drop of rain in the air is a sphere. It is because, physicists tell us, of "surface tension"; because the surface molecules are attracted chiefly by molecules lying alongside and toward the center, and there are not equally attractive molecules outside. There is a thin membrane outside of the egg which doubtless helps keep the egg round. The inside is the more active substance. The interior of the egg is made up of little spheres of shining, fatty substance. This egg floats around in water. It has about the same specific gravity as water. Though not visible in the figure it is certain that a central clearer body, the nucleus, is present. This egg is a nearly typical cell.[1]

In the course of nine months the weight of this speck may increase 1,500 million times. The one cell will give rise to 26 trillion cells. During about fifteen years of growth this speck may, under favoring conditions, increase in length

* Its diameter is about $^1/_7$ of a millimeter, or $^1/_{175}$ of an inch. Its weight about 0.002 milligrams or $^1/_{15,000}$ of an ounce.



1a 1b

FIG. 1a. View just below surface of living human egg, showing general form and the mass of yolk particles.

FIG. 1b. View of same at equator, showing egg membrane. The clearer area at center probably indicates location of egg nucleus. (*Courtesy of W. H. Lewis.*)

FIG. 2. Comparison of a scarcely visible speck with the length of the line (folded to economize space) which represents the grown child, whose length is 13,200 times the diameter of the egg.

13,200 times (Fig. 2). The living speck will become a living man with his complicated tissues, his swirling fluids and cell movements, his vast intellect, of almost limitless comprehension, his ambitions, his emotions of hate and love, and his varying moods. There is no phenomenon in Nature, not even the universe of galaxies, that compares with the marvelous intricacies of development, composition and structure of a child.

It would seem to the non-biological observer quite hopeless to unravel the details of the processes by which this apparently simple egg develops into a child, but biological research has dissipated much of the mystery; at any rate has resolved the total process into hundreds of more elementary processes. We shall have a chance to see some of the things biologists have found out.

MAKING ROOM FOR THE SPERM CELL AND RECEIVING IT

Before the egg can begin to develop into a child something must happen to break the deadlock of slow division of the cell repeatedly into the same thing which had been going on for some cell generations. To develop a child there must be diversification of product—the formation of a complex, greatly diversified city of cells. And first of all an outside cell, the sperm cell, must enter into the egg cell. There it will act as chief planner to build up the city.

However, before the guest can be received, provision must be made for it. And so, before the sperm cell enters the egg, the egg casts out the equivalent of what the sperm brings in. Accordingly, we see the cell forming small buds at one point on its surface. These are called the "polar bodies" because they lie at one pole of the egg (Fig. 3). After the polar bodies are cast off, the sperm cell is ready to enter the egg and its nucleus may then join with the nucleus of the

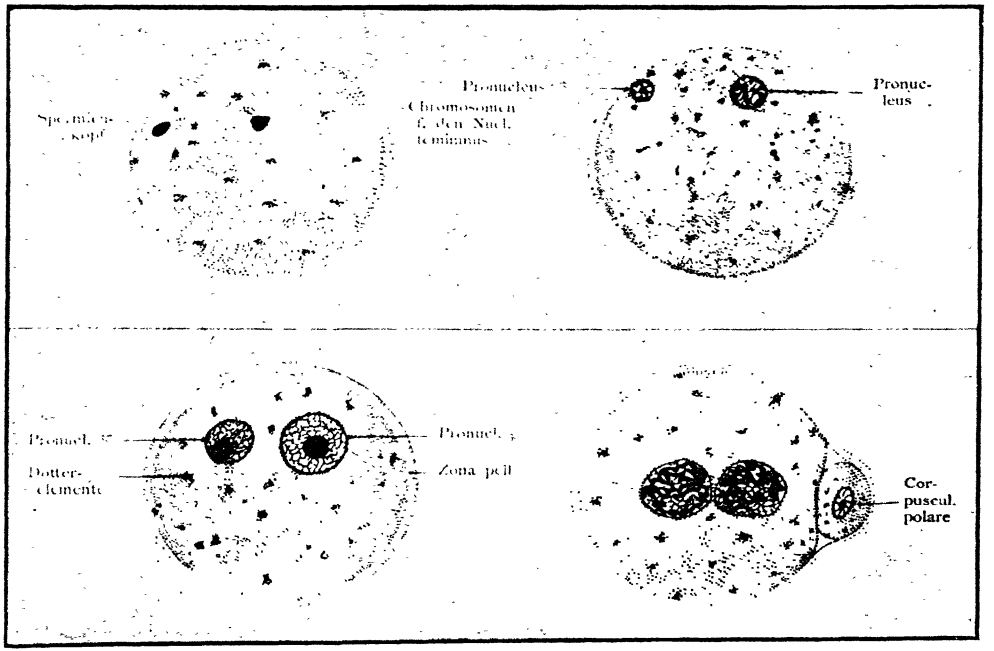


FIG. 3. The egg of a mouse in the act of uniting with the sperm nucleus. The first polar body (corpuscul. polare) is shown at lower right-hand corner. *(From J. Kollmann, "Handatlas des Entwicklungsgeschichte des Menschen," published by G. Fischer, Jena.)*

egg cell and by that means replace in the egg cell the equivalent of what it has thrown out (Fig. 4).[2]

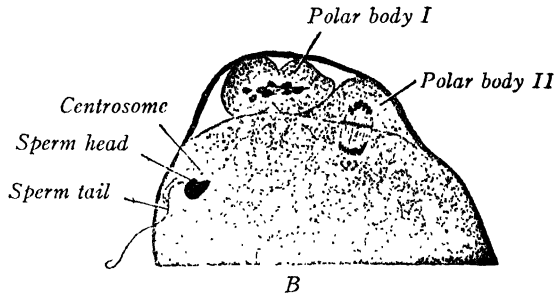


FIG. 4. Separation of the second polar body in the bat after the entrance of the spermatozoön into the egg. The first polar body is beginning to break up. × 500. (*After Van der Stricht, from Arey's "Developmental Anatomy," with permission of W. B. Saunders Co., publishers.*)

DEVELOPMENT IS LAUNCHED; THE EGG DIVIDES

A question often asked is: "Which is more important heredity or environment?" This is regarded by some as the supreme question in social biology. A little reflection shows that it is not easy to answer this question. In such an inquiry heredity is not to be thought of in the abstract, but only in reference to the individual under consideration. Likewise "environment" has always to be thought of in reference to the particular case in hand. The same set of external conditions may be bad for one person; good for another; all depending on the person. Thus, the same associates may attract a boy whose instincts and social conditioning are poor, so that for him they are bad; while they may repel a boy of high ideals who recognizes their conduct as antisocial and to be avoided; so that for him they are good companions, and constitute a good environment.

Again, an heredity that may be good for a boy brought up in a refined environment, say of Boston, may be poor for

a boy brought up in a frontier environment, such as parts of Texas or Montana. In fact, the quality of heredity and of environment are not to be considered apart from each other. They constantly interact and the end product is as much the consequence of that interaction as the effervescence that follows the addition of hydrochloric acid to marble is the consequence of interaction between the two.

There are those who see the importance of "opportunity" in the making of a successful man. No one can doubt the importance of fine opportunities for those who are capable of taking advantage of them. But training in painting is no opportunity for the color blind; training in mathematics no opportunity for those who cannot think in terms of mathematical abstractions. There is no opportunity in college athletics for the congenitally physically defective; no opportunity of advanced study for the mentally defective; no opportunity of musical training for those who cannot discriminate pitch, or who are born deaf. For all these and numerous other classes the door of "opportunity" is no longer open. Indeed, it was closed at the moment when the particular egg and particular sperm united.

Now that the door of opportunity is closed and locked the united egg and sperm (called zygote, from the Greek, meaning yoked together) must begin without delay the business of forming the child. It is a long road from 1 cell to 26 trillion cells, but it can be traversed by the simple process of cell division. One cell divided makes 2; the two divided make 4; the four divided make 8; then 16, 32, 64, 128 follow. Repeat this doubling forty-five times (i.e., 2^{45}) and you have more than the required 26 trillion. However, this possibility is actually not realized. Some of the descendant cells slow up very greatly in their division; others may go on to many more cell generations.

The process of cell division is supremely important. Two cells are to be produced ordinarily as much like the parent as possible in size and content. How can one cell divide into two of the same size as the parent? Obviously only by a doubling of each of the kinds of stuffs in the first cell.

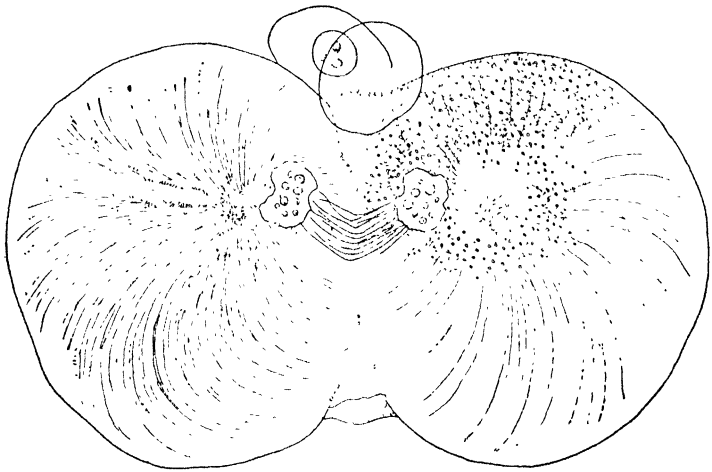


FIG. 5. View of dividing egg of the slug (Limax) showing the two nuclei and the polar bodies above and between the two cells. The centers of the very great activity of the cytoplasm lie near the nuclei. Moving pictures of living dividing eggs show the existence of a great turmoil of disruptive forces in the egg cell accompanying cell division. × 750. (*After E. L. Mark, "Maturation, etc., of Limax."*)

This is the most characteristic property of organisms, that by which each molecule is able to produce two molecules like itself. The division of the spherical egg, called cleavage, is a process unparalleled outside of living organisms. Internal forces have to break the surface tension that keeps the egg a sphere (Fig. 5). The cell elongates, surface tension asserts itself to draw the materials around two centers in place of one. This is not accomplished without a great turmoil in the protoplasm of the egg, powerful internal forces

make their appearance, the two halves are torn from each other, although remaining stuck together at one point, just as Siamese twins retain a connection. The divided cells are not wholly separate and alone in the world; they form part of a community of cells. Even when the body comprises billions of cells these are mostly in organic contact. The separate cells are merely housekeeping units.

THE EGG ENLARGES; BECOMES A TRAVELER; DEVELOPS A GREAT THIRST; BECOMES A PARASITE

The egg, newly escaped from the ovary, is usually met by the sperm in the tube which extends from ovary to uterus (womb). It begins its cell divisions soon thereafter and then starts a leisurely journey of three or four days toward the uterus, cleaving as it goes. It may take four to twelve hours from the time a cell divides until its daughter cells divide again. In the course of three or four days there will be formed a ball made up of smaller spheres (the cells). The mass as a whole has become larger and when magnified looks something like a golf ball.[3]

As the cells get more numerous they are pressed close together inasmuch as each seeks, as it were, the "front row" where it will get the best nutriment. About this time the egg begins to absorb water. This comes to lie at its center and helps the cells maintain their position on the outside. A relatively large amount of water is taken in and the egg grows rapidly at slight expense. It keeps on imbibing water for some days until, after six weeks, the egg is nearly 98 per cent water. By this means the egg comes to weigh about a gram, or nearly 500,000 times its initial weight, the increase being mostly water. Water is an economical material for growth, and it gives plenty of "elbow room" for the great operations that are to go on inside (Fig. 6). Not

less is the importance of water for the chemical processes upon which development depends. For water is the indispensable solvent, the carrier of the proteins and the sugars.

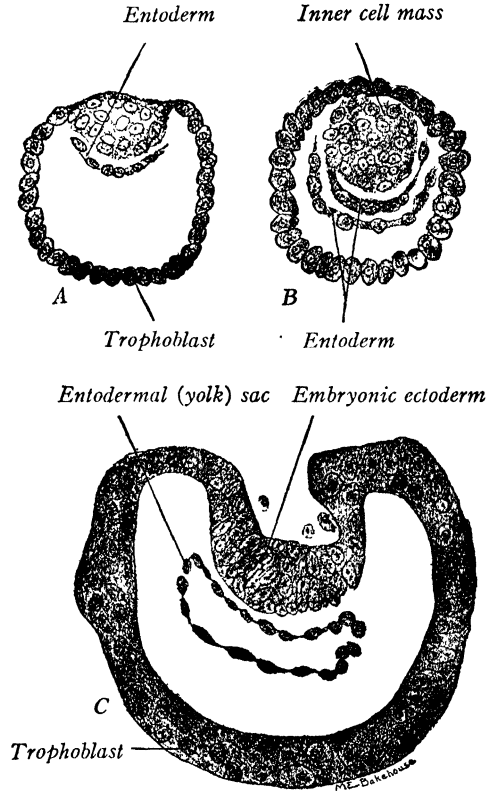


FIG. 6. Section of an "egg" (of a low primate, Tarsius), at a stage when it is a hollow sphere, filled with water, contained within a delicate membrane consisting of one layer of cells. × 260. (*After Hubrecht, from Arey, with permission of W. B. Saunders Co.*)

Before any circulatory system has developed in the embryo these dissolved nutrient molecules and ions that come from the mother must vibrate through the water spaces to reach

the living cells. Also water, with its great heat capacity, conducts the normal heat of the maternal body to every one of the embryonic cells. Water is indeed a wonderful

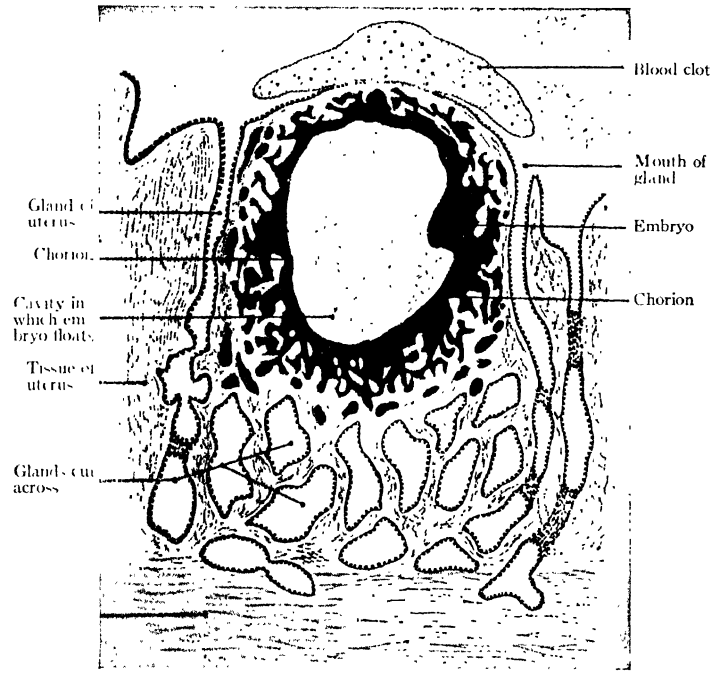


FIG. 7. Section of the wall of the uterus showing how the egg (also seen in section) is implanted in it. The wall of the uterus is richly provided with glands. Most of the embryo, with its large water-filled cavity, is engaged in making a union with the wall of the uterus. At the right of the cavity is seen a swelling of the egg wall. This is the beginning of the embryo proper, which will withhold its development until implantation of the egg is completed. × 18. (*After Peters, from Kollmann.*)

material without which life as we know it would be impossible. And at its very start the embryo makes very free use of it.[4]

Meanwhile the egg has traveled along the egg tube and has reached the uterus. Its wandering has probably been aided by the waving hairlets (cilia) and muscular contractions of the walls of the tube. The egg has now reached a relatively large cavity and is in danger of getting forever lost. It still has to become implanted. Threads of cells grow out from the sphere and burrow into the maternal tissues (Fig. 7). These cells establish the most intimate connection with the tissue of the mother's uterus and soon fine blood vessels extend from the mother's tissue into the threads of cells (now called villi) of the developing egg (Fig. 8). This is the beginning of what becomes in time a huge organ for interchange of body fluids between embryo and mother. This organ is known as the placenta. The young embryo has become, some nine days after fertilization, implanted.

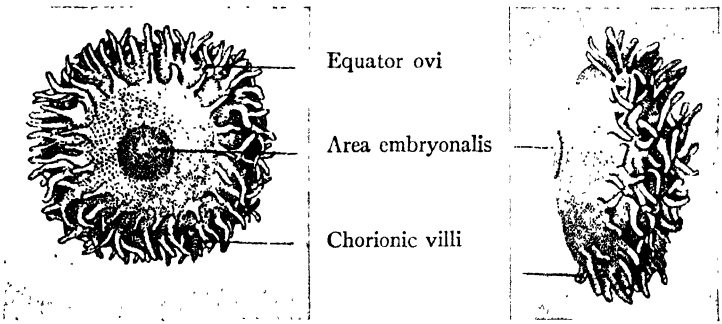


FIG. 8. Two views of the implanted human egg, about 12 to 13 days old. The embryo proper occupies a small area in the center. All around the outside of the egg are seen the villi by which the egg comes into intimate union with the wall of the uterus. This egg is actually about 5½ mm. (1/5 inch) in greatest diameter. (*After Reichert, from Kollmann.*)

All animals that, as embryos, interchange materials with the mother (blood, urea, etc.)—they used to be called viviparous (born alive) as opposed to oviparous (or born as eggs)—have some apparatus for the interchange. This

group includes all (except the lowest) of the mammals—the group to which man belongs. Some fishes and even a kind of toad and a few species of reptiles are viviparous, but in the last group the retention of the embryo in the uterus is probably more for protection than for feeding.

The attachment of the egg to the mother's uterus has important consequences. The number of developing young must be restricted to the capacity of the mother to carry them. The oyster lays up to 50,000,000 eggs in one spawning season; obviously not all of them could develop inside of one oyster. Again, the number of viviparous young does not have to be so great as the number of young of the oyster because of the great protection that the adult mother's body gives. Of the 50,000,000 eggs of the oyster vast numbers are eaten by other marine animals as they are being laid; others fail to be fertilized; the mortality rate of the feeble young is enormous. In the higher mammals, on the other hand, the young are born either practically ready to look out for themselves or else they get maternal care, and consequently only from one up to about twenty young are carried at a time. Maternal care, filial affection, the home, the family, these are all consequences of development of the young in the uterus of the mother and depend in last analysis on the evolution of the placenta.

The attachment of the embryo to the mother is a risky procedure. By this union the embryo becomes, in a way, a parasite upon the mother (Fig. 9). It does not have to find its food, to prepare it for digestion, nor even to digest it. All this is done by the mother. Now it is characteristic of parasites, which live in the body of another species that serves as their host, that they undergo degeneration. Since they do not consume solid food they do not have to digest

their food. They may lose their stomachs and, indeed, the whole food canal may degenerate. Since they do not have to seek for food or mates the organs of locomotion and of sense (eyes, ears and so forth) may degenerate (Fig. 10). Now one might expect, that the human fetus, as a quasi-

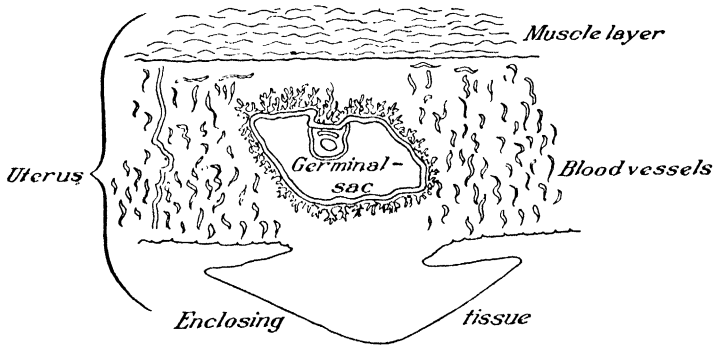


FIG. 9. Section through human egg of age of 2 weeks. The embryo proper with its germ and yolk sac are seen hanging in cavity of the egg. These are attached to the wall of the egg with its villi, and it is through them that the embryo receives nourishment. × 5. (*After Eternod, from Stelz.*)

parasite, would show some consequences of that life in a loss of the feeding and sensory organs. On the contrary, though fed a fluid food and living in the dark, the mouth, stomach and rest of the food canal and the organs of vision and other organs of sense, proceed on their way through a complicated course of development to form organs that have a significance only for a remote future state in the development of the child.

The difference between a typical parasite and the human fetus is, however, twofold. The typical parasite passes to maturity inside of the body of the host and since it at no stage uses its digestive or sensory organs it does not have to develop them. On the other hand, all mammals end their parasitic existence at a relatively early stage and during

their parasitic life are engaged in preparation for their non-parasitic career.

There is one other difference between typical parasites and the mammalian parasitic fetus and that is that the former are located inside of other species than their own,

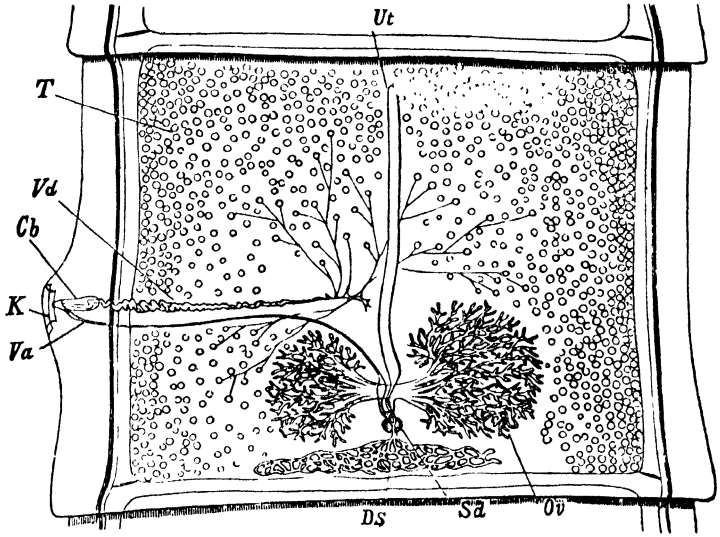


FIG. 10. Drawing of one unit of the chain of units of a human tapeworm. There are to be seen only male reproductive organs (*T*, testes; *Vd*, vas deferens) and the female organs (*Ut*, uterus; *Va*, vagina) and their outlets. *Ov* is the ovary. *Ds* is the gland that furnishes yolk to the eggs. *Sd* is the gland that forms the protecting membrane to the eggs. *Cb* and *K* are the outlets of the reproductive organs. (*After Sommer, from Claus, Textb. of Zoology.*)

whereas the mammalian fetus is a part, as it were, of the mother. It is consequently of much the same chemical make-up as that mother and is, indeed, an organ of the mother. Now, just as an organ of the body, like the brain, does not have to digest its own food or have its own locomotor organs but undergoes its development in its own special way, utilizing the fluid food which is furnished to it

by the common blood, so the human fetus as an organ of the mother goes its predestined course of development and creates organs which are of no use to it during its psuedo-parasitic existence, but do have a prospective value.[5]

---

1. The first photograph of the human egg was taken by Dr. W. H. Lewis of the Department of Embryology, Carnegie Institution of Washington, published in Bulletin, Johns Hopkins Hospital, Vol. 48, pp. 368–372.

2. Polar body formation has been known for a century, having been figured by a German zoologist, Carl Gustav Carus, in a prize essay published in 1824.

3. The early development of the mammalian egg before and during implantation into the uterus wall is being currently worked out in the macaque monkey by W. H. Lewis and C. G. Hartman, of the Carnegie Laboratory of Embryology, with greater detail than hitherto. See Contributions of that Laboratory.

4. The great role of water in early development was first worked out in detail by the author in 1897 for frogs. Vierordt in his *Daten und Tabellen*, 3rd ed., p. 378, cites Bischoff as finding 97.54 per cent water in a fetus.

5. On parasites pioneer work was done by Rudolf Leuckart in the middle third of the past century. Robert W. Hegner is active currently at Johns Hopkins University.

CHAPTER 2

OUTLINING THE GENERAL BODY FORM

PLOTTING OUT THE CHILD

Let us return, now, to where we left the egg attaching itself to the lining of the maternal uterus. Up till now it has developed only a hollow sphere of cells and outgrowths from that sphere to form the villi. Up till now few steps have been made to form the child proper. All these stages have been merely preparing the way. A good deal of time has been consumed in this process, something over a week; but it is time well spent because without the maternal union the embryo cannot develop at all. In the case of the human child the time spent in building a well-developed placenta, as the attachment to the uterus is called, is only a small fraction, perhaps 3 per cent, of its intra-uterine life. But in the case of some other mammals, like the mouse, the fetus spends eight days, or nearly 45 per cent of its intra-uterine life, in becoming attached to the mother and only ten days more are allowed for its development from a small group of cells to an infant mouse which is capable of suckling and of a great variety of movements.[1]

The first indications of the future consist of a thickening of the originally single layer of cells of the hollow sphere to form two or more layers which bulge into the cavity of that sphere (Fig. 11 B, I.C.M.). As this thickening grows into the cavity two hollow spaces arise in it; separated by two layers of cells (Fig. 11 C). The lower cavity occupies the position of the future food canal. The other cavity soon

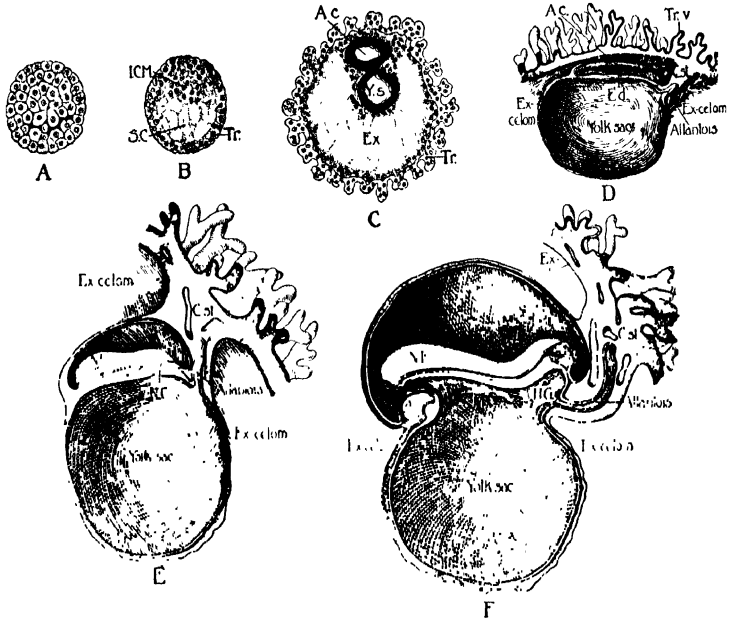


FIG. 11. A series of diagrams illustrating the later changes in the egg and the formation of the embryo. A, a mass of cells derived from cleavage of the newly fertilized egg. B, the fluid-filled cavity (S.C.) is formed, the membrane (Tr.) that comes in contact with the uterine wall; and the inner cell mass (I.C.M.) from which the embryo proper is to arise. C, the formation of the villi, and the further development of the embryo with its yolk sac (Y.s.) and amniotic cavity (A.c.) that comes to surround the embryo proper. Ex., the extra-embryonic cavity, old water space. Tr., the trophoblast. D, a later stage, showing on a much enlarged scale the embryo proper, embryonic disc (E.d.) above and yolk sac below. Tr.v. represents the villi, C.st., the stalk connecting the embryo with the part of the egg uterine wall (nascent placenta); the "Allantois" appears, representing a sort of breathing organ of bird embryos but functionless in the human fetus. E, the embryo is enlarging. The brain and spinal cord are arising from the neural folds (N.F.). N.C., the neurenteric canal between neural folds and yolk sac. F, the gut (M.G., mid gut and H.G., hind gut) is forming. The heart (H) can already be seen. *(Based on researches of Broman, Brödel, Dandy, Eternod, Lewis, Muller and Strecter. From Jackson-Morris, "Human Anatomy," with permission of W. B. Saunders Co.)*

becomes larger than the first and comes to extend over the first cavity as a partly deflated air cushion might. The second part (called cavity of the amnion) becomes filled with fluid and in this way forms an important cushion between the embryo which is being formed and the wall of the

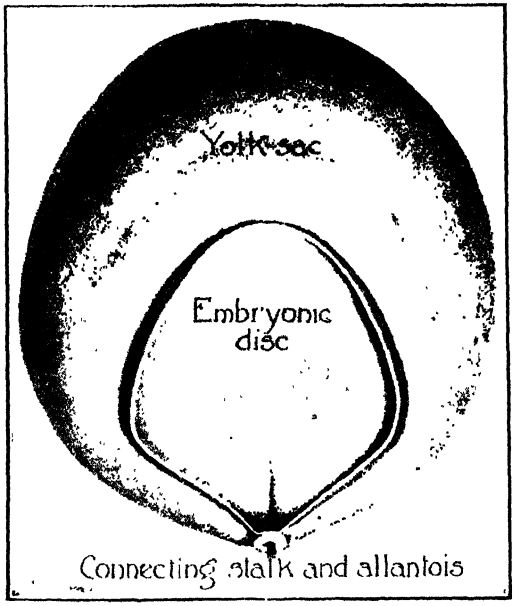


FIG. 12. An upper (dorsal) view of the embryonic disc and yolk sac of a human embryo of the early part of the third week. Note that a longitudinal axis is already laid down. Right and left halves of the body are established. It is out of this disc that the future child is to arise. The stalk connecting embryo with the nascent placenta is indicated. (*Contributed by Dr. George L. Streeter, Carnegie Institution of Washington.*)

uterus from which it is not far removed (Fig. 11 D, E). It eventually forms part of the caul which accompanies the child at birth; but not usually still surrounding it, as happened in the case of David Copperfield.[1]

The two cavities thus established now become lengthened in one and the same axis and in this elongation there is laid down the axis of the nascent child. Thus the beginnings are established of the embryo, suspended, as it were, between the yolk sac cavity below and cavity of the amnion above (Fig. 11 E). In the membrane lying between two cavities, made of its two layers of cells, there soon appears such a thickening of these cells as to form a distinct plate or disc which is known as the embryonic disc (Fig. 12).

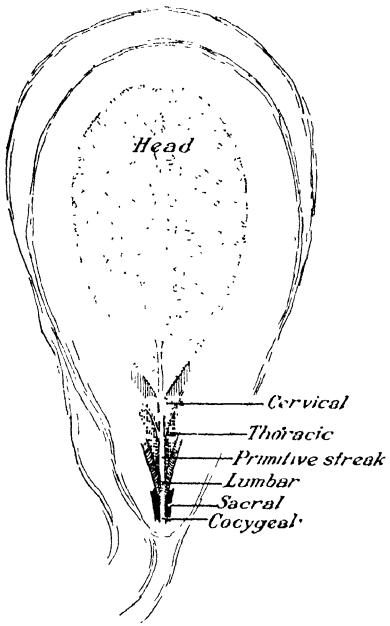


FIG. 13. Dorsal view of human embryonic disc about 18 days old, drawn from a model after C. H. Heuser. The portions of this disc that are to give rise respectively to the head, the neck and the trunk (thoracic, lumbar, sacral) are indicated on the drawing of the model by cross hatching. (*Data supplied by Dr. George L. Streeter, Carnegie Institution of Washington.*)

The disc, at first nearly circular, soon becomes ovoidal, and already in this flat double plate of cells one may locate the sources of the future parts of the body. The embryo has, in a sense, begun to lay out the plan of the child; to plot the job that it has before it in development. In Fig. 13, one sees that already nearly three-fourths of the disc is told off for the production of the head. Immediately behind this is the part of the disc which is to form the neck, the trunk proper and the tail. On the margins of the disc there are areas from

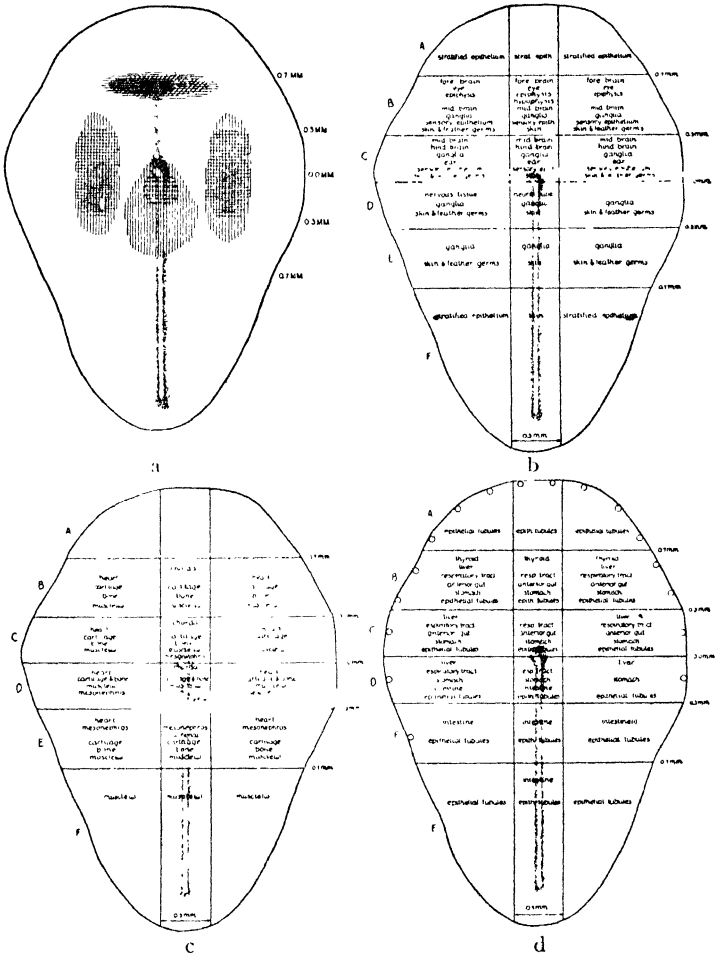


FIG. 14. Outline of the disc of the embryonic chick when about 4 mm. long showing the position of the cells that are to give rise to the different organs. a. Chart showing the position and shape of the areas of the blastodisc that are to form the eye (in front), the heart (on right and left sides), and mesonephros, or second kidney (in middle). The density of the shading within the areas indicates roughly the intensity of the developmental potency. b, c, d. Similar charts showing location of more superficial, middle-lying and deeper-lying organs respectively. (*Contributed by B. H. Willier.*)

which the sides of the head and body wall are to be formed, and from the cells of these margins will arise by a down-folding the under, front or stomach side of the body. From areas at the right and left of the cervical and lumbar regions, respectively, will arise the upper and lower limbs. Thus the future parts of the embryo are at an early stage blocked out in this small disc.[2]

The localization of definite organ-forming areas is shown in still greater detail in the embryonic disc of the chick where the potentiality of each group of cells has been tested by seeing what it develops into when allowed to grow by itself. Such growth is possible by grafting the cells on the embryonic membranes of the chick, a method developed by Benjamin Harrison Willier. The results are well illustrated by Fig. 14.[3]

The human embryonic disc, as we saw, is composed of two layers, the lower one next to the yolk sac cavity and the upper one next to the amniotic cavity. The lower layer is concerned entirely with forming the food canal and its appendages. It is called the inner skin or entoderm. The upper layer is concerned with building the outer skin of the animal and the brain and spinal cord, which are originally part of that outer skin. This layer is known as the ectoderm. The ectoderm and the entoderm are curved membranes that practically touch along the axis of the embryo (Fig. 15). In the interspace, on each side of the axis at which the membranes touch, there arise groups of cells and these are destined to form the muscles, skeleton, and many other organs and tissues of the walls of the body and the limbs. These cells come either to lie in membranes, when they constitute the middle skin or mesoderm; or else they form loose cells, when they are called mesenchyme.

With the establishment of the main axis of the future

embryo, with the formation of its two main membranes, entoderm and ectoderm, and with the production of the intermediate cells (mesoderm and mesenchyme) to form the intermediate parts, the embryo is laid down and ready to begin the development of its various organs.

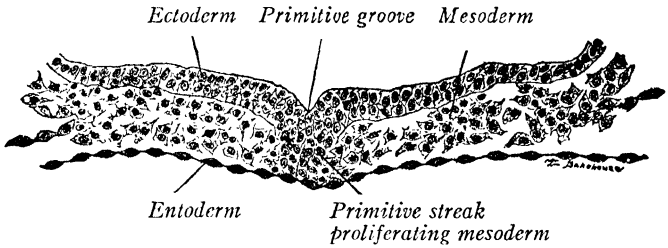


FIG. 15. Cross section of an extremely early human embryo showing the way in which the ectoderm is directly continuous with the entoderm at the primitive streak. At this same line of union the mesoderm is arising from migrating cells. × 185. (*After Streeter, from Arey's "Developmental Anatomy," permission of W. B. Saunders Co.*)

All this development of the future parts is taking place in a disc which is only about two millimeters in diameter or about one-tenth of an inch. The total number of cells involved in this embryonic disc is as yet only a few thousand, and of these small groups of cells are already told off for the special organs. And already the cell protoplasm is different in these diverse regions as it doubtless has been from the beginning.

THE FOOD SAC AND THE FOOD TUBE

The yolk sac cavity is, as we have seen, one of the earliest parts of the embryo to be formed. It is not an entirely closed cavity, but is connected by a slender passage with the cavity of the incipient spinal cord (Fig. 11 E, N.C.). That slender passage is believed to correspond with the neck of the sac that in more primitive forms is pushed down from

the outer layer of cells to form the food sac (Fig. 16). In most animals the walls of this food sac are very thick and full of food particles which supply energy for growth of the developing embryo (Fig. 16). In the human fetus, however, the food does not have to be supplied by the cells that line the yolk sac, for it is imbibed entirely from the mother, and so the wall of the food sac remains thin. As the axis of the future embryo elongates, so does the upper part of the cavity of the yolk sac, forming the gut. The opening into the embryonic spinal cord now becomes closed and in due time the gut becomes provided with a mouth, and is thus changed into a food tube (Fig. 17). Since the fetus does not have to feed on solid food, it will be some weeks, however, before this tube is completed at both ends.

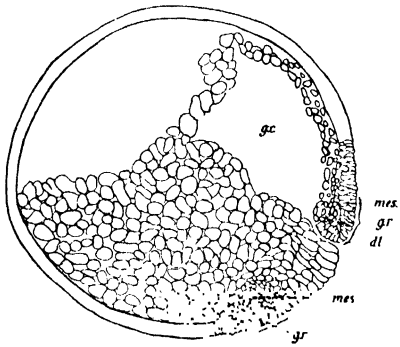


FIG. 16. A section through the middle of the developing egg at the gastrula stage of the salamander Amblystoma. The ectoderm passes directly into the entodermal lining of the digestive cavity (*g.c.*) at the lip of the blastopore (*dl*). The mesoderm (*mes.*) is arising in the region of the blastopore. *g.r.* represents the area of mesoderm formation. (*After Eycleshymer from McMurrich's "Development of the Human Body," permission of P. Blakiston's Son & Co.*)

HEAD AND TAIL

We have seen that as the axis of the future embryo is laid down on the embryonic disc practically three-fourths of it are told off to form the future head, the other quarter to form the body from the head down (Fig. 13). This distribution of space seems unfair to the future lower parts of

the body, but it is an example of a general law in the development of animals, that the head end develops first. This principle is sometimes known as cephalic precocity. Accord-

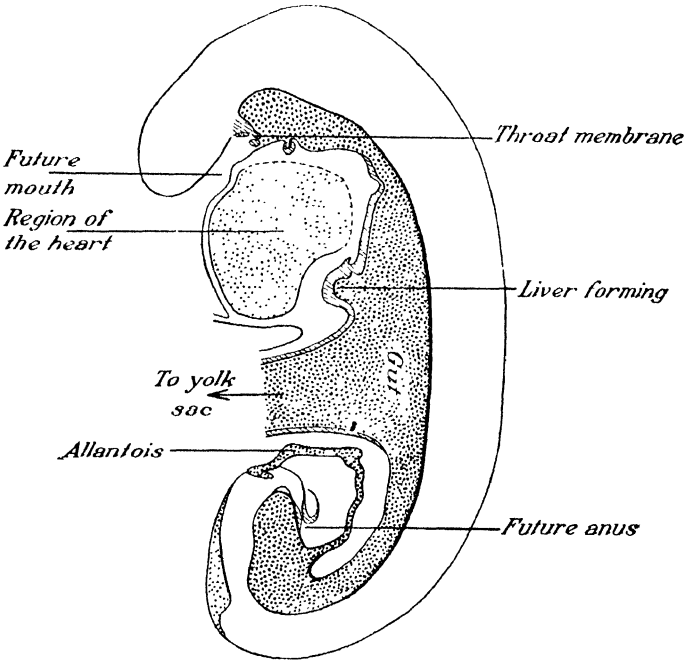


FIG. 17. Graphic reconstruction of an embryo of the third week of development, showing a median sagittal section through the gut. × 40. The Allantois is rudimentary. The cloaca at the hind end of the gut is still closed by a membrane at the site of the future anus. The gut communicates widely with the yolk sac. The pharynx is still closed at the mouth end by a throat membrane. The liver and heart have begun to form. (*After Allen Thompson, from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

ingly, during the middle stages of development, after some weeks have passed and the head is formed, it appears as the most striking feature of the body. Also, the child at birth has a head which is relatively much larger than in the grown person. This appears from the outline in Fig. 18; see also Fig. 19.

The tail end of the embryonic disc, much the slower in making its development, will produce a real tail by which the body is prolonged far beyond the site of attachment of

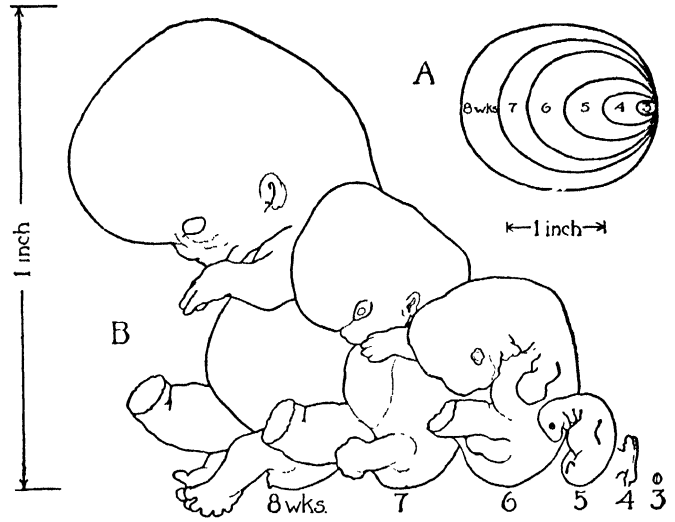


FIG. 18. A. Outlines of the average human "egg" including membranes from 3 to 8 weeks of age, ½ natural size. B. Outlines of human embryos from the third to the eighth week, enlarged 2.5 times. Note: the rapid development of the head with its huge brain, the precocity in development of fingers over toes, the early formation of the eye, the beginnings of the external ear at 7 weeks, as the gill furrows fade away; the late development of facial features. (*After Evans from Jackson-Morris, "Anatomy," permission of P. Blakiston's Son & Co.*)

the future lower limbs, as we see in Fig. 19. Only much later, after the limbs have become well established, does this tail of the human embryo gradually fade away and become more or less absorbed. Eventually it forms the so-called coccyx of the adult. Rarely the tail persists in the infant. It is, however, never functional as in a dog * (Fig. 20).[4]

* James Burnett, Lord Monboddo (1714–1799) was a Scottish judge and anthropologist, who was one of the first to urge the origin of man from the lower Primates. It is stated that on advocating this view before the

The head and the tail, however, do not begin to form until a preceding step has been taken. That step is the formation of a groove (neural groove) on top of the embryonic

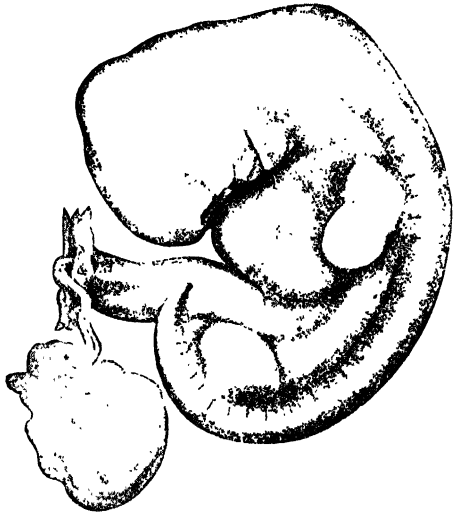


FIG. 19. Photograph of a human embryo, 115 mm. long, diameter magnified five times. This embryo is a little less advanced than the embryo of six weeks shown in Fig 18 (compare hind limbs). The upper limb has two segments but as yet no fingers. It is far advanced over the lower limb. The tail has not reached its greatest length. The muscle masses are blocked out along the axis of the trunk and tail. The gill furrows are beginning to disappear. At the left is the cord connecting the embryo with the placenta, which is partly of embryonic, partly of maternal origin. (*After Minot from Morris-Jackson's "Human Anatomy," permission of P. Blakiston's Son & Co.*)

FIG. 20. External tail, 9 inches long, in a twelve-year-old boy from French Indo-China. (*From A. H. Schultz, 1925.*)

disc running from near the head end down to the tail. The front part of this groove is going to be depressed more and

English king (George III) that monarch wise-cracked: "Show us your tail, Monboddo!" The king was unaware, first that he, himself, once had a tail, and secondly, that the anthropoids, like man, are tailless.

more, and as it gets deeper and deeper its walls get higher and higher and eventually the upper edges of the groove, that is the tops of the lining walls, lean toward each other and thus close the groove and make a tube out of it (Fig. 21). It is from the walls of this neural tube that the brain at the upper end, and spinal cord along the back are formed. It is from these walls that eventually the nerves that supply the muscles of the trunk and the limbs arise.

THE HISTORY OF THE NECK

The neck occupies one of the largest parts of the axis of the future embryo upon the embryonic disc, as Fig. 13 shows. This is the more remarkable since the neck is a relatively unimportant part of the child for some time before birth and after. However, in an embryo that is about one-tenth of an inch (0.25 cm.) long, and has already been developing for several days since the implantation of the egg, it constitutes a very important part of the body. There soon arise upon it four interesting furrows or slits, running almost at right angles with the neural groove already referred to. These furrows are clearly shown in Fig. 18 (5). They agree in position with the row of arches which, in fishes, bear the gills. Between the arches there occur, in fishes, deep slits which pass all the way into the cavity of the throat, so that the water in which the fish is swimming and some of which is almost constantly entering the mouth may pass out through them. At the same time the gills that are on the sides of the slits receive further oxygen. Now in the human embryo the slits are not fully formed, but the arches play an important part, though a transitory one, in development. In those arches are blood vessels, just as there are in the fishes, only since there is no facility in the human embryo for taking oxygen

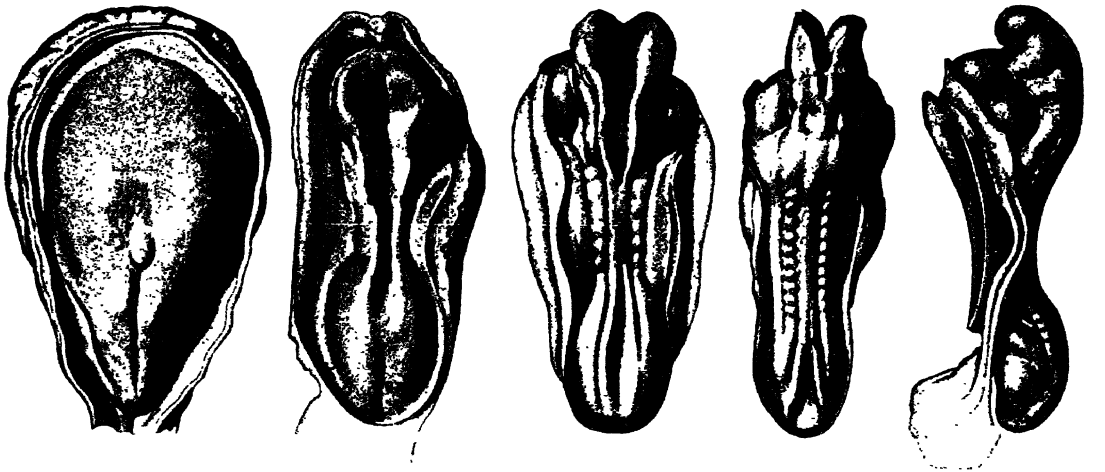


FIG. 21. Photographs of a series of models showing the changes in body form in early human embryos. *A–D*, dorsal views; *E*, lateral. *A*. Embryonic disc with primitive groove. (See also Fig. 12.) × 40 (Heuser). *B*. The neural groove is a deep furrow. × 37 (Ingalls). *C*. The neural groove is closing in the middle of its course between the 7 primitive muscle masses. × 31 (Payne). *D*. The neural tube has now become a canal, still open at its two ends. The walls of the brain are closing. × 31 (Corner). *E*. The stage with 19 primitive muscle masses. The body is rising from the blastodermic plate as a cylinder. The head projects at the upper (front) or anterior end. (*From Arey, "Developmental Anatomy," permission of W. B. Saunders Co.*)

from the surrounding fluid no gills are formed. Accordingly, the blood vessels play a different role and some eventually branch off to the lungs. Thus approximately the same blood vessels which serve for breathing by means of gills in fishes have, by a slight change, come to serve in the respiration of the child.[5]

It may seem remarkable that these gill furrows and arches should appear in the human embryo where they are never to be used for breathing. But they have a use nevertheless. To illustrate this point I may refer to some of the parts which are derived from the different arches. Thus from the first arch arise the muscles used in masticating food, and in it is included the nerve trunk which runs to these muscles. The supporting skeletal parts that arise in the bar give rise to the small bone in the middle of the ear called the malleus. From the cleft, or narrow slit, between the first and second bars there arises the external ear opening, and from the inner part of this cleft there arises the Eustachian * tube the presence of which one feels when one goes up and down in airplanes. Passing rapidly to a high elevation may cause pain in the ear due to the fact that the pressure on the inside of the eardrum is greater than that on the outside. By swallowing, however, or better by holding the nose and blowing, the air on the inside of the eardrum passes into the throat through the Eustachian tube and thus the tension becomes equalized. The outer ear passage and the Eustachian tube thus together represent the first gill cleft of fishes and are the only remnant of those passages from the throat to the outside that we find in fishes.

The second gill arch gives rise to certain muscles of the

* Named for Bartolommeo Eustacchi, anatomist at Rome in the sixteenth century.

face and contains a nerve which innervates them. The skeletal bar gives rise to the body of the hyoid bone which lies at the base of the tongue, also to a part of the third of the small bones of the inner ear, namely the stirrup or stapes. Part of the tonsils are derived from the inner part of the incomplete slit lying between the second and third gill arches.

The third gill arch produces certain muscles which constrict the larynx, and from its skeletal bar is derived an important part of the hyoid bone. From the region of the groove between the third and fourth arches are derived certain portions of the glands of the throat (thymus, parathyroid). Finally, from the last arch are derived certain muscles of the pharynx and the upper part of the respiratory apparatus, and from the skeletal bar is derived, in part, the cartilage of the Adam's apple.* The inner part of the region of the cleft gives rise to a section of the thymus gland. Thus we see that the gill arches are not produced in vain in the child. Having done their work of forming important organs of the neck the surface grooves of the gill arches themselves usually vanish. Rarely, openings persist in the neck of the adult which represent unclosed gill slits (Fig. 22).[5, 6]

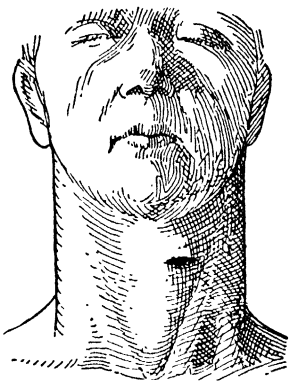


FIG. 22. Drawing of the neck of a man showing the outer end of an open communication from the pharynx to the external surface of the neck. This "fistula" is due to the fact that one of the gill furrows actually formed a gill slit and the open cleft failed to close. (*After Arey, from his "Developmental Anatomy," permission of W. B. Saunders Co.*)

* Legendarily, supposed to have been caused by a piece of the apple which stuck in the first Adam's throat.

THE MACHINERY FOR WALKING AND WORKING

Animals, in contrast to most plants, can move from place to place; or if they are attached at some time of their life they can move their bodies about in reaching for food. These movements they are able to make by virtue of their muscles. In adult man the total muscles of the body make up two-fifths, or more, of its weight. The job of developing them is an important one which starts in very early. Already at the stage of the embryonic disc (Figs. 12, 15) and still more obviously later (Fig. 21, D), masses of cells arise on each side of the axial line. These masses soon form blocks of tissue (called myotomes) arranged in a paired series along the axis and give to the embryonic body the appearance of being made up of a series of rings, like an earthworm, all the way down to the tip of the tail (Fig. 24a). These myotomes will give rise to muscles of the body wall. This ringed condition of the body becomes gradually somewhat obscured as the embryo develops, but it is shown in the body of a slender man, or a thin dog, where the ribs constitute the boundary between the muscular rings. In fishes this ringed condition of the body is still more obvious. Every one knows the series of spinal bones and ribs that make eating of fish somewhat hazardous: the muscles run from rib to rib. In fact the human embryo affords very clear evidence that man is, after all, one of the animals in which the body is made of a succession of rings, like the body of fishes and of earthworms.*

In the trunk region there soon begin to arise (at about the fourth week of intra-uterine life) a pair of stumps, one just behind the gill arches and one at the base of the tail

* Our pious ancestors, who in appealing to the Deity often alluded to themselves as worms, were more properly referring to their remote ancestors than to themselves.

(Fig. 19). These are to produce the upper and lower limbs respectively. Into these little swellings the cells of the mesoderm, referred to above (page 24) penetrate, causing them to become longer and longer. At the same time, in the axis of the swelling other mesodermal cells begin to

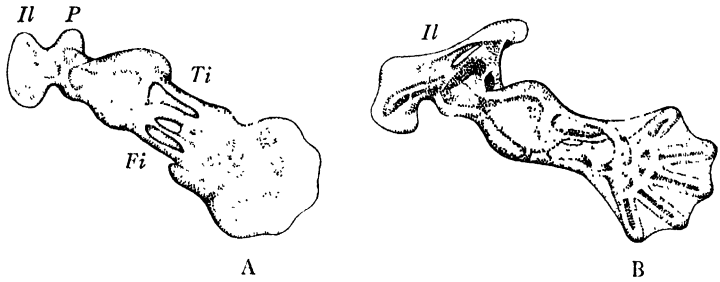


FIG. 23. A. Lateral aspect of model showing an early stage in the development of the lower extremity in the child. At the left is the cartilaginous skeleton of the lower part of the trunk and tail to part of which at a later stage the extremity becomes attached. The limb bones, all in cartilage, show parts as follows: *Il*, the ilium, largest bone of pelvis, forming its brim; *P*, pubic bone, to form front of pelvis. *Fi*, fibula, the outside bone of the lower leg; *Ti*, the main, inside, bone of the leg. To the left of these the humerus is forming. At the figure's right is a plate of tissue which shows 5 cremulations at its outer margin. This is the nascent foot and 5 toes. B. A similar model showing lower extremity at a later stage. The pelvis (*Il*) is already attached to the vertebrae. Beyond tibia and fibula the wrist bone and 5 rays which will eventually form the instep bones and the 5 toes are well laid down. (*After Bardeen, from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

form a skeleton, and as the skeleton begins to elongate by growing at each end the appendage does so likewise. Very soon three segments become obvious. One next to the body gives rise to the attached segment of the limb, the middle segment gives rise to the corresponding part of the finished limb. The outer segment is at first a paddle, but soon on its edges a series of corrugations or lobes appears. Eventually each of these five lobes gains a skeleton, and as the skeleton elongates the fingers (or toes) are formed (Fig. 23).

In each of these fingers, or toes, in turn the skeleton divides into three or four bony segments.

At the same time that the bones are laid down in the limbs, other tissues penetrate. First come, as just mentioned, the mesodermal cells, which elongate and eventually give rise to the muscles that move the different segments upon each other and the limbs as a whole upon the trunk. Hand in hand with the development of these muscles there penetrate into them the nerves that arise from the spinal cord. These nerves attach themselves to the appropriate muscles and make it possible for them to be moved at the demands of the will (Fig. 24, a, b). In the development of the appendages the law of cephalic precocity, referred to above (page 27) still holds, so that the upper limb is formed much in advance of the lower limb, as we see in Fig. 19. Though the upper limb is formed first, yet it eventually falls behind the lower limb in length as we see already in the child at birth.

Let us go back to the muscles that grow out into the limbs, by virtue of which we are able to go from place to place without artificial aid in transportation and to do the work in the industries and farms that require the use of strong arms and hands.

The number of muscles that we have in our arms and legs is pretty well fixed by the internal factors that mold the body; but these muscles are very responsive to use, so that we find the muscles of walkers and jumpers and those of the blacksmith and others who do heavy work, to be far better developed than those of persons whose occupation is almost wholly sedentary, and who make relatively little use of the appendages. Of all the parts of the body the muscles are, perhaps, the most strikingly responsive to the demands made upon them, and the muscles are

developed at a time when there is comparatively little use for them. However, having been formed, the muscles are used by the fetus in rearranging its limbs even as early as the tenth week of development, possibly earlier. This is all in accordance with the principle that the child develops with reference to future needs, and not with reference to current ones. We shall find that in the details of development in the embryo there is constant adjustment to current needs, and that the proportions of parts are constantly changing during development until the adult stage is reached.

The first limb muscles that arise in the lower limb, for example (Fig. 24b), come one from each of the adjacent masses of the trunk. Later, as the limb skeleton is developed in something like its final form the muscles lose their segmental nature, elongate greatly and become attached by their two ends to bone. Already at the age of eight and a half weeks some of the muscles of the adult can be identified. In the thigh, there is the biceps femoris (below) which runs from ischial (or sitting) part of the pelvis to the upper ends of the bones of the (lower) leg segment. This is of use in the adult to help move the thigh back and forth and to flex the leg. The great rectus femoris muscle which runs from pelvis to the patella, has already made connections; and the tensor fascia latae is in place attached to the brim of the pelvis. Another muscle shown in Fig. 24b is the anterior tibial (M. ant. tib.). This muscle runs from its two attachment points, the upper end of the tibia to the base of the great toe. On contraction it extends the great toe. There are still other leg muscles present that move the other toes.[7]

The muscle cells are from their origin elongated. Their ends are associated with the mesenchymal cells that are

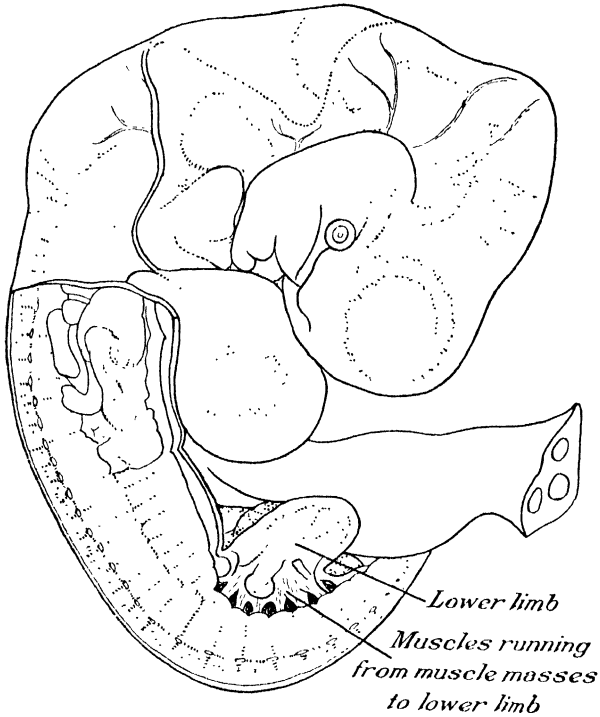


FIG. 24a. Human embryo of 9 mm. length showing the lower limb of the right side and the beginnings of the muscles that are to work the limb. All along the back are the trunk rings—the myotomes—from which the trunk muscles are to be formed. Note traces of the gill bars behind the eye. The upper limb is represented by its skeleton of about the stage of development of Fig. 23, A. (*After Bardeen and Lewis, redrawn from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

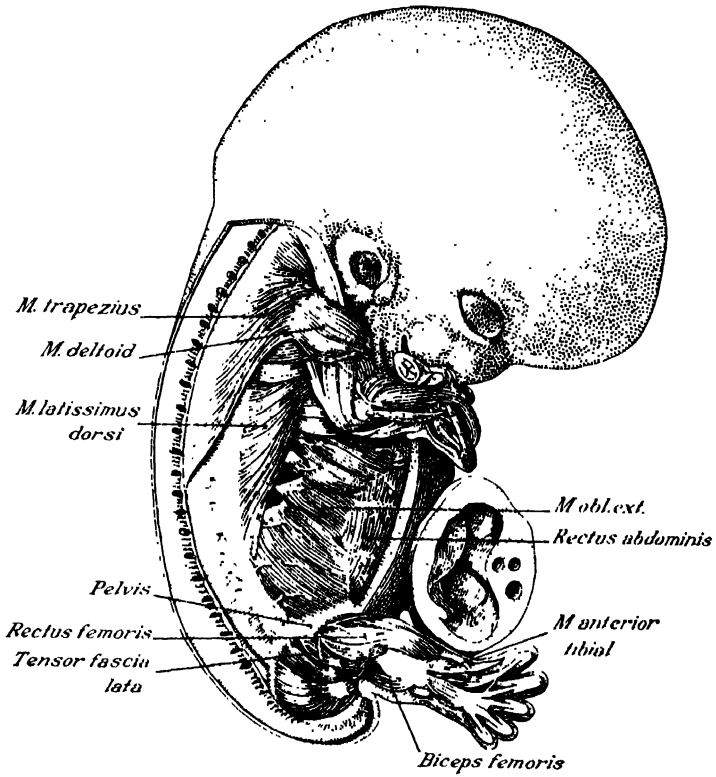


FIG. 24b. Dissection of a human embryo of 20 mm. length (about 8.5 weeks) showing the muscles of the trunk and appendages. In the belly are the long straight muscles (rectus abdominis), which make up the bulk of the abdominal wall. On the flanks are the external oblique muscles (*M. obl. ext.*). On the sides of the back is the great latissimus dorsi which pulls back the fore leg (arm) in the running dog and in the swimming or climbing child. Higher up is the trapezius by which we shrug the shoulders. On the shoulder are already formed the deltoid muscle (*M. deltoid*) which rounds out the angle of the shoulder, and the triceps by which we lift the loaded fore arm and over which the muscular boy brags as he sees the upper arm swell when he flexes it. Other muscles, especially of the leg, are referred to in the text. (*After Bardeen and Lewis, redrawn from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

building bones and tendon, and the terminations of the muscle cells become anchored to the mesenchyme structures by virtue of the perimysium sheaths with which the muscles are enveloped (Fig. 25). At first the muscle cells are plain or "smooth" but contain threads which are

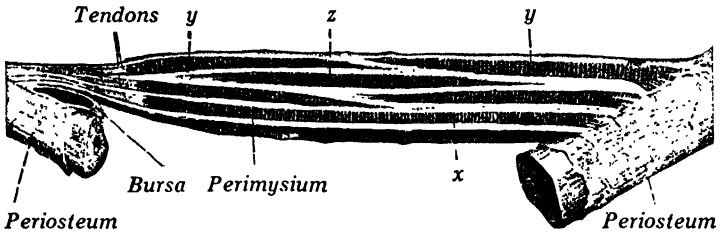


FIG. 25. Diagram showing how the striped muscle fibers, *x*, are connected with the bones to which they are attached through the aid of the connective tissue sheath (called perimysium, i.e., around the muscle) that surrounds the fiber. The perimysium is continuous with the connective tissue sheath of the bone (periosteum, i.e., around the bone). The single muscle cell (of which *x*, *y*, *z*, each represent a bundle) passes, at the left, right into little pockets or grooves of the tendon. Some fibers, e.g., *z*, pass at their ends into the perimysium. (*After Braus, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

deeply stained by dyes (Fig. 26). The latter become attenuated as the cell enlarges, but some of their particles arrange themselves in ranks. These particles enlarge and eventually form the cross bands seen in striated muscle (Fig. 27). Enormously enlarged, the structure of the striated muscle fiber is represented diagrammatically in Fig. 28. Just what each microscopic part of the muscle does to make the muscle contract is still unknown.

Muscles move under the stimulation carried to them by nerves. The nerve cells which accompany the primitive muscle cells arising from the myotomes come to penetrate into the muscle masses as they develop (as just stated, page 36) and each nerve unit finds an end in a muscle fiber (Figs. 29 and 30). The end of the nerve is called motor

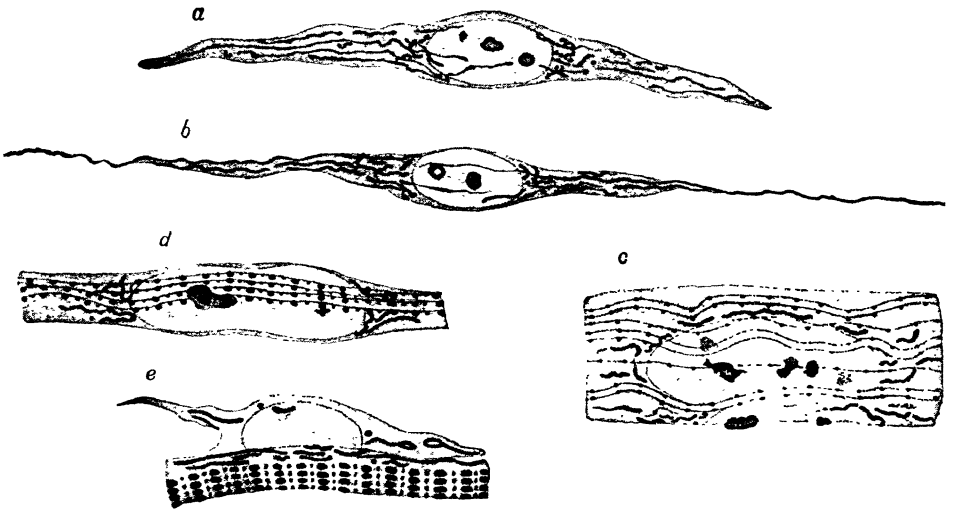


FIG. 26. Development of a striated muscle cell. The origin of the muscle threads (myofibrils) within the developing muscle cell (myoblast), in a chick embryo. *a*, the myoblast of an embryo developed $^{60}/_{432}$ of the way to hatching Nucleus and cytoplasm are distinguishable and, in the latter, deeply staining particles and threads. *b*, from an embryo $^{76}/_{432}$ developed. The cytoplasm and stained threads are elongated. *c*, the middle portion of the muscle cell from an embryo $^{124}/_{432}$ developed. Here the muscle threads run continuously from one end of the cell to the other and alongside of the nucleus (probably not through it as one might infer from the figure). The muscle threads seem to be spun out into extremely delicate, often parallel, strands which have perhaps arisen by splitting of the primitive threads. On these strands the stained threads seem to have broken up into a series of beads, which are the precursors of the so-called Q discs (Fig. 28). *d* and *e* show later stages. Little particles appear between the larger ones. These are the precursors of the Z discs (Fig. 28). Between the deeply staining discs is always a clear ("isotropic") disc. The deeply staining particles come in contact as they enlarge to form the discs of the adult muscles (Fig. 27). (*After Diesberg, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

plate. All of this apparatus evidently conveys to the muscle cell the electric current that is carried through the nerve. The muscle contracts to such current just as it

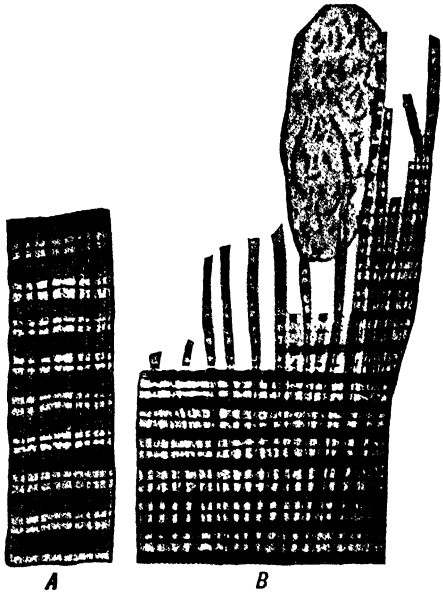


FIG. 27. Section of adult striated muscle showing the anisotropic (dark) and isotropic (light) discs as in Fig. 28, with the thin Z lines bisecting the latter. At the upper end of some of the fibers the myofibrils appear somewhat separated. The nucleus is shown, but it lies in another plane than the myofibrils. × 2100. *A*, fetal. *B*, adult. (*After Levi, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

does when an electric current from a battery is passed through it.

Thus, by the formation of the skeleton of the axis, of the muscles to move the skeletal parts and of the nerves to order the movement of the muscles, the limbs have

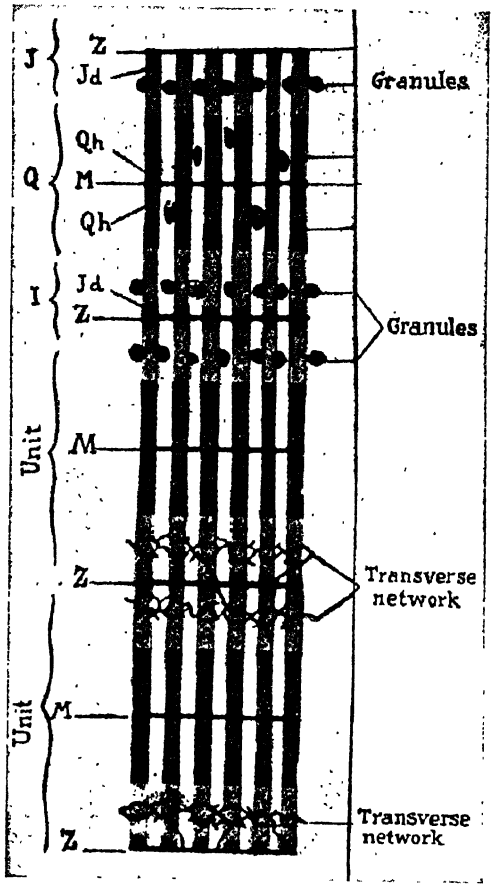


FIG. 28. Diagram of the structure of striated muscle fiber, much more enlarged than in Fig. 27. Dark granules or other structures are shown in the isotropic discs on each side of the Z line. The middle of the dark discs is lighter than the margins and is traversed by a dark line (M). (*After Heidenhain, from Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co., publishers.*)

FIG. 29. Showing the way two muscle fibers, here running vertically, are entered by the ends of the nerves (n) whose impulses they receive. This apparatus of the muscle cell into which the nerve ends is called a motor plate. a, terminal branching of the "axis cylinder," the central filament, of the nerve in the motor plate, a part of the muscle which here lacks striations. The terminal nerve loses its myelin (insulating) sheath (d) as it enters the motor plate. The axis cylinder comes into close relation with a number of nuclei (b) of the muscle cells which are aggregated in the motor plate. c, nucleus. (*After Ramón y Cajal's "Histology," permission of Williams & Wilkins, publishers.*)

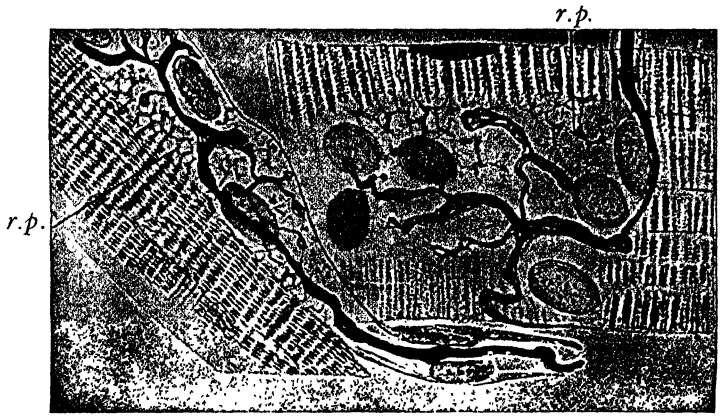


FIG. 30. Enlarged view of a motor end plate (from rabbit tongue). Two axis cylinders are shown entering two bits of muscle. The sheath that surrounds the free axis cylinder is left behind as the latter enters the muscle cell at upper right-hand corner. The letters *r.p.* refer to the protoplasmic network of the motor plate. Note the number of nuclei that are associated with the axis cylinder endings. The axis cylinders contain still finer filaments. (*After Ramón y Cajal, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

become ready for doing the work that is laid out for them to do. It is not long after these parts have become fully formed before they really become active. The first motions occur shortly after the ninth week of intra-uterine life, when the fetus is about 5.5 centimeters (or only an inch and a half) long.

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1. For the intra-uterine life stages of the mouse see E. Carleton MacDowell, Journal of General Physiology, 1927. The early stages of development of the fetus are found described in such treatises as Arey's *Developmental Anatomy* and Kollmann's *Handatlas;* but for greater detail we must await the results on the macaque being worked out at Baltimore.

2. For data on the embryonic disc see Chester H. Heuser, 1932, Contributions to Embryology No. 138, Carnegie Institution of Washington.

3. The experimental studies on localization of organ-forming areas in the blastoderm made by Dr. Willier's pupil, Mary Elbert Rawles, are published in the Journal of Experimental Zoology, January, 1936.

4. Figures of children (post-natal) with tails have been published by Ross Granville Harrison; by Leslie Brainerd Arey in his *Developmental Anatomy;* by Lima de Pires in the Bulletin of the Anthropological Society of Paris, 1927, and by others. A figure of a French Indo-Chinese boy with tail is reprinted in Nathan Fasten's *Origin through Evolution* (1929).

5. Persistent gill slits ("cervical fistulae") have been repeatedly described.

6. An extensive account of the transformation of the blood vessels of the neck is given by E. D. Congdon (1922), in Carnegie Contributions to Embryology.

7. An excellent account of the development of the muscular system is given by Warren Harmon Lewis in Keibel and Mall's *Human Embryology*, and the same author has made the fullest study of the details of development of the appendages and their skeleton in the Carnegie Contributions to Embryology (1920).

CHAPTER 3

GETTING READY TO LEARN ITS WORLD

THE CENTRAL EXCHANGE

Man's large brain is a unique feature. The human fetus would seem to have little need for a large brain; nevertheless the brain develops very early and soon attains a size which surpasses that of other Primates (monkeys and apes) of the same stage of development. See Fig. 31. Thus long in advance of its special functioning the fetus lays the foundation for man's huge (almost monstrous) brain. This brain is of course, just the enlarged head end of the nerve tube.

We have already seen that the front two-thirds of the embryonic disc (Fig. 13) are told off for the head. In this region the ectoderm forms a thick plate of cells along the axis of the embryonic disc, here the neural groove is formed with thick side walls and these eventually grow together on top, as described above (Fig. 21), forming a neural tube whose front end is the nascent brain. The wall of the brain continues to thicken and by the end of the fourth month its cells are arranged in several distinct layers foreshadowing the highly specialized cell layers of the adult brain (Figs. 32, 33, 40).

At the time of closure of the neural groove to form a neural tube certain cells are loosened from the ectoderm in the region of closure and from these most of the sensory nerves of the face arise, while those going to the muscles

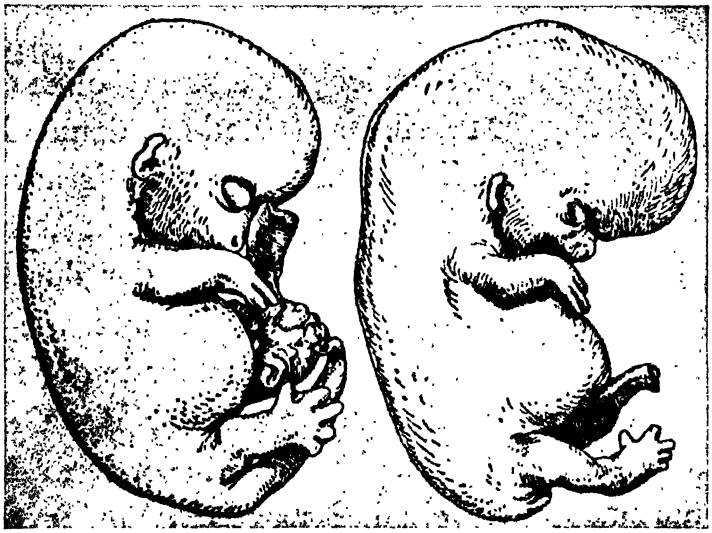


FIG. 31. Side views of the embryos of a monkey (macaque) at left and a human, at right, drawn to same scale and of approximately the same developmental stage. Note many points of agreement and some differences. The head of the human embryo and thus also its brain are already greater than those of the monkey. The belly protrudes further. The navel cord is smaller. Arms and legs of the human are still in the quadrupedal position. (*After Kollmann, from his "Handatlas."*)

of the trunk and limbs eventually arise from the neural cord (Fig. 34). Also, in time, the nerves penetrate into all the viscera and glands of the body to form what is called the sympathetic nervous system, a system which functions in involuntary fashion.[1]

The nerve cells are at first columnar or spindle-shaped. Their ends become greatly prolonged and, at the tips, specialized, according to the function the nerve cell (now called neuron) has to perform. Figure 35 shows a neuron that has to do with movement. The region about the cell nucleus sends out long processes, like the branches of a tree (hence called dendrites). There is one long thread;

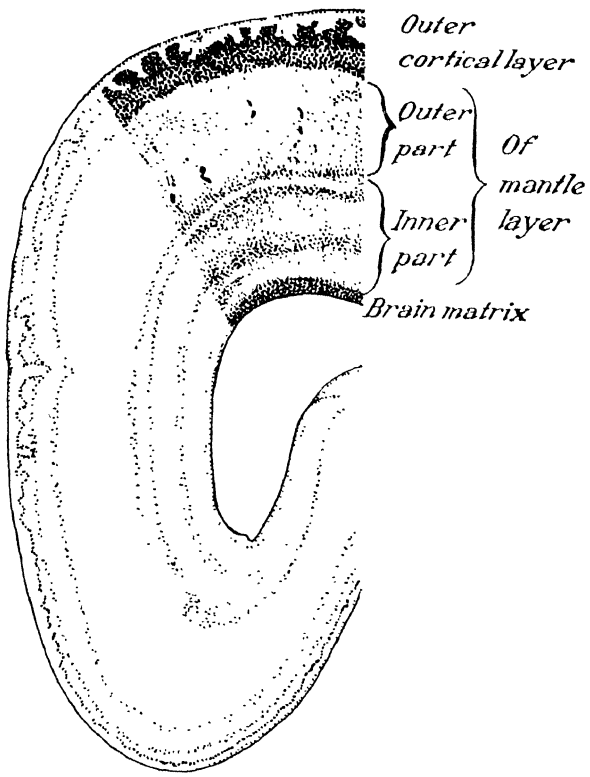


FIG. 32. Section through the wall of the hemispheres of the brain of the human embryo at the end of about 18 weeks. The main layer of the wall is the future white substance of the brain. Its great thickness is due to the rapid multiplication of nerve fibers which lie perpendicularly to the surface. Already four sublayers with ganglionic cells and neurons can be distinguished. From the layer next to the cavity of the brain many neurons leave (or enter) the cortex (rind). The outer layer is the gray matter composed of closely packed ganglionic cells and many nerve fibers running parallel to the surface. Thus 5 months before birth the felt-work of fibers and cells required for the most complex organ of the body and the highest point attained in the evolution of the nervous system is already laid down. (*After His, redrawn from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

this is the nerve fiber proper. It may grow to be many centimeters long. At first the fiber consists only of the protoplasmic prolongation of the cell. It constitutes the axis which becomes ensheathed by other materials. Accordingly it is called the axon. The longer axons become, rather late in development, covered with a fatty insulating sheath, known as the medullary sheath; this results from a condensation of fat droplets appearing about the axon and later deposited all around it. Around this medullary sheath is another sheath made up of a fibrous connective tissue. By the time any neuron is ready to send

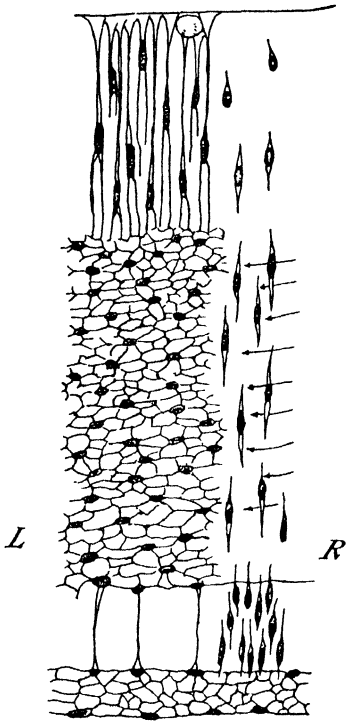


FIG. 33. A diagram of the nerve cell layer of the cortex of the brain at about 13 weeks. The outer layer is at the bottom. The middle zone is thin and not yet differentiated into layers of nerve cells, though at right of figure one sees wandering precursors of nerve cells which will give rise to such layers. This wandering is finished at stage of Fig. 32. (*After His, from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

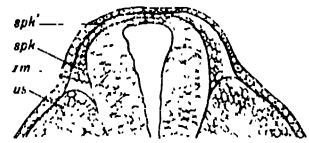


FIG. 34. Cross section through a lizard embryo showing the origin of the dorsal spinal nerves (*spk'*) and spinal ganglion (*spk*) from the region of the newly formed spinal cord (*rm*). At *us* a myotome is cut. (*After Sagemehl, from O. Hertwig, 1888.*)

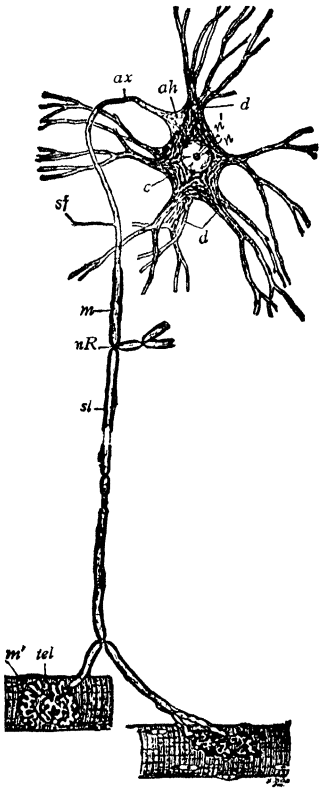


FIG. 35. Diagram of a motor nerve cell from the ventral column of the gray matter in the spinal cord. The ganglionic cell body, above, has its nucleus, *n* (with nucleolus *n'*), and its cytoplasm (*c*) containing a variety of bodies which have become deeply stained. From the cell body dendrites (*d*, *d*) extend out to place the cell in contact with other nerve cells. From a clear area in the cell body (*ah*) starts out the nerve axis, or axon (*ax*), which runs continuously to the striated muscle fibers (*m'*) where it ends in a motor plate (*tel*) Along its course the axon is insulated by a fatty medullary sheath (*m*) and, over all, a delicate membrane or neurilemma (*sl*). The axon may divide as at (*nR*) or send out collateral branches as at *sf*. (*After L. F. Barker, by his permission, from Herrick's "Introduction to Neurology," courtesy of W. B. Saunders Co.*)

messages to a muscle the axis cylinder has usually become ensheathed (Fig. 35). The structure of the axon can be analyzed further into extremely delicate threads which are continuous with a network in the cell center surrounding the nucleus (Fig. 36). In some cases the network is seen to be very complex (Fig. 37). In other cells the dendrites become extremely complicated (Fig. 38). What a marvelously intricate and delicate machinery is the nervous system; how astonishing that it should so commonly be correctly developed!

