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THE CHEMICAL SENSES

THE CHEMICAL SENSES

BY

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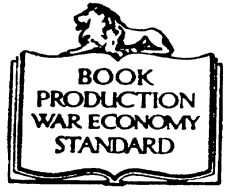
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CHAPTER 1

THE CHEMICAL SENSES—THEIR PART IN LIFE

Taste and Smell

Man is commonly said to be endowed with five senses, sight, hearing, touch, taste and smell. Of these, sight is known to be caused by light waves which are vibrations in the ether, whilst hearing and touch are caused by pressure differences. Sound waves in the air impinge on the ear and bring about rapid changes in pressure on a diaphragm which vibrates and transmits the sensation of hearing to the mind and touch is caused by pressure applied to practically any part of the skin.

Taste and smell, however, are not induced by any known waves in the ether or in the air, but are caused by contact in the case of taste and nearness in the case of smell of certain specific substances. Such substances as salt, sugar, vinegar, quinine, wine or a rose-petal are believed to have a chemical action on the sensory organs in the nose and mouth, hence we speak of taste and smell as the chemical senses. A more precise analysis of the senses shows that smell may be divided into two modalities, first, smell as of roses, night-scented stocks, or mignonette or the less attractive odours of cooking cabbage or the glue works, and secondly an irritation which does not affect only the nose, but also the mouth, eyes, anus and genital apertures, in fact any part of the mucous membrane of the body with which the irritating substance can come into contact. This second sense is spoken of as the common chemical sense and is set in action by such irritants as ammonia or acid fumes. In the ancestry of man the common chemical sense was the first of the chemical senses, and taste and smell are developments or differentiations of it, which, however, occurred at a very early stage of development, somewhere amongst the invertebrates.

These considerations will be examined in greater detail later, for in this first chapter it is proposed to consider the place in life of taste, smell and the irritating chemical sense.

Fundamental Aims of Animals

Biologically the fundamental aims of animal life are

(1) self-preservation ;
(2) preservation of the species.

It is easy to see how taste and smell have been harnessed in the service of, or more properly, have been developed to serve these aims. Self-preservation involves hunting for food, the rejection of poisonous or unsuitable food and escape from dangerous enemies. Preservation of the species involves the survival of some individuals until sexual

maturity is reached, the meeting of the two sexes, fertilization by the male either of the female or of the eggs she has laid, in many cases incubation of the eggs and in the higher animals care of the offspring until they can fend for themselves. The part played by the chemical senses in these activities of life may now be considered.

Hunting

Hunting has progressed far in modern days when big game sportsmen are content to shoot with a camera as a weapon, when the kill, the logical end of the hunt throughout the animal kingdom, is now dispensed with. But whether man hunts for the cinema or for the cooking-pot the necessity of approaching the quarry without giving warning of approach is still the same, and most difficult does he find it to arrange matters so that he is not perceived by smell, although well able to avoid being heard or seen by the animal. This does not apply if man is hunting man as in warfare, for smell is much less sensitive in man generally than in animals. Aboriginal trackers rely more on woodcraft than on smell. Man is said to be microsmatic, keen-scented animals are said to be macrosmatic. When man is hunting animals he uses as much as possible the sense of vision in which he is far superior to most animals, and which being conveyed by ether waves is quite independent of wind or other air movements, and so he places the hunted animal at the biggest possible disadvantage by keeping his position relative to the animal such that the wind blows from the animal to him. The way in which scent is carried by the wind is conclusive proof that it is not a function of the ether but of the air. On other occasions the keen olfaction of the animal world may be turned to good account by man the hunter in his use of bait, the deer for the tiger, the putrefying meat which, dragged behind a boat, will draw sharks from miles away, the worm or the maggot and the ground bait used by the fisherman. Fly-fishing would appear to be independent of olfaction, but this sport is only successful when natural flies are about, luring the fish to the surface to feed. Even so, fly-fishing pays tribute to the visual powers of fish, but I suppose there are relatively few fish with which this method is used, and it also pays tribute to the skill of the angler.

At the other end of the scale the protozoa, consisting of a single cell, simplest of all animal life, pushes forward tentatively a pseudopod, a transitory bulge in its jelly-like body. If it comes in contact with microscopic plants and animals, it engulfs them but rejects inert particles. Such protozoa as the microscopic amœba of fresh-water ponds and the paramecium which roam about bumping into things, taking an avoiding reaction and going off in a fresh direction, have no special sense organs, no cells of taste or smell, but if the water contains irritating chemicals or unsuitable food, another direction is taken. The protozoa have only the most rudimentary chemical sensibility, certainly no taste or smell, yet the chemical sensibility

such as it is, directs the hunt for food. In the search for food flatworms have a highly developed chemical sense, and a piece of meat placed in a spring will soon attract large numbers of small planaria. Earthworms show food preferences, preferring carrot leaves to celery, and celery to cabbage, and appear to be guided by taste. Among the insects bees are directed to flowers at least partly by smell, and other insects like the *Necrophori* to dead bodies and dung on which they feed.

When a dog finds the dead body of a mole and rolls on it, it may be that it will by doing so disguise its own scent and improve its hunting ability, although it may also be simply that the dog derives purely æsthetic pleasure from the odour of the dead mole.

Evasion of Dangerous Enemies

This is the other side of the picture, the rabbit scents the weasel, the fox scents the hounds and is off. The skunk occupies a peculiar position, for the foul scent he spreads is designed to keep his enemies away. The same thing applies to the stink badger of the Philippines (*Mydäus Marchei Huet*) and *n*-butyl mercaptan, one of the foulest substances known, has been found in the secretions of this animal. Even the protozoa appear to have warning by chemical sense of the approach of an enemy and try to make themselves scarce.

Poisoning

How do the beasts reject the poisonous herbs, the birds the poisonous berries? There is little instinctive knowledge of this sort in us; we have to be taught as children which berries to avoid, and a little expert knowledge is generally required before mushrooms are eaten and enjoyed. The relation between the odours and edibility of fungi and the value of odour for identification have been studied by Herrman (*Pharm. Zentr.*, **59**, 1-4, 7-10, 19-21, 1918). The safety of the animals lies in their much keener smell and taste. It is noteworthy that the olfactory region, that part of the nose where the sense organs lie, is always pigmented, yellow in man, darker brown in macrosmatic animals, and the pigment seems to be connected with smell. It is significant that the animals lacking in pigment, for example, white animals, are much more subject to poisoning. In parts of Virginia farmers will only rear black pigs as white eat and are poisoned by roots of *Lachantes tinctoria* which the black pigs leave alone, and in the Tarentino only black sheep are reared as white ones are poisoned by *Hypericum cristum*. Darwin was of the opinion that the black and the white animals ate the same, but only the white were poisoned, but it has since been shown that only the white animals eat the poisonous food. Attempts to stock woods with white rabbits have failed, although as the rabbits are so conspicuous, other factors come into play here. Albinism even in man is associated with complete or partial anosmia. Normally an animal relies on smell to avoid poison, without smell it is lost. Himalayan rabbits are born

perfectly white and remain so for several months, until they are weaned, when pigment makes its appearance just when the necessity to discriminate in food arises.

Man also uses smell to discriminate in food. As he grows older he develops a taste for recherché flavours or, if you prefer, for partly decomposed food, *e.g.* game and cheese. There are limits beyond which he cannot go; if he essays to climb " too high " the nose pulls him down. It has been remarked too that a smell which might be appetising in cheese would definitely condemn an egg. Savages are said to share with civilized humanity the liking for partly decomposed food.

Nutrition

Having found food, an animal must derive nourishment from it. We know from our own experience that the smell of appetizing food starts reflexes it is impossible to control, such as the secretion of saliva and also the secretion of stomach juices to prepare for the digestion of the food when it arrives in the stomach. Incidentally, although the nose and smell do this work naturally, it is not impossible for the ear and hearing to be taught to do it. A dog was always fed when a bell was rung, and after a time the dog's salivary juices flowed when the bell was rung, even although no food was forthcoming. A " conditioned reflex " was set up in the dog.

The odour of onions is pleasant to us when combined with feeding experiences, but unpleasant alone. The odour of roast beef is stimulating, but the same odour occurs in a flower, *Iris fœtidissima*, in our woods and is then nauseating. Such is the power of association.

In the lower animals, too, smell or a chemotropism attracts flies to the meat in which they lay their eggs and on which the maggots will feed. A chemotropism simply means a chemical attraction (positive tropism) or repulsion (negative tropism). As an example of the aid of smell to nutrition there may be mentioned a beetle, the *Bolboceras gallicus*, a little black beetle about the size of a cherry stone, studied by Fabre. As it was similar in appearance to a dung beetle, Fabre at first mistook it for such and offered it the diet esteemed by its supposed relatives, but it would have none of it, and he subsequently found that it fed on truffles and one particular kind of truffle only. A most discriminating epicure. To offer ordure to an epicure ! exclaims Fabre. The truffles, *Hydnocystis arenaria*, are underground and have to be found by the beetle. In the evening it goes abroad, explores the soil, and the sense of smell warns it when the desired object is underneath. It then sinks a well vertically downwards and infallibly reaches the truffle, then feasts happily at the bottom. Fabre also studied it in his laboratory, burying some of the truffles in a tank and he found there was no hesitation, no trial excavations, the insect invariably burrowed directly and vertically to the truffle, usually

about twelve inches below the surface. This is the more amazing when it is remembered that earth is a good deodorizer.

In other cases Fabre found that by exposing the body of a dead mole in the garden he attracted a large number of sarcophagic insects, *Silphidæ*, *Dermestes*, Horn-beetles and *Necrophori*, although these were not previously to be found in his garden. From far away the sense of smell brought the insects to their food.

In some fishes feeding must be initiated by smelling, the olfactory stimulus apparently setting in motion a train of reflexes for the swallowing and digestion of the food. A sole has no recognition of a worm hanging over it, but continues to feel for it aimlessly by the sense of smell although it can see it (Bateson, *J. Marine Biol. Assoc.*, p. 239, 1890). If a dogfish which seeks its food by smell has its olfactory bulb severed it ceases to feed spontaneously (Steiner, " Die Functionen des Centralnervensystems," Abt. 2, 1888). Similarly, in some fishes, e.g. catfishes, feeding will not occur although the fishes are hungry and food is present unless it is started by an olfactory stimulus (Parker, *Bull. United States Bur. Fish*, **33**, 63-8).

Most people will have noticed similar behaviour on the part of a much higher animal, the cat. Although a piece of meat will be within a few inches of its head and it must see it, it takes no notice but goes on searching for it by smell and then having so located it, eats it. Evidently the vision does not combine with the olfaction to produce a perceptual pattern useful to the cat, but the two senses are used largely independently.