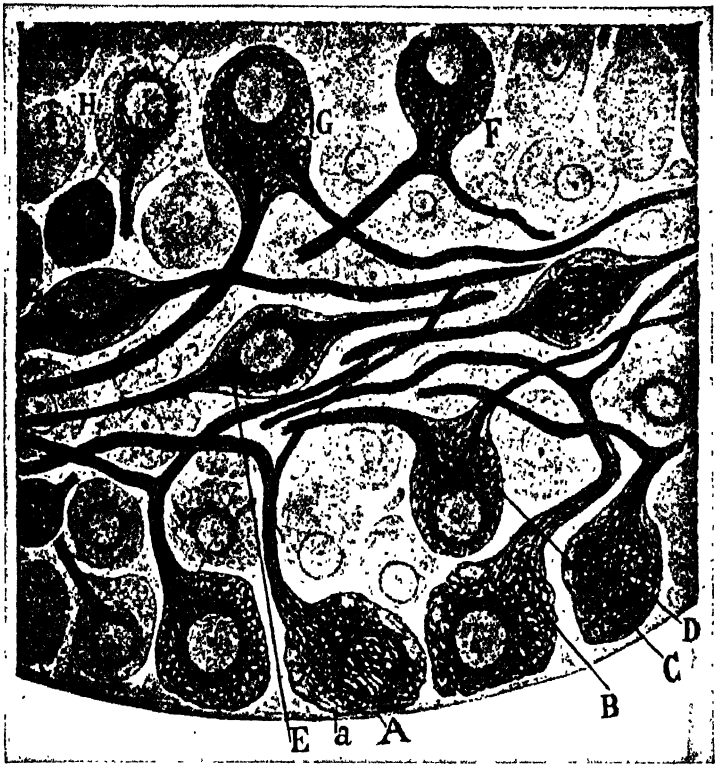


FIG. 36. Nerve cells of a sensory ganglion, or nest of nerve cells. Some, as at A, a, B, D, H, send out the neuron at one pole; others, as at E, are bipolar; others, as at F, G, are of an intermediate type. Note that the axons are made up of a bundle of finer fibers (neurofibrils). In the cell body these neurofibrils unite to form a trestle work which is particularly concentrated around the nuclear membrane, which, we may assume, serves to relay or to reinforce the waves of nerve potentials that are carried along the neurofibrils. (*After Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

In order to convey messages over long distances the neurons must be in communication with each other. Such communication is established when the much divided end

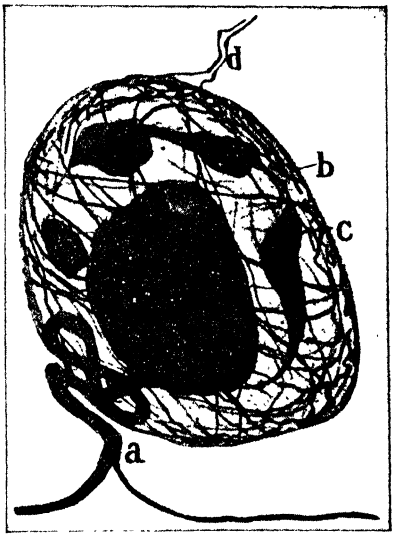


FIG. 37. Drawing of a ganglionic cell body from which emerges an axon (a) which soon branches. A neuron enters the cell at d. This is connected with a only through the mediation of a great network (b) of fibrils which pass around the periphery of the cell like a somewhat frayed ball of yarn. Around the central nucleus the net of fibrillae seems to be especially close and dense. c, dendrites, in the form of a rosary. (*After Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

of the axon of one neuron comes into close relation with the dendrites of another. This close relation is called a synapse. Sometimes the fine branches merely touch each other at their tips; though some investigators think there is a real

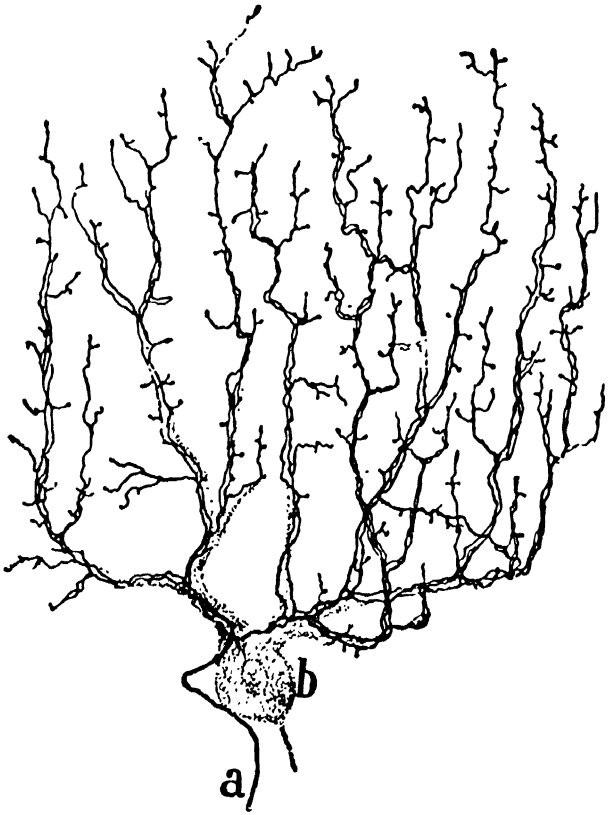


FIG. 38. Drawing of the termination of the axon of a nerve cell where it comes in close relation with another nerve cell. There is, apparently, only close contact and not union between the cells. a is the axon which bifurcates scores of times (probably more times than can be counted in the figure!). The ghost-like cell (b) with which the black branches are in close contact and whose branches they follow is one of the cells lying near the surface of the cerebellum (cell of Purkinje). Such intimate contact is called synapsis. Synapsis would seem to be a device for transferring the nervous electrical impulses from one nerve cell to another (see also Fig. 39). (*After Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

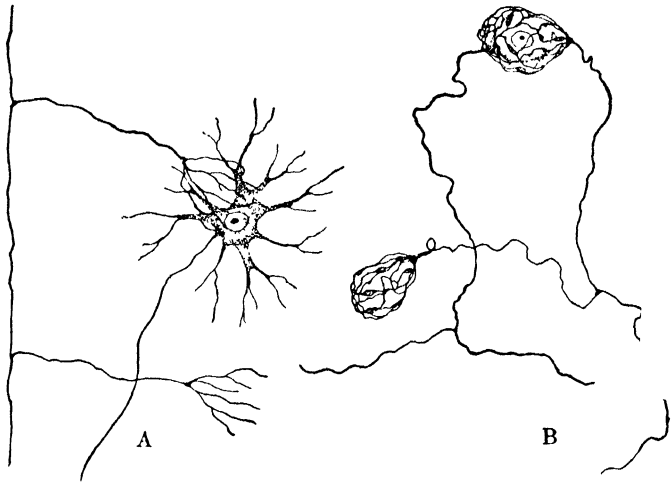


FIG. 39. Diagrams showing the synapsis or termination of axons upon the cell bodies of other neurons. A is from the ventral horn of the spinal cord. B is from the spinal ganglion or dorsal root of the spinal nerve. (*After Irving Hardesty, from Morris-Jackson's "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

union there (Fig. 39). Sometimes the divided axons wrap themselves about the cell body of the following neuron (Fig. 40). This last relation reminds us somewhat of an induction coil; as though the fiber of one cell were inducing current in the next cell.

It is not surprising that the nervous system with its complicated functions (including the mental ones) should have the most complicated cells in the body. The great problem, of course, is: What determines the building of this complex structure of cells, many elements of which are developed long before the fetus can make use of them? What determines that, starting from small cylinders, the nerve cells should differentiate in such a variety of ways as is shown in Fig. 41? We are still far from having gained an answer to these questions.

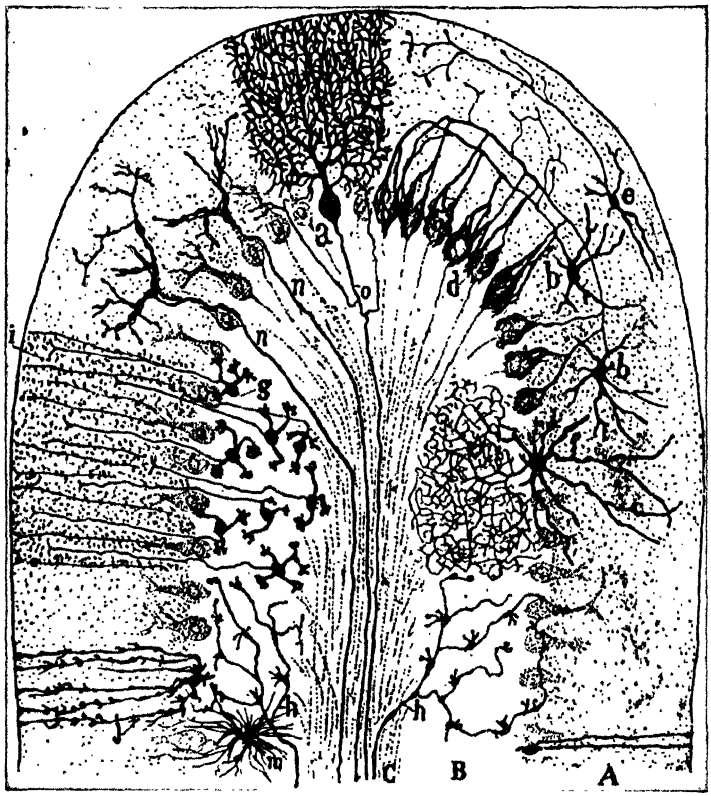


FIG. 40. Semi-diagrammatic cross section of a cerebellar convolution of a mammal, showing different types of nerve cells (neurons) and their endings. The surface layer (A) contains the extraordinarily branched cells (a, d), whose ramifications extend to the surface. These are shown in synapsis with the branched terminals of long axons (n). Other cells of the outer zone are star-shaped (b) and their branches synapse with the terminals of long axons running toward the center. Another type of stellate cell is shown at e. The middle zone (B) contains fewer arborescent cells, as at g, which send axons toward the surface; also some fibers from the center branch as they terminate here (h). Some large stellate cells (f) lie between these two layers. The zone of white substance (C) contains mostly neurons on the way to the more superficial zones. i, j, m, non-nervous supporting cells. (*After Ramón y Cajal, from his "Histology," courtesy of Williams & Wilkins Co.*)

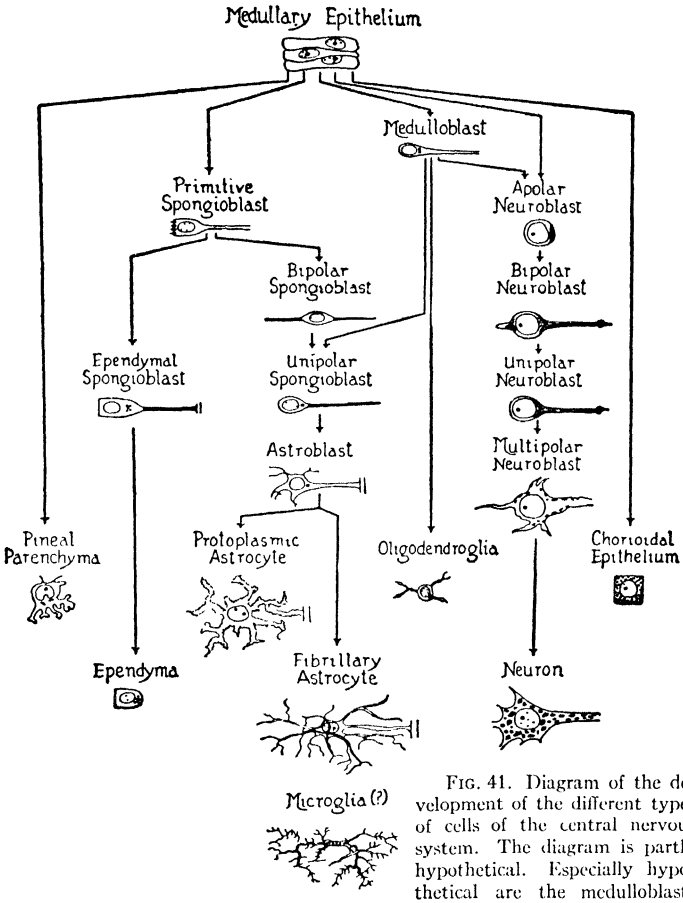


FIG. 41. Diagram of the development of the different types of cells of the central nervous system. The diagram is partly hypothetical. Especially hypothetical are the medulloblasts which are still in an undifferentiated condition. Some such stage must be passed through in the development of the cell type below the medulloblast. The derivation of the microglia (small supporting) cells is unknown.

The column-like cells of the early embryonic neural plate become much elongated to form "spongioblasts." Some of these form the unspecialized building blocks of the brain (ependyma); others become the star-shaped cells (astrocytes) of Fig. 40. Along another line of development arise the neurons with their axons arising at one or two poles. At the extreme left and right of the diagram are special types of cells found in the pineal body and the pigment-coat of the eye. (*After Percival Bailey, from Maximow-Bloom's "Histology," courtesy of originator and the publisher, W. B. Saunders Co.*)

EYES BUT NO LIGHT

Though the embryo lies in a region of complete darkness and almost complete absence of noise, the sense organs, both of sight and of hearing, are very early developed and developed in a way that will enable them on the one hand to see distant objects distinctly, and to recognize different colors; and, on the other, to appreciate the differences in the sound waves, and their varying intensities in pitch and in rhythm. The elements for making these discriminations are all developed weeks, or months, before they can be of any possible use to the child.

Although these sense organs are developed very early—as though it were necessary that, because of their complicated nature, they should get an early start to be completed before birth—probably the earliest of the principal sense organs to be formed is one of the simplest, that of smell. The very front end of the brain is told off for the reception of the sensation of smell, and strands of nerve cells early extend between the brain and the skin at the extreme front end of the body, where a pair of pits has formed at the bottom of which the smell-discriminating cells will arise. Eventually, these pits will become deeper, will be bridged over below by the palate of the mouth, and thus there will be established the tube leading from the exterior to the back of the mouth—the nasal passage. The main point is that the sense organ of the chemical sense of smell is from the beginning developed in the child as in other mammals at the front end of the body (where it can give early information of chemical changes of the medium) and is connected with the front section of the brain.[1]

The first indications of the development of the eye are found in a pair of pockets that push out from the right and

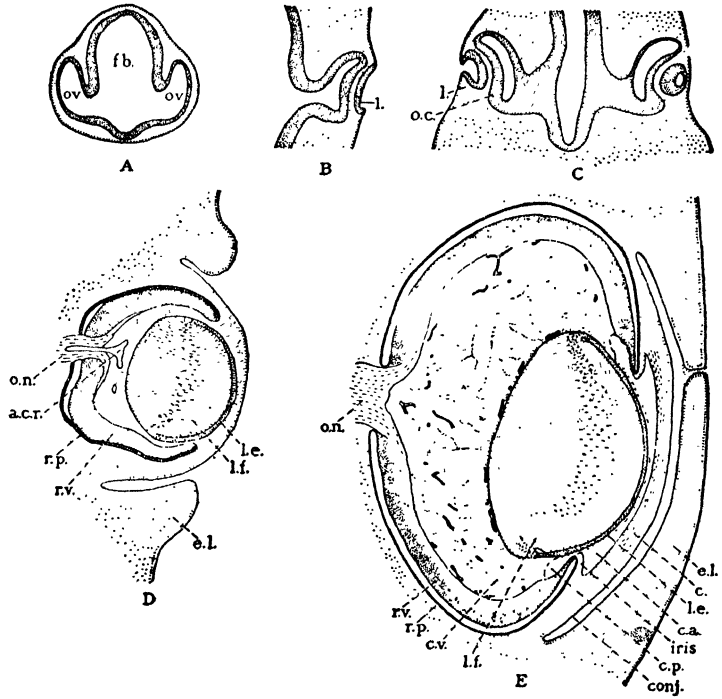


FIG. 42. Above, A, B, C, sections through the head of early rabbit embryos (3 to 5 mm. long) showing the eye forming from outgrowths (*o.v.*) of the brain (*f.b.*) constituting the optic cup (*o.c.*) on the one hand and the lens (*l*) on the other. D, embryo of 12 mm.; E, of 29 mm. *a.c.r.*, central artery of retina; *c*, cornea, connective tissue layer; *c.a.*, anterior chamber of eyeball; *conj.*, conjunctiva, the thin layer of ectodermal origin that covers the cornea; *c.p.*, posterior to iris; *c.v.*, vitreous body of the eyeball; *e.l.*, eyelid; *l.e.*, cell layer forming front of lens; *l.f.*, elongated fiber-like cells of rear of lens; *o.n.*, optic nerve; *r.p.*, pigmented layer of retina; *r.v.*, nervous layer of the retina. (*After W. H. Lewis, from Morris-Jackson's "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

left walls of the neural groove, and in the front half of the thickened region which is to give rise to the brain. They grow out until they come into close contact with the inner face of the embryonic skin (ectoderm). Where these pockets touch the outer embryonic skin remarkable things

happen in this skin; for the skin thickens at this point and later forms a pouch (Fig. 42) that touches the outpocketing of the brain and helps stimulate it to collapse into the form of a double-walled optic cup (Fig. 43). The mouth of the pouch gradually constricts until the pouch is entirely pinched off from the outer skin. The cells of its walls become greatly elongated so that the cavity of the pouch be-

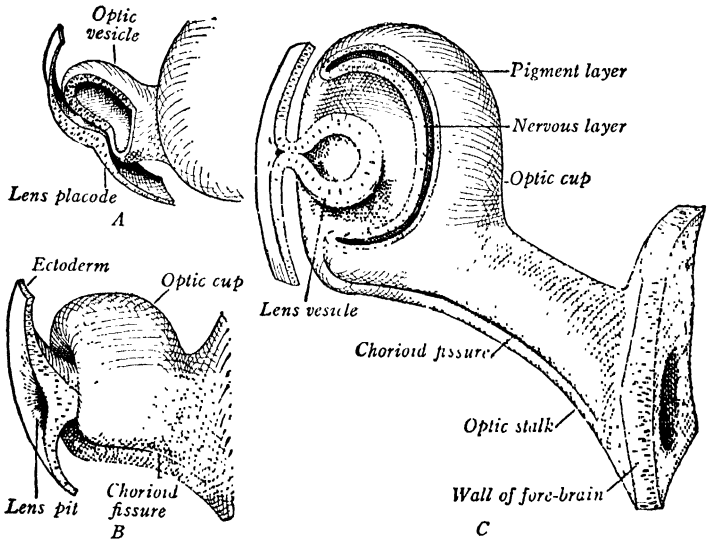


FIG. 43. Models of three early stages in eye formation in human embryos. In all stages the lens is cut through, or near, the middle, and in *A* and *C* the wall of the optic cup has been partly cut away. *A* is from an embryo only 4.5 mm. long, *B* from an embryo 5.5 mm., *C*, 7.5 mm. *A*. The optic vesicle is derived from the brain. The plate of cells that will form the lens placode shows the ectoderm already beginning to thicken. *B*. The optic vesicle has become a cup surrounding the lens vesicle. This optic cup has a crack running down one side, the chorioid fissure, due to the fact that the optic vesicle becomes two-walled by the pushing in of a furrow running its length. *C*. The optic stalk with its chorioid fissure is now elongating. The two layers of the optic cup are shown; the inner producing the retina (nervous layer) the outer the pigmented chorioid coat. The lens is nearly ready to be pinched off from the ectoderm. (*From reconstructions by Mann, after Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

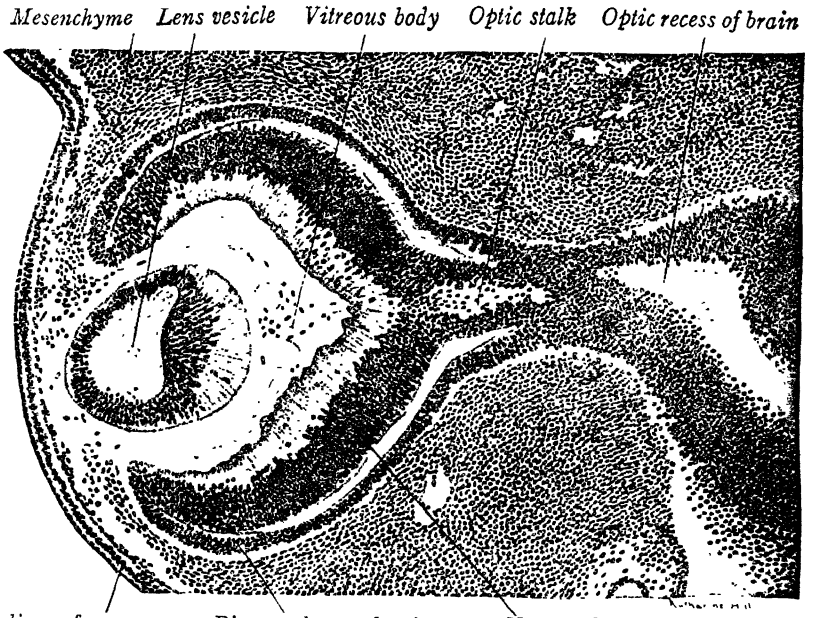


FIG. 44. Section through the eye region of a human embryo 10 mm. long. The wall of the brain is seen at the right. The optic stalk is now a double walled tube, owing to the closure of the chorioid fissure. The nervous layer of the retina is preparing to produce the rods and cones. Note the pigmented layer of the chorioid coat. The lens vesicle has become cut off from the ectoderm and its cells are becoming elongated. Vitreous material is about to be formed between lens and retina and mesenchyme is penetrating between lens and outer skin to form the white cornea of the eye and the aqueous humor in front of the lens. The iris is to arise from the free front edges of the optic cup around the lens. × 100. (*After Prentiss, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

comes quite closed up as they push into it. Eventually a solid body is formed; it becomes the lens of the eye. The optic cup wraps its lips well around the lens and comes to form the retina of the eye (Fig. 43). The part of the pocket next to the brain becomes narrowed to form the optic nerve. From this it will be seen that the retina and optic nerve are merely a part of the wall of the brain. The optic nerve does not have to become attached to the brain as it has been a part of the brain from the beginning.

Between the optic cup and the lens a fluid is now secreted so that the retina falls back from the lens to form a space which is filled with so-called vitreous body or humor. This, as it were, places the screen at the proper focal distance from the lens and thus where the lens will throw a picture upon it. Now it is a striking fact that the form of the lens is soon adjusted to the distance that it should be from the retina, or the retina is placed at the proper focal distance to receive the image cast by the lens. All of this adjustment is made before any use at all is made of the eye.[1]

The part of the embryonic skin lying over the lens later becomes the transparent conjunctiva of the eye and it is continuous with the delicate membrane that lines the lids (Fig. 44). Between the ectodermal layer and the optic cup mesenchyme penetrates and eventually gives rise to the opaque white cornea of the eye.

As the membranes that constitute the main organs of the eye take their proper places, they begin to undergo histological (tissue) differentiation. Figure 45 shows how extensive this is in the retina. The light enters from below, passes through the thick transparent sheet of bipolar cells. In many cases one pole has an arborescent termination of which the ends probably make contacts with other cells. This nervous network transmits impulses from the outer

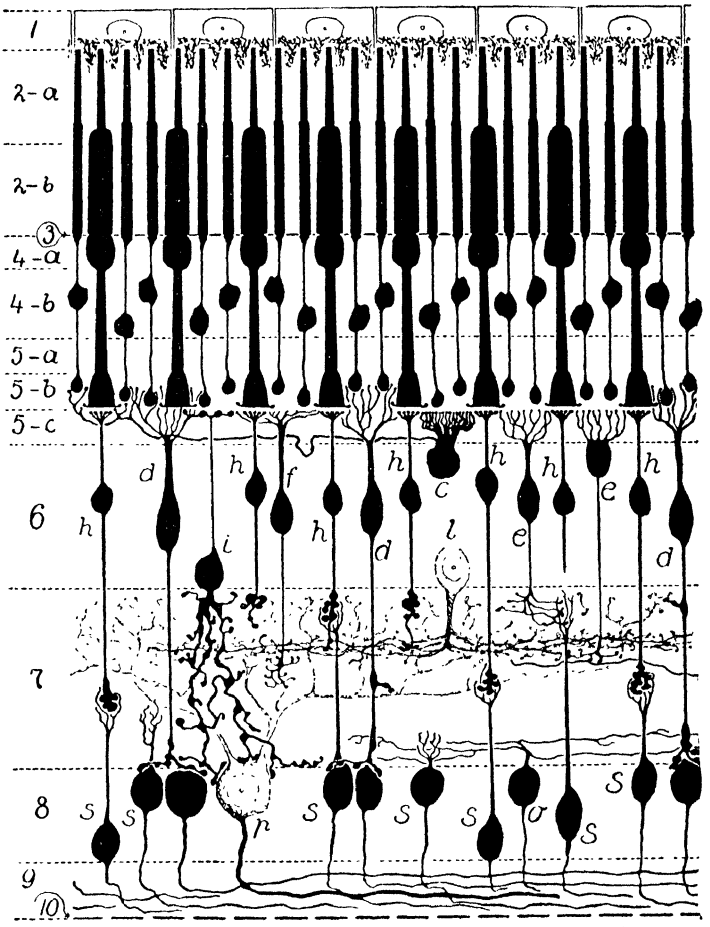


FIG. 45. A scheme of the nervous elements of the retina of a primate (macaque), based on the study of preparations treated according to Golgi's method. The scheme shows the chief characteristics and relationships of most of the retinal nerve cells and their position in the retinal layers: 1, layer of the pigment epithelium, nearest to the brain; 2-a, layer of the outer segments of the rods and cones; 2-b, layer of the inner segments of the rods and cones; 3, outer limiting membrane; 4-a, outer zone of the outer nuclear layer; 4-b, inner zone of the outer nuclear layer; 5-a, fiber-layer zone; 5-b, cone-feet and rod-spherules; 5-c, inner zone of the outer plexiform layer; 6, inner nuclear layer; 7, inner plexiform layer; 8, layer of the ganglion cells; 9, layer of the optic nerve fibers; 10, inner limiting membrane, i.e., nearest to the lens; *c*, horizontal cells; *d*, *e*, *f*, *h*, bipolar cells; *i*, *l*, "amacrine cells"; *o*, *p*, *s*, ganglion cells. (*Generously contributed by Dr. S. Poljak.*)

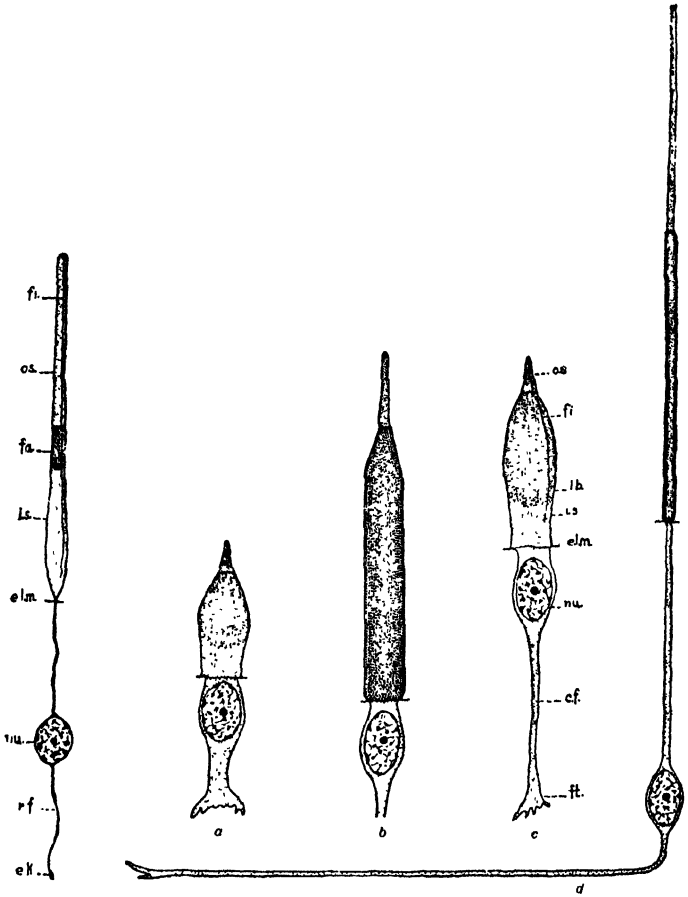


FIG. 46. Left, a rod-cell from the human retina. The nucleus is below at nu. The upper part of the cell is the rod; it points away from the source of light or toward the brain. It is about 50 μ long and 2 μ thick. The outer end (os.) reflects light brilliantly; it is made up of a fatty substance. A fine deeply staining fibrilla (fi.) runs along its surface starting at the middle (fa.). This rod carries the visual purple which is easily modified by light. The inner segment (i.s.) of the rod is thicker. Below it the fibrilla (r.f.) passes down, ending in a small knob (e.k.).

The right four figures (*a–d*) show different types of cone cells of the human retina. *a*, from near the front margin of the retina; *b*, from the region outside the yellow spot (macula lutea) of the retina; *c*, from the margin of the macula; *d*, from the "fovea centralis," center of acutest vision. Letters as above. Also, l.b., lens-shaped body; e.l.m., external limiting membrane; c.f., cone fiber; ft., cone foot. (*After Arey, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

layer of rods and cones to the optic nerve which lies on the inner face of the retina so that light that goes to the perceptive organs must pass through it. Thus the perceptive organs, the rods and cones, lie deep at the rear of the retina. Of the rods there are about 130 million; of the cones about

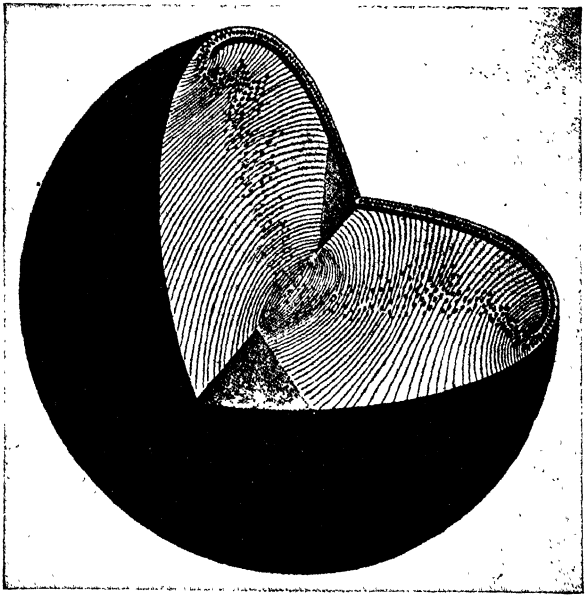


FIG. 47. Diagram of the lens of a human fetus at end of third month. The right quadrant is removed. Note the outer cell layer which at the equator is being transformed into lens fibers. The most central fibers are retarded in growth. (*From Keibel-Mall's "Handbuch d. Entw. d. Menschen.*)

7 million. The rods and cones are specialized ganglionic nerve cells (Fig. 46). The external segments of the rods (but not the cones) contain a red or purple substance, named rhodopsin, which is temporarily bleached where it is struck by the light coming from the outer world. This is believed in some way to start a chemico-physical process that sends impulses to the brain.

The cells of the lens become immensely elongated and clear as glass (Fig. 47). They assume collectively a complicated lenticular form capable of change under the tension of a surrounding capsule held in place by a suspensory ligament and its ciliary muscles. Thus some adjustment can be made for distance.

FIG. 48. Human embryo about 4 mm. long (4.5 weeks) showing at *au* the beginnings of the ear vesicle. *Ul*, upper limb; *Ll*, lower limb; *h*, heart; *Y*, yolk sac; *am*, amnion; *B*, belly stalk. (*After His, from McMurrich's "Development of the Human Body," courtesy of The Macmillan Co.*)

EARS BUT NOTHING TO HEAR

The ear has a development no less remarkable than that of the eye and it, too, is laid down during the first month of development as a pocket of the skin, which comes into connection with the first furrow (Fig. 48).

It must be kept in mind that the ear is a very complicated organ in its origin, as it is in its completed form. Our ears comprise an inner, middle and outer portion. The outer ear is merely a depression in the side of the head which removes the middle ear from the surface. At its outer margin it is ornamented by an organ that we commonly call the ear, but to avoid confusion should call auricle. This arises from six hillocks and a fold (AF) which appear around the first gill

groove. The way these enlarge to form the adult auricle is shown in Fig. 49.

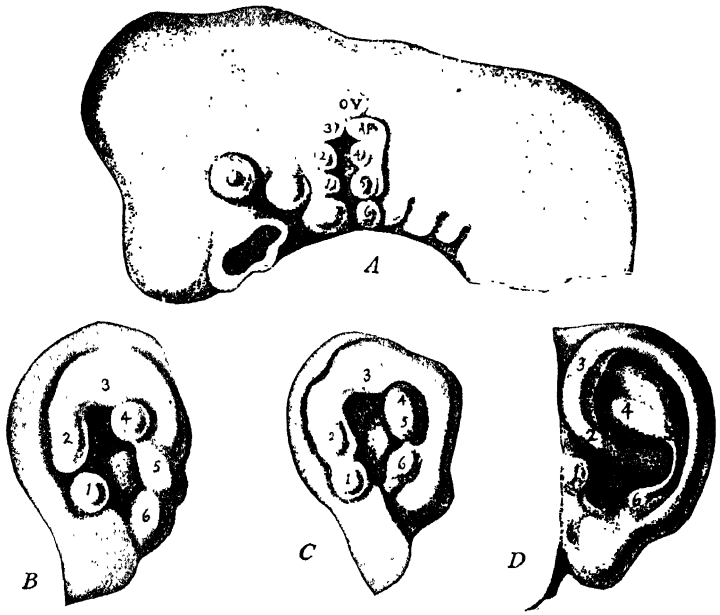


FIG. 49. Stages in the development of the human external ear (auricle). *A*, in an embryo 11 mm. long; *B*, 13.6 mm.; *C*, 15 mm.; *D*, adult. *A* shows the relation of the 9 little tubercles to the gill arches. In *B* and *C* the tubercles grow together and gradually transform into *D*. OV is the ear vesicle whose outer opening comes to be surrounded by tubercles 2–6; 1–3 are elevations in the mandibular (jaw) arch; 4–6 on the hyoid arch. In the adult 1, is called tragus; 2, 3 helix; 4, 5, antihelix; 6, antitragus. (*Partly after His, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

The middle ear is part of the first gill cleft which (as stated on page 32) is continued to the pharynx by the Eustachian tube. At its outer end is a membrane (the outer head of the drum); at its inner end are two membranes in a bony wall; one, the inner head of the drum lying at the upper end of the Eustachian tube; the other, the oval window leading to the inner ear. Three small bones in tandem

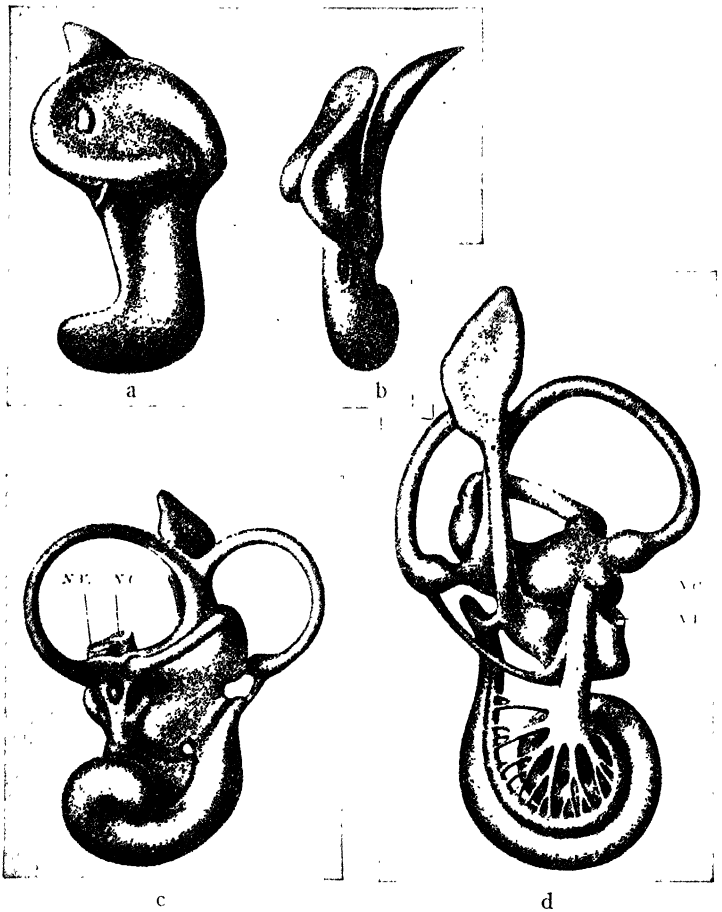


FIG. 50. A series of models showing the development of the internal ear from a simple pouch as at a, b, to a complex organ as shown on bottom row c, d. All views from the side of the embryo. The bottom of the pouch at a elongates and coils to form the snail shell or cochlea, seen at bottom of c and d. The sac toward the top of figures a and b enlarges and the 3 semicircular ducts are gradually separated from each other by grooves that arise through absorption centers. Thus lobes become ducts. The auditory nerves (*N.C.*, *N.V.*) are shown, close to the sacculus, in figures c and d. (*After George L. Streeter, from Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

lead from the tympanic membrane to the oval window. As stated earlier these ossicles are developed out of remnants of the gill bars.

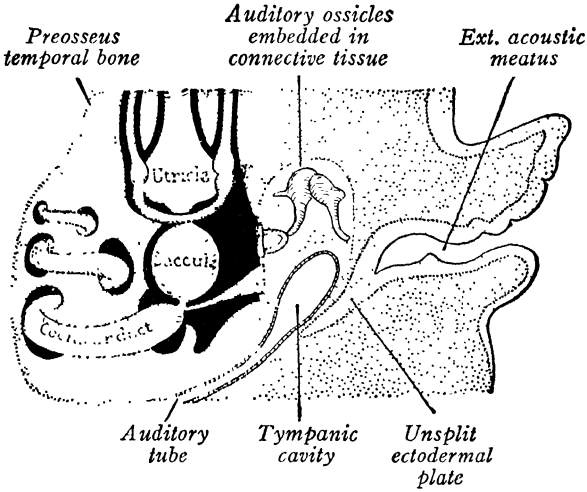


FIG. 51. Relations of the primordia of the external, middle and internal ear, at 3 months, as illustrated partly by schematic sections. The auditory ossicles (which are derived from the first two gill bars) are at first imbedded in connective tissue. This degenerates so that the tympanic cavity extends into this territory and the ear bones come to lie in the cavity of the inner ear. The outer part of the first brachial groove (*Ext. acoustic meatus*) deepens but is always separated from the middle ear (*Tympanic cavity*) by a membrane as seen in the adult. The otocyst (Figs. 48, 50a) in becoming transformed from a simple closed sac to the canals and cochlea, undergoes the complications shown. (*After Arey, from his "Developmental Anatomy," with permission of W. B. Saunders Co.*)

The inner ear (Fig. 50) is that part which contains the ends of the sensory nerves which run to the brain, and by means of which we distinguish intensity, rhythm, and variations of pitch. This inner ear begins development as a pocket from the embryonic skin, at a place indicated in Fig. 48. This soon becomes constricted off as a nearly spherical sac lying close to the embryonic brain, and near

the first gill cleft. An auditory nerve which grows out from the embryonic brain soon places it in connection with the ear sac. From this sphere are pushed out three remarkable curved flat pockets, each of which soon forms one of the three canals (Fig. 50) lying in the three perpendicular planes of space. These are the semicircular canals, which help us to maintain our equilibrium (Fig. 52).

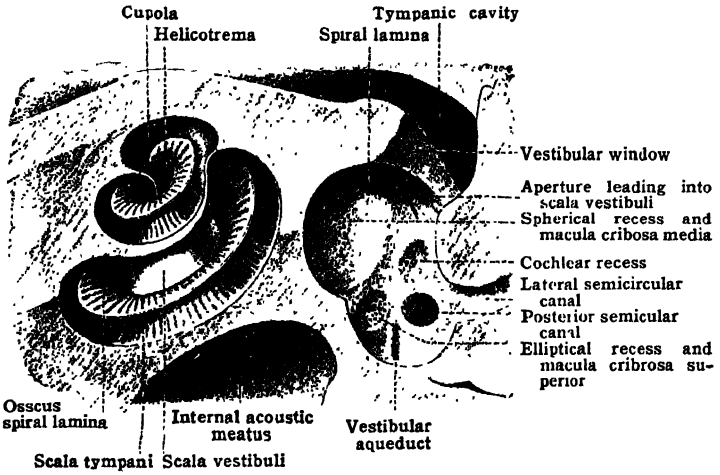


FIG. 52. The right cochlea (left) and vestibule (right), viewed from above after removing the roof of the bony labyrinth. At the left the snail-shaped cochlea is seen from its base to its apex at the cupola. It is imbedded in dense bone. Each turn of the coil is divided into a tympanic staircase (scala) below and a vestibular staircase above, of which the latter connects (as shown on the right) with the vestibule. The partition between the staircases (the bony spiral lamina) is in part formed by the basilar membrane. These two staircases are connected near the cupola by a helicotrema (or hole in the helix). The vestibule, shown at right, connects with the cochlea in front, the semicircular ducts behind and other parts of the inner ear (utricle and saccule) on the side. The depressions in the vestibule provide recesses for lodging parts of the labyrinth. The two "macula cribrosae," are for the passage of nerves through the bony wall. × 5. (*After Testut, from Morris-Jackson's "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

At the opposite pole of the spherical sac a pouch is formed like the finger of a glove. This finger coils as it

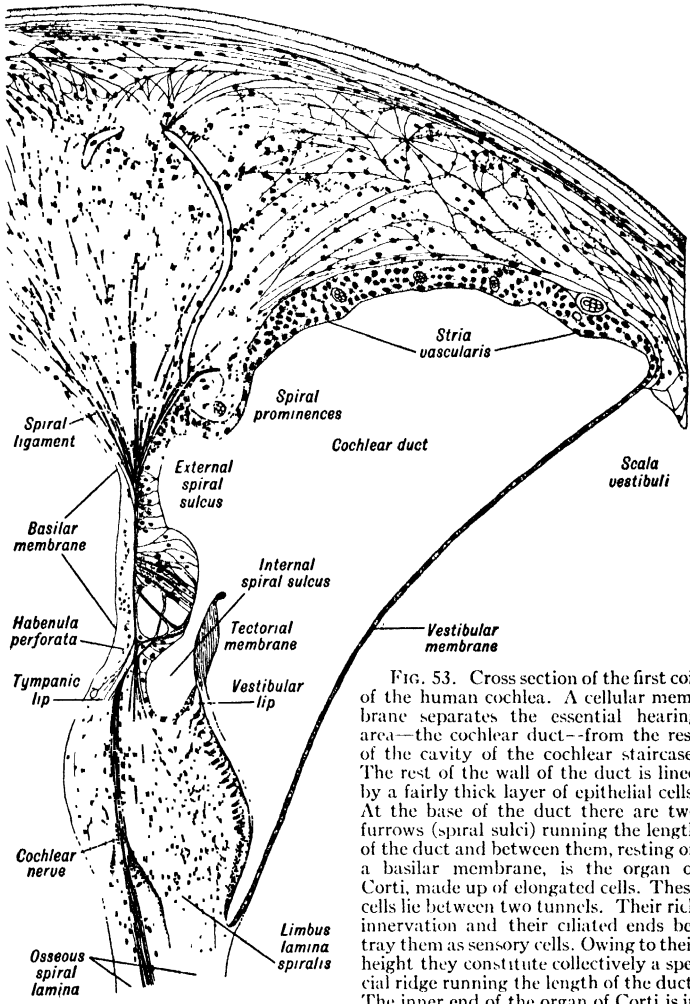


FIG. 53. Cross section of the first coil of the human cochlea. A cellular membrane separates the essential hearing area—the cochlear duct—from the rest of the cavity of the cochlear staircase. The rest of the wall of the duct is lined by a fairly thick layer of epithelial cells. At the base of the duct there are two furrows (spiral sulci) running the length of the duct and between them, resting on a basilar membrane, is the organ of Corti, made up of elongated cells. These cells lie between two tunnels. Their rich innervation and their ciliated ends betray them as sensory cells. Owing to their height they constitute collectively a special ridge running the length of the duct. The inner end of the organ of Corti is in contact with a ribbon-like structure of jelly-like consistency called the tectorial membrane. The basilar membrane is supported between two spiral shelves (the spiral ligament and the osseus spiral lamina at the central edge). The auditory nerve passes through the latter to the organ of Corti. (*After Held, redrawn from Maximow-Bloom, courtesy of P. Blakiston's Son & Co.*)

N.B. To fit the page, the basilar membrane (see Fig. 52) is here placed vertical. The reader would do well to study this figure with the book turned so as to bring the basilar membrane horizontal.

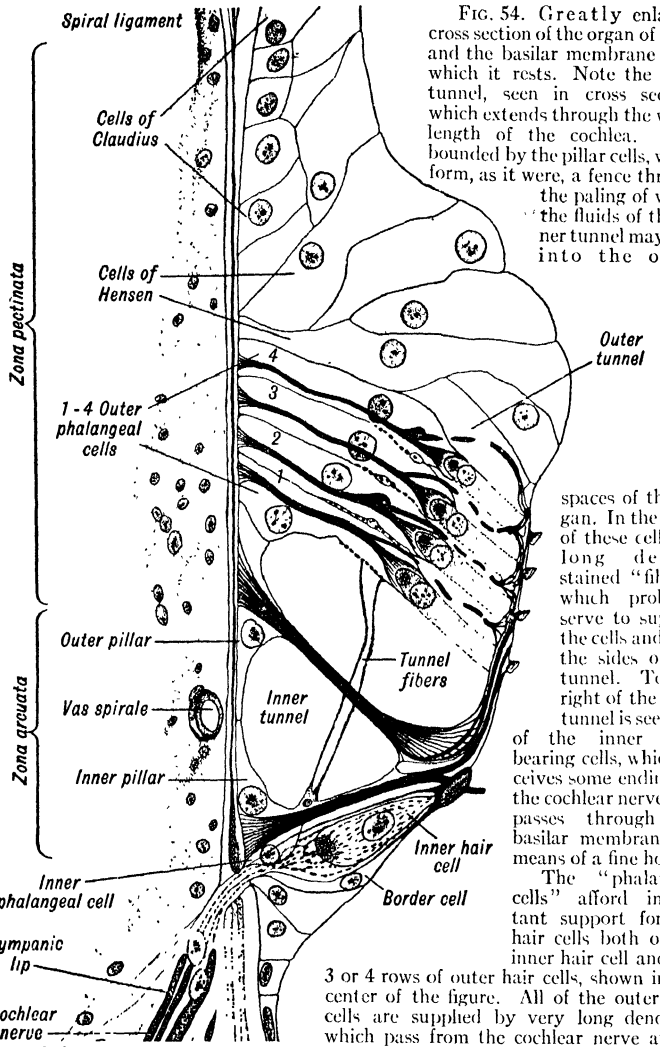


FIG. 54. Greatly enlarged cross section of the organ of Corti and the basilar membrane upon which it rests. Note the inner tunnel, seen in cross section, which extends through the whole length of the cochlea. It is bounded by the pillar cells, which form, as it were, a fence through the paling of which the fluids of the inner tunnel may pass into the other spaces of the organ. In the body of these cells are long deeply stained "fibrils" which probably serve to support the cells and thus the sides of the tunnel. To the right of the inner tunnel is seen one of the inner hair-bearing cells, which receives some endings of the cochlear nerve that passes through the basilar membrane by means of a fine hole.

The "phalangeal cells" afford important support for the hair cells both of the inner hair cell and the 3 or 4 rows of outer hair cells, shown in the center of the figure. All of the outer hair cells are supplied by very long dendrites which pass from the cochlear nerve at the base of the inner hair cell and through the tunnel. The terminations of these dendrites near the hair cells are seen as dots between the outer phalangeal cells. Based on Held, from *Maximow-Bloom*, reproduced by the courtesy of P. Blakiston's Son & Co.

develops (Fig. 50). Within is a winding tube which is known as the cochlea (Figs. 51, 53, 54) (Latin, for snail shell). It is from the beginning associated with the nerve of hearing. Soon the inner lining of the cochlea becomes specialized along one line, since the cells become attached to the nerve at their deep end and bear bristles at the free end (Fig. 54). Later some of the cells become supporting cells for these columnar bristle-bearing cells. Some of the epithelial cells form a membrane of fibrous and gelatinous material at their free ends, and having done this perish and dissolve. Thus the membrane is left as a sort of mantle that

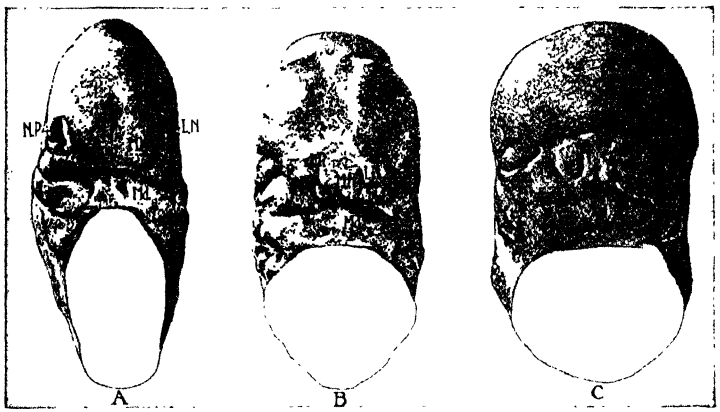


FIG. 55. A series of models showing the development of the face in the second fetal month. The mouth lies between the mandibular process (Md) and the maxillary process (Mx). In Figs. A and B the latter is seen to be paired, but eventually the pair meet below the median nasal process (M.N.) —except in cases of cleft palate. To form the nose a pair of lateral nasal processes (L.N.) arise lateral to the nasal pit (N.P.) and move together toward the middle line below so that the external openings of the nasal pit (nostrils) are brought near together, as at C. Thus the nose is originally a double broad flat structure which eventually becomes narrow and median, but frequently shows some trace of its double origin in a slight vertical furrow at the top of the nose. (*Based on models made in the Department of Embryology, Carnegie Institution of Washington; from Morris-Jackson's, "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

hangs over the highly specialized sensory cells of the organ of Corti (Fig. 53). It is believed to act as a sort of damper to the hair cells below, or possibly is set flapping in its various parts (of varying width) by the sound waves of varied length and intensity.[2]

"THE VERY IMAGE OF HIS FATHER"

It is the usual thing for women who are visiting one's home to see the new baby to exclaim: "The very image of his father." This may be a polite way of assuring the man of the house of his role as parent. It is also a recognition of the importance of heredity, though it may fail to satisfy the father in an aesthetic sense, for the infant at birth has still some fetal characteristics in the face. However, the face is, after all, the part of the body where we are most apt to see resemblance.

Yet the face is a complex of parts so numerous and of such varied proportions that hardly ever do we see two faces that resemble each other closely save in the case of

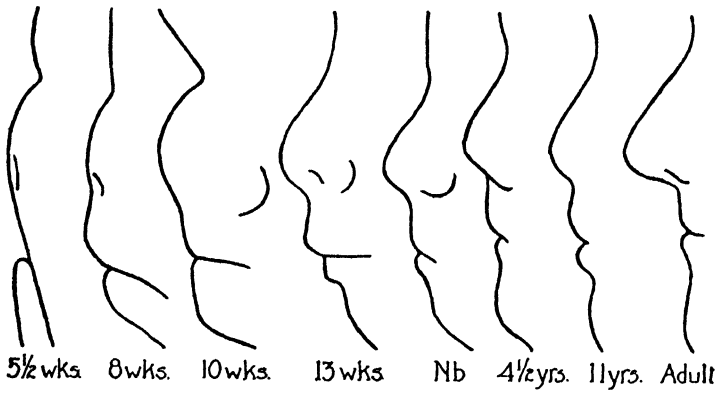


FIG. 56. A series of profiles illustrating the changes in the form and proportion of the face in the developmental period. (*After Peters, from Morris-Jackson, courtesy of P. Blakiston's Son & Co.*)

identical twins. Some of the elements are chin, nose, lips, ears, contour of head. In general, the chin is slow in developing, which is not so strange since it is a recent acquisition of man. It is not found well developed in the horse or dog or even monkey.

The nose is at first represented by a pair of pits on the sides of the head (Fig. 55). These approach each other in front toward the middle plane of the head. The front opening of each of the pits becomes surrounded by a cartilaginous ring, and the pair of rings rise to form a knob (at eight to ten weeks) (Fig. 56). The protruding nose is thus supported by a paired cartilage (Fig. 57). The typical shape of any nose depends upon the way the cartilage grows. The cartilage cells are multiplying, but they are so controlled by internal laws that the nose assumes the familial form, as is strikingly shown in identical twins. (Fig. 190.) At birth the nose has already assumed its more or less typical shape. This external nose takes on a different form in Negroes, Chinese, Semitic, European peoples. Even among Europeans the form of the nose varies—we distinguish the high narrow nose of England and parts of the Tyrol (old Roman type), the concave nose of some central Europeans, the retroussé nose.[3]

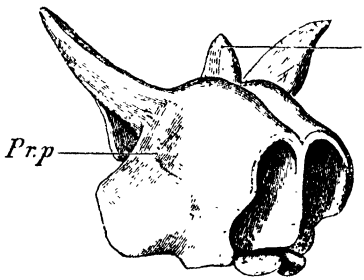


FIG. 57. Reconstruction of the cartilaginous skeleton of the nose of a human fetus of about 12 weeks, seen from in front and somewhat from the side. *c.g.* is the crista galli, which looks like a cock's comb and which ties the nasal cartilages to the frontal bone of the skull. *P.r.p.* points to a process on the side of the cartilage which helps tie it to the upper jaw. (*After Kallius, from Keibel-Mall's "Handbuch der Entwickelungsgeschichte des Menschen."*)

The lips of the child first become separated off by a groove from the jaws at about eight weeks of development. They develop gradually their racial character of great thickness in the Negro and relative thinness in the Whites; but they are very variable even in Europeans. The details of lip-form are molded as truly by the hereditary factors as those of the form of nose and chin (Fig. 64)

The external ears, auricles, are prominent (sometimes too prominent) appendages of the head in man, but not so prominent as they are in other mammals, e.g., the horse or (not to offend the Texans) the mule. The external ears are found only among mammals and differ greatly in size among them. Thus, burrowing mammals, like the mole, have no external ears; but flying animals, like bats, go to the opposite extreme. The elephant seems to use its huge ears as fly swatters.

The head as a whole is, as we have seen, very precocious in its development. The two months' old fetus has a head that equals its trunk in size. But no sooner is the head formed than it begins to grow more slowly than the trunk, and at birth is less than half as large as the trunk.

Not only its size but its form changes. During the first six months of intra-uterine life the head is growing broader. At birth it is markedly brachycephalic, a long word which means short-headed. This is fortunate in a way because in a short head the axes fore and aft and side to side are nearly equal, and so are the diameters of the pelvic outlet through which that head has to pass. So the shortness of the head makes it somewhat easier for the head to pass; and the passage of the head is the most difficult event in normal childbirth. During the process of birth the head is much distorted and reduced in size by the movements of the bones of the cranium which may lap over each other. After birth

the head rapidly resumes its old proportions and then as the child grows up the head elongates—becomes more dolichocephalic, e.g., long-headed. If the child is Chinese or Amerindian the growth in length is slight; if a North European or Negro its growth in length is greater (Figs. 58, 59). How the head shall grow depends upon certain internal hereditary growth factors. The form of the head comes to be the index of the racial or familial type.

FIG. 58. Profile photograph of the head of one of the Dinaric race of the Adriatic region (Albania) showing marked brachycephaly. (*After Josef Weninger.*)

FIG. 59. Profile photograph of the head of a negro from French West Africa, showing dolichocephaly. (*After Josef Weninger.*)

Since family resemblance rests so much upon similarity of chin, nose, ear and head shapes, and since these are molded by internal factors some of which come through the father's germ cell, we understand why even the half-finished child may well show some resemblance to its father.

OTHER ORGANS OF EXTERNAL RELATIONS

I once brought a large jelly fish from the sea and left it over night on the laboratory table. Next morning there remained only a round stain on the table. Its 98 per cent of water had evaporated. That is the danger that any animal undergoes when exposed to the air. The human child with its 75 per cent water meets that danger when it is born into the air. It is by nature protected against it. Its first line of defense is its skin.

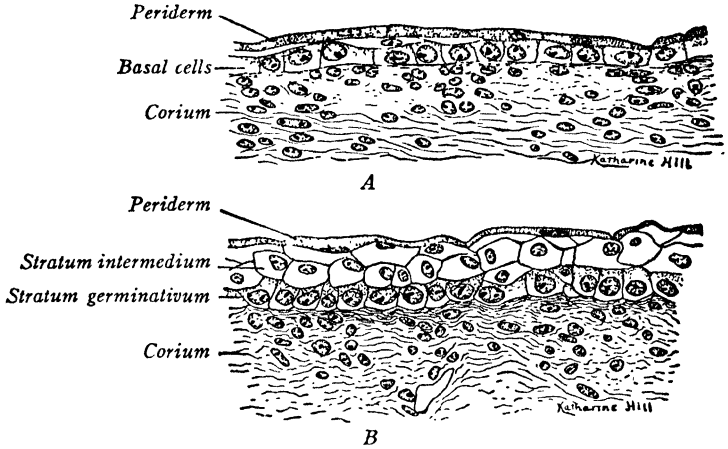


FIG. 60. Section of the skin from a human fetus of 3 months. *A*, from the neck, showing a two-layered epidermis and, at the left, the beginning of an intermediate layer between "periderm" and basal cells. Corium is the deep skin with blood vessels, derived from the mesoderm. *B*, from the chin, with three well-developed epidermal layers lying about the corium. The intermediate layer is here well developed. (*After Prentiss, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

At the beginning of development the embryonic skin consists of only one layer of cells—and that is all that many aquatic invertebrates possess throughout life. At five weeks the skin of the child consists of two cell layers, at four months of three cells layers (Fig. 60). Then many layers

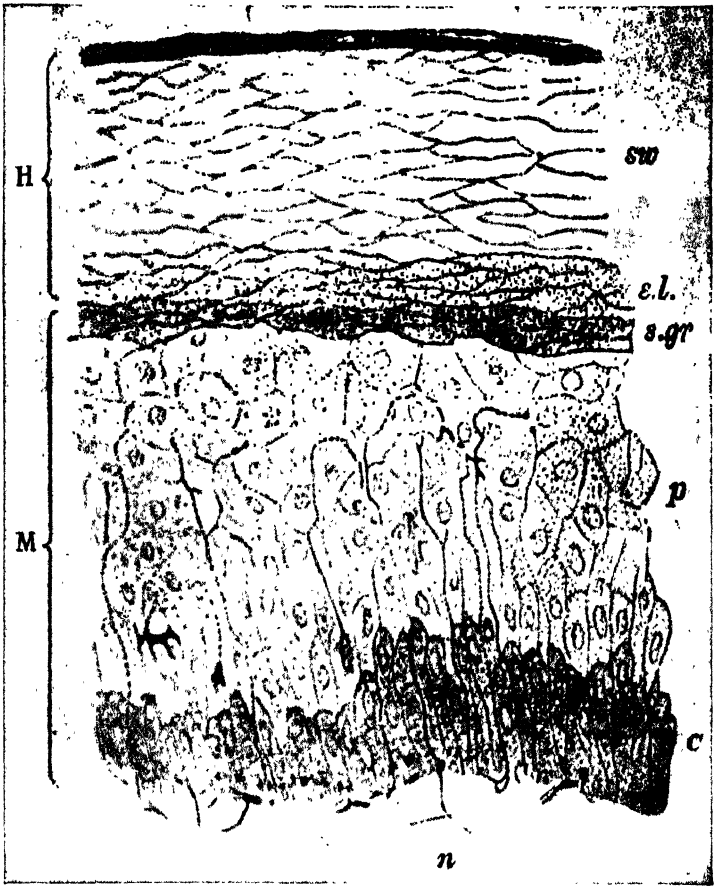


FIG. 61. Section of the epidermis consisting of an outer layer (H), the horny layer of ectodermal origin, and the lower (M) or malpighian layer. The outer layer comprises the flattened horny scales of the surface and the cells (*sw*) that have not yet become flattened. Still lower at *e.l.* the cells are living. In M one sees above at *s.gr* cells that are actively living and dividing and producing layers *e.l.* Below, the cells become more cuboidal (*p*) and are accompanied by nerve fibers (*n*). The cells become elongated below and at *c* are heavily loaded with pigment. (*From Schafer's "Essentials of Histology."*)

of cells of the mesoderm come to lie below the ectodermal layers to add to the thickness of the skin. Also the skin is added to on the outside by layers of dead, flattened, horny cells. Finally, the whole is properly greased, as they grease a channel swimmer, only in less degree, by the skin grease from the sebaceous glands. The result is a series of strata that are almost impervious to water (Fig. 61).

But the skin is a sensory organ and in this capacity is furnished with hairs. Man is not so hairless as commonly supposed. A fine "down" covers the whole body where the

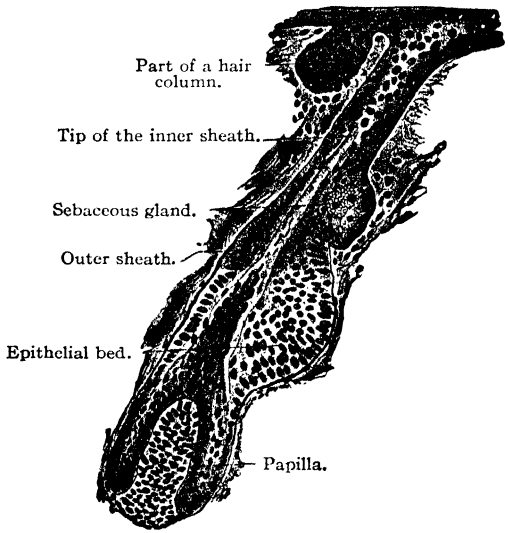


FIG. 62. Vertical section of the skin of the back of a human embryo of 5½ months. × 230. The surface of the skin is above. At the bottom of the obliquely placed hair "follicle" a papilla has formed, bringing blood vessels and nerves to the end of the long bud. The "root of the hair" is forming above. An oil (sebaceous) gland is shown at the middle of the follicle. The "epithelial bed" is a thickened part of the follicle which contributes cells to the forming hair. The hair itself comprises in addition to the axis, which contains pigment, also two or three concentric sheaths of a horny nature (like that of the outer skin). (*After Lewis-Stöhr, "Textbook of Histology," courtesy of P. Blakiston's Son & Co.*)

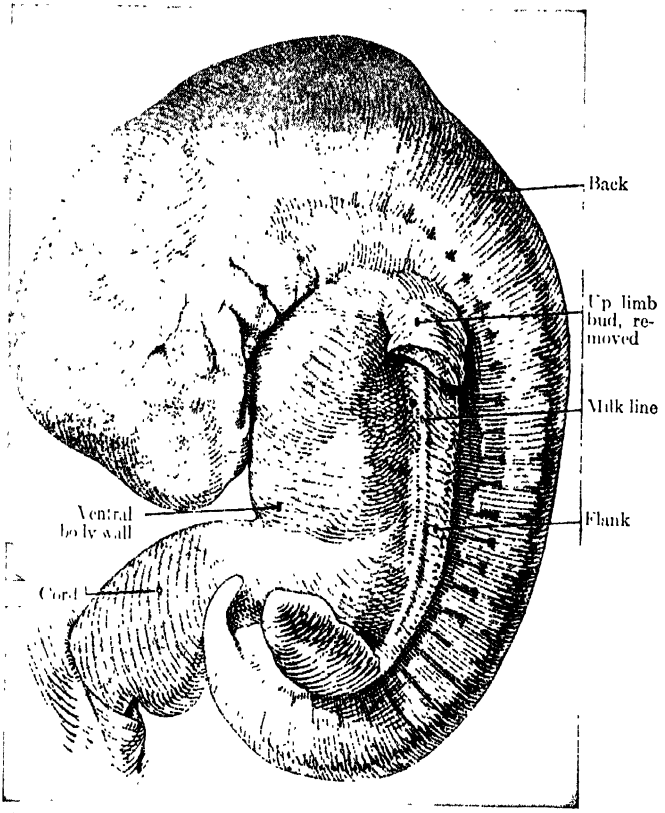


FIG. 63A. Side view of a human embryo of 13.5 mm. (6½ weeks) to show the milk line. This is a thickening that runs from the axilla or arm pit (at upper limb) to the groin. The larger circular dot indicates one of the points where the breasts will arise. These points will migrate toward the ventral side. While in many mammals, like pigs or dogs, many milk glands arise, in man there is typically only one pair, though occasionally one or more extra pairs appear. The beginnings are alike in both sexes; and occasionally the breasts are enlarged in the male. (*After Kollmann, from his "Atlas."*)

hair is not better developed. Thus on the face in either sex there are about 75 to 100 hairs on each square centimeter, or about 600 on a square inch; approximately the same as in "hairy" mammals. The peculiarity of man is that the hairs are mostly so small. Already at the end of the

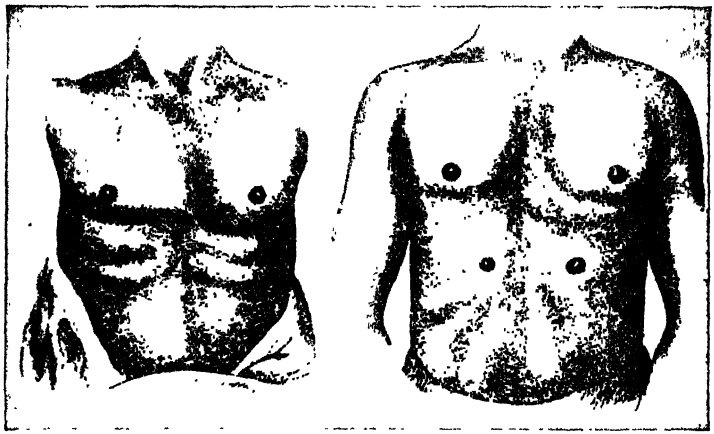


FIG. 63B. Two cases of supernumerary mammae in the male, symmetrical and unsymmetrical. (*After Leichtenstern, from Bateson.*)

second month on the face and a month or so later over the rest of the body at definite points corresponding to the margins of potential dermal scales, like those realized on the tail of a rat, the cells at the bottom of the ectodermal skin begin to multiply and send down a solid cord of cells into the lower skin (Fig. 62). This is called the hair follicle. Later this hollows out to permit the hair proper to form and its tip to move to the surface as new additions to the length of the hair are forming at the base, or root. This hair is formed of modified, horny cells. Some weeks after a hair is formed it is pushed out and replaced by a new one. We are molting, or shedding our hairy coat, all the time.[4]

From the cord of cells that form the hair follicle, or near

this cord, buds arise to produce the grease glands and the sweat glands which are important in heat regulation. So efficient is heat regulation that a grown person can pass from a refrigerator to a warm room without danger, can live in the polar regions or the tropics.

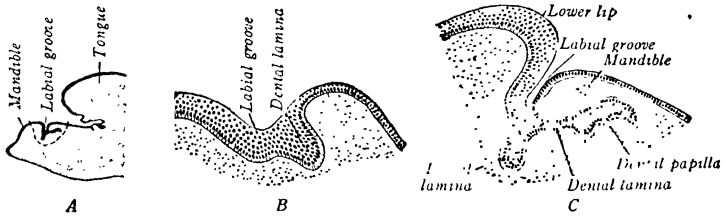


FIG. 64. Course of development and relations of the folds of the membranes that form the beginnings of lips and teeth, as shown by sections through the human lower jaw. *A*, median section, at 9 weeks, to make clear the areas included in *B* and *C*. × 10. *B*, Labiodental lamina at 9 weeks. × 90. *C*, detail at 9 weeks of the area set off in *A* by a broken line. × 47. There are shown: "Mandible" or lower jaw; "labial" or lip groove, cutting off lip from mouth; "Dental lamina," arising from the same epidermal thickening at the lip groove. A dental papilla or germ of a tooth is shown at *C*, developing from the dental lamina. (*After Röse, from Arey, "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

The skin glands gain a special function. A pair of lines of thickened skin run fore and aft between the limb buds of the embryo in the second month. They are found in all mammals and are known as milk lines (Fig. 63A). They persist in the dog and pig and at points along these lines cords of cells grow down to form the milk glands. But in the child, ordinarily, these glands are formed only at the upper part of the chest. However, not infrequently traces of imperfectly formed additional glands are found in the human child along other points of the milk line (Fig. 63B).

Finally, when the skin turns into the mouth to form the jaws a down-growth of the cells of the outer skin takes place along the edges of the whole of the upper and lower

jaws (Fig. 64). At points along this continuous downgrowth further thickenings occur, each of which forms an organ that makes the enamel coat of the tooth (Fig. 65). This covers the dentine of the tooth which constitutes its mass and which is derived by multiplication and secretion of cells of the mesodermal layer—the cells becoming much differentiated in the process.[5]

The beginnings of the teeth are at the end of the second month. At birth the front teeth are already formed with

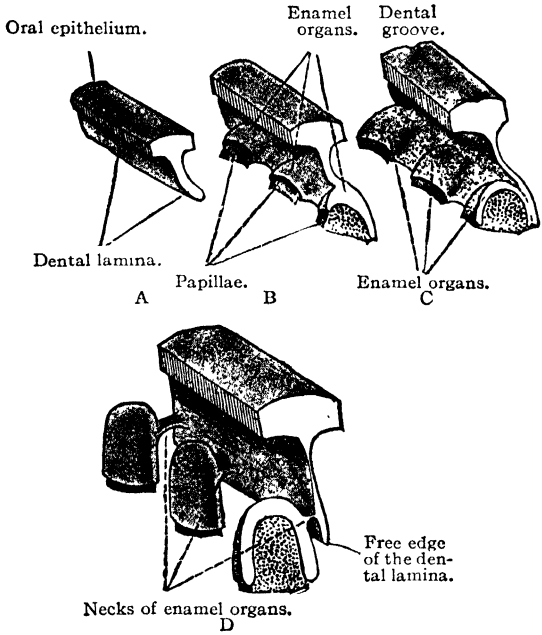


FIG. 65. Diagrams showing the early development of three teeth, the nearest tooth to the reader being shown in vertical section. A shows how the dental ridge (Dental lamina) grows down from the oral epithelium. B shows this ridge developing the enamel organs. At C these are enlarged and papillas are forming the beginnings of the teeth-base (dentine) over which the enamel is to be formed. At D, the tooth germs are nearly finished. (*From Lewis-Stöhr's "Textbook of Anatomy," courtesy P. Blakiston's Son & Co.*)

enamel and dentine and so the trouble that is associated with these marvelous organs begins. The four incisors normally erupt during the first post-natal year, and their eruption is often accompanied by fretfulness. In a few years the first dentition is replaced by a second with additional teeth. The teeth are cut in discomfort, their decay and treatment bring pain, they are pulled out with pain. The two dentitions of man are a remnant of the conditions in sharks where dentitions last only a few weeks and new dentitions are repeatedly formed throughout life.*

NOTES

1. Of the development of the brain and spinal cord a good account is given in Arey's *Developmental Anatomy*, also in C. Judson Herrick's *Introduction to Neurology;* by Irving Hardesty in Morris-Jackson's *Human Anatomy;* and in Maximow-Bloom's *Textbook of Histology.* A special book has been written by Ida C. Mann (1928) on the *Development of the Human Eye* (Cambridge, England, University Press).

2. On the development of the ear one should consult George L. Streeter's (1918) work published in Carnegie Contributions to Embryology.

3. A good account of the development of the face is given in Arey's *Developmental Anatomy*, Chapter V. Facial forms of the different races of mankind are figured in Rudolph Martin's *Textbook of Anthropology*, Jena, 1928.

4. On hair and skin glands look up Charles Haskell Danforth's (1925) book *Hair*, published by the American Medical Association.

5. On teeth consult Lewis-Stöhr's *Textbook of Histology*, published by Blakiston, Philadelphia. Tomes' *Dental Anatomy* is still a standard.

* Let us be happy that we have not so many teeth as the sharks.

CHAPTER 4

PROVISION FOR NUTRITION, SANITATION AND REPRODUCTION

LUNGS, BEFORE AIR

The early embryo travels some distance along its developmental path before it forms lungs. It gets the oxygen it needs from its mother, through the placenta. Also, it is at first more a fish than a mammal. Nevertheless, months before the child will breathe air, before, indeed, the first month of development is finished, the embryo begins to get ready for its terrestrial existence by starting to form the lungs.

Some little distance below the gill arches, the wall of the food canal bulges out toward the heart to form a pocket. The bottom of the pocket divides into two pouches, the beginnings of the two lungs. While these pouches divide again and again to form the many-pouched lungs (Figs. 66, 67), the artery which on either side runs to the last or hinder gill arch takes, as it were, cognizance of the new development that is going on below and sends out a branch to the young lung (Fig. 68). The new organ is so much more important than the useless gill arch that the artery to the lung (on each side) gets bigger and bigger while the main artery to the last gill arch gets smaller and smaller until finally it closes up for good at about the time of birth, when the child becomes a real air-breather.[1]

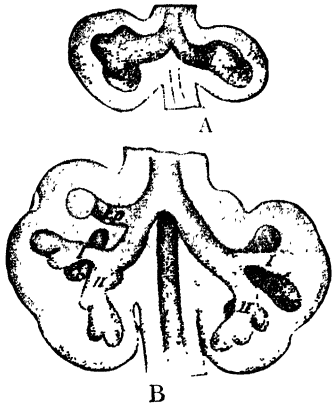


FIG. 66. Reconstruction, showing how the lung grows out of the ventral wall of the pharynx beginning in the third week. The end toward the head remains as the larynx; the opposite end, at first single (trachea) quickly divides into two lobes as at A, the beginning of the pair of lungs. These pockets branch again and again, forming the bronchial tubes, I, II. Embryo A is 4.3 mm. long; B is 8.5 mm.

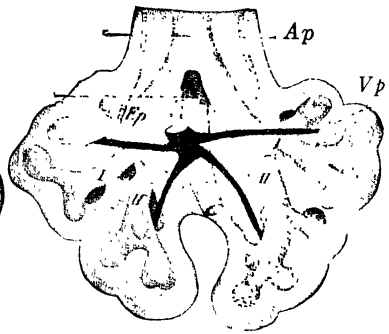


FIG. 67. Later stage in development of the lung. The pulmonary artery, *Ap*, accompanies the further development of the lung. The pulmonary vein (*Vp*) is represented in black. Embryo 10.5 mm. long. (*Both Figs. 66 and 67 are after His, from Morris-Jackson's "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

DIGESTIVE ORGANS, WITH NOTHING TO DIGEST

The food canal is, as we have seen, about the earliest organ developed in the embryo. The beginnings are there before the neural groove is formed. There is no need for such precocity from the physiological standpoint, for the child will not take a meal for two-thirds of a year yet. At the very start the food canal is closed at the ends, but after a couple of weeks an ectodermal pocket at the front end forms a mouth pit, and the bottom of this pouch breaks through during the fifth week to connect the mouth with the pharynx. At the other end is formed as an ectodermal

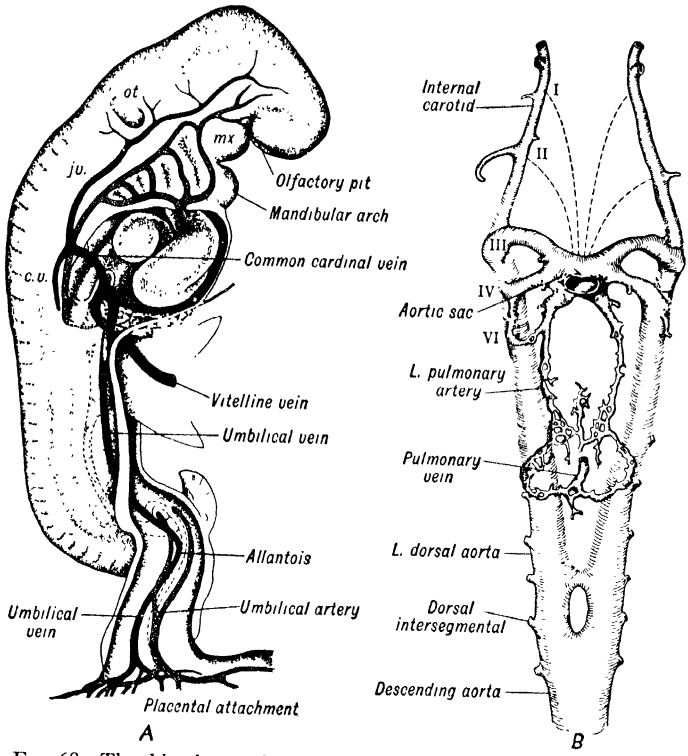


FIG. 68. The blood vessels of early human embryo. *A*, embryo of 4.2 mm., viewed from the right side. The letter and names locate organs that serve as landmarks: *mx*, upper jaw; *ot*, ear capsule; *ju*, jugular vein; *c.v.*, a vein collecting from the lower part of the body. The vitelline vein collects from the yolk sac, the umbilical vein from the placenta. Four arteries are shown passing in the gill arches. (*After His.*) *B*, reconstruction of the arteries starting at the heart and going through gill arches to head and trunk; also to lungs. From a 5 mm. embryo, ventral view. The first two pairs of gill arch arteries (I, II) have disappeared. Arteries III and IV persist. From VI (or V?) arises the pulmonary artery. The parts of the young arteries are named. The carotid is going to the head, the main branches of aorta go to the trunk and unite into one behind. Thus the pharynx passes through a circle formed by the neck arteries, just as in fishes. (*After Congdon; A and B both redrawn from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

pocket a cloaca. Later in the cloaca a partition arises separating the rectum from the urinary apparatus. Finally the bottom of this cloacal pouch breaks through and thus the anal end of the food canal is formed, though not made use of for months to come.[2]

Along the food canal many essential structures arise: the teeth, the tongue, the salivary glands of the mouth that lubricate the food and start its digestion, the esophagus, stomach and intestines, large and small, including the vermiform appendix which may be the locus of appendicitis. One of the great glands of the food canal, the liver, begins as a pouch within two or three weeks of the time the embryo proper has begun to form (Fig. 69). Nature is forehanded. The liver is, indeed, a huge organ which at birth weighs 4.5 per cent of the body, and it takes some time to build it (Fig. 70).

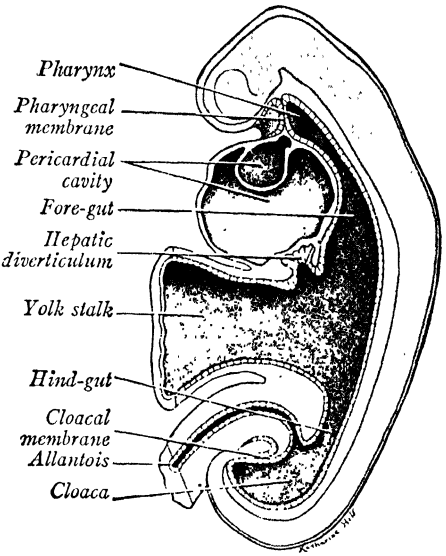


FIG. 69. Human embryo split in half along the middle plane showing the beginnings of liver formation from the gut, at "Hepatic diverticulum," just behind the heart area. The mouth and pharynx have not yet united; nor is the gut open at tail end, embryo 2.2 mm. (*After His, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

First, the gall bladder (Fig. 70) has to be separated off from the liver proper. The gall bladder and liver move away

from the food canal and are connected by long tubes, or ducts, which in the adult may get stopped up by solid particles from the gall bladder, and cause much pain. But the long liver duct is necessary to allow the great liver freedom to adjust itself to any available space in the cavity of the body. And it needs the space, for it is the reservoir for much of the recently digested food.

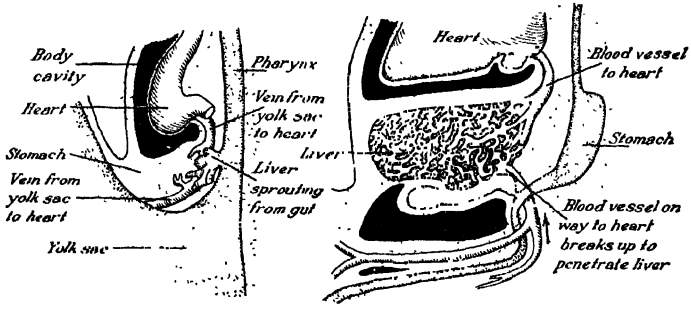


FIG. 70. Diagrams illustrating early stages in the development of the liver. A is from a 4.0 mm. human embryo. Liver beginning to form from the Pharynx just behind the Heart in close contact with the yolk vein. B is from a 12 mm. pig. The two veins (at bottom) unite to enter into the liver whose connection with the duodenum, or lower part of stomach is shown. The liver is thus a compound structure made up of blood spaces and gland and storage cells derived from the wall of the gut. Finally, the blood spaces unite to form a vein that carries blood to the heart. (*Redrawn from Lewis-Stöhr's "Textbook of Histology," courtesy of P. Blakiston's Son & Co.*)

The developing liver comes in contact with some veins that lead to the heart and, as it were, lures them to enter into its substance. They soon break up into many thousands of very minute blood spaces in the midst of the liver mass. This relation is so intimate that each cell of the liver lies on one side next to the incoming blood space (portal vein), that comes from the food canal, on the other side next to an outgoing blood vessel (hepatic vein) that carries blood to the heart (Fig. 71). Next to many liver cells is a little tube that

eventually, after uniting with other like tubes, empties into the main liver duct and so on to the food canal, to which it carries the useful digestive ferments known as bile. The same liver cells store up the digested products of starchy foods with which the blood is loaded after a meal and give them out in driblets to the blood stream all through the day and night. It takes a long time to perfect this relationship of gland and vessels.

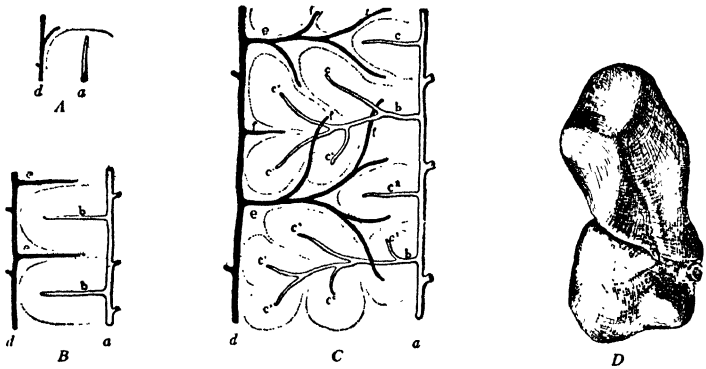


FIG. 71. Diagram showing the method of formation of hepatic lobules. *A*–*C*, diagrams (by Mall). *a*, the liver vein which later subdivides into *b* and *c*. *d* is the portal vein (carrying to the liver) which later branches into *e* and *f*. B is a whole lobule from a fetal pig (with the blood vessel entering). × 35. One sees what a great part in development is played by division of lobules as indicated also at *c'*. (*After F. P. Johnson, all figures from Arey, "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

The pancreas begins to form at about the same time as the liver by two outpocketings of the middle gut. The lower, smaller, pouch enters into the larger pocket, taps it and carries away its secretion via its own duct to the gut. The lining cells gain a great size and become filled with the trypsinogen or enzyme producer (in the form of numerous globules) (Fig. 148). This substance is transformed in the gut into important digestive agents.

Some of the cells in the pancreas get cut off from the walls of the ducts and form islets. They secrete into the blood vessels and not into the gut a special material called insulin. This insulin regulates the breaking up of sugar in the blood, preparatory to its absorption by the tissues.

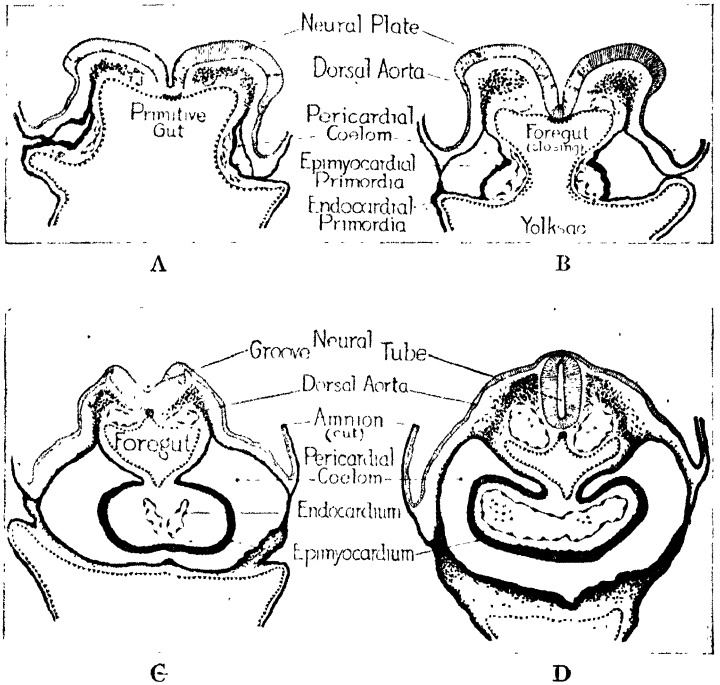


FIG. 72. The development of the human heart out of paired elements. A. Longitudinal section of an early embryo, neural groove wide open, with blood spaces, "endocardial primordia," on each side of the yolk sac. "Epimyocardial primordia," foundations of the outer heart; "pericardial coelom," cavity around the heart, inside the pericardium. The dorsal aorta is still paired. B. The fore gut is closing and the cardial elements are approaching. C. The membrane from which the heart muscles arise now form a closed sac or tube. D. The neural tube is closed. The inner and outer layers of the heart together form a closed tube; and blood corpuscles appear in the lumen. (*After Patten, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

BUILDING THE PUMP AND LAYING PIPES FOR THE CENTRAL HEATING PLANT AND COMMUNITY FOOD DISTRIBUTION

Since the human embryo carries almost no food of its own and consequently must receive food from the wall of the maternal uterus, the provision of pipe lines from uterine wall to incipient embryo is one of the earliest developmental operations. The loose mesodermal cells which have insinuated themselves between ectoderm and entoderm arrange themselves in threads which hollow out to form minute tubes that lie over the yolk sac, in the stalk that connects placenta and embryo, and eventually in the body of the embryo itself. In the front part of the trunk near the neck a pair of these tubules arise and then come together into one (Fig. 72). This is the inner lining of the heart. The muscles of the heart come from

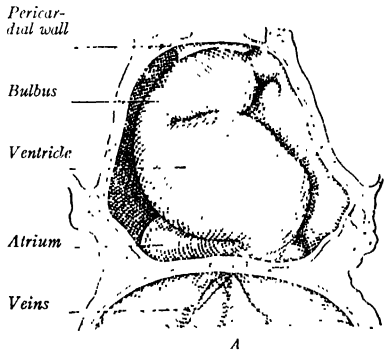


FIG. 73. Human heart in early flexion, in an embryo $3^{3}/_{10}$ mm. in diameter, about 4½ weeks. The venous blood enters the heart tubes from behind, passes into the venous sinus, to atrium, to ventricle, and thus to the bulbous aorta and the arterial system. × 60. (*After Davis. This figure is from Arey's "Developmental Anatomy," reproduced by courtesy of W. B. Saunders Co.*)

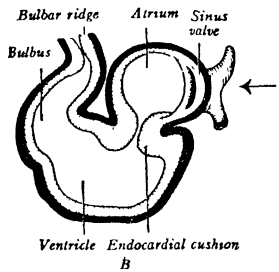


FIG. 74. Diagrammatic sagittal section of the heart and pericardium at about the stage of Fig. 73. (*After Frazer, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

the right and left mesodermal membranes which line the cavity of the body.

By the end of the third week * the heart begins to beat, at first probably feebly and irregularly, and then with increasing vigor and great regularity. Now the oxygen and dissolved nutritive substances that pass by osmosis through the membranes of the placenta are pumped from the placenta through the heart to the head and trunk. The blood which has given up most of its oxygen now returns to the placenta and thus circulation, oxygenation and nutrition are secured.

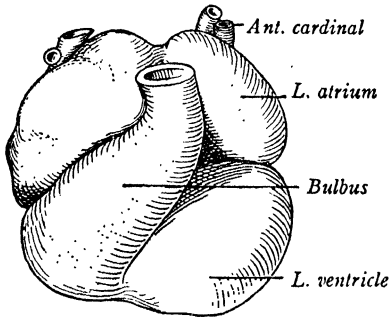


FIG. 75. Human heart in late flexion, at 5 mm. (about 5 weeks). The ventricle is forced away from the head while the atrium lies nearer it. Thus the heart tube has undergone an S-shaped twisting. × 33. (*After Ingalls. This figure is from Arey's "Developmental Anatomy," and is reproduced by courtesy of W. B. Saunders Co.*)

The heart at first is a simple tube as in fishes; then it forms a loop. Thus the segment of the heart which originally received the venous blood from the tail is placed in front (Figs. 73, 74, 75) and the segment that sends the blood forward is placed behind. Each of these two segments divides into a right and left half. The right half receives blood from the body and sends it on to the lungs; the left side receives blood from the lungs and pushes it forward to the head and trunk. This right and left stage is the latest, the perfect one. For a while, even until after birth, the body of the fetus receives in consequence of incomplete separation of right and left sides a somewhat mixed blood.[3]

* Data communicated by Dr. Davenport Hooker.

As the central pumping plant becomes perfected the blood vessels improve their walls. In the arteries, a layer of muscle cells is formed combined with elastic fibers, gradually built up around the lining. In the larger veins muscle bundles appear. The whole blood-circulatory system is now ready for any reasonable pressure.

This system of blood vessels eventually carries the digested food from the intestine to the liver where it gives up any extra burden of food. Thence it leads to heart and, after birth, through the lung circulation, through the heart again and on to the body tissues, carrying oxygen and food.

PLANS FOR THE SEWAGE SYSTEM AND THEIR REVISION

The chemist at his laboratory mixes reagents to get the new ones he is seeking and always in the process he obtains many products that he throws away. If he wants the precipitate he throws away what passes through the filter. So in a great city ships, trains and trucks bring in materials for use as food or for other purposes; the sewers and incinerators take away the refuse. Just so in our bodies, of the food that we consume and that gets into the cells of the body only a part participates in chemical reactions there and some of the by-products are wasted. They pass out into the blood; they are carried to selective filters and secreting cells in the kidney, and the rejected residue, water, urea, various inorganic salts, sundry acids, a group of substances called purins, creatinine (containing much nitrogen), dissolved gases, pigments, etc., are passed to the bladder and intermittently thrown out from the body. This sewer system has thus very intimate relation with the system of blood vessels.[4]

This sewer system of man has had a long and devious history which is reflected in the developmental history of

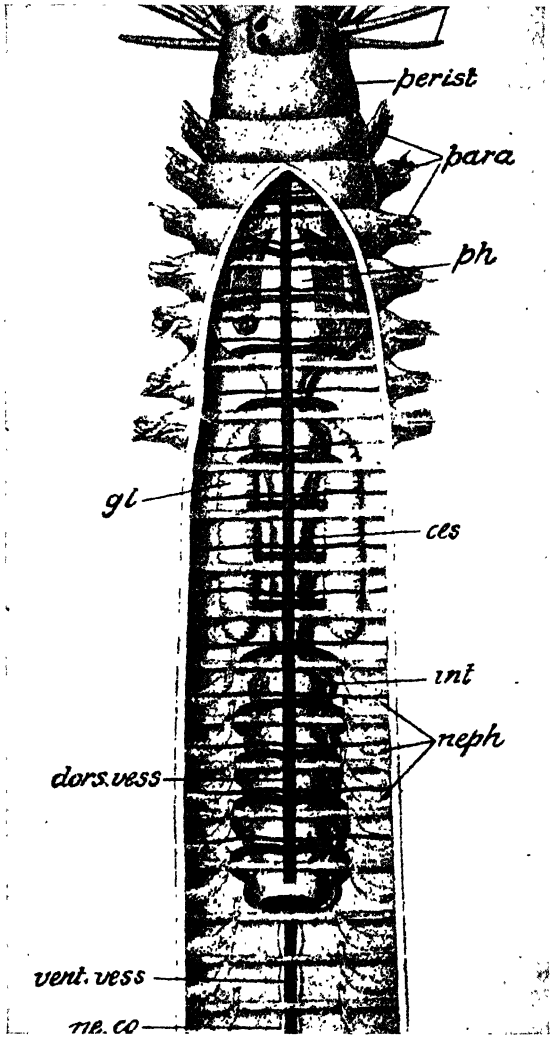


FIG. 76. Dissection of a marine sand worm (Nereis). Head at top. The body-wall along the back had been removed. One sees the gut (*ph, ces, int*) in the axis, surrounded by blood vessels; nerve cord (*ne.co*) below. In the lower part of the picture is the double row of kidney tubules (*neph*) of which there is a pair to each compartment (corresponding to a myotome). About natural size. (*From Parker and Haswell, courtesy of The Macmillan Co.*)

the kidney. First of all it appears that since both renal excretions and sex cells have to be thrown out of the body the same organ can be used for both purposes. And this is the case in the lower organisms, such as earthworms. In such worms the excretory organs are tubes running from the body cavity to the exterior (Fig. 76). Of these a pair lies

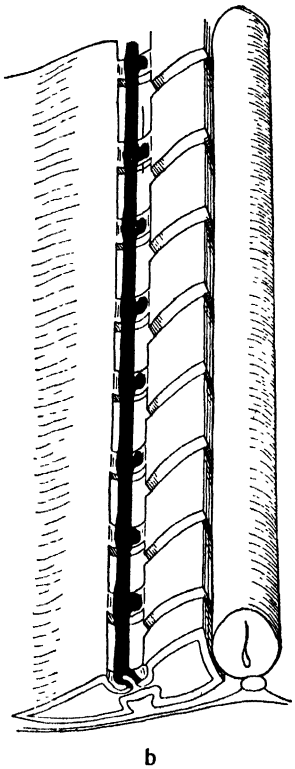


FIG. 77. Diagram explaining the development of the first kidney. The spinal nerve is at right of figure, and to its left is a series of mesodermal somites, each hollow and communicating at the left with the body cavity. The primitive excretory canal, in black, develops from a series of tubes arising from mesoderm of the flanks of the animal as shown just above "b." Each of these tubes grows tailward, until it reaches the next following tube. Then these tubes fuse together forming a collecting duct (main black band in figure). The duct remains, by means of the several primitive segments of the embryo. (*From Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

in each ring, or segment, and the pairs are thus repeated many times. Eventually, as we shall see, in the most highly developed form of the kidney, the two functions are more separate but the organs are still somewhat connected.

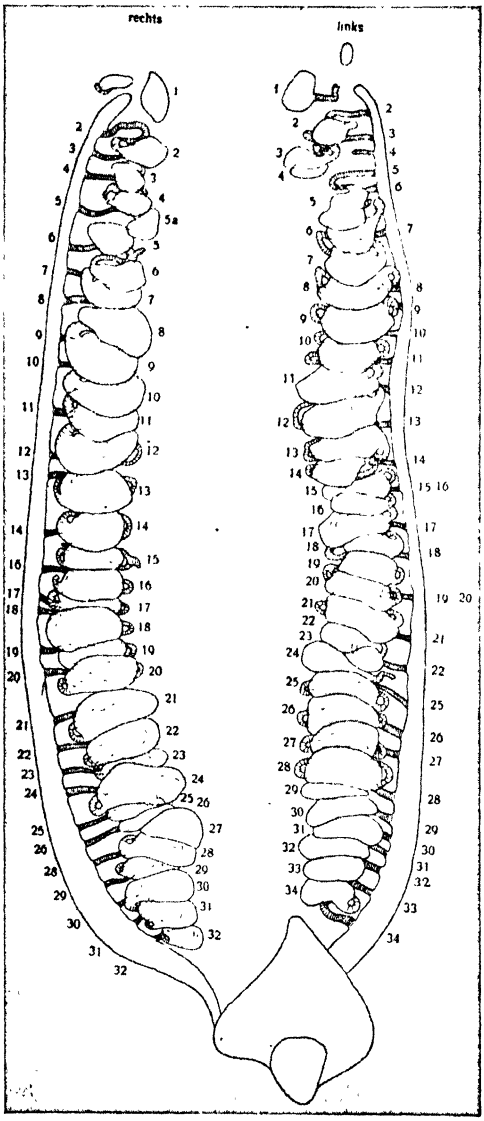


FIG. 78. Model of the second kidneys from an embryo of 9.5 mm. (5¾ weeks). The two second kidneys take a slightly curved course, concave toward each other. The separate canals are closely compressed, so that the ovoidal bodies (numbered 1 to 34 next the middle line), which serve as filters of the blood, come to form a compact body, while the canals themselves are greatly twisted as they pass from the filters to the main collecting canal (1–34 at the side, right and left). After this temporary kidney has been fully formed it begins to degenerate, the units separate off from the main duct, beginning at the upper end. The main ducts widen below and unite into the urinary bladder. (*After Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

In the child, during the third and fourth weeks of development indeed, as the successive mesodermal segments (myotomes) are laid down from the head end tailward, a series of pairs of little tubes are formed in the neck region (Fig. 77). A pocket from each tube opens into the body cavity. Instead of each opening by a hole in the skin to the outside (as happens in ringed worms), the ends next to the skin grow together to form on each side a long duct or tube (Fig. 77) that continues to grow back to the tail end of the body and opens to the exterior there. All of this constitutes the first kidney.

The little segmental tubes are temporary. They soon pass away as development proceeds but the pair

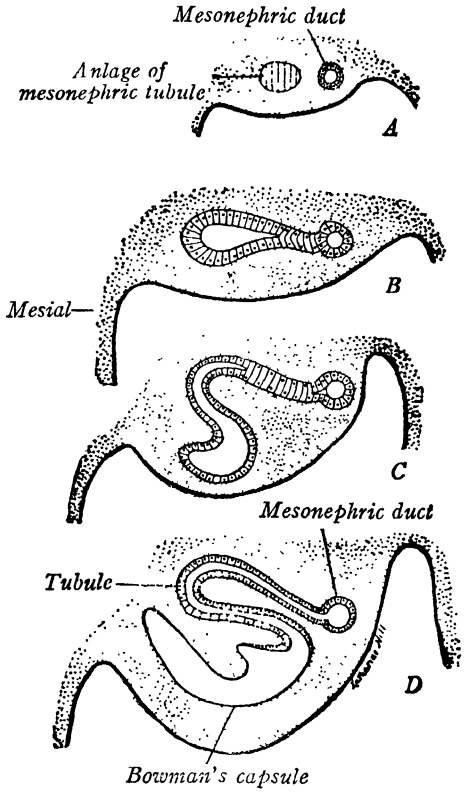


FIG. 79. Details in the development of the tubule of the second kidney, shown by a series of diagrams. *A*, a mass of cells appears near the duct. *B*, it elongates and fuses with the duct. *C*, it elongates further and enlarges at its mesial end. *D*, it unites with the duct and forms a filter (Bowman's capsule) at the other end. (*After Felix, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

of ducts we still carry in our adult bodies. These are called Wolffian ducts from their discoverer, Caspar Friedrich Wolff (1733–1794), whom we shall hear of again. The Wolffian ducts will persist as the ducts that carry sperm from the male germ gland to the exterior. They will play a part in forming the permanent kidney. But before that they have an important role to play in the early embryo.

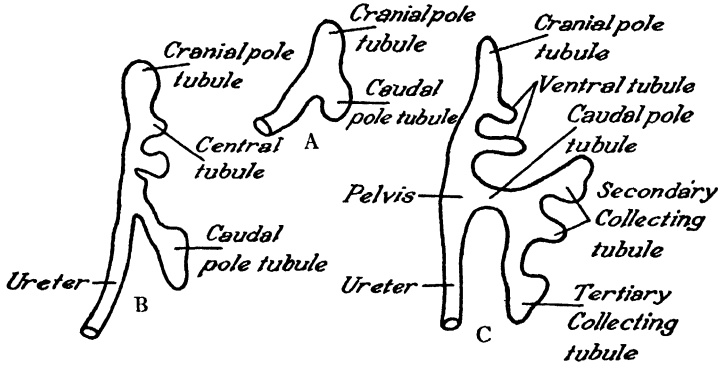


FIG. 80. The development of the primitive buds from the ureter to form the permanent kidney. At A the beginnings are shown of two tubules at the head and tail ends of the series respectively. B, the ureter elongates; a central tubule appears. C, these tubules increase in complexity and as they multiply form the beginning of a kidney body in an embryo of 20 mm. (7½ weeks). (*After Felix and Schreiner, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

As the segmental tubes of the first kidney wither away, in the segments of the body that lie behind them (that is nearer the tail) new little tubes arise on either side of the body near the Wolffian duct and come to connect with it (Fig. 78). Blood vessels come to the tubes preparatory to filtering into them (Fig. 79). Thus in the second month of development is formed our second kidney. This corresponds in structure with the permanent kidney of the fishes and Amphibia (salamanders, frogs and toads). But in the child it is gradually re-

placed at the beginning of the third month by a third kidney; while of it, itself, part is saved for a more specialized function.

The third kidney strikes out for itself in a new line. To be sure, in this case each of the pair of kidneys makes use of the outlet of the Wolffian duct, out of whose wall it has grown as a bud and then a branch. The branch produces a vast number of little tubes (as it were the twigs of the branch) into which the blood vessels grow (Fig. 80). Thus is formed on each side of the body a compact, bean-shaped body, the kidney which serves so useful a function in our grown-up bodies.

To illustrate the succession of sewage apparatus in the developing child let us imagine that a number of families had settled on a meadow near the sea. As the meadow was too wet at times a large main of sewage pipes was run through the axis of the settlement which received the water from a number of side ditches. This corresponds to the first kidney. The ditches soon fill up, as ditches will, and are abandoned; and accordingly a series of lateral sewage pipes is laid tributary to the main. This corresponds to the second kidney. As the community grows into a large village the main is found inadequate except for the end where it opens into the ocean. Accordingly a new and larger main is built using the end of the old main while a vastly more complex and adequate system of drain pipes run under all the side streets and connects even with the leaders that carry water from the roofs of the houses. This corresponds to the third, or final, kidney. It will be observed that this last kidney makes use still of a little part of the main of the first system.[4]

BOY OR GIRL?

As the nine months of pregnancy are drawing to a close the paramount question in the mind of the parents is: Will

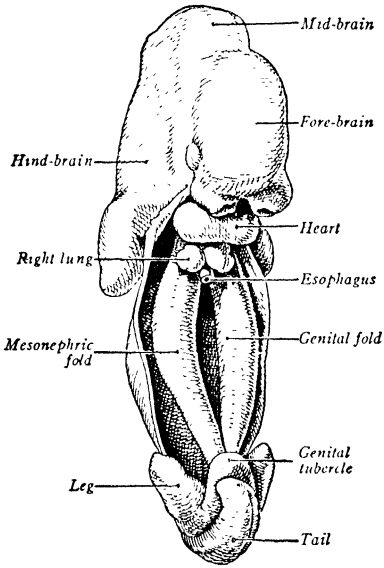


FIG. 81. Kidney-genital folds of the human embryo. Dissection of an embryo of 9 mm. (nearly 6 weeks) seen in ventral view after removing the overlying body wall and viscera. × 11. (*After Kollmann, from Arey.*)

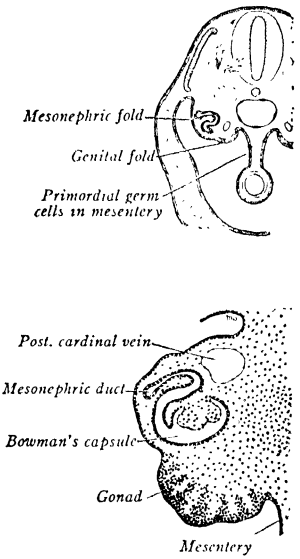


FIG. 82. Above, cross section through an embryo of 5 mm. (5 weeks) showing the position of the right kidney-genital fold. The genital fold is distinguished by a thickening of the membrane lining the body cavity. Single germ cells are shown lying in the nearby mesentery (which supports and surrounds the gut). × 35. Below, transverse section in greater detail through the right urogenital fold, showing the gonad with the thickening epithelium, and the coiled mesonephric duct and glomerulus (Bowman's capsule). × 75. (*Figs. 81, 82 from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

it be a boy or girl? I have even heard of a mother who believed in the supreme control of "mind over matter" (whatever that jingle of words may mean) and who wished for a boy a month before she bore a son. Accordingly she was strengthened in her belief. But, as a matter of cold fact the sex of the child is anatomically established already in the second month of development. It was, indeed, practically determined at the

moment the sperm entered the egg cell. For, though all eggs are alike in their potentiality for sex, the sperms are of two kinds, male-forming and female-forming. And these are of equal numbers. It is an even chance that a given egg will be fertilized by a male-forming or a female-forming sperm; so it is (nearly) a fifty-fifty bet that the unborn child will turn out to be a boy.

The beginnings of the differences between a boy and a girl become externally recognizable in the second month of

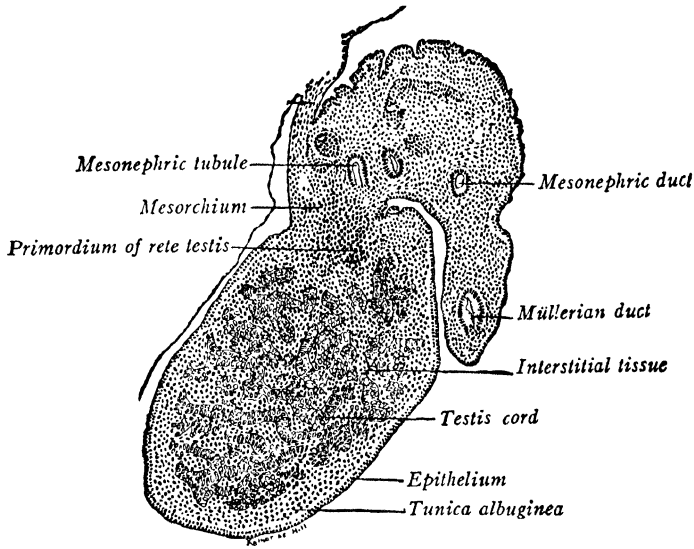


FIG. 83. Cross section of the left genital fold of a 20 mm. (7½ weeks) human embryo showing the beginning of differentiation of the testis. The remains of the mesonephric tubule and cross section of the mesonephric duct are seen above. The Müllerian duct, which in the female develops into the oviduct, is seen at the right. The cords of the testis are seen below, they seem to arise from the surface epithelium. The loose tissue between the cords of the testis is called "tunica albuginea." The "rete testis" is the network of ducts that will carry sperm to the mesonephric duct. This figure illustrates the method of development of tubes and other tissues out of a solid mass of cells. × 25. (*After Prentiss, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

intra-uterine life. The germ gland (or "gonad") arises in either sex as a thickening of the membrane lining the cavity of the body in the region of the upper part of the secondary kidney (Figs. 81, 82). In the case of the boy, there grow into this thickened mass from the superficial membrane finger-like cords of cells, and these later, some time after birth, become tubes, whose walls produce the sperm cells (Fig. 83). Now a remarkable thing happens. The nascent testis lies close to the old Wolffian duct. Some of the former tubes of the secondary kidney grow into the testis and connect with the cords of the testis. They serve later to carry the sperm from these cords, or tubes, to the Wolffian duct. This duct serves then, even in the adult, to carry sperm from the testis outward. To go back to the comparison with the sewage system of a village, the old first main, abandoned for sewage purposes in favor of the later (final) system of drains, is now tied up with the internal house system of pipes. Accordingly we now have two systems leading to the cloaca near the sea; the system of field drainage, corresponding to the third kidney, and the system of house drainage corresponding to the testis and the ducts that lead out from it. So much for the male glands and ducts (Fig. 84).

In the potential girl the gonad (sex gland) is at first quite like that of the male and it arises in a corresponding point of the body. In the ovary, also, cords grow from the surface of the gonad into the anterior; it is probably from these tubes that the eventual eggs are formed. Also, some of the tubes of the secondary kidney grow into the gonad. During the second month, however, there is formed from the lining of the body cavity starting near the gonads and progressing tailward, a pair of tubes with a wide open mouth close to the gonads. This paired tube is known by the name of its

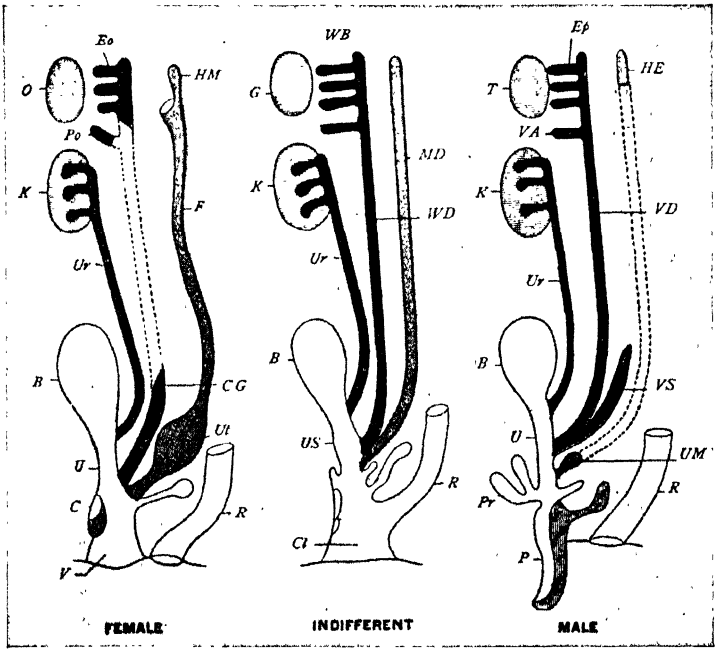


FIG. 84. Diagrams illustrating the transformation and interrelationships of the Mullerian and Wolffian ducts. At an early stage of fetal development there are present (middle figure) the Wolffian body (*WB*), the second kidney, including its duct (*WD*). Also present is the Müllerian duct (*MD*). From this indifferent condition the female (left) is derived by the transformation of the Müllerian ducts into the female oviducts and uterus, and the Wolffian body into a mere rudimentary appendage of the ovary, *O*. The rest of the Wolffian ducts degenerate except for a rudimentary piece near the bladder (*CG*). In the male (right) the Müllerian ducts degenerate and disappear almost wholly, except for fragments *HE* and *UM*. The Wolffian duct, on the other hand, carries sperm from the testis via the "epididymis" (*Ep*) as the vas deferens (*VD*). In all figures *B* is bladder; *U*, urethra; *R*, rectum; *K*, kidney; *Ur*, ureter. In the male, *Pr*, prostate gland; *UM*, uterus masculinus; *HE*, "hydatid" of epididymis; *P*, penis. (*Modified after Huxley from McMurrich's "Development of the Human Body," courtesy of P. Blakiston's Son & Co.*)

discoverer (Johannes Müller, a German physiologist, anatomist and embryologist of the first half of the last century) as Müller's duct. This tube arises in both sexes. Under the influence of the differential in the male-producing sperm, referred to on page 103, the Müllerian duct becomes in that sex a mere rudiment, like our appendix. But under the influence of the future female it gets larger and serves to carry the eggs from the gonad (ovary) to the uterus—it becomes the oviduct. Apparently the urinary duct is large enough to carry sperm but not to carry out the large vertebrate egg, so that for the eggs a special tube is, from the first, reserved.

But what becomes in the female of the Wolffian duct which serves in the male to carry the product of the gonad (sperm) to the outside? In her the Wolffian duct gradually gets smaller and functionless. The tubules of the second kidney which entered into the ovary can still be seen about the ovary of the adult but they become in the female rudimentary. To return to our figure of the village sewage system, it is as though half of the houses (say, on the north side of Main Street), still used the old primitive drains, the other half of the houses ran a new set of drains parallel to the old one and let the old drain in them fill up and become useless. It is noteworthy that in building the new in the body the old type is first formed; then, though improvements are necessary, the old is made use of as far as possible.

The boy and the girl can be easily told apart by the way their excretory and genital ducts end. During the early part of the second month these ducts all empty, together with the food canal, into a common cloaca. Such a cloaca is found in birds, reptiles and amphibians. From this cloaca passes a temporary embryonic tube whose accompanying blood vessels constitute an excretory con-

nection with the mother. At this time the mother has to excrete for two.

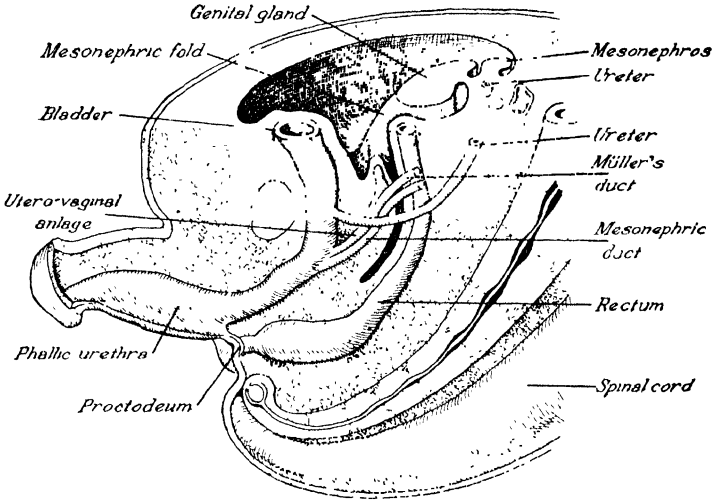


FIG. 85. Completed division of the human cloaca in the male embryo, and other associated changes, as shown by reconstructions viewed from the left side. Right half of the caudal end of an embryo of two months showing the rectum in the middle in front of the vertebral column opening at *Proctodeum*. To the left of rectum is the *Bladder*, continuous with the *Phallic urethra* of the male, opening at apex of phallus (penis). Into this bladder open the *Ureter* (from kidney), the *Müllerian duct* and the mesonephric (or Wolffian) duct. The *Mesonephros* is seen above and the *Genital gland* nearby, projecting into the body cavity. The right *Müllerian duct* is enclosed by the *Mesonephric fold*. (*After Keibel, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

Before the end of the second month as we have seen (page 89) the end of the gut becomes cut off from the rest of the cloaca. A little later the Müllerian ducts which are united and enlarged at their lower end are separated off as uterus and vagina from the bladder and its duct. But in the male the Woffian duct (which carries sperm) opens into the bladder duct (urethra) and the common duct of both is prolonged into a tubercle (Fig. 85) which later grows into

the intromittent organ (penis). Thus at the beginning of the third month, a difference is found in the external genitalia of the boy and the girl. During the next two or three months the testes, which formerly lay like the ovaries high up in the body cavity, begin to migrate and before birth come to occupy a pouch already prepared for them at the very bottom of the body cavity. The ovary also moves down slightly to take a position in the shelter of the pelvis.

It is not to be forgotten that the function of the testes is not merely to produce sperm and of the ovary merely to produce eggs. On the contrary, both glands throw into the blood substances (hormones, in some cases sterols) that are carried to all parts of the body and serve markedly to differentiate the general physiology and the behavior of the two sexes.

NOTES

1. On lung development Flint (American Journal of Anatomy, Vol. 6) and George S. Huntington (American Journal of Anatomy, Vol. 2) have made distinguished studies; as W. S. Miller has on the finer lung structure.

2. On the development of the digestive system see Arey's *Developmental Anatomy* and references at end of chapter. See also papers by Johnson in the American Journal of Anatomy, 1913 and 1919.

3. The early development of the heart has been traced by Bradley Patten in the American Journal of Anatomy, Vol. 48, and by Carl Lawrence Davis (1927) in the Carnegie Contributions to Embryology. In the same Contributions are papers by Florence Sabin, George L. Streeter and L. D. Condon.

4. The remarkable development of the kidney systems has been worked out with great pains in all groups of vertebrates during the past 100 years and only gradually did its true meaning become understood. Francis Maitland Balfour, 1876, and Adam Sedgwick, 1882, were among the early Englishmen to synthesize these scattered studies. See Balfour's *Comparative Embryology* and later textbooks of embryology like Keibel-Mall and Arey.

CHAPTER 5

PUTTING ON THE FINISHING TOUCHES

THE SKELETON IS REBUILT

Vertebrates have to have a skeleton to hang their muscles on; and the human child is no exception. The muscles, in the shape of the muscular rings (myotomes) which we have already considered (Figs. 21, 24), begin forming toward the end of the first month. At this time there is a delicate rod lying in the axis of the body where the backbone comes later to lie. Migrating cells penetrate between the myotomes eventually to form the ribs, and around and above the axial rod eventually to form the backbone or vertebral column. This is the cellular stage of the skeleton, properly, mesenchymatous stage. (Fig. 86.)[1]

In the middle of the second month of intra-uterine life these migrating cells begin to form a first trunk skeleton out of cartilage. That is, the migrating cells band together and then secrete between themselves a cheesy substance that hardens into the consistency of gristle (Fig. 87). Thus the primitive ribs and vertebral column are preformed in cartilage.

Similarly, the migrating cells penetrate into the limb buds and give rise at first to a mesenchymatous anticipation of cartilage (Fig. 86). Then a week or so later (at six to seven weeks after fertilization) cartilage begins to be formed by these wandering cells. The whole lower part of the skull develops in like fashion with the vertebrae. But

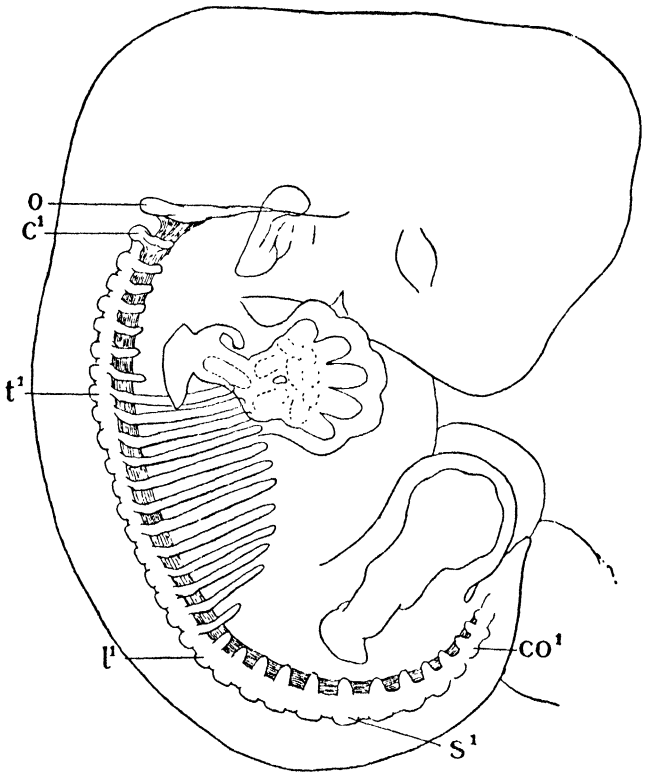


FIG. 86. A diagram outlining the areas in which the mesenchymatous (wandering cell) precursors of cartilaginous bones are already formed. These areas and masses include, in an embryology of 11 mm. length, the vertebral column (c^1, t^1, l^1, s^1), certain ribs, certain masses in the upper limb, the hinder part of the skull (O); CO^1, temporary vertebrae of the tail. (*After Keibel-Mall's "Handbuch d. Entw. d. Menschen."*)

the developing upper brain becomes surrounded on its sides and above by the migratory cells and they form a felted membrane about it, but never any cartilage. Thus, before the end of the second month one can, by properly clearing the tissues of the embryo and dyeing the cartilage, get a good view of the cartilaginous skeleton in place. It has,

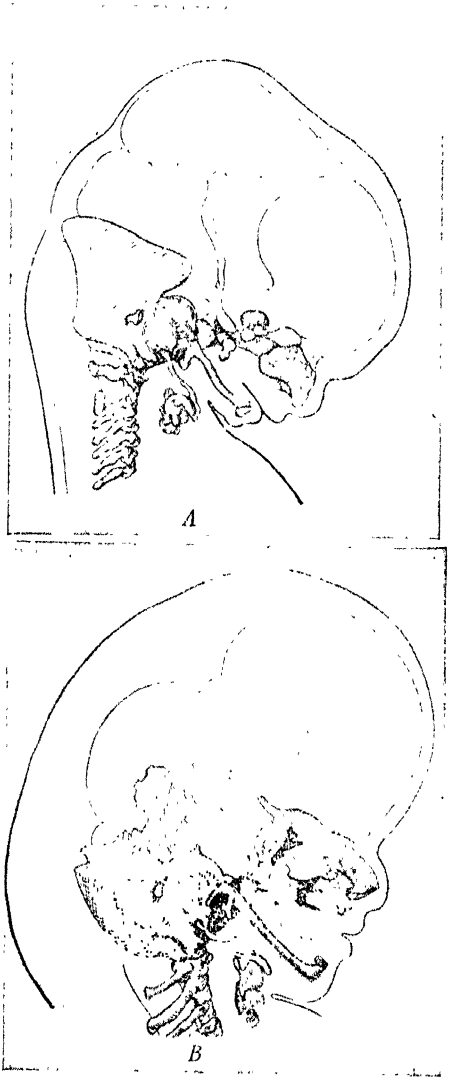


FIG. 87. Diagrams outlining the cartilaginous bones of the human fetus. *A*, during the eighth week. × 5. (*After Lewis, modified*). *B*, at ten weeks. × 3. (*After Macklin.*) The membrane bones are in stipple. (*Both figures from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

It will be noted that at 8 weeks the upper vertebrae, hyoid bone, jaw bones and base of skull are formed. At 10 weeks the cartilaginous base of skull has increased and the bones of the face are forming.

except for the membrane bones, much the distribution of the bony skeleton which will not appear until later (Fig. 87).[1]

This cartilaginous skeleton has some clear advantages. It is light, highly flexible, elastic, easily repaired. The sharks and other lower fishes have only a cartilaginous skeleton (Fig. 88) and they are among the most powerful of swimmers and the most savage of fighters.

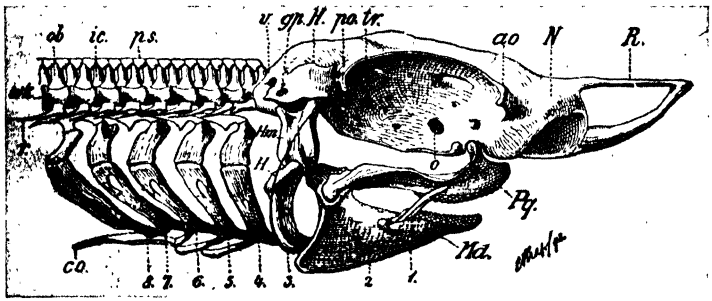


FIG. 88. Cartilaginous skeleton of adult shark, showing vertebral column, arches, skull. *ao*, antorbital process; *co*, rib coupling; *gp*, *tr*., *v*, holes for nerves; *H*, ear capsule, also hyoid; *Hm*, uniter of hyoid and mandible; *ic*., intercalated pads; *Md*, mandible; *N*, nasal capsule; *o*, passage for optic nerve; *ob*, arch over spinal nerve with process, *ps; po*, postorbital process; *Pq*, upper jaw; *R*, beak; *r*, ribs, *wk*, vertebrae, 1–8 arches of mouth and gill bars. (*From J. S. Kingsley; Holt & Co.*)

But cartilage has a certain disadvantage as skeletal material for terrestrial animals. It is not quite rigid enough. You need rigidity for attaching powerful muscles and supporting the body from the ground. When rigidity is lacking in the nature of the material the skeleton has to be greatly thickened to give rigidity by massiveness.

In the middle Paleozoic period, a great invention was hit upon in vertebrates, and became a permanent possession of most of the later representatives of the class. The cartilage still formed, as it is in the child, but at a certain stage (in the embryo child at the end of the second month) there appeared in the cartilage centers at which the matrix of the cartilage was dissolved and replaced by bone.

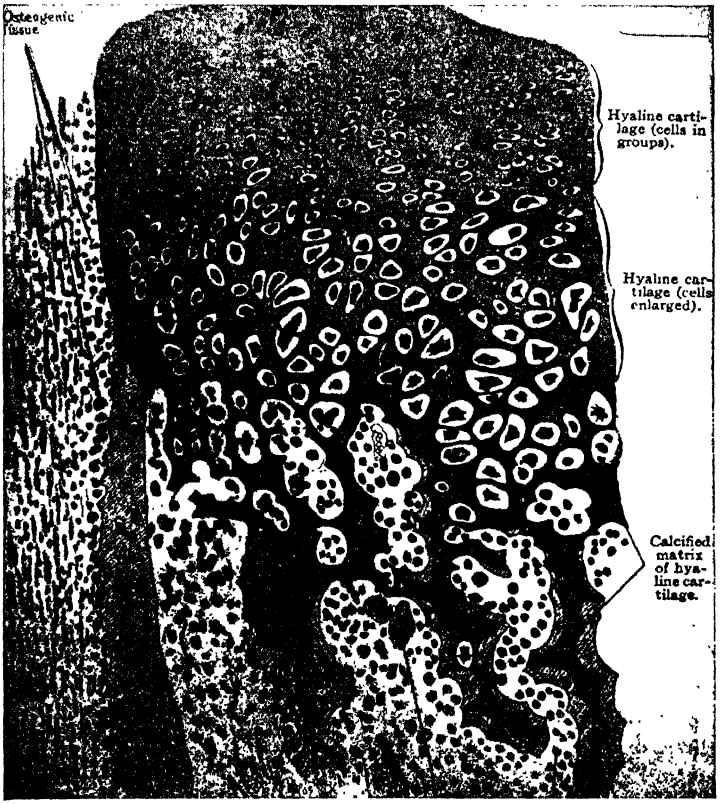


FIG. 89. Longitudinal section of one of the finger bones of a human embryo of the fourth month showing bone forming out of cartilage. × 220. The periosteum is the connective tissue sheath around the bone. The osteoblasts are the cells of the periosteum which form the bone surrounding the cartilage (perichondrial bone). This "osteogenic," or bone forming, tissue is thus forming bone that has not been preformed in cartilage The rest of the figure has to do with bone formation out of cartilage. The upper part of the figure represents cartilage. On top the cartilage cells are still in files, in the order in which the cells divided before they became encapsuled in the collagen that they secrete. At "Hyaline cartilage (cells enlarged)" one sees the collagen being dissolved around the cells. Below, blood vessels are seen penetrating into the mass and bringing in osteoclasts (bone destroyers) which help make great spaces in the cartilage into which the osteoblasts (bone formers) penetrate and begin to secrete the solid material (p. 272) of bone, around the blood vessels as centers. Many free migrating cells (marrow cells) lie within the forming bony walls. × 220. (*From Lewis-Stohr's "Textbook of Histology," courtesy of P. Blakiston's Son & Co.*)

This is a dramatic process, well pictured in Fig. 89. The cartilage, it appears, is always surrounded by mesenchyme which has not become cartilage. At about two months of age this mesenchyme begins to form a sheath of bone around the cartilage and to send cells into the cartilage which gradually dissolve it. The space may be more or less filled by bone or some space may be left to form the bone marrow that is found in long bones, like the leg bones. Eventually most of the old-fashioned cartilage of long bones is replaced by bone, but there is gristle in the body that is never ossified—such as the cartilages of the lower ribs, of the Adam's apple and windpipe, and of the prominent part of the nose (Fig. 57). Either these parts do not have to support a great muscular pull or else (as in the lower ribs) too great rigidity would be a disadvantage.

But not all bone is preformed in cartilage. In our bodies there are certain superficial bones, like those of the cranium (and of the teeth if one may call so particular a structure bone) that never pass through a cartilaginous stage but are derived directly from cells that may have formed mesenchymatous tissue, or may be from simple epithelium. Such are called membrane bones.

The invention of bone had important consequences. It made it possible for vertebrates to come on land as the frogs and salamanders and even certain fishes do temporarily. It made possible the terrestrial reptiles, the aerial birds and the mammals that travel on the ground, burrow into the ground, swing from branches of the trees, fly into the air, and have even returned to that ocean whence the vertebrate phylum arose. Blessed bone! The "outs" about bone are that it is heavy and brittle and its spaces may harbor many parasites. Bone is normally rigid and yet elastic and possessed of a marvelous capacity for

repair. For all bones are penetrated by blood vessels and living cells, and they are ensheathed by a tissue that is very much alive and active. All of these active cells are "standing by" throughout life to replace worn out or diseased bone, to meet special stresses that a bone may be called upon to bear, to repair a break that may occur. The bone in the living body is not at all like the dry bone of the bone yard or museum of skeletons. It is active, sensitive, plastic, one might almost say highly intelligent.

THE EMERGENCY DEPARTMENT

The adult body is well adapted in its organs for the maintenance of the ordinary affairs of life. But there are crises that must be met, such as the threatened assault of enemies—other men or animals—and as childbearing, childbirth and lactation. There is the episode of rapid growth during the later months of intra-uterine life and the adolescent spurt of growth when a boy may increase in height four to six inches in twelve to eighteen months. For such crises special bodily provision has to be made; hence in part has arisen the system of internally secreting, or endocrine, organs.[1]

The list of endocrine organs is a long one (pineal, pituitary, parathyroid, thyroid, thymus, pancreatic islets, suprarenals, gonads) and I am not going to dwell on the development of each. They are made up mostly of odds and ends of more or less discarded organs, the gonads of course excepted. For the gonads, as the oldest of all and as carriers of the immortal reproductive stuff, are self-perpetuating.

As for the others, they are functionally more or less tied together. The pituitary stimulates the thyroid and also a gland that lies over the kidneys, hence called suprarenal.

FIG. 90. Photograph of part of a row of midgets and dwarfs taken by Harry Hamilton Laughlin at the "Century of Progress," Chicago, 1934.

If the first is deficient the child fails to grow adequately; remains a dwarf. There are a good many dwarfs in the country, enough to form a fairly large "Midget City" at the Century of Progress Fair in Chicago and to keep the circuses and amusement places well supplied in addition (Fig. 90). And of course these cases are only a fraction of all, since most of them remain at home. What is the

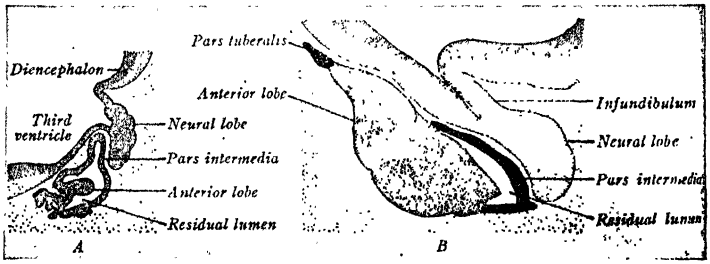


FIG. 91. Development of the human pituitary body (hypophysis) shown by mid-sagittal (median) section. *A*, at 8 weeks, showing: "Third ventricle," or cavity, and "Diencephalon," or wall, of middle brain; "Neural lobe," or posterior lobe of pituitary body; "Pars intermedia," intermediate segment; and "Anterior lobe." *B*, the same region at 11 weeks. The neural lobe lies at the bottom of a deep depression at the bottom of the brain wall. × 35. (*Adapted after Atwell, from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

nature of this pituitary gland, which with its collaborating gland has such an effect on growth and other qualities of build? Of this pituitary one part (the anterior) is formed shortly after the mouth is folded in, by a deep dimple in the roof of the mouth pointed toward the base of the brain. This comes to lie just in front of a depression in the floor of the brain. These two pouches make the pituitary gland (Fig. 91). On the top of the brain, above the pituitary, an up-growth occurs and this forms an organ known as the pineal gland. The philosopher, Descartes, who was seeking the site of the soul, hit on this as the goal of his search—

because it was a single body and had thus the unity of the mind and soul. Comparative anatomists, however, reached another interpretation for they found that in reptiles the organ, or part of it, formed an eye in the middle of the head (Fig. 92). Shakespeare had some hint of this fact, apparently, for he speaks of a jewel in the head of a toad. This gland is supposed in man to have some relation to the development of secondary sex characters, especially to restrain the maturation of the reproductive organs.

How these organs at the top and bottom of the brain originated is a subject for speculation. Some have suggested that in the ancestors of vertebrates the gullet ran through the brain, as one may see it does in the earthworm. For such persons the pituitary and pineal bodies are remains of such a gullet. Whatever the facts may be this interpretation is in accord with the typical origin of endocrine glands from remnants.

The role of the endocrines as the emergency department of the body is well illustrated by the function of the suprarenal gland. This is made up of remnants from two distinct tissues. Walter Bradford Cannon of Harvard demonstrated that when a dog is excited by a cat it keeps up the excitement even after the cat has jumped over the fence and disappeared from the dog's view. And he proved that the reason is that the excitement makes the suprarenals excrete into the blood a substance (hormone) which keeps up its effect on the nervous system for some time. He got the proof first by showing a barking dog to a cat for a few minutes and then testing the cat's blood. He found that a sample of this blood would prevent the muscle from the gut of a rabbit from contracting as it did when the blood was unexcited. The conclusion is that excitement causes the suprarenal gland to yield its hormone and this increases

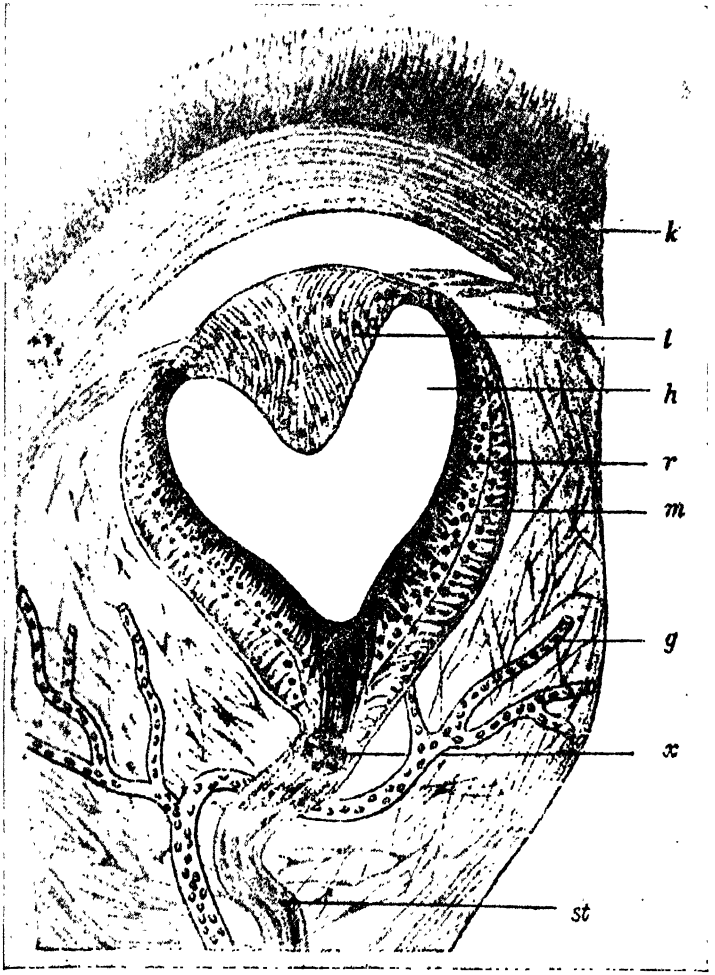


FIG. 92. Vertical section of the pineal eye of a lizard-like reptile, called Hatteria, that lives in New Zealand. Above is the scaly skin and a connective tissue covering (*k*) which are both transparent. Below them lies the eyeball proper, comprising a lens (*l*), a humor-filled space (*h*), a retina, *r* and *m*. The optic nerve has degenerated (*st*, *x*) in the adult. Various blood vessels (*g*) surround the organ. (*After Baldwin Spencer, from Parker and Haswell's "Textbook of Zoology," courtesy of The Macmillan Co.*)

the amount of sugar in the blood and this increases muscular vigor, energizes the individual and gives him added power to escape or fight, or to excel in physical prowess in competitive games. It brings "intestinal fortitude."

In the same way the gonads and pituitary produce various hormones that play an important role in connection with the periodic functions of reproduction and the intermittant function of lactation. So long as our endocrine glands are in good working order our bodies can stand enormous strains. As the engineers say we have a large "factor of safety."

PUTTING ON SIZE

By the end of the first twenty weeks of intra-uterine life, at a time when the period of development in the mother's body is half finished, the human child shows the special traits of its species. It can no longer be mistaken for one of the lower primates. Indeed, a European fetus can be distinguished from that of a Negro. The head is relatively large while the legs are very short. Its nose is broad and bridgeless. It is now, however, a functioning organism. It responds to contact by a reflex muscular contraction; some neuro-muscular complexes function completely. The heart and vessels carry the stream of nourishing food from the placenta to all parts of the body.

At twenty weeks the fetus is still small, weighing about 280 grams, or somewhat more than a half a pound. It must increase to about 3,500 grams during the next twenty weeks; so that growth is one of its principal occupations during that period. And this growth has an ever increasing absolute velocity. For example during the sixth lunar month the increase is about 300 grams; in the seventh about 400 grams; in the eighth about 500; in the ninth 800;

in the tenth 1,300. Just before birth the fetus is growing at a faster rate than it will grow at any future period of life. And this rapid growth is one of the things that determines the precise onset of parturition. Comparatively helpless as it is at birth the neonate has at least size in its favor.[2]

During the second half of intra-uterine life the internal organs also are undergoing a differential development.

The female hormones of the mother might be thought of as prejudicial to the development of the sex organs of the male. However, the hormones produced by the male fetus are very vigorous and probably protect it against the female hormones of the mother. In the case of cows when twins of opposite sex develop the placentae of the two grow together and the circulation of the two becomes common.[2] Under these circumstances the hormones of the male calf inhibit the full development of the sex organs of its twin sister. There are, however, at present no facts that justify us in thinking that anything like that occurs among human twins of opposite sex, apparently because the circulations of the two placentae rarely unite. One effect of the sojourn of the female fetus in the mother's body is the extraordinary development of its uterus two or three months before birth. But immediately after birth the weight of the fetus's uterus decreases again, presumably because the supply of maternal hormones has ceased.

Finally, a word may be said about the hair coat of the fetus that is nearly ready to be born. Man is the least hairy primate. But nearly all of the skin bears fine hairs (down) about as abundant as, though much finer than, those of other primates. In the fetus, however, this coat of down (lanugo) is very pronounced and nearly uniform over the

body. The neonate is for a brief time a fine-hairy mammal. With the loss of the lanugo the baby assumes, for a time, a nearly hairless appearance except for the head hair.

The skeleton takes a growth spurt in the last two months of prenatal life, hand in hand with that of the musculature. The mother appreciates the increasing restlessness and vigor of the unborn babe. The central nervous system, which is precociously developed in the embryo, falls relatively behind the other organs in fetal development. Likewise the viscera grow less rapidly than the skeleton and musculature. During the second half of intra-uterine life more of the reflexes become well established. The grasping reflex, so very important for the primate immediately at birth, gradually increases in complexity and vigor up to birth. The young monkey, in the very act of being born as soon as its arms are free, grasps firmly the hair of its mother. The neonate human baby, when startled, throws up its arms as if to grasp the mother's body. Protective reflexes appear as early as, if not before, the nursing reflex.[3]

The few weeks immediately before birth are precarious ones for the fetus and many a baby is still-born. Boys are especially apt to die before birth. This has been interpreted as due to the fact that, as compared with the female child, the male child is in a "foreign" and not altogether friendly environment in the female body of its mother. For the fetus receives not only fluid food from the mother but also hormones and among these are the female hormones. Apparently it is some of the same hormone that stimulates the enlargement of the mammary glands of the mother that gets into the fetus of both sexes and causes that temporary enlargement of those glands which is found in the new-born.

THE CHILD IS BORN, HALF MADE

After nine months of expectancy, ordinarily after some hours of labor, including severe labor pains (frequently relieved by anaesthetics) the child is born. Within a few minutes it has changed from an aquatic animal to a terrestrial; from a quasi-parasite to a mouth feeder. If it is

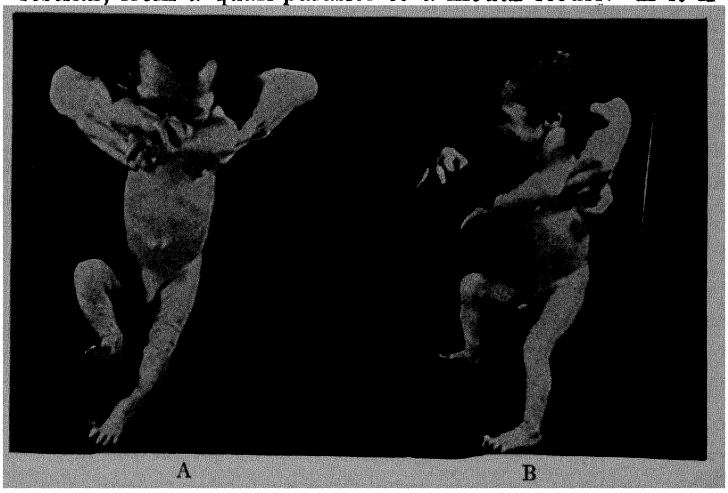


FIG. 93. Posture of a new-born babe whose feet are brought into contact with the floor. A. General flexion of upper extremities, lower extremities and neck; note lateral contact of feet with floor, resembling the club-foot attitude of anthropoid apes. B. A little later the trunk is held forward, extension developing in upper extremities, contact chiefly with the toes. These contacts set up the reflex stepping movements of the new-born. (*Contributed by Dr. Myrtle B. McGraw.*)

well made, and it is one of the most remarkable facts of Nature that most babies are born well made, it can ingest, digest, breathe, feel, see, recognize agreeable stimuli, use its voluntary muscles, secrete and excrete. The new-born child is an independently going machine.

Within the first few hours after birth the child reveals the possession of special machinery for certain reflex move-

ments. If placed in a tank of water it will make effective swimming movements; if it is held so that its feet are permitted to touch the floor it will make progressing steps; if supported by a belly-band it may propel itself by its lower limbs; if a rod is placed in its hands it will grasp it so firmly that it can be lifted by the rod; if it is startled by a blow on the bed it will make a grasping movement with its arms. In general the arm action is more developed than the leg action. The lower limbs are apt to be kept flexed for some weeks in the way they were in the uterus. Cephalic precocity shows itself (Fig. 93).

Despite all it is able to do the baby is only a half-made representative of the human species. It has only about one-third of its eventual adult stature, one-twelfth of its eventual weight. Its skeleton is far from complete. The long bones of the limbs are still growing rapidly. The caps (epiphyses) that limit their growth are still unattached to the body of the bone. The wrist bones are unformed. The shoulder blades are largely cartilage and will not be completed for eighteen years still. The skull will change its shape markedly, becoming more elongated. The adult facial features can hardly be forecast from their rudiments on the babe. The heart is still partly reptilian, so that a mixture of arterial and venous blood may occur in the heart. Some traces of the fetal circulation may persist after birth. The upper walls of the great brain hemispheres have at birth a complex structure, but nevertheless the structure increases in complexity for years * (Fig. 94). The eyes seem to be nearly completely functional at birth, except that the movements of the eye muscles are not properly co-ordinated. The eardrum is still filled with tissue which only gradually withers away; but even so the baby

* Agduhr, E. '28. Kon. Akad. v. Weten. Amsterdam, Vol. 27.

reacts to a shrill whistle. Doubtless the sense of taste is well developed, so that the quality of good milk is highly agreeable, while bad-tasting milk is rejected as disagreeable. Even fetuses react to ammonia as well as to contact three to five months before due to be born.

The muscular system is feeble; especially of the lower part of the body and lower limbs, though these limbs may be flexed after stimuli. The baby is thus not quite helpless but soon learns to use its arms for a variety of purposes and to move about in bed. Some months are required to enable it to stand on its lower limbs and take the first steps. Indeed, the baby is a weak, uncompleted creature; its importance lies in its potentialities.[1]

THE LONG, LONG ROAD OF CHILDHOOD

By the time the infant has learned to walk, its rate of growth has greatly slowed down and after two years the child

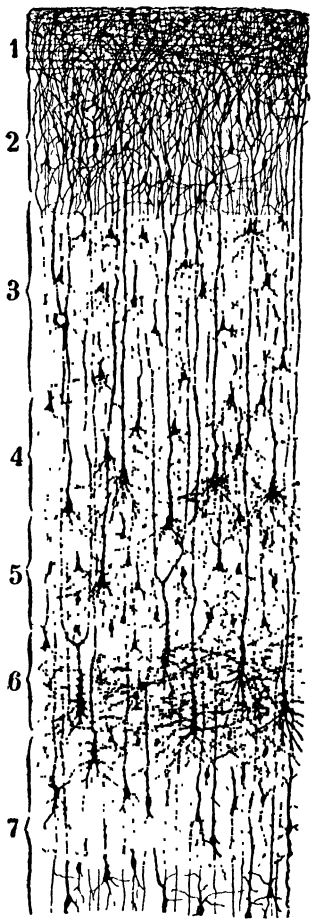


FIG. 94. Section from the cerebral cortex (outer brain rind) of a human infant, with the neurons impregnated by the method of Golgi. There are here recognized 7 layers (so numbered). In the outer layer (1) the fibers run largely tangentially. (*After Ramón y Cajal, from Herrick's "Introduction to Neurology," courtesy of W. B. Saunders Co.*)

adds, on the average, only about 2.5 kilograms (five pounds) a year for the next eight years. Hence one-tenth to one-seventh of the human life span is spent in getting ready. Hardly another organism is so slow to develop as man! The elephant, which lives to be 150 to 200 years old, attains maturity at 20 to 30 years of age; but this period is proportionately to the life span not longer than that of man who matures at about 15 years. If the length of the post-natal premature period is expressed in percentages of total life span we get a table like the following:

Species	Maximum Length of Life, Years	Percentages		
		Prematurity Period	Reproductive Period, Female	Post-Reproductive
Man	80	20	40	40
Horse	35	14	76	10
Bull	30	13	77	10
Dog	11	10	80	10
Guinea pig	6.7	7.5	93.5	0
Mouse	3	15	75	10

During these years of childhood the boy or girl has to be as active as any other young animal. And the direction of its activities is determined by its structure and instinct. It climbs, it swings, it jumps, it sprints and it wrestles, like any young anthropoid ape. When the affectionate but somewhat distraught mother says "you little monkey," she speaks a half truth, as we shall see more in detail later.

Meanwhile the child's brain is developing. He exercises his newly found language capacity. Two of us, small boys, went to the cobbler's shop and as he wasn't quite ready waited for him to finish our shoes. Finally, he drew a deep sigh. "What is the matter?" I inquired. "It's an awful death to die," he replied, "to be talked to death." Branden-

berg's six-year-old child asked 397 questions per day. The boy wants to know how things are made. He dissects his sister's talking doll; he takes the clock to pieces. He begins to explore his world. He may have all the neighbors looking for him in consequence of half a day's disappearance. He has to learn numbers in order to count his marbles and puppies. His social instincts develop. He wants to go with other boys, and later he will organize his gang and pit it against an enemy-gang.

By the time he is ten years old the normal boy has learned his surrounding world adequately and accurately. He sees all, he remembers all, and his knowledge is uncannily precise. "Sherlock Holmes" knew that he could rely on his "Baker Street gang."

The girls, too, jump rope, they learn the technique of child and household care with dolls, and helping at home.

But just because of these long years of childhood with intense mental and physical development, those grown folk who love to organize things have come to insist on school for all children. Some children, probably most, are thrilled by the opportunity to learn more of their world; many others find the work unsuited to them and therefore irksome. But the steamroller of an educational system insists on mass culture, alike for nearly all.

THE ADOLESCENT EXPLOSION

The long period of childhood is ended more or less abruptly by a metamorphosis that is almost comparable with that from the tadpole into the frog. This is best seen in the boy; just because, on the average, the boy has to change more in stature and weight to get to be a man than a girl has to become a woman. Before the main episode there is frequently a preliminary rumble. Frequently at

the age of ten or eleven years a growing boy will break the lock step of one inch (2.5 cm.) per half year and jump up to four centimeters. This is the juvenile spurt in growth. Then follows a year or two, or three, of reduced growth and then inside of one or two years, at about age fourteen to sixteen, an increase of growth velocity up to five centimeters (2 inches) per half year. This is the adolescent spurt. After this explosion growth slows up strikingly, and is nearly finished at eighteen to twenty years (Fig. 95).[5]

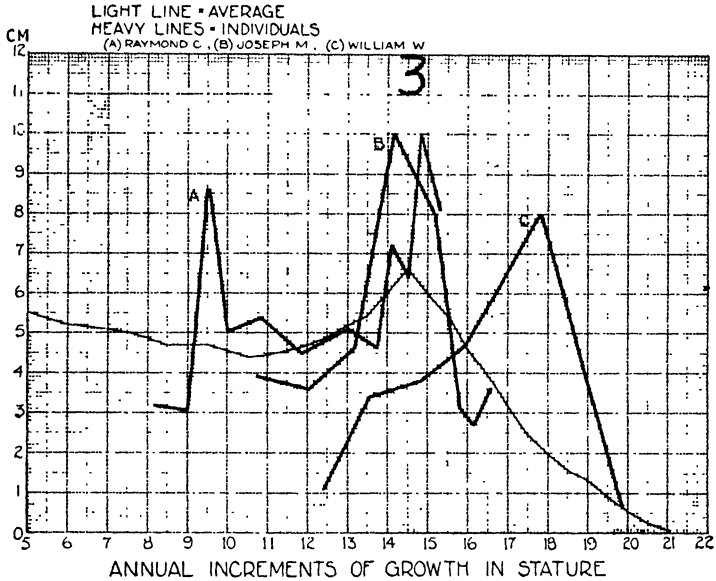


FIG. 95. Growth of three boys in one family. The horizontal distances from the left indicate age. The vertical distances, rate of growth, expressed as centimeter increments of stature in one year. Note the spurt of growth at 14, 15 and 18 years respectively.

The age of most rapid growth is, for boys, centered at around 14.5 years. For girls at about 13.0 years. Of boys of a given height at thirteen years, those whose adolescent

spurt comes early will be relatively short men. If the adolescent spurt comes late they will be tall men. If their adolescent spurt is very vigorous, that is, if they add many inches to their stature in one year, they will probably become taller men than they will if they have no strikingly great adolescent spurt.

Parents whose children at adolescence are growing so fast that they visualize the necessity of reconstructing doors and stairways in the house may take comfort in the knowledge that generally that rapid rate of growth does not last long. Let me cite one example of rapid growth of a son and daughter in standing height (stature) that caused the parents undue concern. The father is 76½ inches (194.3 cm.); the mother 67½ inches (171.4 cm.) tall.

This is the way the boy and the girl grew:

Boy (in centimeters)			Girl (in centimeters)		
Age Years	Stature	Increase per ½ Year	Age Years	Stature	Increase per ½ Year
12½	172.3		9	145.5	
13	176.7	4.4	9½	149.1	3.6
13½	182.0	5.3	10	151.8	2.7
14	186.2	4.2	10½	154.1	2.3
14½	187.5	1.3	11	157.5	3.4
			11½	162.2	4.7

The boy had practically stopped growing at fifteen years. The girl is growing rapidly, but she is not so tall as her mother. However, since her father is very tall she will probably eventually exceed her mother in stature.

The adolescent spurt is a period of rapid growth of the limbs and of corresponding awkwardness in handling the limbs. The boy outgrows his clothes before they are worn out; so they become the heritage of a younger brother. If

not replaced the coat sleeves soon come only to the middle of the lower arm and the trousers to just below the calf, so that the boy is quite humiliated. At the same time the voice changes, the fuzz on his face gets more prominent; the shoulders continue to broaden, the external genitalia enlarge and pubic hair appears; new ambitions, new longings surge, the opposite sex becomes more attractive.

In the girl the growth, though rapid, at twelve to fourteen years is typically not so extreme as in the boy. The onset of sexual maturity is heralded by the first menstruation. Numerous psychic and emotional changes occur at this time, well described by G. Stanley Hall in his book on *Adolescence*. The period of adolescence is one of such rapid physical growth and emotional changes that each child who is passing through this stage deserves careful consideration by parents, school teachers or principal and the athletic director.

GROWN UP AND READY FOR HIS WORK IN THE WORLD

By eighteen years in the case of the boy and sixteen in the girl, on the average, adulthood is practically attained. With the acquisition of long thighs and a high foot arch the youth becomes fitted for long walks or for running. The newly adjusted segments of the arm (page 379) fit him for working with tools. He seeks and finds a mate; settles down to do his work in the world, for which his special gifts and brains fit him. He rears a family and helps to establish the continuity of that series of generations whose beginning go back to the origin of life on earth, hundred of millions of years ago.

SUMMARY

The development of a child starts with the microscopic egg, loaded with a vast variety of materials for the upbuild-

ing processes. The egg unites with the male sperm cell, begins to divide into a sphere of cells, migrates to the uterus, locates in the uterine wall as a quasi-parasite, expands greatly by imbibing water. The developing egg provides first for the securing of food from the mother and then begins to form the embryo proper. The axis of the trunk is first laid down. The head end develops rapidly while the tail end is much retarded. On the neck appear furrows located like the gill slits of fishes. Though not used for respiration they are essential to the development of many structures that are found both in fishes and man. Of the limbs the arms develop somewhat earlier; muscle, nerve and bone develop within them, hand in hand. The brain enlarges and the peripheral nerves grow out to muscles and acquire nervous connections with the incipient sense organs. Organs of smell, sight and hearing develop all their marvelous complexity long before they can function. The facial features are worked out in detail, carrying family resemblances. The outer skin becomes tremendously thickened and the cells become horny; hair and grease are produced in the skin. These things all help to protect the body from the drying influences of the air. The lungs are relatively late in development. Some of the blood vessels that start in the gill furrow region now turn toward the new center of respiration.

Along the food canal many essential structures arise such as the teeth, the tongue, the salivary glands, the great glands of the food canal, liver and pancreas, each with its intricate structure and complex functions.

The heart passes through stages of increasing complexity and the blood vessels which arise at first as strands of cells become hollowed out and more and more perfected and strengthened to meet the work they have to do.

The provision is made for carrying waste products from the body to the exterior. Three different systems are successively established for this purpose.

Sex of the child is determined at the moment that the egg is fertilized, and in the second month of development the sex organs become differentiated. Besides the blood vessels a system of vessels that manufacture and carry lymph arises which serves not only in nutrition, but especially in bodily defense, in that the white blood cells serve as scavengers. Before the body is ready many finishing touches have to be made.

The skeleton is complex in origin, beginning with a dense mat of loose cells which sometimes become transformed directly into bone, in other cases become, first, cartilage and then bone. The bone formers seem, as it were, dissatisfied with their work; tear down and reconstruct repeatedly. As the body gets larger the need for integration of its activities becomes more obvious; different organs send out "messages" (hormones) to one another, which arouse special, sometimes periodic, activities.

The child at birth is a feeble organism. Though provided with some fundamental instincts of tenacious grasping, swimming and stepping these are lost after a few weeks, and later these functions have to be learned. Growth in size and differentiation of parts continue for some years. Indeed, the human child has relatively the longest period before maturity of perhaps any mammal. This is the period which is utilized for schooling. Finally, at about twelve years in a girl and fourteen years in a boy, extraordinarily rapid growth begins, accompanied by important changes in the mental and emotional life. At the end of this spurt of growth physical development is practically completed.

NOTES

1. For the skeletal system details may be found in Arey's *Developmental Anatomy*, Chapter XII, where references are made to the foundation researches. The endocrine organs have been the objects of especially active research during the present century; their functions are being slowly worked out and all textbooks 25 years old are somewhat out of date. Dr. Lewellys F. Barker in 1922 edited a 5-volume treatise on *Endocrinology and Metabolism*. William Engelbach's *Endocrine Medicine*, Baltimore, 1932, in 4 volumes, has the advantage of being more recent.

2. The growth of the fetus has been traced by Mall and by Streeter and the curve of average growth has been published by the latter in the Carnegie Contributions to Embryology, Vol. XI. The inhibition of the development of the female sex organs by the male twin in the cow has been described by Frank Rattray Lillie (1917) in the Journal of Experimental Zoology.

3. For the grasping reflex of monkeys during parturition, see Hartman on the macaque.

4. Of the movements of new-born babes see Myrtle B. McGraw's experiments with Johnny and Jimmy as set forth in her volume, *Growth*, 1935, Century Co.

5. For the adolescent explosion data are given by the present author in the Proceedings of the American Philosophical Society, 1931, and elsewhere. Franz Boas has afforded data in *Human Biology*, 1932, concerning the correlation between the age of rapid growth and eventual size attained.

PART II

THE MACHINERY OF DEVELOPMENT

CHAPTER 6

THE CELL AS A CHEMICAL FACTORY

SPECULATIONS BEFORE KNOWLEDGE

Development, whether of the chick from the egg or of the child in the uterus, is a common fact of life. The contemplation of its meaning, and the search for the causes, the consideration of the mechanism by virtue of which are achieved the amazing results of development, have engaged thoughtful minds from the earliest recorded period. It may be worth while to consider some of the early views.

The earliest recorded speculations date from long before the Christian era. Thus it is stated that Diogenes of Apollonia, in Crete (about 420 B.C.), "believed that the embryo in the uterus was developed by the warmth of the mother out of semen of the father." Empedocles (also of the fifth century B.C.) held that "in reproduction the embryo received some parts of the body from the father's and the others from the mother's seed." These speculations were vague; based on incomplete observations.

The conclusions of Aristotle (384-322 B.C.), teacher of, and later subsidized by, Alexander the Great, marked a decided advance over the earlier speculations, based as Aristotle's were on extensive first-hand study and dissection of animals. He argues that the developing organism cannot exist ready-made in the semen or seed; yet the agent that directs development must be internal (i.e., in the seed). In accounting for the successive stages of development Aristotle says, "Is it possible then that A should move B,

and B move C; that, in fact, the case should be the same as with the automatic machines shown as curiosities? For the parts of such machines while at rest have a sort of potentiality of motion in them, and when any external force puts the first of them in motion immediately the rest is moved in actuality. As then in these automatic machines the external force moves the parts in a certain sense (not by touching any part at the moment, but by having touched one previously), in like manner also that from which the semen comes, or in other words that which made the semen, sets up the movement in the embryo and makes the parts of it by having first touched something though not continuing to touch it. Plainly, then, while there is something which makes the parts, this does not exist as a definite object, nor does it exist in the semen at the first as a complete part.

"When the material secreted by the female in the uterus has been fixed by the semen of the male (this acts the same way as rennet acts upon milk, for rennet is a kind of milk containing vital heat, and the relation of the semen to the catamenia is the same, milk and the catamenia being of the same nature); when I say the more solid part comes together, the liquid is separated off from it, and the earthy parts solidify membranes all round it.

"In the female is the material from which is made the resulting product. Not only must the mass of material exist then from which the embryo is formed in the first instance, but further material must constantly be added that it may increase in size.

"The male does not emit semen at all in some animals, and when he does this is no part of the resulting embryo: just so no material part comes from the carpenter to the material, i.e., the wood in which he works; nor does any part of the carpenter's art exist within what he makes, but the

shape and the form are imparted from him to the material by means of the motion he sets up. It is his hands that move his tools, his tools that move the material; it is his knowledge of his art, and his soul, in which is the form that moves his hands or any other part of him with a motion of some definite kind, a motion varying with the varying nature of the object made." (Translation by Arthur Platt, 1910.)

Crude as some of Aristotle's expressions seem, the theory as a whole is an extraordinary anticipation of modern ideas. Substitute for "semen" genes acting as enzymes, and for material secreted by the female "cytoplasm" or "substrate," and you have in outline something approaching the most reasonable theory of development.

The views of Aristotle were in a way opposed by Averroes (or Ibn-Rushd) an Arab born in Cordova, Spain, in 1126. He taught that "nothing is potential that does not exist in reality, in however undeveloped and therefore disguised a form it may be; the plant already exists in the seed, in however undeveloped a state, just like the animal in the embryo." Thus early appeared a difference of view as to the nature of development—a difference that at a later time became formulated in the phrase "epigenesis vs. preformation," epigenesis being the development of an egg that is not preformed in its parts.

At the opening of the Renaissance, interest in the problem of child development was revived. And the most distinguished propagandist of the epigenetic doctrine was William Harvey, the discoverer of the circulation of the blood, who set forth his conclusions in his book, *Exercitationes de generatione animalium* (1651). These conclusions were based on his observations on the development of the chick within the egg shell. These led him to support the view of Aristotle that the chick was not preformed in the

egg, but was gradually developed, one part succeeding another; and by the "additament of parts budding one out of another."

But Harvey's general views of the beginnings of development were very vague. He suggested, because the wall of the uterus so nearly resembles the surface of the brain, that the development of the child there was like the development of a conception in the brain. The male introduced the conception and from this "conception it cometh to pass that the female doth produce an offspring like the male genitor." Thus not merely child development but also paternal inheritance was to be accounted for.

Despite the great weight of the names of Aristotle and Harvey, the doctrine of epigenesis had, even in Harvey's time and later, little standing in the science of that day. Men properly found the epigenetic explanation "unsatisfying." Among these was the eager young naturalist, Jan Swammerdam (1635–1680), of Amsterdam, who gained well-deserved fame for his extraordinary dissections and figures of the anatomy of insects, and who observed the metamorphosis of a butterfly from a chrysalis, and chrysalis from a caterpillar. These observations led him to insist that the butterfly is indeed preformed in the chrysalis, and by dissection one could prove its presence there, wings, antennae, legs and all. This demonstration seemed incontrovertible and a series of writers who had not the observational basis of Swammerdam adopted the view of preformation; and, indeed, of preformation of the embryo in the egg. On the vertebrate side Swammerdam received great support from Malpighi, an excellent observer (considering the means at his disposal) of the development of the chick. Though he observed well he concluded that the embryo pre-existed in the unincubated egg.

The hearty acceptance of the doctrine of preformation led some to the logical conclusion that the female developing in the egg must already have in her ovary eggs that contain females preformed, whose ova in turn carry preformed females, and so ad infinitum. To those who protested against so ridiculous a conclusion, the rejoinder was made that just as the microscope was revealing hitherto unknown organisms of exceeding smallness, so there was logically to be put no limit on the power of the Creator in the direction of infinitesimality. Thus was defended the theory of "emboîtement," the box-in-box or encapsulement theory. In its extreme form it held that the ovary of Eve contained the preformed bodies of all of her descendants that were to be, only of small size, so that only growth, but no epigenetic development, was necessary. On this hypothesis males counted for little as progenitors. Those who held these views were called ovists.

But not all preformationists found the preformed embryo to lie in the egg. The old idea that the egg was merely food stuff for the embryo would not die without defenders. With the invention of the compound microscope (by the Jannsens of Middeburg about 1590) and of improved simple lenses by Anton van Leeuwenhoek of Delft, Holland (at the end of the seventeenth century), naturalists began to look for a more concrete basis for reproduction of the child. Leeuwenhoek's attention having been called to the existence of sperm animalcules in the fertilizing fluid he concluded (1683) that they impregnate the egg and grow in the egg into the fetus. This fact was seized upon as incontrovertible evidence of the all-importance of the sperm. So arose the group of "animalculists" who found in the sperm the preformed embryo. If observation was required it was forthcoming. Hartsoeker (1694) published a drawing of the

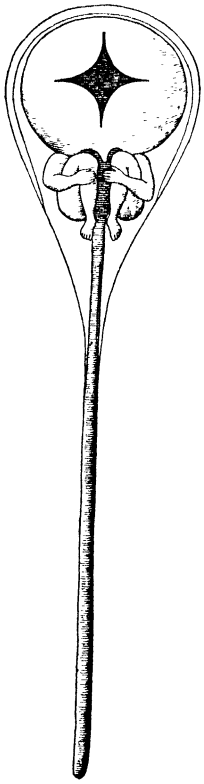


FIG. 96. Reproduction of a drawing of a human spermatozoon published by Hartsoeker about 1708, showing the homunculus in the head of the sperm. The star in the head evidently represents the frontal fontanelle, or unossified region of the skull. Hartsoeker speculated that this homunculus must carry sperm in each of whose heads lies a still smaller homunculus, and so ad infinitum. (*From W. His, "Arch. für Anthropologie," 1870.*)

human sperm cell with a large-headed fetus in the sperm-head (Fig. 96). Others, until within less than a century ago, were able to demonstrate to their own satisfaction the human organs in the head of a spermatozoon (Figs. 97, 98). These animalculists held that their theory was based on observation.

Between the ovists and the animalculists there waged during the eighteenth century a hot discussion. Most of the vigorous proponents of one side or the other made no observations of their own; but occasionally a naturalist who had won repute as a careful observer lent his authority to one school. Thus Réné Antoine Ferchault de Réaumur who was born at Rochelle, France, in 1683, and made wonderfully fine additions to the knowledge of the anatomy of insects, was able to distinguish eggs not only in the chrysalis but also in larvae some time before metamorphosis. This experience led him to favor the preformation doctrine and, indeed, inclined him toward the side of the ovists. This was in 1734. Thus till the middle of the eighteenth century preformation held sway, with a difference of opinion as to whether the preformed embryo was in egg or sperm.[1]

The advance of careful *observation* was now to introduce a new attitude toward generation. Although Harvey had examined, before 1650, the development of the chick and concluded that the organs were formed successively out of an unorganized egg, the work needed to be carried further, more analytically and with better glasses. And so it came about that when Caspar Friederich Wolff, about 1750, started a further study of the development of the hen's egg it bid fair to yield important results for the theory of development. Embarking on this study Wolff found no minute chick in the unbrooded egg, but only yolk globules of various kinds. As incubation proceeded he could see strings of tissue running out from the central disc and becoming hollowed out to form blood vessels. Gradually the spinal nerve, head and tail appeared and the muscle masses (myotomes) could be seen (Fig. 99). Wolff concluded that some organs arise from the homogeneous egg as secretions; new parts are formed from the tissue of the already established central mass, and parts once started increase by means of fluids which form in them and, by increasing in amount, enlarge the spaces in such organs. There is much in Wolff's statement that is crude and incomplete, but at least he saw accurately and reported faithfully what he saw. The great contribution of Wolff was not the new facts he collected, but the establishment of the principle that speculation without observation may get you to the wrong place in biological science.

FIG. 97. Reproduction of a drawing made by "Delapatius," (whose civil name was de la Plantade) of the metamorphosis of a spermatozoon as seen by him. The extremities are represented as fully developed but the head shows no features. (*From W. His, "Arch. fur Anthropologie," 1870.*)

It was Karl Ernst von Baer, who was born in Esthonia

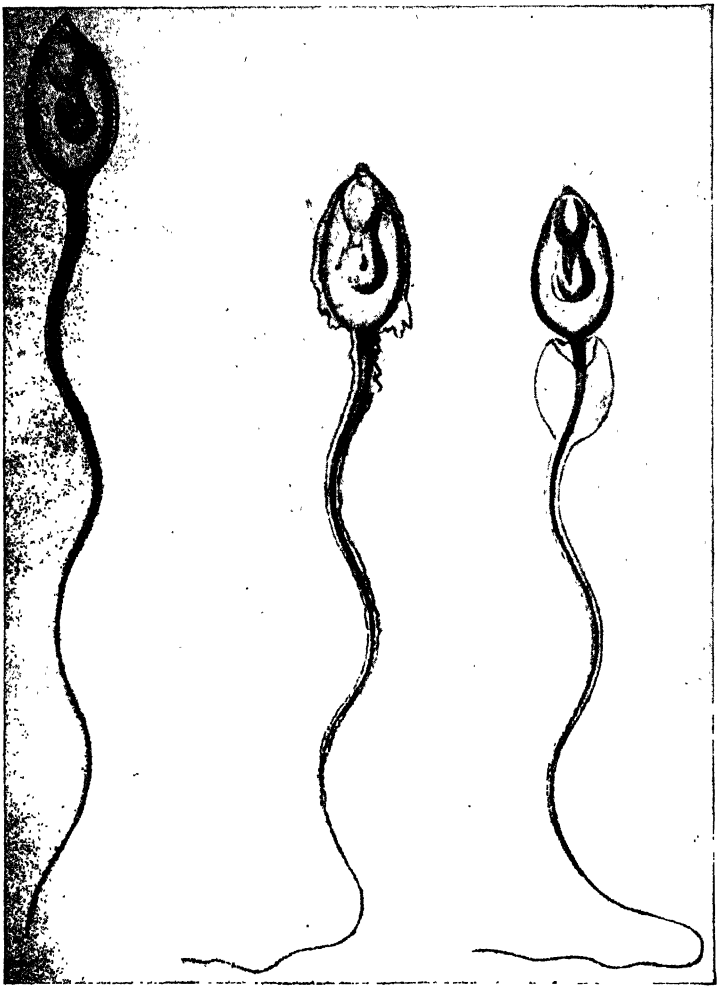


FIG. 98. Reproduction of a drawing published by Felix Archimède Pouchet as late as 1847. Assuming that there must be an organization in the spermatozoon he finds in the head a tubular organ which he says may be interpreted either as the nascent fetus or else as a parasite with mouth or sucker. This is followed by a stomach-like enlargement and that, in turn, by an intestine-like tube. (*From F. J. Cole, "Early Theories of Generation," courtesy of the Clarendon Press, Oxford.*)

(1792) two years before Wolff died, who first discovered the egg of a mammal—a dog (1827); showed in great and accurate detail how the hen's egg develops, noted the gill bars of the chick embryo and recognized that they repeated the condition found in fishes. Von Baer published his find-

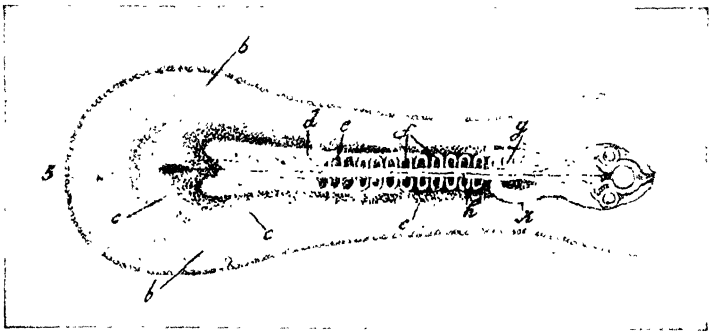


FIG. 99. Drawing of the embryo of the chick as made by Caspar Friedrich Wolff in 1759, illustrating the progress in the microscopic study of the embryo. The embryo is from an egg that has been incubated for 36 hours. The embryo has been removed from the yolk and the light shines through it from below. The author's description given in Latin may be translated in part as follows: At the head appears something of a snout and the front and hind part of the brain, upon which on both sides the optic nerves are attached which go forth from the eyeballs; further the cerebellum, which continues into the elongated medulla which in turn stands in union with the spinal cord. *h*, spinal cord; *g*, neck vertebra; *f*, vertebra of back; *e*, the hinder still incomplete vertebra of back; *d*, fundament of the vertebra of loins; *c*, very transparent substance which consists of little globules that are scarcely adherent, which surround the vertebrae and are thicker together close to the keel (axis) and in the upper part. This shows the first traces of the extremities. *b*, cavity of the amnion. (*From a German translation, cf. Wolff's "Theoria Generationis" by P. Samassa.*)

ings in a large volume entitled *Uber Entwicklungsgeschichte der Tiere, Beobachtung und Reflexion* (1828); that is,—*On the Development of Animals, Observation and Reflection.* Observation and reflection form a combination in research that must never be dissociated.

The proper relation of sperm and ovum, the facts of

fertilization of the egg as we now understand the process, were not made clear until many years later when Oscar Hertwig in 1875 traced the head of the sperm into the egg and saw the nuclei of both germ cells unite on an equal footing. This conclusion received great additional support in 1879 from animal material by Hermann Fol of Geneva (the son of wealthy parents, he became professor of zoology at Geneva), and in the same year by Friedrich Schmitz, from studies in plants. Thus the dispute concerning the primacy of egg or sperm in development was settled by the demonstration that they both play equally important roles, although not precisely the same role.

We have seen how, from the time of Aristotle, the battle waged between the preformationists and the epigenesists. At one time the preformationists were in the ascendancy. They had logic on their side. From nothing, nothing can come. From a homogeneous egg fertilized by a homogeneous sperm the specific heterogeneity of a particular individual with its galaxy of family traits can hardly arise. But observation seemed to favor the epigenesists. If you look at the egg or at the sperm you do not find the individual there in miniature. The egg looks homogeneous.