If we hold our nose, smell can be eliminated and only taste remains, and we find that practically all our food sensations were due to smell, and only a small part to taste and also some to touch. By holding the nose it is found that grated apple, grated onion and grated turnip all taste alike—slightly sweet. A cold in the head does pretty much the same thing and makes food seem flavourless.

Reproduction

The general view is that the chemical senses play only a minor part in the mating of mankind. With the four-footed animals the position is obviously different, but this is because olfaction is the main and most highly developed sense they have, usually surpassing vision and hearing, and it is only to be expected that this sense should bring the sexes together. As low in the animal world as smell is found, it probably initiates copulation, which is consummated by tactile-temperature and visceral sensations. Before olfaction had developed, the common chemical sense played a similar role. Birds are an exception, their courtship is based on an appeal to the eye and the ear. How perfect such a courtship with the plumage of the peacock or of the cock chaffinch and the melodious notes of the thrush seems to us, but probably the attractiveness is due to the preponderance of the senses of vision and hearing in ourselves, and if olfaction were our

preponderant sense such a courtship might easily seem low and better avoided.

Insects, however, depend on olfaction for their coupling. Kellogg stated that as soon as the silkworm moth issues, the male seeks a female and succeeds as well in the dark as in the light, but if one antenna is cut off the male describes circles and takes a long time to find a female. This is a case of positive chemotropism.

Remarkable instances of insects drawing their mates long distances were recorded by Fabre. It will be necessary later to go into this in greater detail, but some of his observations may be noted here to illustrate the dependence of the sexes meeting on the sense of smell. A female Great Peacock moth hatched out in his laboratory one morning, and the same evening about forty male Great Peacocks invaded his house, although they were a rare variety in the neighbourhood. The same thing happened on subsequent nights until after several days the female lost her allure. In another case a female Oak Eggar or Banded Monk was hatched and nothing happened until the third day, when sixty male Oak Eggars arrived. Evidently, said Fabre, the nubile female emits an odour of extreme subtlety imperceptible to our own olfactory sense organs. The most remarkable feature of these experiments was that the insects were rare in the neighbourhood of Fabre's house and must in his estimation have travelled some kilometres, so that the smell which lured them must have been highly attenuated.

Nature has endowed certain animals, notably the musk-deer and the civet cat, with pouches of extremely odorous material situated near the genital glands, by means of which these animals can find their mates over long distances. In the musk-deer only the male has the secretion, but in the civet cat both sexes have it, the male in greater quantity. These substances, musk and civet, have been borrowed by man, or rather woman, and used as bases on which to build up subtle perfumes. In man the perfume of a woman's hair may cause distraction by its suggestion of closer intimacy. The aim of the perfume manufacturer may be to stir the instinct of courtship, but withal scent and smell play a very subsidiary part in human sex relations.

The Influence of Civilization

There can be no doubt that the main influence of civilization on the chemical senses has been to blunt them. We have examined how these senses are used in the primitive activities of life, and with the coming of civilization life is less hazardous. There are no wild beasts to be avoided, food is plentiful and does not have to be hunted, knowledge and experience teach what is to be avoided, marriage is organized. These changes have taken place gradually, but equally the senses of smell and taste have lost their sharpness. The process is slow, but gradually they dwindle to a shadow of what they were.

They have, however, at the zenith of their powers made such a powerful impression on the central nervous systems of our ancestors that their power astonishes us. Particularly is this so with memory. A scent—perhaps a sweet-briar—recalls a childhood incident, and the scene stands out in the memory with amazing clarity and detail. We see the use of this as one of our ancestors eats fruits which may have a pleasant or alternatively a disgusting effect, then the next time he smells the fruit the associated experience of pleasure or disgust is clearly displayed to him and he reacts accordingly in the light of experience, but without conscious thought. The nose is superior to the eye and the ear in one respect. With increasing age, sight and hearing fail, but not smell nor taste. Work on smell can bring charm and pleasure and, on the other hand, can enable dangers to be perceived and by opportune action avoided.

But there is another side to the question. Simultaneously with the loss of sensitiveness the types of odour, and particularly the associations possessed by the odours have grown tremendously. One of the purest emotions is the pleasure derived from smelling a flower, and on that civilization has built the whole perfume industry. Religion, medicine and science all broaden the applications of olfaction. Civilization has brought, too, countless olfactory problems which belong to the realms of Public Health and Hygiene. The provision of abundant pure water and food supplies, the effluvia of modern industries, the disposal of sewage and garbage, odorous occupations, all these have brought problems in their train, and often unpleasant odours and tastes or irritating chemicals which had to be endured whilst the source of the trouble was located and put right. Some of these aspects will be examined, and some illustrative examples of the type of problem encountered will be given.

Æsthetic Enjoyment

One of the pleasures, possibly one of the most exquisite pleasures on a plane higher than that of instinct, is to be found in the garden. Roses, lilies-of-the-valley, violets, tobacco plants, night-scented stocks, jasmine, azaleas, what delight to smell these, but how soon is our capacity for enjoyment exhausted! We smell the violet with enchantment, but we plunge our nose into a bunch and the smell is gone. Appreciation of flowers changes, and for a period the beauty of scent was forgotten, and roses of glorious appearance but without scent appeared, such as the most perfect white rose, Frau Karl Druschki, perfect in everything but scent which it lacked entirely. Where also is the old sweet-scented musk, *mimulus moschatus*, which seems to be scentless now?

The scents in a garden are intensified after a shower of rain, partly because the moist atmosphere is favourable to olfaction and partly as the raindrops have dispersed the odorous vapours half-contained by the flower, but liberated by the knocking of the raindrops.

The Chemical Senses

On a lower plane the enjoyment to be derived from eating sweets and fruits and succulent meats and drinking tea, coffee, cocoa, ale, cider and wines is not to be despised. Such delights give much of the happiness of life to most of us, and a rarer if not quite unsung ecstasy to the epicure and connoisseur.

Religion

Havelock Ellis has stated that during religious excitement a real and pleasant odour is discernible in the atmosphere.

It will be recalled that the wise men from the East selected as treasures with which to commemorate the birth of Christ " gold, and frankincense, and myrrh " (Matthew, Chapter ii, verse 11). The inclusion of the last two shows that they rated odours highly.

Mohammed loved scents, and the Koran commands the believer to say, " O God, make me to smell the odours of Paradise, and bless me with its delights, and make me not to smell the smell of the fires of hell." Mohammed is reputed to have possessed an extraordinarily acute sense of smell.

Five thousand years ago Chaldean priests burnt incense to their god Zeus at an altar outside the temple of Bal Marduk in Babylon.

In the book of Daniel we read that Nebuchadnezzar fell upon his face and worshipped Daniel, and commanded that they should offer an oblation and sweet odours unto him.

Isaiah mentions " houses of the soul," small boxes containing rich perfumes attached to necklaces. Excavations have shown that these were worn by Egyptian women too, with an image of the goddess Themei engraved on them. Also in Isaiah we read that incense was an abomination. Sacrifices had become too prevalent.

The Romans strewed their tombs with roses, the Greeks with myrtle, and the funeral pyre consisted of sweet smelling woods, cypress and yew.

The Aztec belief in offering sacrifices to their gods was that unless the latter were abundantly refreshed with the smell of human blood they would languish and discontinue their work on the crops.

During confessionals at Rome, consecrated roses that exhaled ambergris and musk were used to denote secrecy, hence our phrase " sub rosa."

The burning of incense in places of religion originated in the desire to drown the unpleasant smells of the abattoir where the animals were slaughtered for sacrifice.

The sulphurous stink of the Evil One is legendary.

Medicine

Olfactory methods were common in early medical practice. The belief at one time was that a disease was due to a demon having entered the body of the patient, and the logical course was to make things as unpleasant as possible in the patient's body so that the demon

would evacuate. Accordingly fumes were generated around the patient by burning hair, horn, feathers, sulphur and odoriferous wood near him. Doctors carried camphor and musk to ward off infection. Evil-smelling asafœtida (devil's dung) was used for hysterical conditions. On the other hand, the pleasant smelling carminatives dill, aniseed and peppermint have long been used. The old method of driving out the demon, if possible without killing the patient, bears a striking resemblance to modern medicine where a drug is used which destroys the dangerous bacilli and inflicts the minimum of damage on the patient. The drug in the blood stream has taken the place of the offensive smokes. Many of the drugs prescribed to-day would be instantly rejected by the body through nausea and vomiting, but the medical profession with the collaboration of the pharmaceutical chemists delude the chemical sensibility of the patient and sugar-coat the pill. Such a device would clearly be less practicable with the pungent fumes of sulphur.

Odour is helpful in diagnosis. Physicians used to speak of typhus having a close mawkish odour, and the smell of smallpox is horrible. The odour of diphtheria is nauseating. An acid smell is indicative of acute rheumatism, and according to McKenzie the odour of chaff can be detected in cases of nephritis. There is a smell of mice in the disease known as "Favus," and the smell of a big hæmorrhage is unmistakable and ominous. The sweet-smelling breath of diabetics, due to acetone, is well known. Curiously enough a sweet smell was said to attend the plague, but what was counted sweet then might not be so now. The patient is always unaware of his own malodour. The bad breath of a chronic drunkard or the pleasant ethereal atmosphere around the moderate wine-bibber may indicate to the physician the cause of the trouble. Crompton (*Birmingham Med. Rev.*, **2** and **3**, 1873-4) wrote "on the use of the nose, or rather the sense of smelling, in the diagnosis of disease."

In cases of hay fever known to be brought about by the pollen of certain plants acting on susceptible subjects, it appears to be the naked nerve fibrils of the common chemical sense, the trigeminal nerve, which are affected. People suffering from asthma cannot go near horses as there is a protein in the blood of horses which irritates such subjects.

Chemistry

The schoolboy's synonym for chemistry is "Stinks," which indicates how perceptible is the close relation between chemistry and olfaction. On the one hand, the chemist derives immense help from olfaction, as many substances are instantly recognizable by a sniff, alcohol, ether, chloroform, aldehyde, benzene, naphthalene and countless others. The ability to identify substances by smell varies greatly, some chemists apparently having the sense impaired, but in others with practice a stage of development is reached which is

miraculous. On the other hand the contribution of the chemist to the perfume industry and to the fertilization of the soil and extermination of pests in fruit and flower-growing industries is a contribution to human contentment. Of the vile odours, products of the laboratory, it need only be said these are properly confined to fume-cupboards and should not be loosed on humanity.

In a leading article *The Times* of 8th February 1937 pokes fun at the " chemist's nose." A case of alleged contamination of dresses by paint odour was brought, and an analytical chemist who gave evidence claimed to possess " a chemist's nose."