And so the discussion has come down to us to the present time. But it has taken a new form. All recognize that there must be a mechanism in the germ cells to produce the specific predictable organism. What is its nature? Surely the preformationists were wrong when they said they saw a miniature embryo in the egg or sperm. Is the true mechanism visible?

HISTORY OF THE CELL THEORY

The biological studies of the past century have gradually revealed a mechanism in the gametes (germ cells) that

might conceivably in some way or other act to direct the development of the child. Let us first consider the mechanism; then its interpretation.

The fact that there are cells in plants and animals was known over two centuries ago,* though the general theory that organisms were made up of cells and their products was first established by two Germans, Matthias Jacob Schleiden and Theodor Schwann, who published their observations in 1838–1839. A few years earlier (1831) a Scottish botanist, Robert Brown, had told of finding as a constant essential organ of the cell an "areola" or, as he also named it, a nucleus. That cells divide was also known at this time. Soon the generalization was established that cells arise by the division of pre-existing cells and in no other way. This led to the theory elaborated in 1858 by the great pathologist of Germany, Rudolph Ludwig Karl Virchow, that cell life forms a stream that has flowed without a break from the beginning of life on earth to the present.

Then came the great discovery by Rudolf Albert von Kölliker (1845) and Wilhelm Hofmeister (1847) that the nucleus also divides in cell division. Much later it was shown by Anton Schneider (1873), then in greater detail by Otto Bütschli, Hermann Fol, Eduard Strasburger, Edouard Van Beneden, Walter Flemming and Oscar Hertwig (all of Continental Europe), that the division of the nucleus is accompanied by the formation of peculiar thread-like bodies that become deeply colored by certain dyes and are hence

* In 1664 Robert Hooke, a resident of London, first introduced the word cell when he wrote: "I took a good clear piece of Cork and with a Penknife sharpen'd as keen as a Razor, I cut a piece of it off, and thereby left the surface of it exceeding smooth, then examining it very diligently with a Microscope, me thought I could perceive it to appear a little porous. . . . These pores, or cells, were not very deep, but consisted of a great many little Boxes. . . ."

called chromosomes (color bodies). Quickly the conclusion was drawn that the cell nucleus is the bearer of heredity—directs in some way the course of child development. Here was the long-sought machinery that determines the history of development from the egg to the adult.

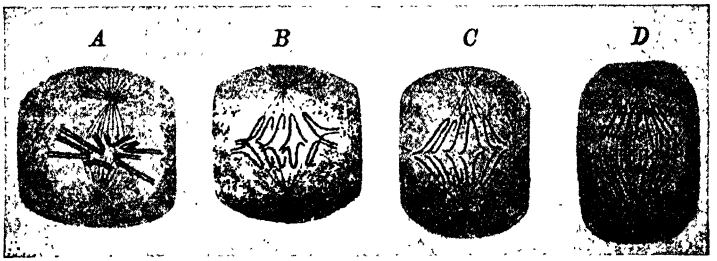


FIG. 100. Reproduction of one of the earliest drawings of chromosomal division (mitosis) during cell division, as made by Walter Flemming, 1879. *A*. The chromosomes lie at the equator. *B*. The chromosomes split, half of each going toward the respective poles. *C*. Splitting completed. *D*. The chromosomes are nearly segregated at the poles.

Knowledge of the nucleus in cell division advanced rapidly. The chromosomes were found to divide each into two equal threads (Fig. 100), one going to each daughter cell. The threads (chromonemata) came to be regarded as the specific carriers of heredity. More recently it has become recognized that the chromonema threads are made up largely of discrete particles—the chromomeres—and these particles are of definite number, form and position in the chromosomes and contain smaller, ordinarily invisible genes. These genes have been regarded as determiners of special organs; but they have also general developmental functions. Thus in late years has been revived a preformation of a refined sort.[2]

THE CELL, A WONDERFUL MECHANISM

The child arises, as we have seen, from a single cell, and development is accompanied by cell division and cell

differentiation. While body form is probably controlled to a certain extent by general forces exerted throughout the body as a whole, the cell is obviously the metabolic unit and the center of important factors that build up the body. It is the arena for the interplay of genes, chromosomes and the rest of the cell, called cytoplasm. Consequently, to show that interplay in proper setting we must consider the salient facts of the cell.

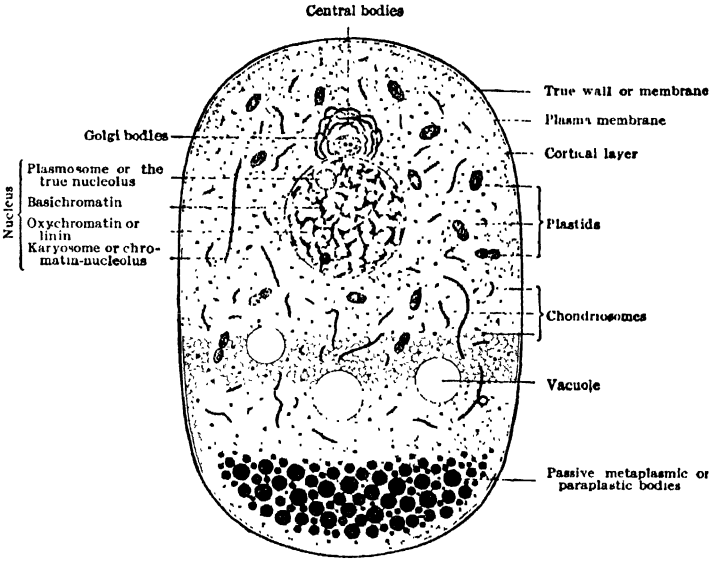


FIG. 101. General diagram of a greatly enlarged cell. In the "resting" or metabolic nucleus one sees particles with unlike electric properties—acid and basic. In the cytoplasm is shown a granular (colloidal) meshwork or framework of which the interstices are probably filled with water and dissolved substances. In the meshwork are suspended granules of varied kinds, threads and other formed components. (*After E. B. Wilson, "The Cell," courtesy of The Macmillan Co.*)

The idea of the cell (Fig. 101) comprises a cell body separated from other cell bodies by a cell wall. The cell is filled with protoplasm, which is usually about 85 per cent

water, and is found chiefly filling the interstices of a great framework or trestle-work made of more active, moving, colloidal (glue-like) substances. There are many larger or smaller cell inclusions, some of a mucilaginous consistency, some of a more solid nature. In or near the center of the cell is a vital part of its activities, the cell nucleus. The cell cannot survive long and does not ordinarily divide to produce new cells without the nucleus. The nucleus is usually nearly spherical and is bounded by a delicate membrane. The contents of the nucleus may be called collectively the nucleoplasm; the extranuclear part of the cell, the cytoplasm.[3]

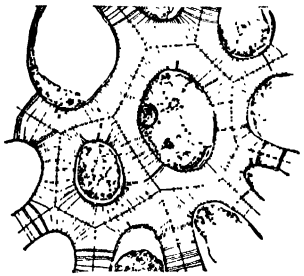


FIG. 102. Cells of the inside of the seed of persimmon showing the thick cell walls, with fine passages through them, establishing living connection between the cells. (*After Quisumbing, from Sharp's "Introduction to Cytology," courtesy of McGraw-Hill Book Co.*)

Let us consider in turn each of these elements of a typical cell and discuss its role in development.

THE CELL WALL

As viewed under the microscope the cell wall varies in different cases from a thick "wall" as in many plant cells (Fig. 102) to a delicate membrane like that shown in the idealized animal cell (Figs. 101, 103). In extreme cases, as in mesenchyme cells (page 24) and the blood corpuscles, one can hardly speak of a wall. The limiting membrane may be only two or three molecules thick.

The cell boundary is a region of the greatest importance for the cell. Here it comes in contact with the world without, upon which its existence depends and to which it is constantly reacting. For the living cell, at each face of the cell

wall in contact with the medium there is a change of phase, namely from a semi-solid to a fluid. And such a change of phase is everywhere the field for electric-chemical phenomena. If the more solid part of the boundary consists of positively charged ions, there is in contact with it a layer of negatively charged ions or molecules oriented with their negative poles toward the solid layers. Outside of this the molecules of the fluid medium are moving toward this solid layer and, again, away from it as they exchange their charges. In the fluid the molecules are in constant, rapid motion, bombarding, as it were, the solid phase (Fig. 152). Inside of the limiting membrane is a supplementary layer of protoplasm.

FIG. 103. Figure drawn from a culture of leucocytes from the blood of a guinea pig. The enlarged leucocyte (forming a macrophage) is transforming into a fibroblast. The nucleus is shown, together with numerous stained bodies (mitochondria) in the cytoplasm. There is no obvious cell membrane, though the cytoplasm at the surface is denser than that nearer the center. × 750. (*After Maximow-Bloom in "Textbook of Histology," courtesy of W. B. Saunders Co.*)

Where the solid walls are thick, as in many plant cells, they might seem to afford an obstacle to ingress and egress of molecules; but in these cases the walls are sometimes, if not always, perforated by so-called intercellular bridges, perhaps only 0.2 or 0.3 μ in width (Fig. 104).

The solid cell walls of plants are frequently composed of small particles which we may call micellae. The combined micellae form a supporting framework of which the elements may be pushed apart by migratory cells as indicated in Figs. 105, 106. These micellae form, as it were, the bricks of the wall. They are of the order of 2,500 to 10,000

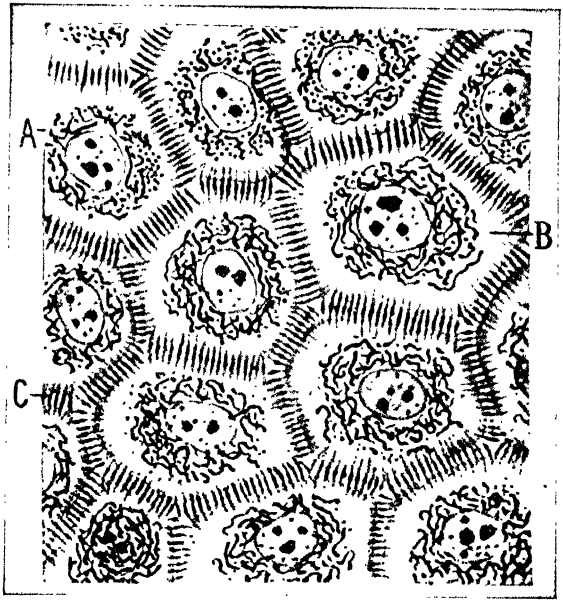


FIG. 104. Cells of the human epidermis, full of stained bodies (mitochondria) grouped about the nucleus. The cell walls are perforated, as at C, permitting the passage of protoplasmic threads. A, B, refer to cells with chondriosomes. (*After Rio-Hortega, from Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

Ångstrom units in length and are laid in a mortar of a sticky substance, called pectin.[4]

When the cell membrane is, as in most animal cells, only a few molecules thick it is believed to be made up, in part, of molecules of fatty substance, because fats penetrate it so readily. The membrane is probably made up in part of molecules of water since molecules that dissolve in water pass through it also. The water may be thought of as filling the interstices of the fatty molecules.

The passage of molecules through artificial membranes is generally determined by certain rather simple factors,

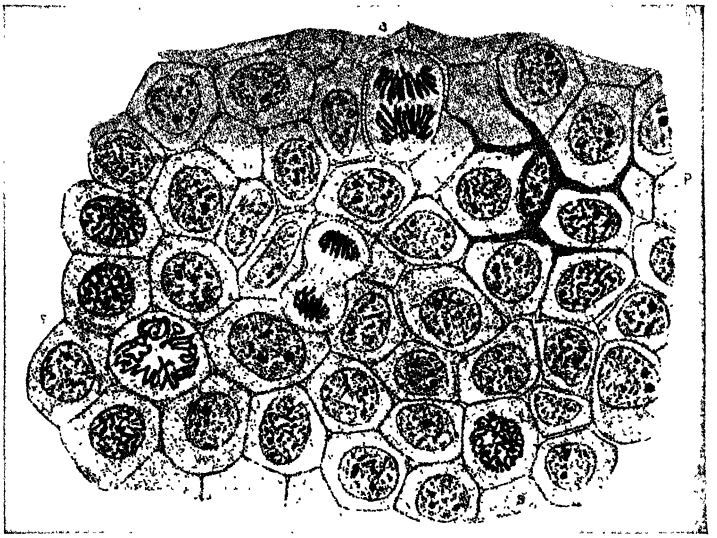


FIG. 105. A small portion of the epidermis of a larval salamander. Most of the nuclei are in the "resting" (metabolic) state; but several are in mitotic division. Near *p* is a branching, granular pigment-cell that has crept up from below, forcing its way between epidermal cells. Delicate strands of protoplasm pass through the cell walls. × 550. (*After Wilson, from his "The Cell," courtesy of The Macmillan Co.*)

such as the size of the pores in the membrane in relation to size of molecules in the solution, the difference in concentration of salts on the two sides of the membrane, or the capacity of the molecules to be dissolved in the membrane. That electric potentials at the faces of the membrane are also important is shown by the fact that fractions of the molecule (ions) having the same charge as the membrane pass through the membranes more readily than do those of opposite charge.

In the membranes of living cells, usually several molecules thicker than artificial membranes are, the passage of molecules or ions is much more complicated. Thus for a living cell, like a red blood corpuscle, in the medium con-

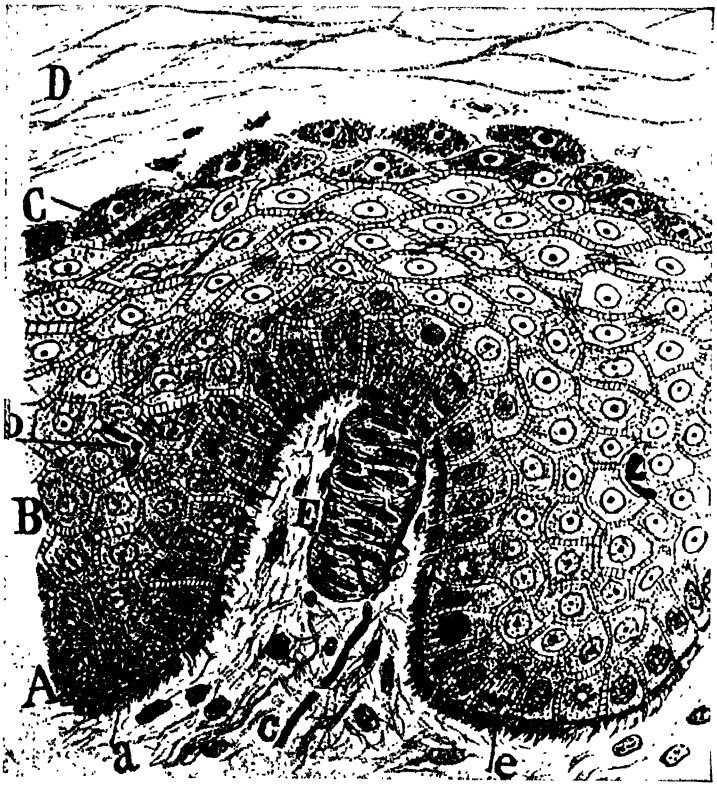


FIG. 106. Section of epidermis of the skin of the finger, cut perpendicularly to the surface. A is the layer of actively multiplying epithelial cells. These get less action in successive stages B, C, D. At E is a tactile end organ. The point of special interest is at b, where a white blood corpuscle has emigrated from the derma through cell walls. (*After Ramón y Cajal, from his "Histology," courtesy of Williams & Wilkins Co.*)

taining various salts in solution, the potassium is found much more concentrated in the cell than in the medium, while the opposite is true in the case of sodium. This is to be explained on no mechanical ground, like that utilized in explaining diffusion through artificial membranes, but

rather by this, that the protoplasmic layer which lies in contact with the inner face of the cell membrane, by its complex composition and electrical states, exerts a selective action upon the passage of molecules or ions. To secure the necessary proportions of the different kinds of molecules they require, the protoplasmic membranes have acquired a trick or two beyond those shown by artificial or dead organic membranes.

THE SOIL AND ITS SEEDS

The Cytoplasm. The cytoplasm is composed of a fluid (water and dissolved substances) and solids. Let us consider what is known about the visible solid bodies. According to one theory, which has much to support it, the cytoplasm is a sort of foam work consisting of films surrounding spaces. The spaces are probably filled in some cases with solutions, in others with masses of special building materials. Some of these are fat globules, some are rather large spheres that are not fatty, some are very tiny granules combining fat and phosphorus. The cytoplasm of most cells contains special fatty-phosphorus bodies which vary in size from small spherical granules to rods, or threads. In the living cell they are typically changing position, uniting into threads and networks and breaking down again into small pieces. They are believed to play specific roles in cell metabolism (or chemical change). These bodies bear the long name of chondriosomes (from *chondrion*, granule and *soma* body).* These chondriosomes have been thought responsible for forming many cell structures, such as the contractile elements or threads in muscle cells—

* Which recalls the story of the old woman who appreciated the great work of the astronomers in discovering new stars, but what bothered her was to understand how they learned the names of these stars.

even the thread-like structures that run in nerve fibers and carry impulses. But not all observers are agreed about this. It is especially important that one or more chondriosomes are carried by the sperm cell and these may intermingle with the chondriosomes of the egg cytoplasm. Also there is evidence that these bodies on occasion divide (just as chromosomes do); so that chondriosomes pass from a mother cell into its two daughter cells.

Special bodies in the cytoplasm apart from the chondriosomes are known. They are called collectively plastids. This term is commonly applied to bodies found in plant cells, but there are similar bodies found in animal cells. Of the latter the most striking are known as the bodies of Golgi (after Camillo Golgi, an Italian student of cells, who discovered them at the end of the last century). They occur in great numbers in the cytoplasm of nerve, epithelial and many other kinds of cells. There is some evidence that these bodies divide as plant plastids and as chondriosomes apparently do.[5]

The water in the cytoplasm is immensely important, especially because of its great solvent power; because it permits the ionization of molecules, i.e., their separation into their acid and basic fragments. Upon this separation depends the acidity of the cell. This acidity is measured by a convenient artificial scale known as pH values. In this scale 7 is the neutral point. Values below 7 indicate degree of acidity; the more acid the greater the departure from 7 and toward 0. Values above 7 measure degree of alkalinity. Professor Robert Chambers has determined that the cytoplasm is slightly acid (pH about 6.7 to 6.9). If the acidity departs far from this near-neutral point the cell will die. But the cytoplasm gathers and stores substances that protect against sudden and marked alterations in pH. These

are called buffers. To this class belong bicarbonates (such as people use to counteract acidosis) and others.

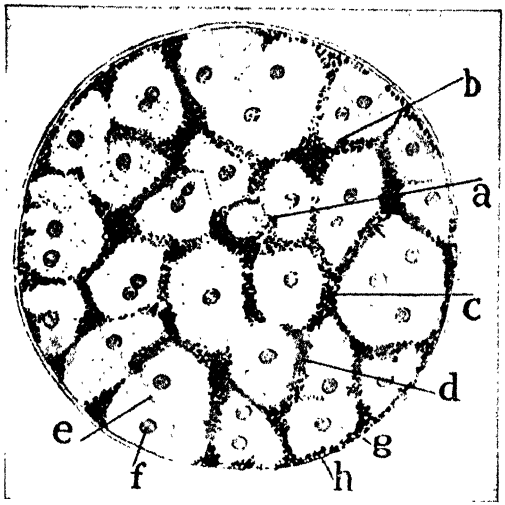


FIG. 107. Diagram of the morphologic structure of the nucleus. a, true nucleolus; b, false or chromatic nucleolus; c, basi-chromatic substance, taking a deep stain; d, oxy-chromatic substance, taking a light stain; e, "linin" filaments; f, pale granules in the meshes of the chromatic reticulum; g, nuclear membrane; h, peripheral chromatin ("chromatic cortex"). (*After Ramón y Cajal, from his "Histology," courtesy of Williams & Wilkins Co.*)

Of course the cytoplasms of different cells differ, thus permitting their specialization in the different tissues and glands—for example, blood cells, cartilage cells, muscle cells, nerve cells, lymph cells, the various endocrine-gland cells, the digestive gland cells, the excretory cells, the germ cells, the cells of the special sense organs and those that form the skin and its organs. All the kinds of cells in the body are not known yet. There must be hundreds of such kinds. Each kind has its specific structure and composition.

THE FERTILIZING MATERIAL—THE NUCLEUS

During the past one hundred years the importance of the nucleus in cell physiology has been increasingly recognized. The nucleus is typically spherical, doubtless due to internal pressures at all parts of its limiting membrane. It consists largely of water with substances in solution, indicating its great chemical activity. It may even be so densely crowded with colloidal particles as to be a jelly. Near the outer boundary run many threads containing granules that react diversely to chemical dyes. These threads seem to form a network, with larger granules or accumulations at the nodes. Details are shown in Fig. 107. A deeply staining, solid nucleolus is commonly present; of its structure and function little is known. Such is the nucleus, the center of the cell's metabolic activity, whose materials fertilize, as it were, the soil of the cell.[6]

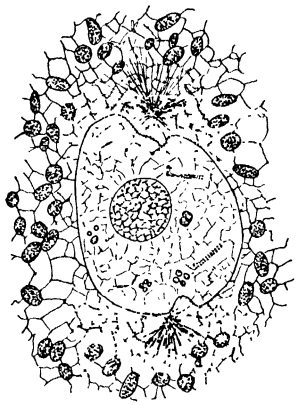


FIG. 108. An early stage in cell division when extranuclear centers of activity depress the nucleus at opposite poles. (*After Mottier, from E. B. Wilson's "The Cell," courtesy of The Macmillan Co.*)

The nuclear membrane is of variable thickness and distinctness in various cells. In some cases it may be only one molecule thick; in other cases it resists the pressure of a fine needle, and may crumble into corrugations if some of the nuclear fluid be sucked out by a fine pipette. Its form may be disturbed by pressures arising in the cytoplasm (Fig. 108). The nuclear membrane disappears at the time of nuclear division (Fig. 109). Its presence is at the same

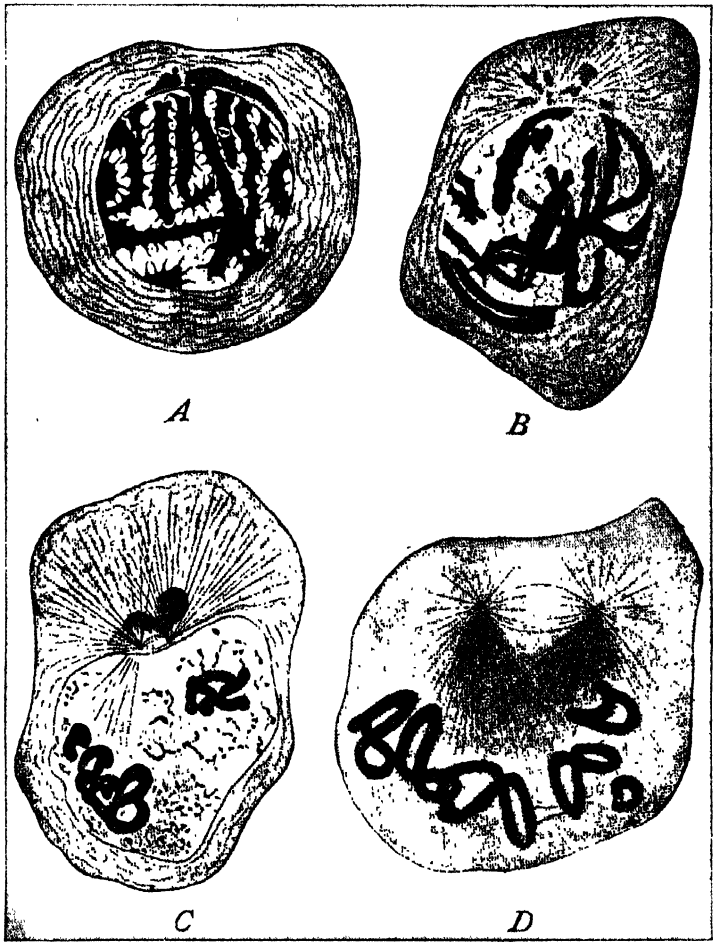


FIG. 109. Cell in very early stage preceding nuclear division. The chromatin is seen aggregated at the surface of the nucleus in the "spireme" stage. The nuclear membrane has disappeared at stage *D*. (*After Meves, from E. B. Wilson's "The Cell," courtesy of The Macmillan Co.*)

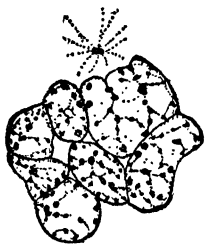


FIG. 110. Chromosomal vesicles in the embryo Fundulus, as they are enlarging and becoming pressed together to produce the metabolic nucleus. (*After O. Richards, from Sharp's "Introduction to Cytology," courtesy of McGraw-Hill Book Co.*)

time evidence of metabolic processes going on in the cell and of part of the machinery by which metabolism is being effected.

The nuclear membrane arises in some if not all cases by these changes:—the chromosomes at the end of mitosis (see page 162), i.e., in the telophase, become vesiculated and these vesicles (Fig. 110) press closely together to form the nuclear membrane. Thus many if not most of the genes are brought to the surface of the nucleus at the interface with the cytoplasm (Figs. 111, 112). As the next nuclear division begins the genes draw away from the nuclear membrane (of which they form an important part), consolidate to form the chromonemata and enter into the make-up of the chromosomes. At the same time the membrane begins to disappear (Fig. 109). This relation is shown diagrammatically in Fig. 113. Thus the nuclear membrane cannot be regarded as necessarily constituting an obstacle between nuclear and cytoplasmic elements but, at times at least, it becomes the in-

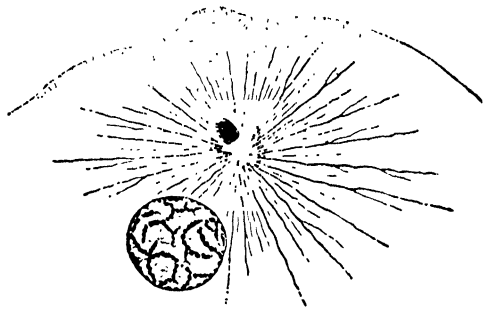


FIG. 111. Nucleus of the sperm cell (of a sea urchin) is entering the egg. Chromatic material at surface in contact with the nuclear membrane. (*After Wilson, from his "The Cell," courtesy of The Macmillan Co.*)

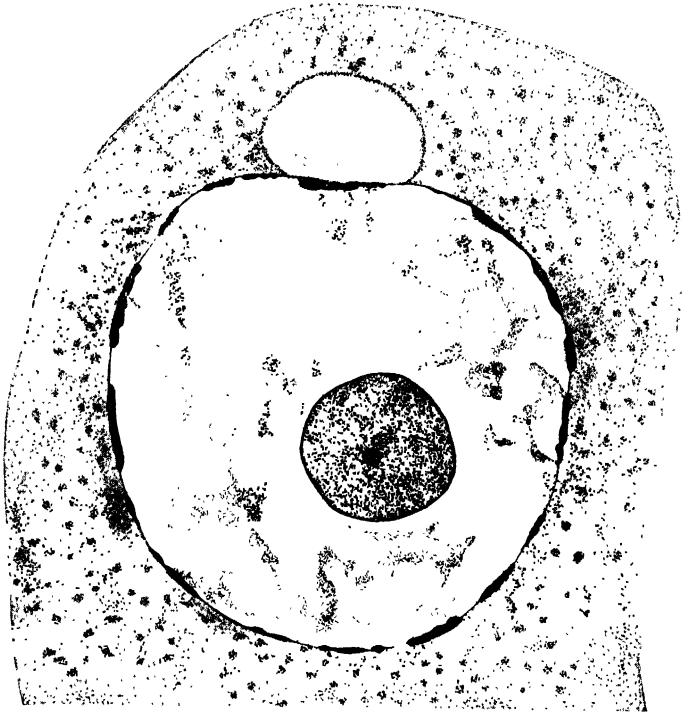


FIG. 112A. Sectional view of the nucleus of a sperm-forming cell of a spider showing the regular arrangement of stainable material at the nuclear membrane. (*After Sokolow.*)

strument for bringing the two into closer relationship.[7]

SHARING THE FERTILIZERS—NUCLEAR DIVISION

The most striking constituent of the nucleus is a quantity of exceedingly fine granules lying in the substance of a network or a coiled thread located near the nuclear membrane. Some of this material is deeply stained by dyes like iron hematoxylin, or acetic acid carmine, and by many aniline dyes. This stainable material has been called

chromatin. The threads of the nucleus are outstanding among all the organs of the cell because of the great changes in position that they undergo in preparation for cell division. The cytoplasm certainly is affected by cell division, but not so strikingly. The nuclear changes in cell division are called mitosis.* To a description of the process of mitosis we turn next.

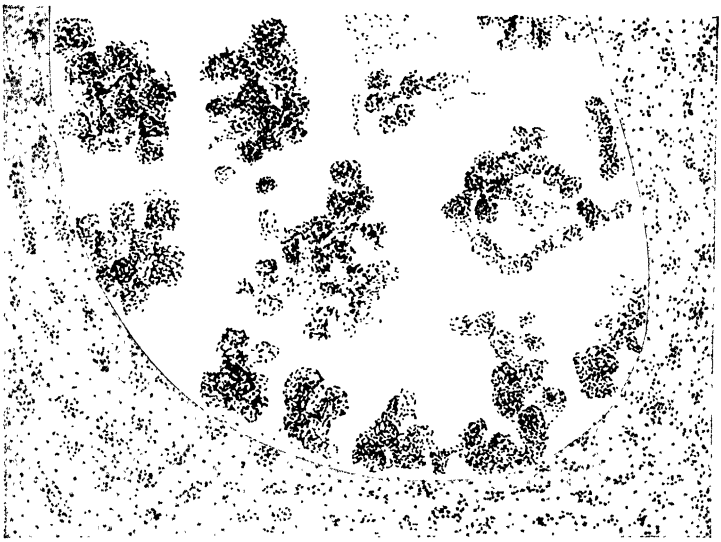


FIG. 112B. Surface-view of the same nuclear membrane as is shown sectionally in Fig. 112A. The stained particles are arranged in more or less regular groups on the nuclear membrane. (*After Sokolow.*)

The sequence of events in mitosis is shown diagrammatically in Fig. 113. Although the strands of the nuclear network look somewhat alike they are really of two kinds: the main threads, and the secondary cross fibers that tie the main threads together. In Stage 2 these minor fibers have broken and the main threads are thus rendered some-

* From the Greek, mitos, a thread.

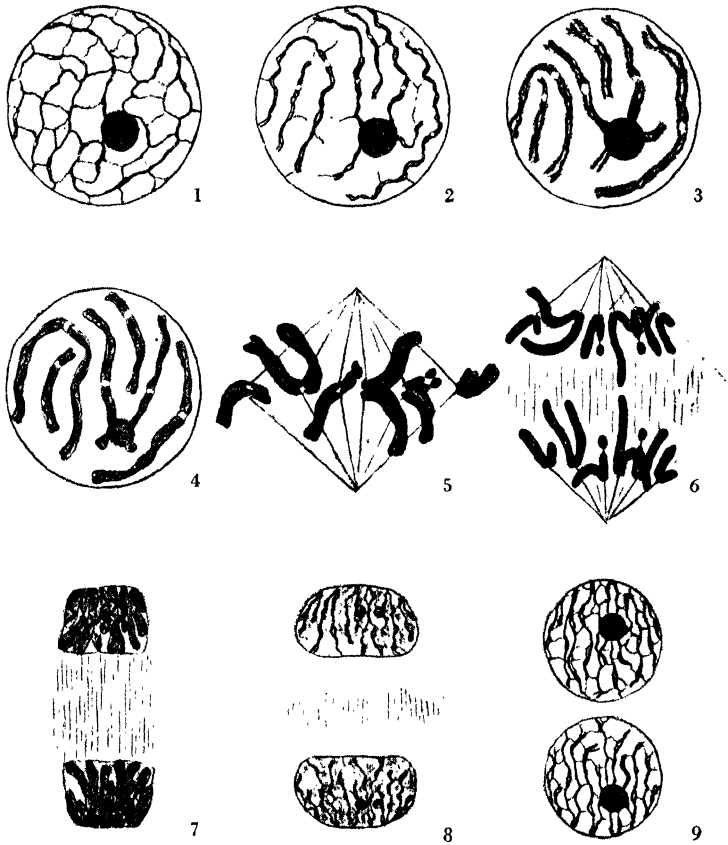


FIG. 113. Semi-diagrammatic representation of somatic mitosis based on species with large chromosomes. 1. The metabolic stage of the nucleus. Certain strands of the network are thickening in anticipation of chromonemata formation. 2. The chromonemata are freed; already show doubling; 3. Some are tied to nucleolus. 3 and 4. Chromonemata are straightening and thickening. 5. Metaphase chromonemata (now *chromosomes*) thicken and gather at the equator. 6. Anaphase, chromosomes divide and move apart to two poles. 7. Early "telophase." 8. Median telophase—the nuclei becoming reconstructed. 9. Later telophase, the nuclei larger, approaching stage 1. (*After Sharp, redrawn from his "Introduction to Cytology," courtesy of McGraw-Hill Book Co.*)

what independent. There are in the figure six threads: two are joined to a large round deeply staining sphere (nucleolus); two are free and long, and two are short. Thus there are two threads of each kind and three pairs altogether. One element of each pair is derived from the egg cell and one from the sperm that united with the egg to start the individual to which this cell belongs. Each thread has also split lengthwise. These split-off threadlets are made up of deeply staining particles (which, we may anticipate, indicate the position of genes, the units of inheritance) joined together by, or suspended in a clear substance. A split threadlet is called a "chromonema" (meaning colored thread).

In Stage 3 the twisted chromonemata begin to accumulate stuff around themselves which in Stages 4 and 5 become so strongly stainable that each of the pairs of chromonemata which have become coiled and shortened, become transformed into a dark, sausage-shaped body. Each such body is called a chromosome (colored body).

Probably in Stage 5, or shortly after, the chromonemata divide again and become quadruple, only the separate threads are obscured. The nuclear membrane is dispersed. Two poles appear in the cytoplasm and from each a non-staining fiber runs to near the middle of each chromosome. The chromosomes split lengthwise into two half chromosomes and the components of the pair move toward opposite poles (Stages 5 and 6). From each of the two groups of chromosomes thus established a new nucleus is reconstructed.

Just what makes the cell divide has been much studied. The prevailing view is that tractive forces arise in the star-like centers. The equatorial zone between these centers gains a reduced surface tension and the cell membrane

wraps itself about the two star-like centers as the new cells separate.

The different stages in Fig. 113 have received distinguishing names. Stages 2, 3 and 4 are spoken of as the prophase (or "before" phase); Stage 5 is the metaphase (beyond the prophase); Stage 6 is called anaphase ("up-along" phase; the chromosomes moving up toward the poles). After the metaphase comes the telo- (distant or end) phase. In the metaphase the chromosomes are most distinct and easily counted. Consequently this is the stage most commonly studied. But it has one great disadvantage, the structure of the threads is obscured by the deeply stained sheath of chromatin. Other stages of the chromosomes deserve as much attention as the metaphase.

As Fig. 113 shows, the pairs of chromosomes differ from one another in length. This difference is ordinarily a constant one in a given species. The elements of each pair are ordinarily of the same length. There is in many species an exception to this; since there is a particular pair of chromosomes the members of which are unlike in the sperm cells; while they are alike in the egg cells. Partly because of this difference in the sexes this pair is known as the sex chromosomes and this appellation is justified by the special role they play in controlling the development of certain traits correlated with sex.

THE CHEMISTRY AND ARCHITECTURE OF THE CYTOPLASM; ESSENTIAL TO DEVELOPMENT BUT TOO SLOW

Because the genes are important in development it must not be concluded that they are the sole actors in that drama. Development may be compared not to a monologue, but to a dialogue. The genes by themselves are incapable of any vital activity; it is in relation to the cyto-

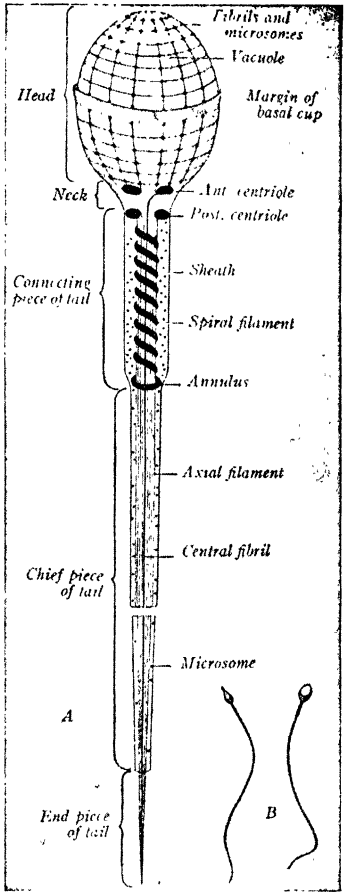


FIG. 114. Human spermatozoon. *A*. Semi-diagrammatic representation of internal structure, showing vacuoles and minute particles on head; and 2 pairs of larger granules in neck, with one or more fibrillae passing out into tail. Connecting piece of tail, with an axial filament about which is wound spirally a filament of mitochondrial origin and outside that a sheath containing stainable particles. The chief piece of the tail follows with axial filament and delicate sheath, with microsomes (small stainable particles). × 6,500. (*After Stieve.*) *B*. Living appearance in edge and flat view. × 700. (*Both from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

plasm that they do their work in a way that we shall see presently. Meantime we must turn our attention to that cytoplasm and see what is its nature and history. And first it must be pointed out that the sperm brings in but little cytoplasm to the egg (Fig. 114); the cytoplasm is mostly in the egg before fertilization. The cytoplasm affords the building stuff, the genes activate it, as Aristotle, indeed,

suggested. Or, the cytoplasm affords the soil and seeds; but it can do little without specific fertilizers.

What do we know about the reagents that are in the cytoplasm of the egg? Naturally, very little is known about the chemistry of the minute and rarely seen human egg, but something is known about the chemistry of other eggs. We know most about the stuffs in the hen's egg; but that knowledge does not interest us so much since those stuffs are mostly pure food materials and little concerned in building up the *specific* organs of the body. However, let us see what we can glean from what has been learned about the chemical materials in the cytoplasm of the egg, hens' eggs and others.

First, there are the albumins, which, as everybody knows are represented in the white of the hen's egg. The hen stores a lot of this around the egg proper (or yellow yolk) before forming the shell. But these albumins are in the egg cell proper, also. The albumins are soluble in pure water. Second, there are certain fats and oils and fatty acids, including lecithin, that are not soluble in pure water. There are also eight or more kinds of inorganic ions, including potassium, sodium, magnesium, calcium, iron, sulphur, phosphorus and chlorine.

A list of all the numerous kinds of substances that have been found in the hen's egg would be tedious. It is obvious that the undeveloped, indeed the unfertilized, egg contains a great variety of them. And out of them are derived by a devious path the various chemical substances that make up the various organs and tissues. And these organs are to a large degree what they are because they owe their chemical properties to the substances that are in the egg. These substances have in some way become transformed into the specific tissue sub-

stances, and got into (helped create) those tissues at the right time and place.[8]

The contents of the cytoplasm of the egg of any mammal are unknown chemically. It seems probable that this egg content is in part like that of certain invertebrates whose egg resembles the mammals' in having little or no yolk.

With the aim of finding what chemical stuffs are in a nearly yolkless egg a group of Bryn Mawr students, headed by Professor David Hilt Tennent, studied the minute eggs of sea urchins which can be got in considerable quantities. They found fatty substances combined with sugar such as occur in the human brain and nerves (cerebrosides); also fatty substances combined with phosphorus (phosphatides) which are found in the fluids of all cells of our bodies; things called sterols which also occur in all of our cells and especially in nerve cells. This is quite a stiff lesson in chemistry, I know; but it illustrates how biologists are striving, though against great difficulties, to find out what is the nature of those substances that are packed away in the egg, and what relation they have to the materials of which the fully developed body is made.[9]

There is no doubt that there are many kinds of molecules in the cytoplasm ready to take part in the building up of the organism. But are they equally distributed to the various early cells from which the different organs are to arise? The human egg is not very suitable for answering this question just because the materials in it are very minute and appear under the microscope more or less alike. As shown in Fig. 1 no clear difference in the substances of different parts of the egg appears. Yet by focusing at different levels of the egg one does find that the particles are not distributed entirely uniformly throughout the egg. Those at the sur-

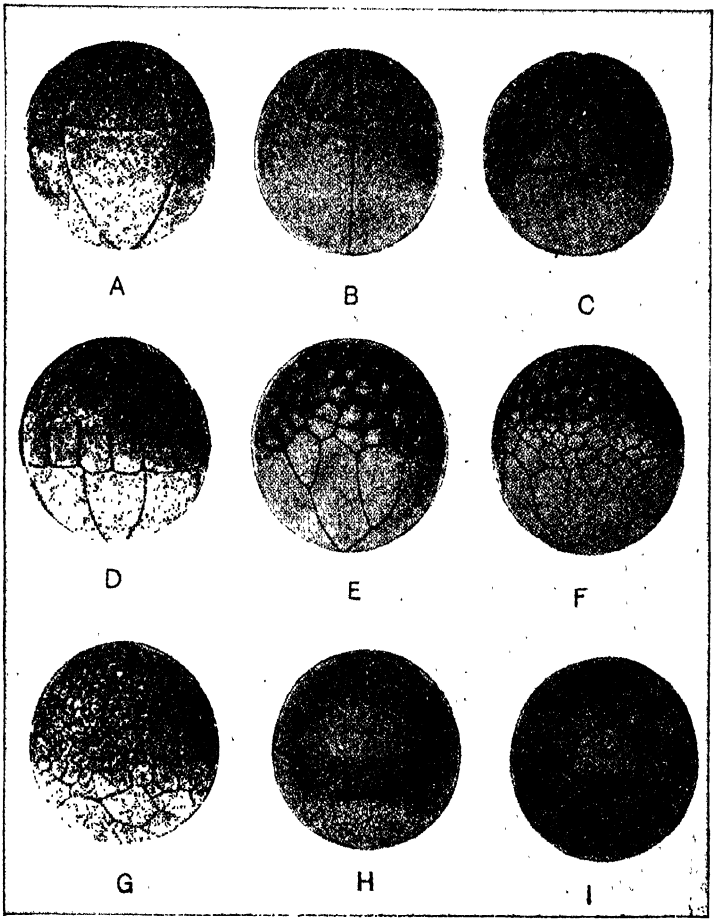


FIG. 115. Segmentation of egg of the frog. A, 8-cell stage. B, beginning of 16-cell stage. C, 32-cell stage. D, 48-cell stage (unusually regular). E, F, two sides of same egg in later cleavage. These figures A–F show the stratification of the egg into fine pigmented materials above and coarse yolk-laden stuffs below. H, I, beginning of formation of the entoderm by gastrulation. (*After Morgan, in his "Development of the Frog," courtesy of The Macmillan Co.*)

face are relatively large; many smaller particles are interpolated between the larger ones. There is no doubt a specialization of the material of the egg such that the embryo must begin to form not just anywhere but at a particular pole of the egg.

If one looks widely over the animal kingdom and compares eggs from different groups one finds that in many cases, if not in all, the materials of the egg are not laid down uniformly, that already different parts of the future embryo are foreshadowed in the egg. This is very clearly seen in the egg of the hen. When the shell of an unincubated egg is broken open you see on top a whitish spot resting upon the large yellow mass, or yolk, of the egg. This white spot is going to produce the main axis of the embryo chick, its brain and spinal cord and its masses of muscles. The rest of the egg is going to form at first a part of the food canal, and will be eventually absorbed by the food canal and by the blood vessels which reach out from the embryo proper and penetrate into the yellow mass. It is impossible to make the brain and spinal cord arise from any other part of the egg except the white spot.

The different appearance of the various parts of the egg is illustrated again in the frog's egg (Fig. 115). Here one pole is dark and floats upward; the other is white and lies below. The first two planes of division of the egg run nearly vertically, so that the first four spheres have both white and black poles; but when these four cells divide by a horizontal division plane there result four black cells above and four white cells below; and the lower cells are the larger. Obviously the cytoplasms are different in the upper and lower cells, and as a matter of fact they produce very different organs. The dark cells produce mostly skin and nervous system; it is impossible to make the brain arise first in the

white surface of the egg. The white cells give rise to the food canal and its glands, they will not produce skin. The muscles and bones arise from cells lying between the other two. Thus the future organs are probably already blocked out in the egg.

This probability is a demonstrated fact in some lower animals, especially those called Ascidians (from the Greek meaning a purse, so named because of their shape). These Ascidians, also called "sea squirts," occur at the seashore mostly attached to stones or seaweeds, but are not to be overlooked as of little significance for man. As a matter of fact they seem to lie close to man's primitive vertebrate ancestors. Now in an egg of this group (Fig. 116) one can see a crescent near the bottom (marked m) which is a region that forms chondriosomes and from which muscles will arise; another, opposite, full of yolk granules (y) from which the entoderm cells of the larva will arise; and, in the middle, a transparent cytoplasm from which the ectoderm will arise. By careful observation other regions can be distinguished which give rise to the neural plate (brain and cord, page 172); to the mesenchyme of the trunk and to the mesenchyme of the tail. If these parts of the eggs be mixed

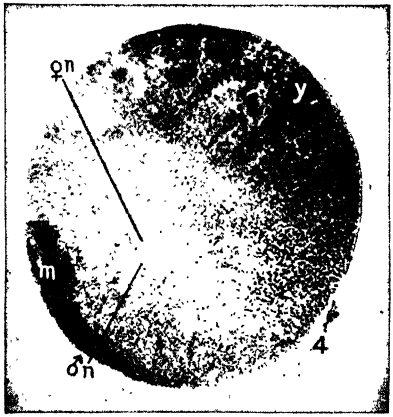


FIG. 116. Section in the median plane of the egg of the tunicate Styela, showing the egg nucleus, ♀n, and sperm nucleus, ♂n, in contact; cross section of the mesodermal crescent (m) full of mitochondria; and the yolk on the opposite side. × 550. (*After E. G. Conklin.*)

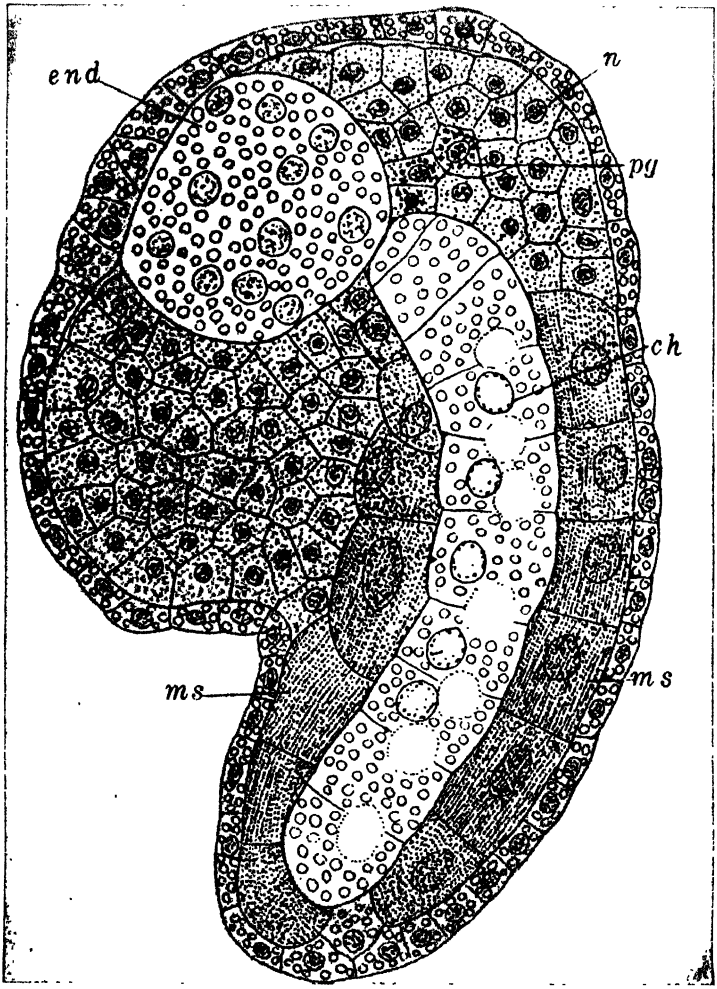


FIG. 117. Drawing of a nearly normal larva of the tunicate Ciona developed from an egg that had been centrifuged for ½ minute just before the first cleavage and "fixed" or killed, 17 hours later. Normal except for absence of brain vesicle. The pigment for eyes is located in 3 cells at *pg* in the midst of a solid mass of nerve cells *n*. The notochord is at *ch*. The muscles, containing mitochondria, are shown at *ms; end*, endostyle (precursor of our thyroid gland). (*After E. G. Conklin, 1931.*)

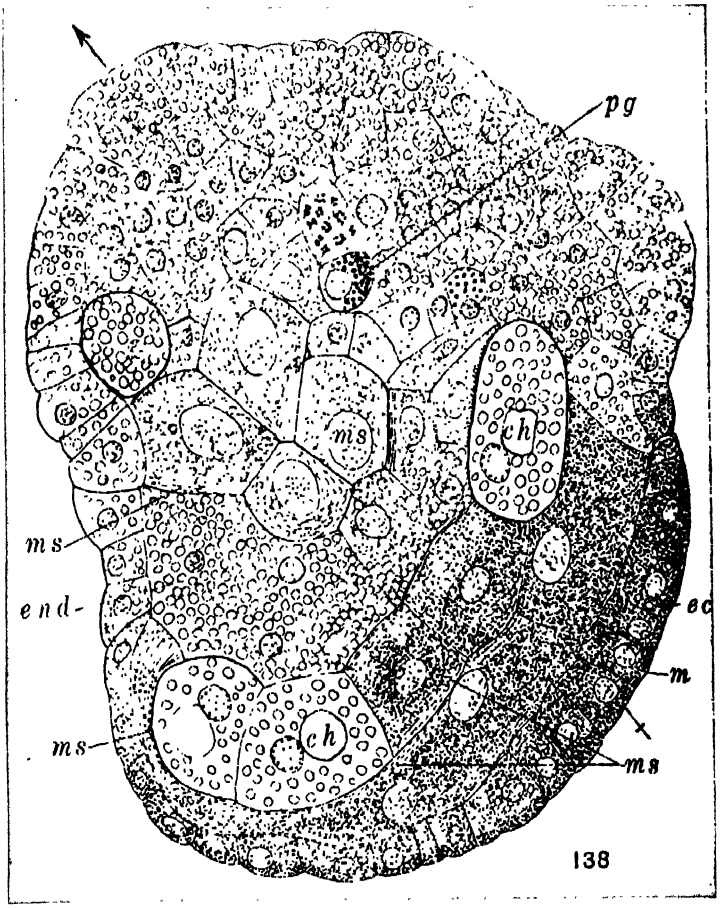


FIG. 118. Drawing of a larva like that of Fig. 117 except that it had been centrifuged for 2 minutes but before egg-cleavage had started; then fixed at 7 hours later. The chorda (*ch*) is in pieces. The muscle cells (*ms*) are scattered. The cells of the pigment spots (*pg*) are dispersed. The larva could not possibly function, if it could grow up. The ectodermal cells (*ec*) contain many mitrochondria (*m*). (*After E. G. Conklin.*)

up by whirling the eggs in a centrifuge * (something like that used to separate butter-fat from the buttermilk) then the organs of the body may indeed start to arise but are so badly displaced that the bodily machine can't function, just as would be the case if in an automobile the stearing wheel were attached to the pulley of the fan belt and half of the pistons were connected with the exhaust. Figure 117 shows the nearly normal larva. Figure 118 shows a larva after exposure of the egg to a large centrifugal force. The primitive backbone is in three different places, muscle cells are in bits that can't work together, while the brain doesn't form at all or is replaced by the gut.[10]

Such distribution of dissimilar cytoplasms in different parts of the egg is, as stated, probably widespread. But during the early stages of development (egg cleavage) the materials are segregated in diverse fashion. In Fig. 119 different types of zonal distribution of cytoplasmic materials are shown. *A* is the immature egg before the cytoplasmic stuffs have been segregated. In *B* is shown diagrammatically a stage of the egg with a stratification of stuffs. *C* is the cleaving egg. *D* shows a type of division in which only one of the two cells has the lower zone (heavy yolk). *E* shows a type in which all the zones pass to each cell. In a case like this the two cells may be separated from each other and each will produce the entire organism, only it will be of small size. In *F* a hypothetical type is represented in which in the first division the lowest and next to lowest zones are segregated into different cleavage spheres. Of course, in this case the single isolated sphere or cell could not develop into an entire organism, nor would the first cleavage plane separate the right and left halves of a symmetrical organism, but

* From studies of Edwin Grant Conklin published in 1931 in the Journal of Experimental Zoology, Vol. 60.

one cell could perhaps form the front, the other the hind end of such an organism.

What these facts show is that the cytoplasm of the egg that is about to start developing is not made up of uniform and uniformly distributed material, but that this material is diverse in different parts and that, under proper conditions, these different parts will contribute to the formation of their respective organs.

It will be seen that these studies incline toward the position of the preformationists, and, indeed, toward the position of the ovists. The difference is that the new ovists do not find miniature adults in the egg, but only organ-forming substances. Nor are these cytoplasmic substances able to form organs alone by themselves, for if the nucleus be removed from the egg it will not develop at all.

Since the modern preformationists have rejected the box-in-box theory they have been put to it to explain the recurrence of the embryo from the egg in successive generations. How do they account for the recurrence of these strata? First of all it has to be recognized that the stratified structure is so simple that no box-in-box hypothesis is required. You can slice a layer cake by parallel vertical planes into as many pieces of like composition as the area of the cake will permit, but you cannot so slice an onion. The stratified structure can pass in the ovary to each egg by simple cell division.

There is another apparent difficulty, and that is that the eggs of the new generation are usually formed in an ovary and that ovary has been derived from one of the cleavage spheres of the egg. And if the cleavage spheres are formed by the scheme of Fig. 119 *F* then no one of them would receive all of the kinds of egg stuffs. It would seem doubtful if Fig. 119 *F* is realized in Nature. If it is realized there must be

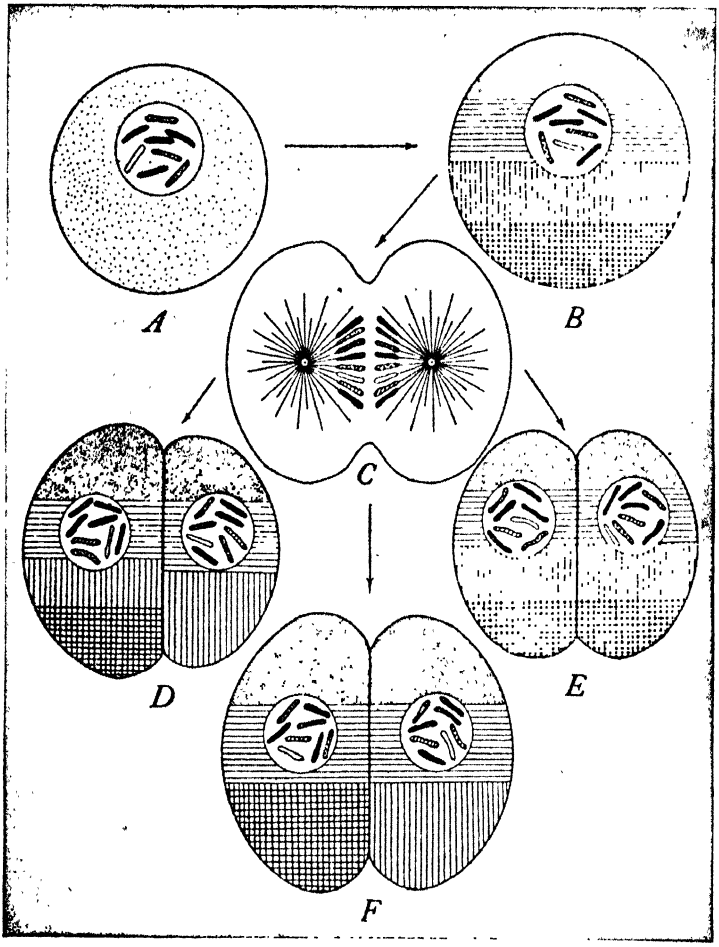


FIG. 119. Diagram of protoplasmic zones and their distribution at the first cleavage in different forms. *A*, immature egg, assumed to be without definite zones of cytoplasmic materials. *B*, mature egg with cytoplasmic materials in horizontal strata. *C*, first cleavage division of the chromosomes. *D*, *E*, *F*, different types of the two-cell stage; *D*, the lower zone isolated in one cell; *E*, equal division of the zones. *F*, hypothetical type with complete separation of two zones at the first cleavage. (*After Wilson, 1905.*)

some still unknown way by which any zone lost in a line of cells that is going to produce the ovary in the young can be constructed out of the remaining zones.

In general, it is probable that the ovary is derived from some one cleavage sphere which has retained all of its strata and passed them on through the generations until such time as the ovary is formed. When, as in the case of certain plants, a single cell or group of cells from a leaf can reproduce the entire plant it is probable that it contains all of the requisite stuffs for development. There are some animals of which a piece will form the missing parts. Here, too, there must be cells with all the necessary cytoplasmic stuffs. But of this more later.

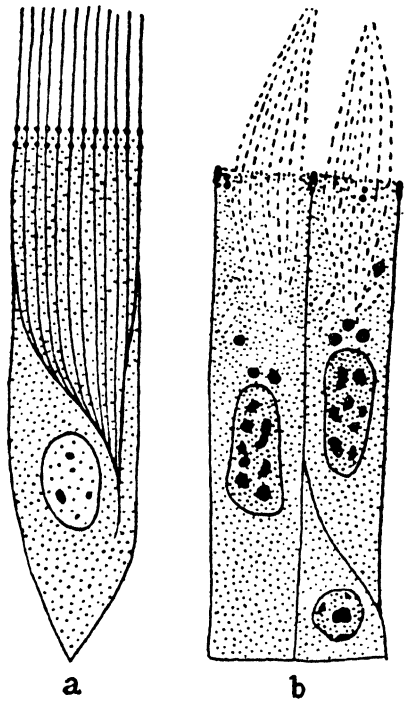


FIG. 120. a, diagram of a ciliated cell, showing vibratile cilia. (*After Prenant.*) b, cells of the human epididymus, showing non-motile cilia. (*After Fuchs, from Lewis-Stöhr, "Textbook of Histology," courtesy of P. Blakiston's Son & Co.*)

One kind of cells carried in the body may under special (abnormal) conditions produce all tissues while in the body. This is the ovum and probably other cells of the ovary. These cells may grow rapidly, form fluid-filled cysts in whose walls appear all of the body tissues, brain, muscle, car-

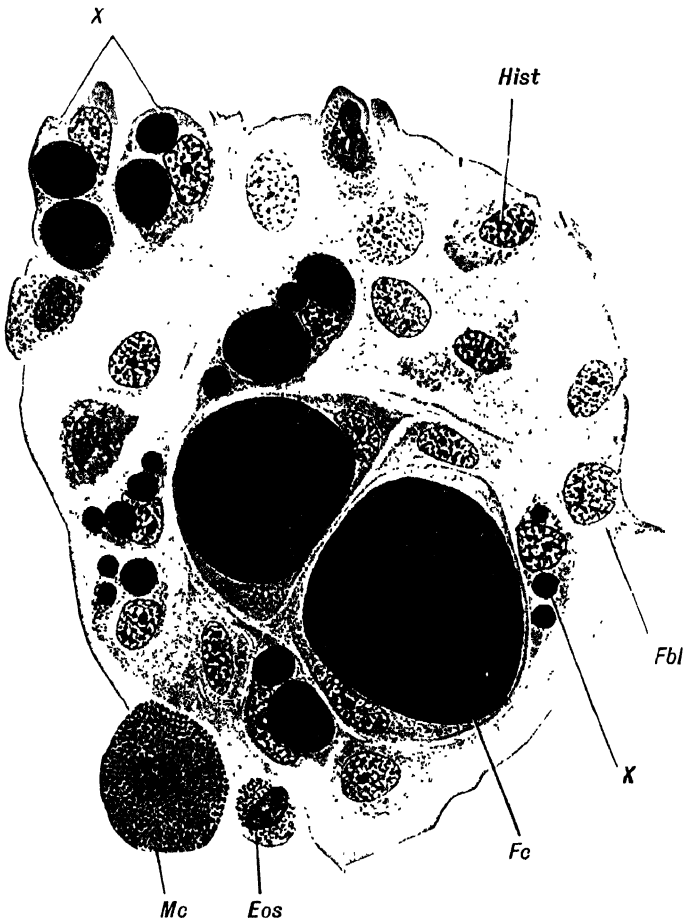


FIG. 121. Several fat cells (*Fc*) from the loose connective tissue of a rat. Other cells are indicated by letters as follows: *Fbl*, fibroblast (cf. Fig. 103); *Hist*, macrophage, large devouring cell; *Mc*, mast cell, crowded with granule which stain deeply. *Eos*, eosinophile leucocytes, small cells with brilliant yellow granules, and large nucleus; *X*, developing fat cells. The fat has been stained black by osmic acid. × 1,000. (*After Maximow-Bloom, "Textbook of Histology," courtesy of W. B. Saunders Co.*)

tilage, bone, teeth, glands, skin and hair. Thus the cells of the ovary, retaining all necessary building stuffs and genes of the nucleus may under special, still unknown, conditions, produce all tissues, but the regulators of proper time and place are absent. In our own bodies single tissue cells (other than of the ovary) cannot reproduce the whole body, but can reproduce or repair themselves, as when wounds heal. In such case the cytoplasm probably retains stuffs for the building of the particular tissue injured and no others.[11]

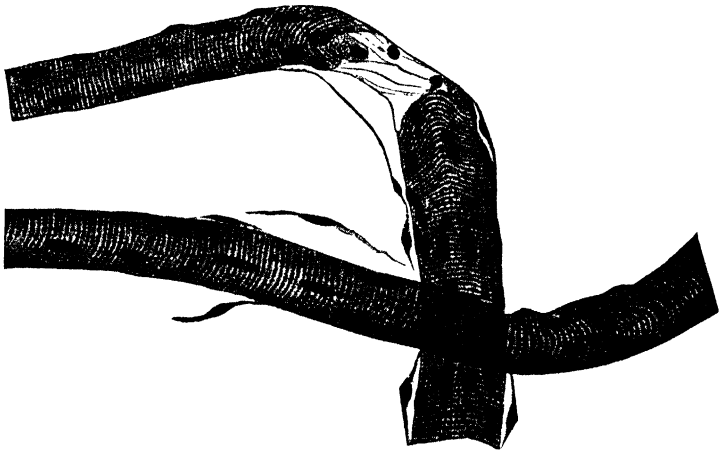


FIG. 122. Two striated muscle fibers of man from a teased preparation, with the nuclei stained. The upper fiber is crushed in the middle and shows the sarcolemma (muscle sheath). Between the fibers are several spindle-shaped connective tissue cells. × 250. (*After Maximow-Bloom, "Textbook of Histology," courtesy of W. B. Saunders Co.*)

We are thus led to the conclusion that the cytoplasm of most cells gradually undergoes change during development. It is because of such change that the different tissues of the body arise; each with its special form and quality of cell. When a piece of one of these tissues is grown under appropriate nutritive conditions in a glass container it will, if it

grows at all, form in general only the same kind of tissue as the original piece. This indicates again that the cytoplasms of these different tissues are different and specific and each incapable of producing anything else than its particular kind.

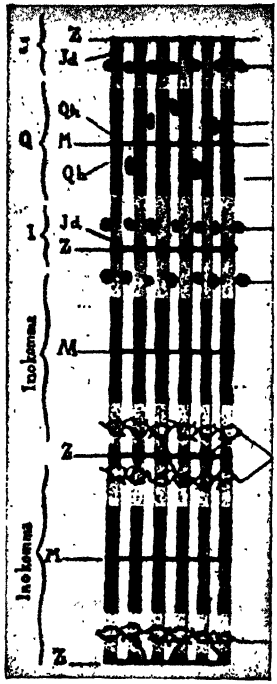


FIG. 123. Diagram of the structure of striated muscle fiber, much more enlarged than in Fig. 122. Dark granules or other structures are shown in the isotropic discs on each side of the Z line. The middle of the dark discs is lighter than the margins and is traversed by a dark line (M). (*After Heidenhain, from Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

And how different the cells of these tissues are! Figure 120 is one of the cells that make up the wall of one of the body tubes. There are delicate "hairs" (called cilia) which are constantly beating to carry fluids in one direction. Figure 121 is a cell used for the storing of fat. The cytoplasm is pushed quite to one side; the rest of the cell is fat. Figure 89 shows how cartilage cells lie in the clear, tough, gristly substance they have formed and how this dissolves and is reconstructed to form bone (seen on side). Figure 122 shows a part of a muscle fiber cell with its remarkable cross stripes. If you look at them with the highest power of the microscope they appear even more remarkable (Fig. 123). Figure 124 shows a nerve cell with its long fiber covered by a sheath and its terminal branches. The way these new fibers end in a muscle cell is, as we have seen, striking, since the fibers divide again and again in the midst of

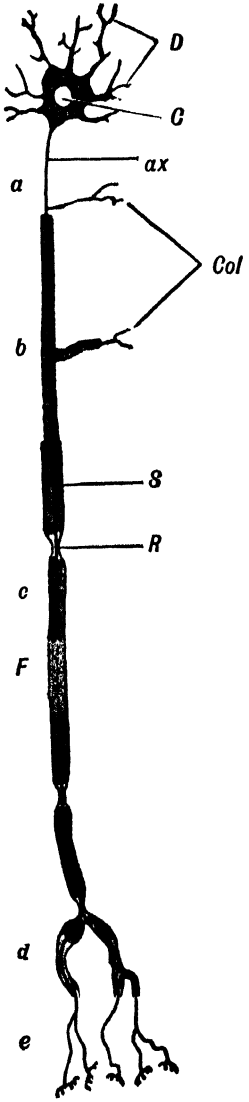


FIG. 124. Diagram of a motor neuron from the periphery of body. *C*, cell body with its nucleus; *D*, dendrites; *ax*, axon; *Col*, collateral branches; *S*, nerve sheath; *R*, node where sheath thins out; *a*, area of the naked axon (no myelin); *b*, area of axon covered with myelin; *c*, area covered with both myelin and sheath. *F*, dotted lines indicate that fiber is broken here, because of its great length, since it is desired to show the two ends; *d*, area in which the axon is covered only with sheath and nuclei; *e*, area of the naked axon, ending in an arborization. (*After Maximow-Bloom, "Textbook of Histology," courtesy of W. B. Saunders Co.*)

FIG. 125. Different stages in the development of the motor plates in muscles of a human fetus at full term. a, plate formed by ramification or branching of the tip of the neuron; d, plate formed by increase of complication of the terminal enlargement; b, c, by both methods; f, e, terminal enlargements in which branching is being started. (*After Tello, from Ramón y Cajal, "Histology," courtesy of Williams & Wilkins Co.*)

the muscle cell (Fig. 125). The endings of the nerve fiber in the brain are no less remarkable (Fig. 126). We have already seen the specialized sperm cell. The fertilized ovum is capable of producing all of these kinds of cells. But each kind is an end product and can produce only its own kind. We shall consider later more in detail the way these tissue cells are produced.

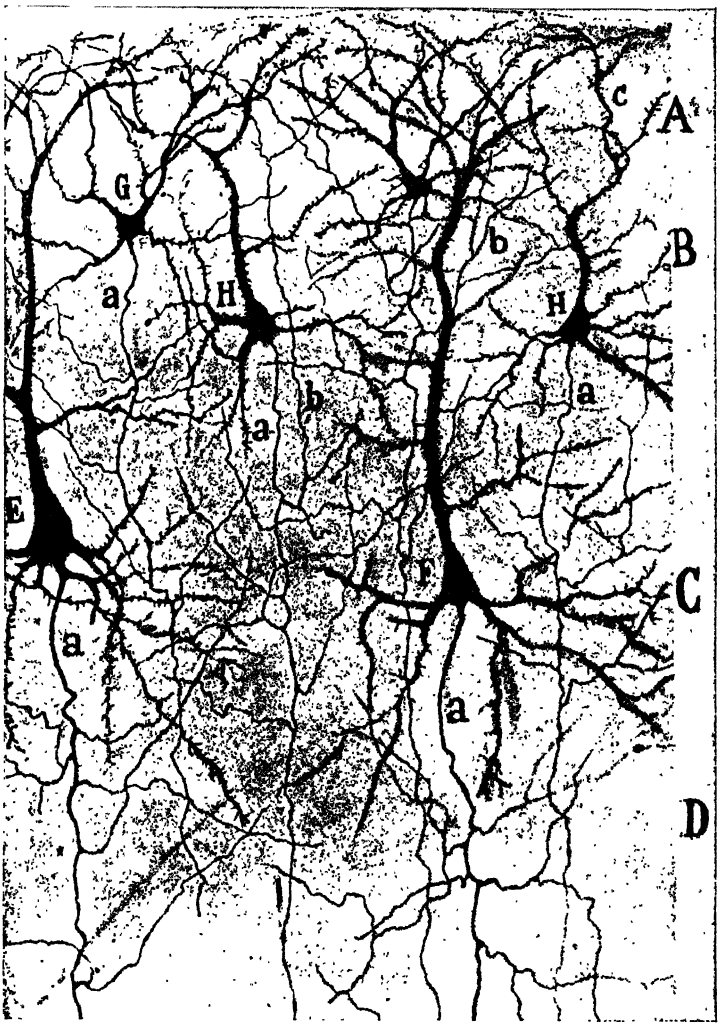


FIG. 126. Details of three layers (A, B, C) in the visual region of the cat's cerebrum brought out by the Golgi method. There are shown different types of pyramidal cells, with abundant branching of the cell body (dendrites) and axon (a). b, collaterals of the axon. D, lower cortical layer. (*After Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

NOTES

1. For a fuller account of speculation on sexual development see F. C. Cole's *Early Theories of Sexual Generation*, Oxford: Clarendon Press, 1930 (230 pp.).

2. An adequate history of the development of the cell theory has, apparently, still to be written. Some material for this history is to be found in Eric Nordenskiold's *History of Biology*, English translation (1928). A historical sketch is given in Chapter 26 of Lester W. Sharp's *Introduction to Cytology* (1934).

3. Good accounts of the general structure of the cell are given in Edmund Beecher Wilson's *The Cell in Development and Heredity* and Sharp's *Introduction to Cytology.*

4. For a further study of cell walls and their behavior see Cold Spring Harbor Symposia on Quantitative Biology (edited by R. G. Harris), Vols. I and II.

5. Bodies in the cytoplasm are described in greater detail in *General Cytology* edited by E. V. Cowdry, University of Chicago Press.

6. The constitution of the nucleus and its functions when "at rest" (that is, not dividing) are described very fully in the review by Georg Tischler, *Der Ruhekern* (i.e., resting nucleus), a book of 630 pages of which 130 pages are a bibliographic list of titles. This is a monument to German literary industry, to be read only by the serious student. It is worth while to call attention to it here as showing the vast amount of research that has been done on the nucleus in recent years.

7. Nuclear division has excited more interest since it was first observed about 60 years ago by Anton Schneider than any other cell phenomenon and properly so since it is essential to heredity.

8. The chemistry of the egg has been treated in extenso by James Needham in his 3-volume work on *Chemical Embryology.*

9. The investigations of Tennent and his students are published in *Studies from the Tortugas*, of the Carnegie Institution.

10. The fundamental studies of Edwin G. Conklin on stratification of the cytoplasm of the egg have been made not only upon Ascidians but also in a mollusc and in the worm-like pre-vertebrate called "Amphioxis." The last named studies are published in the Journal of Experimental Zoology, 1933; those on centrifuged Ascidians in the same Journal, Vol. 60.

11. Further details about ovarian dermoid cysts can be found in any medical encyclopedia.

CHAPTER 7

THE GENES AND HOW THEY DO THEIR WORK

THE ACCELERATORS: THE GENES, EARLY GUESSES ABOUT GENES

Let us now return to the chromosomes to consider what has been learned of their more intimate nature, and especially of their genes. And, first, it is important to recognize that our knowledge rests on a solid foundation, both of indirect or experimental proof and of direct observation. This knowledge has been acquired in the past thirty years and the acquisition constitutes one of the finest achievements of biology. It will be of interest to trace the history of that achievement.

The theory that development is under the control of particular units in the protoplasm is a very old one. In 1748 Pierre Louis Moreau de Maupertius offered the speculation that in both females and males there is a seminal fluid composed of a multitude of germs which, by uniting, form the fetus. A very similar speculation was offered by Erasmus Darwin (1810), the grandfather of Charles Darwin. These germs are formed by the parts of the body and partake of the nature of the parts from which they come and consequently cause to develop in the fetus the respective parts which originated each of them.

The English philosopher, Herbert Spencer (1864), postulated elements of a third order lying between the cells and the molecules. These he called physiological units. Though small they are very complex. They represent the smallest particles that can live. Existing in the cell in im-

mense number, they determine its form by their arrangement. They consist of chemical molecules grouped in very complex aggregates; and since the least change in the nature, number or arrangement of the constituent molecules modifies the structure, the number of kinds of physiological units can become almost infinite. Spencer supposes also that the units are polarized but in complex fashion and when the polarity is altered by external agents the cell shape is thereby altered. During child development, while the units remain the same, form undergoes changes. This is because the form is determined by the ensemble of the diverse units. If the proportion of the different kinds undergoes variation, as it does during development, the form will vary.[1]

Charles Darwin proposed in his *Animals and Plants under Domestication*, of which the second edition was published in 1876, a theory of Pangenesis. This assumes that "all the units of the body, besides having the universally admitted power of growing by self-division, throw off minute gemmules which are dispersed through the system." These gemmules grow, multiply, and aggregate themselves into buds and into the sexual elements. How they shall develop depends on what kind of other nascent cells or units they unite with. Thus an organism does not regenerate its kind as a whole, but each separate unit generates its kind. "The development of each being . . . depends on the presence of gemmules thrown off at each period of life, and on their development, at a corresponding period, in union with preceding cells."

Some years later Professor Hugo de Vries, of Amsterdam, wrote a book on *Intracellular Pangenesis* in which he also postulated an hereditary substance, made up of "Keimchen," for which word he also substitutes the classical term "pangenes." These are the bearers of hereditary qualities.

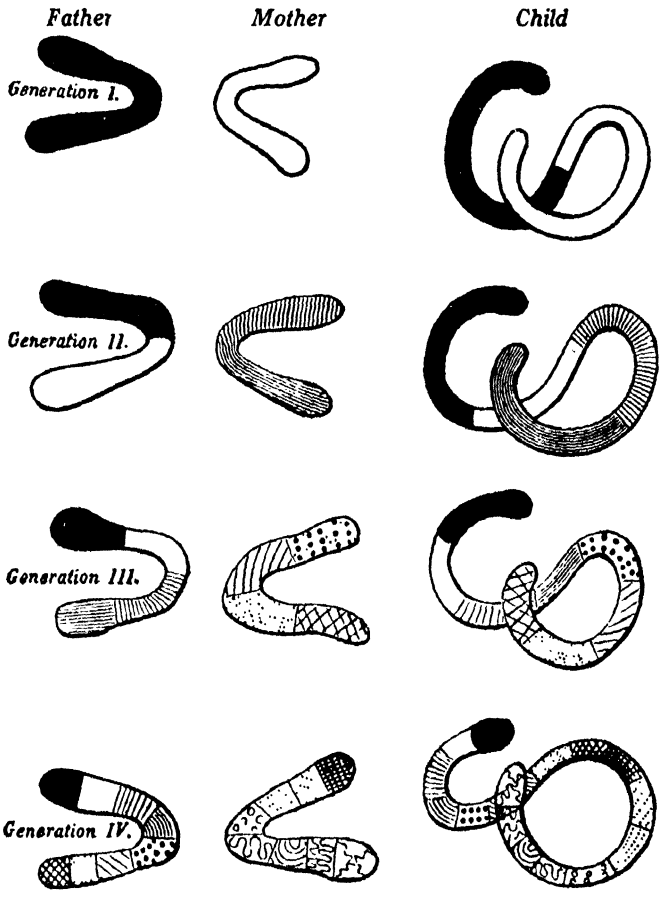


FIG. 127. Hypothetical structure of chromosomes according to Weismann. In the first generation the unlike chromosomes of the parent unite in the child. In the grandchildren the chromosome becomes still more complicated and in the later generations still more so. This is the first attempt to indicate the composition of the chromosomes out of linearly arranged ids or, as we say now, "genes." (*From Weismann, "Das Keimplasm," 1892.*)

August Weismann also accepted the theory of hereditary units or determinants, grouped into "ids" which he located in the chromosomes ("idants"). In successive generations the idants, each being made up of ids from different parents, tend to become more and more complex (Fig. 127). The Dutch naturalist, Wilhelm Ludwig Johannsen, introduced the simplified term "gen" for the units of de Vries and of Weismann. The most recent development of the gene theory is that of the former Columbia University group (including Professor Thomas Hunt Morgan, Alfred Henry Sturtevant, Calvin Blackman Bridges and Hermann Joseph Muller), which has established the presence of genes strung along the chromonemata, like beads on a necklace. It has been shown that each gene has not only a general function in the metabolism of each cell of the body, but each has also a prevailing specific effect on the development of a particular cell, tissue or organ. These genes have passed from the realm of hypothesis to that of demonstrated fact.

MENDEL'S DISCOVERY

It had been known since the early part of the last century that by crossing of plants you could get new combinations of their characters. And it was known that you could improve a domestic plant variety by introducing into it a valuable character of another variety of plant by hybridizing it with that other variety. In the middle of the last century a monk at Brünn, Austria (now Czechoslovakia), by the name of Gregor Mendel, began a new kind of hybridizing, not with the aim of improving the variety but of finding how traits are inherited. His work with peas was particularly successful, yielding scientific results. He crossed varieties of the pea plant that differed in color of

the seed (green vs. yellow), in the form of the seed (smooth vs. wrinkled), in the length of the plant stem (tall vs. dwarf) and still other traits. For example, he crossed tall with dwarf varieties and found that the progeny of the first filial generation (F_1) were all tall. When these F_1's were crossed together or allowed to self-fertilize there were obtained tall and dwarf forms in the second generation (F_2). Mendel counted and recorded the proportion of each type and found there were three of the talls to one of the dwarfs. Mendel continued the experiment by getting the F_3 generation through the self-fertilization of the plants of the F_2 generation. He found that all of dwarfs, self-fertilized, produced only dwarf plants. But the talls, self-fertilized, were of two kinds: those that produced only tall progeny and that that produced three talls to one dwarf, and these kinds were in the proportion of 1:2 (Fig. 128). The study of this trait and that of others that gave similar results led him to call the trait that appears alone in the F_1 generation the dominant trait; while the one that does not appear but recedes from view in the developed plant he called recessive. The fact that in the third hybrid generation you get pure recessives, pure dominants and a mixture of the two in the ratio of 1:1:2, or 1:2:1, led him to conclude that there were two opposed determiners, call them A (dominant) and a (recessive), which reappeared in such proportions as would result from multiplying the determiners together: $(A + a) \times (A + a) = A^2 + 2Aa + a^2$. The terms with capital letters are dominants, the other recessives, and the exponents of the terms are 1:2:1. Another conclusion followed from these results namely, that when the two opposing traits were combined (as in F_1) in one individual they did not blend and lose their identity but, on the contrary, they both reappeared

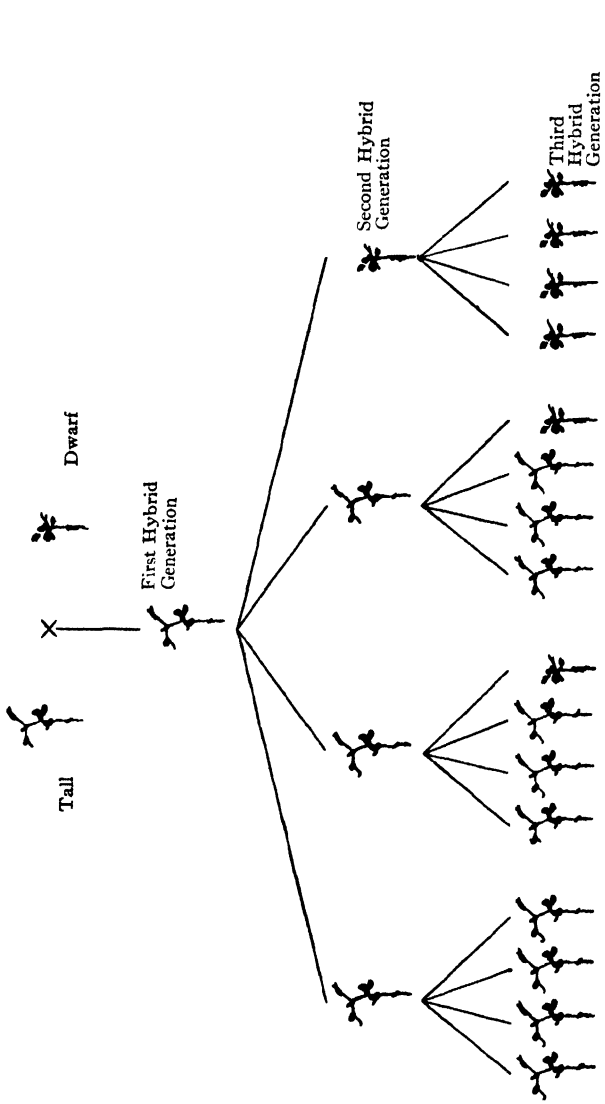


FIG. 128. Diagram to illustrate the Mendelian inheritance of tallness and dwarfness in the culinary pea; illustrating the results obtained by Mendel with the same material. Top row, the parents. Second row, first hybrid generation, tall; tallness is dominant. Third row, second hybrid generation, 3 tall to 1 dwarf. The dwarfs, inbred, produce only dwarfs Two-thirds of the talls, inbred produce talls and dwarfs in the proportion of 3 to 1. One-third of the talls, inbred, produce only talls. (*After A. D. Darbishire, "Breeding and the Mendelian Discovery." Permission of Cassell & Co.*)

in equal numbers in the germ cells produced by that individual. If two such individuals were crossed these germ cells (which may be called *A* germs and *a* germs) unite equally in the combinations: egg *A* + sperm *A*, egg *A* + sperm *a*, egg *a* + sperm *A*, and egg *a* + sperm *a*. There was complete *segregation* of the determiners in the germ cells of the hybrid. The pair of contrasting or opposing determiners came to be called allelomorphs or (for short) allels. The union of germ cells gives rise to a zygote and the zygote that bears only one kind of determiners (e.g., *AA*) is called homozygous. The zygote that bears both different determiners (e.g., *Aa*) is called heterozygous. The conditions of the individuals that we see are called phenotypes. Thus *AA* and *Aa* are of the same phenotype. But, the genetic constitution as determined by breeding reveals the genotypes. Thus *AA* and *Aa* are of different genotypes.[2]

Having determined how one pair of allels is inherited it became of interest to learn how two pairs of allels carried in the same parents would reappear in their children and grandchildren. This mating is known as di-hybrid mating. Thus, it will be instructive to follow the consequences of the mating of a tall pea yielding yellow peas with a dwarf pea yielding green peas, both of the traits of the latter being recessives, and not showing in the F_1 hybrids. Since the tallness and yellowness are independently inherited, when these hybrids form germ cells these will obviously be of four sorts, equally common: tall-yellow (*Ty*), tall-green (*Tg*), dwarf-yellow (*dy*), dwarf-green (*dg*). When the F_1 generation is inbred, the germ cells of both parents will be of the same four sorts and the combinations and their frequencies will be got by multiplying the formulas together (or squaring them):

$$\begin{array}{cccc} TY+ & Tg+ & dY+ & dg \\ TY+ & Tg+ & dY+ & dg \end{array}$$

The product is as follows:

$$\begin{array}{cccc} TYTY+ & TYTg+ & TYdY+ & TYdg \\ & TYTg+ & & \\ & & TYdY & \\ & & & TYdg \end{array} \qquad \begin{array}{ccc} TgTg+ & TgdY+ & Tgdg \\ & TgdY & +dYdY+dYdg \\ & & Tgdg+ \quad dYdg+dgdg \end{array}$$

$$TYTY+2TYTg+2TYdY+2TYdg+TgTg+2TgdY+2Tgdg+dYdY+2\,dYdg+dgdg$$

Of these 10 classes the fourth and the sixth have the same allelomorphs. Combining them we get the following 9 classes:

$$TYTY+2TYTg+2TYdY+4TYdg+TgTg+2Tgdg+dYdY+2dYdg+dgdg.$$

Recalling that recessive determiners do not show when their dominant allelomorph is present, the phenotypes of four kinds are as follows:

TY	IIII IIII	=	9
Tg	III	=	3
dY	III	=	3
dg	I	=	1
			16

That is to say, in F_2 there are for every 16 offspring 9 tall yellow seeded, 3 tall green, 3 dwarf yellow, 1 dwarf green seeded. Extensive breeding of peas since Mendel's day confirm expectation.