" It (the nose) must have thrown a flood of light on many a dark problem ; yet it was not, so far as we know, a luminous nose like that of the Dong or like the nose of Bardolph, which had saved Falstaff a thousand marks in links and torches, walking in the night betwixt tavern and tavern ; nor was it like the nose of Slawkenbergius about which the less said the better, nor like the nose of Edward Lear's Old Man with a Nose. . . . It owed nothing, we must conclude, to outward show and gave no visible sign of its exceptional quality. Its virtues lay within. And the virtue of a chemist's—or at any rate of that chemist's nose is that which would naturally be expected in an analytical chemist. Like number TWO in Master Hugues of Saxe-Gotha's fugue, it discepts and distinguishes. When the layman (the mere man with a mere nose) smells a composite smell, he only smells a smell. The analytical chemist's analytical nose can analyse the smell into its parts. It is able, we can well believe, to determine even the percentages of the constituents, so that the analytical chemist may write them all down and add them up and make them come to one hundred."

Well, except for the last bit about the quantitative side of the matter, it is all true.

The poisonous nature of many of the chemist's synthetic products may be noted. Poisonous natural products are generally distasteful and the nose or mouth rejects them, and, conversely, repulsive smells are usually better avoided.

Human excrement is dangerous, lice which carry typhus germs flourish in evil-smelling places. The smell of infectious disease is often mawkish. As a rule man obeys the dictates of his nose and keeps away. But when he comes to the half-million synthetic products of organic chemistry, the nose cannot cope altogether satisfactorily with this new load. True, it perceives many of the products, for example, coal gas, the smell of which was unknown even to our near ancestors, but other synthetics may smell like natural products such as camphor, and the nose gives no indication of danger. Such bodies as benzene, toluene and xylene can be breathed as disperse vapours in the air for long periods without discomfort, but perhaps after years a condition known as " aplastic anæmia," often fatal, sets in. Dioxan has a faint sweet smell, but when breathed as a dilute

mixture in air it is deadly. The smell of hydrocyanic acid gas in dangerous concentrations is not at all unpleasant.

Hygiene

Personally, no one is aware of his own aura. The Eastern races have a peculiar smell which we find unpleasant, and they find us similarly distasteful. It has been suggested that when we instinctively like or dislike someone when first meeting him, it may be due to his aura or personal odour seeming pleasurable or disgusting to us without, however, reaching the threshold of our consciousness, so that we are at no time conscious of his odour. However that may be, a pleasant personal odour, or at the least freedom from unpleasantness, is a social *sine qua non*.

Haggard and Greenberg (*J. Am. Med. Assoc.*, **104,** 2160-3, 1935) investigated breath odours after eating onions and garlic, and found that the odours were due entirely to solid particles which remained in the mouth. They found garlic contained 0·19 per cent. diallyl sulphide and onions 0·049 per cent. Five minutes after eating two grams of garlic the expired air contained 0·003 mg. of oil per litre. Brushing the teeth and tongue and rinsing the mouth with a 3 per cent. solution of chloramine banished the odour.

We instinctively keep away from repulsive odours such as in dung, lice and disease, but it may not be the odour itself which is dangerous, it may just be Nature's warning that the material from which the bad smell comes is dangerous.

Winslow and Greenberg (*Proc. Soc. Exp. Biol. Med.*, **15,** 123-4, 1918) investigated the problem with guinea-pigs. They kept some young guinea-pigs under normal conditions and others of similar age in a hutch through which they circulated foul air which had been passed over human and dog fæces. They found that during the first week the guinea-pigs exposed to the foul atmosphere did not grow so much as the controls, but that during the second week of exposure they grew more and caught up with the controls. Apparently the olfactory apparatus was fatigued, either through inattention of the central nervous system or through exhaustion of the peripheral sensory organs. The general inference is that a foul smell *per se* has no permanent ill-effect on growth.

In " Public Health Laboratory Work," p. 167, Kenwood points out that odour is a very valuable guide to purity of air. Perception of odour is influenced by temperature, moisture and agitation; low temperatures, dryness and quiescence of the air being unfavourable to odour detection. Common atmospheric impurities are organic matter, empyreumatic and tarry matters, ammonium sulphide, sulphuretted hydrogen, ammonia, coal-gas and carbon disulphide, but carbon dioxide, carbon monoxide and methane, the last two particularly dangerous, are inodorous.

There is no doubt that the acuteness of olfactory sensation varies.

The bazaar smells of India, and the musk redolence of China would not be tolerated in the West. But this finickiness of ours is a new development. At the beginning of the last century London streets were strewn with human and animal slops and ordure.

That sweet odours ward off pestilences is an old belief, and rue and rosemary have long been strewn at the Old Bailey as prophylactics against jail-fever which the prisoners might otherwise communicate to the other parties concerned.

Public Health

Disraeli's law defining a bad smell as a nuisance became law in 1875. Until the early part of the nineteenth century it had been the custom to empty the house slops into the streets at night with a warning cry of Gardy-loo (Gardez l'eau). Edinburgh was no better than London. Anyone who could go back in time to the eighteenth century as Peter Standish did in " Berkeley Square " could not be insensitive to the polluted atmosphere. Now, of course, things have been put right by underground sewers and sewage disposal farms, but mankind did not exercise foresight nor take the necessary steps until they were long overdue and forced on him.

The provision of air-conditioning plants in which the air is filtered and cooled or warmed as may be necessary in public buildings and factories shows how far we have progressed now.

The necessity for the safe disposal of human fæces is shown by the situation in the East, where the use of such material as manure has kept fertile the same soil for thousands of years and formed an essential part of the national economy. The Chinese walk barefoot in the flooded paddy fields and are attacked by a parasite which has hatched from eggs in the fæces and has suffered a transformation using a snail as an intermediate host. In Japan the trouble has been largely overcome by chemically poisoning the snails, but in China millions live an emaciated dreary existence due to infection. In the Southern States of America the " poor white trash " was also infected with a parasite from excrement, and the disease was virtually exterminated by building a hundred thousand privies.

With regard to the control of odours from sewage plants the two first essentials are liberal design and proper placing of the plant (Skinner, *Surveyor*, **67**, 499-500, 1925). Good effluents from sewage plants should have no offensive odour after being kept in a stoppered bottle for five days at 80° F. (Edmondson, *ibid.*, **54**, 183, 1918). Last traces of odour are usually due to sulphuretted hydrogen, and the presence of this substance is dependent on (1) presence of sulphates, (2) sulphuretted hydrogen-producing bacteria, (3) certain temperature conditions, and (4) a certain time interval required by the bacteria. The addition of chlorine removes the bacteria and so prevents odours. Residual chlorine is not necessary in the effluent. Less than one part per million of sulphuretted hydrogen is not objectionable (Cuslow,

ibid., **73**, 1834, 1928). A layer of activated carbon on racks above the weirs has also been found effective in eliminating odours liberated by offensive liquids (van Benschoten, *Eng. Contract. Record*, **49**, 728-30, 1935). These two methods of removing odour by chlorine and by activated charcoal are of general application and of great importance. Stuart, in *Water Works and Sewerage*, **81**, 327-8, 1934, points out that taste and odour can be eliminated in three ways, by prechlorination and by activated carbon treatment as just discussed and also by chloramine treatment, a method which he says is extending. Alternatively, combinations of all three methods may be used.

An interesting case was furnished by the grachten or drainage canals of Leyden. These have been troublesome as a source of offensive odour since the fourteenth century. Lately (Korswagen, *Pharm. Weekblad.*, **64**, 229-39, 1927) the trouble has been traced to anaerobic fermentation giving off gases when the *p*H value falls below 7·1, i.e. really when an acid condition supervenes.

In a discussion on the sanitary significance of odours Earp (*Am. J. Pub. Health*, **13**, 283-93, 1923) points out that odours are not ordinarily considered a menace to health but nuisances. They may be eliminated by the following means : (1) removal of the source of offence ; (2) removal of putrescible by-products by sedimentation, filtration, skimming, biological treatment, or oxidation ; (3) oxidation of offending gases in solution by combustion, by aeration, or by chemical agency ; (4) removal of offending gases by specific chemical reactions ; and (5) filtration of offending gases.

In countries where the mosquito is a disease carrier and a serious pest it has to be fought. It has been found (Crumb, *Entomol. News*, **35**, 242-3, 1924) that certain odours attract the ovipositing mosquito. The mosquito, *Culex pipiens*, lays its eggs into water containing sulphuretted hydrogen and methane. Old yeast infusions and old diluted urine were also attractive. Probably the attractive principles are bacterial decomposition products.

Water Supplies

Water for drinking must be free from taste and odour. Much is done by control of the ground from which the water is collected, by the prohibition of bathing and fishing and by filtration.

Water, unless contaminated, cannot possibly have a taste or smell, as it is always present in the moist membranes of our nose and mouth and is, together with air, the neutral substance by which we judge the smell and taste of all others.

The methods of removal of taste and odours are those discussed in the section on Public Health, viz. chlorination and activated charcoal, and in addition aeration, lime treatment and sedimentation.

As an example the water supply of Cumberland (Md.) developed a cucumber flavour, due to the presence of an organism, *Asterionella*, in it. By feeding Nuchar, an activated charcoal at a rate of 0·3 grain

per gallon ahead of the filter, the taste was eliminated in one day (Bruce, *Am. City*, **47**, No. 5, 75, 1932).

Another case concerned the water supply of New Castle, Pa., which takes its water from the Shenango River. The stream rises in swampy ground and flows through an industrial part before the city. Odour complaints were avoided by doses of activated charcoal of 0·5 to 1·0 grain per gallon, and the cost of the treatment was estimated at 70 cents per million gallons (Johnson, *J. Pa. Water Works Operator's Assoc.*, **4**, 43-52, 1932).

Fair and Wells (*Water Works Eng.*, **87**, 1051-5, 1934) worked on the determination of odour in water and devised an osmoscope or smell-measuring instrument. The basis of the method was to draw air from above the water, dilute it with an equal quantity of pure air, then to dilute this mixture with its own volume of pure air again and so on, until the threshold value is reached, that is, until the odour is only just discernible and slightly more dilution causes it to vanish completely. The number of times that dilution must be carried out in order to reach the threshold value is called the *p*O value, by analogy with the *p*H value, which is an inverse logarithmic evaluation of hydrogen ion concentration used by the physical chemist. Clearly a high *p*O value indicates a bad sample of air or water and the lower the *p*O value the better the purity.

Unwanted Odours in Foods

Everyone is familiar with the fishy egg which may be quite fresh and wholesome but is unacceptable to the palate, and is due to feeding too much fish meal to the fowls.