Similarly, a trihybrid mating may be made. In 64 offspring there will be phenotypically: 27 triple dominants, 9 of each kind with one recessive and two dominants, 3 of each kind with only one dominant and 1 with all three recessive allelomorphs.

It will be observed that, as the number of allelomorphs considered simultaneously in any mating increases, the number of classes and combinations increases rapidly and the less the chance of making a correct prediction as to the combination that is to be expected in any individual.

Mendelian expectation is still further complicated by the fact that in mammals and especially in man a single trait may depend for its expression upon many simultaneously acting determiners. Accordingly, the analysis of the inheritance of human traits proceeds slowly. Nevertheless, there exists a considerable body of human traits whose inheritance has been successfully studied so that recurrence in later generations may be predicted.

This point must, however, be emphasized. Heredity in man follows precisely the same laws as in peas. Thus brown eye color is a dominant trait with absence of brown (pure blue) as its allelomorph. Also curliness of hair is dominant over straight, in European matings, and brown hair is dominant over red hair. In the mating of a brown-eyed, brown- and curly-haired individual of a stock that for generations has shown these traits (if such a person exists) with a blue-eyed, red- and straight-haired person, the progeny will all resemble the first (or dominant) parent. But in the F_3 generation the same kinds of combinations

will appear in 64 persons of that generation as in the case of peas, cited above. Heredity follows the same laws in man, horses, insects and plants. We are just a piece of the universe of organisms.[3]

OUTGROWTHS OF MENDELISM

The leading English investigator of the shuffling of determiners, William Bateson, early noted that in some cases the recombinations were not random, but that two characters were inherited together. This phenomenon he called coupling. Later Morgan concluded that coupling of two traits in inheritance was due to the fact that the genes for both were located in the same chromosome. Leonard Doncaster had previously noticed that sex and certain color markings were associated in moths. This suggested that a determiner for sex lies in one chromosome and that other determiners of traits that are linked with it lie in the same chromosome. This chromosome came to be called the sex chromosome.

FIG. 129. Chromosome groups as seen in the early testis cells of the male vinegar fly, Drosophila melanogaster: X, Y the sex chromosomes. (*After Bridges, from Wilson's "The Cell," courtesy of The Macmillan Co.*)

By using a rapidly reproducing organism (the vinegar fly, Drosophila melanogaster) it became possible to list the linked traits of that organism. They fell into four groups. A long list of sex-linked characters; two long lists of non-sex-linked characters, and a very short list. When the chromosomes were examined it was found that there were three long and one short (Fig. 129) and that one of the long ones differed in size in the sperm and the egg and, therefore, must be the sex chromosome.

As the work progressed it was found that for many a pair of traits, the genes, *A* and *B*, which were ordinarily inherited together (linked) were occasionally inherited separately (segregated). Let us consider a specific example. The recessive trait, black body color, of the fly (instead of the normal gray), and recessive vestigial wings (instead of normal long wings) are usually inherited together; and since they are not sex-linked and were linked with numerous other traits they belonged to one of the long non-sex chromosomes that came to be called the second chromosome. As stated, the traits of the double recessives when crossed with normal sometimes did not appear together in the second hybrid generation. To be precise, in 17 per cent of the progeny there were either black-bodied large-winged, or gray, vestigial-winged flies. There occurred a predictable proportion of failures of linkage. This result was explained on the assumption that, during the formation of the germ cells, something special happens to this second chromosome. Now at that stage the chromosomes pair up, one of the members of the pair coming from the father and one from the mother. The chromonemata of the several pairs twist about each other slightly like the strands of a rope and may stick together at a point of contact. Where the chromonemata separate it is sometimes found that each component of the chromonema pair is now in part derived from the chromonema of one parent and in part from that of the other. There has been a "crossing over" between the parts of the paired chromonemata.

Next, the fact appeared that in matings of double recessives certain other genes of the second chromosome did not cross over with the same frequency of 17 per cent, but, on the contrary, some with a smaller, some a larger

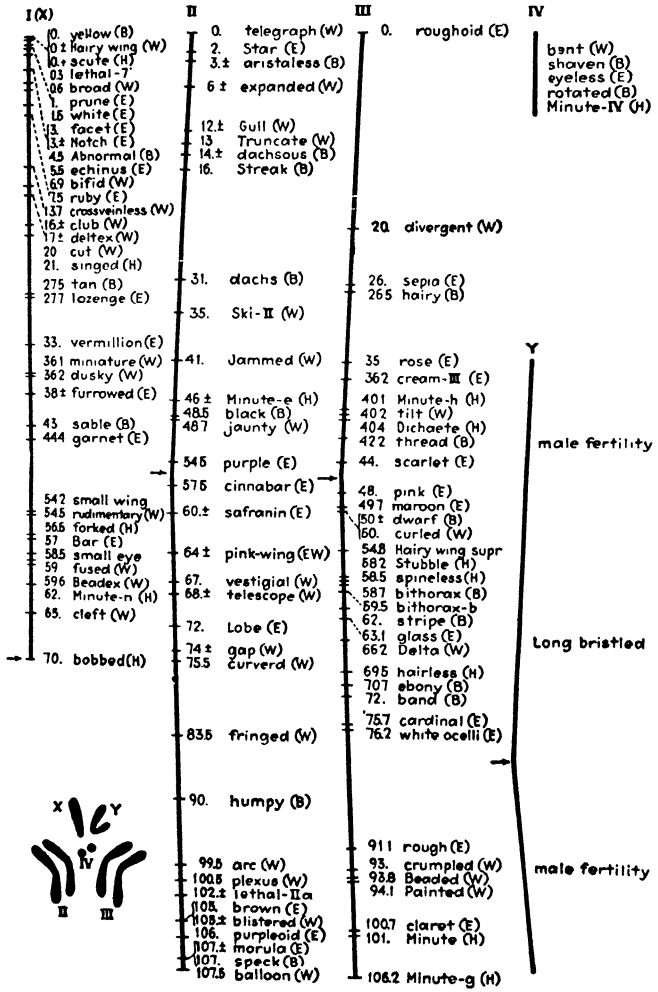


FIG. 130. Linkage map of Drosophila melanogaster, showing relative positions of many of the known genes in the chromosomes as determined genetically. The letters in parentheses indicate the portion of the fly's body in which the character appears. B, body; E, eye; H, hairs; N, wings. The arrows indicate positions of spindle attachment regions. In the Y-chromosome "long bristles" which is the normal allel of "bobbed" and the two factors for male sterility have not been precisely located. In Chromosome IV the genes are all very closely linked. (*Adapted from Morgan, Sturtevant and Bridges, 1925, and Stern, 1929, from Sharp, "Introduction to Cytology," courtesy of McGraw-Hill Book Co.*)

per cent. Then the idea arose that when the genes are close together in the chromosomes a crossing over is less apt to occur between them; when far apart more apt to do so. That made it possible to determine the relative distance apart of the genes for all pairs of traits, and eventually to draw up a chromosome map in which all the genes of all of the chromosomes (not the second chromosome merely) are shown at their proper distances apart. Such a chromosome map for the four chromosomes of Drosophila is shown in Fig. 130.

Still another step has been taken. It is possible, by bombarding the chromosomes with X-rays, so to alter them or their environment as to inactivate certain genes or even a longer part of the chromosome. The affected part of the chromosome cannot be ordinarily seen because the gene is invisible, being beyond the resolving power of the microscope with blue light, which can show as distinct two points only when they are about 2,000 Ångstrom units, or 0.2 μ apart. The locus of the gene is generally indicated, to be sure, by a small visible body called the chromomere (colored part), but this is obscured by the chromatin in the chromosome. The location of the affected gene in the chromosome map is, however, known by breeding methods. Naturally, it would be a fine thing if the affected chromomere could be seen.

An opportunity to see a particular chromomere has been afforded by the discovery of the extraordinary chromosomes in the salivary glands of the Drosophila, and other flies. A photograph of one of these chromosomes is shown in Figs. 131 and 132. (The photograph in Fig. 131 is not from Drosophila, but from another fly.) Strictly this is not a chromosome, but a combination of the chromonemata which form the essential part of a chromosome. The ap-

FIG. 131. Photograph of salivary gland chromosome (compound chromonemata) of the fly Sciara, showing bands, commonly regarded as indicating loci of genes. (*Courtesy of Dr. C. W. Metz, Carnegie Institution of Washington.*)

FIG. 132. Photograph of a segment of a salivary gland chromosome of Sciara, very greatly enlarged, showing granules each of which may represent the site of a gene. (*Courtesy of Dr. C. W. Metz.*)

pearance of bands in this figure is due to the circumstances that there are in the particular cells from which this photograph is made many identical chromonemata joined side by side. If we should split the chromosome lengthwise into its constituent chromonemata then we should have threads, or longitudinal bands, in which the crossed stripes are reduced to mere dots. It is the combination of the minute chromonemata that are attached to each other so that the same genes lie alongside of each other which causes the chromomeres to appear as bands. This result might be visualized by imagining that we are viewing from an airplane an army in which the different ranks were made up of the same number of individuals, for example eight, and these were marching across the plain in eight files. Let us imagine further that in some of the ranks all the soldiers were dressed in bright colors and these ranks were interspersed among the troops that were clad in khaki uniform. Then we should see in these long-drawn-out files a series of bands of bright colors against the more uniform khaki background. (What it is that causes the genes of the same kind always to lie next to each other in such bands is one of the problems not yet solved. Perhaps there is a linkage between molecules.) The entire army would thus be compared to a chromosome and the individuals in it, at least those that are brightly colored, would correspond to individual genes. Now, just as in its evolution the army might break up into its individual files so the compound chromosome of the figure might be regarded as capable of breaking up into its elementary lines or files. Each of these would be one of the chromonemata, which we have already considered.[4]

Now in these compound chromosomes it is possible to identify the gene loci that have been inactivated by X-rays

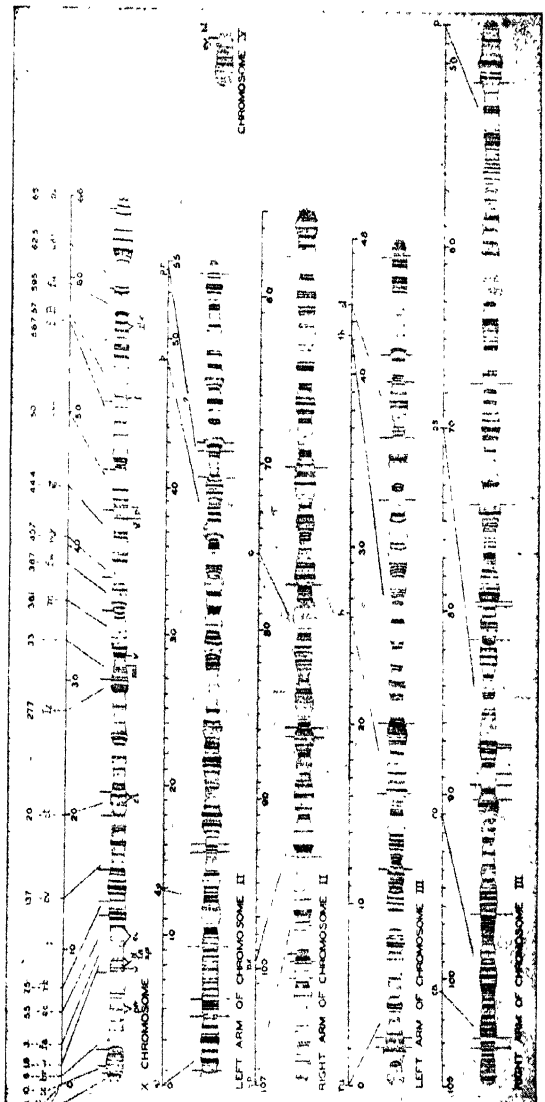


FIG. 133. Maps of the chromosomes of Drosophila melanogaster, as found in the salivary glands. The sex chromosome occupies the top line, chromosomes II and III, 2 lines each, and chromosome IV is given at the right. On the top of the figure a successful attempt is made to identify some of these prominent bands with mutant genes (indicated by letters such as *y*, ac, sc, br, w) whose order and spacing are known from breeding evidence. This attempt supports the hypothesis that the dark bands indicate the positions of zones made up of identical genes. In cases where, from breeding evidence, it is known that genes have dropped out from a chromosome the salivary gland chromosome shows a defect at the precise spot determined by breeding (see Fig. 134). (*After Painter, Journal of Heredity, 1934.*)

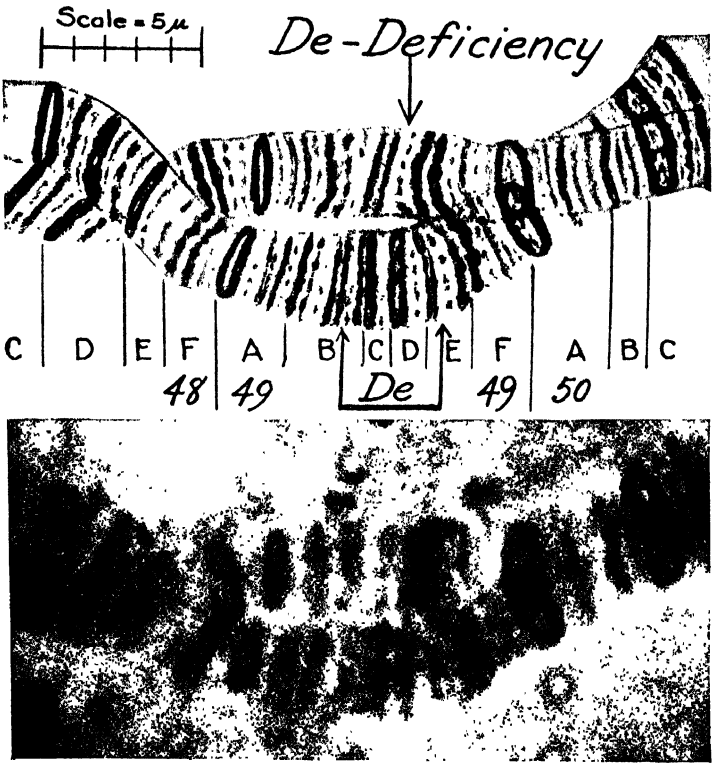


FIG. 134. Giant chromosome (compound chromonemata) from a salivary gland cell of Drosophila melanogaster. Photograph and drawing of a very short section from the right limb of the second chromosome, showing the normal mate (below, in both figures) with its characteristic series of dark bands and lines across the chromosome. The other mate of the pair (above) is "deficient" (at the arrow) for a section of about 10 distinguishably distinct lines. The deficiency includes the loci for the three genes at "*De*," namely "vestigial," "scabrous" and "lethal-Curry," at and near 67 on the linkage map of the second chromosome. In heterozygous forms (i.e., in which the deficiency is present in only one of the pair of chromosomes, as in this figure) this deficiency removes the hairs from the thorax and legs of the fly, hence the name "Depilate" for this deficiency. (*Information and illustration through the courtesy of Dr. C. B. Bridges.*)

(page 197), and thus to see the locus of the gene that is responsible for any particular character of the adult fly. The beginning of this identification is shown in Figs. 133, 134.

The number of bands in the entire set of compound chromosomes, in Drosophila melanogaster, is by count about 2,500; and this compares closely with an estimate of the number that is obtained by the method of breeding flies after single genes had been eliminated by X-ray bombardment.

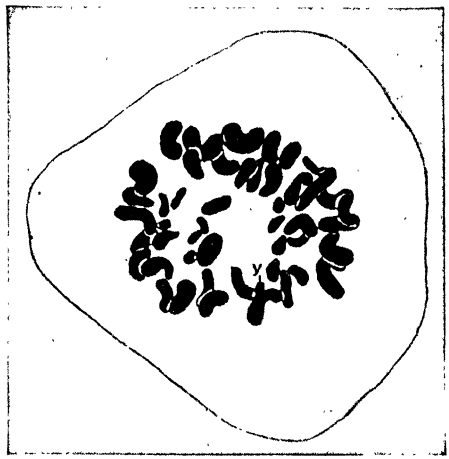


FIG. 135. Cell from the testis of man showing 48 chromosomes, including the small Y-chromosomes. (*From Painter.*)

Human chromosomes have been studied carefully only in the middle phase. Here it is determined that the number of chromosomes is twenty-four pairs (Fig. 135). They are shown, each unit separated from the other, in Fig. 136. It is seen that some are large, at the left; others small, at the right. Some are tenuous; others rounded. These forms are fairly constant and clearly the differences are important.[5]

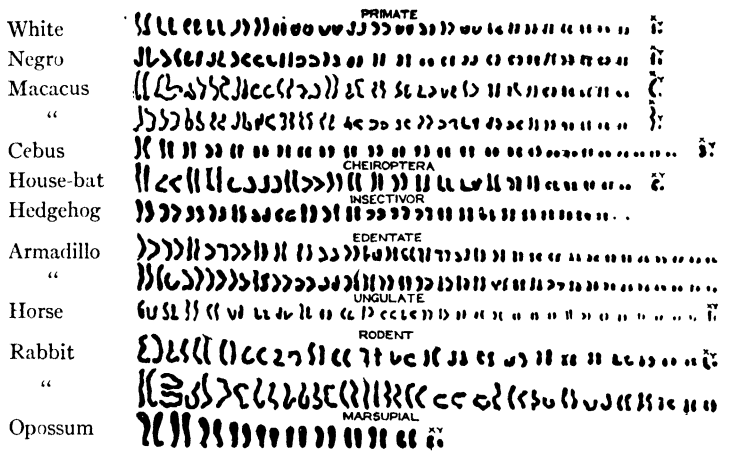


FIG. 136. Chromosomes of various mammals placed in a row in order of size for ease in identification. The primates, including man, are placed on top; below them the Cheiroptera (bats), then the Insectivora (shrews, etc.), edentates (sloths, etc.), ungulates (e.g., the horse), rodents (e.g., mice), and marsupials (like the opossum). (*From T. S. Painter, American Naturalist, 1925.*)

One pair, *XY*, deserve special notice. It consists of one large chromosome like the upper part of an exclamation point, the other member of the pair is like the dot of the exclamation point. This pair constitutes the sex chromosomes.[5]

The reason why detailed studies on genes in the chromonemata have not been made and mapped in man is because the difficulties in studying genetics in man are so great. Such maps will not be made for a long time yet. But there is no doubt that the general principle established for Drosophila applies to all multicellular organisms including man. The probability is enhanced by the fact that in recent years a chromosome map has been worked out, in part, for rats by William Ernest Castle and his associates of Harvard (Fig. 137). And, since the chromosomal mech-

anism in all mammals is much alike we may conclude that man's twenty-three pairs of chromosomes, plus the sex chromosomes, contain a specific series of genes, each influencing the development of a particular part of the organism. Already we know several sex-linked characters and any chromosome map of man will probably start (as did the Drosophila maps) with the sex chromosome. The pioneer work on Drosophila has developed a technique for analyzing the chromosomes and it presents a challenge for similar work on man.

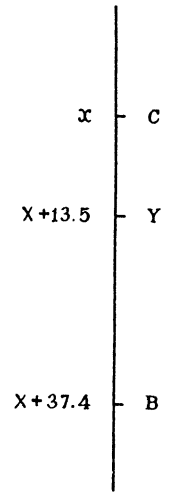


FIG. 137. Preliminary map of three genes in one of the chromosomes of the rat. The mutant genes are C, whose absence causes albinism; and Y, involved in yellow fat production. The crossing over in the interspace C–Y is 13 p.c. Finally, B is involved in brown pigmentation. The crossing over in the interspace C–B is 37 p.c. (*Courtesy of W. E. Castle.*)

The demonstration that the various genes determine to a large extent the specific character of the organism is an important one. And it is hardly to be wondered at that those who had shown the relation between characteristics of organisms and the genes of their chromosomes should conclude that the problem of heredity had been solved. But instead of the problem being entirely solved a new problem has been formulated, namely how do the genes do their work in controlling the course of the development of specific parts, and, indeed, of the body as a whole?

HOW GENES DOUBLE THEMSELVES

Nature of the gene.[6] The gene is not a guess, its importance in heredity is not a mere hypothesis. Its reality is assured by the same criteria as satisfy us of the reality of the nu-

cleus itself. For genes can be measured and counted and the place which they occupy can be seen. These genes tend to form about themselves a deeply staining substance which is to the gene as the husk is to the hickory nut, or possibly as the pulp of the grape is to a single grape seed. It is the pulp, the chromomere (page 197) that enables us to locate the gene. However, the late John Belling, who had the most profound knowledge of how to get the highest powers of the microscope to yield their utmost, believed that by crushing the pulps he could in one case see the central gene within, as shown in Fig. 138.[7]

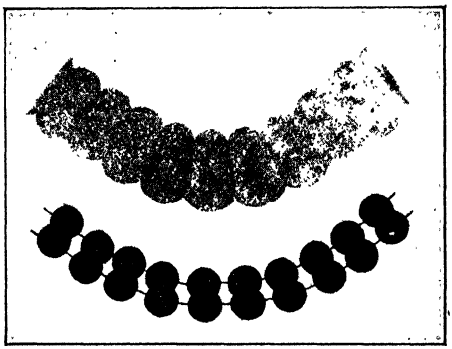


FIG. 138. Upper, double row of chromomeres in the pollen mother cells of Allium (of the onion family) as seen under the microscope greatly enlarged. The chromomeres have been squeezed flat showing that there is an extremely minute particle in each, which the author was inclined to identify as a gene. Lower, a drawing representing the above double string of deeply stained chromomeres before destaining and squeezing flat. (*After John Belling.*)

What is the nature of the gene? First of all it is extremely minute. But on the question whether the gene is a molecule or group of molecules, there is little agreement. Surely, from its size alone the gene may well be only a single molecule; and if it is a single molecule then some genes must be of a complex nature. The reason for concluding this is that one may by various agencies succeed in altering the work that the gene does without altering its position. By means of X-rays and other radiations the quality of a gene may be made spontaneously to

change. Thus the gene in one locus may, under some circumstances, influence the production in one fly of red eye pigment, in another rose-colored pigment; again, a light pink, cream, and even white. The best hypothesis to account for this series is that the molecular structure of one gene has been changed in serial fashion or else the milieu has undergone a series of changes, e.g., by oxidation or reduction.

Each gene performs not only a special function in development, but also participates in the development of the body as a whole. So no one gene can be spared and, indeed, usually, where the gene is entirely wiped out from the long chain of genes in a chromosome, one finds that the cell which has suffered the loss dies. Each gene thus plays an indispensable part in cell activities and life. One must conclude, therefore, that in the fruit fly there are at least 2,500 functional units playing, separately or collectively, an essential developmental or metabolic part.

Doubling. One of the most striking facts about the gene is its power of self-duplication. In the original fertilized egg cell (zygote) there are probably not more than four genes of each kind. Since each time a cell divides the number is doubled these four genes of each kind must have become several billions of each kind in the adult. How is this repeated doubling brought about? Modern chemistry cannot answer this question definitely. But it is approaching a point where the answer seems imminent. Perhaps it will be worth while to formulate a hypothesis about this self-duplication.

The gene is probably a protein. The protein molecule is now believed to consist of a series of parallel chains of units (also called residues or submolecules). These units are amino-acids, e.g., glycine, or amino-acetic acid, which

has the formula $CH_2 - NH_2$ (with COOH below the CH_2). All of the amino-acids have the NH_2 group (or at least NH) and an acid (COOH) and one or more hydrocarbon radicals. The units in any chain are bound together by the NH and CO radicals. The parallel chains are loosely tied together thus:

```
|      |
CO....NH
|      |
NH....CO
|      |
CHR...CHR
|      |
CO.....NH
|      |
NH....CO
|      |
CHR...CHR
|      |
```

While the simplest of proteins, called protamines, found in fish sperm, have a molecular weight of about 2,000 times that of hydrogen and contain only about 14 bonds, the more complicated proteins, like egg albumin, have a molecular weight of 34,500. Hemoglobin from red blood cells has double this weight. Other proteins have three or six times the molecular weight of egg albumin. Much more complicated proteins are known, even up to a weight of 5,000,000 times the weight of hydrogen.[8]

Now it would seem possible that in the case of molecules made up of many parallel chains bound together by secondary forces, as in the above diagram, rupture between

chains would require little energy. And it has been suggested that a chain adds new units until a disrupture occurs. From the weight, on the average, it is computed that a protein molecule is about 5,000 Ångstrom units long. Immediately, however, the parts were separated, each piece would restore the whole with its weight of 34,000. Then there would be two like molecules in place of one. There is, however, no experimental evidence on this point.

Again, in plants the principal type of molecule is cellulose, one of the carbohydrates. In carbohydrates, says Gortner, is the fuel which serves to carry on vital processes. They constitute three-fourths of the dry weight of the plant world. To this group belong glucose, the granddad of all the compound sugars and sucrose, maltose, starch, glycogen and cellulose. And cellulose forms the outer wall of plant cells and constitutes nearly the whole of such plant fibers as linen and cotton. These fibers grow rapidly as their cellulose molecules multiply. How do these multiply?

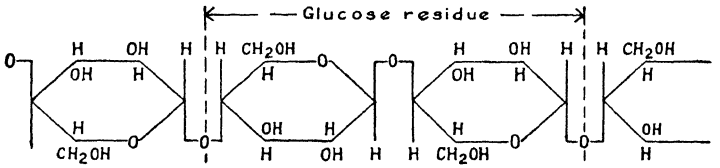


FIG. 139. Diagram of a unit and two half unit sections of the cellulose molecule showing one of the links of the chain of glucose residues or submolecules. The carbon atoms at the angles of the hexagonals are omitted, being assumed. (*After G. L. Clark, Cold Spring Harbor Symposia, 1934.*)

Chemists and physicists working in co-operation have concluded that the cellulose molecule, much like the protein molecule, is made up of a chain of submolecules (units or residues), which are glucose molecules (Fig. 139). Several of these chains of units may lie parallel (Fig. 140). The chains are linked by oxygen bonds. Were these bonds that

unite the glucose units broken, each chain would make two of half length, but their structure would be immediately restored by union with free glucose molecules. Or the division might take place lengthwise. Thus, growth of the chain and self-division seem to constitute the method of self-proliferation.

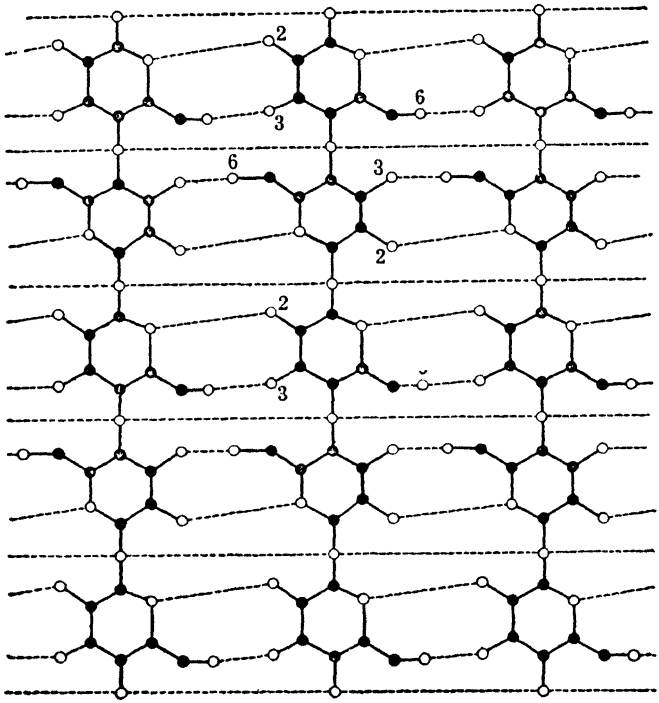


FIG. 140. Diagram of structure of cellulose, derived from a tangential section through a ramie fiber showing 3 glucose units. Dark lines indicate primary valence bonds. Broken lines indicate probable general direction of secondary valence forces. (*After Sponsler and Dore, from Gortner's "Outlines of Biochemistry," courtesy of John Wiley's Sons.*)

If we can use these facts to answer our question as to the basis of the wonderful capacity of organisms to duplicate

indefinitely the stuff of which they are composed, we may conclude that it probably inheres in the capacity of the cellulose and protein molecules to form long chains and a lattice-work of like links, which may break by mechanical stress, when they become too long; and which may then quickly regenerate.

CONFLICT BETWEEN THE GENISTS AND CYTOPLASMISTS

That there are particles in the nucleus that determine the traits of the developing young has been long suspected. Weissmann, indeed, located in the chromosomes, or what he called the germ plasm, the determiners of the course of development. He and many other naturalists focused their attention upon the chromosomes as the principal agents of development because of the remarkable way in which the chromosomes divide in producing new eggs or sperm, or in helping build up the developing body. The group of naturalists who emphasize the importance of the gene may be called the genists. Of present-day genists, the most important school is that of the Drosophilists, a group that we associate with the name of Thomas Hunt Morgan. He was able to demonstrate the important role played by individual particles arranged along the axis of the chromosome.

On the other hand, there have always been voices crying, as it were, in the wilderness, that the cytoplasm of the egg is also important in directing the course of development. It has been pointed out by a score of embryologists that the cytoplasm of the egg is, indeed, not homogeneous, but is different in different parts. The studies on the diversity of the cytoplasm in the egg have yielded figures of which examples have been already cited from Edwin Grant Conklin (Figs. 116, 117, 118), Edmund Beecher Wilson (Fig. 119) and others. In Fig. 13 we have seen that, at an

exceedingly early stage in the formation of the embryo—the stage which is known as the blastodisc (because the new bud, or blastus, of the embryo forms a disc)—already the location of the head, neck, trunk, sides of the body, and the future appendages are blocked out, though none of these things are seen in the form that they possess in the child at birth. There is every reason, as we shall see later, for believing that materials in this blastodisc that are to form the head are not the same as the materials that are to form the trunk and the muscles of the side of the body or the limbs. The blastodisc is already differentiated even as the adult is.

The discussion between the genists and the cytoplasmists reminds us, in a way, of the feud between the ovists and the animalculists, and just as in the latter case both were wrong in maintaining that the embryo arises exclusively from the one kind of germ cell or the other kind of germ cell, so in the former case both would be undoubtedly wrong in maintaining, on the one hand, that the genes alone are responsible for directing the course of development, or on the other hand, that the cytoplasm is primarily responsible. Just as the development of the individual depends upon the interaction of the egg and the spermatozoon so the development of each cell depends upon the interaction of the genes and the cytoplasm in a way which we shall discuss shortly. To say now that both genes and cytoplasm are important is not to minimize the value of either, but to enhance the value of interaction of the two agents.

EVIDENCE FOR THE ROLE OF CYTOPLASM IN DEVELOPMENT

That the genes play an important part in directing development need not be argued, since all geneticists are

agreed upon this point. That the cytoplasm plays a no less important role is less obvious. One line of evidence as to the importance of the cytoplasm is, however, of great importance. This evidence is derived from reciprocal crosses. A reciprocal cross, it should be added, is one made between two species *A* and *B*, in which *A* is used first as mother and then as father.

Let us assume two species, *A* and *B*, that differ in one or more traits. Now if these species be crossed so that sperm *a* of species *A* enters egg *b* of species *B* any offspring will develop under the combined influence of the nucleus (*N*) of *a*, (*Na*), and *b*, (*Nb*), and of the cytoplasm (*C*) of the egg *b* (*Cb*). The cytoplasm of the sperm (*Ca*) can be neglected, first because the sperm cell (Fig. 114) carries little cytoplasm except of the tail; second, because the tail is generally left outside of the egg and has no influence on development. If the cross is made reciprocally the offspring will develop under the combined influence of $Na + Nb$ and cytoplasm *C* of the egg, *a*. Thus the developmental factors in the two cases may be recapitulated as follows:

First cross, $Na + Nb + Cb$.
Second cross, $Na + Nb + Ca$.

It is clear that the cytoplasms *Ca* and *Cb* are the differentials in these reciprocal crosses. If the cytoplasm plays an important role in development the reciprocal crosses should produce offspring that differ in that the product of the first cross should incline toward the *B* species; those of the second cross toward the *A* species.

Now, by and large, reciprocal crossings have not been found to give offspring that differ strikingly. The reasons for this are not difficult to understand. First, crosses between markedly different species are mostly infertile.

Consequently reciprocal crosses are usually confined to cases in which the genes of the nuclei and the materials of the cytoplasm are harmoniously adjusted. Also, it seems probable that cytoplasmic constitution does not change as rapidly in passing from species to species as the genic constitution does. Accordingly we may not look for as obvious differences in offspring traits due primarily to cytoplasmic changes as in offspring traits due primarily to gene changes. Another reason why differences have not been ordinarily recognized in reciprocal crosses is because such hybrids usually do not develop to maturity, especially among animals; while differential characters most commonly appear in the later stages of development. Also, differences in reciprocal crosses have usually not been looked for very critically.

A difference in reciprocal crosses has, however, been found in so large a number of cases that such difference may be regarded as normal. A few examples follow:

Funaria is a typical moss, such as you find on moist soil of the woodland. Fritz von Wettstein of Göttingen made four types of crosses of mosses of this and related genera.[9]

First, he crossed strains of the species Funaria hygrometrica. Any strain could be crossed with any other. In no case did the offspring of any cross differ from its reciprocal.

Second, he crossed the distinct species, Funaria hygrometrica and Funaria mediterranea, using first one species and then the other as mother. The progeny were very different in the reciprocal cross, though the same two parents were involved; in any cross the mother's traits were the more strongly inherited by the hybrid progeny. Obviously the dissimilar egg plasmas constituted the differential.

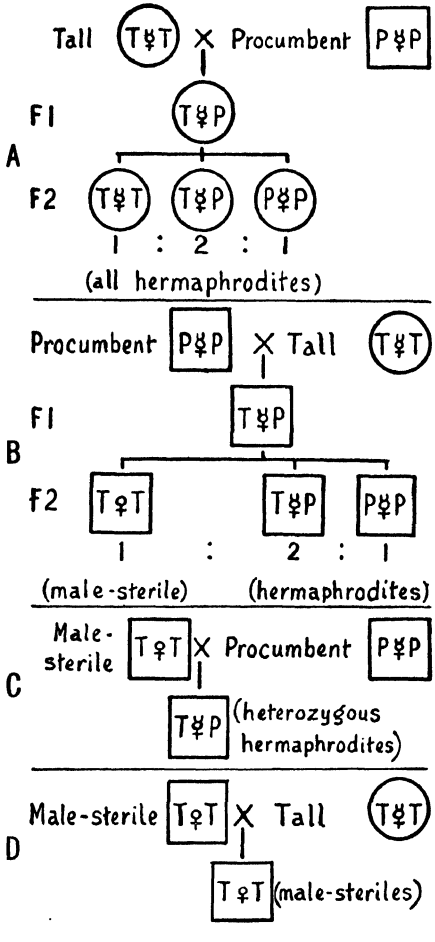
Third, Funaria was crossed, both ways, with another

genus, Physcomitrium. The reciprocal hybrids are substantially similar but when their spores are sown the progeny showed no plants like the father but only numerous plants like the mother. Apparently all spores that carried paternal traits were sterile. In this case the sperm genes could not function at all in the foreign cytoplasm and so died.

Fourth, two still more dissimilar genera were crossed. The sterility was still greater; the few spores that could develop at all produced plants of the mother's type. In all other cases the introduced sperm died in the foreign cytoplasma. In these last cases the genes of the foreign species could apparently not act upon the cytoplasm into which they were introduced.

Another case may be cited; this time involving the flax plant. In this species the flower carries both male and female organs. Two strains of the species are known, differing in their form of growth. One is called Tall; the other Procumbent. If the ovules of Tall are fertilized by Procumbent sperm (pollen) there are produced seeds and eventually plants that have the normal flowers carrying both ovules and anthers. Self-fertilized, such plants produce again normal offspring.* If, on the other hand, Procumbent ovules are fertilized by Tall sperm the resulting offspring have, indeed, both ovules and anthers, but if the ovules of such offspring be self-fertilized some of the seeds will develop plants that carry female organs only (Fig. 141B). Apparently the genes of Tall finding themselves (as may happen in the second hybrid generation) alone with Procumbent cytoplasm are unable to build up the male organs in the flower. If those flowers that have Tall genes (and no others) and Procumbent cytoplasm are fertilized with Tall sperm from normal flowered plants, again seeds are produced which grow

* Fig. 141A.

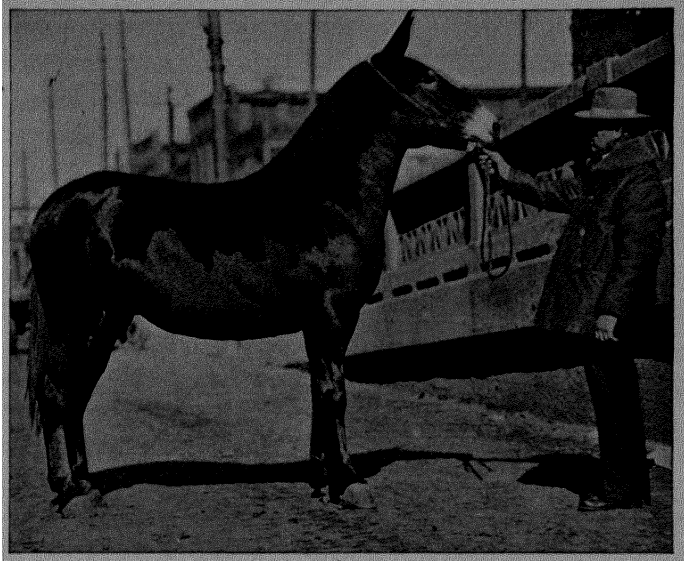


O = cytoplasmic constituent of the Tall.
□ = " " Procumbent.
T = a gene, or group of genes, of the Tall.
P = a corresponding gene, or group of genes, of the Procumbent.

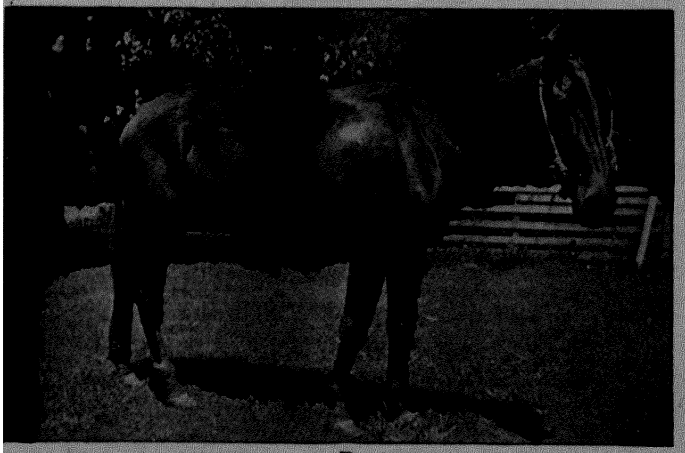
FIG. 141. Diagram of the pedigree of short and tall strains of flax, as described in the text. (*After Chittenden and Pellew.*)

into flowers which again have no male organs (Fig. 141D). Thus, again, Tall genes will not produce male organs in Procumbent cytoplasm. The reverse is not true. The cytoplasm is the differential.[10]

In animals also reciprocal crosses may give rise to dissimilar results. Thus in the famous tiny wasp known as Habrobracon (a name without etymology) there are, at the temperature of 25°, two races, a dark and a light. In each race the male is darker than the female. The male offspring have only female parents; the female offspring are biparental. When the races are crossed reciprocally the females of the two kinds of matings differ in pigmentation of which the degree inclines toward



A



B

FIG. 142. A, photographs of mule (progeny of a male ass and a mare) and B, hinny (progeny of a stallion and a female ass) to illustrate the problem of reciprocal crosses. (*Kindness of the U. S. Dept. of Agriculture and P. D. Sanders, editor of Southern Planter.*)

the mother's. That is, they are darker if the mothers are of the dark race; lighter if of the light race. Thus, the degree of development of the pigment is determined, in part, to be sure, by the genes of the nucleus, but also by the constitution of the cytoplasm.[11]

In mammals, also, the constitution of the cytoplasm of the egg plays a differential part in development. Thus, the hinny, whose mother is an ass, differs in several characters (size of ear, body build) from the mule whose mother is a mare (Fig. 142). William Ernest Castle crossed, reciprocally, a race of large rabbits with one of small rabbits. When the large race were used as mother the young grew to be 5 per cent heavier than when the small race was used as mother. Castle is not quite certain whether egg cytoplasm or difference in contribution from the mother's blood during gestation is responsible.[12]

The foregoing are examples merely. Cases could be multiplied several times. The facts suffice to demonstrate that the cytoplasm contributes in important fashion to the characters of the progeny; they support the conclusion that development is the interaction in some way or other between genes and cytoplasm.

WHERE THE GENES DO THEIR WORK

In order to get more light in detail as to the way the genes do their work let us look at the special relation between nucleus and cytoplasm as revealed by the cytologists or students of the cell.

First of all, the life of a cell may be divided into two stages. One is the dividing stage where the chromosomes become evident, go to the equator, divide and pass off to opposite poles. The second stage follows the division of the cell. The nucleus rounds off and goes into a stage sometimes,

unfittingly, called the resting, sometimes, more properly, the metabolic stage. The relative time spent in these two stages depends upon conditions. In the early development of a plant the metabolic stage is relatively short. Thus in the growing tip of an onion root the metabolic stage of the

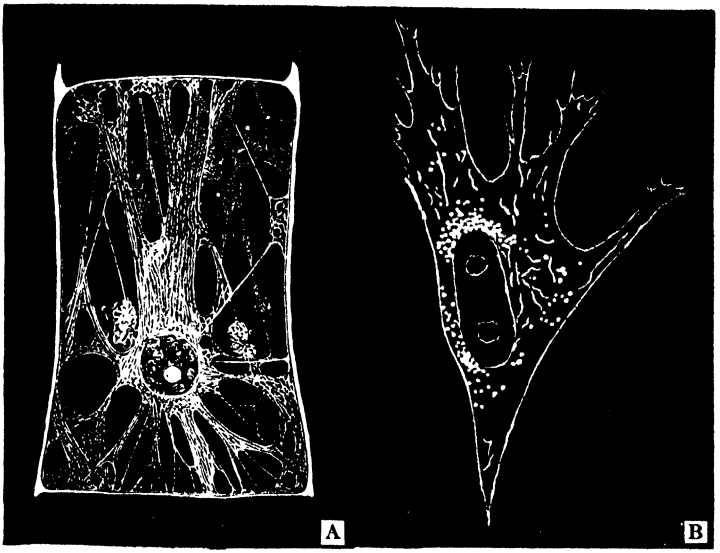


FIG. 143. Living cells as they appear under dark-field illumination. A, cell from hair of squash. The cytoplasm lines the cell and extends in strands through the vacuolar matter; nucleus in lower center. (*After Heidenheim, 1897.*) B, cell from chick embryo in tissue culture. The cell is adhering to the underside of a cover slip. Near the nucleus are numerous fat globules; note also filamentous chondriosomes. (*After Strangeways and Canti, 1927, from Sharp's "Introduction to Cytology," courtesy of McGraw-Hill Book Co.*)

nucleus lasts, at 20° C., about two-thirds of the time (240 minutes) required to complete the cycle from one stage of division to the next recurrence of that stage; i.e., the resting stage is about 160 minutes, or, to express it in round numbers, 10,000 seconds. In the adult, the resting stage is enormously prolonged. The extreme case is that of the

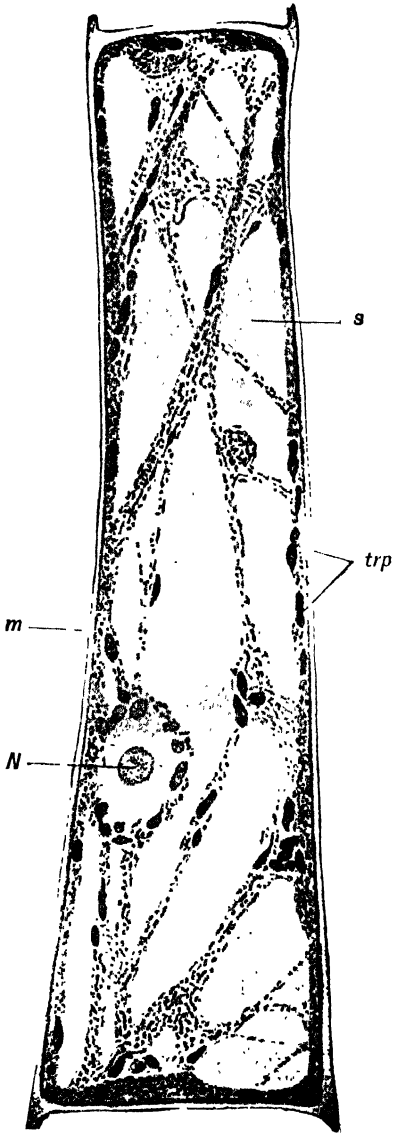


FIG. 144. Living cell of epidermal hair of pumpkin. *m*, cell wall; *s*, cell juice separating the cytoplasm into streaming protoplasmic bars of various shapes containing mitochondria and trophoblasts (*trp*); *N*, nucleus. × 500. To illustrate the accumulation of cytoplasm around the nucleus and the streaming lines of cytoplasm directed toward it. (*After Mavimow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

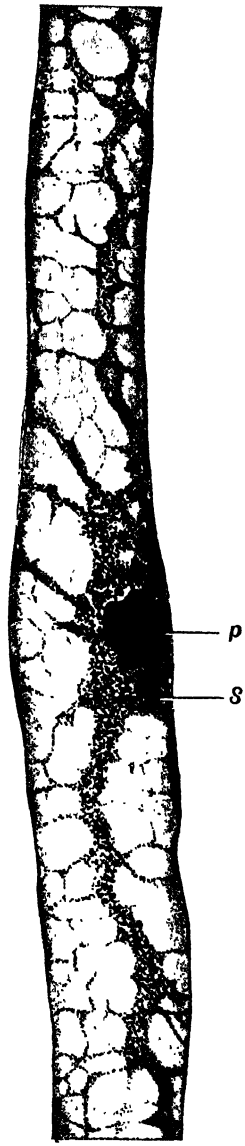


FIG. 145. A nerve fiber from the tail of a cat. *p*, nucleus and *S*, granular cytoplasm aggregated about it. The main stream of cytoplasm seems directed toward the nucleus. (*Redrawn after Nemiloff, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

nerve cells of the adult brain which divide practically not at all. At this stage the cell activities are largely confined to maintenance. The dividing stage is always brief; the resting stage is always longer, may continue indefinitely.

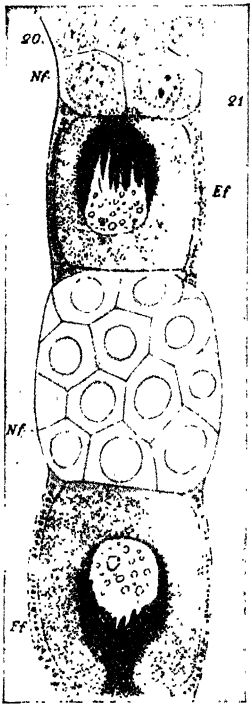


FIG. 146. Two eggs, *Ef*, from the ovary of a beetle with the nutritive cells lying between and above. In the upper nutritive cell group (*Nf*) granules are being richly prepared and passed to the egg cell. The two egg nuclei send processes: one forward (upward), one backward; both toward the dense food granules. (*After Korschelt, 1889, "Morphol. u. Physiol. des Zellkernes."*)

Let us now examine the nucleus at the metabolic stage. The genes that were in the chromosomes have become dispersed. The method of dispersion is shown in Fig. 109. Each chromosome takes up fluid and becomes a vesicle. The vesicles by mutual pressure produce a spherical nucleus. By this process some of the genes come to lie in, and apparently to form part of, the nuclear membrane.

Many figures could be cited that show this. Thus Fig. 110 shows the nucleus of a sea urchin egg. Apparently the genes in the chromatin are all at the surface. Figure 112 shows the staining substance (partly genic) at the nuclear membrane of a spider's sperm cell seen in optical cross section of the nucleus at the resting stage. It appears to form little groups there. In Fig. 113, 2 a spirene is forming; apparently at the nuclear membrane. This membrane occurs at change of phase between the cytoplasm, on the one hand, and the nu-

clear "sap" on the other. The chromatic material is drawing away from that phase boundary (nuclear membrane) to begin mitosis. The diagram (Fig. 113, 1) is, perhaps, faulty in showing so thick a nuclear membrane where the

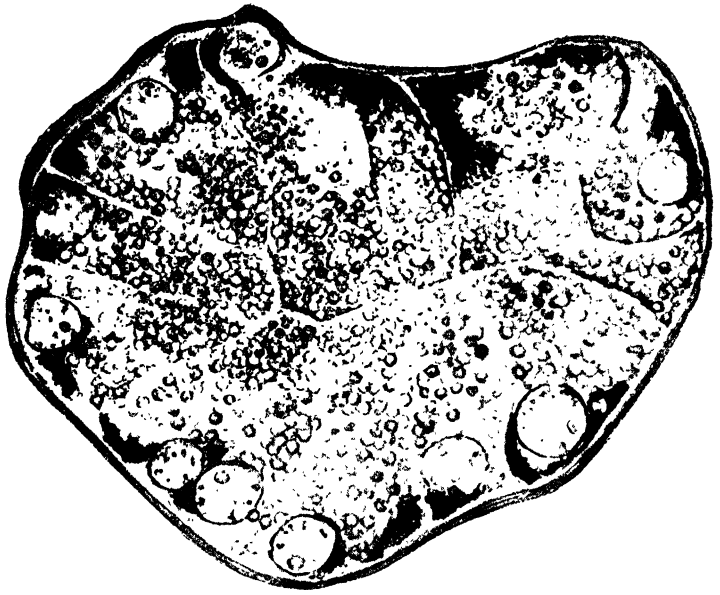


FIG. 147. A cross section of a branch of a human submaxillary gland showing chromophil (color-loving) substance (black) and zymogen granules. Treated with acid fuchsin and toluidene-blue stains. × 1,640. (*After R. R. Bensley, from Maximow-Bloom, with permission of originator, author and publisher, W. B. Saunders Co.*)

chromosomes have begun to form; but in any case the surface tensions at the membrane are soon broken and the cytoplasm surges around the chromosomes (Fig. 113, 6).

During the metabolic stage the nuclear membrane with its crowd of genes is the site of the greatest activity of the cell. This appears from numerous studies that have been made. In Figs. 143, 144, 145 we see the cytoplasmic streams centered on the nuclear membrane.

Great events are going on there. Masses of stuffs are being manufactured. We get some idea of how great the product is by some of the drawings or photographs in which the special materials are brought out by differential staining.

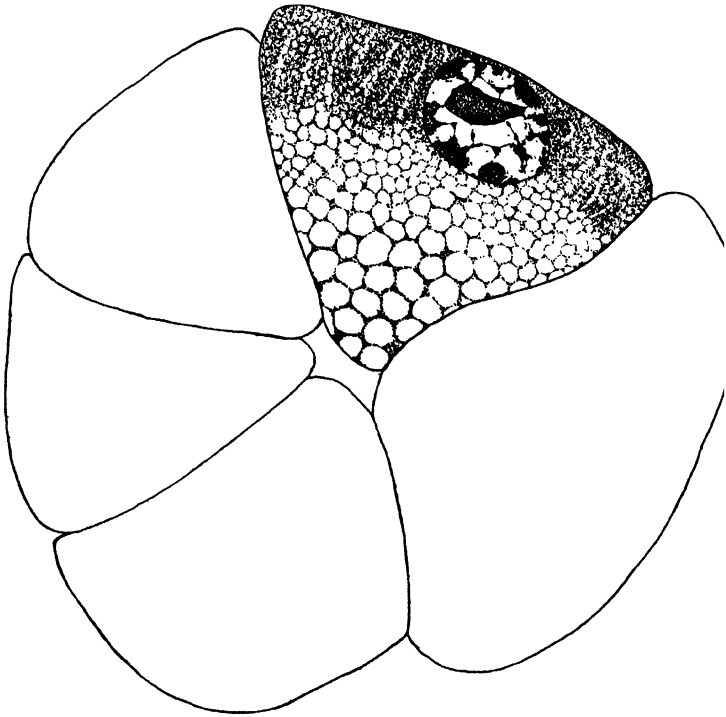


FIG. 148. Section of a branch of the pancreas of a guinea pig showing the homogeneous basophil (base-loving) substance in which the light streaks represent unstained mitochondria. In the central portions are the zymogen-secreting granules. × 1,550. (*Redrawn after Bensley.*)

Figure 146 shows the nuclear membrane of an egg nucleus losing its spherical form and, indeed, sending out processes toward the particles that stream in from the adjoining nutritive compartments.

In Fig. 147 are shown cells of the glands that lie under

the jaw and get more conspicuous when we have mumps. The cells are seen distended with granules ready to be thrown out into the duct. These granules are regarded as zymogen granules (i.e., enzyme producers), the antecedents of ptyalin, the enzyme of saliva that acts upon starch. The nucleus is crowded back in the cell and may show an irregular form. Around the nuclei is a substance which stains deeply with basic dyes, hence is itself acid. It looks as though this base-loving substance is the material which is acted on by the nucleus to produce the zymogen granules. These granules constitute the major part of the cell. They are renewed after each meal and perhaps more frequently. The nucleus must act very rapidly upon the cytoplasm to produce zymogen up to 20 times the volume of the nucleus, inside of about 5 hours or 18,000 seconds.

Figure 148 shows some of the secreting cells of the pancreas. Here again the mass of each cell is made up of enzyme-generating substance. The nucleus at the base of each cell is in the center of basiphil substance. This affinity of the granules around the nucleus for basic stains indicates that the granules, too, are acid.*

Finally may be shown (Fig. 149) the picture of an ovum developing in the ovary. It is at this stage that the ovum is growing rapidly and organizing its cytoplasmic content. Around the young egg is an envelope of follicle cells. They too are hard at work providing stuffs to go into the ovum; stuffs out of which are to be manufactured in time and in complex

* Some insight into the electric potentials of particles in the cell may be gained by the use of acid or basic dyes which are absorbed by or enter into chemical union with particles of an opposite charge. Electro-negatively charged (acid) dyes: trypan blue, Bordeaux red, eosin-blue, light green, blonde Lyon, picric acid, azocarmine, indigo carmine, Scharlach R, echt rot. Electro-positively charged (basic) dyes: methylene blue, safranine, Nile blue sulfate, gentian violet, Janus green, neutral red, methyl green, toluidine blue, azure II, pironin, dahlia, basic fuchsin, thionin.

fashion, and with the aid of the genes, the various tissues of the body. One notes the concentration of stainable materials around the nuclei of the follicle cells, and the concentration of other granules around the nucleus of the developing ovum.

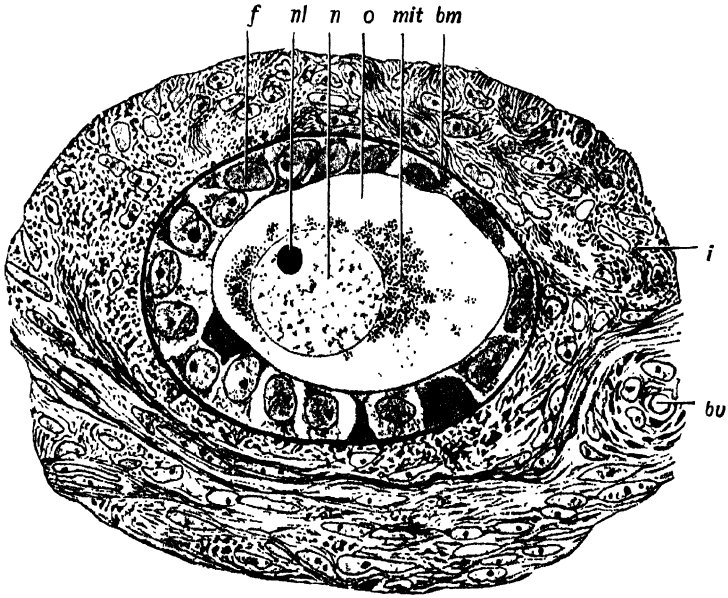


FIG. 149. Follicle in the first stages of growth, from ovary of adult woman: *f*, follicular (nurse) cells with mitochondria; *nl*, nucleolus of ovum; *n*, nucleus of ovum; *o*, cytoplasm of ovum; *mit*, accumulation of mitochrondria around the nucleus; *bm*, basement membrane; *i*, filling connective tissue; *bv*, blood vessel. Structures revealed by acid fuchsin stain. × 780. (*After preparation of C. M. Bensley, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

From these facts and indeed in general from the observations of the most careful cytologists the conclusion seems justified that in the metabolic stage the genes lie in, and form an important element of, the nuclear membrane. Around this membrane the cytoplasmic particles swarm and the opportunity is afforded for enzymatic action.

HOW THE GENES SPEED UP THE ACTIVITY OF THE CYTOPLASM

Various general considerations and especially the facts of reciprocal crosses and the pictures of the metabolic nucleus lead to the conclusion that genes and cytoplasm must interact in individual development.

First of all let us consider the probable nature of the gene. The conditions are these. The gene is a particle of about 1/100 to 5/100 of a μ in diameter (100 to 500 Ångstrom units, as estimated from the bombardment with X-rays). Molecular groups, such as the largest protein molecules, may reach the same size. The molecule of egg albumin with a molecular weight of 34,000 has a diameter about 185 times that of hydrogen, or 185 Ångstrom units, or 1.85/100 of a μ. Many protein molecules have 6 times to 150 times the weight (say 2 to 5 times the diameter) of the molecule of egg albumin. Accordingly the size of the gene is that of some protein molecules, and it seems probable, as we concluded a little while back (page 206) that a gene is such a molecule.[13]

Second, if a gene has a molecular weight of 150 times the molecular weight of egg albumin it would be about 100,000,000 times as heavy as an atom of hydrogen. That would give the gene a weight of about 2/10,000,000,000,000,000(2×10^{-15}) of a gram. So it is quite small. But it is very efficient; for it does its work on a cell that weighs perhaps 1/1,000,000,000(10^{-10}) of a gram and acts during perhaps 10,000 seconds. The gene is not used up in the process. It doubles in anticipation of cell division and each new gene, unchanged, goes on with the work.

Third, the only class of substance that the chemist knows capable of such a performance is the class of catalysts. Catalysts can perform the most marvelous chemical

feats without becoming themselves used up. The German chemist, R. Willstätter, found an organic catalyst which activated 1,000 times its weight of hydrogen peroxide per second to do an oxidizing job. There can be no doubt that a gene is a catalyst. Catalysts are of two sorts, inorganic and organic. The organic catalysts are called enzymes. The gene would be called by a chemist, without hesitation, an enzyme. And some enzymes belong, as John Howard Northrop has shown, to the group of protein molecules.

Enzymes have long been known as ferments. The action of ferments has been known since early man became not only a contemplative animal, but also a bibulous animal. He early learned that the juices of certain plants when exposed to air would undergo a process called fermentation, by which was produced a product which when imbibed considerably elevated the spirits of the user. However, the term ferment is somewhat ambiguous. On the one hand it refers to the organisms which we now know get into the plant juices to produce alcohol from them. On the other hand, the chemist thinks of a ferment not as the organism, but as the substance produced by the organism which reacts upon the plant juices to produce alcohol. These substances, to avoid confusion, are now commonly spoken of as enzymes. Enzymes may thus be said to be organic activators or accelerators of chemical reactions. All fermentation, as of cider or wine, is due to enzymes. Every person who makes bread makes use of the enzymes of yeast to accelerate the reactions in flour. One might even say that the process of development of a child is something like the process of making bread, only much more complicated.[14]

The number of enzymes that have been found in the adult human body is very great. There are nearly 100 enzymes, or groups of enzymes, already known in man, and

these do a great variety of things. Some of them do their work by causing the substances on which they act to gain or lose oxygen. Others cause a shifting of the water radical into different relations in the new molecule. Enzymes form an important part in the manufacture of certain chlorophylls, certain sugars, aldehydes, alcohols, products of pepsin, lactic acids of milk, various black pigments; and these substances play a role in the life processes of the body and in localized metabolism upon which growth of particular parts depends in the development of an organism.

Now, as we have just seen, we have every reason to believe that the genes in the nucleus are enzymes and, indeed, we may believe that at the beginning of development the enzymes are more or less completely confined to the genes in the nucleus. The reason for such conclusion is that the genes of the father seem to play the same role in controlling development of the young as do the genes of the mother. Yet the father's contribution in the sperm contains few substances outside of the nucleus (page 166).

If we examine the sperm cell under the highest power of the microscope we find a body with a structure such as is shown in the Fig. 114. If we look at this figure carefully we shall find in the head no such microscopic human body as did the speculators of two centuries ago. We find, on the contrary, a head which contains almost exclusively the nucleus. Also, a long tail which possesses a contractile thread but which sometimes does not enter the egg at fertilization. Connecting the head and tail is a neck which has certain particles which do indeed not belong inside of the nucleus, but play an important part in the division of the nucleus. But of yolk particles like those of the substrate (see page 167) upon which the enzymes act we find practically nothing at all. The sperm, therefore, brings in

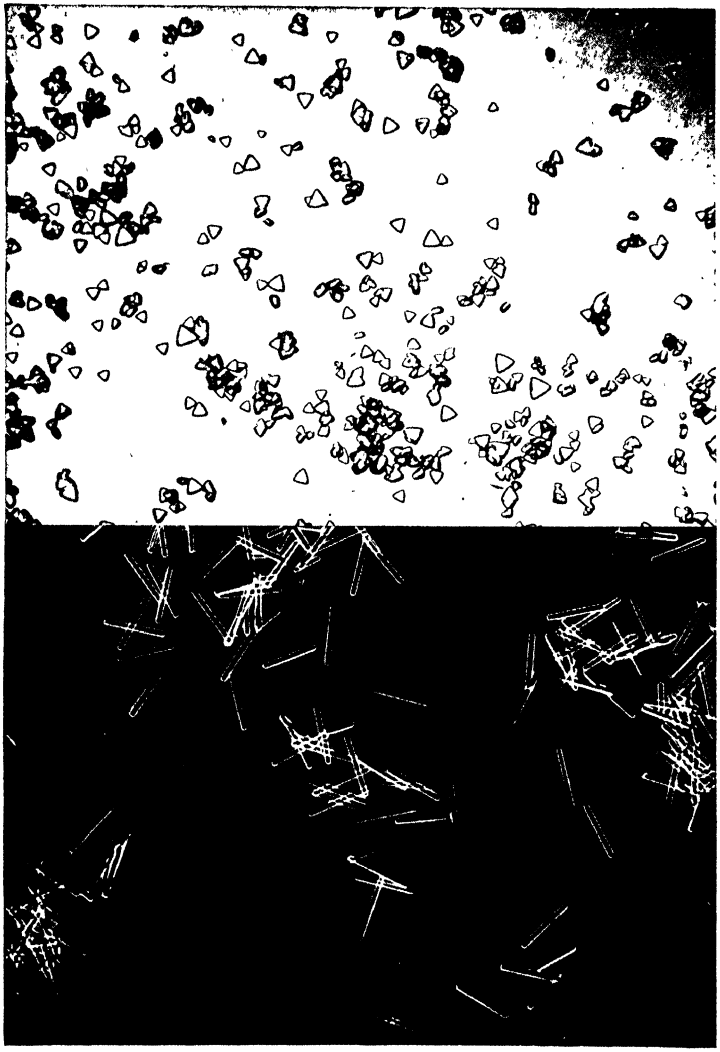
almost exclusively the enzymes. In coming into the egg it merely adds its quota of enzymes to that already possessed by the egg.

Since the sperm adds no new materials to the egg plasma why is it, if the egg is already provided with a full quota of enzymes, these enzymes do not proceed to act upon the substrate and begin the development of the new individual? Why the human egg is not capable of independent development nobody knows. The eggs of some of the lower vertebrates are capable of developing without the entrance of the sperm nucleus. Even eggs which ordinarily wait for the entrance of the sperm may (as in the case of the frog) be incited to begin development by chemical or even physical stimulation. Evidently the entrance of the sperm into the egg in some way overcomes an inertia or inhibition. It certainly doubles the enzymatic activity.

The enzyme catalyst is produced only in living cells. It is commonly found in living cells, though it may be thrown out from living cells into the body. Thus there are enzymes in the milk which come from the cells of the milk gland. Similarly there are enzymes floating in the food canal which have been derived from cells which throw their products into the food canal. Enzymes then are inseparable from vital processes. They have never yet been produced in test tubes; although, of course, one would not dare say they never will be.*

Any enzyme does its work by accelerating some particular chemical process in materials with which it is in contact. The materials thus acted on constitute the substrates.

* A more concrete idea of an enzyme will be gained by looking at Figs. 150, 151. These show above crystals of trypsinogen from pancreatic juice. This substance has no enzymic action. But if it comes in contact with even a trace of juice of the intestine called enterokinase (which acts like an enzyme) it becomes itself extremely active as the enzyme trypsin.



FIGS. 150–151. Fig. 150 (above). Crystals of the zymogen trypsinogen which is produced in the pancreas and is inactive. But when in the intestine it comes in contact with enterokinase it becomes the intensely active enzyme trypsin (Fig. 151, below). (*Courtesy of Dr. J. H. Northrop.*)

For the gene as enzyme the cytoplasm constitutes the substrate. The processes activated are specific. One kind of gene can accelerate only one kind of chemical process that is going on in the substrate. Such a process cannot be accelerated in the absence of a suitable gene. If not accelerated it will probably fail of accomplishment in the rapidly moving events of development.

The exact way by which the genes do their specific work in each cell is still not precisely known. However, the problem is fundamentally that of catalytic action in general. Accordingly, we can use the best thought of physical chemists as to catalytic action to develop a reasonable hypothesis.

We have already seen evidence that many, if not all, active genes lie in the nuclear membrane (Figs. 146–149), and that the cytoplasm is carried to the nuclear membrane which is the center of chemical activity (Fig. 149). In Fig. 152 I offer a diagram on a huge scale suggesting in detail the activities going on at the nuclear membrane. At A the streaming protoplasm is carrying particles to the nuclear membrane; other particles, at B, are carried away.

In the figure are represented three genes, *x y z* in the nuclear membrane having the specific key-notch form suggested by a leading student of enzymes, Emil Fischer. The theory is that the gene particles have a charge which in the example is assumed to be negative. Positive particles in the cytoplasm (*a*) are attracted but only those that fit the key notches of the catalyst (*z*) come into union. After the union there may remain a residual positive charge. That will attract the negatively charged particles of the cytoplasm (*b*) and those that fit unite with the positive (+) particle and neutralize it or give it a residual

negative (−) charge. There is thus repelled from the gene the new molecule, *ab*, altered, we may assume, in form

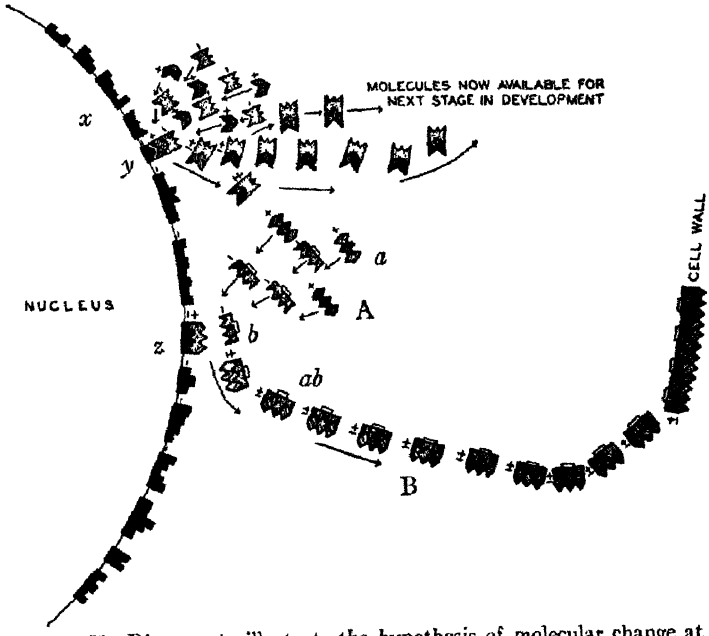


FIG. 152. Diagram to illustrate the hypothesis of molecular change at the nuclear wall. The particles (genes, by hypothesis) which make up a large part of the nuclear membrane are supposed to be carrying a weak negative charge. They have, following E. Fischer's theory of enzyme action, specific form. Ions, positively charged, move toward them, and may form chemical union if of suitable conformation. The resulting combination has still a weak residual positive charge so that ions with negative charge and appropriate conformation may unite with the first molecule. The charges are satisfied and the neutral molecule may join the stream that carries such molecules to the cell wall, to help build it.

In similar fashion, under the influence of another gene appropriate molecular unions may occur which may not be utilized now but may become available for the next stage in development.

from either of the parent molecules. It may be of a zymogen class. The gene *z* is now ready for a repetition of the process.[15]

The whole process goes on with enormous rapidity; probably one or more thousands of the zymogen particles being formed in a second. Assuming that 1,000 particles are produced in one second and that each zymogen particle has the diameter of 5/1000 μ, the particles produced in a second would fill the space of $\frac{1}{8}$ of a cubic μ. In the period of $2\frac{2}{3}$ hours or, 10,000 seconds, then would be produced 1,250 cubic μ. This amount would fill a fair-sized cell, yielding perhaps as much substance as is shown by the granules in a single cell of Fig. 147.

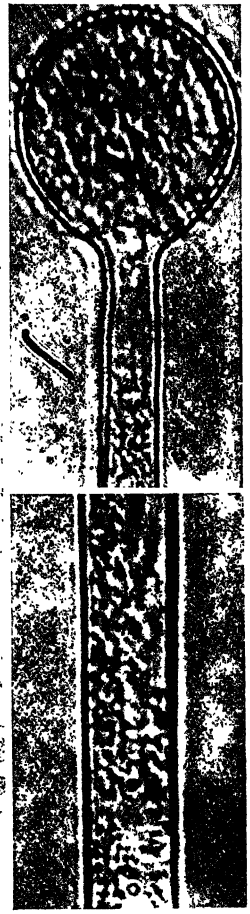
It may well be that two dissimilar genes are active at the same time, as is indicated at *y* and *z* in Fig. 152. But the two genes are accelerating different chemical unions, making different substances in the cell. Most of the kinds of genes, like *x*, are, at any moment, not active. The above illustration fits the specific case of a secreting cell, pouring its products into ducts or blood vessels.

The case of cells that are growing and building up the cell body by adding new organic particles or micellae is no different in principle. The different materials that go to make up a muscle cell or nerve cell are manufactured from available materials with the aid of enzymes that play a specific role, as most enzymes do. Complex molecules are being constantly built up and probably break up as protein molecules appear to do, when they reach a certain size (page 210). By regeneration of the molecule two full molecules will exist where one was before.

The processes by which a cell organ is built up are perhaps best illustrated by looking at the tip of a growing cotton fiber as worked out by Dr. Wanda K. Farr, at the Boyce Thompson Institute, in collaboration with George L. Clark, chemist at the University of Illinois. Figure 153 shows the tip of the fiber, magnified 1,020 diam-

153

154



155

FIG. 153. Tip of a cotton fiber showing the minute ellipsoidal particles forming in chains in the middle and moving to the cell wall to increase its length and thickness. These particles are cellulose and have been regarded by some chemists as giant molecules of that substance. × 1,020. (*Courtesy of Wanda K. Farr.*)

FIG. 154. A bit of cotton fiber some distance behind the tip showing the chains of cellulose particles that go to strengthen the cell wall. × 1,495. (*Courtesy of Wanda K. Farr.*)

FIG. 155. Developing spore-bearing stalk of the vinegar fungus showing increasing thickness of the cellulose cell wall in the lower portion. Polarized light. × 1,700. (*Courtesy of Wanda K. Farr.*)

eters. One sees the swarming cellulose particles and sees them arranging themselves to form the cell wall, possibly under the influences of electronic forces. Figure 154 shows even more clearly the particles forming the cell wall. Figure 155 shows how the cellulose wall of the spore-bearing thread of a fungus thickens by the addition of more cellulose particles. The particles are about 4,000 Ångstrom units in length.

As remarked, it is one of the striking qualities of organic catalysts that their action is specific; that each accelerates (or initiates) only a specific chemical reaction going on in the environing material —called the substrate. If the genes are the principal catalysts that direct development it follows that any one kind of gene can do its job only as the cytoplasmic set-up (substrate) affords it material for chemical processes which it is to accelerate. As soon as this material is exhausted that particular gene ceases to function at this time. There is now a different chemical set-up in the cytoplasm. Further chemical change will depend upon the presence of some other gene capable of accelerating (or initiating) it. For example, if cellulose exists in the substrate it will be hydrolyzed in the presence of water and the enzyme cellulase, producing cellobiose. The enzyme (gene ?) cellulase can no longer act after all the cellulose is transformed. But if there be present the enzyme cellobiase, that can act upon cellobiose, producing glucose. Once the cellobiose is all transformed into glucose, the cellobiase is, as it were, put out of business. If, however, the enzyme maltase is present it acts upon the glucose, accelerating its transformation to starch. After this transformation is complete the maltase is no longer used but if the enzyme amylase be present the starch in water can be transformed to *X*-maltose or *B*-maltose, depending

upon the particular form of amylase, *X* or *B*, that is present.

This series of reactions can be expressed diagrammatically thus:

Enzymes:	*Substrates*
	Cellulose
1 cellulase	↓
	Cellobiose
2 cellobiase	↓
	Glucose
3 maltase	↓
	Starch
4 amylase	↓
	Maltose

The foregoing is an illustration, merely, of the successive action of a series of enzymes upon the substrate. It illustrates the way in which a set of hundreds of genes may (if we assume them to be catalysts) act differentially (although all are present in every cell) owing to a differentiation in the cytoplasm. This hypothesis satisfies the need for a *cellular set-up that shall produce a particular kind of cell content—a particular tissue—at a particular time. Thus an essential feature of the developmental process would be provided for.*

DEGREE AND VELOCITY OF SPEEDING UP

The products of each cell are determined by the reaction between one or more of its genes and certain elements in the cytoplasm. Now it is a law of catalyst action that the velocity of the reaction varies with the enzyme concentration. Accordingly, the more numerous the active molecules in the nucleus the more swiftly will its work be done.

Now the genes in the nucleus are ordinarily paired, since one set of genes comes from the sperm and one from the egg. But if any unit in the gene complement is different in the paternal and maternal chromosomes, as happens when the parents show racial differences, then such gene will be single instead of paired in the developing child. When this is so the particular trait that depends on the presence of this gene will develop more slowly and incompletely than when the gene is paired. Thus, in eye color, the pigment of the iris appears shortly after birth in the case of pure-bred South Italian children. But in a child of Nordic origin the eyes are for some months blue, even if one parent is brown eyed, and the brown pigment, if any, forms late, slowly and imperfectly; the child eventually has light brown or hazel eyes.

A good illustration of the effect of genes that vary both in number and vigor is given in a study of the gipsy moth made by Richard Goldschmidt of Berlin. Here the moth becomes a female if there is present only one set of the genes that determine sex (those of the *X*-chromosome). It becomes a male if there are two sets. The *XX*-genes produce a male; the *X*-gene produces a female. But races of the gipsy moth differ in the strength of their sex-determining genes. If the mother belongs to a race in which the sex gene is weak while the father belongs to a race in which it is strong, then the female which gets its (strong) gene only from the father will receive an *X*+ gene and will go beyond the ordinary *X* (female) condition toward the *XX* (male) condition. That is, the *X*+ gene starts out to produce a female but, under the stimulus of more or stronger *X* stuff, it begins to develop male characteristics and begins the earlier and goes the faster toward maleness the stronger the *X* stuff derived from the father is.[16]

Also, in other species, in which maleness depends on X and femaleness on XX, if by accident the female gets a third X it becomes a super-female, at least if the rest of the chromosomal garniture is normal in amount. If the rest of the chromosomal garniture is triple (instead of the normal double) while the X-genes are only doubled then the individual fails to achieve normal sex and becomes of intermediate sex.

These illustrations will serve then to enforce the general conclusion that the rate of development and the size the organ eventually achieved vary among other things with the amount of vigor of the catalysts in the nucleus.

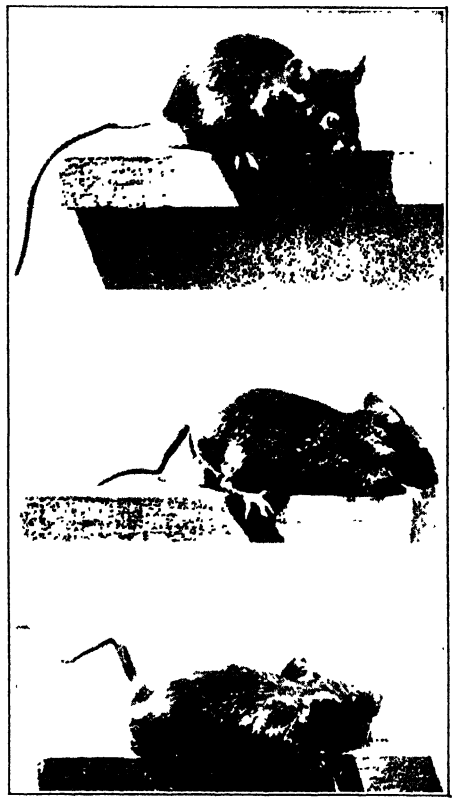


FIG. 156. Flexed-tailed mouse. The tail is shortened and tends to form a spiral at its base. (*Courtesy of H. R. Hunt.*)

BEGINNINGS IN THE DEVELOPMENT OF A TRAIT

When we first observe the development of a trait in a child we are apt to think of the trait as having just been formed. But usually this is not so. The beginnings may go

far back toward the beginning of embryonic development. Thus the number of fingers or toes is not first determined as the fingers are arising from the paddle at the tip of the appendage, but the beginnings were laid probably before the appendage had begun to develop.

The principle is well illustrated by the case of the flexed tail in certain mice (Fig. 156). The flexed tail looks like a slight thing. It would scarcely be noticed by one unfamiliar with mice. The flexed tail may be very short and badly bent; or it may be little affected. Yet it proves to depend on changes that arose early and were of a fundamental nature in the mouse development. Thus the discs between the tail vertebrae are abnormally wedge-shaped instead of being flat pads. The vertebrae develop abnormally. Indeed, at the stage when the notochord—earliest embryonic representative of the vertebral column—is forming, this shows irregular swellings (Fig. 157). This results in a shorter axis than normal in the region where the tail is laid down. The embryo thus develops badly from the very start.[17]

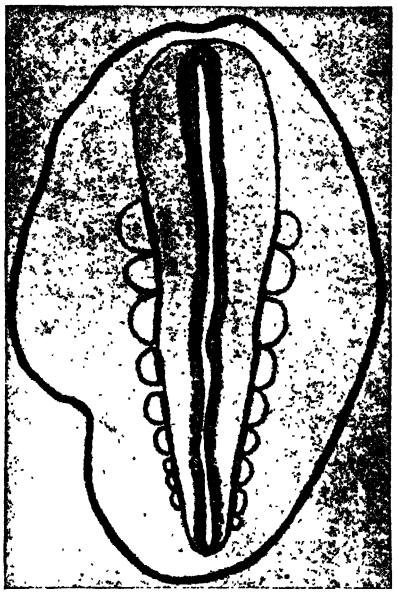


FIG. 157. Diagram of frontal section through neural tube of 15-day-old flexed-tailed embryo, showing the irregular waves of the walls of the nascent spinal cord. The semicircles on each side represent the primitive muscle masses (myotomes). (*After Kamenoff, 1934.*)

This is a single example. It is probable that most marked bodily characters show their beginnings in the first few days of development. If we knew enough they might appear in the very cytoplasm of the egg cell before fertilization. There is a gene peculiarity also; however, the gene peculiarity cannot be seen but its effects will be seen as the affected organ develops.

In general, traits of adults are often a by-product of developmental processes that have an unsuspected meaning. To understand a trait, especially a new or abnormal trait, seek its earliest stages.

NOTES

1. Herbert Spencer's speculations are published in his *Principles of Biology*. August Weismann's theory of the chromosomes was fully developed in his book *Das Keimplasma*. W. L. Johannsen introduced the term "gen" in his *Elemente der exakten Erblichkeitslehre* (genetics). Morgan's first general exposition of his investigations with Sturtevant, Muller and Bridges is set forth in their book, *The Mechanism of Mendelian Heredity*, N. Y.: Holt & Company (revised ed., 1923).

2. Mendel's paper was first published in the Proceedings of the Natural History Society of Brünn, in 1866. The paper has been reprinted in English by Bateson in his *Mendel's Principles of Heredity*, 1909 and 1930, and by W. E. Castle (1916) in his *Genetics and Eugenics*.

3. Heredity of human eye color as a Mendelian character was worked out by C. C. Hurst and by the author and Mrs. Davenport in 1907. (See Science, Vol. 26, p. 589.)

4. The extraordinary chromosomes of the salivary glands of flies have long been known, but their significance has only been recently brought out in this country by Theophilus S. Painter of the University of Texas, by C. B. Bridges of Pasadena, California, and by M. Demerec of the Carnegie Institution at Cold Spring Harbor. See Genetics, Vol. 19, pp. 174, 448 (1934), also Journal of Heredity, 1933.

5. On human chromosomes see T. S. Painter, *American Naturalist*, 1924.

6. A book on *The Gene* has been published by Morgan.

7. Belling's figures of the ultimate structure of chromonemata—the genes or chromomere cores—were first published in the University of California Publications in Botany, 1931. Our figures in the text were taken from the News Service Bulletin of the Carnegie Institution, 1932.

8. On structure of the protein molecule see Ross Aiken Gortner's (1929) *Outline of Biochemistry;* also Meyer Bodansky, 1934, *Introduction to Physiological Chemistry.* On the glucose molecule see George L. Clark in Cold Spring Harbor Symposia on Quantitative Biology, 1934, p. 28; also Mrs. Wanda K. Farr in the same publication, pp. 34–38.

9. The studies of Fritz von Wettstein were published in Bibliotheca Genetica, Vol. X, 1928.

10. The studies on the flax plant by Reginald J. Chittenden and Miss C. Pellew were first published in 1927, in *Nature.*

11. The work on Habrobracon was done by Alfred Kühn of Göttingen and published (1927) in the reports of the scientific society of that city.

12. Castle's results on rabbits are published in the Proceedings of the Nat. Acad. Sci., 1934.

13. On size of gene see M. Demerec, Journal of Heredity, Vol. 24, p. 369.

14. A good summary of our knowledge of enzymes up to the time of its publication is given in J. B. S. Haldane's *Enzymes,* London, 1930.

15. For Emil Fischer's theory of enzyme action see his papers in German periodicals, such as Zeitschrift f. physiologische Chemie, Vol. 26, 1898. See also Alexander and Bridges, Science, Vol. 70, p. 508.

16. Goldschmidt's (1927) *Physiological Theory of Heredity* (Berlin, Springer) is a work of outstanding merit, based upon nearly a lifetime of experimentation and observation on insect genetics in different parts of the world. A. L. Hagedoorn (1911) wrote on genes as autocatalysts in Roux's *Vort äge Entwick. Mechanik, XII.*

17. The history of the flexed tailed mouse has been told in great detail by Paul Chesley (1935), Journal of Experimental Zoology, and by Ralph J. Kamenoff (1934, Columbia University).

CHAPTER 8

THE MASTER BUILDERS

CELL DIVISION

The development of a child starts from a single cell, the fertilized egg. The grown child comes to be made up of about twenty-six trillion cells. The increase is brought about by repeated cell divisions. What makes the cell divide and divide again and each daughter cell divide until eventually some cells cease while others go on developing more slowly? What makes the cell divide at all?

There is some evidence that cell division occurs when the cell gets too big; when disruptive forces of internal pressure exceed those of surface tension. This increase of internal pressure may be due to imbibition of water or to an increase of cytoplasmic particles (micellae). There is some reason for believing that the element sulphur as found in glutathione plays an active part in cell metabolism and by accelerating nuclear growth, expedites nuclear division. There are those who suggest that the sperm brings in sulphur which starts the fertilized egg dividing.

IMBIBITION OF WATER

Water plays a vast role in chemical processes in general and in none more than in those of biology. It doubtless plays a part in cell division; for, as the cells multiply they are kept apart from each other and crowding is prevented by the formation of water spaces between the cells. Thus during the early cleavage of the egg, water comes to occupy

the center of the sphere, as air does the middle of a hollow rubber ball (Fig. 158). There is thus formed a wall, or membrane, of living cells in which future developmental processes will take place. It seems probable that the imbibition of water that makes this hollow sphere is an osmotic effect. That is, pure water enters into the center faster than the central solution can diffuse out.

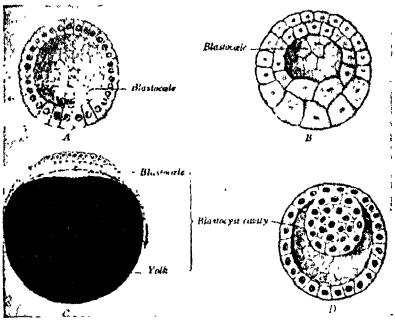


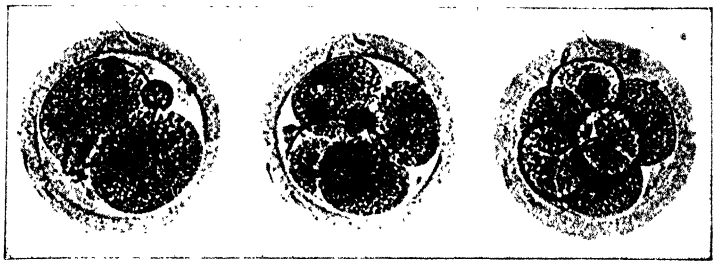
FIG. 158. Stereogram of blastula types in vertebrates. *A*, amphioxus; *B*, amphibia; *C*, reptiles and birds; *D*, mammals. To show imbibition of water. (*From Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

Local imbibition of water plays an important part in causing foldings of membranes, and in opening up spaces in cell masses, as we shall see a little further on.

DIFFERENTIATION

The course of development can be roughly divided into two stages. First the stage in which the cleavage spheres are essentially alike; second, that in which the cells are essentially dissimilar. In man the first stage is probably very short. However, so little is known about the early development of the human egg that we have to go to the lower organisms to learn about this first stage. In the Rhesus monkey the first eight cells derived by three cleavages are practically alike in size and form (Fig. 159). Probably out of one of these cells will arise the entire embryo and fetus. Indeed, it is quite probable that, where the first four spheres are all alike, any one of them isolated may

produce the entire individual. If one of the first eight spheres should be isolated it would ordinarily develop only a little way, if we may draw an inference from the experiments that have been tried in lower forms. Possibly in the human egg, where cytoplasmic materials are pretty uniformly dispersed, one of the first eight spheres does regularly produce the embryo proper, while the other seven go to form the group of cells that help to make a union with the wall of the mother's uterus. In general, the rule may be stated, that isolated cleavage spheres that are capable of developing the entire embryo are undifferentiated, i.e., unspecialized.



A B C

FIG. 159. Cleavage of the living monkey egg, cultivated in plasma and recorded by photomicrographs by Lewis and Hartman. × 225. A, 2-cell stage; B, 4-cell stage shown 8 hours later than A; C, 8-cell stage, 12 hours later than B. (*Courtesy of Carl Hartman.*)

After the eight-cell stage the cells are differentiated so that one alone cannot, when isolated from the others, produce the whole organism. Why is this? It might be because the nuclear gene-complex has become changed; it might be because the cytoplasmic cell contents are different in the eight cells.

Whether the gene-complex changes in successive cell generations is not fully established. What evidence there

is indicates that it does not, ordinarily, change. Thus in the vinegar fly, Drosophila, in cells of the salivary gland many cell generations removed from the egg, the genes seem to be exactly the same as in the fertilized egg. It has been shown, also, that all the genes are ordinarily necessary to each of the developing cells even in late stages, so that if one drops out completely the organism usually dies.

There is evidence that at an early stage of development of some species the cells that are to give rise to certain parts of the body, like the skin, may lose part of their chromatin (stomach worm of the horse; and the fly Sciara). Such cells would seem to be differentiated early as a result of nuclear change. But this seems to be highly exceptional. Indeed, it is probable that the lost chromatin is a rudimentary organ; has lost its usefulness.

If the genes do not, in general, become different in different cells of the developing child then it must be the cytoplasm that becomes different. We have seen (page 175) that even the unfertilized egg is composed of a variety of materials and these are arranged in stratified fashion; that the first division plane cuts through all of these strata; that the second, perpendicular to the first, also cuts through all of the strata. Later divisions, however, produce cells that get different materials from the egg. Indeed, one may predict that particular kinds of cells will arise from particular parts of the egg with its particular preformed substance. This we have already seen to be the case in Ascidians. By the dividing up in qualitative fashion of the cytoplasmic stuffs to the various cells of the developing organism differentiation is brought about. The stuffs thus segregated are not the final cell stuffs but are the stuffs which through many chemical transformations give rise at the appropriate time and place to the final cell stuffs.

Embryonic membranes and their foldings. Because the group of early cleavage cells imbibes water into the center of the group the cells surrounding the vesicle come to form a membrane, or skin, at its surface. We are now talking about a new kind of membrane, different from the nuclear membrane. This is a membrane of cells. It is one of the principal building materials of the embryo. This is readily understood. If you have a four-inch solid rubber ball you can't make much out of it but a rubber ball. But if you have a four-inch hollow rubber ball you can make a lot of things out of it. You can make a double-walled cup out of it. You can make a rough tube out of it by putting your finger in the double-walled cup and folding the edges of the cup around your finger. Your finger lies in the hollow of the tube. Or you can perhaps gather together the edges of the double-walled cup and make a double-walled ball. Now a large part of the early developmental processes by which a child is built up consists of making from a membrane a double-walled cup, a tube, or a double-walled ball.

Or, if you have a piece of sheet rubber you can make many things out of it. You can make a deep depression or cup at one point (by pressing into it with your finger); or you can make a long trough from the sheet (by placing your finger on it lengthwise). You can fold the sheet around your finger and make a tube; you can gather the edges together and make a tobacco pouch or a toy balloon. A flexible membrane is well adapted for making things. And so Nature has found it; and accordingly extensive use has been made of this material; and cupping, folding, gathering is the order of the day, as the embryo develops.

But other things can be done with a flexible membrane. A hole can be made in it. The living membrane can thicken

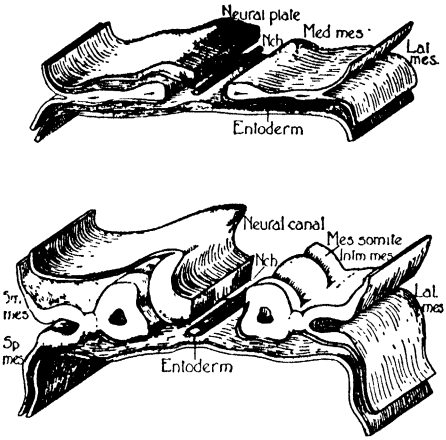


FIG. 160. Sections of solid models of parts of the human embryo illustrating the early changes in the mesoderm. The parts shown are along the mid line of the back (dorsum). The axis (Nch, for notochord) is the precursor of the backbone. Immediately above, the ectoderm is forming the neural plate which becomes transformed into the neural canal, and eventually into the spinal cord.

Between the ectoderm and entoderm is the mesoderm, in which one can distinguish a median and a lateral portion. From the median part arise the primitive muscle masses, myotomes or mesodermal somites (Mes. somit.) as a series of somewhat segregated blocks of cells. These are connected by intermediate mesoderm (Intm. mes.) with the lateral mesoderm (Lat. mes.) which now forms two leaves, a leaf next to the ectoderm which produces the muscular layer of the skin (Sm. mes.) and a leaf next to the viscera (Sp. mes.) which produces, among other things, the muscular layer of the gut. The space between these two layers is the body cavity. (*From Morris-Jackson's "Human Anatomy," courtesy of P. Blakiston's Son & Co.*)

at particular spots and cavities can arise in the inside of the thickened membrane as though the lath and plaster and the wall which it covers should separate from each other. Let us see how these principles are used in the development of a child.

Figure 158, *D* (like Fig. 11, B), shows the human egg with a cavity in the middle and a thickening of the wall above. Two cavities will arise in this thickening. From the roof of the upper cavity is formed the double embryonic protecting membrane (Fig. 11). From the floor of the upper and the roof of the lower cavity the embryo child will arise. And one of the first events occurring in this floor of the upper cavity (the outer ectodermic layer), is a groove at its bot-

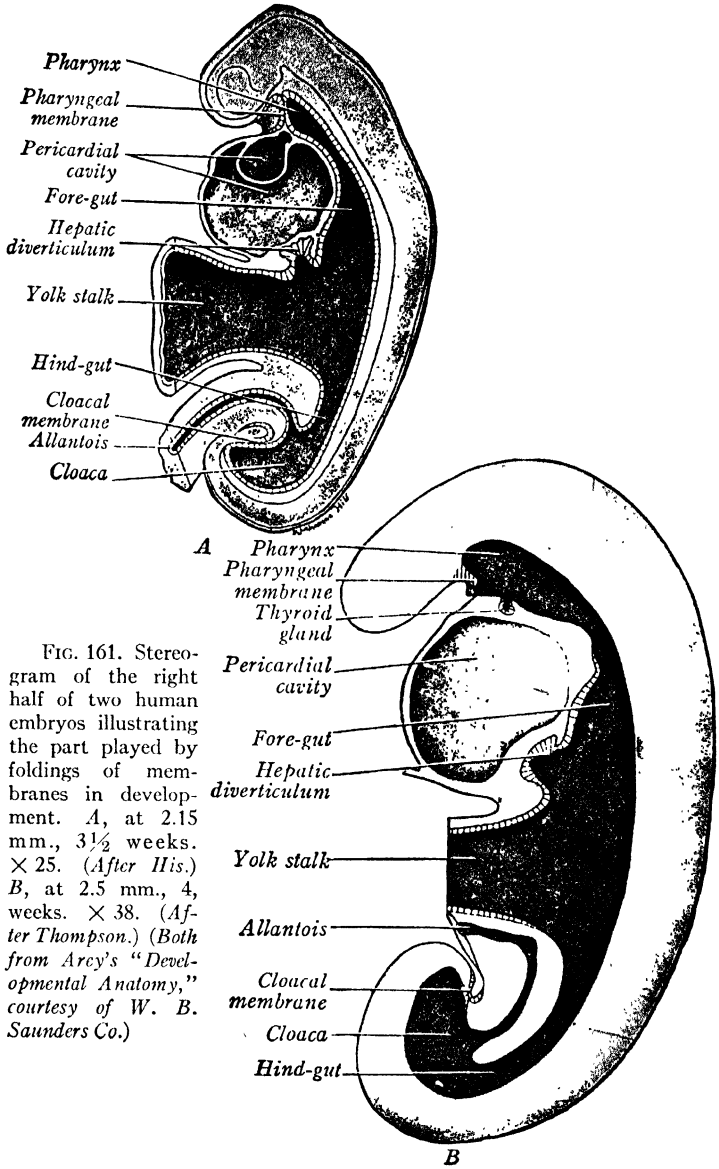


FIG. 161. Stereogram of the right half of two human embryos illustrating the part played by foldings of membranes in development. *A*, at 2.15 mm., 3½ weeks. × 25. (*After His.*) *B*, at 2.5 mm., 4, weeks. × 38. (*After Thompson.*) (*Both from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

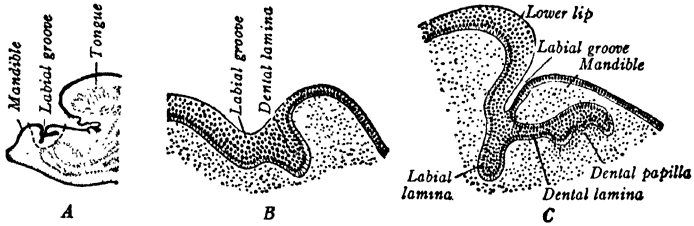


FIG. 162. Formation of the layers of the lips and tooth germ, shown by sections through the lower human jaw. *A*. Sagittal section, at 9 weeks, to explain the areas included in *B* and *C*. × 10. *B*. Lip-tooth layers at 7 weeks. × 10. (*After Rose.*) *C*. Detail at 9 weeks of the area in *A*, set off by a broken line. × 45. (*After Rose.*) (*Both from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

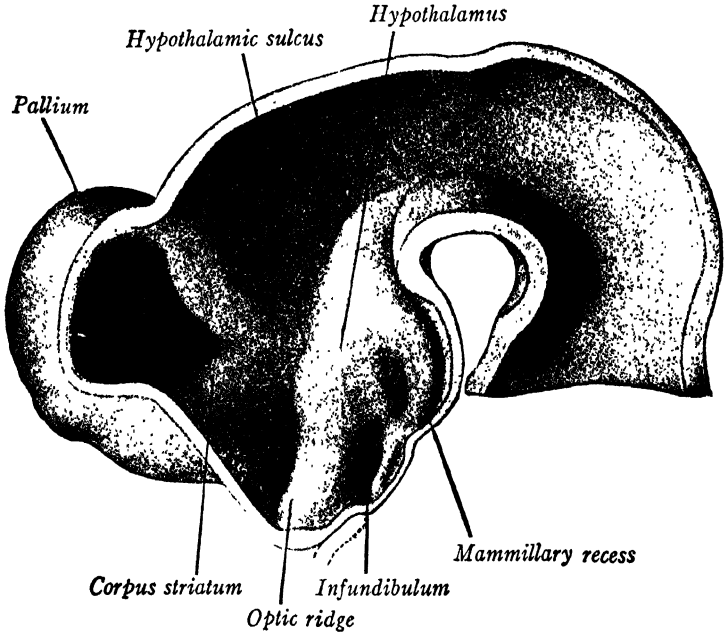


FIG. 163. Median section of the fore and mid brain of a 10 mm. (6 weeks) human embryo, looking into the right half. To illustrate the part played by foldings of membrane. (*After His, from Arey.*)

tom corresponding to the future axis of the embryo (Fig. 160). This is made by a fold in the floor.

A little later the outer embryonic cell layer, or membrane, continues to down-fold ever deeper in the middle line, and the top of this groove closes in to make a tube (Fig. 21). Thus the brain and spinal cord are laid down. The important part that the foldings of membranes play even in later development is indicated in Figs. 161 to 165. See also Fig. 80.

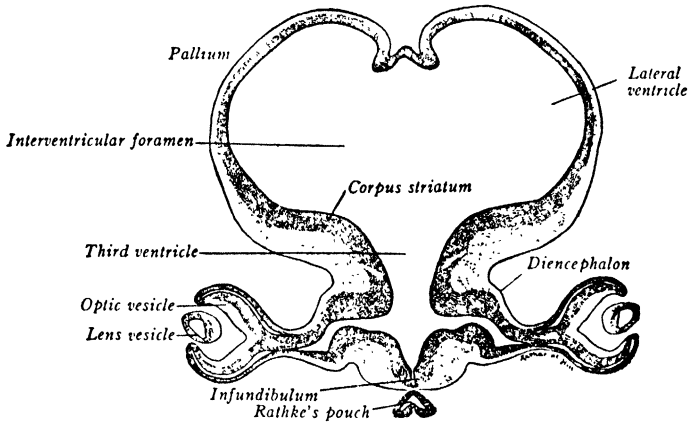


FIG. 164. Cross section through the brain of a 10 mm. (6 weeks) human embryo, at the level of the eye stalks and infundibulism (posterior pituitary); to show foldings of membranes. × 61. (*After Prentiss, from Arey.*)

How does the membrane fold? If we look at a folding membrane we shall find that in the cells that are to enlarge and fall out of the general level of the membrane the nuclei tend to move to the deeper part of the cell. This then becomes the center of activity. This part of the cell becomes enlarged and the resulting wedge- or pyramid-shaped cells tend to slip behind (Fig. 165). At the deeper level there is probably a differential imbibition of water or accumulation of products of cell activity that causes the enlargement.

The cause of local imbibition of water is not certain, but in general depends on a well-known group of organic reactions. Many colloids (i.e., non-crystalline substances, like white of egg) such as are found in embryonic cells are lyophilic (dilute-solution lovers) and tend to imbibe great quantities of water, with change of acidity.

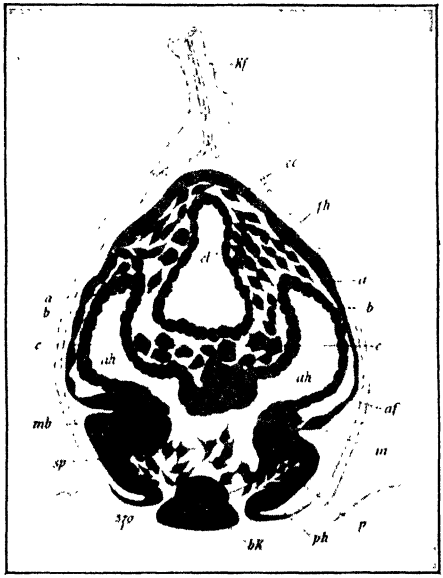


FIG. 165. Cross section of embryo of the tunicate, Salpa; showing the role of spaces and foldings of membranes and migratory cells in development. For our purposes the letters may be disregarded. (*After Heider.*)

In other cases a membrane, or two membranes at point of contact, may get thinner so that finally a hole is made. For example, the mouth cavity is made by infolding of the embryonic skin; this pocket comes to touch the wall of the primitive gut. The two walls gradually get thinner where

they meet, until an opening is made in the region of the back of the mouth (Fig. 161). When contact has been made, no further growth occurs and as the embryo grows larger the membrane stretches until it breaks. Possibly more active agencies are at work causing an absorption and eventual rupture.

THREADS AND TUBES

The body contains many organs that grow out in thread-like fashion. Such are the nerves and the blood vessels. Nerves arise from certain cells of the primitive spinal cord (Fig. 166). These cells give rise to neurons with long nerve fibers. Such fibers go to the skin and sense organs on the one hand, or else to the muscles on the other. An interesting question is: How do the nerves find their way to make the proper attachments? Thus from the lower neck region nerves extend to the upper limbs to supply their muscles. How did they originally find their way there from the spinal cord? Or was there a nervous connection, as some maintain, from the time the limb bud arose? The latter hypothesis is not necessary. It has long been known that if in the embryo a nerve is cut a new nerve will grow out from the old stump and will make its way to the organ that its predecessor supplied. Even if a limb be removed from a salamander larva before nerves have grown into it and be reimplanted four or five segments (metameres) behind its original site the nerves which ordinarily go to that limb will go to it even though in doing so they have to grow back four or five segments. But if the transplanted limb be older, so that nerves have already entered into it, then the reimplanted limb will receive nerves from four or five segments behind those whence come the nerves that ordinarily supply the limb. But in both cases the nerves that grow out

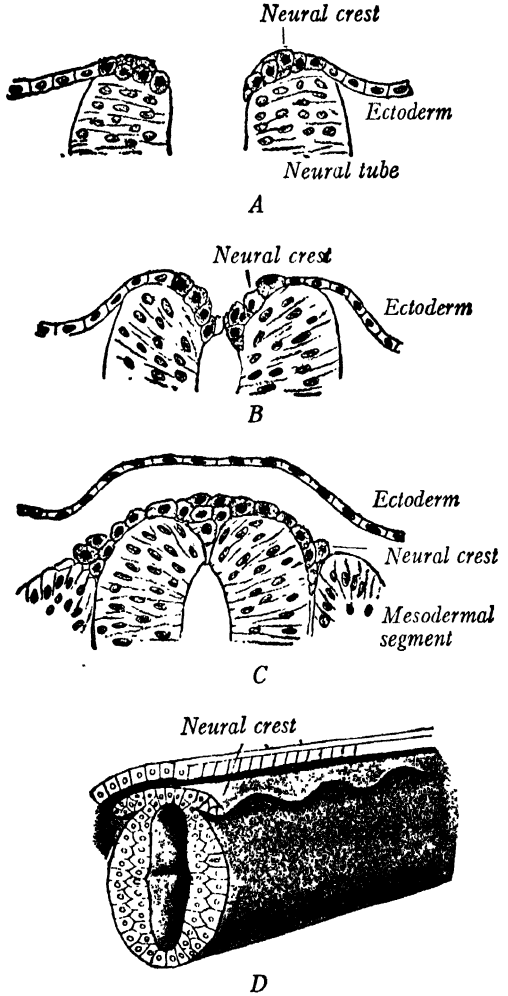


FIG. 166. Drawings and models showing the development by foldings of the neural crest in human embryos. *A–C*, transverse section of 2.5 mm. (28-day-old) embryo. (*After Leubossék.*) *D*, Stereogram of the early spinal cord and beaded neural crest. (*Kingsley.*) (*Both from Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

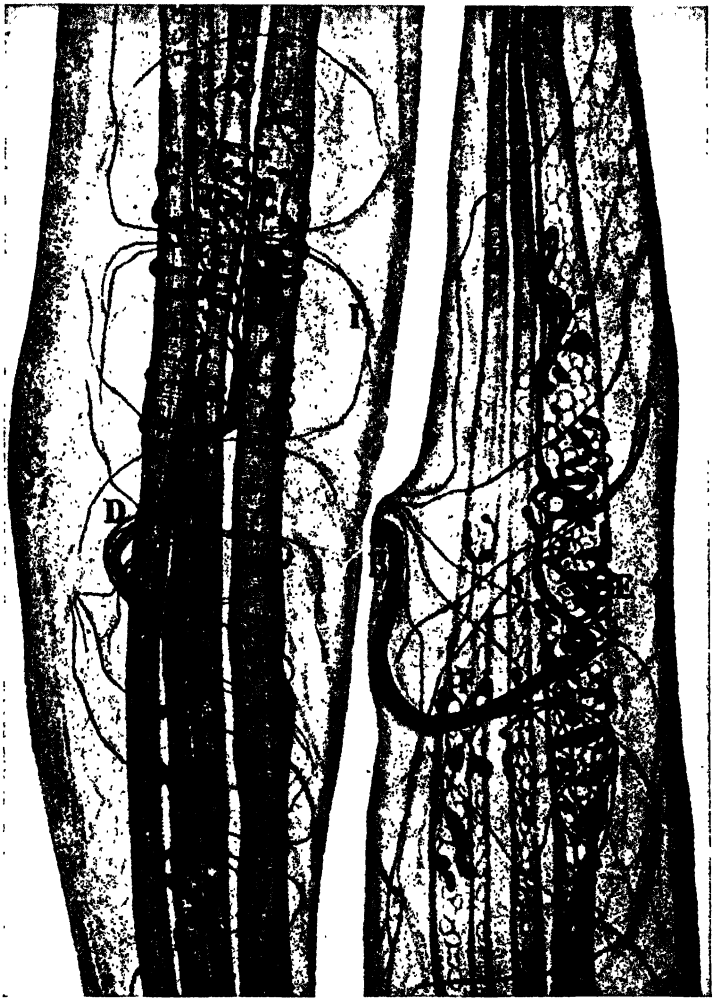


FIG. 167 The union of nerve and muscle in a human fetus of 6 months. A, a large fiber which sends out ramifications like claws at G. B, a fiber which ends at E in ivy-leaf-like expansion. C is the connective tissue covering of the muscle. H, muscle fibers. I, fine nerve fibrillae. (*After Tello, from Ramón y Cajal's "Histology," courtesy of Williams & Wilkins Co.*)

from the spinal cord find their way to the young muscles of the limb and attach themselves to these muscles, so that the muscles thereafter move normally. How intricate that union of muscle and nerve is is shown in Fig. 163. In the case of certain nerves, as of the lower limbs, the end of the nerve must grow out and travel down considerable distance to get to the end of the limb. Reaching there it must make appropriate connections with the muscles already developed and then send out branches to other muscles as the toes are formed. Marvelous is the attraction between a particular nerve and the muscle that it has to supply (Fig. 167).[1]

The blood vessels begin to form toward the end of the first month of development as elongated blood spaces on each side of the body. A pair of these blood spaces unite below to form the heart. Fine blood spaces appear in the upper and lower limbs as soon as they begin to bud. As the limbs elongate and their muscles become larger, certain strands of the network become definite tubes to carry the blood to and from the tissues. Some of the minor strands give rise to the smaller blood vessels; other minor strands fade away. From the very method of origin of these minor vessels out of a network, just which elements of the network shall become permanent is uncertain and in the adult the minor blood vessels are, as might be expected, extremely variable. Indeed in the smaller vessels the network condition still persists in the adult; and this is very fortunate, for if a vessel going to a tissue becomes clogged up by some accident the blood can still reach the tissue by a new route. Indeed, some of the medium-sized blood vessels may be artificially closed, as happens in many surgical operations, and new courses for the blood will soon be established.

Thus nerves and blood vessels find their way to the tissues they are to supply by quite different methods: One

apparently by virtue of a directive influence emanating from the organ which is to receive the nerve (as bees are lured to flowers); the other by a sort of struggle among the elements of a network by which the more successful elements become main vessels or principal branches.

The role of gene-cytoplasmic interaction in these cases is somewhat uncertain. Doubtless such interaction determines the quality of the nerve cell and its organs; its axial fiber, and the sheath that surrounds the fiber (Fig. 34). The main body of the nerve cell is sometimes seen to be crowded with fibers, just as the telephone wires concentrate at the telephone building in a city, and especially at the exchange switchboard (Fig. 36). Since the energy of nerve transmission is electrical, these fibers doubtless behave as telephone wires do to carry electrical waves or impulses. The gene-cytoplasmic interaction yields the substance for fibers. Probably some electronic forces arrange the particles of this substance end to end so that the fibers grow in length. Probably also the genes determine the sensitiveness in reactibility of the neuron.

In the case of blood vessels the gene-cytoplasmic reaction doubtless determines the production of elastic fiber and muscles in the cells of the wall of the vessel. In the heart these muscle cells become striated (Fig. 168). The nature of this striation is still a mystery.

Still a second system of vessels or spaces in the body carries lymph throughout the body. This system starts as large spaces between the membranes of the embryo; gradually the spaces narrow, become better defined and gain walls of their own. The process is something like that of blood-vessel building, but even less definite. From existing lymph vessels cells, singly or in groups, may form new fine vessels by a sort of budding process. This is a response on the part of

FIG. 168. Section of human heart muscle, showing discs lying between separate muscle cells. × 450. (*After Heidenhain, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

migratory cells to the demand of certain tissues from lymph vessels. The responsiveness is probably determined by genes.

TRAMP CELLS AND THEIR MIGRATIONS

Very early in the history of folding of the young membranes, loose cells (mesenchyme) are detached from the

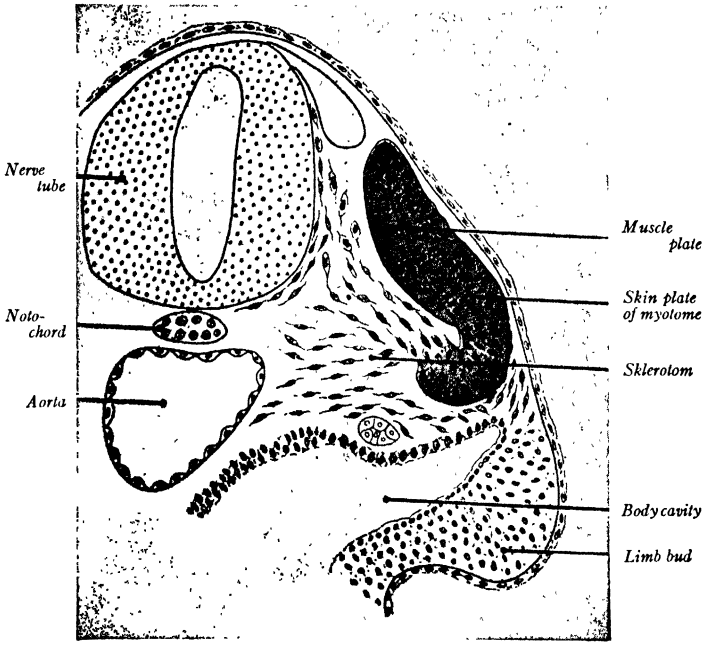


FIG. 169. Cross section through a human embryo of the third week taken at the level of the upper extremity. The nerve tube is seen above, closed; below it, the notochord and then the main blood vessel. At the right is one of the primitive muscle masses (myotomes) and to the left of it numerous migrating cells ("sklerotom") on their way to start forming the skeleton; especially the vertebral column. (*From Kollmann's Atlas. Courtesy of G. Fischer, Jena.*)

membranes to go wandering through the body spaces (Fig. 169). These are to give rise to the connective tissues,

such as fibrous tissue, cartilage and bone, to the blood vessels, to the smooth muscle cells which surround vessels, to the small lymph vessels. The mesenchyme cells seem to be free to migrate in all directions; actually they proceed rather definitely to the work that is allotted to them in the production of their respective tissues. For example, as shown in Fig. 169 they come to surround the spinal cord, brain and chorda to form the vertebrae. These cells penetrate between skin and muscles to form blood vessels.

How do they find their places? That is one of the puzzles of development. We cannot doubt, however, that these migratory cells are acted upon by the regions to which they have to go; that they migrate to them as surely as a sperm cell to an egg or as a dog to his master. Some of the work that these migrating cells do is marvelous. One job is done as follows: In one of the Tunicates (a group lying at the root of the vertebrate phylum) that lives floating free at the surface of the sea, long chains of individuals are attached to a long runner, or stolon, something like a strawberry runner. However, these individuals do not arise from the stolon as the buds on a strawberry stolon do. They start on their career by budding off from a runner on the belly of the parent. And therein arises a problem; for the stolon upon which the buds are to develop further and from which they are to receive their nutrient lies far away on the opposite, or dorsal, side of the parent (Fig. 170). How are the buds to be transported, while still more helpless than a newborn babe, over the body of the mother to their permanent home? Each bud is, as a matter of fact, transported by two migrating cells precisely as ants may convey the carcass of a cockroach to their home, by pulling it concertedly in the right direction.[2]

This well-directed action of the migrating cells is seen

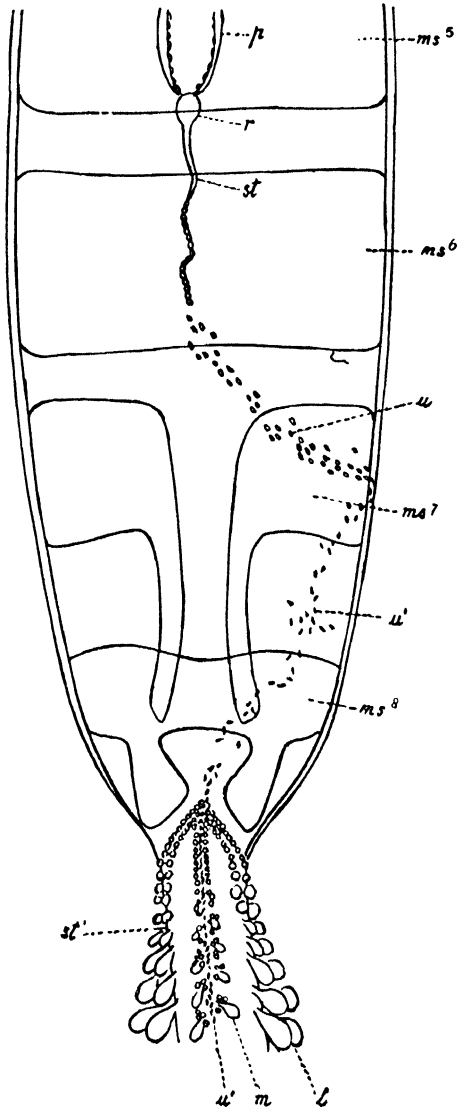


FIG. 170. Dorsal view of the hinder part of the body of a large Doliolum "nurse." Below, the stolon (*st'*) on which are buds (*l*, *m*, *u*, *u'*). These have not arisen from the stolon to which they are attached, but from buds that have arisen from a stolon (*r*, *st*) on the opposite side of the body and much further forward. The buds produced here are transported to the hinder stolon (*st'*). ms^5–ms^8, fifth to eighth muscle bands. (*After Barrois, from Korschelt and Heider, 1893.*)

in perhaps its most extraordinary fashion in some observations made first by Henry van Peters Wilson on the cells of sponges. If a living marine sponge (not a bath sponge, of course, which is only a dried skeleton) be squashed through fine bolting cloth, the cells of which it is composed will become separated from one another. If they are allowed to fall into a glass containing sea water and if left undisturbed for twenty-four to twenty-eight hours, it will then be seen that little new sponges have begun to form out of some of these cells. The new sponges arise for the most part from migrating cells that lived in the parent sponge, which, as soon as they have fallen into the container, begin to multiply, forming new little sponges. They incorporate into these nascent sponges some of the other, more specialized cells, of the parental sponge.[3]

Thus the varied histories of migrating cells in our bodies and those of other organisms indicate that these tramp cells have a very marked sensitiveness to stimuli that fall upon them from certain tissues, and by virtue of their responses play an important part in the development of the child.

Just how is this behavior of wandering cells controlled by the genes? Evidently the genes do not directly lead the migrating cells and set them down in this place or that. It is probable that the genes determine the quality of the stimulus emanating from any attracting tissue or organ, and doubtless also the specific reactiveness of the migrating cells. This explanation is not so far removed from daily experience. Just as different children are born with differing hereditary attractions toward color, form, contacts, mechanical movements, so single migrating cells may well differ in the genetic basis for their specific movements.

Notes

1. The growth of nerves from the cells of the neural tube has been demonstrated by Ross Granville Harrison in the Journal of Experimental Zoology, 1910, and by C. C. Spidel in the American Journal of Anatomy, 1933.

2. The migrations of buds in the Tunicate Doliolum was worked out by a careful observer, Jules Barrois in 1885, who published in Jour. anatomie et physiologie, Paris.

3. The movements of dissociated sponge cells have been described by Wilson in Journal of Experimental Zoology, 1930, and earlier. M. W. de Laubenfels (1928) has repeated some of this work and carried it further (Year book, Carnegie Inst., No. 26).

CHAPTER 9

HOW THE SEVERAL TISSUES ARE MADE

We have now to consider by what means the cells of the body have come to form differentiated tissues during development. In this inquiry I will take up first the chemical differentiation of certain of the best-studied tissues. [1,2]

BRAIN

The brain and spinal cord are among the earliest organs to become differentiated, as they are among the largest and weightiest tissues of the body. The materials of the brain, apart from water (which decreases from over 90 per cent to about 75 per cent during development, and loss of which may cause senescence) are largely fatty substances.

The first of these is lecithin. This is a fat that contains phosphorus and nitrogen and is found in the yolk of birds' eggs and probably in the human egg. Lecithin is, indeed, a constituent of all cells and is doubtless of first importance for life. The lecithin of our brain does not have to come from lecithin in our food since the brain cells can make (synthesize) lecithin out of an acid-containing phosphorus, alcohols and a salt of the nitrogen-bearing choline.* The synthesis is doubtless effected by some still unknown

* Choline is oxidizable to muscarine which is found in a deadly mushroom, Amanita muscaria. Amanita caesarea is edible. The two Amanitas look alike. When Caesar wished to rid himself of some rivals he invited them to dinner, had himself served A. caesarea and his guests A. muscaria. That night his guests mysteriously died.

enzymes which become active during brain development. Lecithin is so abundant in the brain that it certainly plays an important role there. There are reasons for thinking that it helps build up the walls of any nerve cell and increases its permeability.

Cerebrosides. These are non-phosphorous-containing fatty substances which occur particularly in the brain. The molecule of a cerebroside contains a sugar, galactose, which is readily split off; also a fatty acid, called cerebronic acid; and another, nervonic acid. Galactose for the cerebrosides can be obtained in adequate amount from the sugar of mother's milk, lactose. For, when lactose is acted upon by the enzyme lactase, galactose and glucose are formed. Probably this enzyme, lactase, is derived from a gene. From these products, with fatty acids and alcohols, the cerebroside can be built up. Just what relation these fatty-sugars have to the particular form and function of cerebral tissue has not yet been worked out, but without doubt there is such a relation.

Cholesterol. This substance is widespread among eggs and tissue cells, but it is found in exceptionally large quantity in the brain. There is reason for thinking that cholesterol is formed in cells by the action of the enzyme cholesterase upon cholesterol esters.* The esters are probably especially abundant in the cytoplasm of the ectodermal cells from which the brain is formed and we may assume that one or more genes become active in each brain cell at an early stage in the development of the brain wall and thus give the brain cells the exceptional number of cholesterol molecules that we find therein.[3]

The combination of nitrogenous, sugary and phosphoric

* An ester (an invented word, just as "gas" is) is made up of an organic acid and a radical of the alcohol series.

fats found in the brain cells constitutes the cream of the stuffs that are characteristic of living cells; stuffs that are highly nutritive and highly changeable. During the course of development of the brain the sugar- and phosphorous-containing fats increase in amount, while the other fats and oils remain in about a constant proportion.

MUSCLE

The picture of the chemical constitution of muscle is quite different from that of brain; just as the two tissues differ in form, structural content and function. The lecithin content of muscle is indeed high. But most striking is the protein myosin, one of the globulins, which, unlike albumin, are all insoluble in water. This myosin is a simple protein, i.e., yields when decomposed only amino-acids or their derivatives. It has a remarkable property of holding water. And that is fortunate, for when a person has to go for a long time without water the muscles still conserve a supply and continue active. You are still able to walk in the desert hunting for water while "dying of thirst."

Just how myosin is built up (doubtless under enzyme action) in the muscle cell is unknown. It is largely located in the muscle fibrillae; indeed these fibrillae are probably composed chiefly of the muscle globulins. It is stated that myosin is already present in the human fetus of five months, because at that age *rigor mortis* occurs after death. Indeed, the muscles of the fetus are active at eight to ten weeks after the egg is fertilized.

In its earliest development the muscle starts as a simple cuboidal cell. This elongates. In the midst of the cytoplasm there appear fine parallel threads. These can be seen in smooth muscle fibers. In striated muscle these threads thicken at equal intervals and, in the parallel threads, at

the same cross plane, in a way described in more detail on page 41. Thus muscle fibrillae with the striations arise (Fig. 25). Just what chemical changes lie at the basis of this fibrillar formation we do not yet know. It is possible that a series of enormously long molecules placed end to end is involved. Such molecules are known in rubber and give to it its contractile property.

CONNECTIVE TISSUE

Anyone who handles meat in the kitchen or carves it at the table has observed that the skin is attached to the

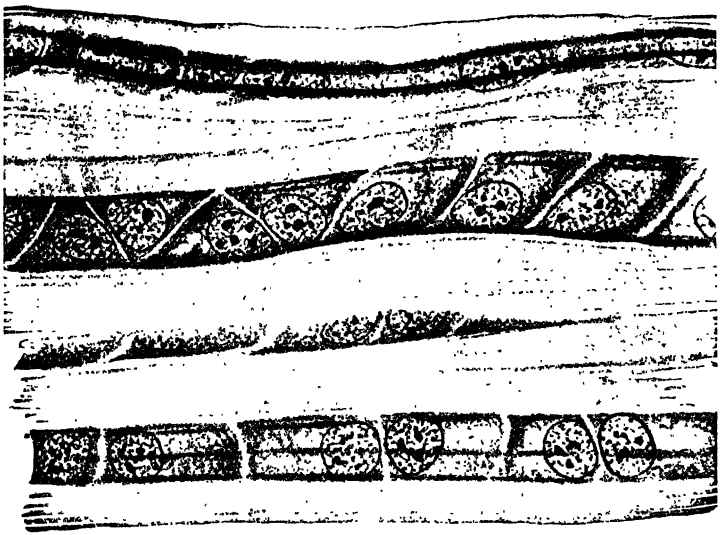


FIG. 171. Freshly teased out tendon of the tail of a rat, stained with methylene blue. The rows of tendon cells run between bundles of collagenous (gluey) material. × 520. (*After Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

muscles and the muscles are bound together or are attached to bones by fibrous tissue and tendons. These tissues that tie together organs are called connective tissues. These

tissues are made up of amazingly tough and elastic materials. A picture of a tendon (Fig. 171) shows the metabolizing cells and bundles of secreted material between them. These latter are not cellular material, but are the product of the cells. They have a definite and remarkable structure; namely, in most cases, of nearly parallel fibers. In some cases the fibers are in spirally

FIG. 172. Longitudinal section of a part of the great neck ligament of an ox. The thick, bright, gleaming elastic fibers form most of the tissue. Between them are dark fibroblast nuclei and wavy collagenous fibers. Eosin-azure stain. × 330. (*After Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

twisted bundles and such elastic tendons are capable of great extension. Such are found in the neck of a cow and permit her to stretch the neck to graze while they uphold the heavy head (Fig. 172). In these connective tissues the cells, having formed the secretions between the cells, yield to them in functional importance.

Connective tissues are largely composed of two chemical substances: collagen and elastin. Both are albumin-

like simple proteins, very insoluble in all neuter solvents, of a very complex molecular structure that is probably of elongated form and capable of stretching and contracting; something like the long molecules of rubber. In relaxing, the fibers sometimes become contorted. This contortion of the fiber may well be due to a twisting of the relaxed molecules. Just how, out of the numerous mesenchyme cells that are liberated in the embryonic body, it comes about that just these cells shall produce such elastic molecules, is still uninvestigated. Also, little is known about the way in which, with the co-operation of enzymes, they are synthesized.

BONE

Bone, like cartilage, is built on a foundation of a protein collagen, which is not readily dissolved. Bone varies greatly in different parts of the body. In one of the two main types the bone is formed directly from a loose connective tissue, in the other it is preformed in cartilage. However, the two types of bone formation may co-operate in the building of a single bone.

Figure 173 shows stages in the formation of a skull bone (connective tissue type). One sees at the upper margin ordinary mesenchyme cells that are elongating to form fibrous connective tissue. At *a* one sees the early secretions between the cells. These are much like the secretions found in cartilage (gristle) and consist largely of collagen, as it occurs in fibrous connective tissue. Gradually in this tissue the collagen fibers at the middle become thicker, denser and interpenetrated with molecules of calcium phosphate and other salts of earthy elements. It is thought that the enzyme phosphatase occurring in the nuclei of bone cells hydrolyzes * organic phosphorous-containing and calcium-

* I.e., causes disruption of molecules as they take up water.

FIG. 173. Beginning bone formation from mesenchymatous cells (membrane bone formation). Obtained from the skull of an embryo cat of 5.5 cm. *Bg*, ordinary connective tissue cells (fibroblasts); *a*, collagenous (gluey) interstitial substance; *b*, homogeneous, thickened collagenous fibers which become the interstitial bone substance; *Ob*, connective tissue cells, with processes, which become osteoblasts and later bone cells. Eosin-azure stain. × 520. (*After Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

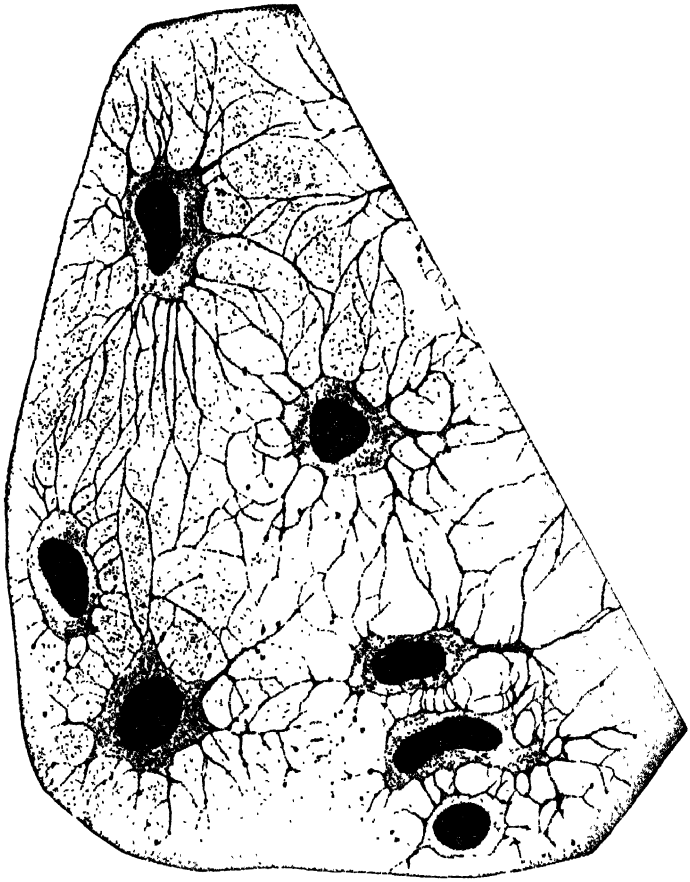


FIG. 174. Thin, transparent membrane bone of a white mouse, stained while alive with methylene blue; studied in glycerine. The substance between the cells appears homogeneous; the angular bone cells with their nuclei fill the cavities. From the cells arise anastomosing processes which lie in minute canals and in cross section appear as dots. × 1,040. (*After Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

containing acid esters (page 169) causing them to deposit calcium phosphate and carbonate. As they are formed, the molecules probably pass out of the cell into the space between cells. The cells retain their connection with each other (Fig. 174).

In the case of the long bones, where especial strength is required, a somewhat different method of bone formation occurs. The bones are first formed in cartilage. The cartilaginous rods become surrounded by regular bone-forming cells, and a thick outer bone is produced. Meanwhile some of the cartilage cells in the interior rebel, as it were, dissolve the cartilage, and make spaces. Blood vessels penetrate into these spaces. Bone-forming cells arrange themselves around the vessels. Bone spicules and fibers are laid down in layer after layer of bone plates or cylinders all concentric with the blood vessel. Thus are formed compound cylinders of bone with an axial blood space (Fig. 175). This is called an Haversian system, after the former English anatomist Clopton Havers. The bone-forming cells lie between the layers of the cylinders and are connected with each other by fine processes that can be traced in successive relays of cells back to the central space with its blood vessel (Fig. 176).

After one set of Haversian systems has been formed the bone substance becomes dissolved, probably by the secretions of the cytoplasm of certain cells that are found in the dissolving region and are called osteoclasts (or bone destroyers). Before the first set of Haversian systems is totally destroyed a new set of systems is formed whose elements are usually eccentric to the elements of the first. Finally, this process of replacement may occur still another time. The result is that, in the adult bone, the latest Haversian systems are seen to lie in the midst of remains of

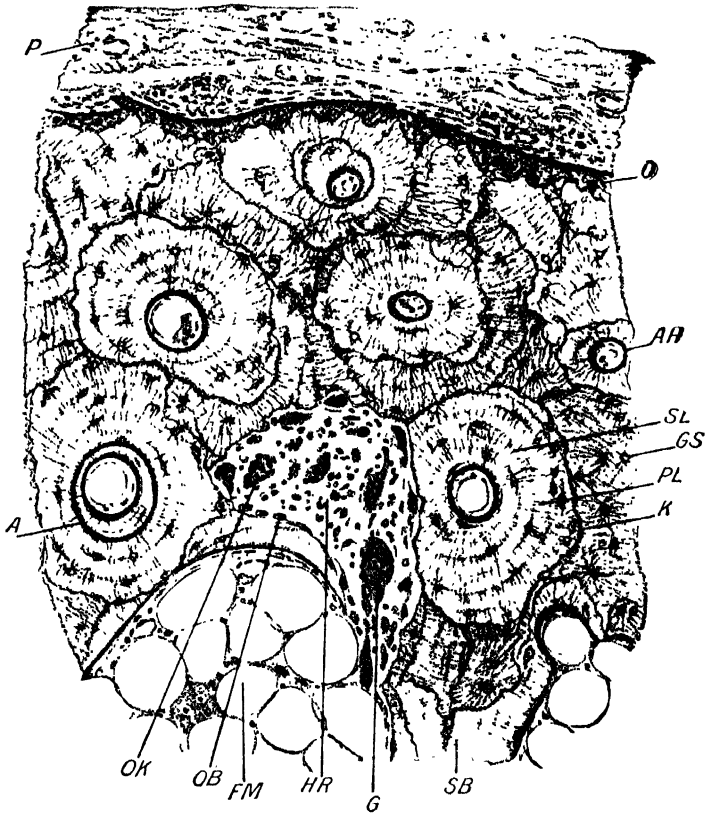


FIG. 175. Cross section of the second joint of a human middle finger. *A*, line of junction; *AH*, border of a blood vessel canal; *FM*, fatty marrow; *G*, blood vessel; *GS*, limiting membrane of a lacuna (containing a bone cell); *HR*, Haversian space with red marrow; *K*, cement line; *O*, superficial network of bone; *OB*, osteoblasts or bone formers; *OK*, osteoclasts, or bone destroyers; *P*, periosteum (connective tissue covering of the bone); *PL*, longitudinal fibrillar lamella or plate; *SB*, layer of spongy bone; *SL*, a circular fibrillar lamella or plate. × 110. (*After Schaffer, from Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

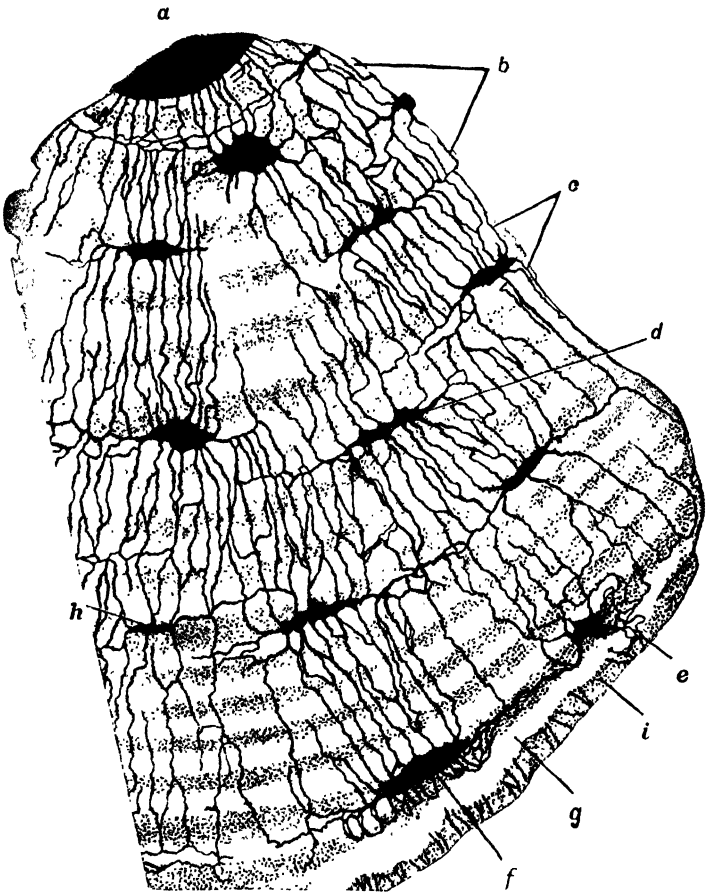


FIG. 176. Sector of a cross section of an Haversian system of a macerated human hip bone. The cavities and canalicules are filled with a dye; hence black. *a*, lumen of Haversian canal; *b*, longitudinally fibrillated plates; *c*, circularly fibrillated plates; *d*, lacuna which lies in circularly fibrillated plates and is therefore seen in the long profile; *e*, connection of canalicules of the Haversian system with those of an intermediate system; *f*, looped, external canalicules of the Haversian system; *g*, cement line bordering an Haversian system; *h*, confluent lacunae; *i*, intermediate system, i.e., between Haversian systems. × 520. (*After Maximow-Bloom's "Textbook of Histology," courtesy of W. B. Saunders Co.*)

older systems (Fig. 175). These Haversian systems are marvelous in their strength, elasticity and lightness. Think of a series of cylindrical sheaths of limy salts wrapped one around another, like the layers of an automobile tire. In the successive cylinders the fine spicules and fibrillae run, now lengthwise of the cylinder, now circularly. These cylinders contain living cells kept in communication with the central canal and its blood vessel. The center of the long bone contains a large marrow cavity. This is filled by the creators of the blood cells, both red and white, and is very rich in blood vessels. Thus the bone is very much alive.

The whole arrangement just described provides economy of material; greatest strength combined with lightness. As every one knows a hollow column is much stronger than a solid one of the same weight. At the upper end of the thigh bone, which is very large and would be heavy if solid, the bone is laid down in plates like a great truss with spaces between the plates. The plates are laid down as an engineer might plan them to receive in best fashion the weight of the heavy trunk with least use of material. If, by chance, the thigh bone is broken and reset so that the

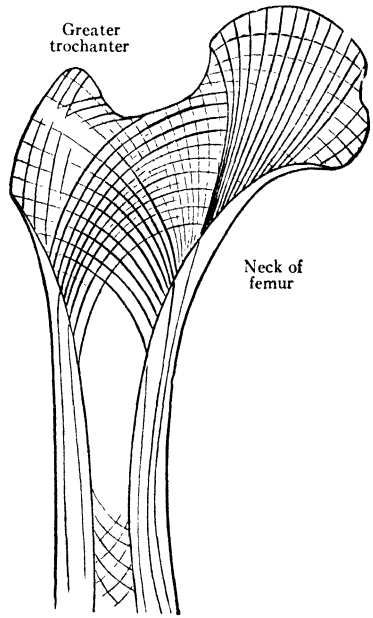


FIG. 177. A, diagram to show the pressure and tension curves of the femur. (*After Wagstaffe.*)

axis of the upper bone is inclined to its normal position the old plates of bone are resorbed and new plates are developed so as to receive in best fashion the stresses that fall along a new line (Figs. 177, 178). So marvelously responsive are even the bone cells to the demands of the body as a whole!

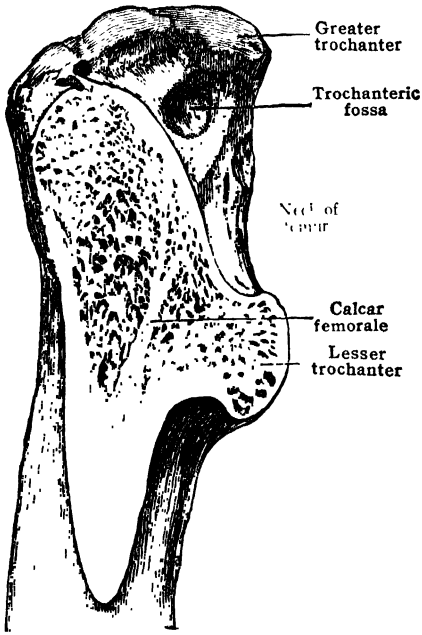


FIG. 178. Section of the upper end of the femur to show the compact truss of bony tissue that passes into the neck of the femur to help support the weight borne by the head of the femur. (*From Morris-Jackson.*)

The genes may determine the responsiveness of the bone-forming cells, but surely cannot anticipate all possible kinds of breaks in the bones. There can, however, be no doubt that the tendency to form Haversian canals is under genic control. Indeed, by a gene mutation there are human families which lack the gene for forming such systems. The long bones of such people are very brittle. A child of such a family who falls out of bed breaks a limb; a boy with this defect cannot slide to base at baseball; a fall on the ice may be very serious. Such persons are called "brittle boned."

We often regard the bones as the most fixed, least alterable parts of the body just because, from the nature

of the supporting work they have to do, they are so rigid. But many facts, besides that of the reorganization of the head of the femur, show that this is an error. The bones are capable of great changes in form and structure to meet changing conditions. This conclusion is well supported by studies made many years ago by the English anatomist and surgeon, W. Arbuthnot Lane. There fell into his hands for autopsy the body of a man of seventy-three years who had been for most of that time a cobbler. Now the old-fashioned cobbler had a variety of operations to perform but the most laborious was hand-sewing. "In sewing the boot the last is held firmly between the front of the chest and the upper surface of the thigh; an awl is used for making holes, through which the waxed threads are passed and then pulled tight, an operation which requires much force, pressure against the chest and great extension of the arm. The head at the same time is thrown forwards and downwards."

The body of this shoemaker showed numerous changes associated with his occupation. First, the lower half of the sternum, or breast bone, was covered with thick connective tissue forming a huge pad. It was produced by an enormous thickening of the ligaments that connect ribs and sternum. The upper part of the sternum was greatly broadened and strengthened; and two sections of the sternum could be moved upon each other as by a hinge joint—a wholly new structure. The lower tip of the sternum was pushed in so far that it was only three-quarters of an inch from the spine. Into this narrow passage the liver and diaphragm were squeezed.[4]

The spine in neck and shoulder region was likewise altered. The first vertebra, the one which holds the skull (and is called atlas, from the Greek god that held the globe)

had become excavated in front by the blows of a bony process of the second vertebra which impinges against the atlas. The atlas, as it were to strengthen itself, had become higher in front, and the bony process of the second vertebra was similarly altered. To make a long story short, the bones of the shoulder joint, arms and hand all showed changes largely of such sort as would strengthen the skeleton to meet the special repeated and somewhat violent stresses that it had to meet.

The above cited case is not isolated. Special modifications have been described in the skeleton of coal heavers, porters and others. The building of bone is partly determined by genetic factors, partly by tissue response to stimuli. But the latter also is determined by a specific constitution due to genes.

SKIN

The skin of the adult is derived from two sources. On the one hand its outer cells arise from the ectoderm of the embryo; on the other its deeper lying cells, with their blood vessels, connective tissue, and muscle endings are of mesenchymatous origin. The outer layer of cells undergo a change by which they become horny, i.e., form keratin. The keratinized cells are found not only in the outer skin, but also in the finger and toe nails, in horns and hoofs of cattle, in hair, wool and feathers. Keratin belongs to a group of substances (albuminoids) that are insoluble in neutral solvents and also dilute acids and alkalis. The keratin molecule is a very complex protein one. It is perhaps derived from glutathione which is present in many food stuffs and by reduction-oxidation processes yields cystine which is used to make keratin. It is remarkable that the same group of substances should, on the one hand, yield the

delicate, contracting fibers of muscle and, on the other, this extraordinarily resistant keratin, which protects the delicate muscles from desiccation in the air of the desert

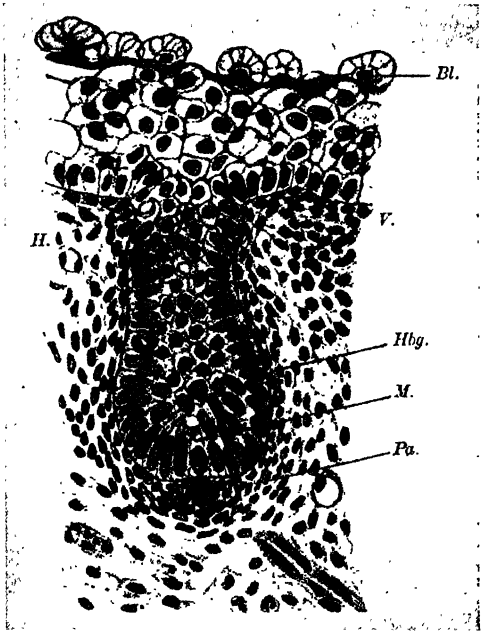


FIG. 179. The hair plug, beginning of the hair follicle, from a human embryo. *M*, center of formation of the hair (matrix). *Pa*, the beginnings of the hair papilla; *Hbg*, connective tissue about the hair follicle. *Bl*, vacuolated cells of the outer skin. *V*, front surface of hair follicle; *H*, hinder surface of the follicle where an oil gland is to arise. × 430. (*After Keibel-Mall's "Handbuch d. Entwickelungsgeschichte des Menschen."*)

or of steam-heated rooms, protects the fingers of the worker with alkalis and acids and even of the biologist who handles the tissue-hardening formaldehyde.

Hair is a localized keratinized organ of the outer skin.

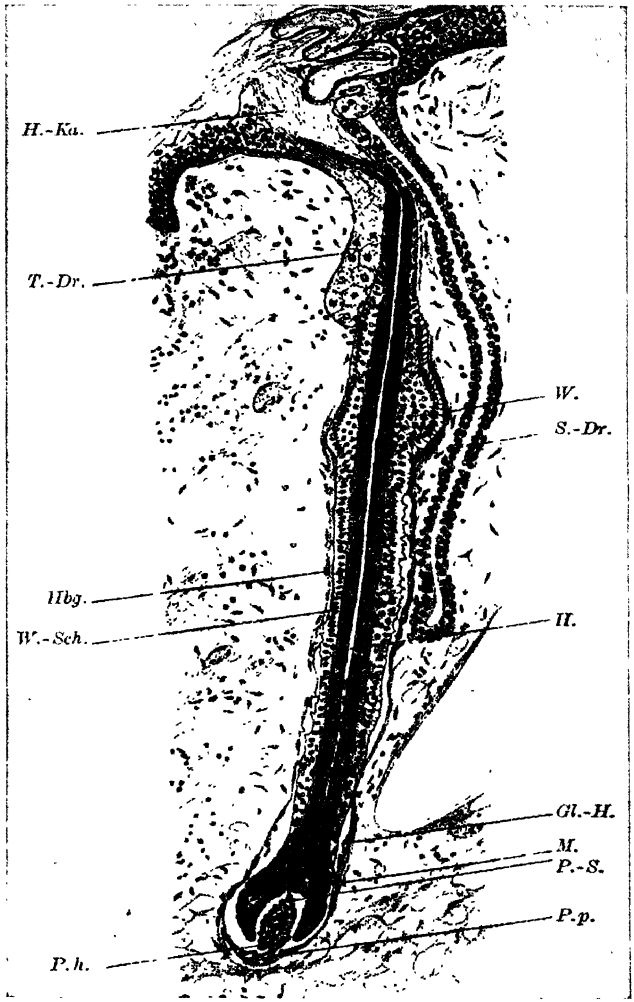


FIG. 180. Fully formed lanugo (fetal hair) from an 8 months old male fetus. *P.p.*, pad of the papilla, *P.h.*, neck of the papilla; *P–S*, apex of the papilla; *M*, hair matrix; *Gl.–H*, "Glashaut" or transparent shiny skin layer. *H*, shaft of hair; *W–Sch*, outer sheath of root; *Hbg*, connective tissue of hair follicle; *S–Dr*, sweat gland; *W*, pad; *T.–Dr*, sebaceous gland; *H.–Ka*, hair canal. Black, inner sheath of hair root cuticulae. × 120. (*From Keibel-Mall's "Handbuch der Entw. des Menschen."*)

At definitely limited and regularly arranged points in the skin (points that are determined by certain creases in our skin that are the remnants of the lines along which the scales of reptiles' skins are imbedded) the ectoderm thickens and finally sends a finger-like growth into the lower skin (Fig. 179). The cells in the axis of this pocket become keratinized (Fig. 180). Their color (like that of the iris) is determined by a reaction between a substance in the cytoplasm (tyrosin) and an enzyme, probably in the gene (tyrosinase). The gene catalyzes the tyrosin which becomes oxidized to form melanin which is the basis of the dark pigment of hair and skin. In the case of Negroes the tyrosinase catalyst is freely active. In Europeans the reaction may be interfered with by an anticatalyst.

In eastern Asiatics a yellow pigment is found abundantly in the skin. This is probably a carotinoid (giving carrots their color). As such it may presumably be derived from the action of a still unknown carotinase upon a substrate. At any rate the production of yellow pigment as seen in red hair is a genic character and accordingly requires the presence of an enzyme in the nucleus of the pigment cells.

Thus the skin and its organs constitute man's natural defense from drying air and penetrating sunlight. Man's genes and cytoplasm working together have been able to protect him against these extreme conditions.

BLOOD

Most animals have a large fluid-filled space between gut and body wall (the body cavity). Through this cavity nutritive substances can pass to all parts of the body. In the higher animals the fluid has to be made to circulate by pumping. Hence a heart, and the confinement of the

circulatory fluids to tubes (blood vessels). The fluid that circulates in the vessels is the blood. Thus blood circulates in a practically closed system. However, the walls of the tubes are liable to rupture. Blood may thus be lost in part or whole. Without some defense the organism would bleed to death. It is, accordingly, advantageous that the blood, which must circulate freely through the minutest capillaries, should solidify when it comes in contact with the air. This process of forming a jelly-like solid is known as clotting. The first step in clotting is the formation in the blood of threads. These are made by the aggregation of a protein colloid present in the normal plasma. This colloid is called fibrin. It is believed to result from the action of an enzyme, thrombase, upon fibrinogen which is carried in the blood fluid. In consequence, the fibrinogen is split into fibrin and a globulin of the blood serum related to the fiber-former of the muscle. Thus the clot is quickly made.

Why does not thrombase cause coagulation in blood of uninjured vessels? Apparently the thrombase becomes active only in the presence of conditions (air, etc.) which are unusual and hazardous to the blood.

That some such enzyme as thrombase is formed from a certain gene is quite clear, since in the absence of such gene the blood will not coagulate. This is the case in "bleeders" or those affected with haemophilia. Families may suffer through generations with this defect. The most noted case is seen in the much intermarried royal family of Europe. The late tsarevitch of Russia was an example of such a haemophiliac. Genetic analysis shows that this condition is due to a change in a gene that is located in the sex chromosome.

Blood is a very complicated tissue. One of the most important elements in blood is the red blood corpuscle.

This is a cell that has lost its nucleus. It is thus doomed to sterility, like the worker bees, but like them is essential to the life of the organized body. The blood corpuscle contains an extraordinary substance incorporated in or attached to the protein molecule. This is hemoglobin, which has the remarkable property of taking in oxygen when oxygen tension outside the corpuscle is high (as in the lungs) and yielding it out when oxygen tension is low (as in the tissues). This property is probably in part due to the iron the molecule carries. The molecule of hemoglobin is a huge one, weighing about 68,000 times as much as a molecule of hydrogen.[5]

The most characteristic part of hemoglobin is a substance, hemin, comprising an iron atom. This hemin is formed also in all plants and animal cells; but in them it is usually not united with the protein globin. Probably there is in blood cells an enzyme that unites them. The constitution of the hemin is very similar to the central group in the molecule of leaf green (chlorophyll). Commenting on this fact Gortner says: "It is highly improbable that the close similarity in the structure of these two vital pigments is one of chance, but it appears more probable that in the processes involved in organic evolution, the essential nucleus of the earlier vital pigment, chlorophyll, became modified so as to assume new functions in the developing animal kingdom, the magnesium in the chlorophyll being replaced with iron in order to care for the new function as an oxygen carrier."

It is generally agreed that hemoglobin, like chlorophyll, does not act as a catalyzer, but as a sort of shuttle device for conveying oxygen or carbon dioxide between the outside world and the tissues. Apparently this intermediary substance has a chemical constitution that is not unique,

but comprises a specially modified molecule that is nearly universal in cells and is perhaps in the fertilized egg. For respiration is a fundamental function of living protoplasm. In the evolution of the higher organisms some slight though highly efficient adjustments have to be made to meet the complications introduced by great size of the body.

As this is not a treatise on embryology I shall not attempt to describe the mechanism of the development of all of the organs of the body. There are hundreds of centers of developmental activity in the body. The most marvelous fact about development is the way in which the developing centers work together and so often produce a normal child.

NOTES

1. On the tissues and their chemical differentiation the reader will find certain textbooks of aid. On the morphological side reference may be made to the excellent textbook, *Histology*, of Philipp Stöhr, rendered into English and much added to (in several editions) by Frederick T. Lewis of Harvard Medical School and others.

2. Another excellent *Textbook of Histology* is that of Alexander A. Maximow, late Professor of Anatomy at the University of Chicago, and William Bloom. The illustrations are mostly new and fine.

3. On the chemical side assistance can be gained from the textbooks of Gortner, *Biochemistry*, and Bodansky, *Physiological Chemistry* (both published in New York by John Wiley & Sons).

4. The work of W. Arbuthnot Lane on the shoemaker was published in 1888 in the (English) Jour. of Anatomy and Physiology. There are other contributions by him in the same Journal.

5. Such a molecular weight for hemoglobin has been found by numerous investigators, such as Adair in 1925, Svedberg, Vickery and Northrop, subsequently.

CHAPTER 10

MEETING STRESSES AND ACCIDENTS

MAKING EMBRYOS DEVELOP ABNORMALLY

From a fertilized egg normally arises a single embryo. But why only one? Under what conditions can two or more be produced? The experiment has been tried on a frog's egg at the two-cell stage of tying a hair around it and constricting it in the plane that separates the right and left halves of the embryo. Under these circumstances each half tends to produce a whole; but actually the embryos are united—the heads alone are double. Apparently the permanent distortion due to tying causes the head ends to round off and form two distinct centers of development. Here there is no gene change but merely a mechanical displacement of the cytoplasm.

Even with less mechanical treatment the course of development of the embryo may be profoundly changed, as we have seen in speaking of the development of the centrifuged Ascidian egg (page 174). Indeed, if the distribution of cell fluids is interfered with by modifying the salts in the medium in which the embryo is developing, it may be caused to develop abnormally, since the normal processes of fluid imbibition upon which membrane foldings depend are altered. In fact it is in general true that normal development, normal interaction of gene and substrate, normal relations of cell division, water imbibition, cell movements and tissue differentiation can all be disturbed by a large number of chemical and physical modifications

of the surroundings of the developing embryo, and this may happen when the gene-complex is quite normal.

HOW PART ACTS ON PART

"In the course of development," said Aristotle, "part acts on part as in the automaton." In recent years Aristotle's dictum has been proven to be true.

We have seen how the eye is formed of two portions; (1) outpocketing of the primitive brain region to form the optic cup; (2) inpocketing of the ectoderm to meet (1) and eventually form the lens of the eye (Fig. 43). Does (1) induce (2)? Years ago Warren H. Lewis, now of the Carnegie Institution of Washington, answered this question experimentally by studies on tadpoles. He cut off the end of (1) and inserted it beneath the ectoderm at a place where a lens ordinarily does not form. He found that at this new place the ectoderm thickened and formed a lens. Again, in an otherwise undisturbed embryo just before the lens was to arise, he removed the ectoderm just over (1) and, borrowing some ectoderm from another part of the body, implanted it in place of the removed ectoderm. This new ectoderm now formed a lens; a thing it certainly would not have done had it not been for the stimulus afforded by the underlying (1). The formation of a lens is induced by the developing brain outpocket.

Again, in the frog embryo (as in humans) there appear grooves on the neck which in the frog produce gill slits. Now if at an early stage, before the grooves appear, the ectoderm of the gill grooves be removed and replaced by ectoderm from another part of the body, then later, at the time the gill slits should arise, they will appear at the proper place though made up, in part, of this foreign tissue. The fate of this ectoderm is determined by its position in relation

to other organs. What the ectoderm of frogs at this young stage will do depends upon what it is called on to do by adjacent embryonic organs.[1]

Again, it is known that, as the tadpole of the frog is about to undergo its metamorphosis into a little frog, and hence from a gill-breathing to an air-breathing organism, the gills become covered on each side of the head by a fold of skin that extends back over the gills. An opening persists behind so that water that has passed through mouth and gill slits can pass out again. Some time later the fore limbs, arising from an area of the skin that is covered by this operculum, break through a special opening in the operculum. This is not merely a mechanical result, since a glass bead implanted in the skin near the limb does not cause perforation of the operculum. It is not that the operculum has an internal tendency to perforate. For if it is transplanted sometime before perforation has begun to another part of the skin, it will not perforate. If, on the other hand, the operculum is removed and skin from the tadpole's back is ingrafted in its place that also undergoes a perforation. Hence the tendency to perforation is not resident in the operculum, but depends on the *position* of the opercular tissue. The growing limb might be the agent for opercular perforation. To test this the limb was removed at its earliest appearance. Still the operculum became perforated. So the limb was not the cause of the perforation. Again, pieces of gill tissue undergoing degeneration were grafted under normal skin of the back or under opercular grafts placed there and the integument became perforated. Hence it was concluded that the atrophying gills of the metamorphosing larva are the immediate cause of the opercular perforation. Perhaps a digestive ferment is given off by the atrophying gills that destroys the tissue of

the operculum and thus frees the limbs. On the other hand, the atrophy of the gills and the growth of the limbs are both dependent on secretions from the thyroid gland. In any case, the perforation of the operculum is beautifully

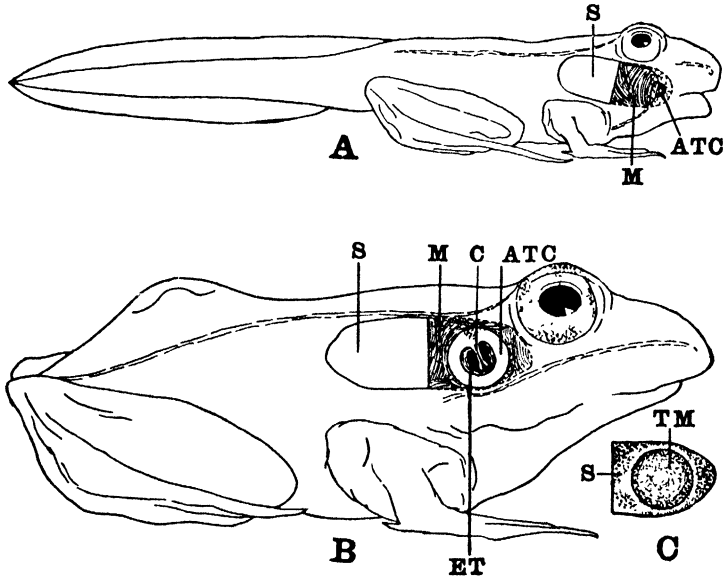


FIG. 181 A. Side view of a tadpole showing the annular tympanic cartilage, ATC, below the eye; muscle, M, behind, and the flap of skin, S, which had been removed. B. Adult frog showing annular tympanic membrane (ATM), with tip of columella (C) and opening to Eustachian tube (ET). C. The tympanic membrane, TM, in place. (*From O. M. Helff.*)

timed by the enzymes of the atrophying gills to open the door for the growing limbs. Thus part acts on part in development.

Again, as Helff has also shown, behind the lower jaw of the frog tadpole in the region of the ear pocket a cartilaginous ring is formed. The skin over this ring becomes thinned to form the eardrum membrane, supported by the cartilaginous ring (Figs. 181, 182). What makes the

skin go thin in the region delimited by this ring? Is it because of the specific hereditary nature of the cells of the skin of just this part? No, for if skin from the back or sides

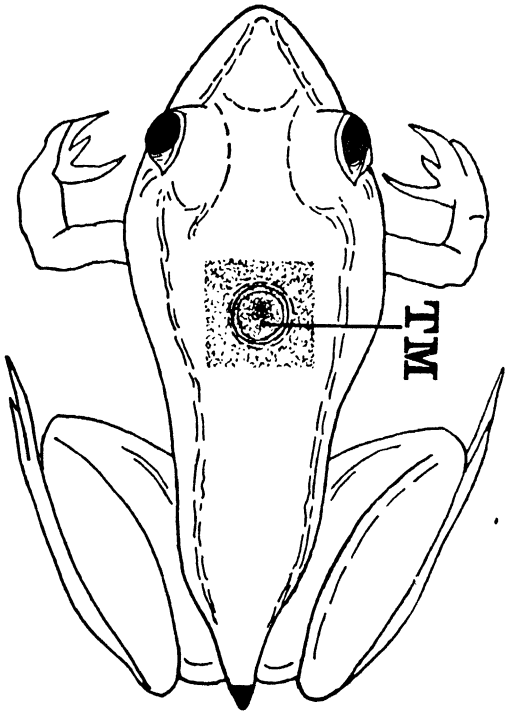


FIG. 182. Drawing of a frog showing the formation of a tympanic membrane in skin of the back underneath which an annular tympanic cartilage had previously been transplanted. TM, tympanic membrane. × 4. (*After Helff.*)

of the larva be substituted for skin normally occurring at the ring, such transplanted skin will form the eardrum membrane. If the ring be transplanted under the skin of the tadpole's back, that skin will form a drum membrane inside of the ring. Or if the ring be extirpated over the ear, then no drum membrane will be formed. The con-

clusion is reached that the change from skin to eardrum is the result of influences exerted by the cartilaginous ring, doubtless through chemical agents arising from the cells of the cartilage.

The amphibia are wonderful creatures to illuminate this question of the action of part on part. If a piece of the young embryo of a salamander, taken very early from the place at which part of the neural plate ordinarily arises, is transplanted in an entirely different part of the body it will sink beneath the surface and induce the ectoderm in the new place to form a neural plate, brain, eyes, etc., where they would not otherwise be formed. The presence of the underlying tissue at any point is what calls for the neural fold, just as the contact of the optic vesicle when it touches the ectoderm calls forth the lens. And it is noteworthy that the transported cells have within themselves the power of self-determination, as well as that of organizing the cells in their new environment.

These illustrations will have to suffice to demonstrate the principle in differentiation that in some cases the fate of certain cells is already determined early in development by combination of cytoplasmic and genic content; while in other cases cells have a constitution that permits them to respond to the stimuli of other organs by a specific type of differentiation. Similarly, the muscles make their way to the skeleton as it is forming, and the muscles become attached, at the proper points, to the elements of the skeleton. Likewise the nerves that grow out from the spinal cord make their way toward the muscles that they are destined to establish relations with and enter into those muscles. One part of the developing organism acts upon another part and stimulates it to co-operative action. Development is not a grossly mechanical process, but a

matter of mutual co-operation, mutual response to the stimuli received by one part from another.

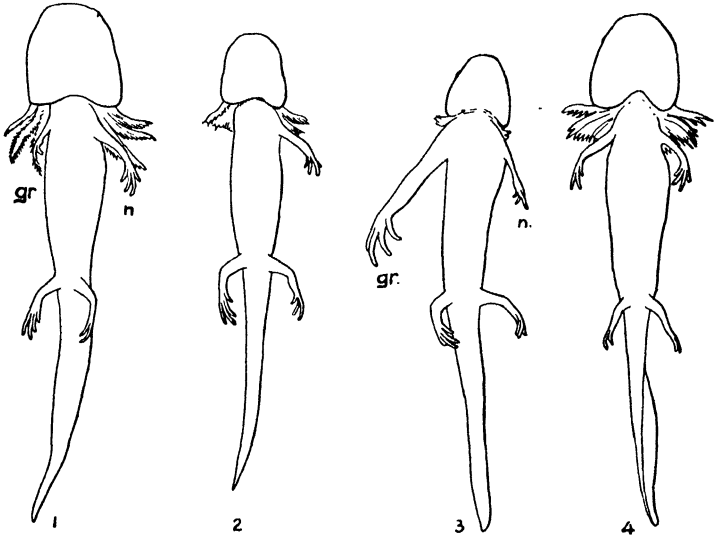


FIG. 183. Photographs illustrating Harrison's transplantation of limbs in salamanders. 1, larva of Amblystoma tigrinum, with a punctatum fore limb (*gr*) on the right side; *n*, normal limb. Specimens preserved 76 days after operation.

2. Larva of A. punctatum, the donor of the limb shown in 1. Regeneration of the lost limb has not occurred 76 days after operation.

3. Larva of A. punctatum showing a gigantic, but otherwise normal, tigrinum limb (*gr*), grown to this size, after having been grafted in the limb bud stage; *n*, normal limb, 72 days after operation.

4. Normal control larva of A. tigrinum of the same age. All figures magnified 1.4 diameters. (*After R. G. Harrison.*)

Another type of control of developmental process shown by salamanders may be presented since it reveals the interaction of the self-determining factor and that of interdependence. There are two salamanders hereabouts: one, large, which we may call *L* *; and one smaller, *S*.† The limbs of the *L* larva are normally retarded in development,

* Amblystoma tigrim; † A. puntatum.

while those of the *S* larva are precocious. At an early stage, before limb buds could be distinguished as such, one incipient limb bud of one species was exchanged by Ross Granville Harrison with that of the other, and this was done reciprocally (Fig. 183).

Now it turned out that the limb of the rapidly growing *S* type implanted on the *L* embryo soon surpassed the slow-growing *L* limb. When, on the other hand, the *L* limb was grafted on *S* it remained small while the undisturbed *S* limb grew rapidly. However, shortly after, the grafted *L* limb grew far more rapidly than it would have done had it been left in place. After about two or three months (Fig. 183) in the *L* species the engrafted *S* limb was very small. In the *S* species the engrafted *L* limb was huge; much larger than the *L* limb on the normal *L* individual.

The results may be explained as follows: Both species have in their appendages a growth potential (*G*) which is the greater in the *L* species. This growth potential is determined by genetic factors. The other factor is a regulator (*R*). This does not reside in the tissue cells. It is "in the circulating medium and is probably a hormone" derived either from the pituitary or the thyroid gland, or both. This *R* factor is probably more efficient in the *S* species since this undergoes its metamorphosis the earlier. The *R* factor makes the *L* limb transplanted to *S* eventually become huge. Here it is seen that the end result, size, is determined in part by genetic, in part by endocrine factors. This result is of general significance, as appears from the next section.[2]

NATURE'S PLASTIC SURGERY

When a clean cut is made in the skin the wound will soon heal so that the cut edges adhere. And when tissue

has been destroyed (as by a large boil) the lost tissue will be replaced by a new growth of skin and connective tissue. This replacement is called regeneration. If a piece of diseased liver is removed by a surgical operation new liver tissue will be reproduced by multiplication of liver cells. The smooth muscles that surround intestine or stomach may regenerate to a limited extent after a surgical operation. Nerve cells that have lost their fibers may regenerate new fibers. Pancreas, spleen and suprarenal gland regenerate tissue to a greater or less degree, probably from cells that are themselves not secreting but are embryonic cells, which are lying low, as it were, ready for this emergency. Lung tissue regenerates very little, so that healing after tuberculosis is mostly a filling in of cavities by connective tissue cells.

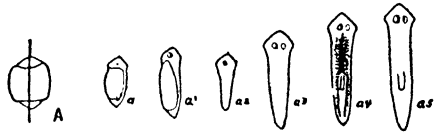


FIG. 184. Outline drawings of the flat worm, Planaria. A, a band cut across the middle and allowed to regenerate; then cut in two lengthwise, as indicated by the line a–a^5. Regeneration of left half at successive stages. (*After Morgan, "Regeneration," courtesy of The Macmillan Co.*)

In general the higher vertebrates have a limited power of regenerating lost parts. A lizard can regenerate a lost tail, without normal vertebrae, but with muscles, nerves and skin. A salamander can regenerate not only tail but also limbs, parts of the jaw, the gills, even the eye. The capacity that an organ has for regeneration is a function of the available embryonic cells it possesses.

In invertebrates the capacity for regeneration is widespread. When an earthworm is cut in two each piece, kept in the habitat that earthworms like, can grow into a whole one. The robin that breaks an earthworm in two trying to pull it out of the sod may get several meals from the same

earthworm during the course of the season. Some worms may be cut into many pieces, each of which will grow into a normal individual (Figs. 184, 185); indeed some divide themselves regularly as a standard method of reproduction. Many of the lowest organisms reproduce in this way—have nearly cut out romance altogether. In some plants even a bit of a leaf may develop into an entire individual.

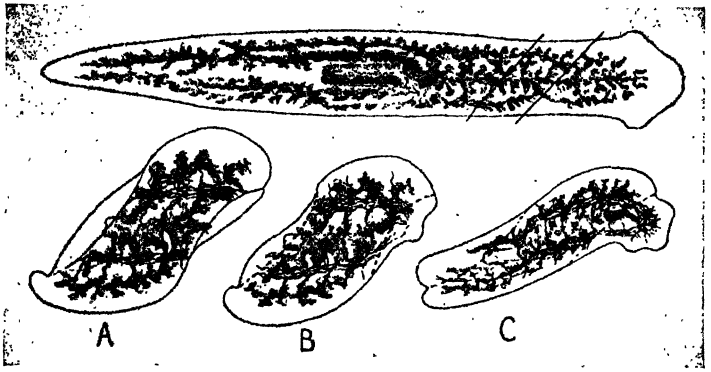


FIG. 185. Development of an oblique cross piece taken from in front of the pharynx of Planaria. A, 28 hours after removal; B, 48 hours after removal; C, 96 hours after removal. (*After Bardeen, 1901*)

Regeneration (the biological as contrasted with the theological kind) is possible because in almost all parts of the body there are cells that are not strictly tissue cells but are available for replacement of lost parts. They are not ova and can ordinarily not produce a whole embryo; possibly their cytoplasms are so exhausted of substrate materials that each of them can produce only the particular tissue in which it is located. It is remarkable that these cells lie quiescent until called forth by some sort of injury.[3]

There is some reason for thinking that many tumors are due to the growth of these replacement cells when there are really no lost parts to regenerate. The replacement cells

have, as it were, mixed their cues and started to grow before they were needed.

Development in general and the healing of injuries and regeneration of lost parts, in particular, are guided in their progress by factors that reside in the body as a whole. And, as the late Jacques Loeb pointed out, the body does not form these extra parts so long as they are parts of the whole. But only when the continuity of the body is interrupted do the latent processes of growth and development start up anew.

Finally in regeneration the fact of polarity has to be taken into consideration. This is well shown by one of the species of attached marine animals called hydroids as well as by plants in general (Fig. 186). Such a hydroid has a lower pole which is attached to the substratum by a stolon (see page 165), from which it may send up a new shoot, and each such shoot becomes transformed into a "head" bearing a crown of tentacles. If, however, the piece of the hydroid be reversed, after cutting off the heads, the stolon will grow out of the end in contact with the bottom of the glass vessel. In this case polarity seems to be a function of position in relation to gravity or contact.

If the head end of an earthworm is cut off a head ordinarily reforms; if the tail end is removed a new tail arises, but it is possible by ingenious cuts to secure a reversal of the usual process. Polarity has a limited potentiality.

In the ordinary development of a child, as of any mammal, the head end is early distinguished from the tail end. The head end grows more rapidly (Fig. 26) as we have already seen. From this fact the principle of cephalic precocity has been deduced (page 27). The tail is the last part of the organism to complete its development; the tissues remain embryonic there longer than elsewhere. It has been

shown by Charles Manning Child that metabolism goes on more rapidly at that end which becomes the head and that is why it grows the faster.

The conclusion from these observations is that behind the activities of genes and cytoplasm lie certain forces that

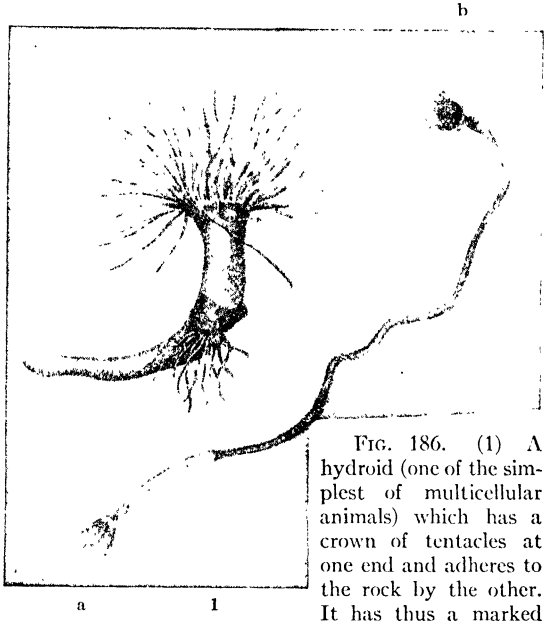


FIG. 186. (1) A hydroid (one of the simplest of multicellular animals) which has a crown of tentacles at one end and adheres to the rock by the other. It has thus a marked polarity. However, when a piece, a–b, was cut out of the middle of the stem and both ends were left free in the water, tentacles arose on both ends. The polarity is relative to the solid substratum.