Bottled food has been known to develop abnormal flavours and odours, and Bidault and Hinard (*Ann. fals.*, **23**, 30-6, 1930) found that they were mostly attributable to poor grade rubber gaskets. The rubber of which the gasket is made should not have been vulcanized, especially not with sulphur chloride. Food showed a mouldy odour after cold storage in certain rooms. This was found to be due to moulding of the insulating material, which was cork. The remedy lay in the destruction of all nutritive value in the cork by dry heat (Jurges and Reichard, *Gesundh. Ing.*, **51**, 304, 1928).

A "boar odour" was noticeable in male pig flesh, and Keller (*Z. Fleisch-u. Milchhyg.*, **47**, 174-6, 1937), who investigated it, found that it could be largely removed by using a little more sodium nitrate in the pickling. The source of the odour was concentrated in the salivary gland of the lower jaw.

A skunk-like odour was developed by butter, and was traced to the presence of an organism which was called *Pseudomones mephitica* and which was isolated from it. When pasteurized butter was inoculated with this organism it also developed the skunk-like odour (Claydon and Hammer, *J. Bact.*, **37**, 251-8, 1939). The water supply to the cattle is an important factor affecting the taste, odour and

colour of the butter (Moore, *Natl. Butter Cheese. J.*, **31,** No. 5, 18, 1940). The pleasant flavour of butter is due to the presence of biacetyl. This disappears on storage, but the butter can be freshened and the flavour restored by adding biacetyl (Tapernaux, *Lait*, **12,** 1043-55, 1932). The biacetyl is formed by oxidation of acetylmethylcarbinol, which is produced by the micro-organisms used as butter starters. These soon lose their power, but biacetyl is readily made artificially, and the addition of 5-10 parts per million of butter hardly endangers health but improves the flavour. It has the disadvantage of making the butter turn rancid sooner, and butter for export is always well washed to remove biacetyl (Monier-Williams, *Perf. Ess. Oil Record*, **27,** 4).

In October and November when beet-tops are used for cattle feed an offensive odour may appear in milk and butter and is due to trimethylamine from the betaines (Post, *Pharm. Weekblad.*, **67,** 1309-13, 1930).

Beers can acquire flavour by absorption of odour without contact with the odoriferous material. When sample lots of wort were fermented in an atmosphere permeated by chlorine, gas tar, coal tar or disinfectant, the characteristic flavour was transmitted to the beer, whilst turpentine gave a fruity taste. On the contrary, phosphorus, carbon disulphide, sulphur-dioxide, sulphuretted hydrogen and mineral naphtha did not communicate a flavour to the beer, although the last two made it hazy (Murphy and Mason, *Bull. Bur. Bio. Tech.*, **2,** 165-71, 1927).

An odour in goat's milk like that of the buck was traced by Koestler and Wegmuller (*Landw. Jahrb. Schweiz.*, **48,** 842-52, 1934) to be due to caproic and caprylic acids together with an unidentified complex substance. An odour of amyl alcohol in milk was due to the presence of white and orange micrococci in the cattle's bedding (Cunningham, *Proc. World's Dairy Congress*, 1931, *Copenhagen*, Sec. 2, 1-5). Dairy products generally are susceptible to the absorption of foreign flavours and odours, and this is chiefly due to the fat in the milk which absorbs odours. Skimmed milk which has lost most of its fat is not so susceptible.

Fish living in a tidal river which contains large numbers of *Actinomyces* acquired an earthy taste. If they were removed from the river and kept in other water for five days, then they lost the flavour (Thaysen, *Ann. Appl. Biol.*, **23,** 99-104, 1936).

British Patent 260,960 describes the use of furfuryl and methyl mercaptans to flavour substitute coffee; 100,000 parts of the corn coffee from burnt wheat, rye, etc., is treated with the vapours of 0·3 part furfuryl mercaptan and 0·5 to 0·8 part methyl mercaptan. Now mercaptans have most offensive smells when concentrated, but in great dilution they are here used to improve the flavour of food. It is a general principle, and many of the most highly prized perfumes which enchant in dilution only disgust in higher concentrations. Whilst discussing coffee is it not remarkable how the delicious strong odour of roasting coffee (genuine) so signally fails to appear in the beverage ?

Industrial Odours

The Public Health Acts now forbid the proximity of evil-smelling works to towns. The most offensive industries are bone manure, blood boiler, blood drier, fat extractor, fat melter, flock maker, gut scraper, knacker, rag dealer, rag-picker, soap drier, tanneries, glue works, rendering factories and size factories and sizing rooms in textile factories. After a time workers in these odorous occupations become used to the smell and do not notice it. Nevertheless they carry it with them on their clothes and, whilst unaware of their own aura, are by no means pleasant to others.

In an investigation of the odours of Paris, Boudouard (*Compt. Rend.*, **154,** 238-40) attributed them largely to the manufacture of fertilizers, phospho-guanos and animal superphosphates. He found that climatic conditions have a great effect, higher temperatures intensifying the odours as well as sudden changes in the electrical condition of the atmosphere. Dried fertilizers were more objectionable than moist.

In our country the linoleum works at Lancaster used to advertise their presence, so that one could recognize Lancaster in a thick fog without difficulty.

At one time artificial silk works had a bad name in this respect, but give no offence now. Bailey (*Chem. Age*, **20,** No. 519, 1929) investigated the subject, and found the trouble was due to the action of sulphuric acid on small particles of carbon disulphide from the churns giving sulphuretted hydrogen. Complete boxing in of the machines was impracticable. A tower of caustic soda washed out some but not all of the odours. Chlorine and sulphur dioxide were tried unsuccessfully. Some improvement was brought about by adding absorbents such as glucose which combine with the sulphuretted hydrogen during the process.

Odours from Oil Refineries may create a nuisance. Weston (*Proc. Am. Soc. Civil Eng.*, **51,** 854-83, 1925) suggested that the best method of controlling and eliminating is to collect them at all possible points of discharge by a vacuum collecting system and then burn them in the furnaces.

Klason (*Paper Trade J.*, **79,** No. 2, 30-6, 1924) investigated a case in which a paper mill was surrounded by an odour of decayed cabbage. He considered the smell was due to traces of mercaptans.

The foul odours of retting flax may be minimized by steeping the raw fibre in an alkaline solution before the retting operation (Tobler, *Faserfoschung.*, **2,** 9-21).

Nowadays the best method for removal of bad odours from effluent gases is to pass them up a tower packed with activated charcoal, preferably cokernut charcoal, which has a very high affinity for organic aromatic substances. When the carbon has become so saturated that the gases passing from the tower still carry an odour, then the incoming gases are switched from the first to a second tower, whilst the

carbon in the first tower is revivified by passing steam through it. The steam takes the odorous substances from the charcoal and is condensed and sent to sewer. The charcoal is dried by warm air, and the first tower is ready for use as an absorber again as soon as the second tower begins to pass odorous gas. The whole business is simple, cheap and efficient.

Another general method of removing odours from effluents is to add chlorine. The process is described by Henderson and Haggard (*J. Ind. Eng. Chem.*, **14,** 548-51, 1922).

The use of a similar method at the New Bedford Garbage Plant is described (Springborn, *Public Works*, **52,** 442-3, 1922). With a 7-second contact 900 lb. of liquid chlorine deodorized the vapours from 4,000 tons of garbage.

In general the avoidance of foul atmospheres near factories rests on these principles :—

(1) Efficient draught by fans to keep the gases under control.
(2) Passing the effluent through a furnace if possible to burn the odorous bodies.
(3) Prevention of mould or bacterial growth.
(4) Neutralization of the odour by the addition of chlorine.
(5) Removal of the offensive materials by passing the gases through active charcoal.

Odour as a Warning

It is easy to imagine how many accidents would happen and probably fatalities too if coal-gas had no smell. Fortunately its smell is very noticeable and gives ample warning of leaks or escapes of the gas.

Other gases met with in industry, particularly carbon monoxide, are poisonous and odourless and therefore a source of grave danger. It has been suggested to use an odour as a warning in case of danger in mines (Katz, Allison and Egy, *Bur. Mines Tech. Paper*, **244,** 1-27, 1920). A strongly smelling substance, with a distinctive disagreeable odour, should be injected into the compressed air line.

Of the odorants tried those found most promising were ethyl and butyl mercaptans, amyl acetate, butyric acid and valeric acid.

Natural gas is used as a fuel in America, and the addition of an odorant to act as a warning has received considerable attention. Holtz (*Gas Age Record*, **66,** 341-5, 1930) states that 3 gallons of Cal-Odorant No. 3, made by the Standard Oil Co., per million cubic feet of gas is satisfactory. United States Patent 1,732,516, James (1929), suggests that gas for heating or lighting should be odorized by the addition of aliphatic aldehyde-like compounds such as are formed by the oxidation of aliphatic and naphthenic hydrocarbons. U.S. Patent 2,094,270, Hampton and Rutherford (1937), suggests the use of organic cyclic sulphides of the saturated ring heterocyclic type containing three or more carbon atoms and sulphur as the hetero atom. An oil containing these is made by the decomposition of a sludge from another

process, and is used as a signal odour in gas. An Austrian Patent 133,526, Fischer (1933), suggests a mixture of garlic and tobacco previously heated with aqueous ammonia and arranged in the gas main with a moistening device, but such a method is obviously inferior to present-day practice.

The Sharples Solvent Corporation in America now market " Pentalarm," a red liquid, and the makers describe its use as follows: " Pentalarm, the Sharples warning agent for fuel gas, is composed principally of amyl mercaptans. The odour imparted to gas by Pentalarm is distinctive in nature and is such that it invariably suggests the presence of gas. This odour may be classed as unpleasant, but not nauseating—an ideal combination.

" Because of the extremely small quantity of Pentalarm required for odorization, the odour does not persist for an appreciable length of time after the gas leak has been repaired. The extremely small quantity required is advantageous also because less than 3 grains of sulfur are introduced per thousand cubic feet of natural gas. This is far below the maximum for purified manufactured gas.

" The physical properties of Pentalarm make it especially well suited for vapor phase introduction into the system. In this method of odorization a small but accurately proportioned amount of the gas to be odorized is by-passed through the odorizing equipment. Here it picks up or absorbs the odorant required for the remainder of the gas flow and carries it back to the main, completely vaporized. The gas flow through the odorizer is controlled solely by the flow in the main line, which means that uniform odorization is assured at all times regardless of the volume of gas flowing. This uniformity of introduction prevents the waste of odorant, and eliminates trouble and expense that invariably arise from unwarranted leak complaints due to unevenly odorized gas. As Pentalarm is essentially amyl mercaptans, it is insoluble in water, and thus the odour is not decreased when the odorized gas comes in contact with water. It has been used for years without damaging equipment in or connected to gas-distributing systems and without injury to persons or animals.