(2) A polyp with a normal head (h) and a 3 months old head forming around a slit made in the side wall. Tentacles and mouth have already developed; but only on the upper side of the cut. (*After Jacques Loeb, 1891.*)

act throughout the body as a whole. These doubtless help direct the more isolated cell functions so as to establish co-ordinate local growth processes and establish the form of the body as a whole. In how far this polarity is determined

by the polarity of the egg and the stratification of its stuffs is not yet precisely determined.

INTRAMURAL MESSAGES: ENDOCRINE GLANDS

While in the simpler organisms, like insects, the relation between genes and traits is fairly direct, in many vertebrates and especially mammals, the relation is more devious.

FIG. 187. Photograph of a group of dwarfs (short-legged folk) and midgets (uniformly reduced folk) exhibited at Luna Park, Coney Island, 1915. From left to right: Irwin Emmer, Samuel Goldstein, Louis Comadori, Baron Magri, Addie Frank, Joseph Zaino, Helen L. Haskell, Elsie King, Joe Short, Nona Appleby, Helen Linoner, Patrick McGoff, George Laible, Annie Nelson (Mrs. George Laible). (*Photo by Chas. Nesensohn.*)

Thus, tall stature is inherited. But we are not to think of genes that determine tallness directly. We have already seen (page 117) that stature is influenced by the secretions, called hormones or messengers, which are sent out by various internally secretive glands into the blood, and carried by it to the tissues that can make use of them; or, in other words, that can read the messages and respond to them. In the particular case of stature the pituitary gland at the

base of the brain sends out a message to the thyroid and this becomes active, throwing its secretions into the blood. Also, the signal is transmitted to the suprarenal gland and its outer layer begins actively to secrete. The germ glands, or gonads, may become involved as we see they are at the time of most rapid growth of boys and girls. The entire resources of the body are, as it were, called upon at that time to do their best to expedite growth.

But these glands are built under the direction and control of the genes; and what the quality of the glands shall be depends on these genes. Hence an hereditary line of small pituitary glands will be a line of dwarfs (Fig. 187); a line with poorly functioning thyroid glands will be short and fat. Our build is largely determined by our internally secreting glands and their quality, in turn, is determined by the enzymic activity of the cells of the developing embryo. See page 228.

MISTAKES OF THE BUILDERS

The study of child development clearly reveals the vast complexity of that process. We have seen that the normal course is determined by interaction between a set of genes, which must all be represented, and a set of cytoplasmic materials which seem, likewise, to be all indispensable at the start; but probably become different in the various completed tissue cells. Also at every stage one part acts on a responsive part and normal development requires a normal stimulus and a normal ability to respond. That a viable child should so often result from a fertilized egg would well be considered Nature's greatest achievement were it not so common.

First of all, however, the children who are born are only a fraction of all fertilized eggs. It is probable that most em-

bryos die during the first or second month of intra-uterine life. This is no fault of the uterus or the mother but it is the fault of the genes or cytoplasm, which are not adequate for normal development. Intra-uterine deaths at this stage are frequently entirely unnoticed and are not regarded as miscarriages.

Of children who are born about 3 per cent are born dead or die within three days after birth. The question is often asked: Why did they die at birth? And attempts are made to explain "on the ground of syphilis of the parents, of narrow pelvis of the mother, etc." These are doubtless real causes of death; but it is probable that the greatest cause of still-births is a defect in the genes or the cytoplasm of the germ cells that produce a fetus that is simply so badly developed that it cannot stand the transfer to a terrestrial life which most fetuses withstand easily.

The number of defects causing death or interference with development is very great. An abbreviated list may be hazarded. Beginning with the head, this may develop so badly that the neural tube does not close and there is practically no brain at all. Or the brain case may close and the child become a microcephalic idiot. Then the neural tube may fail to close in the small of the back so that the tube remains permanently a furrow (spina bifida). The two lower limbs may grow together, and so may individual fingers and toes. Of the viscera, one kidney may fail to form, the kidneys may be united. The heart may show a large persisting opening in the interventricular wall (causing a "blue" baby). In cows, but not humans, if there are twins of opposite sex the hormones from the male twin prevent the normal development of the sex organs of the female twin.

The defects that children show, physical and mental, are largely due to errors in development. These "errors,"

however, often go back to mutations in the genes or cytoplasm and so, if not fatal, may be reproduced in successive generations.[4]

TWINS

When the nurse announces to the awaiting father that "they are twins," the news brings mixed emotions: the

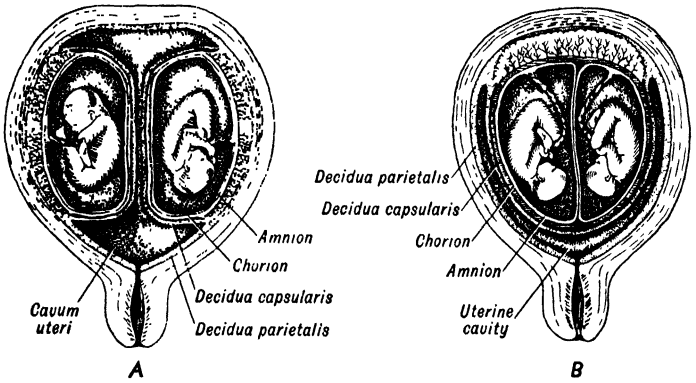


FIG. 188. Uterine relations in the two types of human twins (Corning). *A*, ordinary, double ovum twins with separate membranes. *B*, identical, single ovum twins within a common chorion. (*Redrawn from Arey's "Developmental Anatomy."*)

pride of parentage, the prospective economic burden. In any case curiosity is aroused as to the reasons why his family should have been thus distinguished. For roughly slightly more than 1 per cent (about 1 in 88 births) of cases of child delivery are cases of twin births.* A happening that occurs only once in about a hundred times demands some special explanation.

* Triplets occur about once in 88^2, or 7,744 times; quadruplets once in 88^3, or 681,462; quintuplets about once in 88^4, or 60,000,000 births. Thus the Dionne quintuplets are properly distinguished as a rare phenomenon.

The first fact to be recognized is that there are two kinds of twins. One kind is due to the circumstance that two ova have ripened in the mother and passed into the oviduct at one time, and have been fertilized there This kind is called fraternal twins They may be both of the same sex or of different sex. They are just two children of the family,

FIG 189 Photograph of a pair of ordinary uniovular twins (S) Profile view for comparison of features, form of hair, etc A dissimilarity is to be noted in several characters (*ERO archives*)

with the ordinary origin, who have developed in the mother at the same time (Figs 188 *A*, 189).

The other kind of twin has another and more striking history. This kind starts out as a single fertilized egg At some time early in development two embryos begin to start on this single egg. There is only one implantation upon the wall of the uterus; consequently only one set of embryonic membranes except for the amnion, or caul, which is double —one amnion for each of the twins. Since these twins of this

called identical twins, draw their nourishment through the same placenta it sometimes happens that one twin steals more and more than its share of the common blood and may even deprive its twin of any food. Consequently the latter dies and may even be absorbed. Many a child born singly was started as one of twins.

The exact moment when the two embryos begin to develop on the egg is uncertain. It is probably not true that the first two cleavage spheres separate to undergo independent development, for in such case there would probably be two placentas and chorions instead of one. It is after the egg is implanted and the inner cell-mass begins the work of developing an embryo that that mass divides into two masses (or more, in the case of multiple births of a higher order) and each such mass starts to develop into a child. It forms its own neural groove and body axis. Two (or more) individuals thus arise from the same egg (Fig. 188 *B*).

The special interest in one-egg twins (also called duplicate or monozygotic or monochorial twins) is that since they are derived from the same fertilized egg, they should have the same genes as activators and the same substrate, and should be as like as the right and left sides of the body, or perhaps more alike. They are, of course, always of the same sex. Apart from accident, such as the stealing of nutriment by one of the twins, and possible difference in available space in the uterus, the twins ought to be as alike as the same internal chemico-physical forces could make them, considering their marvelous complexity. By a comparison of identical twins we gain some idea of how near the same internal mechanism, working on the same materials, can come to producing exactly the same thing.

We have all had experience with identical twins brought up in the same household. They are often cause of much

confusion, especially if they dress alike. When I was a teacher of Zoology at Harvard I had a student who was rather striking in his looks, of large frame, with red hair and finely chiseled features. We would, of course, nod as we met passing through the yard But once when I encountered him he met my smile with a stony stare I felt hurt and

FIG. 190 Photographs of profiles of a pair of identical (uniovular) twins Note resemblance of form of nose and other facial features. (*ERO archives*)

wondered how I could have offended him Shortly after I saw the two walking together and understood

Such identical twins are adapted for an investigation into the degree of detail that the genes can control Certainly, identical twins ordinarily resemble each other closely in body build, in bodily proportions, in features, pigmentation and so on (Fig 190) How do they differ? Consider the patterns at the tips of the fingers (Fig. 191), of which it is said that no two are alike, or at least that never an identical set of patterns appears on the hands of any two

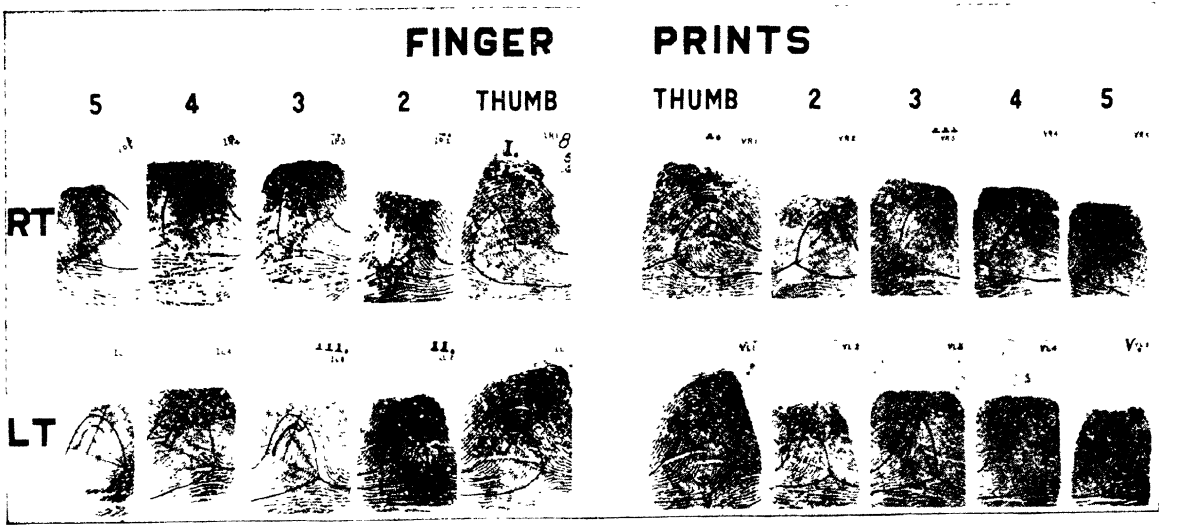


FIG. 191. Fingerprints of the **E twins.** Compare the cores of the prints, as outlined, recalling that right and left hands have the cores reversed. Ina E's prints at left; Yyma's prints at right. Right hands above; left hands below.

persons. Since the patterns are not precisely alike on the corresponding fingers of the right and left hand we should not be surprised to find them not precisely alike on the corresponding fingers of the twins Actually there is much the same close similarity of patterns in corresponding finger tips between identical twins as between right and left hands of the same person Usually the general type of pattern is the same; but the details differ (Fig 191) The same genes cannot determine precisely the same number and form of ridges with the same number of openings of the sweat glands Thus there is a limit to the hereditary or genic control

Again, the question may be raised In how far is the resemblance of identical twins due to similarity of bringing up? To be sure, boy and girl twins brought up together are usually not more alike than a son and daughter two years apart in age.

FIG 192 Photographs of twin boys reared apart since infancy The boy at the right (Raymond) was adopted when 14 months old by a well-to-do physician in a large city, the other boy (Richard) was adopted at 1 month by a truck farmer in Southern Illinois. The photograph was made when the twins were 10 years old. At 13 they were still as closely alike as identical twins reared together (*After H H Newman, courtesy of Journ. of Heredity.*)

Still it would be interesting to learn what would be the effect upon their resemblance of rearing identical twins apart.

Light on this problem has been thrown by Horatio Hackett Newman of the University of Chicago in a series of studies published in the *Journal of Heredity* in recent years. The cases are those of twin children, orphans or of

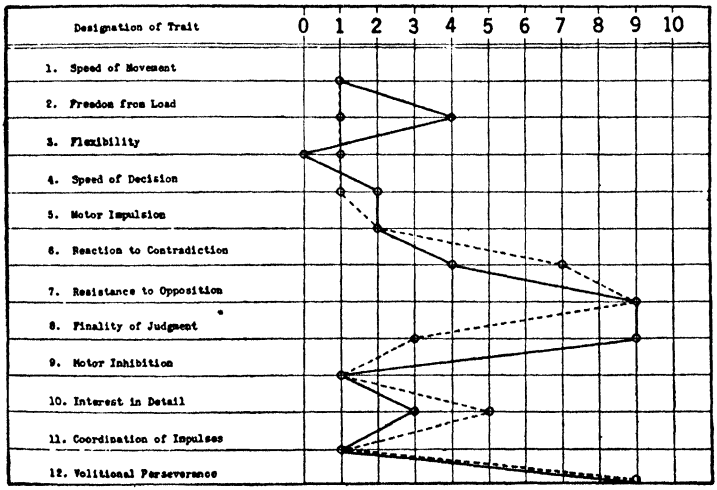


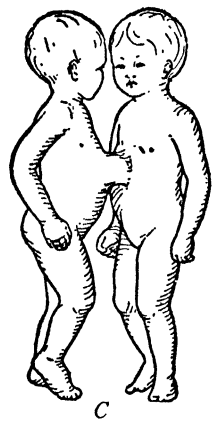
FIG. 193. The Will-Temperament profile of a pair of women, uniovular twins, reared apart. The 12 traits listed at the left are graded (in 10 degrees) at the right. For example, in 6, Reaction to contradiction, the twin represented by the heavy line scored 4; the twin represented by the dotted line scored 7. Except in No. 8 the scores are fairly close. (*After Newman, Journ. of Heredity, 1932.*)

overcrowded families, the two members of each pair of whom have been sent to foster homes, often of quite different sort. Some ten years or more later the twins are studied physically, mentally and temperamentally. In general they maintain the resemblance they had as children. Although their environments were very diverse they re-

mained alike, since both chose unconsciously, as it were, the elements of their environments that their similar constitutions permitted them to use (Fig. 192).

The Will-Temperament profile (Fig. 193) is taken as a measurement of temperament. This is a rough test; but the parallelism is, even so, striking. The pattern of reaction is set before birth and little altered in its fundamentals by different experiences during post-natal life.

It sometimes happens that the twins that develop on one egg are not entirely separate. Hence arises the type of Siamese twins, who may survive (Fig. 194), also the types in which one is so reduced as to be a mere appendage of the other. Finally, there are the types in which the heads and chests are united and these fortunately die very early. They are called Janus monsters, from Janus, the two-faced Roman god, who looked (like the month of January) backward to the past; and forward to the future.[5]



C

FIG. 194. Outlines of symmetrical twins joined at the breast bone. They are of the type known as Siamese Twins. (*From Arey's "Developmental Anatomy," courtesy of W. B. Saunders Co.*)

SUMMARY

As the guesses of the classicists were replaced by the observations of the nineteenth century the problem of development was seen to be centered in the cell. For the cell is the link in the chain of life which extends back to its beginning on earth. The cell wall is at the same time the guardian and the portal of the cell. The cytoplasm affords site and material for vital reproductive operations—it provides the soil and the seed. The nucleus with its genes provides the special fertilizer for the

cytoplasmic field. At the nuclear membrane the fertilizer is delivered to the cytoplasm. The division of the nucleus provides for the exact transmission to each new cell of the precious fertilizing nuclear enzymes.

The cytoplasm of the egg provides all the raw materials out of which the tissues are to be built. But its operations are too slow; the acceleration of enzymes is required. The genes are these enzymes, and they provide hundreds of different kinds arranged in the nucleus in orderly fashion. Each kind of gene is useful to the organism as a whole; it also plays a special role in organ development. The gene molecules double again and again with all the precision of the protein and the cellulose molecules, to reproduce themselves with all their properties at each cell division.

Gene and cytoplasm are not contrasted or alternative in development. They co-operate. At the nuclear membrane the genzymes * accelerate the chemical operation going on in the cytoplasm. The duplication of the genes that occurs at fertilization of the egg increases the velocity of development.

Development proceeds under the operation of a few principal factors: Cell division, imbibition of water, and differentiation in form brought about by foldings, by thickenings and thinnings of membranes, by the spinning of threads and the laying of tubes, by migratory cells, and by the production of the specific cellular and formed substances which characterize the different tissues. Throughout development part acts on part and preserves unity in the process; and in the later stages intrasomatic messages are transmitted between distant parts. Repair is possible through the presence in all parts of the body of cells that remain in a more or less embryonic condition. Such cells

* Genzyme may be used as an abbreviation for gen-enzyme.

are stimulated to developmental activity by injury to or removal of parts.

On the one hand errors in development occur through defects in the developmental machinery, rendered more common by the very complexity of development. On the other hand, marvelous similarity shows itself in the product—identical twins—when the genes and cytoplasm are alike.

NOTES

1. Studies on the amphibia showing the influence of part on part were made early in the century by Hans Spemann of Würtzburg and R. G. Harrison of Yale. Their pupils are carrying on the work thus brilliantly started. Much of it is published in the Journal of Experimental Zoology of which Dr. Harrison is editor.

2. The experiments on limb grafting, made by R. G. Harrison and pupils, are summarized in a paper on "Heteroplastic Grafting in Embryology" published in the Harvey Lectures, 1935.

3. On plastic surgery see the book by T. H. Morgan, *Regeneration*, The Macmillan Company.

4. The importance of lethal (fatal) factors in development was early pointed out by John Hammond of Cambridge, England, in domestic animals and by H. J. Muller in Drosophila. Dr. Otto H. Mohr (1926) of Oslo has made a study of lethal factors in domestic animals and man (Zeit. für induktive Abstam. u. Vererbungslehre).

5. The literature on twins has grown greatly during the past two decades. Horatio Hackett Newman has published the *Biology of Twins* (1915), Univ. of Chicago Press. In Germany O. von Verschuer has led in researches on this topic and has published in the Zeitschrift für induktive Abstam. u. Vererbungslehre, 1917, 1932, and elsewhere. In England Francis Galton gave a great impetus to the study of twins by the chapter on History of Twins in his *Inquiries into Human Faculty* (1883), reprinted in Everyman's Library. A charming book.

6. On the skin is a good chapter by Charles R. Stockard in Morris-Jackson's *Human Anatomy*. On blood consult W. H. Howell's *Textbook of Physiology*.

PART III

HISTORY OF THE ORIGIN OF THE MACHINERY OF DEVELOPMENT

CHAPTER 11

THE HISTORY OF OUR GENES AND THE MECHANISM BY WHICH THEY HAVE BEEN HANDED ON TO US

We have traced the course of development of the child and have looked into the machinery of that development. We have now to consider the history of that machinery.

The machinery is, as we have seen, a device of catalysts in the nucleus and substrate in the cytoplasm by which the materials of the cell are manufactured. Also, a responsive cell protoplasm such that part acts on part and secures an appropriate reaction; also, a device by which part of the formative processes are early turned over to intermediary agents, the endocrine glands. In addition there is a polarity that affects the organism as a whole. Thus there is not merely a single kind of factor active in child development, but several potentialities of the protoplasm are utilized.

The history of the machinery of development is so long, complicated and little studied that it would not be profitable for us to attempt to consider all parts of that history. Three topics only will we attempt to consider. These are: First, the history of the germinal stuffs, genes and cytoplasm. Second, current changes in the germinal stuffs as indicated by mutations and their inheritance. Third, the well-worn path of vertebrate development which directs the development of the child.

We have examined the genes, have considered the role they play as catalysts and the way they are passed on from cell to cell by the chromosomes. We have now to inquire

what has been the probable history of the gene-complex and the chromosomes? I say *probable* history, because the studies in this field are still very incomplete.

As we have seen (Fig. 135) man's body cells contain twenty-four pairs of chromosomes. Europeans, Japanese and Negroes have the same number of chromosomes and the arrangement of genes in them is probably the same. In how far there has been a change in chromosome number in the anthropoid section of the Primates to which man belongs cannot be said. The chromosomes of the Rhesus, or macaque, monkey of India and Japan, comprise also twenty-four pairs, as Fig. 136 shows. There are certain resemblances in the sets of chromosomes of man and Rhesus, especially there is in both a very large pair, also a pair of very unequal size (placed at the right in Fig. 136) which constitute the sex chromosomes or the *XY* pair. The chromosomes are such flexible objects that it is hardly feasible to make successfully a detailed comparison of the two series. The chromosomes of a third species of Primates, the American monkey, Cebus (Fig. 136), have been studied and twenty-seven pairs found. Consequently even inside the group of Primates the number of chromosomes has undergone a change.

In other mammals the number ranges from six (kangaroo) to thirty (goat) pairs. On the whole, the number increases from the lower mammals to the higher, six to ten pairs being common among the marsupials of Australia. There has probably been an increase in the chromosome number in the course of the evolution of mammals.[1]

Whatever may be the case with the chromosomes it is certain that the kind and probably the number of genes has increased with the differentiation and increasing complexity of mammals in passing from the lowest to the highest

forms. And even in the different races of mankind the distinguishing differences are evidently genic differences, a point to be discussed later in more detail.

To get the history of the evolution of the gene-complex we must go to the lowest organisms. And here we meet with an initial difficulty: What are the lowest organisms? What is the essential property that enables us to distinguish the lowest forms from the inorganic? Perhaps for our purpose it will suffice to call organisms those which contain particles that are capable of self-proliferation.

Starting out with this definition what do we find in the way of self-proliferating genes in each of the simplest organisms?

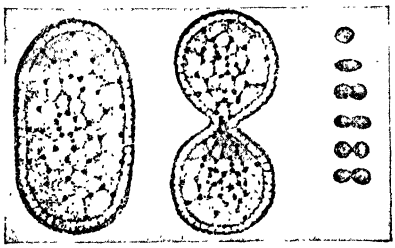
BACTERIOPHAGE

First, let us examine what is known concerning the bacteriophage. This particle is regarded as having a diameter of 50 to 200, or even 600 Ångstrom units. If the smallest estimated diameter were accepted as correct there would perhaps be only 1 molecule, having a diameter of 50 Ångstrom units. Using the middle estimate the bacteriophage might comprise 100 molecules. As Rahn says: "The bacteriophage has almost no 'characters'; it is formless and structureless, has neither 'size' nor color, consists of 1 molecule or very few, which hold together by some sort of attraction. The only character inherited from organism to organism is apparently that of transforming the albumin of the host into its own albumin. One can regard the bacteriophage as an organism with a single gene." This gene seems to be very destructive of the cytoplasm of bacteria upon which it appears to act by breaking up their molecules with water. Some of the resulting units it transforms into its own kind of molecule; which, as it increases in size, divides

into one or more parts. Here is a vital process of chemical interaction between two organic particles which are not in the same individual, with self-proliferation of one of them. It is life in its simplest form.[2]

VIRUSES

Next, let us consider the filterable viruses, some of which are responsible for some of our worst diseases, such as smallpox and influenza, yellow fever, poliomyelitis, foot and mouth disease in cattle. These viruses are larger than the bacteriophage. Some of the largest should appear on photographs made with ultra-violet light and are, say, 1,000 Ångstrom units in diameter; the smallest are not bigger than bacteriophage. They may well each comprise 500 to 5,000 molecules. A large share of these molecules must be organic catalysts, interaction of which with the particles in the blood (hence outside of themselves), results in the production of virulent toxins. Isolated, the virus may not be "alive" but its interaction is of the nature of a vital process.



A *B* *C*

FIG. 195. Structure of a bacterium, Achromatium species; *A*, resting; *B*, in division. Numerous pigmented granules are seen. These are believed to divide as at *C*, but they do not form chromosomes. (*After Schewiakoff, from E. B. Wilson's "The Cell," courtesy of The Macmillan Co.*)

COCCI AND BACTERIA

These are various forms of the world's greatest ferments. Thus acetic acid bacteria by interaction with fruit juice form vinegar; lactic acid bacteria cause milk to go sour; others cause fermentation of silage, upon which dairymen feed their cows; some

forms of alcohol and aldehydes are commercially produced by bacteria. Decay of organic matter is largely brought about by them. Some of them are the great enemies of living tissues. As they act enzymatically or zymogenetically upon such tissues they produce poisonous toxins that may kill the largest hosts. They divide with such rapidity that, if growth is not limited, 1 bacterium at the body temperature will produce in 72 hours 4,772 trillion bacteria. Of course growth is eventually limited (else we should all be pushed off the planet) through exhaustion of food and accumulation of noxious excreted products. The rate of increase eventually slackens and finally decreases to zero.

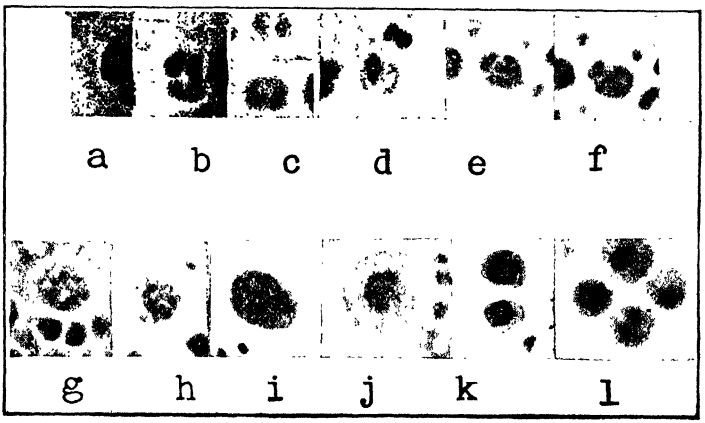


FIG. 196. Division of genes and cytoplasm in a bacterium—(a) The diplococcus (double coccus). This is one of the smallest of bacteria. (b) The diplococcus has divided across the plane of its septum to form four cells. (c) Separation occurs along the plane of the original septum to form two daughter diplococci. (d) There now appears in each cell a deeply staining spot, the "nucleus." The nuclei unite as the pair of cells blend. In later stages (e, f, g, h) stainable particles appear, probably chromidia, each with a gene at center. Finally, these condense, forming a thread, and become covered with chromatin. (i) The "chromosome" thread now divides into two (j, k) and one piece goes to each daughter cell. The threads condense into the nuclei seen in each cell (l) as in Fig. d, also. (*Contributed by Dr. Carl C. Lindegren.*)

The special enzymatic material of bacteria is, by hypothesis, the genes, and these must multiply as the cells do. These genes at their metabolic stage seem to be grouped in some cases at the inner surface of a nuclear membrane; in other cases there is no such membrane (Fig. 195). In the

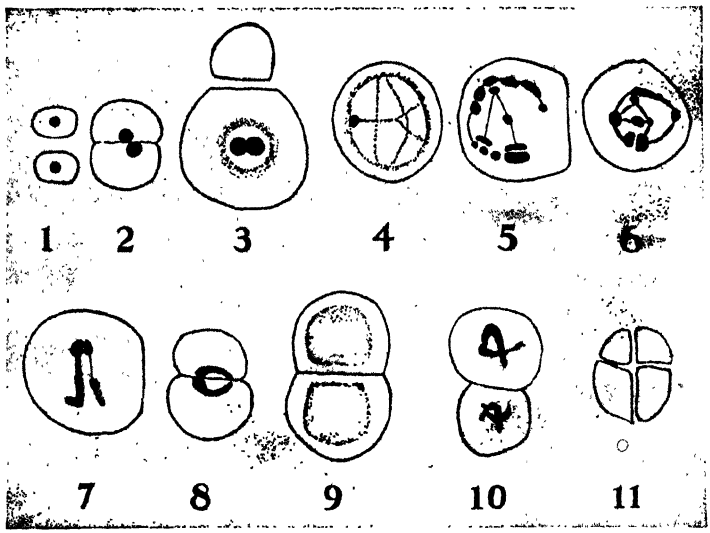


FIG. 197. More diagrammatic figures from the tubercle bacillus; showing phenomena that suggests a sexual mechanism in this bacillus. 1, 2, 3, two cells come together and their nuclei blend. 4, perhaps a "resting" stage of the nucleus; 5, 6, 7, deeply staining particles come together to form a chain, or chromosome (?); 8, the cell divides and so does the chromosome; 9, diffuse stage of chromatin; 10, 11, a second cell division. (*From Lindegren and Mellon, 1932.*)

former case the genic material comes to form rods in the cell center and these divide, crossways, more or less precisely. In other cases in the division of the cell body the scattered genes are segregated with approximate equality by first aggregating in an axial thread (Figs. 196, 197). Since the bacterium has so few organs perhaps we may say that

it needs and probably has few *kinds* of genes and many of one kind; so that division of the genes is in them quantitative rather than qualitative.

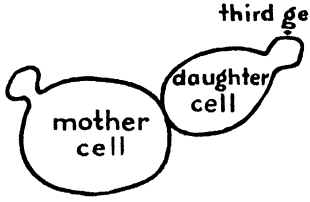
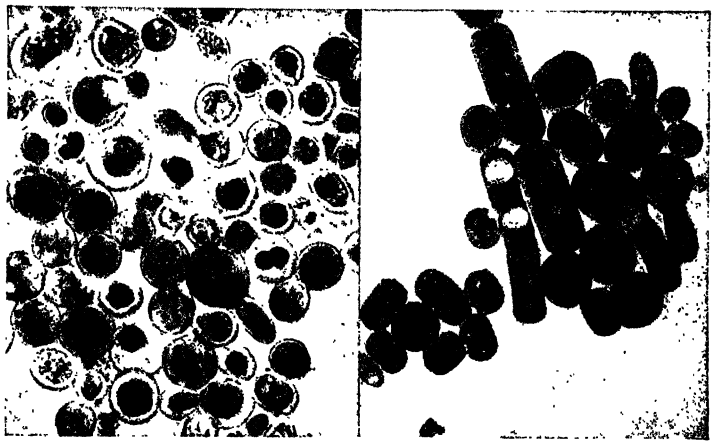


FIG. 198. Outline drawing of yeast cells in act of reproducing by budding instead of fission as in the case of bacteria. (*After Rahn, Cold Spring Harbor Symposia, 1934.*)

YEAST

Yeast is the enzyme producer par excellence, in fact the word enzyme is derived from the Greek, meaning, in yeast. The ferment resides in small cells, about 6 microns in diameter. It is estimated that a



A B

FIG. 199. (A) A photomicrograph of cells in a common type of yeast illuminated with wave length of 2,750 Ång. Many of the central vacuoles contain strongly absorbing material. Magnif. ca. × 2,700. (B) Similar ultra-violet pictures of living cells in another yeast which shows a tendency to produce threads. These cells are more opaque than those of (13). (*After Ralph W. G. Wykoff, Cold Spring Harbor Symposia, 1934.*)

yeast cell contains at any moment between 15,000 and 150,000 molecules of the enzyme called invertase and about

20,000 molecules of catalase. One yeast cell with a volume of about 200 μ^3 and weighing (at the specific gravity of water) 5×10^{-9} grams ferments 50 million sugar molecules per second to alcohol and CO_2.* Even so the yeast cell ferments less than 1/10,000,000,000 of its weight per sec-

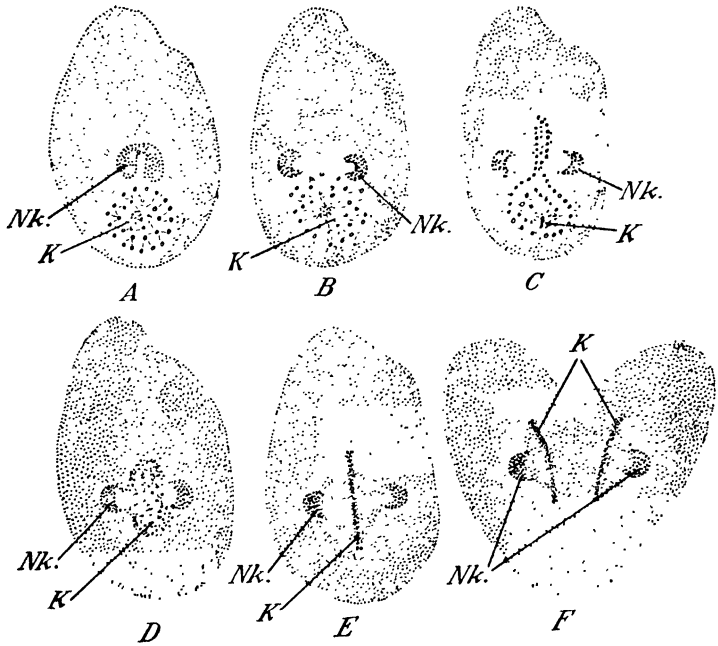


FIG. 200. Division of the cell body of the protozoan, Paramecium. The nucleus is at *K*, center of division appears early at *Nk*. As the latter doubles and takes the bipolar position the staining particles of the nucleus come to lie between the poles and the one nuclear plate divides into two with the division of the cell. × 1,500. (*Redrawn after Schaudinn, 1896.*)

ond; but, of course, only a small fraction of the weight of a yeast cell consists of enzymes.

How are these enzymes passed on to the rapidly increasing number of yeast cells? First, the yeast cell does

* O. Rahn in Symposium on Quantitative Biology, Cold Spring Harbor, Vol. II, p. 63.

not ordinarily multiply by division into equal cells but by budding (Figs. 198, 199). What this means is hard to say. Each bud is believed eventually to become a full-sized cell capable in time of producing buds. Each bud has a nucleus in its cell which divides at the same time with the cell. Second, the chromatic material apparently masses itself before cell division and then divides without the mitotic figure and without the appearance of chromosomes. Thus in the lower organisms the chromosome has apparently not yet evolved and the number of kinds of genes is small.

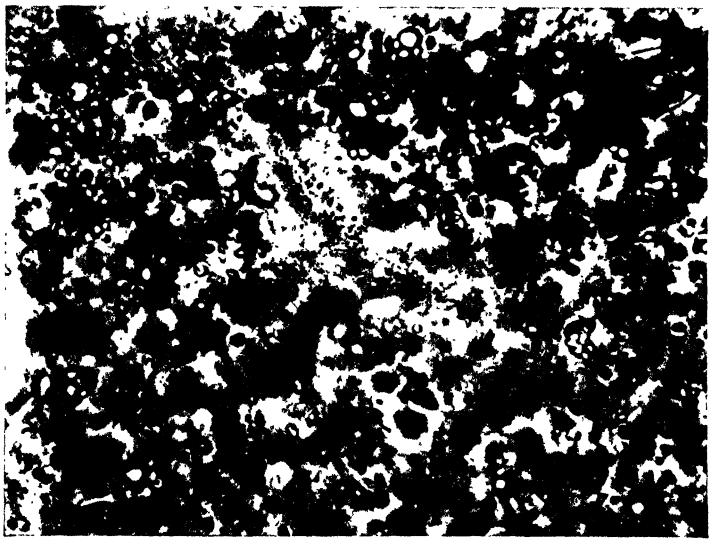


FIG. 201. Photograph of Amoeba proteus in the act of dividing, showing the assemblage of chromidia at the equator, without assemblage into chromosomes. × 2,000. (*Contribution of H. W. Chalkley.*)

PROTOZOA

Passing next to the simplest animals, let us consider the Amoeba (Figs. 200, 201). Probably the particles which correspond to genes are those that come to be arranged

at the equatorial plate to secure a more equable distribution to the two poles. But there is no evidence of an arrangement of the genes into chromosomes that undergo a precise splitting as in the higher forms. The particles seem to be identical with those chromomeres that are shown in

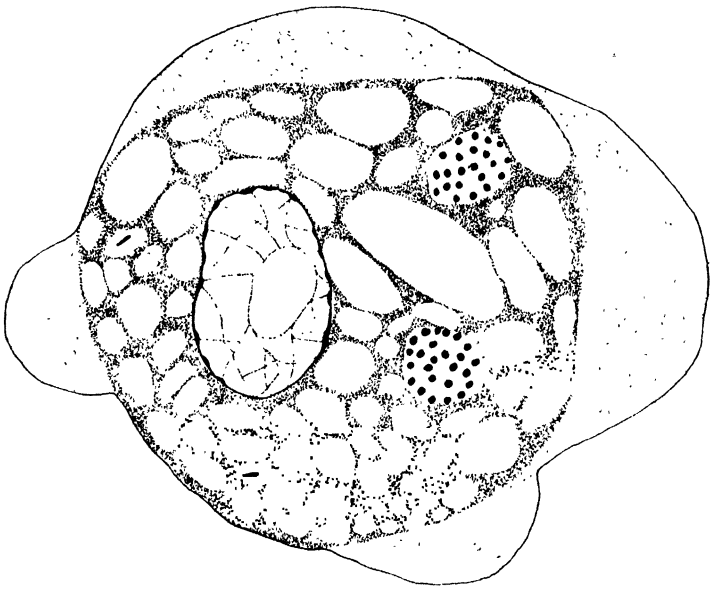


FIG. 202. Drawing of a parasitic Amoeba (Councilmania), showing stainable particles (chromidia) at nuclear membrane. (*After Kofoid and Sweezy, redrawn.*)

Fig. 132 as making up the cross bands of the salivary gland chromonemata. As shown in Fig. 202 these particles apparently assemble at the nucleus membrane in the metabolic stage of the nucleus. In some of the higher Protozoa (Fig. 203) the genes apparently come to lie in threads which break in two in the middle, half going to each daughter cell. In one of the highest Protozoa types (Fig. 204) the dispersed genes arrange themselves in linear series looking like

chromosomes, each series divides crosswise and the halves go to the prospective daughter cells. This set-up more nearly approaches that of the higher organisms.[3]

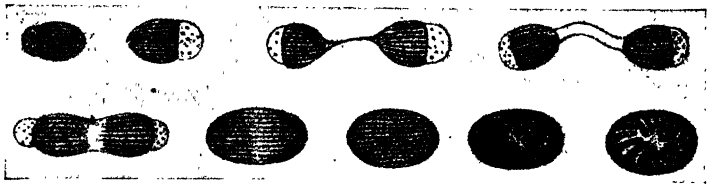


FIG. 203. Division of the nucleus in a ciliated protozoan (Spirochona gemmipara). Stainable granules (chromidia) are seen to arrange themselves in double rows nearly parallel to the line of division. They tear apart in the middle and the separated ends go to the two poles. (*After Balbiani, 1895.*)

Finally, in the higher plants and animals a mitotic figure with exactly dividing chromosomes is practically universal.

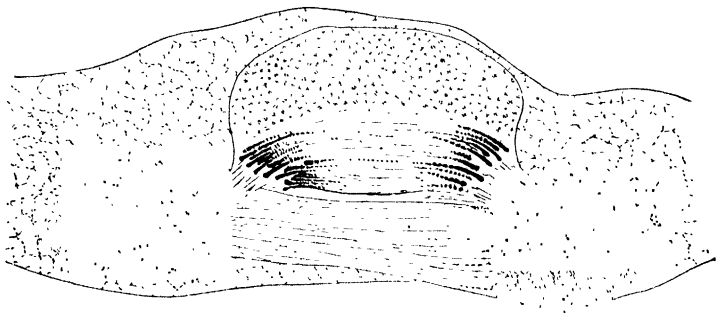


FIG. 204. Nuclear division in one of the highest of the Protozoa (Noctiluca). The chromidia assemble in lines parallel to the axis of division. They break in the middle and the ends go to the two poles. (*After Calkins, 1898.*)

What is the significance of the chromosome? The hypothesis may be offered that it is a device for securing the precise qualitative division of all the kinds of genes that in its evolutionary history the nucleus has accumulated.

The increasing complexity of the organism is correlated with more kinds of catalysts. Any device that cells offered in the way of securing the more precise qualitative division of all the kinds of genes and transmission of them to all daughter cells would lead the offspring built up of such cells to survive. On the other hand, as Demerec has shown, the complete loss of some one gene may be fatal. Thus the more efficient mechanism of the chromosome became established by selection. Thus have the mitotic figure and the chromosomes of the child, as the directors of our development, come to be our heritage.

HOW WE CAME BY OUR GENES

And what, in broadest outlines, can we say about the history of the human genes? First, there has been an unbroken line of gene-stuff from the earliest organisms to the highest.

Second, the more numerous the genes have become the greater the number of cells in the body and the greater their histological differentiation. A mammal with its muscular, nervous, glandular, bony tissues has certainly a more complicated genic structure than an Amoeba or a segmented worm.

Third, the numerous and multifarious genes must have evolved from the smaller number of genes in the lower organisms. The increasing complexity of the tissues in the high forms is an index of the increasing number and kinds of genes. Also, the increase in kind of these genes has permitted the evolution of organisms from the simple to the complex. But chance change in the genes has not been the sole directive force in evolution. Probably not one in a million of such changes was able, in times of stable environment, to show such an improvement in the soma as to give

its possessor any advantage in its relation to the world about it. Most changes generally led to the death of the nascent individual who was unfortunate enough to experience them. Selection of viable and indeed superior genes has been the order of evolution.

It appears, then, that some of man's genes are as old as organic life on earth though they have undergone change in number and quality. Man's genes are the highly selected hereditary units that have resulted from aeons of modification and selection. It is amazing that man so little appreciates their value that he so often refrains from reproducing them. The farmer and the stock breeder at least appreciate the value of the gene, because success in their business depends upon that appreciation. How keen that appreciation is is shown by the fact that $150,000 has been paid for a single race horse which had, indeed, passed his prime as a racer. He was purchased not for racing, nor for the meat market, but solely for breeding. The purchaser was really expecting to make use of a few effective sperm cells, each with some tens of thousands of genes. Suppose a million of these genes actually are required to start a control of the development of 40 offspring, then the combined weight of all these genes would be 2×10^{-10} grams, or 2/10,000,000 of a milligram, valued at the rate of $750,000,000,000 per milligram. Surely there is no other material than the gene that can command so high a price. Some genes are the most valuable material in the world.* Of course, not all germ cells are very valuable; some, indeed, may be responsible for traits that are prejudicial to the social order. Accordingly society may properly decide

* I have known a wealthy childless man who had in his youth and middle-age wasted the genes of his sperm cells and who in later years would have given a million dollars to have had one of them effective in the development of a child and heir.

that, through sterilization, persons carrying such pernicious genes shall not become parents.

HOW WE CAME BY OUR CYTOPLASM

We have already learned (page 167) something of the complicated chemical structure of the egg. A thoughtful consideration of that structure should give us added appreciation of the egg. It is not merely an accumulation of "food stuffs," as it were the cold victuals and water which the beggar had picked up from the neighboring cells. The cytoplasm has a much deeper meaning than that. For the cytoplasm has not only nutritive materials but also its plastids, chondriosomes, Golgi bodies, vacuoles and central bodies which control cell division. Where have these varied constituents of the cytoplasm of the egg cell come from? We have already considered this matter (page 156), and found that evidence is accumulating that chondriosomes, plastids, Golgi bodies and some vacuoles divide and pass into the cytoplasm of the daughter cells just as the chromosomes and their constituent genes do. From this point of view these elements of the cell and the cytoplasm in general, have the same sort of continuity from generation to generation, indeed the same hoary antiquity, that the genes have. Also, they are not merely gene-fodder, but they are the real builders of the developing child that make use of the specific catalytic properties of the genes to regulate and expedite their chemical operations.

It is known that there are certain ants which cultivate in their burrows a certain fungus upon which they feed. Whenever the colony divides some of the spores, or threads, of this fungus are transplanted to the new subterranean homes. In like fashion the cytoplasm through the generations has carried with it the nucleus-packets containing a

complete assortment of these precious genes without which reproduction of its kind would be impossible. Since the number of kinds of cytoplasmic materials in the egg is probably small as compared with the number of molecules of each kind it is not necessary that the cytoplasm should have a special device to ensure that each kind of molecule in about the right amount should be transmitted to each daughter cell or each egg of the ovary.

The hypothesis of continuity of the cytoplasmic inclusions does not fail to recognize that new nutritive particles or molecules are being absorbed by the ova in the ovary and by all the cells during development. What the nature of these nutritive particles or molecules shall be and what they shall become is determined by the nature of the cytoplasm and especially of the cell wall and by temperature, oxygen tension, etc., especially during the later steps of development of the embryo. Much of this food stuff may be of the nature of raw material which may pass through one or more processes in the ovarial ovum before becoming available for the specific action of the genes. The action of the genes, as we have seen, is probably concerned especially with manufacturing the materials for the different tissues and organs; materials which have to be elaborated with relatively great velocity.

Thus the cytoplasm is to be conceived as made up of, or including, self-reproducing material of specific nature. It carries along with it through the generations also the especially precious genes contained in that nucleus which is at the same time their stronghold and their workshop.

HOW DID THE CELL ORIGINATE?

Reviewing the facts of evolution of the chromosomes and cytoplasm and viewing their interrelation and mutual

dependence we may hazard a speculative suggestion as to how this association was first brought about before the organic world was in existence. It seems most probable that an (inorganic) catalyst entered into relation with some primitive carbon dioxide + water + nitric acid + hydrogen disulphide ($CO_2 + H_2O + HNO_3 + H_2S$) compound or mixture and that out of these the precursor of a glucose or glycine molecule was formed. In time some cellulose or protein molecule evolved and the catalyst was attached to that. Eventually new catalysts were formed and new kinds of protein and cellulose molecules arose. Thus would life originate. For life is the product of the interaction of a special enzyme and suitable substrate. "Living substance" is that which is capable of generating life.

That cellulose can be formed out of H_2O and CO_2 in the absence of sunlight by the sulphur bacteria as well as some Protozoa (Mast) is well known. Perhaps it is not a great step back to the stage when the precursor of the enzyme of the sulphur bacteria, before there was any cell body, was able to perform this synthesis. As glucose and glycine strings begin to form and grow, a breaking up of the strings becomes inevitable and new self-perpetuating units are formed. Such a synthesizing machinery once started would continue, under the operation of selection of successful additions to the machinery, until the modern world of organisms should be brought into being.[4]

NOTES

1. To our knowledge of chromosomes of mammals, especially Painter has made a series of contributions, largely published in the Journal of Experimental Zoology.

2. On the bacteriophage, virus and bacteria a handy reference book is that of A. D. Gardner, 1931 (London: Methuen). Our

figures of yeast are taken from Cold Spring Harbor Symposia, Vol. II.

3. A good book on Protozoa is that of Gary N. Calkins published by The Macmillan Co., N. Y.

4. On synthesis of organic matter out of inorganic by Protozoa see S. O. Mast and D. M. Pace (1933), in Protoplasma, Vol 20.

CHAPTER 12

THE CHANGING WORLD OF ORGANISMS; MUTATIONS AND HOW THEY ARE HANDED ON

We have considered the way in which the genes and cytoplasm co-operate in the production of an individual. We have seen the great precautions that the cell takes to secure the transmission from generation to generation of each gene and a typical sample of the cytoplasm. We understand from these facts how the children come to resemble the parents; and how the species is continued through the ages.

Yet, were this the whole story we should be unable to understand how the different races of mankind have arisen and the fact that families show family differences. All blood lines even the most inbred are undergoing change. What is known about the phenomenon of genetic change or mutation?

ORGANIC CHANGE

So complicated a molecule as the protein molecule can hardly persist indefinitely without change, and experience shows that it does not. Even a weak organic acid in distilled but alkalized water kept hermetically sealed in a safe for years may, at the end of the time, reveal many products. Yeast of a given strain, similarly held living at a low temperature and reproducing only very slowly will, in the course of years, produce enzymatically new strains. It is

not amazing to find that seeds kept long may show new gene characters (mutations); or that by special treatment (X-rays) the normal rate of occurrence of such mutations may be accelerated.

"Sports" have long been observed in cultivated species. Smooth-skinned nectarines came suddenly from peaches. The Concord grape mutated from a wild species. Trotting and pacing are mutations of gait in horses that have been observed in captivity and that have been eagerly seized upon by horse breeders and allowed to reproduce. The different traits of the various kinds of dogs, cats, poultry, have been discovered, often fully made, by breeders who have looked for them and once having found them have continued to breed and improve those mutations which they regarded as valuable. Mutation is found also by all who breed feral animals and plants and carefully consider the traits of each generation. They are found to be practically infinite in quantity and kind. They lie at the base of organic evolution.

We shall in a moment consider what is known about gene change. We must here consider what is involved in such change, during hundreds of millions of years.

Genes can be modified without losing their identity. This is demonstrated in the phenomenon of multiple allelomorphism.* Thus in the coat color of guinea pigs are shown such modifications as intense pigmentation, slightly dilute pigmentation, fuller dilute pigmentation, red-eyed dilution, incomplete albinism (pigmentation of extremities). These stages of coat color are due to the *same gene*, slightly altered. In the human family there are such

* Allelomorphs (now frequently shortened to alleles) are contrasted or opposing traits—other forms which may replace each other in heredity, e.g., blue and brown eyes.

alleles of which the best-defined case is that of the AB blood groups, of which more below. Now, what do these alleles tell us about the nature of the gene?

There can be little doubt that the gene is, like most organic catalysts, a protein molecule, or at least is attached to a protein molecule. Some protein molecules are very complicated, made up of elementary complexes that are easily dissociated. Change of elementary complexes might well produce quantitative changes in the work done by the one gene. By more profound molecular changes greater quantitative changes in the gene will occur.

Mutation. Experimentation has revealed an unsuspected capacity of organisms to change or mutate more frequently than usual when placed under special conditions. The means used are high temperature, radium, ultraviolet rays and especially X-rays. These agencies acting upon the germ cells or even young embryos may cause such modification of the genes as will lead to important somatic changes in great number. The changes that occur are conditioned by the structure of the genes that are affected. They are of the same kind as occur spontaneously, i.e., without special treatment; but the treatment accelerates greatly their appearance.

The number of different mutations that have arisen in the fly, Drosophila (the organism that has been most studied genetically), is about 300 (Fig. 205). Some of those affect body color, eye color, size and form of wings, form of body, form and number of appendages, bristles and internal organs. Many mutations cause the early death of the fly, probably because vital organs are affected. Probably any part of the body may have its development affected by mutation.

Mutations are of a number of types. They are to be

expected, independently occurring, both in the cytoplasm and the genes, but they have been carefully studied only in the latter case. Mutations of the genes involve either the

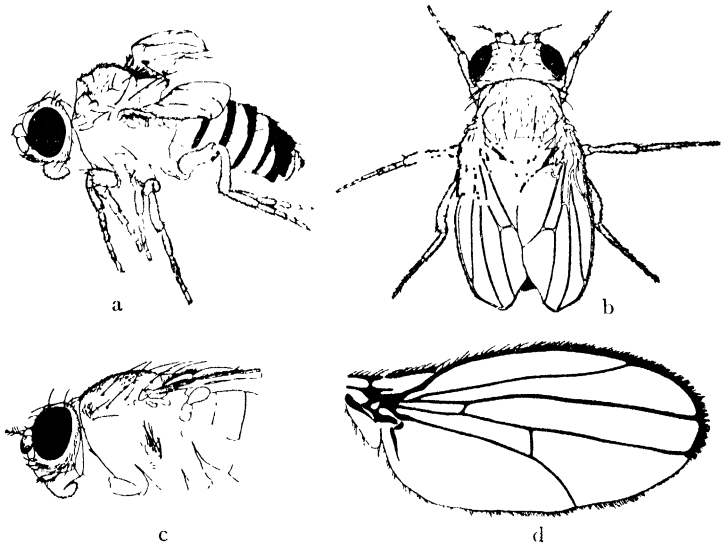


FIG. 205. Mutant races of Drosophila melanogaster. a, "humpy," a second-chromosome recessive, where the most obvious changes are the very rough body surface and the much shortened curved wings, but where all parts of the body are apparently changed to some degree (multiple effects). b, "miniature," a sex-linked recessive wing change, apparently not accompanied by significant changes elsewhere (simple effect). c, "sternopleural," a second-chromosome dominant mutant, having extra numbers of bristles in one small area. Lethal when homozygous. d, "fused," a sex-linked recessive change in venations, entirely sterile in females but with normal fertility in males. (*Illustrations and information through courtesy of C. B. Bridges.*)

gene groups, or chromosomes, on the one hand, or single genes on the other. Of the chromosomes one or more may become tripled; or all may be tripled, quadrupled or multiplied more times. The quadrupling is often effected without interfering with normal development; the resulting individuals merely have all their cells of double size and so the

whole body becomes of double size. In other cases the gene string is fragmented; the fragments may come to be replaced with ends reversed; or they may make abnormal unions with fragments of dissimilar chromosomes. Some of the chromosomal mutations permit the individuals to survive, but usually altered in form. In many cases the individuals develop badly or die early.

Mutations that affect single genes are the commonest. The differences between races and families are largely due to such. And when strains carrying dissimilar gene mutations are crossed, as happens all the time in our vastly mongrelized human species, intermediate traits occur. These intermediate traits are partly due to the fact that one gene will develop traits more slowly and less completely than two genes of the same kind (page 238).

Now when a gene mutates the organs or tissues of the body that depend upon its activity show a change. Indeed the differences between people are chiefly due to the fact that, as between them, one or more of their genes have become different. When a family shows a striking family resemblance it indicates that all of the children have received from the germ cells of one or both parents one or more modified genes; that is, genes that induce an idiosyncrasy.

These idiosyncracies may be of body size, proportions, form of features, pigmentation, chemical constituents of blood, endocrine glands, resistance to disease and so on. It may be worth while to illustrate this point by citing a number of human mutations and indicating the probable genes involved and the type of inheritance shown. A full catalogue would be impossible, for mutations in human development are almost limitless, affecting every organ directly or indirectly.[1]

STATURE

The range in height of the races of humans is very great; and these differences depend upon genes, which work probably chiefly in determining the activity of certain

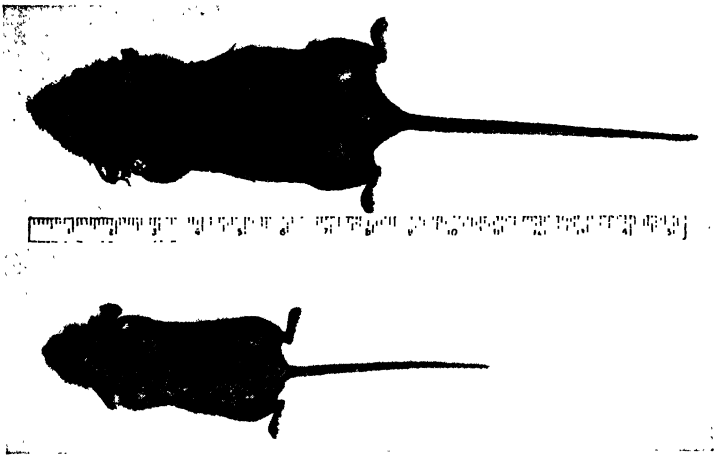


FIG. 206*A*. Photographs about $^{11}/_{20}$ natural size and at the age of 84 days, of two mice litter mates, both of which are congenital dwarfs. No. 17 (below) was untreated and grew practically not at all after 2 days following birth, remained at 6 grams weight. No. 18 (above) was given forty implants during 50 days of fresh anterior pituitary gland. No. 18 increased in weight from 6 to 17 grams in about one month; or at about the same rate as normal mice of the same strain, as shown in the growth curves at Fig. 206*B*, where the full, nearly horizontal, line at the bottom is the growth curve of the dwarf; the rapidly rising broken line with solid points, is that of her treated sister (No. 18), and the unbroken line that of another dwarf mouse similarly treated. (*After P. E. Smith and E. C. MacDowell, courtesy of Dr. Smith.*)

endocrine glands. The shortest race on the globe is the Pygmies of Africa whose males average 141 centimeters or about 56 inches. The tallest is the Negroes of the Lake Chad region of Africa. There the males are, on the average, 182 centimeters or 73 inches tall. The Scots of Galloway are almost as tall (179 cm. or 72 inches).

Now, if a full-blooded tall mutant should mate with a

full-blooded short mutant the children would be mostly below the average in stature, because the factors that make for shortness are, on the whole, dominant. A child who receives the dominant stunting factors will have

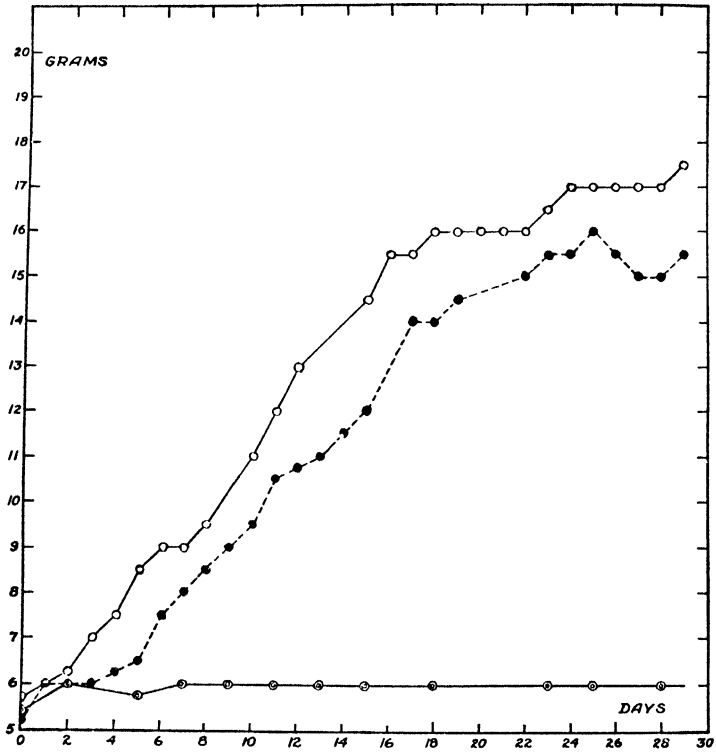


FIG. 206*B*.

probably a smaller or less active pituitary gland than one who does not receive the stunting factor. Active pituitary gland means active thyroid and active suprarenals. For, abundant hormones from all these glands collectively stimulate metabolism and cause the child, and especially its extremities, to grow rapidly.[2]

The experience of Edwin Carleton MacDowell (of the Carnegie Institution) and Philip E. Smith (of Columbia University) with a dwarf infertile family of mice is instructive. The adult dwarfs were about one-third the size of non-mutated mice of the same general strain (Fig. 206*A*, *B*). They were found to have rudimentary anterior pituitary glands; their thyroid glands were devoid of the globules of secretion that fill the active glands; of the suprarenal glands the outer layer which is normally made up of high cells, showed only small flat cells; the mature individuals were infertile. These mice were given anterior pituitary hormones daily and after two weeks or so extraordinary changes occurred. The mice began to grow, the thyroid began to make its hormone, the suprarenal outer layer thickened, the males became fertile. But the pituitary gland itself had not developed; it

FIG. 207. Side views of two children (O. R. and N. C.), the boy (left) 14, the girl (right) 12 years of age. They are of about the same mentality (I. Q.) and have for about the same number of years been reared in the same institution, under nearly similar conditions. *a* is of pure Italian stock, *b* of pure Danish stock. Photographs on same scale.

had no need to, since its function had been artificially furnished.

Figure 207 shows the difference in stature of two children, *a* and *b*, of the same age. The father and mother of *a* were respectively very short and very short; of *b*, tall and tall.

FIG. 208 Photographs of "Miss Allen" at the ages of 4 and 23 years, respectively, giving evidence of the persistence of an early juvenile type of fleshy build (*ERO archives*)

a is of three generations of Italian ancestry on both sides; *b* of three generations of Danish ancestry. The children were reared in the same institution under as nearly similar conditions as possible. The shorter one is a boy. It is the genes of South Italian and of Danish stock respectively that are determining by however circuitous a route, that the one child shall grow slowly; the other rapidly.

In some children growth stops at about seven years—such become ateliotic dwarfs (Figs. 90 and 187). Probably in these cases the pituitary gland ceases to function properly

at that time. Pituitary extract has been given to such dwarfs. In some cases growth has then started up again, but as ateliotics may start growing at adolescence without

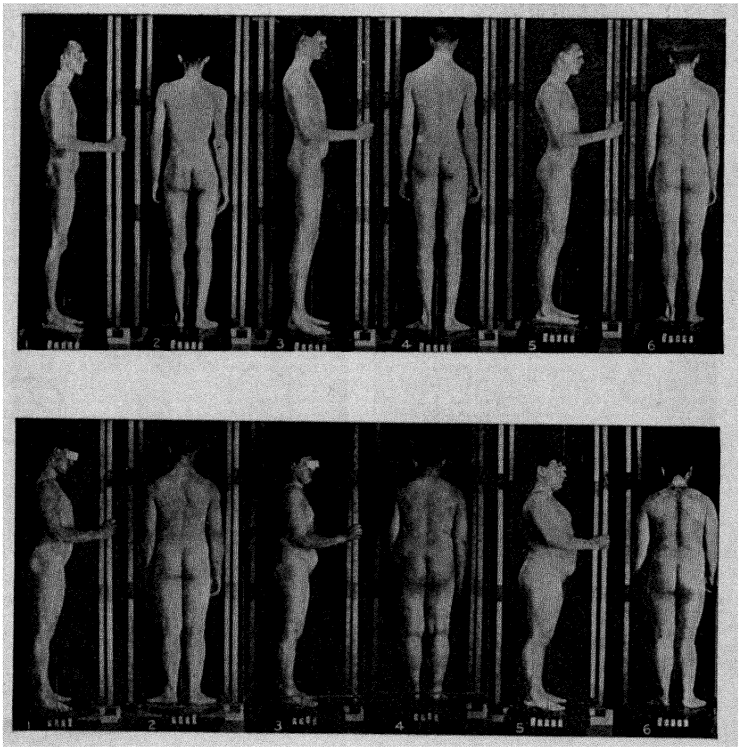


FIG. 209. Side and rear aspects of a series of men representing a standard scale of body build. Top row: 1, 2, below average of very slender group; build index 1.6; 3, 4, average very slender build, build index 1.65; 5, 6, slender build, index 1.98. Bottom row 1, 2, medium build, index 2.3; 3, 4, fleshy build, index 2.7; 5, 6, very fleshy build, index 3.5. (*Carnegie Institution Publ. No. 329, also ERO archives.*)

treatment the efficiency of the treatment is uncertain. However, in ateliotics some internal secretions are obviously at fault.

BODY BUILD

Some children develop a slender body build; others a fleshy build (Fig. 208). The genes for body build act largely through the endocrines; the thyroid and pituitary are also involved here. If both parents belong to slender stock all the children will ordinarily tend to be slender. If both parents are very fleshy the offspring will vary, fleshy and very fleshy predominating. The greater variability of the offspring of matings fleshy by fleshy, as compared with slender by slender, suggests that the genes of the former are dominant, so that the offspring of "fleshy" matings occasionally reveal the recessive, slender condition. Fleshy persons ordinarily belong to fleshy strains by virtue of special genes or cytoplasm. Occasionally, however, by some post-natal disturbance in the endocrine balance, it is possible that a pathological gauntness or obesity may result that is not strictly racial but pathological (Fig. 209).[3]

CEPHALIC INDEX

For a long time mankind has recognized important differences in head proportions of the different races. The "round-heads" in the British parliament of Cromwell's time were called so merely because they cut their hair short. But long-headed Englishmen have long been recognized, and regarded as shrewd. Indeed, looking mankind over, the races are divided into (1) long-, (2) middle-, and (3) short-headed (Fig. 210). (1) includes the Negroes of Africa and certain East Indian tribes. (2) includes among the longer-headed the Nordic Europeans and certain East Indian tribes; among the shorter-headed the Dutch and Letts, the Burmanese, some Chinese and some Amerindian tribes and Eskimos. Of the shortest heads (3) ex-

tremes are found among Lapplanders, Dalmatians, Serbs, many Asiatic peoples, some Polynesians and many Amerindian tribes, especially Apaches. The fact that these differences in skull-form are racial (when not artificially caused) implies germinal differences

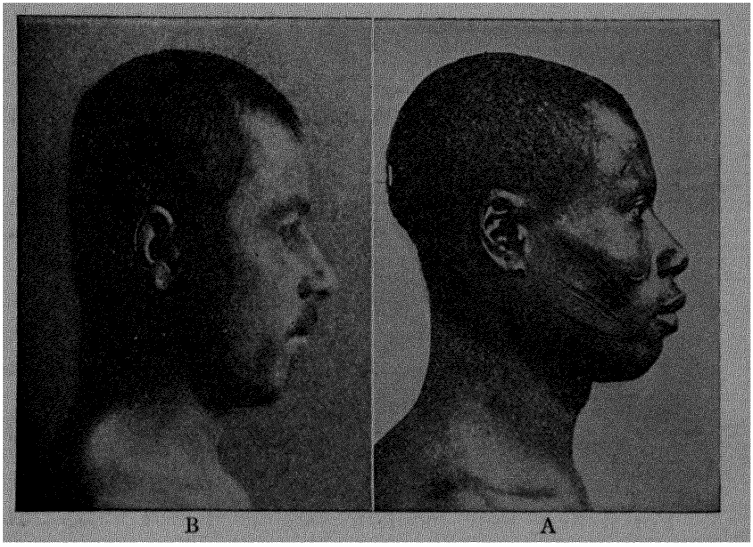


FIG. 210 A, profile photograph of the head of a negro from French West Africa, showing dolichocephaly B, profile photograph of the head of one of the Dinaric race of the Adriatic region (Albania) showing marked brachycephaly (*After Wensinger*)

The ratio of head width to head length of anthropoid apes, from birth on, is high and that of the human child at birth high also, like that of young anthropoids. But during later development additional genes become active, directly or indirectly, to induce a longer, narrower head. If one parent comes from broad-headed and the other from long-headed stock, the children tend to be broad-headed, suggesting dominance of the broadening factors. On the

other hand, if the young mammal (rat) is supplied with insufficient vitamins the head fails to gain its typical length Thus the development of the genetic tendency for head-form may be retarded by inadequate nutritive conditions.[4]

SKIN COLOR

The different races of mankind differ greatly in skin color, from the deep black of the Australian aboriginal to the clear blond of the Nordic and the pink skin of the albino All children are born with white skin, however, so that sunlight plays a role in developing the color potentialities as we see also in the fact of tanning of the skin in the summer time. The capacity for tanning in South Europeans depends upon the presence of a gene cytoplas-

FIG 211 Photograph of a family of Bermuda colored people, including a light colored mother (in middle) and her seven children (and one dog) The father (not shown) was the son of a colored woman by a white man. Note the variation in skin color The mother has 17 per cent black in her skin. The children range from 26 per cent to 8 per cent black Three of them have 18 per cent black color This photograph demonstrates segregation of skin color and supports the conclusion that two pairs of genes determine negro skin color (*Photograph by Miss Florence H Danielson, RKO archives.*)

mic reaction which does not occur in Nordic blonds. It is practically certain that there is a reaction between tyrosin in the cytoplasm and tyrosinase presumably produced by a gene. Negro skin color is probably due to two pair of extra genes or doses of tyrosinase. Consequently, the skin of the Negro child rapidly darkens after birth, even in diffuse daylight. In mulattoes there is only one extra pair of genes and so they attain only a half color. Among a large number of offspring of two mulattoes (in the strict sense) one will find about 6 per cent who have entirely white skin and about the same who are deep black (Fig. 211). The other children are of various intermediate grades of skin color as they carry 1, 2 or 3 tyrosinase genes. Thus, this racial character is a matter of chemical reaction.[5]

HAIR COLOR

In man and anthropoid apes the pigment of hair ranges from black to flaxen (white in albinos) and also presents various grades of red and golden. The black or brown pigment is believed to be a melanin; the red or golden a carotin-like substance, so that the appellation of "carrot top" to a red-haired boy has a better chemical justification than intended. Hair color forms a graded series from the darkest to the lightest shades. So there must be several genes responsible for the melanin reaction (tyrosinase + tyrosin) in the darkest hair color. In general, it seems to be true that when one parent has dark hair and the other light hair the hair color of the offspring inclines toward that of the darker parent. However, in the case of such a mating of light and dark the full pigmentation is retarded in development. Many a tow-headed youngster gains a dark brown head of hair after adolescence. And many a red-haired child comes to have glossy black hair later in life

in consequence of the development of a melanin pigment that overlaps the red. Hair color is thus determined both by the duration and the vigor of chemical action.

EYE COLOR

The ancestral eye color of humans was doubtless like that of all the apes, a dark brown. The absence of brown pigment in the Nordics results in a blue iris; in which the blue is probably due to the breaking up of light on small opaque particles of the iris. The tyrosinase of the cells of the iris acts slowly even in the presence of sunlight, especially if the individual is not of pure brown-eyed stock. So, in this case, the child is born blue-eyed and the brown pigment, if any, is slow in making its appearance; perhaps delaying six to twelve months.

If one parent's germ cells carry the full equipment of enzyme and substrate for brown iris pigment, and the other parent's germ cells are without (since he comes of blue-eyed stock) then the children will nevertheless make brown iris pigment, though tardily and in small amount. But if neither parent brings in either the enzyme or the substrate for making brown pigment the children will be like their parents, blue-eyed.

Dark hair, dark eyes and dark skin usually go together, but occasionally one finds Irish girls with black hair and violet eyes. This fact is sufficient to prove that there are separate genes for pigment in hair and eyes. Persons with bright red hair have a skin that usually burns in the sunlight and they, like blonds, must be careful about prolonged exposure to the sun. Gradual exposure gives them no graded protection; they only burn and burn again and again. In some races, however, the weakly pigmented skin becomes protected by another pigment which produces

FIG. 212. Portraits of Rob Roy (albino, left) and his wife (albino, middle) and their son, Prince Roy (also albino, right), illustrating inheritance of albinism. (*ERO archives.*)

freckles. Thus body pigmentation is a complicated matter depending upon and controlled by a variety of genes for tyrosinase or other pigmental factors that do their work at specific times and places.

ALBINISM

Particularly unfortunate is the entire loss of pigment, shown by albinos. The albino's retina is not protected from the strong rays of the sun and he keeps his lids partly closed in the sunlight. His skin burns and blisters if not protected. Albinos occur in all of the major races of mankind, either in a complete or partial (freckled) condition. Albinism occurs in many wild and domestic mammals, lower vertebrates and plants. It is a widespread mutation.

Albinism is apparently usually due to the absence of the tyrosinase gene, rather than the absence of tyrosin in the cytoplasm. For adding tyrosin to the albino organism does not yield color. If the tyrosinase be lacking in sperm and egg it will be lacking in the progeny also. The offspring of two albino parents are all albinos (Fig. 212). But if only one parent is an albino the young are pigmented. Thus albinism is a recessive trait, due to absence from the cells of the pigment-producing enzyme.

HAIR FORM

Hair, which is found only in mammals, occurs in many forms, bristles, as in swine; wool as in sheep; and straight, curly, or "wooly" hair, as in the diverse races of mankind. The anthropoid apes have straight hair. The curved-hair types are, among the higher Primates, strictly human mutations. Among higher Primates straight hairs develop in a straight follicle and are nearly circular in cross section; curly hairs are more oval in cross section, while wooly

hair is still more flattened and its follicle is curved. In any case the beginning of the hair is found in the formation of a follicle (page 281). In straight hair this follicle is nearly circular on cross section; in curly hair more elliptical. In American Indians, Mongolians, Eskimo, the single hair is coarse and straight; in Nordics fine and straight. In some East Indians and Australian aborigines the hair is wavy. In Negroes, Negritos and Melanesians the hair is wooly. In Bushmen and Papuans the hair is twisted or close kinky. These different forms of the hair (Figs. 213, 214) are referable to different forms of the follicle and the form of the follicle is determined by the reaction between genes and cytoplasm of the skin, controlling the multiplication of specific cell groups.

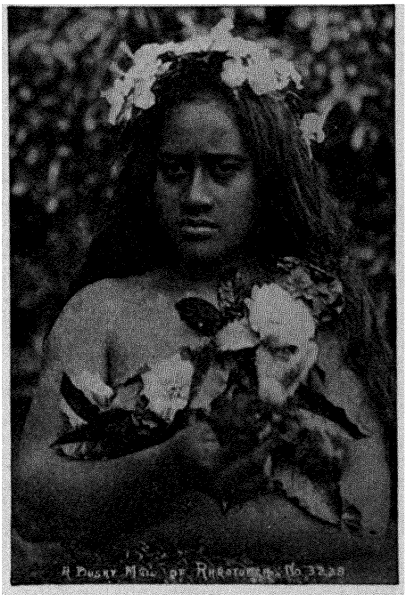


FIG. 213. Portrait of a girl from Raratonga, Southern Polynesia, illustrating slightly wavy type of hair. (*ERO archives.*)

In the hybrid between a European with straight hair and a Negro, the hair is typically curly; between straight and curly Europeans it is wavy. It is probable that both a difference in a particular gene and a difference in the cell cytoplasm are responsible for the difference in form of these hair follicles, and so of the hair. In the hybrids these

differences are blended because the reagents involved are diluted.

HAIR LENGTH

Man's hair coat, as already pointed out, differs from that of other Primates in size and persistence of individual

FIG. 214. Family groups from Papua, showing kinky type of hair. (*ERO archives.*)

hairs. However, we do carry on our heads the same type of hair as the chimpanzee, for example; namely hair that is of large caliber and persists, continuously growing, for months or years. Mutations in size and persistence of hairs are common among mammals. The body hair of a horse is being constantly shed, and most rapidly in the spring. But the hair of the mane and tail persist in growth for a longer time. In some families they may grow exceptionally fast and throughout life (Fig. 215A). That sometimes happens in humans with head hair, as in the "Seven

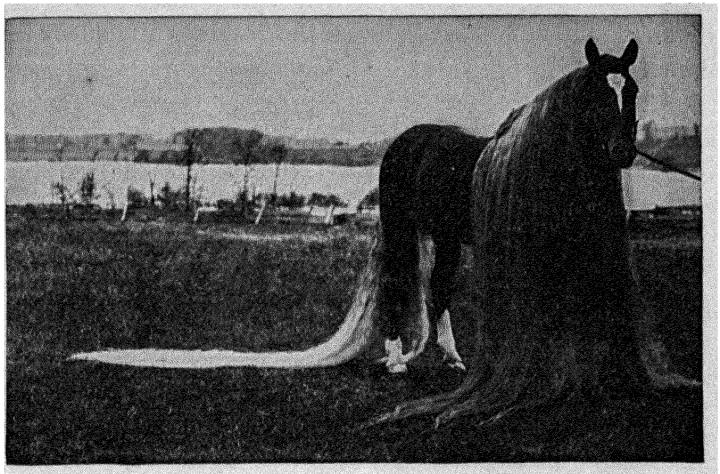


FIG. 215A. Photograph of horse, "Oregon Wonder," belonging to a race that is characterized by persisting growth of hair of mane and tail. (*Author's coll.*)

FIG. 215B. A Japanese print of the Tosa fowl of Japan, a race of birds that illustrate the persistence of growth of hackle and tail feathers. (*Author's coll.*)

Southerland Sisters." Likewise the body hair, under the influence of the secretions of perhaps the pituitary and suprarenal combined may grow to be as heavy as in the lower Primates. A somewhat similar mutation is found in the Tosa fowl race of poultry, in which the tail feathers grow nearly a tenth of an inch (2½ mm.) a day and do not molt, so that they may come to be two or three yards long and would get longer except that they tend to break on account of their length (Fig. 215B).

BLOOD GROUPS

If the blood of two persons be mixed, as occurs in blood transfusion after an accident, either one of two things may happen. The bloods may mingle without change or they may interact disastrously, resulting in a clogging of the smaller blood vessels. The reasons for this difference were in time found to be as follows: The red blood corpuscles usually carry a specific enzyme called agglutinogen. This by itself is harmless unless the blood serum is able to form a corresponding substance, or antibody, in which case the corpuscles will gather in clumps. Since normal blood does not form the fatal antibody we are able to "carry on" despite the possession of this dangerous cell enzyme.

There are, however, two principal kinds of these cell enzymes. These may be designated as (1) agglutinogen *A* and (2) agglutinogen *B*. Each has in the serum its opposite antibody. In case (1) it is antibody *b*, in case (2) antibody *a*. Persons may be classified, or grouped, according to the presence of the *A* or the *B* blood. If now the corpuscles with agglutinogen *A* (1) are mingled by transfusion with serum containing antibody *a* (2) then the cells clump; the blood is agglutinated (Fig. 216). The matter is still more complicated. It appears that in some persons the blood

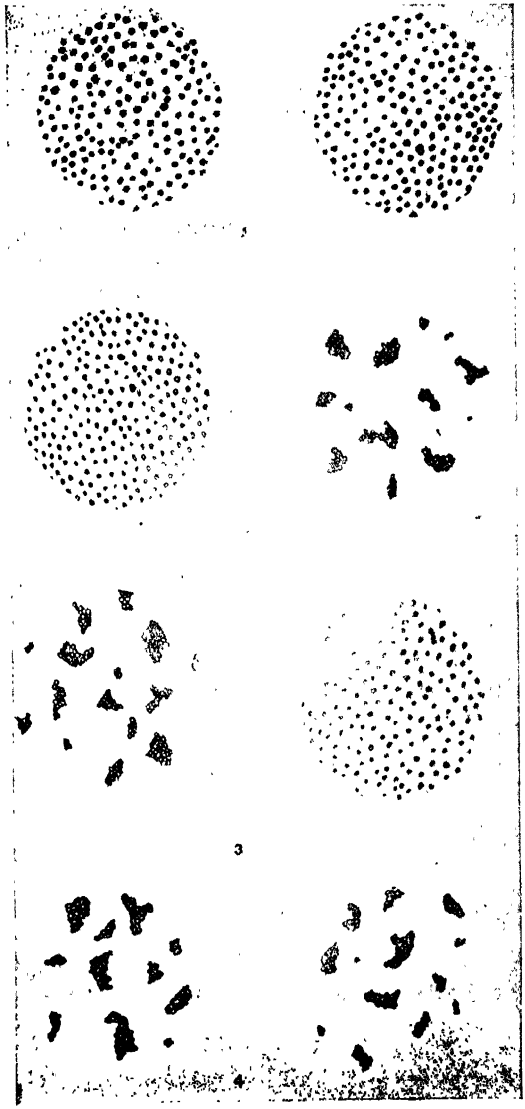


FIG. 216. Diagrammatic appearance of the four blood groups, as seen under the microscope. Serum of group *A* on the right; serum of group *B* on the left. Row 1, when cells of group *O* are added to either serum, no agglutination. Row 2, when cells of group *B* are added, agglutination with group *A* serum. None with group *B* serum. Row 3, when cells of group *A* are added agglutination with *B* serum but not with *A* serum. Row 4, when cells of group *AB* are added agglutination both in serum of group *A* and that of group *B*. (*Based on Snyder's "Principles of Heredity," by permission of author and D. C. Heath & Co., publishers.*)

cells produce both of the two kinds of agglutinogens, *A* and *B*; they belong to group *AB*. Such blood introduced into persons of any group will cause agglutination—in the *A* group by the antibody *b*; in the *B* group by the antibody *a*; in the *O* group (see below) by both antibodies *a* and *b*. Such persons make highly dangerous blood donors in blood transfusion operations. On the other hand, there are persons whose corpuscles carry no agglutinating enzyme, neither *A* or *B*. They belong to group *O*. Naturally the blood of such persons will not induce agglutination in any blood no matter what antibodies it may contain; they make preferred blood donors.

The distribution of persons belonging to the groups *A*, *B*, *AB* and *O*, is not without interest. The Nordics of Europe and also the Australian aborigines belong largely to group *A*, the Gypsies and many natives of India and northern China belong largely to group *B*. The Africans and Malaysians belong largely to the *AB* group. The full-blooded North American Indians are almost wholly of the *O* group. Through mixing in past time peoples of the four groups are found in nearly all populations.

These agglutinating enzymes get into a person from the genes of the germ cells that have united to form the zygote. If the gene for *A* be present in both gametes, or one gamete only (the other being without such either type of enzyme), the offspring will produce the agglutinogen *A* in their red blood corpuscles. Similarly with *B*. If one parent produce only gametes with gene for *A* and the other only gametes with gene for *B* then the children will belong to the *AB* group. If the gametes of both parents are devoid of either gene *A* or *B* then the children will belong to group *O*. Genes *A*, *B* and *O* are merely different forms of the same supergene, and occupy the same place on the chromo-

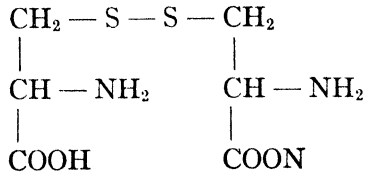
some. The nature of the antigene in the blood is fixed by the nature of the gene. So, how the child's blood shall react to a particular blood infusion depends upon the germ cells he received from his parents.

The fact that the full-blooded North American Indian carries no agglutinating enzyme is interesting. It has been suggested that the race left Asia before such enzymes had, as we may say, been "invented" by the human organism. But since the agglutinating enzymes have been found in even the chimpanzee we must conclude that they are of ancient origin, and some other hypothesis must be sought to account for the relative absence of such agglutinogens in the Amerindian.[6]

MUTATIONS IN METABOLISM

We have seen that the process of metabolism by which urea and carbon dioxide are eventually derived from protein food stuffs involves the action upon those proteins of a series of enzymes. Thus proteins are first broken up by hydrolysis into nitrogen-containing acids, amino-acids. These amino-acids are further acted on by enzymes until uric acid results. For example, if guanine is produced, this may be acted on by guanase, resulting in xanthin; this may be acted on by xanthine-oxidase yielding uric acid, which is excreted in the urine.

Of the amino-acids cystine is one that contains sulphur. Now cystine has the formula:



If the S is replaced by S — H the molecule falls into two molecules of a substance called cysteine. This ordinarily is oxidized to urea and certain sulphur compounds. But if the factor (enzyme ?) which splits the cystine molecule into two cysteine molecules is absent or insufficient or if certain other defects in metabolism occur, cystine will appear in the urine. There are certain families in which this regularly occurs. The pedigrees indicate that more than one factor (enzyme ?) is abnormal. This abnormal condition is called cystinurea. The mutation that makes cystinurea possible may be comparatively recent in man and may have occurred at various times. It is known, however, to occur in other mammals (Fig. 217).

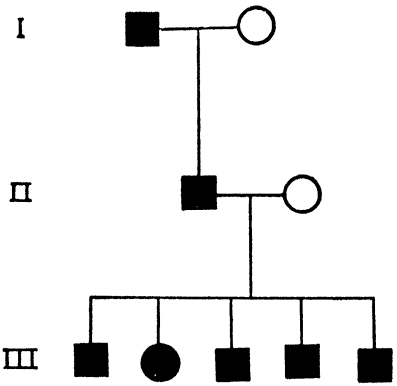


FIG. 217. Pedigree chart of a family with cystinuria (abnormal excretion of cystine—a sulphur-containing acid radical of protein—in the urine). The defect occurred in three generations (I–III) as shown; and included three sibs in the third generation. Squares, males; circles, females; black symbols, affected individuals; short horizontal lines, matings; long horizontal lines, fraternity lines from which hang the sibs. (*After Abderhalden, from Baur, Fischer and Lenz.*)

There are other mutations affecting metabolism. One of the amino-acids into which protein breaks up is phenylalanine. Phenylalanine yields a certain amount of tyrosin. Ordinarily both of these substances are oxidized and produce clear products. But in an alkaptonuric individual they interact, form an acid which when excreted and allowed to stand turns black. There is probably absent in the gene an enzyme which

oxidizes this blacking material before it is excreted. And this absence (doubtless of a gene) through the generations may be inherited by certain members of a family who fail to receive the gene.

There are many other mutations affecting metabolism, only two will be considered.

Diabetes mellitus. Sugar is carried by the blood to all the tissues. It is a valuable food and not to be wasted.

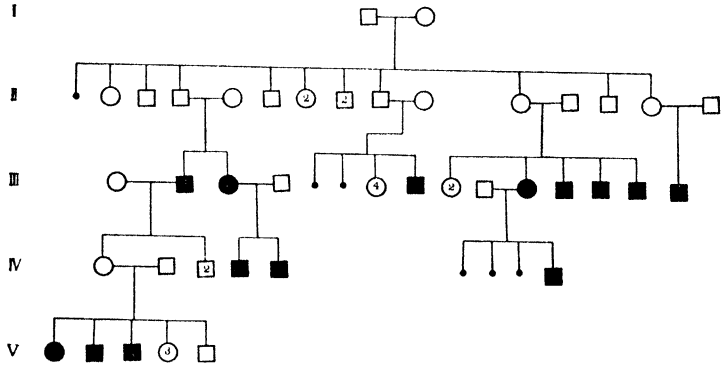


FIG. 218. Family of diabetics, symbols in black represent diabetics. The two persons of the I generation are said to have been normal; and no diabetes is known in generation II. Diabetes is known only in the two lines of descent shown. In the III generation death occurred at about 70 years. In generation V the 3 children marked in black died at 14, 17 and 23 years respectively. (*ERO, A08505.119.*)

But sometimes it is excreted in the urine in such large amounts as to threaten the patient with starvation. This disease is known as diabetes mellitus. In this disease there is insufficient secretion of the hormone insulin from the pancreas. Since the tendency to diabetes is partly racial (Jews being affected in larger proportion than others), and certainly runs in some families, we must conclude that in diabetics the development of the pancreas or rather of the islands of Langerhans in the pancreas, is inadequate, doubt-

less due to a defective genic (possibly, also, cytoplasmic) condition (Fig. 218).