" The odour producing ability of Pentalarm is such that only three-fourths of a pound is required to odorize 1,000,000 cu. ft. of gas so that a mixture of $\frac{1}{2}$ of 1 per cent. of the odorized gas in the air may be readily detected. This degree of odorization provides a factor of safety of 8, since the lower explosive limit of natural gas is approximately 4 per cent. This safety factor is generally considered sufficient for adequate protection."

It may be noted that as 12 oz. of Pentalarm odorize 200,000,000 cubic feet of air-gas mixture, the quantity of Pentalarm in 3 cubic inches of air-gas mixture which is about the quantity taken in, in one inspiration or sniff is less than one twenty-millionth part of a grain. This means that one-quarter of an ounce of amyl mercaptans suitably diluted with air would enable every man, woman and child on earth to smell it, always excepting those suffering from anosmia.

War Gases

Normally our common chemical sense is not brought into play very much. Its more highly specialized differentiations, taste and smell, do most of the work. An onion will start it working and bring tears to our eyes, and if we happen to come in contact with ammonia or acid fumes, or if a particle of caustic or corrosive substance such as lime or creosote should find its way into our eye, we know all about it. Irritants finding their way to the nose induce the reflex of sneezing to get rid of them as soon as possible. Nevertheless these occasional experiences, particularly when connected with the eyes, are very painful and temporarily incapacitate us.

Various gases and vapours which bring on distressing symptoms have been used as tear gases. Such are chloroacetophenone which smells like furniture polish, bromobenzyl cyanide with a bitter sweet spicy odour, and ethyl iodoacetate which smells like pineapple, known commonly as C.A.P., B.B.C., and K.S.K. respectively. These are all absorbed by activated carbon gas masks. Many people will have noticed when testing gas masks in a gas chamber containing a tear gas that whilst the mask effectively protects the eyes, nose and mouth, a tingling or prickling will be felt under the chin where shaving has made the skin a little tender. Another method of causing discomfort through the common chemical sense is by nose gases, usually arsenical smokes, such as diphenylchloroarsine (D.A.), diphenylcyanoarsine (D.C.) and diphenylaminochlorarsine (D.M.), and these also are filtered out by an efficient mask. These smokes are irritant. Choking gases like chlorine are deadly but unmistakable. Phosgene, with a smell like musty hay, can be breathed without discomfort, but fatal consequences may ensue a few hours later. In addition to chlorine and phosgene, diphosgene (musty hay smell) and chloropicrin (pungent) are lung irritant gases. The dreaded blister gases are recognized by the sense of smell. Mustard gas, dichlorodiethyl sulphide, or Yperite is variously described as like onions, garlic or horse-radish. Lewisite, chlorovinyldichlorarsine, smells of geraniums. Another war gas is arsine which poisons the blood stream. It is odourless except in high concentrations when it is said to have a garlic smell.

Whilst the smells are unmistakable when known samples are examined, smell is inadequate for identification of unknown gases, particularly as there may be mixtures. For example, a tear gas would quite drown the smell of a blister gas if both were present, but the blister gas would be the more dangerous of the two. The difficulty of recognizing poison gases by odour was emphasized by Muntsch in *Gasschutz u. Luftschutz*, **2**, 273-5, 1932.

Terminology

The science of smell is " Osmics " (ὀσμη osme = a smell), and the words " osmophoric " and " osmyls " relate to odorous substances. Inability to smell is known as " anosmia." The act of smelling is

" olfaction " and its derivative is " olfactory." I suppose " odour " and " smell " are more or less synonymous, although the latter may carry a suggestion of unpleasantness in common use, whilst " odour " is more neutral. Certainly " odorous " is more neutral than " smelly." " Gustation " bears the same relation to " taste " as " olfaction " to " smell." The common chemical sense has no terms peculiarly its own. Perhaps " pungent " is the nearest.

In the opening passage of " Aromatics and the Soul " McKenzie writes, " I sing of smells, of scents, perfumes, odours, whiffs and niffs, of aromas, bouquets and fragrances, and also though temperately and restrainedly I promise you, of effluvia, reeks, fœtors, stenches and stinks."

Smells may be pleasant or unpleasant, feeble, faint, strong, bland, pungent, mawkish (Scotch mawk = maggot), fruity, dank, arid, stuffy, mephitic or sulphury, aromatic, ethereal, balsamic, acid, fragrant, ambrosial, burnt, repulsive, nauseating, fœtid, penetrating, distracting, alluring, seductive, soft, heavy, sharp, alliaceous, rancid, spicy, flowery, resinous, foul, and so on. Now most of these words are not peculiar to the sense of smell in the way that " red," " blue," " green " are to sight, or " sour " or " bitter " to taste, or " shrill " to sound. On the other hand, some of them, such as " pungent," " mawkish," " stuffy," " mephitic," " aromatic," " fragrant " and " fœtid " definitely suggest smell, and others, such as " alliaceous " and " rancid," are the joint property of taste and smell. There are only four tastes—sweet, bitter, sour, and salty—so the vocabulary of taste is complete. There are, though, thousands of odours. There are thousands of colours and thousands of sounds, but we have well-defined names for only a few, which crude analysis has separated, for example, " red," and by a later and more critical analysis " vermilion," " crimson," " carmine " and " scarlet." We have to agree that " stuffy," " mawkish " and " pungent " do not carry the same degree of definition as " red," " blue," or " yellow." There are, however, clear differences between " scent," " bouquet," " stench " and " fœtor."

I think the descriptive terminology is not so poverty-stricken as often made out. It is true that we usually describe odours as " like something," e.g. like oranges, or roses, or camphor, or cucumber, but what else could we do ? A descriptive definition of each smell would require a new language of thousands of words. Only when we find the real source of odour and can measure it, as we can analyse light with the spectroscope, will it be possible to nail each variety and give it a systematic name or number.

CHAPTER 2

STRUCTURE OF THE CHEMICAL SENSE ORGANS AND THEIR CONNECTIONS

Location of the Receptors

We know from experience that we smell through the nose, taste with the tongue and perhaps other parts of the mouth, and that the parts of our bodies most liable to chemical irritation are the eyes, nose, mouth, anus and reproductive openings. The logical inference is that these parts of the body contain some specialized receptor apparatus absent from other parts. Such specialization is a corollary of our high stage of development. Lower forms of life have the receptors or receiving stations for taste and chemical sensibility distributed over large areas of the body. For example, many fishes have taste organs on their flanks, and become aware of the presence of food by taste sensations transmitted through the flanks. In man, taste and smell are very definitely localized, although the chemical irritability is more widespread.

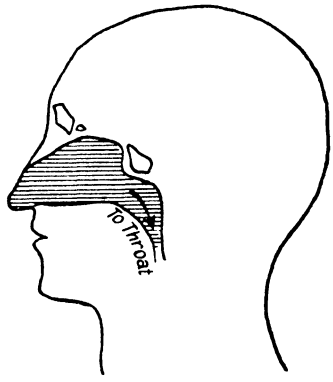


FIG. 1.—The shaded portion shows the extent of the nasal cavities.

The Nose

Whilst the nose is a prominent feature of the face, it is not confined to the excrescence normally visible, but penetrates inwards for about two and a half or three inches where it joins the top of the throat or pharynx. In Fig. 1 the shaded portion indicates the extent of the nasal cavities in the inside of the nose which is not ordinarily visible. The two paired openings—the nostrils—are the anterior nares, and the openings at the back of the nose to the throat are the posterior nares or choana. The inside of the nostrils, called the vestibule, is lined with a delicate continuation of the skin or epithelium which covers the outside of the nose. The middle partition of the nose which separates the two nostrils is the nasal septum. Apart from smelling, the nose has the task of warming and filtering the air we breathe before it passes to the lungs, hence the desirability of nose breathing as opposed to mouth breathing. In this connection it is interesting to note that the inhabitants of countries with hot climates have flat noses compared with the long noses of the inhabitants of colder countries where the air requires more warming. The osseous part of the nose extends downwards

to the bridge. The lower part is cartilaginous and will take up shocks due to sudden blows without permanent damage, at the same time protecting the inner and operative parts from even temporary damage.

The bones of the nose are the vomer and ethmoid. The vomer forms the lower and back portion of the nasal septum or middle division which is cartilaginous at the front. The ethmoid bone is at the top of the nose and extends as far downwards as the bridge. In addition the superior turbinate is bony.

The frontal bone which extends downwards from the forehead to the top of the nose, and the ethmoid bone and the upper jawbone contain air spaces or sinuses. These communicate with the nasal passages, and are lined with a continuation of the mucous membrane lining the interior of the nose.

The cartilaginous material on the inside lateral walls of the nose is arranged in a scroll-like form which offers a large surface, as is desirable for conditioning the air we breathe. The cartilaginous material is arranged in three nearly horizontal folds known as the inferior, middle and superior turbinated bodies. The inferior is that nearest to the nostrils and the superior is that highest up the nose. Of the turbinated bodies, also sometimes referred to as conchæ, the superior is truly bone but the middle and inferior are cartilaginous. The superior turbinate is an extension of the ethmoid bone. In some people, and especially in macrosmatic animals, there are more than three conchæ and those in addition are called the supreme conchæ. In others there are only two. Normally there are three, with a fourth, higher up than the superior concha, fairly common. Between the superior concha and the middle septum of the nose, right at the top of the nose is the olfactory region, or more descriptively, the olfactory cleft, the seat of the smell receptors.

The interior of the nose, the nasal septum, the vestibule and the turbinated bodies are lined with a delicate mucous membrane—the Schneiderian membrane. Except in the olfactory cleft the general colour of the interior of the nasal cavities is reddish.

The lining of the back of the nose, the naso-pharynx, is covered with adenoid tissue. When this becomes hypertrophied, the condition known as "adenoids" results and interferes with breathing, voice production and appreciation of the flavour of foods.

The inferior and middle turbinates are vascular, composed of erectile tissue which may expand to restrict air ingress. The passage ways along which the air travels between the turbinated bodies are known as inferior meatus, middle meatus and superior meatus. The nasolachrymal duct which drains the eye into the nose (one on each side) opens into the inferior meatus. The connection is well illustrated by introducing some drops of a suitable stain into the eye and observing after perhaps ten minutes the appearance of the stain in the nasal mucus. The nose is provided with small muscles to assist with breathing under unusual conditions and to provide facial expression.

To summarize the structure of the nose :

(1) The opening of the nostrils (anterior nares) continues inwards and meets the top of the throat (pharynx). The openings at the back of the nose are the posterior nares or choana. The nasal septum is the median portion dividing the nostrils.

(2) The cartilaginous interior of the nose is arranged in horizontal folds, conchæ or turbinated bodies, the highest of which is bony. The function of these is to condition the air for the lungs.

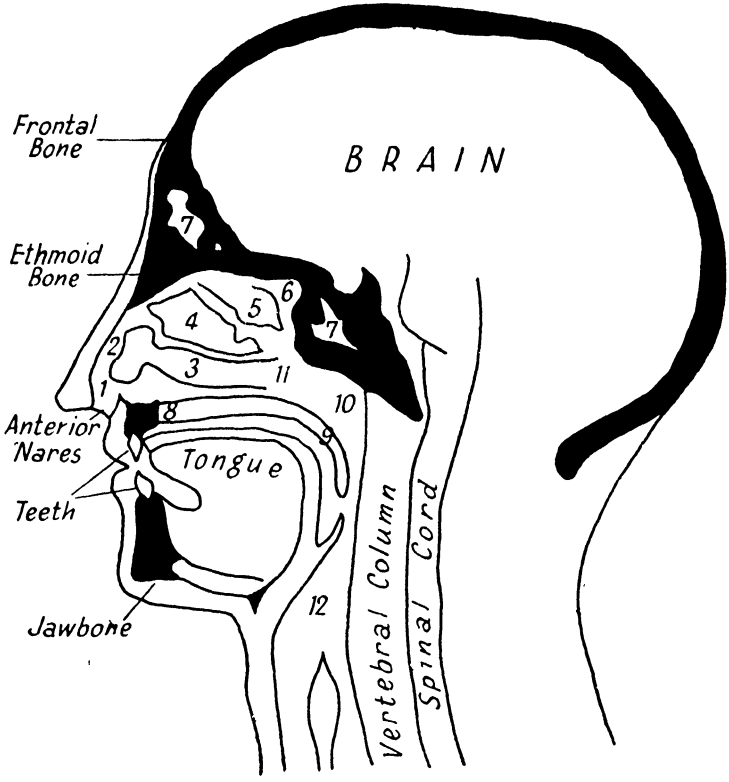


FIG. 2.—The nasal passages.

(1) Vestibule.	(7) Sinuses.
(2) Antrum.	(8) Hard palate.
(3) Inferior turbinate.	(9) Soft palate.
(4) Middle turbinate.	(10) Naso-pharynx.
(5) Superior turbinate.	(11) Posterior nares.
(6) Olfactory cleft.	(12) Pharynx.

(3) The olfactory cleft—the seat of the sense of smell—lies at the top of the inside of the nose between the median septum and the superior turbinated body.

Fig. 2 is a cross-section of a head cut through its plane of symmetry

and is drawn to show clearly the internal structure of the nasal orifices.

Fig. 3 is an end-on view showing the scroll-like formation and the large surface offered to the inspired air by the turbinated bodies.

The Olfactory Region

The olfactory cleft is situated as already described between the median septum and the superior turbinated body. It is yellow in colour, due to the presence of pigment, whereas the main interior surface of the nasal cavities is reddish. The pigment appears to be connected with the mechanism of the olfactory apparatus.

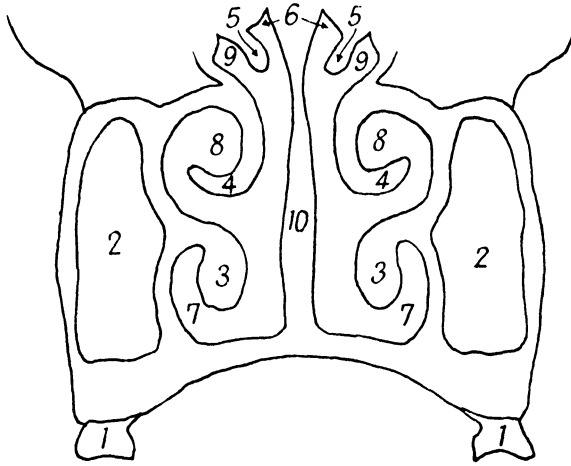


FIG. 3.—Section across the nasal cavities showing the scroll-like structure of the turbinates.

(1) Molar teeth.
(2) Antrum.
(3) Inferior turbinate.
(4) Middle turbinate.
(5) Superior turbinate.
(6) Olfactory cleft.
(7) Inferior meatus.
(8) Middle meatus.
(9) Superior meatus.
(10) Nasal septum.

Read (*Amer. Jour. Anat.*, **8**, 17-47, 1908) showed that the region spread over the superior concha almost to its free edge and over the median septum to one-third of its extent. The back to front spread of the region is twice that of its depth on either septum or concha. The total area of the olfactory region is about one square inch in each nasal chamber in an adult. The epithelium of the nerve area consists principally of ordinary epithelial or sustentacular cells which are broad and blunt, and of delicate olfactory cells which are confined to this area and are supported by the epithelial cells. The olfactory cells are pigmented and are long and narrow, and arranged with their length perpendicular to the plane of the nasal cavity. This region has few if any goblet cells which are numerous in the Schneiderian membrane. The types of cell are illustrated in Fig. 4. Attached to each olfactory

cell are five or six or perhaps eight olfactory hairs, fragile protoplasmic filaments which project through the cuticular membrane covering the area. It is generally believed that the hairs are affected by odorous particles and set off the train of events culminating in our perception of odour. They are kept moist by mucous material from adjacent parts of the nose which are supplied with goblet cells. If the mucus thickens, as when we have a cold or in catarrhal conditions, the olfactory hairs are incapacitated and our sense of smell is impaired. The olfactory hairs are better developed in animals, particularly amphibia and reptiles, than in man in whom they have probably degenerated. They are also referred to as *flagella* or lashes.

The simplicity of the olfactory receptors, which are simply pigmented cells with long protoplasmic filaments extending into an open air passage, is most marked when compared with the structure of the

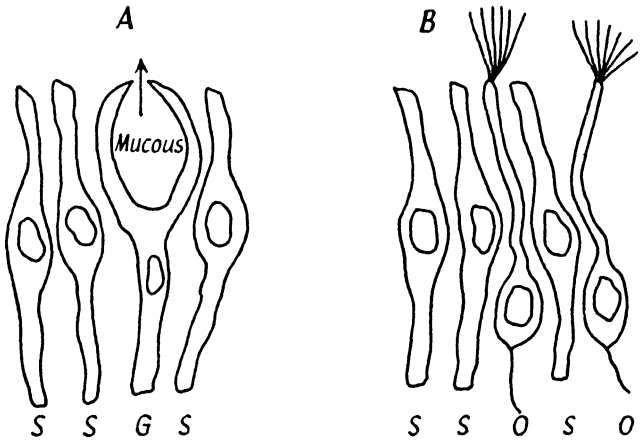


Fig. 4.—Cell structure of the internal nasal surfaces.
(A) Respiratory area. Goblet cells (G) feeding mucus supported by epithelial or sustentacular cells (S).
(B) Olfactory region. Olfactory cells (O) surrounded by epithelial cells (S).

eye or ear, and it gives few clues to the nature and mechanism of olfactory reception. A complicated receptor end-organ when studied will indicate the nature of the processes, but what can be deduced from microscopic filaments projecting directly into the nasal air passages ? The olfactory hairs are very delicate and easily destroyed, for example, by cold water.

Such is the apparently simple design of the end-receptors of the olfactory processes.

The Olfactory Nerve

The messages picked up, or the information gathered by the olfactory region in the nose, has to be carried to the brain. By itself, the olfactory region is no more able to function usefully than an aerial

without a wireless set. Continuing the analogy the nerve may be likened to the lead-in. The olfactory nerve itself is large enough to be visible to the naked eye, but is composed of some twenty fibres which can only be seen adequately with a microscope. Nerve fibres are usually covered with a sheath or are "medullated," but in the olfactory nerve they are naked or non-medullated. Non-medullated fibres also occur in the body but usually in connection with internal, e.g. visceral, body conditions, where the same speed and precision of reporting to the brain as is found in the sense organs does not seem to be required. The thousands of different fibres which compose a large nerve trunk behave individually, and certain stimuli will cause some individual fibres to respond but will leave others quiescent. Also, the nerve trunk consists of two different kinds of fibres, "afferent," carrying information from the end-organ, in this case from the olfactory cells, to the brain, and "efferent," giving the reply from the brain, which may cause reflex action if urgently necessary, or otherwise voluntary action.

Each fibre, called the axis cylinder, is a long thread of protoplasm. Where the medullary sheath exists it is a complex fatty substance. The diameter is usually about 0·01 mm.

The olfactory region contains in addition to the olfactory cells, certain free nerve endings, naked ends of nerve fibres, the ends alone being without a medullary sheath. Early workers had difficulty with these and confused them with the olfactory nerve, but it is now known that they are quite separate from the olfactory nerve and are connected with the trigeminal nerve. They respond to chemical irritation but not to true olfaction.

The Olfactory Bulb

The olfactory nerve travels from the olfactory cleft, high up in the nose, to the olfactory bulb of the brain to which it transmits its messages. The position of the olfactory bulb in the brain has a certain significance. The frontal areas of the brain are those considered to be concerned with higher psychic interests, associations and reflections, and the olfactory nerves are the most frontal of any of the twelve pairs which leave the brain. Accordingly the olfactory nerve is known as the First Cranial Nerve. The Second Cranial is the optic nerve, the Fifth, the trigeminal, deals with the common chemical sense, the Seventh with facial expression, the Eighth is auditory, the Ninth is the glossopharyngeal and deals with taste as do also the Tenth and Twelfth, and the others deal mainly with the control of body muscles such as those of the eye.

The Central Nervous System which receives messages from the external receptors and transmits messages to the muscles, as well as being responsible for conscious thought and intelligence, consists of the Brain and Spinal Cord. From the Cord another thirty-one pairs of nerves separate. The encephalon or brain weighs about 3 lb., very heavy or very light brains being associated as a rule with idiocy.

The chief parts of the central nervous system are the Cerebrum or forebrain which in man is much the largest part, the Cerebellum which controls activity and muscular movement, the Pons Varolii, the Medulla Oblongata which is the respiratory centre, and the Spinal Cord. Just as the brain is protected by the skull, the cord is protected by the bony case of the vertebral column. Fig. 5 illustrates the relation of the different parts of the Central Nervous System to one another.

The Cerebrum is the highest part of the brain, and of the twelve pairs of cranial nerves, only one pair, the olfactory nerve, joins the cerebrum. This nerve is responsible for the sense of smell, and consists of diffuse collections of fibres which lead into the brain from microscopic receptors in the upper part of the nasal passages. The cerebrum is the seat of intelligence, and it is to be expected that its importance increases as we ascend the scale from the lower to the higher animals. Fishes from which the cerebrum has been removed lose the sense of smell and do not feed voluntarily, but otherwise their behaviour is normal, but a decerebrate pigeon appears to doze all the time although it can fly all right. A decerebrate dog appears to have lost its intelligence and to be incapable of learning anything. It will avoid a shadow in the same way as it avoids a substantial obstacle.