Goiter. This condition is that of an enlarged thyroid gland. Goiter is related to the thyroid as diabetes is to the pancreas. The thyroid gland (built up in part of the floor of the pharynx in part out of rudiments of the gill area) secretes about one milligram of its specific secretion (thyroxin) each day into the blood. This hormone has important relations to metabolism. The activity of the thyroid varies, however, but ordinarily secretes enough for the body's needs. But in regions where iodine is scarce in the ingested water or food, the thyroid, in many families that are characterized by poorly developed glands, functions inadequately. The gland seems to compensate by enlarging. In some places goiter is said to be endemic, i.e., constantly present in a large proportion of the population. Always, however, certain blood lines are especially affected; others are immune.

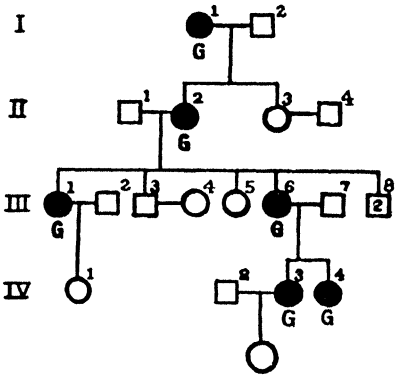


FIG. 219. Pedigree of a family of Western Maryland, showing high incidence (6 cases) of a thyroid disturbance which results in an enlargement of the gland, called goiter. (*ERO archives.*)

Thyroxin is derived from the protein molecule. It is an amino-acid, built somewhat upon the plan of tyrosin, with iodine atoms replacing some hydrogen. It is probable that thyroxin is produced in the cells of the gland, accumulated in vesicles and periodically discharged. The appropriate cell genes, acting as catalysts, and the cytoplasm must co-operate in perform-

ing this specific cell function. If the catalyst or the cytoplasm is inadequate the production of thyroxin is restricted. This is obviously in part a genic, hence an inheritable, trait. It is probable that one gene lies in the sex (*X*) chromosome, so that defective women suffer more than men.

Without question a special degree of activity of the thyroid runs in a given family. This has been demonstrated in most convincing experimental fashion in families of pigeons. And the endocrine glands function in birds and mammals, including man, always in the same fashion (Fig. 219).

DEFECTS OF HANDS AND FEET

The hands and feet develop at the extreme ends of the limbs, far from the starting points of the limb buds. There is an opportunity for many mutations to occur in the multiplying cells of the limb before fingers and toes are finished off. And defects are especially apt to show if the developmental factors are not vigorous, or not all present.

One of the commonest defects is a failure of the web between the toes to be cut back deeply. It is the second and third toes that are especially apt to be joined by a web. Also, the web between the fingers may be extended far up on the fingers. In some cases the bones of the fingers are more or less united; in other cases extra fingers may be present. In these cases the limbs apparently develop normally until the digits are to be formed. Then, instead of the five definite cremulations which initiate the finger formation, there are numerous small irregular cremulations. In such case eventually three to seven cremulations get the upper hand and so those numbers of fingers begin to develop, but usually more or less deformed. Various terms are given to the defect produced. Zygodactyly refers to extension of the web, syndactyly refers to the bony union

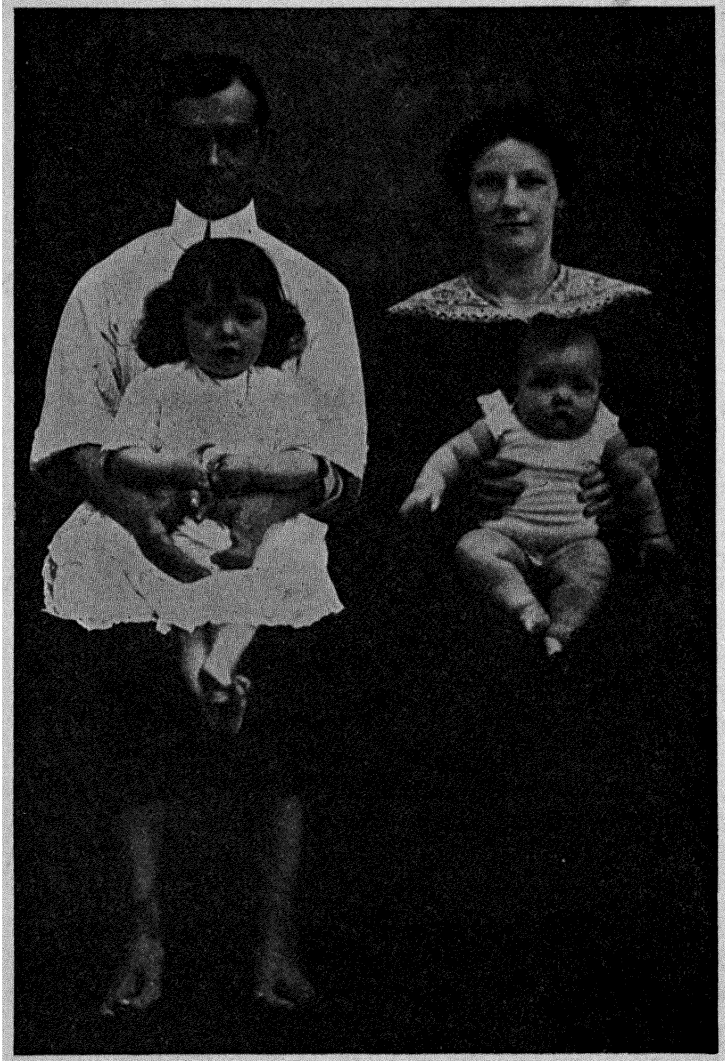


FIG. 220. Photograph of a family showing irregularly developed hands and feet, a condition known as syndactyly, or union of digits. (*ERO, A211–60.*)

of the fingers, polydactyly to the presence of one or more extra fingers. These defects run in families, usually without skipping a generation. The defect (Fig. 220) is said to be dominant.

Beyond that we cannot go. We do not know what normally determines the five points of cell multiplication at the margin of the limb paddle which eventually produce the fingers or toes (Fig. 23). Whatever the process is, it is a very ancient one; for five fingers are standard for most mammals, reptiles and amphibia. However, this standard is often not attained; and often it is definitely modified by reduction in a species or group of allied species. Probably, the same sort of factors that determine the number and location of the limbs act in determining the number and location of fingers. It is probable that the number of fingers is determined early, at least by the time the limb bud appears, by the setting aside to this end of five cells or cell groups (Fig. 23).

EYE DEFECTS

The eye is a very complicated organ; and if all of its parts are not perfectly formed and adjusted to each other the eye will be decidedly defective. It is not strange then that there are so many imperfect eyes. Also, it is plain that these defects do not occur at random even when some of them can be accounted for on the ground of an environmental factor of eyestrain. For some eyes are more readily altered by eyestrain than others. We may consider some of these defects in detail.

Corneal degeneration. The mesenchyme penetrates between the lens and the ectoderm to make the cornea (page 62). This mesenchyme tends to become glass-clear by a special secretion at the end of the fourth fetal month, so

that light can pass through uninterruptedly at birth. But in certain families the secretion is so poorly made, either through the nature of the cytoplasmic material or the genes, that the cornea tends to become opaque in earlier or later life in smaller or larger areas. Sometimes, indeed, the child is born with a cornea whose secretions are not at all transparent. There is a corneal cataract.

Coloboma of iris. The iris is the thin circular edge of the optic cup. But this cup has a groove running down the

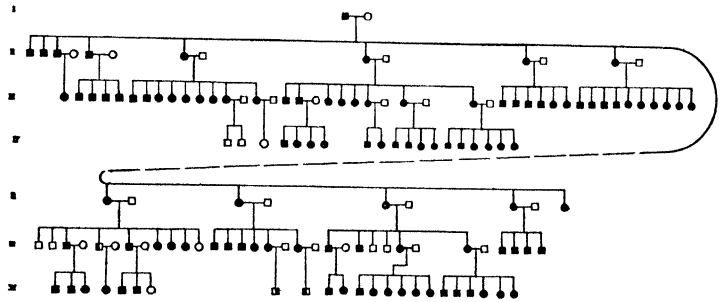


FIG. 221. Pedigree chart of a family in which the optic cup fails to close around the lens normally, producing a condition of imperfect or absent iris. (*After Dr. S. D. Risley, from Jour. Amer. Medical Assn., 1915.*)

optic stalk (Fig. 43). Ordinarily the groove closes to make the iris a complete ring. But in some families the groove fails to close and the iris is incomplete. This is what is called a coloboma (which is a Greek word meaning imperfection). Something in the cytoplasm of the cells of the optic cup or in the weakness of the genes fails to give the required stimulus to the closing of the optic cup. Whatever it is, it is usually, or frequently, hereditary—the defect is in the germ cells.

Allied to the foregoing is the case found in certain families in which the iris fails to form at all. One of the most striking familial cases is that described by S. D. Risley

(Fig. 221). In this case most members in the blood line for three generations are without an iris. The genes that direct the building of the iris must be absent altogether in this family.[6]

The lens. Like the cornea the lens must be clear to be effective. The cells of the embryonic lens ordinarily lose even their nuclei at the end of the second fetal month. In some families the lens does not clear up perfectly, or perhaps in middle life begins to go opaque again. This gene-defect does not skip a generation—is a dominant. In some families the lens, having started to form in the edges of the optic cup at the time of its origin, fails to become properly located at the mouth of that cup when finished. It is out of place (ectopic). Naturally such a misplaced lens produces distorted images. In these families there seems to be no proper responsiveness during development between lens and retina. The remote causes of this developmental defect are quite obscure. In wild species the strains that possessed this defect would surely be quickly eliminated.

Retina. The retina, which stands beween the lens and the brain partakes somewhat of the nature of both. The perceptive rods and cones are elongated cells like those of the lens (page 63). Near the optical axis of the eye in the retina is the yellowish macula believed to be especially sensitive to light. In some families the macula may undergo a progressive degeneration. In others, the color-discriminating property is at least partially absent. We do not know on what color discrimination depends, but if upon the molecular condition of the cones then it is probable that in some persons (the color blind) the molecular structure that is affected by the red and the green rays of the spectrum fails of development. This failure of development

is doubtless due to the absence of the nuclear catalyst upon which its production depends. Such catalyst, or gene, is located in the X-chromosome, which is single in males. Consequently males are more apt to show a defect in color discrimination (color blindness) than females. For in females the defect in one X-chromosome will be made good by its presence in the other.

In some families an excessive pigmentation of the retina may develop; in other families the optic nerve tends to atrophy; in still others tumors tend to form on the retina; again, the nerve fibers of the retina may gain medullary sheaths, rendering parts of the retina opaque in several members of the family. Such retinal defects occur often late in life after the following generation has been started. Consequently they are not weeded out in mating.

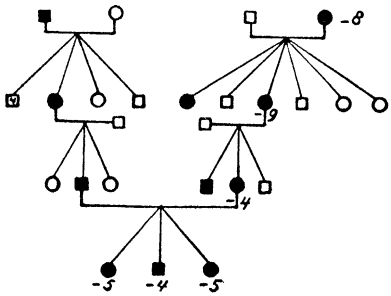


FIG. 222. Pedigree chart of a family characterized by shortsightedness (myopia). All individuals indicated by black symbols are nearsighted. (*From "Waardenburg," 1932, Das menschliche Auge und seine Erbanlagen.*)

Myopia. The retina is a curtain on which the image formed by the lens must be brought to a focus if vision is to be clear. Sharp focusing implies an ideal distance from lens to retina. The distance is not a rigidly fixed one because of powers of adjustment (within narrow limits) of the lens and iris. If the optical axis of the eyeball is too long or the lens too curved the image will be thrown in front of the retina, and thus the object will be seen out of focus. Persons who have this defect are said to be myopic.

Now there are families in which the children are myopic from infancy or become myopic in youth (Fig. 222). In these families the lens and cornea may be badly formed. Typically the lens is at first nearly spherical; then new lens cells are produced at the margins of the lens and these new cells grow over and behind the older ones, increasing the depth of the lens in the optical axis. Still later as equatorial growth continues, the lens expands in its equatorial axis. The myopic lens is too spherical; the lens retains a fetal form. Also the eyeball at birth has a relatively shorter axis than it has in the adult. If the wall of the eyeball is too weak to resist the pressure of the fluids inside of the eye the globe may become elongated from in front backward, and thus myopic. Thus the myopic eye is an immature eye, a weakly built eye or an overstrained eye. And some or all of these factors arise in part, at least, from genetic defects.

MUTATIONS IN THE MENTAL SPHERE

A child may be a good animal and yet not be satisfactory to his teachers because he has trouble with his arithmetic or spelling. He is backward at school. The school indeed assumes that every child shall have a certain set of intellectual capacities. Yet experience indicates that some children are defective in one or more mental processes. They may have a good general intelligence, but be deficient in special lines. It often happens that a leading college will "forgive" a brilliant student one of his entrance requirements as he comes to graduation after repeated failures to make good his deficiency. Special defects are no more remarkable than extraordinary "gifts" in respect to music, painting or mathematics. All are, commonly, due to mutations, hereditary modifications in the process of development of the brain.

The invention of special mental tests and their application to school children has revealed an unanticipated range in general mental capacity. If on the numerical scale of general intelligence the average standing of a child of a given age is 100, then it appears that there is occasionally a "phoenix" (defined by Samuel Johnson as a "rare bird")

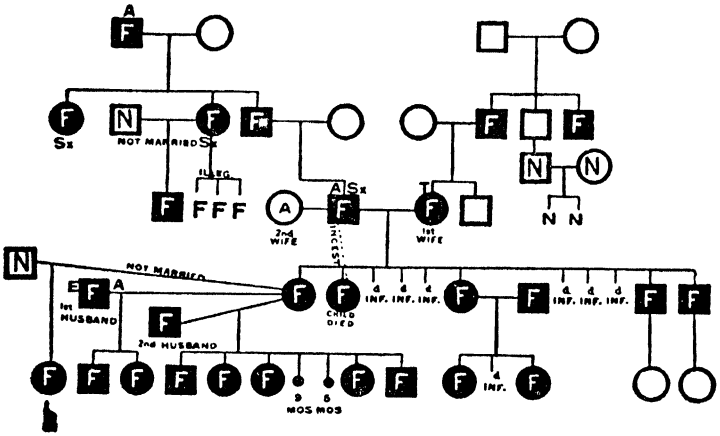


FIG. 223. Pedigree chart of a family showing hereditary feeblemindedness. All individuals indicated by black symbols are affected. (*From H. H. Goddard.*)

who has a rating of close to 200. John Stuart Mill is an example. Son of a Utilitarian philosopher, Mill began to study Greek at three years; at seven read Plato; at nine was studying algebra. He wrote a history of Rome at six and a half. At the age of five he discussed with Lady Spence, wife of the First Lord of the Admiralty, the comparative merits of Marlborough and Wellington. The other extreme is below 50 per cent, applicable to certain imbeciles who are able to survive only by institutional care, or by life in the hills where they are not touched by the hazards of civilization. In school they make no progress; remain quite illit-

erate. Often they belong to a family whose members have survived under similar circumstances (Fig. 223). In some cases the low mental status can be traced for four or five generations until one wonders if the strain does not reach back, unimproved, to Neanderthaloid ancestors.

DISEASE RESISTANCE

Some families are characterized by the long life of the individuals composing them; others by short life. We think of the long-lived families as resistant to many or most disease-inducing factors; the others as susceptible.

That resistance vs. susceptibility is a real phenomenon is well shown in the case of leucaemia in mice. Leucaemia also occurs in humans; often in children. It has been best studied experimentally by Edwin Carleton MacDowell in strains of mice that have been so long inbred that each has become marvelously pure-blooded. In one strain of such stock leucaemia appeared as a regular cause of death in old mice. This leucaemia is characterized by enormous multiplication in old mice of the white blood cells from bone marrow and spleen until the blood vessels become fatally clogged.

Now if some of these white blood cells be transferred into even a young mouse of the leucaemic strain that mouse will die of leucaemia within ten days. But if some of the same cells are inoculated into a mouse not of the leucaemic strain nothing happens. The malignant leucaemic cells soon die. There is in this case a natural resistance to leucaemia, as in the other strain there is a susceptibility. It has been shown that in the susceptible strain there is something that promotes the development of the leucaemic cells or at any rate does not interfere with their development. In the resistant strain the introduced cells

are obviously destroyed. Clearly the resistant and the susceptible strains are chemically unlike; this unlikeness is connected with a chemical unlikeness in the genes of the two strains.

Susceptibility is usually, as in the foregoing illustration, specific. And so it comes about that we have families susceptible to tuberculosis, to cancer, to pneumonia, to skin disease of various kinds, to dental caries. That susceptibility to tuberculosis has an hereditary basis is shown by the higher incidence of tuberculosis in both of twins when they are identical than when they are fraternal; also by the higher incidence between parent and child (with a common heredity) than between the two parents (unrelated).

By chemical tests one distinguishes individuals who are resistant to diphtheria, scarlet fever, tuberculosis, etc. These specific chemical reactions depend in part upon specific qualities of the genes which are responsible for such protection.[7]

That respiratory diseases, especially pneumonia, have an especially high incidence rate in certain families has been repeatedly observed. Raymond Pearl tells of a family of thirteen brothers and sisters all of whom have had broncho- or lobar-pneumonia one or more times. Some of the thirteen died of it. One certainly, one other probably, has tuberculosis of the lungs. Certainly 100 per cent of pneumonia in a large fraternity is a rare condition. A study of the 202 blood relatives of this fraternity reveals that, on the father's side, there is a high incidence of pulmonary tuberculosis (6.25 per cent). On the mother's side there is a high incidence of respiratory illness. The combination of parental traits is responsible for the high incidence of pneumonia in the early years of the children.

Variation in resistance, or susceptibility, of persons to

bacteria is a well-known fact which is considered in text-books under the head of natural immunity. Referring to the bactericidal activity of the blood serum and the phagocytic powers of leucocytes and other cells, Hans Zinsser says: "They may vary in different species, races or even individuals in potency against any given infectious agent."

One species of mammal is ordinarily resistant to the pathogenic organisms of other species. In man, races differ in susceptibility. Thus Eskimos transported to civilization, and colored persons who live in the white man's country, are very susceptible to tuberculosis. To Polynesians measles and influenza are as dangerous as smallpox formerly was in Europe. Smallpox and syphilis are relatively mild diseases in Mexico. Negroes are less susceptible than whites to yellow fever. Even individuals of the same race differ in susceptibility, as numerous family studies show.

Natural immunity has been ascribed both to differences in the activity of the leucocytes and to differences in the bactericidal properties of the blood. It is not improbable that the resistant substances in the blood serum are derived from the leucocytes. If so, then it is probable that enzymes of these cells are producing with the co-operation of the cytoplasm an especially active protective material in the blood. Thus natural immunity is to be thought of as genzymatic in nature.

NOTES

1. A very full account of sports as known at his time is given in Charles Darwin's *Animals and Plants under Domestication.* But since Darwin's time the number recorded has increased manifold. See Herbert Spencer Jennings' *Genetics*, 1935, for the modern point of view about organic change and mutations.

2. On stature, the author published in Genetics, Vol. 2 (1917), a paper that extended Galton's work on the same topic in his *Natural Inheritance* (1889).

3. On body build see a book by the present author published by Carnegie Institution in 1923.

4. The cephalic index is fully treated in Rudolf Martin's *Anthropologie.*

5. Skin color inheritance is considered in a Carnegie Institution publication (1913).

6. Blood groups in man have been intensively studied for the past 20 years. See books on the subject by Laurence H. Snyder (1929, Baltimore) and by A. S. Wiener (1935). Risley's paper appeared in the Journal of the American Medical Ass'n, Apr. 17, 1915.

7. The details of inheritance of human mutations are given in a number of books such as R. R. Gates' (1929) *Heredity in Man*, Macmillan Co.; Otto L. Mohr's (1934) *Heredity and Disease*, N. Y.: Norton; C. P. Balcker (1934), *Chance of Morbid Inheritance*, Baltimore: Wood; *Human Heredity*, etc., Baur, Fischer and Lenz translated by Paul, N. Y.: Macmillan Co., 1931.

CHAPTER 13

THE PAST AND THE FUTURE

ANCIENT DEVELOPMENTAL PATHS

We often think that human development is an affair of the human species. Were we to take so narrow a view we might well wonder how so complex an organism could have acquired all of the marvelous developmental potentialities that man has acquired even in the 500,000 or more years that man, as such, has lived on earth.

But the fact obviously is that man is a Primate and Primates have dwelt on the earth for perhaps 10,000,000 years. Also, man is a mammal and mammals have been on the earth 50,000,000 years. When a child develops he develops along the lines of a Primate, with the accumulated experience of ten million years. It is only the specific human traits that differentiate him from the other Primates (such things as larger cerebral cortex, reduction in hair coat, loss of grasping form of foot, modification of facial features) that have had only half a million to a million years to evolve in. The path that the human child goes through in early development is the well-worn, through 50-million years-trod, highway of the mammal; and then it branches off to go to the 10-million-year-old Primate road; and finally it takes the distinctly human path traversed for the past half million years. Still later it diverges to the racial trail started some 50,000 years ago. The study of the course of development of the child will give some clues concerning the path followed in its evolution (Fig. 224).[1]

MAN AMONG THE VERTEBRATES

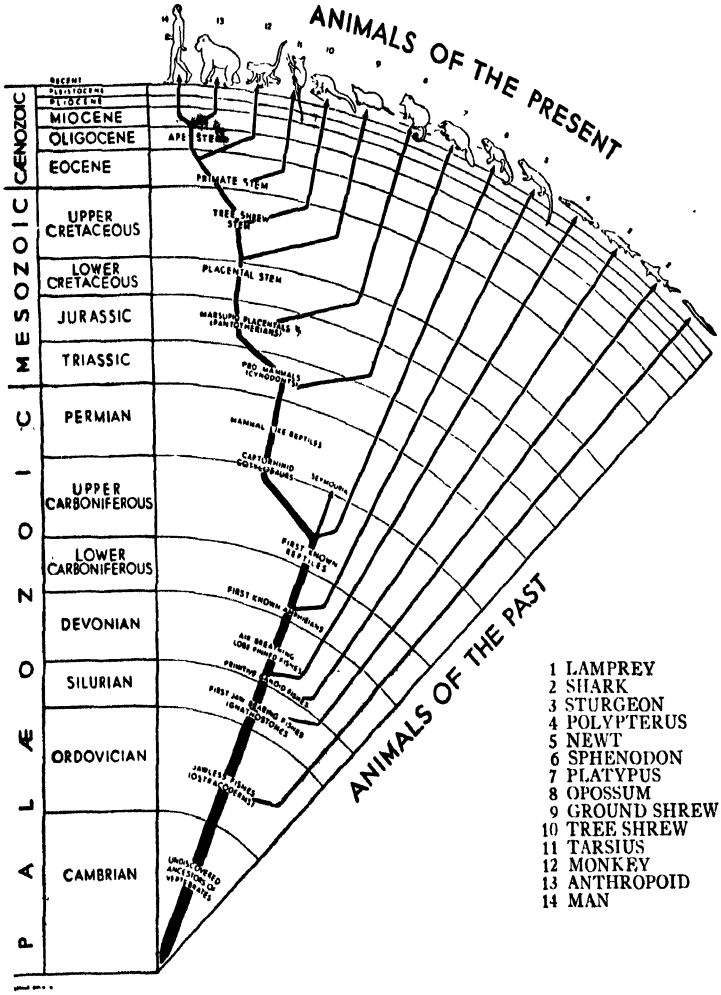


FIG. 224. Diagram of the vertebrate subkingdom, showing the course of its evolution through the geologic ages and especially that of man. (*Courtesy of American Museum of Natural History and the author, William King Gregory.*)

We have seen that some of the changes which the embryo undergoes have apparently little meaning for the adult human. They do remind us of stages found in the development of the lower vertebrates. Such are the tail and the gill arches, so like the corresponding organs of the young fish. There can be no doubt that the reason why the gill arches are formed is because that is the way that the vertebrate young have always been developed from the beginning of vertebrate history. In the fishes the neck goes on to produce gill slits and gills as well as the muscles which work them, and glands on the side of the gill bars. In the case of mammals the arches are formed just the same, but the gill filaments are not formed; i.e., the gills are not completed but their supports are used, in part, to form muscles and important elements of the skeleton and glands of the neck region. Since all organs have to be made out

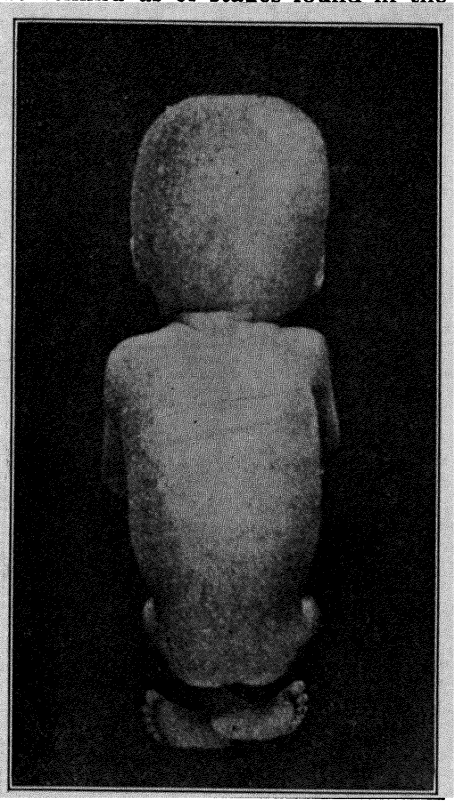


FIG. 225. Human embryo toward the end of the first half of pregnancy showing slight development of pelvis and legs. (*After Kollmann, from his "Handatlas."*)

of earlier formed parts there would be no other way for these organs to develop excepting by the formation of the gill arches. It is easy to show in detail that the human fetus and infant pass through many stages that are characteristic of the young of other mammals and especially of other Primates; and these stages may even persist into the adult stage of these other species, though they disappear in the adult stage in man.

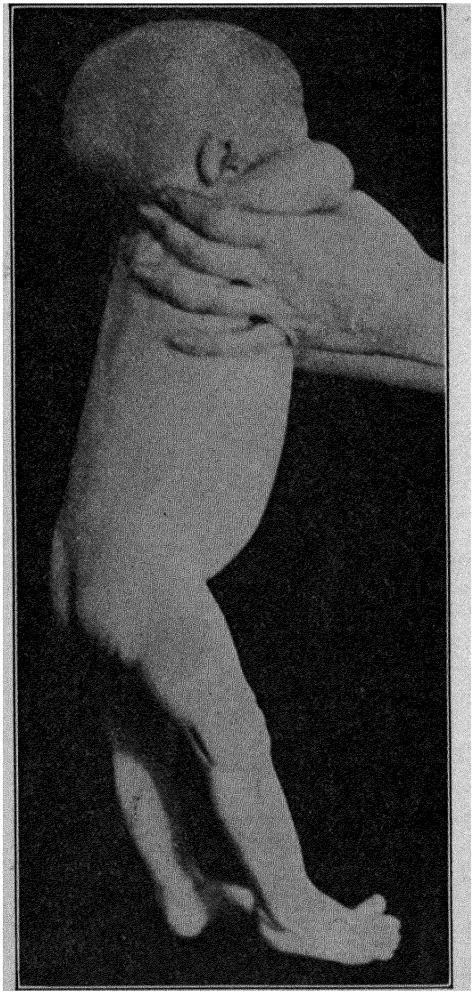


FIG. 226. Photograph of a baby, at about one month after birth, showing the slight development of the buttocks. (*Contributed by Normal Child Development Clinic of Columbia University, courtesy of Dr. Myrtle B. McGraw.*)

For example, a child before birth (Fig. 225) and for some weeks thereafter (Fig. 226) has the great gluteal masses (or buttocks) relatively undeveloped, and on this account cannot walk. This stage is that of

the chimpanzee (Fig. 227) which cannot walk well upright either.

Again, the relatively long arms and short legs of the human fetus (Fig. 228) are very similar to the early formed arms and legs of the chimpanzee fetus, which persist in the adult chimpanzee, though the arms become relatively short in the adult human (Fig. 229).

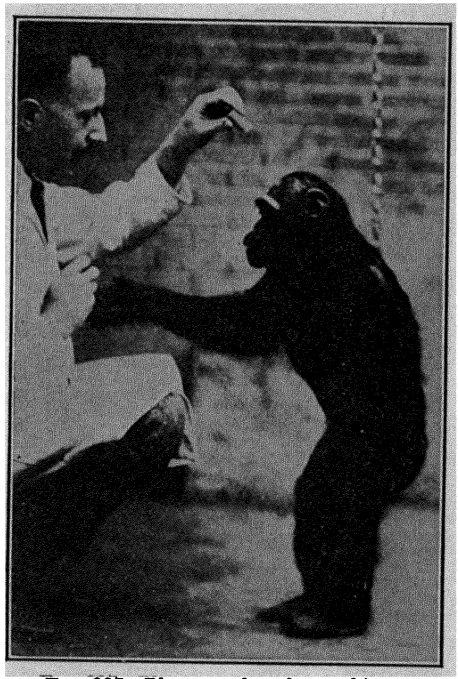


FIG. 227. Photograph of a chimpanzee showing slight development of the buttocks. (*After A. H. Schultz.*)

Light is thrown on the relatively long arms of the infant as compared with the adolescent by a consideration of the relative arm and leg length of other mammals. As is well known, in mammals that run on all fours there is an approximate equality in length of all four appendages. On the other hand, in mammals that progress by leaping and that use the fore extremities little for locomotion, those extremities become relatively short. This generalization is illustrated by the cases of the kangaroos and jumping mice (Fig. 230). For, since the running relatives of the kangaroos and mice doubtless represent an ancestral condition, we may say that the semi-

upright position of the kangaroos and jumping mice is in some way related casually to that of the short front legs. So, too, in man. There is every reason to assume that the ancestral type to man used the arms for locomotion in the trees, and these arms were doubtless longer than the legs as is true of the adult orang, gibbon, gorilla and chimpanzee; and of the human fetus. In further development, man, in connection with his upright posture has departed from the anthropoid type and come to have his relatively short arms.

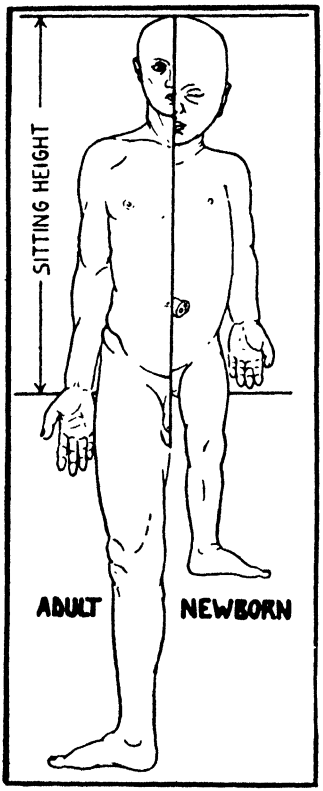


FIG. 228. Outlines of adult and new-born human, being a diagrammatic comparison between the exact bodily proportions of each, both reduced to the same sitting height. It is to be noted that while the leg has doubled in length the arm has increased only about one-third. The arm of the new-born is precociously long. (*After A. H. Schultz.*)

Indeed, the child at birth is far from having completed its physical development. It goes on showing changes which had been anticipated in intra-uterine life until eventually the proportions of the adult are acquired and growth gradually slows down at, or before, the end of the second decade. I will give a few examples.

The change in proportions of arm and leg is brought out in the graph of Fig. 231, in which time (age) in years is marked along the base and

the size of the index (arm length/leg length) is indicated by the length of the verticals—leg length being taken as 100.

One sees that in the embryo at the third month the arm is one-quarter longer than the leg; at birth the two are

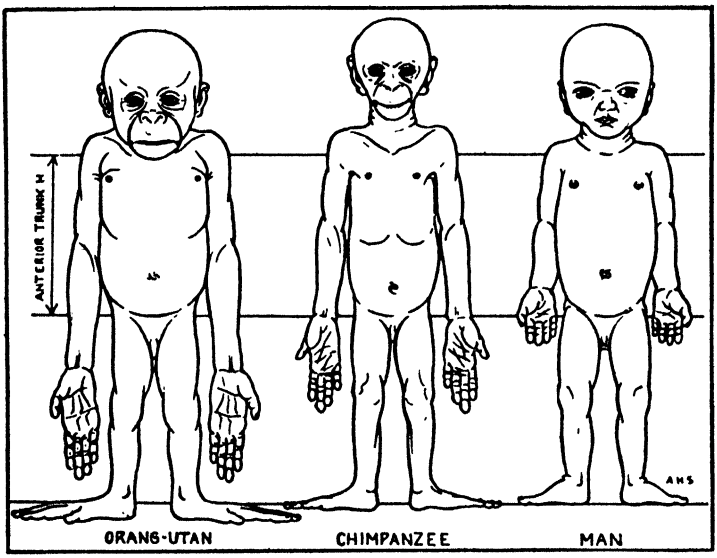


FIG. 229. Diagrammatic representation of the exact bodily proportions of the new-born orang, chimpanzee and man, all reduced to the same anterior trunk height. Note the different lengths of the limbs. (*After A. H. Schultz.*)

nearly equal in length, that thereafter the legs grow relatively faster and faster, until, in the girl at about twelve and the boy at about fourteen years, the arms are about four-fifths as long as the leg. After that the legs nearly stop growing and the arms keep on growing for a little while longer. The relatively short arms of man are associated with his upright position. Other mammals which do not run on all fours acquire short fore limbs (Fig. 230).

Another example—the chest of the child at birth (Fig. 232) is very nearly a cylinder with approximately equal axes. If one thinks of the dorso-ventral axis as 100, then at birth the transverse axis is about 112 (Fig. 233) but

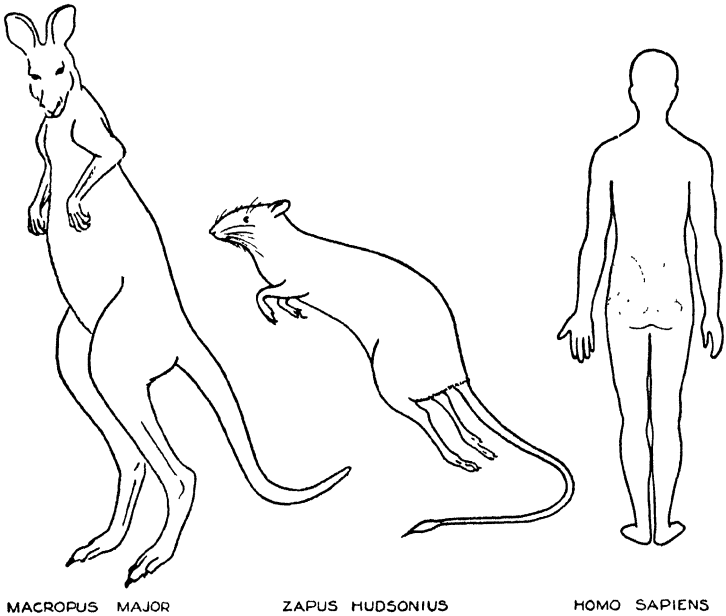


FIG. 230. Outline drawings of three mammals that use predominantly their posterior (lower) appendages only for locomotion, showing the tendency toward reduction in anterior appendages. The comparison of these three types suggest that if the human upper appendage has undergone an evolutionary reduction comparable with that undergone by the other two, man's ancestors must have had long arms and probably brachiating habits. The species represented (in different scales) are named below the drawings.

increases rapidly to about 130. After that it slows up and after fourteen years falls behind, while the dorso-ventral axis increases for a year or so, but eventually this axis stops growing and the transverse axis continues its increasing breadth. Thus, there is in the development of

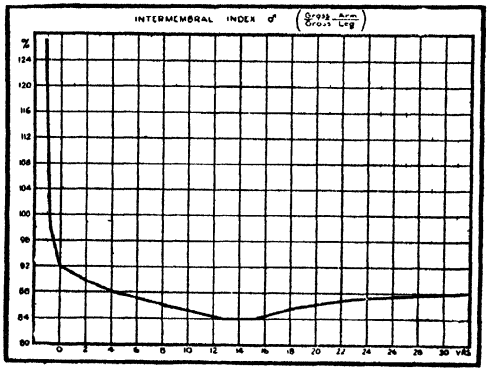


FIG. 231. Curve showing the changes in the intermembral index in the male, for different ages from before birth to 32 years, as indicated along the horizontal base. The index is the quotient of total arm length divided by total leg length and the various values of this quotient are indicated on the scale at the left. Thus, the length of the arm in successive years (that of the leg being 100) as represented by the curve is indicated by the numbers of that scale.

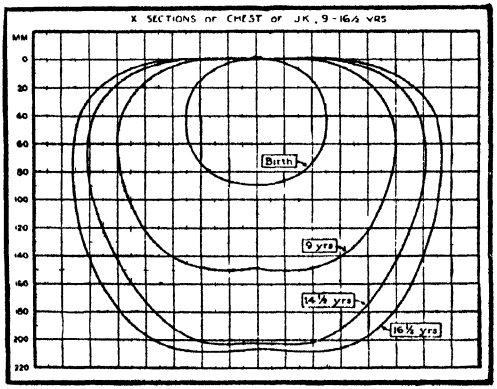


FIG. 232. Cross section of the chest at the level of the nipples. The inner circle indicates the average cross section at birth. The remaining 3 near-ellipses represent changes in the chest form of the same boy at 9, 14½ and 16½ years of age. These outlines show the changes in relative length of the transverse and sagittal diameters.

the child a rhythm in growth, producing changes in proportions. There is, as it were, a struggle between old historical and new human tendencies. The cylindrical chest is the generalized form that is found in the fetuses of all Primates. While in some lower mammals like the horse

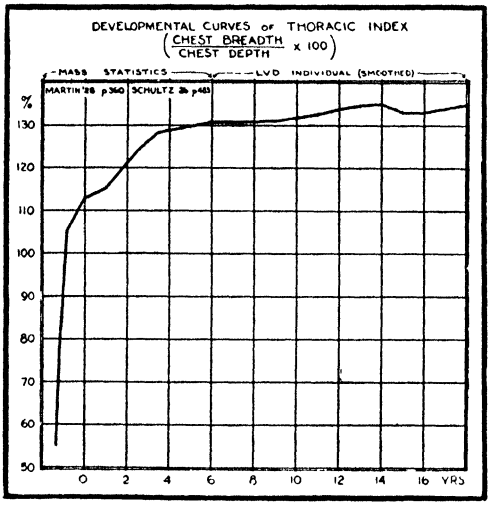


FIG. 233. Curve of the development of the thoracic index, or the breadth of the chest when the chest depth is taken as 100. The curve shows the varying index (scale to left) from before birth to 18 years of age (age scale at bottom). (*Based on Martin, Schultz and new data.*)

the dorso-ventral axis is the greater, in man it is the transverse axis that comes to be the greater. This last form is certainly better fitted for a creature that walks upright and uses his arms in all directions.

Again, the upper extremity has two principal segments, the upper arm and the forearm as far as the wrist. The relative length of the lower to the upper segment is the one which changes during development. At about the third month of gestation the relative length of the forearm

to upper arm (the length of the upper arm being taken at 100) is 74. The ratio rises rapidly to about 90 at birth. It then falls as shown in Fig. 234 to about 13 years in the case of boys and 12 years in the case of girls. Thus there is a very peculiar discontinuity in the developmental curves of this ratio. The question arises: What does it mean?

If we examine the very limited data that we have upon the changes of the brachial index during gestation of other

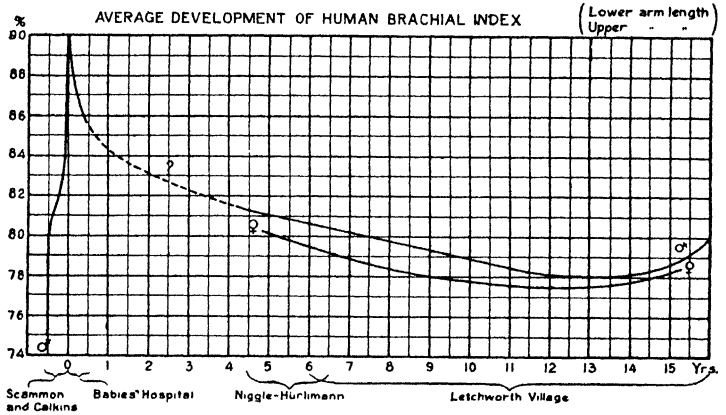


FIG. 234. Average development curve of the brachial index (i.e., lower arm length divided by upper arm length) (scale at left) from intra-uterine life to puberty as indicated on the age scale at bottom. Data from various sources; those from ½ to 5 years are sparse.

Primates,* then it appears that in the lower Primates also the brachial index rises during gestation to 80 or 85 (Fig. 235). However, in the apes the ratio continues to increase until in the adult chimpanzee it is about 94, in the gibbon, 107. In its intra-uterine course, therefore, the human child passes through a series of changes of the index which are closely comparable with those of the anthropoid

* As given by Schlaginhaufen and Mollison.

apes, but instead of maintaining the large ratio acquired at birth, as the anthropoid apes do, the human arm undergoes a rapid reorganization, such that the lower arm falls behind in relative length from birth to adolescence. We thus

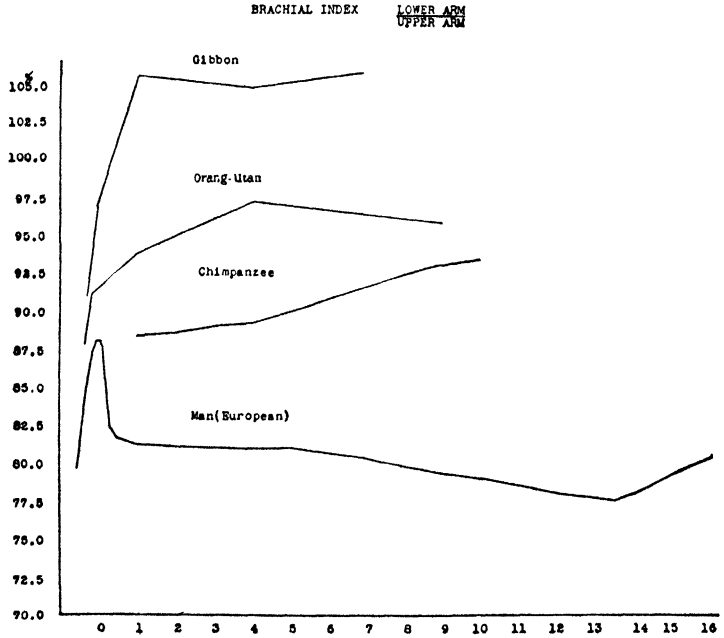


FIG. 235. Comparative curves of changes in the average brachial index (i.e., 100 × lower arm length ÷ upper arm length) at different ages in intra-uterine and post-natal life, shown for gibbon, orang-utan, chimpanzee and man (European).

obtain an interpretation of the human individual development curve of the brachial index, in that the prenatal part follows the general Primate trend, preparing the child, as it were, for an arboreal, brachiating, life; but from birth on the brachial index deviates more and more from the brachiating plan, and acquires that of adult man.

This resemblance of certain stages of development of the child to later stages, and sometimes even adult conditions, in the lower vertebrates was the thing which led Karl Ernst Von Baer to the generalization that in recapitulations of ontogeny the child passes through steps that lie along the lines on which man is supposed to have evolved.*

It is obvious that the child does not generally develop the (often specialized) forms which are found in the *adults* of the lower vertebrates. It is, however, true that the lower vertebrates and the child pass through similar stages in early development, and that at a certain point the line of development of the human child diverges from that of the line taken by some of the lower forms, so that the adult conditions of the two become very different, as, for example, in the transitory embryonic gill arches.

We may say, in general, that the early developmental stages of the vertebrates show many organs in common, though these organs may be only temporary in their appearance in the higher forms. They represent, as it were, the scaffolding necessary to the erection of the building, but something that is of no further use, once the building is completed. Accordingly, when the building is finished the scaffolding is removed.

The similarity in the development of the human fetus and the young of other Primates and other mammals and vertebrates is, however, clearly one of the strongest arguments for the conclusion that these are all related, and it is only in the later stages of development that they have become different from each other. The development of a child can take place only along a narrow path, and for some

* During his researches Von Baer found the labels missing from two small embryos that he had preserved in alcohol. He was unable to decide whether they were very young lizards, birds or mammals.

distance that path is a well-worn one that has been trod by its ancestors and which is still being trod by many related mammals.[2]

The mutations which ordinarily first appear in the germ plasm show themselves by alterations in the form of the individual that arises from that germ plasm and they are reproduced in the subsequent generation, because the subsequent generation arises from that modified germinal plasm. The relation of the germ plasm and the change in the adult may be visualized in a diagram (Fig. 236) in which is shown a series of mutations in the germ protoplasm *A*, *B* and *C*. The bodily modifications that they induce recur in successive generations that arise from the modified germ plasm. Most of the mutations that survive affect last-formed organs. Mutations of early stages would probably cause death.

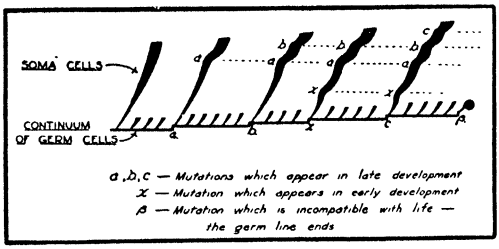


FIG. 236. Diagram showing at the base the continuum of germ cells that passes through the ages; also the somas that arise from them (only five represented in extended form). Illustrates the inheritance and piling up of inheritances of mutations in the individual soma. For simplification the illustration is drawn from a parthenogenetic species (like the water "flea," Daphnia); so it is not complicated by sexual reproduction. Time is indicated along the base line passing from left to right.

WHAT OF THE FUTURE?

The human child reveals in its development the past history of the race. Is there any way of predicting the future course of human development? Apparently it is much easier to resurrect the past than anticipate the future.

Nevertheless, we have in the palaeontological history of various mammals hard-earned information of the course of evolution of various genera and families.

First, the early species were of small size. The later species increased in volume up to a maximum after which they disappeared. This is the history of the camels, which started with an animal about the size of a jack rabbit. The primitive horse was three feet long. The early rhinoceros was a small animal. It gave rise to a species that became extinct in the post-Pliocene age of Europe. It was fifteen feet long. The Titanothere, on which the late Henry Fairfield Osborn wrote a monograph, began as an animal weighing about 150 pounds. The largest of its descendants weighed about 6,000 pounds. The primitive elephants were relatively small; the last and largest forms still survive (partly in consequence of domestication). They have nearly reached the physiological limit of size for a terrestrial species. Similarly the lizards of the Miocene mostly started small, advanced to a gigantic size and then became extinct.

Now man has had a long history, but we have few remnants that enable us to say whether or not he has increased in size from eolithic times. Man belongs to the largest and highest group of Primates. His nearest relatives (in the Anthropoid apes) are all rather large. The Gorilla certainly surpasses man in weight if not in height. The others are not as tall as man. The whole group of Anthropoids and man comprise huge individuals. It seems probable that they are near the end of their evolution. As for man, he still seems to be getting larger. What the end is to be we know not.

In the same direction points man's huge brain. Perhaps significant of the human trend is the phenomenon we see today of thousands whose brain function becomes impaired

in later life. With an appalling increase of persons receiving state care as insane, we wonder what the future will bring forth in respect to brain break-down, and how rapidly present-day tendencies will progress.

Apparently man is to be compared with great horny and armored Dinosaurs, the Great Elk and many fossil Nautili in which an exaggeration of a part was followed by extinction.

On the other hand, there are some extraordinary properties of the human species that may enable it to resist extinction for another 100,000 years: (1) its widespread dissemination; (2) its resistance to disease, resulting partly from crowding; (3) its study of the laws of development and sanitation. In a word, the knowledge that it has acquired and put to use. These may all postpone the day of extinction. But inherent laws of mutation and evolutionary change will work themselves out eventually and man will in time go the way of all other species.

SUMMARY

We have now traced the long, long history of the human genes to the beginning of life on earth when, perhaps, an inorganic catalyst, entering into a favorable combination of molecules of carbon, hydrogen, oxygen, nitrogen and sulphur, assisted in the formation of some simple carbohydrate and amino-acid. Thereafter the catalyst entered into union with one of its products and thenceforth lived combined with it. Together they started on the career that has led to the genes and substrate (cytoplasm) which has given rise through the ages to the world of living organisms as we know it.

Under the influence of external energy the unstable genic and cytoplasmic elements have undergone a more or

less constant mutation. Mutations that were adapted to conditions, or that could find conditions adapted to them, survived and were continued. Even inside of a species, like the human, mutations have occurred of which the less innocuous have been able to survive. Thus has arisen that great variety, often apparently meaningless, which characterizes each group of organism and none more so than man. The interaction of gene and cytoplasm, themselves constantly varying under impact of external energy, provide the vast variability that has made evolution possible.

The new mutations affect first of all the organs that arise relatively late in child development. Accordingly, the child follows the line of development of his ancestors until it comes to the development of the new trait. As new characters are added to the old the former become constantly relatively older. Nonetheless, the child in development passes through these stages though at a relatively early age. Thus the relative age in development at which a trait appears is roughly parallel to the relative time of its appearance in the evolution of the race. And as the new traits are built upon the old in tracing the course of development we are able to get some clue as to the way our ancestral types developed. Thus always the more recently evolved species are forced to travel in their individual development the familiar well-worn paths that the ancestral species have also trod.

NOTES

1. On human evolution one may consult the books of Henry Fairfield Osborn on fossil man, also G. Elliot Smith (1927), *The Evolution of Man*, Oxford University Press; Earnest A. Hooton (1931), *Up from the Ape* and Richard Swann Lull (1929), *Organic Evolution.* No doubt there are humans, even of European stock, who can read

these books and remain unconvinced that the first man was not made out of clay. For such the reading of these books is a waste of time.

2. On infants read Arnold Gesell (1928), *Infancy and Human Growth*, N. Y.: Macmillan Co., and Myrtle B. McGraw, *Growth*, N. Y.: Century Co. On the morphological changes of the developing child see scattered papers by Adolph H. Schultz and the author in recent years.

INDEX AND GLOSSARY

acidity, 156, 225.
Adam's apple, 33, 114.
adolescence, 128–130.
adolescent spurt, 115, 128–130.
adrenals (see suprarenals).
agglutination, sticking together, especially of the red blood cells under abnormal conditions, 350–353.
Albania, 341.
albinism, lack of pigment, 346.
albumins, 167.
Alexander the Great, 137.
alkaptonuria, from alkali + Gk. haptein, to possess. A reducing substance in the urine causing it to darken on standing, 354.
allantois, 20, 27.
allel, Gk. allelon, reciprocally. One of the pair of similar genes occupying the corresponding loci in the pair of chromosomes; same as allelomorph, 191 (see multiple allels).
amacrine, Gk. a, not; makros, long; is, inos, fiber. Type of unipolar cell found in the retina and elsewhere, 63.
amino acids, from ammonia, an acid containing NH^2 obtained from protein by hydrolysis, 207, 353.
amnion, the delicate membrane surrounding the embryo, 21, 66, 300, 301.
amoeba, 322.
amphibia, 100, 106, 290, 309.
anaphase, Gk. ana, up. The phase in nuclear division when the chromosomes, after division, move to the two poles, 163, 164.
Ångstrom unit, vii.
animalculist, 142.
antigen, a substance which in the body stimulates the production of an antibody, 350.
ants, fungus growing, 326.
anus, 89.
aorta, 92.
appendicitis, 89.
aqueous humor, 61.
arboreal life, 374, 380.
Aristotle, 137–140, 146, 166, 286.
arm, 130, 373–375, 378, 379.
arteries, 88.
ascidian, one of the divisions of tunicates (q.v.).
auricle, L. dim. of auris, ear. The external ear or pinna, 66, 67, 76.
Australians, 347.
automaton, 138.
Averroes, 139.
axis of body, 21, 22.
axon, Gk. axon, axis. The long unbranched process of a nerve cell, usually ending in a dendrite, 44, 45, 50, 53–55.

bacteria, 316–318; 328; sulphur, 328.
bacteriophage, 315, 328.

Balfour, F. M., 108.
Barker, L. F., 133.
basi-chromatic, 157.
basic dyes, dyes which owe their coloring properties to the base which has contributed to their composition as a salt, 225.
Bateson, W., 194.
beginnings of a trail, 239, 241.
Belling, J., 206, 242.
Beneden, E. Van, 147.
bile, 91.
birds, 106.
birth, 123.
Blacker, C. P., 368.
blastodisc, Gk. blasto. The germinal disc, 212.
blastopore, 26.
bleeders, 282.
blood cells, 92; clotting, 282; groups, 332, 350; sugar, 92; vessels, 88, 94, 95, 253, 256.
blue baby, 299.
Boas, F., 133.
Bodansky, M., 242.
body build, 340, 368.
bone, 112–115, 269–278; cartilaginous, 272; diseased, 115; formation of, 109–115; mesenchymatous, 269, 270.
Bowman's capsule, 102.
brachial index, L. brachium, arm. The ratio: length of lower arm divided by upper arm, 379.
brachycephaly, short-headedness, 76, 77.
brain, 28, 30, 31, 47, 49, 56, 110, 264, 383.
Bridges, C. B., 188, 241.
brittle-bone, 276.
Brown, R., 147.
buffer, a substance that tends to preserve unchanged the grade of acidity or alkalinity of another substance, 157.
Burnett, J., 28.
bursa, L. purse. A fluid filled sac, often developed where it will reduce friction, 40.
Bushmen, 347.
Bütschli, O., 147.

Calkins, G. N., 329.
Cannon, W. B., 118.
carbohydrates, 209.
carotid artery, 88.
carotinoid, 281.
cartilage, 109–114, 180.
cartilaginous skeleton, 110–112.
Castle, W. E., 204, 218, 241, 242.
catalyst, Gk. katalysis, dissolution. A chemical agent that accelerates a reaction without itself being destroyed in the process, 227, 236.
cataract, Gk. kataraktes, to knock down. Opacity of the lens or adjacent organs, 361.
caul, 21, 301.
Cebus, 314.
cell, 147–149, 177, 178, 184; division, 9–11, 162–165, 243; kinds, 157, 180, 219; number, 3, 25; origin, 327, 328; velocity of division, 219; wall, 150–152, 184.
cellobiose, a sugar of the biose (disaccharide) class, obtained from cellulose, 237.
cellulase, an enzyme that acts on cellulose, accelerating the formation of cellobiose, 237.
cellulose, 209–211, 236.
centrifuge, 174.
cephalic index, 340, 368.

cephalic precocity, 27, 36, 124, 295.
cerebral cortex, 125.
cerebronic acid, 265.
cerebrosides, 168, 265.
cerebrum, 49, 56, 125, 183.
Chambers, R., 156.
chemical differentiation, 264.
Chesley, P., 242.
chest, 376, 377.
chick, 145, 170.
Child, C. M., 296.
child-behavior, 123, 126, 127.
childbirth, 123.
childhood, 126, 127.
child-inquisitiveness, 127.
chimpanzee, 373, 374, 379.
chin, 75.
Chinese, 75.
Chittenden, R. J., 216, 242.
chlorophyll, leaf green, 283.
cholesterase, an enzyme that acts upon cholesterol, 265.
cholesterol, an alcohol found in bile, egg yolk and nerve tissue, 265.
choline, Gk. chole, bile. A base, widely distributed among all kinds of organisms, combined in the lecithin molecule, 264.
chondriosome, Gk. chondros, a granule. A minute body of granular or thread-like shape, found in cells, 155, 156, 171, 326.
chorioid, 60, 61.
chromatin, Gk. chroma, color. A deeply staining cell-substance, found enveloping chromosomes, 159, 162, 165.
chromidia, 317, 320–323.
chromomere, the ultimate visible unit in the chromonemata, 148, 197, 322.
chromonema, one of the fine thread-like bodies forming an essential organ of chromosomes, 148, 155, 160, 163, 164, 188, 195, 197, 200.
chromosomal duplication, 148, 164, 333.
chromosome, one of the group of deeply stainable small spherical or elongated bodies which contain the genes, 148, 149, 160, 164, 165, 187, 197, 200, 204, 205, 211, 314, 323, 333, 334.
chromosome, human, 203–204; salivary, 197–203.
chromosome-map, of Drosophila, 196, 197; of the rat, 205.
cilia, 177, 180.
Clark, G. L., 234, 242.
cleavage, 169, 176, 244, 245.
cloaca, 89, 106, 107.
coal heaver, bones of, 278.
coat color, 331.
cobbler, bones of, 277–278, 284.
cocci, Gk. kokkos, berry. Minute spherical bacteria, 316, 317.
coccyx, L. cuckoo. Rudiment of tail in man, 28.
cochlea, L. snail shell. The spiral canal of the inner ear, 70–73.
Cold Spring Harbor Symposia, 184.
Cole, F. C., 184.
collagen, Gk. kolla, glue. A gelatin-like protein, 113, 268, 269.
colloids, ordinarily, non-crystalline substances which do not readily diffuse through membranes, 150, 252; lyophilic, 252.
coloboma of iris, Gk. koloboma, a defect due to mutilation. Fis-

sure of the optic cup, especially at the iris, 360.
Condon, L. D., 108.
cones of retina (see retina).
conjunctiva, 59, 62.
Conklin, E. G., 174, 184, 211.
connective tissue, 256, 267.
cornea, L. corneus, horny. The transparent outer covering of the eyeball, 59, 62.
corneal degeneration, 359.
Corti, organ of, 71, 72, 74.
cotton fiber, 236.
cow, twins, 299.
Cowdry, E. N., 184.
creatinine, 95.
crossing over, 195, 197.
cysteine, a decomposition product of proteins, 354.
cystine, Gk. kystis, bladder (because first found there). An amino-acid found in horn, in hair and, exceptionally, in urine (cystinuria); a cleavage product of protein, 278, 353, 354.
cystinuria, 354.
cysts of ovary (see ovarian cysts).
cytoplasm, Gk. kyto, cell + plasma, a plastic material. The part of the cell surrounding the nucleus, 149, 155, 162, 165–176, 179, 184, 211 ff., 246, 313, 326, 327.
cytoplasm, continuity of, 326, 327.
cytoplasm, distribution zones of, 176.
cytoplasmists, 211.

Dane, 338.
Danforth, C. H., 85.
Darwin, C., 185, 186.
Darwin, E., 185.
Davis, C. L., 108.
deficiency, 202.
Delapatius, 143.
Demerec, M., 241, 242, 324.
dendrites, Gk. dendron, a tree. Branching terminals of nerve axones, 49.
dentine, L. dens, tooth. The limy substance forming the mass of a tooth; ivory, 84, 85.
dermoid cysts, 184.
Descartes, R., 117.
development, abnormal, 285, 286.
de Vries, H., 186.
diabetes mellitus, 354, 355.
diameter, gene, 227; protein molecule, 208.
differentiation, 244 ff.
digestive system, 108.
dihybrid, 191.
Diogenes of Apollonia, 137.
Dionne quintuplets, 300.
dolichocephaly, Gk. dolicho, long, narrow. Long-headedness, 77.
dominance, the bodily expression of the more active of two allels, 189, 193.
Doncaster, L., 194.
doubling of chromosomes, 164; of gene, 207; of molecule, 207.
Drosophila, Gk. drosos, dew; phila, lover of. A small fly frequenting fermenting fruits, 194–203, 246, 332, 333.
dwarfs, 116, 117, 297, 298, 337.
dwarf mice, 335–337.
dyes, acid and basic, 225.

ear, 32, 66–74, 85.
ear bone, 32, 33, 69.
ear drum, 124; of frog, 289.

earthworm, 97, 118; regeneration of, 293.
ectoderm, the outer embryonic membrane, 24–26, 171.
educational system, 127, 130, 132.
egg, ascidian, 171; frog, 169, 170; hen, 167; human, 3–6; ovarial, 226; sea urchin, 168; size of (see size, egg).
egg cleavage, 174.
elastin, L. elasticus, propulsiveness. An albuminoid constituting elastic fibers, 268.
electric potentials, 153, 155.
electronic forces, pertaining to the electron, or elementary charge of negative electricity, 236, 257.
embryonic disc, 20–25, 28, 30, 31, 45, 47.
Empedocles, 137.
enamel organ, 84.
encapsulement theory, 141.
endocrine glands, 115–120, 133, 297.
Engelbach, W., 133.
entoderm, the inner embryonic membrane, 24–25, 171.
enzyme, Gk. en-zyme, in yeast. Any organic catalyst, 228–232, 237, 242.
enzyme-action, specificity of, 236; velocity of, 237–239.
enzyme-product, 225.
epidermis, outer skin, 79.
epigenesis, the theory that the embryo is formed *de novo* from the unorganized egg, 139–146.
epiphysis, 139.
Eskimo, 340, 367.
esophagus, 89.
esters, compounds made by replacing the acid hydrogen of an acid by a hydrocarbon radical, 265, 272.
European, 120, 340, 341.
Eustachian tube, 32, 67.
evolution, the doctrine that organisms show progressive changes and have done so since remotest times, 385.
excretory duct, 106.
excretory organs, 95–101.
experimental teratology, 285–292.
extremity, 34–37.
eye, 58–66, 124; ball, 59–62, 362; color, 193, 344; defects, 359–363; lens of, 59–62, 65, 361–363; lid, 59.

face, 73, 74, 85, 111, 153.
face of membrane, 153.
Farr, W. K., 234, 242.
fat, 180, 265, 266.
fat cell, 178.
fatty-phosphoric bodies, 155, 264–266.
feet, 357.
ferment, fermentation-producing agent, 228, 287, 316.
fermentation, change due to enzymes produced by living organisms, such as yeast or bacteria, 228.
fertilization, 146.
fibrin, fibrous protein resulting from action of thrombin upon fibrinogen, 282.
fibrinogen, a soluble blood-protein which, acted on by the enzyme thrombin, yields fibrin, 282.
fibroblast, or primitive mesenchymal cell from which connective tissues arise, 270.

finger bones, 113.
finger prints, 304.
fingers, 35, 358.
Fischer, E., 242.
fishes, 34, 88, 100.
flax, 215, 216.
Flemming, W., 147, 148.
flexed-tailed mouse, 239, 240.
Flint, J. M., 108.
Fol, H., 146, 147.
foldings of membrane, 247–253.
follicle, L. folliculus, a small bag. A bag-like organ or depression, like that of hair or the egg capsule in the ovary, 279, 280.
food canal, 87.
foot, 34–36.
fovea centralis, L. a small pit, centrally located, 64.
fraternal twins, 301.
frog, 169, 286–290; eggs of, 169.
Funaria, L. funarius, of a rope. A genus of mosses, characterized by a peaked cap to the spore-cup, 214.
fungus ants, 326.

galactose, Gk. galakto, milk. A crystalline sugar, $C_6H_{12}O_6$, 265.
gall bladder, 89, 90.
Galton, F., 309.
ganglionic cell, 52, 53, 56, 57.
gastrula, 26.
Gates, R. R., 368.
gemmule, 186.
gene, 148, 149, 165, 166, 185 ff., 246 ff., 313, 314; as molecule, 206, 227; bacterial, 316–318; change, 331; defect, 299; dispersion, 160; distribution in nucleus, 159–163; human, 325; loci of, 196; number, 203, 207; size and weight, 227; value of, 325.
gene-cytoplasmic reaction, 257.
genists, 211.
genital duct, 106; fold, 102, 103; gland, 106.
genius, 363.
genotype, 191.
George III (King), 29.
germ cells, 146; gland, 104.
Gesell, A., 386.
gibbon, 374.
gill arch, 30, 32, 33, 67, 86, 88, 371; atrophy, 287, 288; bars, 38, 67–69; furrows, 30, 286; slit, 33.
gills, 30, 32, 287.
gipsy moth, 238.
globin, a cleavage product of the hemoglobin of the blood, 283.
globulin, a group of proteins (e.g., myosin) insoluble in pure water but soluble when salt is added, 266.
glucose, a sugar ($C_6H_{12}O_6$) of which dextrose is one form of the three in which it occurs, 209, 210.
glutathione, a sulphur-containing organic compound obtained from yeast, blood and other tissues, 243, 278.
gluteal masses, muscles of the buttocks, 372.
glycine, Gk. glyks, sweet. A sweet-tasting amino acid, 207.
glycogen, a carbohydrate related to starch and dextrin, sometimes called animal starch. It is stored in the liver, 209.
goiter, 356.
Goldschmidt, R., 238, 242.
Golgi bodies, 63, 326; method, 63, 156.
gonads, organs that produce the

eggs or the sperm, respectively, 115, 120, 298.
gorilla, 374, 383.
Gortner, R. A., 209, 242, 283.
grafting of limbs, 290.
grasping reflex, 124.
growth, 120, 121, 126, 128, 132, 133, 317.
Gypsies, 352.

Habrobracon, 216, 242.
haemophiliac (see bleeders).
Hagedoorn, A. L., 252.
hair, 80, 85, 121, 193, 279, 346–350; color, 343; fetal (see lanugo); follicle, 82, 279; form, 346, 348; length, 348–350; number, 82; red, 343.
Haldane, J. B. S., 242.
hand, 35, 357.
Harrison, R. G., 46, 291, 292, 309.
Hartman, C. G., 18.
Hartsoeker, 141, 142.
Harvey, W., 139, 140, 143.
Havers, C., 272.
Haversian system, 272, 274, 275.
head, 26–29, 31, 76, 77, 295.
heart, 92–94, 108.
Hegner, R. W., 18.
Helff, O. M., 288.
hemin, a derivative of hemoglobin, 283.
hemoglobin, Gk. haima, blood + L. globus, globe. The respiratory pigment in the red blood cells, 283.
hen's egg, 143, 145, 167, 170.
hepatic lobules, 91; vein, 90.
heredity, 148.
heredity vs. environment, 8.
Hertwig, O., 146, 147.
heterozygous, Gk. heteros, other. Derived from gametes unlike for a given gene, 191.
hinny, 217.
Hofmeister, W., 147.
homozygous, Gk. homo, like; zygote, gamete. Derived from union of gametes alike in respect to a given gene, 191.
Hooke, R., 147.
Hooton, E. A., 385.
hormones, Gk. hormoein, to excite. An internal secretion, carried by the blood from one cell group to another, 120.
Howell, W. H., 309.
Hurst, C. C., 241.
hybrids, 214.
hydrogen, 208.
hydroid, hydra-like, belonging to the group that contains the freshwater polyp, Hydra, 296.
hydrolysis, Gk. hydro, water + lysis, a dissolution. Chemical decomposition involving the use of the elements of water H_2O, 236, 269.
hyoid bone, 33, 111.

id, 187, 188.
idant, 188.
idiocy, 299.
imbecile, 364.
immunity, 367.
implantation of egg, 13, 14, 18.
India, 347.
infant, 386.
insulin, L. insula, island. A secretion of the "islands" of Langerhans,—cell masses of the pancreas, 92.

intercellular bridges, 151.
interface, 151–155.
intermembral index, 377.
intestine, 89.
intrauterine deaths, 299.
intrauterine life, length of, 19.
iodine, 356.
iris, 59, 61, 238, 344.
Italian, 238, 337, 338.

Janssens, 141.
Janus monster, 307.
Jennings, H. S., 367.
Jews, 355.
Johanssen, W. L., 188, 241.
Johnson, F. P., 108.

Kamenoff, R. G., 242.
keratin, Gk. keras, horn. The chemical basis of horn, hair, etc., 278, 281.
key-notch theory, 232.
kidney, 95–101, 105, 106, 108; first, 97, 99; second, 98, 104; third, 101; tubules, 96.
Kölliker, R. A. von, 147.
Kühn, A., 242.

lactose, L. lactis, milk. A sugar ($C_6H_{22}O_{11}$) present in milk, 265.
land life, 114.
Lane, W. A., 277, 284.
language, 126.
lanugo, 121, 280.
larynx, 87.
Laubenfels, M. W. de, 263.
lecithin, Gk. lekithos, egg-yolk. A waxy, crystallizable, phosphorus-containing fat, 167, 264, 266.
Leeuwenhoek, A. van, 141.
leg, 373–375.
lens of eye, 59, 60–62, 65, 66, 286, 361.
leucemia, Gk. leukos, white—emia, blood. A tumor of the white cells of the blood, 365.
leucocyte, a white blood cell, 365.
Lewis, W. H., 18, 46, 286.
ligament, 268.
Lillie, F. R., 133.
limbs, 34–45, 66.
limb transplantation, 291, 292.
Lindegren, C. C., 317, 318
linkage, 195, 196.
linkage map, 202.
lips, 76.
liver, 89, 90, 94; cells, 91; regeneration, 293.
lizard, regeneration in, 293
Loeb, J., 295, 296.
longevity, 126.
Lull, R. S., 385.
lung, 86.
lymph, 257, 259.

macaque (see Rhesus).
MacDowell, E. C., 335, 337, 365.
macula lutea, 64.
Mall, F. P., 133.
malleus, 32.
Malpighi, 140.
maltase, 237.
maltose, 209.
mammal, 360.
mammals, chromosomes of, 204.
man, genes, 203, 204; evolution of, 369.
marrow cavity, 114.
Martin, R., 368.
Mast, S. O., 329.
maturity, 126.
Mauperitus, P. L. M. de, 185.
McGraw, M. B., 133, 386.
medullary sheath, a myelin layer

which surrounds certain nerve fibers, 50, 51.
Melanesian, 347.
melanism, Gk. melas, black. Excessive formation of black pigment, 343.
membrane, cell, 153–155; embryonic, 247; foldings of, 247–253; nuclear, 223; perforation of, 87, 89, 252, 253.
membrane bones, 111, 270, 271.
Mendel, G., 188, 241.
Mendelism, 188–194.
mental defect, 364.
mental gift, 363–365.
mesenchyme, loose migrating cells of the middle embryonic layer, 109, 110, 114, 150, 171, 259, 260, 270.
mesoderm, middle embryonic membrane, 25, 26.
metabolic nucleus, 219, 222, 322.
metabolism, Gk. meta, beyond; ballein, to throw. Sum of the vital, oxygen-consuming processes of the body, 219, 353.
metamorphosis, human, 127.
metanephric, relating to the middle or second kidney, 23, 103.
metaphase, or after phase, a stage in nuclear division immediately preceding the anaphase, 163, 164.
mice, dwarf, 335–337.
micella, L. mica, morsel, grain. Units of microscopic size in colloids, 151, 243.
microglia, Gk. glia, glue. The mass of small adventition cells scattered throughout the brain, 57.
microscope, resolving power of, 197.
Midget City, 117.
midgets, 116, 117, 297.
migration of cells, 259–263; of buds, 261–263.
milk glands, 81.
milk lines, 81, 83.
mitochondria, Gk. mitos, thread; chondrus, granule. Chondrisomes, 151, 152, 226.
mitosis, Gk. mitos, a thread. Nuclear, especially chromosomal, division, 148, 162, 163.
Mohr, O. H., 309, 368.
molecular weights, 208, 209.
molecule-doubling, 207, 234.
molecules, large, 210, 211, 236, 269, 283.
Monboddo, Lord, 28.
monozygotic twins, from one zygote, 302.
Morgan, T. H., 188, 194, 211, 241, 309.
motor plate, 40–42, 45, 51, 182, 255.
mouse, dwarf, 337; flexed-tailed, 239, 240.
mouth, 73, 87, 89.
movements, muscular, 45.
mulatto, 343.
mule, 217.
Muller, H. J., 188, 241.
Müller, Johannes, 106.
Müllerian duct, 103, 105–107.
multiple allel, 207, 331, 332.
multiple allelomorphism (see allel). The presence of several related genes at one locus, 207.
muscle, 34–46, 109, 171, 258, 266; fiber, 39–45, 179, 180, 257, 266, 267; fibrilla, 42, 43; -nerve union, 255, 256; regeneration, 293.
muscular system, 125.

mutation, L. mutatio, change. A genetic variation, which reproduces itself, 313, 330–332, 382; chromosomal, 332, 333; genic, 334; induction of, 332; in man, 335, 338–367.
myelin, the fatty material which makes the medullary sheath of nerves, 44.
myopia, shortsightedness, 362–363.
myosin, Gk. mys, muscle. A simple protein found in muscle, 266.
myotomes, the segmented embryonic cell masses which give rise to the trunk and appendicular muscles, 29, 34, 38, 97, 109, 149, 248.

nasal passage, 58.
Neanderthal man, 365.
neck, 30, 46.
Needham, J., 184.
negro, 120, 281, 335, 340–343.
neonate, 121–123.
nerve, 36, 253; auditory, 70; fiber, 49, 50, 181, 182; ganglion of, 52, 53; optic, 62; sensory, 263; spinal, 50.
nerve cell (see neuron), 180, 257.
nervonic acid, found in nerves, 265.
neural fold, 290; groove, 28, 30, 31, 47; plate, 171; tube, 29–31, 47.
neurenteric canal, 20.
neurofibrils, 52.
neuro-muscular complexes, 120.
neuron, 48, 51, 57, 181.
Newman, H. H., 309.
Noctiluca, 323.
Nordenskiold, E., 184.
Nordics, 343, 344, 352.
Northrop, J. H., 22.
nose, 73–75, 114.
notochord, 248.
nucleoplasm, the basic substance of the cell nucleus, 150.
nucleus, L. kernel. The body in the cell which is center of metabolism and reproduction, 147, 149, 150, 158, 184, 213, 214.
nucleus, metabolic stage of, 219–226.
nucleolus, a conspicuous, deeply staining body in the nucleus, 157, 158, 164.
number of cells in body, 3; of rods and cones, 65; of hairs per sq. cm., 82; of genes in Drosophila, 203, 207.

operculum of frog, 287.
opportunity, 9.
optic cup, 59, 60.
optic nerve, 61, 62.
orang, 374.
organ-forming areas, 24, 46.
organizer, 290.
organs, 87.
Osborn, H. F., 383, 385.
osteoblasts, 113, 273.
osteoclasts, Gk. osteo, bone + klastos, broken. Large migratory cells that destroy bone to form canals, etc., in it, 113, 272, 273.
otocyst, 69.
ovarian cysts, 177, 178.
ovary, 108, 177, 179.
oviparous, producing eggs that hatch outside the body, as opposed to viviparous, 14.
ovists, 141, 142, 175.
ovum, 145, 226.

oxy-chromatic, 157.
oyster, 15.

Painter, T. S., 201, 203, 204, 241, 328.
palate, 73.
Paleozoic, Gk. palaio, ancient + zoe, life. The earliest of the three life eras, 370.
palm prints, 306.
pancreas, 91, 92, 224; islets of, 115, 355; regeneration of, 293.
pangenes, 186.
pangenesis, Darwin's theory that all cells of the body throw off minute generating granules, 186.
pangenesis, intracellular, 186.
Papuan, 347.
Paramecium, 320.
parasitism, 15–17.
parathyroid, an internally secreting body lying adjacent to the thyroid, 33, 115.
part-on-part, action of, 138, 139, 286–292, 298.
Patten, B. M., vi, 108.
pea, 188, 193.
Pearl, R., 366.
pectin, 152.
Pellew, C., 242.
penis, 106.
periosteum, 113, 272.
phagocytosis, 367.
pharynx, 89.
phase, change of, 151, 222.
phenotype, 191.
phosphatase, an enzyme that expedites the hydrolysis of phosphoric acid compounds, 269.
phosphatides, 168.
phosphorus, 264, 266.
Physcomitrium, 215.
physiological units, 185.
pigment, 79, 281, 331.
pigmies, 335.
pineal bodies, 118; eye, 119.
pineal gland, L. pinea, pine-cone. An internally secreting body forming part of the roof of the middle brain, 115, 117.
pituitary gland, L. pituita, phlegm. A vascular internally secreting gland lying at the base of the brain (the formation of nasal mucus formerly ascribed to it), 115, 117, 118, 120, 297, 336, 337.
placenta, Gk. plakons, flat cake. The disk-like mass by means of which connection for nutrition is established between mother and fetus, 19, 94, 121.
plastids, Gk. plastides, molder. Certain small bodies lying in the cytoplasm, 156, 326.
Platt, A., 139.
pneumonia, 366.
polar bodies, 6.
polarity, 295.
polydactyly, many fingeredness, 359.
Polynesian, 347, 367.
portal vein, 90.
porter, bones of, 278.
post-reproductive period, 126.
potassium, 154.
Pouchet, F. A., 144.
preformation, 139, 141, 146, 175.
prematurity, 126.
primates, principal, chief, the order of mammals that includes man, apes, monkeys, lemurs, 204, 314, 369, 379, 380.
primitive groove, the equivalent of the blastopore of the lower vertebrates, 25, 26, 31.

prophase, earliest stage in mitosis, 165.
protamines, simple proteins found combined in acid proteins in ripe sperm, 208.
protein, any of the class of extremely complex unions of amino-acids essential to all living cells, 207, 208, 211, 228, 330, 332.
protein, molecular weight of, 208, 209.
protoplasm, the totality of the fundamental living substances of cells, 149.
protoplasmic zones, 176.
Protozoa, the group that contains the simplest animals, 321; as synthesizers, 328, 329; genes of, 321–324.
ptyalin, Gk. ptyalon, spittle, saliva. A starch-splitting enzyme of saliva, 225.
purins, 95.

rabbits, 218.
race horse, 325.
radium, 332.
Rahn, O., 319, 320.
rats, 204.
reaction to stimulus, 40, 120, 123–125.
Réaumur, 142.
recessive, that member of an allelic pair of contrasted genes that is eclipsed in inheritance; opposed to dominant, 189, 193.
reciprocal crosses, those in which the one of the varieties that is being crossed is used alternately as father and as mother, 213–215.
red hair, 343.
reflexes, 120, 122–125.
regeneration, generating anew; restoring lost parts, 293–295.
reproductive period, 126.
reptiles, 106, 114, 118.
residues, 209.
resistance to disease, 365, 384.
respiration, 94.
retina, 59–65, 361.
Rhesus macacus, the macaque monkey, 18, 48, 133, 244, 314.
rhodopsis, Gk. rhodon, rose + opsis, sight. The visual purple of the retina, 65.
ribs, 34, 114.
Risley, S. D., 360.
rods of retina (see retina).

Sabin, F., 108.
salamander, a kind of tailed amphibian, 114, 153, 291–293.
salivary gland of Drosophila, 197–199, 202; of man, 225.
scarlet fever, 366.
Schleiden, M. J., 147.
Schmitz, F., 146.
Schneider, A., 147, 184.
Schultz, A., 386.
Schwann, T., 147.
Sciara, 198.
Scots, 335.
sebaceous glands, L. sebaceus, grease forming. Skin glands that secrete an oily material at base of hairs, 80.
secreting cell, 225.
Sedgwick, A., 108.
segregation of genes, 191, 195.
selection of genes, 325.
self-duplication of molecules, 208, 209.
semen, viscid fluid containing the sperm cells, 137, 138.

semicircular canals, 70.
Semitics, 75.
sense organs, 58–74.
sewage system, 95–108.
sex, 102–104, 108, 121, 132; chromosome, 165, 194, 204, 205; determination, 102, 103, 238; intergrades, 238, 239; linkage, 194, 205.
sexual development, 184.
Shakespeare, 118.
sharks, 112.
Sharp, L. W., 184.
Siamese twins, 307.
simplest organisms, 315–319.
size, bacteriophage, 315; cellulose particles, 236; egg, 3; embryonic disc, 23; intercellular bridges, 152; gene, 227; micella, 151, 152; virus, 316; yeast, 319, 320; zymogen particle, 234.
skeleton, 35, 109, 122, 124, 132, 133.
skin, 78–83, 85, 131, 157, 278; color, 342, 368.
skull, 111, 124; shape, 76, 77.
smallpox, 367.
smell, organ of, 58.
Smith, G. E., 385.
Smith, P. E., 335, 337.
Snyder, L. H., 368.
specificity of catalysts, 230, 232.
Spemann, H., 309.
Spencer, H., 185, 186, 241.
sperm cell, 104, 144, 145, 166, 229, 230.
spermatozoön (see sperm cell).
spina bifida, 299.
spinal cord, 30, 264.
spleen, 365; regeneration of, 293.
sponge, 262.
sports, 331, 367.
staining, 225.
stapes, stirrup-shaped bone of middle ear, 33.
starch, 209.
stature, 297, 335, 336, 338.
stepping reflex, 123.
sterol, any one of a class of the higher alcohols, highly distributed in organisms, especially important in reproduction, 108, 168.
still birth, 122, 299.
Stockard, C. R., 309.
stolon, a runner (like that of strawberry plants), 261.
stomach, 89.
Strasburger, E., 147.
Streeter, G. L., 21, 22, 108, 133.
Sturtevant, A. H., 188, 241.
submolecule, 209.
substrate, 230, 236, 237.
sugar, 209.
sulphur, 243.
suprarenal gland, an internally secreting gland lying above each kidney, 115, 118, 298, 337.
suprarenals, regeneration of, 337.
surface tension, 3.
susceptibility to disease, 366, 367.
Swammerdam, J., 140.
swimming, 124.
sympathetic nervous system, the nervous system of the viscera, 48.
synapse, the contact region at which the nervous impulse passes from one nerve cell to another (in cytology, the pairing up of like chromosomes), 53–55.
syndactyly, union of digits, 358, 367.

tadpole (see frog).
tail, 26–30, 46, 110; flexed, 239, 240.
tapeworm, 17.
taste-sense, 125.
teeth, 84, 85.
telophase, 160, 163, 165.
tendon, 267, 268.
Tennent, D. H., 168, 184.
teratology, the science of marked deviations in development, 299.
testis, 103, 106, 108.
thigh, 130.
thigh bone, 275, 276.
thoracic index, 378.
threads, 253.
thrombase, an enzyme which acts upon fibrogen to form fibrin in blood clotting, 282.
thymus, an internally secreting gland that lies in the upper part of the chest and secretes a substance that influences growth and differentiation, 33, 115.
thyroid, a gland lying in the neck which conserves and disburses iodine essential to metabolism, 115.
thyroxine, an amino-acid, containing iodine, found in the thyroid gland; a regulator of metabolism, 356.
Tischler, G., 184.
tissues, 264–284.
tongue, 89.
tonsils, 33.
trachea, 87.
tramp cells, 259–262.
transfusion, 350.
transplantation of limbs, 253, 291.
trihybrid, 193.
trophoblast, 20.
trypsin, 230, 231.
trypsinogen, 91, 230, 231.
tuberculosis, 366.
tunicates, a group of invertebrates that lies at the base of the vertebrate series (see also ascidian), 171, 172, 246, 285.
twins, 75, 300–307; identical, 302–304; in cattle, 121.
tympanic membrane, 67, 69, 289.
tyrosin, Gk. tyros, cheese. An amino-acid released from protein by digestion, etc., 281, 354.
tyrosinase, the enzyme which accelerates the oxidation of tyrosin, 281, 343–346.

umbilical vein, 88.
urea, 95.
urethra, 106.
uric acid, 95, 353.
urinary bladder, 98, 105; duct, 100–108.
urine, 353.
uterus, the womb, 14; of fetus, 121.

vacuole, 326.
vagina, the caudal end of the reproductive duct in mammals, 107.
veins, 90.
velocity of cell reaction, 225, 234, 237–239, 334; of cell division, 219, 317.
vermiform appendix, 89.
Verschuer, O. von, 309.
vertebra, 109.
villi, 14, 19.
Virchow, R. L. K., 147.

virus, filterable, 316, 328.
vitelline vein, 88.
vitreous body, 59, 62.
viviparous, giving birth to more or less developed offspring; opposed to oviparous or egg laying, 15.
volume of cell, 234.
Von Baer, K. E., 143, 381.

walking, 124.
wandering cell, 260–262.
water, 252, 266.
water of organisms, 3, 11–13, 18, 78, 95, 156, 243, 244, 264, 266, 285, 326.
weight of egg, 3; of embryo, 11, 120, 121; of gene, 227.
weights, molecular, 227, 283.
Weismann, A., 187, 211, 241.
Wettstein, F. v., 214, 215, 242.
Wiener, A. S., 368.
Willier, B. H., 23, 24.
Willstätter, R., 228.
will-temperament profile, 306.
Wilson, E. B., 176, 184, 211.
Wilson, H. v., 262.
Wolff, C. F., 100, 143, 145.
Wolffian duct, the duct that carries urine from the second kidney, and later serves to conduct sperm from the testis, 100, 101, 104–107.
worms, ringed, 99.

xanthin, Gk. xanthos, yellow. A yellow coloring matter found in flowers, 353.
X-rays, 203, 332.

yeast, 319, 330.
yellow fever, 367.
yolk sac, 20, 25, 26.

Zinsser, H., 367.
zones of egg, 169, 171, 176.
zygodactyly, union of digits by a web, 357.
zygote, the fertilized egg and the embryo derived from it; united gametes, 191.
zymogen, an unactive form of an enzyme. Acted on by the enzyme kinase it is changed to the active enzyme, 224, 225, 233, 234.