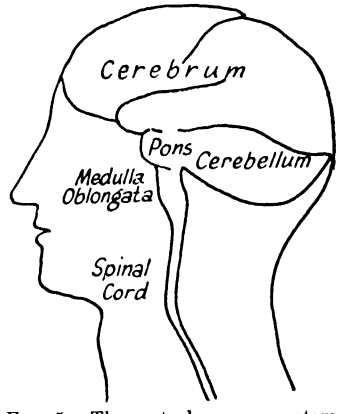


FIG. 5.—The central nervous system.

If, on the other hand, the cerebellum be removed from a pigeon instead of the cerebrum, the bird appears startled and alarmed and quite wide-awake, but when it essays to fly it meets disaster for it has lost the ability to control its flight and balance and flutters helplessly.

The brain, in man, is never completely at rest, but is kept moving in a constant state of surge by blood going into it. The blood churns round in the brain, feeding and cleaning it. During sleep the brain has a lower content of blood which goes to the extremities. Warm feet draw the blood from the brain and induce sleep.

The Cerebellum is the hind brain and occupies the back part of the base of the skull. The Tentorium is a membrane which forms a tent over the cerebellum and keeps the pressure of the posterior lobes of the cerebrum from it. The Pons Varolii lies on the top of the Medulla and connects it to the Cerebrum and Cerebellum and is the cross-roads of the brain. The Medulla Oblongata is the upper end of the spinal cord expanded into a club shape.

The Cortex is the grey matter on the outside of the brain and is a layer about $\frac{1}{4}$ inch thick. It is an aggregation of neurons with the

axones leading out of the brain to some part of the periphery, but with the branching processes or dendrites in intimate association with their neighbours. As animals increase in intelligence the cortex grows and changes, becoming more wrinkled so that its area is greater. The human embryo at six months has a perfectly smooth layer of grey matter in the cortex, and soon this begins to wrinkle and form fissures. The ability of an individual is due not to the size of his brain but to the depth and number of the wrinklings and the multiplicity of the associated neurons. The wrinkling gives an enormous increase in area. It has been estimated that the area of activated charcoal used for the surface absorption of gases and vapours is of the order of 2000 square metres for each gram. This is the type of carbon used in a gas-mask. If, for amusement, we postulate that the ratio area/weight of brain matter is of the same order as that of active carbon, then the area of the brain of a normal individual is about one square mile. If we further postulate that a sensation, a perception, an emotion or a thought may be accompanied by a chemical change in a microscopic nerve fibre and by no other physical change, then we may see a physical interpretation of the scope in each one of us for perception, memory, reflection and intelligence, a vast field of possibilities we need have no fear of exhausting but which the more it is tilled the more fertile will it become. We catch a glimpse of the material nature of thought, and recognize as the converse of this proposition the philosopher's old story that matter is thought and has no existence separate from it.

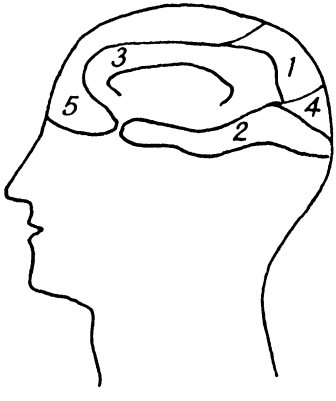


FIG. 6.—The relative positions of the centres of the brain.

(1) Parietal.	Skin sensation.
(2) Temporal.	Hearing.
(3) Limbic.	Taste and smell.
(4) Occipital.	Vision.
(5) Frontal.	Higher psychic centre.

To revert to the structure of the central nervous system, we remember that this is the authority to which the peripheral sense organs dispatch their information.

Beneath the grey matter in the cerebrum is a large mass of white matter, the Corpus Callosum, which consists of medullated fibres which cross from one side of the brain to the other, from one part of a hemisphere to another part. The cerebrum is divided by a deep fissure into two symmetrical hemispheres.

The cortex of the cerebrum is the receiving station for information and is the centre for determining and initiating the necessary responses. It consists of a variety of nerve cells, some of which receive messages by afferent or sensory axones, whilst some send out instructions by efferent or motor axones. Each sense organ, eye, ear, nose,

has its own place where messages are received—skin sensation in the parietal area, hearing in the temporal, taste and smell in the limbic area and vision in the occipital. The higher psychic centres are in the frontal lobe. Fig. 6 shows the relative positions of these areas.

It may be added that the cortex cerebri was built up phylogenetically on the sense of smell. It does not participate in instinctive actions which are based on lower centres.

To summarize, we have followed the perception of odorous material from the olfactory hairs, through the olfactory cells and along the olfactory nerve to the olfactory lobe of the brain, and have examined the significance of that part of the brain and its relation to the other parts. This line of thought will be followed up in the Chapter on Sensation. Meanwhile in this chapter we are concerned with structure, and will now consider that of the receptors for taste.

Taste Receptors

Complicated end-organs of taste occur in the tongue and soft palate of man. It has been estimated that there are about 9,000 of these taste-buds in man. They also occur on the epiglottis and the beginning of the gullet but they do not occur in adult man on the underside of the tongue, in the middle of the upperside of the tongue, on the inside of the cheeks, on the lips, on the tonsils or the uvula. It is different in the child where taste-buds are found over the whole upper surface of the tongue and on the insides of the cheeks. Hence the partiality of children for sweets, whilst the adult prefers flavours in which the odorous factors play a significant part. In the human fœtus the taste-buds make their appearance at three months, and are more widespread in the embryo than in the child, just as in the evolution of man the widespread taste-buds in his ancestors have become more localized.

Within the taste-bud are a number of elongated cells each of which ends in a minute hair-like process—the gustatory hair, which projects through a minute pore in the surface of the taste-bud, which is called the gustatory pore, into the mouth cavity. Direct stimulation probably takes place on the hairs and the impulse passes through the gustatory cells to the nerve fibres and thence to the brain. The end-receptors it will be seen are in essential respects similar to the olfactory end-organs.

Taste as we usually speak of it is a complex perception which takes into account odour, temperature and touch. By closing the nose apertures and tasting aqueous solutions at the temperature of the body we can reach an irreducible minimum of four tastes, sweet, bitter, saline and sour, and possibly, as will be discussed later, two more, alkaline and metallic. Whilst it seems clear that some taste-buds react to only one taste, such as sweet and not to sour, bitter or saline, it is impossible to distinguish the different types of bud by appearance. The only way they can be distinguished is by applying to them sweet, sour, etc., solutions and observing if there is a response.

Most of the taste-buds are situated in the tongue. The tongue is a very mobile muscle changing in shape at every contraction. Besides taste, it has to do with speech, mastication and insalivation. It is very sensitive to touch, heat and cold. It is covered with a mucous membrane and is about 3½ inches long. The tongue is composed almost entirely of striped muscle fibres. It is attached by its root to the floor of the mouth and to the hyoid bone, whilst the tip is free. The upper surface or *dorsum* is thickly studded with papillæ, little projections which make it rough. There are four kinds of these projections: (1) *filiform papillæ*, which are conical and cover the whole of the dorsum as well as the tip and borders of the tongue. These are not concerned in taste. They reach a high stage of development in some of the feline *Carnivora*, where they make the tongue rough like a rasp so that bones can be licked clean of flesh; (2) *fungiform papillæ*, which resemble button mushrooms in shape. These are less numerous and generally contain taste-buds; (3) *circumvallate papillæ*, which are usually seven to ten in number and are much the biggest. They lie towards the back of the upper surface and each is a flat mound with a little moat round it, the outer wall of the moat being a little higher than the surface of the tongue. Both sides of the moat have taste receptors embedded in; (4) *foliate papillæ* are only vestigial in man and consist of vertical ridges on the edge at the

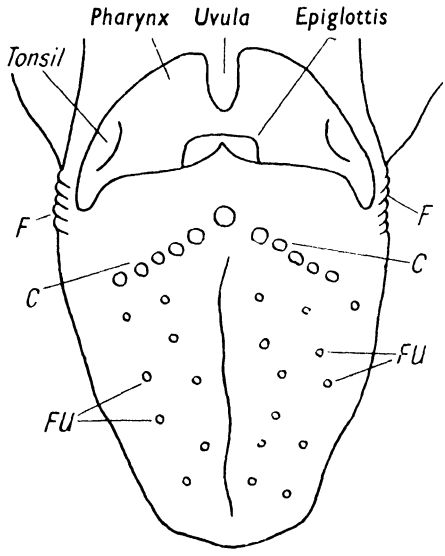


FIG. 7.—Upper surface of the human tongue.
F. Foliate papillæ.
C. Circumvallate papillæ.
FU. Fungiform papillæ.
Very small filiform papillæ are also scattered over the surface.

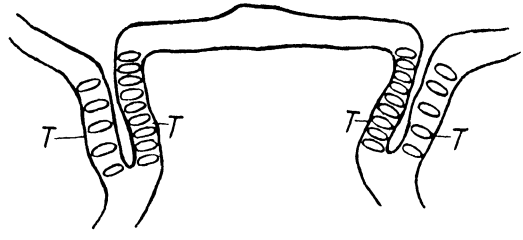


FIG. 8.—Enlarged view of circumvallate papilla. Vertical section. Note position of taste buds (T) on either side of moat.

back of the tongue, just in front of the attachment of the anterior pillars of the fauces. Fig. 7 shows the position of these papillæ together with the general dispositions of the tongue, whilst Fig. 8 shows the position of the taste-buds relative to the papillæ. The foliate papillæ are highly developed in rodents and here the circumvallate are reduced to one each side. It may be noted that in the *lemurs* an under-tongue or *sub lingua* is found in addition to the main tongue. In birds the tongue is usually covered with a horny skin and is poorly supplied with muscles. It is highly developed in reptiles, for example, the forked tongues of snakes and lizards and the telescopic tongue of the chameleon. In fishes it is an immovable swelling on the floor of the mouth, and in some, such as the hag (*Myxine*) and the pike (*Esox*), teeth are developed on the tongue. In mammals the tongue is always movable and covered with papillæ.

Whilst the centre of the tongue is devoid of taste-buds in the adult, the distribution of the sour-sensitive, sweet-sensitive, saline-sensitive and bitter-sensitive is irregular. The sweet taste is most easily sensed at the tip of the tongue, the bitter at the back, the sour at the edge and the saline both on the tip and the edge. Fig. 9 illustrates this distribution.

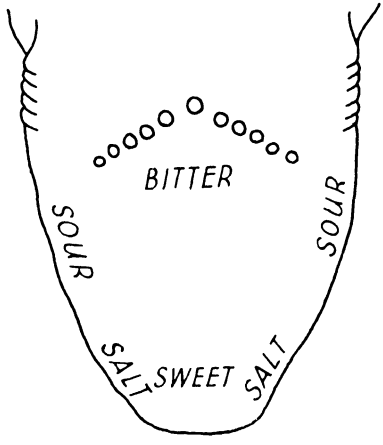


Fig. 9.—The areas where the four tastes are most easily sensed. In these areas the taste buds are very numerous. All four tastes are also sensed, but less readily over all the areas.

The Taste Nerves

Whilst taste is a simple sense in that there are only four main tastes compared with the countless varieties of odour, its innervation is more complex than that of smell. With olfaction there is the olfactory nerve, the first cranial nerve, which conveys all the messages to the brain, but with taste at least three of the cranial nerves are concerned. The back and sides of the tongue, particularly the circumvallate papillæ, are served by the glossopharyngeal or gustatory nerve (9th cranial) whilst most of the front is served by the lingual nerve, which is made up of the lingual branch of the trigeminal (5th cranial), and the *chorda tympani* of the facial (7th cranial). A few twigs of the superior laryngeal branch of the vagus or 10th cranial nerve go to the pharyngeal surface of the tongue. The 12th cranial nerve, the hypoglossal, is the motor nerve of the tongue. That the buds on the circumvallate and foliate papillæ towards the back and on the edge of the tongue are served by the glossopharyngeal has been proved by loss of taste in these regions in persons in whom the ninth cranial

nerve has been cut. Severing of the trigeminal nerve does not, however, permanently cause loss of taste, and it is probable that the trigeminal is not concerned in true taste sensation any more than it is in olfaction although it was once considered so to be. All these nerves concerned in the transmission of taste messages to the brain intercommunicate through fine branches near their roots.

The Common Chemical Sense Receptors

These are not so localized as the organs of taste and smell, but neither are those for temperature or touch. There is evidence that the chemical sense is primitive and that in lower and particularly in aquatic animals large areas of the body are covered by receptors to chemical action. The chemical sense is lost over those parts of the epidermis which become horny. The receptors are free nerve endings. There is no complicated end-organ corresponding to the taste-buds or even to the olfactory cell. The axones shed their medullary coverings and the free endings of the nerves pick up the chemical irritation. The type of irritation most commonly experienced is caused by ammonia or acid fumes, which usually cause reflex action, such as an instinctive movement out of the irritant zone, closing and watering of the eyes, coughing and sneezing. The irritant action on the eyes feels different from that on the mouth, and we conclude that different modalities of this sense are involved. These free nerve endings are served by the trigeminal (5th cranial) nerve which reports to the medulla oblongata.

The chemical sense is primitive and probably developed with the tactile sense. Possibly both are differentiations of some elementary diffuse sensibility. Taste and smell are higher differentiations or developments of the chemical sense.

The Vomero-Nasal Organ

This is a nose within a nose. It is rudimentary in man, but apparently active in lower animals, particularly reptiles. Similarly, it is more prominent in the human embryo than in man.

Its function cannot be determined from experience as it is inoperative in man but has been variously suggested as (1) an olfactory organ for substances in solution as opposed to substances which have vaporized in air, but this is unlikely as the vomero-nasal organ has been found to be filled with air in freshly killed animals; (2) an instrument by which an animal tests its own secretions or juices; (3) a receptor which notes atmospheric conditions in accordance with which the vascular tissue of the nose expands to restrict air ingress; (4) a subsidiary olfactory organ. The last is considered the most likely. In man there are at least two kinds of vision, black and white vision in poor lights and colour vision in good lights, but in some animals, particularly nocturnal, there is only one of these kinds. By analogy, although man only perceives odour in one way, there is no reason

why other animals should not perceive it in more ways, and possibly the vomero-nasal organ is the receptor for some such olfactory sense. In man the paired organs are situated on the median septum of the nose, near the bottom and towards the front. In a newly born child they are tubular processes from 0·5 to 2·5 mm. long and the organ opens into the nasal cavity by means of a minute pore in the septum. The tubular part of the organ ends blindly and is not innervated in man. In adult man the organ sometimes disappears but many have grown and reached an extreme length of 8 mm. In animals, e.g. sheep, rabbit, rat, cat and snake, nerve fibres join the vomero-nasal tube or duct and apparently mingle with the true olfactory fibres. It is interesting that it is well developed in lizards and snakes and in the lower mammals such as the Australian duckbill, *Ornithorhynchus*, the egg-laying mammal.

The vomero-nasal organ is also known as the Jacobson Organ.

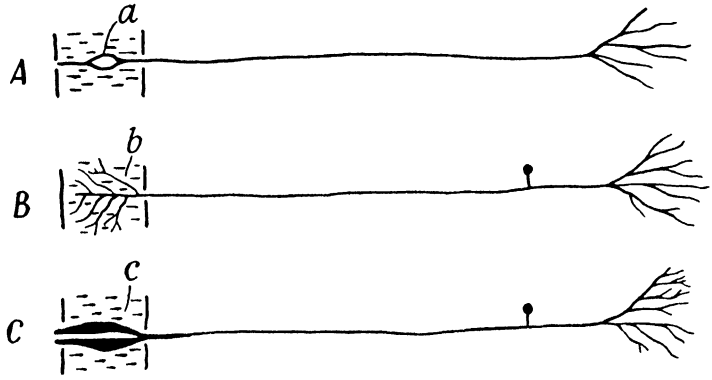


Fig. 10.—(After Parker). Receptor systems of
A. Olfactory and vomero-nasal organs. (*a*) Olfactory cell.
B. Common chemical sense. (*b*) Free nerve endings.
C. Taste organs. (*c*) Taste buds.

Comparison of Olfactory, Gustatory and Chemical Sense Receptors

The common chemical sense receptor consists of free naked nerve endings in the mucous membrane of the mouth, nose, eye, etc., and axones or nerve fibres proceed from these into the central organs and are provided with deep-seated cell organs. In taste the taste-buds are composed of receptive cells and again the axones have deep-seated cell bodies. In olfaction, however, the neurons have cell bodies in the receptive area and their axones extend as nerve fibres into the brain. The structure of the taste and common chemical receptors with their deep-seated cells is a typical vertebrate structure, whereas the olfactory structure with the peripheral sensitive cell and the neurone passing without a deep-seated cell into the central system is

typical of invertebrates. Parker suggests that the vertebrates are descended from ancestors whose integument was like that of the sea-anemone, and that as the skin thickened over most of the body to give protection to the changing animal, one small portion remained unchanged and became the olfactory region of the vertebrates. The integument of the sea-anemone is rich in receptive cells similar to the olfactory apparatus in vertebrates. It may be, however, that a deep-seated cell of the olfactory nerve wandered into the brain when olfaction was so highly developed in our ancestors and that this is the reason for its apparent absence. Whilst the sense of smell is a differentiation of the common chemical sense, it certainly developed early and is found in invertebrates. The conception of a small part of the skin of our ancestors of millions of years ago remaining unchanged whilst the rest of the body developed from some such lowly form as a sea-anemone captures the imagination. Fig. 10 (after Parker) illustrates the structural differences in the receptor systems for the different chemical senses.

CHAPTER 3

SENSATION

Irritability

A fundamental characteristic of all living organisms is irritability. From our own experience we know that irritation of various organs such as the skin, eyes and tongue is followed by the sensations of pain or touch, vision and taste. The irritation may give a pleasant sensation such as a sweet taste or an unpleasant one such as pain. We also know that certain kinds of irritation do not produce sensation but instead, reflex action. For example, something approaches the eye and we close it hurriedly, although we have no idea what the approaching object is like and have not consciously assessed the danger and decided to close the eye as a safeguard. In fact we have not seen the object, but the eye has closed automatically. In another case, such as the contraction of the pupil in bright lights, the action cannot be controlled by the will. In a third case sensitive receptors pass information to the central system by which equilibrium is maintained. A dummy of a human being is a most unstable affair, but ordinarily we are quite unconscious of any effort to maintain our balance. The parts of our body which are open to irritation are the receptors, and these pass information to the cord or brain so that the result may be sensation or reflex action or bodily re-arrangement.

The receptors constantly flood our central system with a never-ending, except to a large extent in sleep, stream of impressions. These make up our mental life, and all our consciousness rests on the basis of these messages sent to the brain from the receptors. Without them thought would not be possible, although it would be so to an individual who had experienced the sensations from receptors which he had subsequently lost. If we try to define sensation we are in difficulties. Is it the message that the receptor sends to the central system, or has the message no existence other than as the thought it evokes ? We can at least say that a sensation is the accompaniment of certain brain processes. Certain changes, possibly physico-chemical, take place in the brain matter and we experience sensations. Beyond that we have hypotheses but we lack proof. Who can say at the present stage of our knowledge why a change in the brain matter should produce sensation ? Some say that the two are the same thing looked at from different points of view, but inasmuch as the sensations are responsible for all our conscious life they are facts to be reckoned with, and all knowledge is derived from them. Usually the brain processes are accompanied or preceded by activity of the peripheral sense organs, the skin, tongue, eyes, nose, ears. The sensation expressed by " I see a tree " is ordinarily stimulated by activity of the eyes, but not necessarily so, for the same sensation may be experienced in a dream

when the eyes are inactive, or in hallucinations when the experience of other individuals indicates that there is no tree to activate the eyes. Evidently the brain processes and the experience of sensation may take place without stimulation of the peripheral receptors.

It seems certain that there is good general correspondence between the sensations of different individuals, as the general laws of nature in mathematics, physics and all the sciences are comprehensible to all mankind, whilst if there were serious differences between the perceptions of individuals of the same set of circumstances, for example, the appearance of equal angles, the shape of triangles, the temperature of water and so on, there would be great differences in behaviour, and natural laws comprehensible to one individual would be rejected as untrue by another. True, there are minor differences, some prefer one taste to another, some find a scent agreeable, others find it distasteful, but these are subtle differences of a high degree of differentiation and in no way invalidate the conclusion of uniform sensation and perception in humanity.

When we come to the lower animals we are much less sure of our ground. It is generally agreed that reflective thought and consciousness of self have not developed yet in animals. It is clear from their behaviour that the higher animals with which we are familiar, particularly the mammals, such as cats, dogs, horses, sheep, rabbits and so on, can see, hear, smell, taste and feel, and as their peripheral receptors are similar in structure to ours it is reasonable to think of their sensations of sight, hearing, etc., as similar in quality to ours, although differences even at this high stage are patent. The dog hears a whistle pitched so high as to be inaudible to us; it follows a scent we cannot smell at all, and it is apparently unaffected by scents, such as the sweet herbage through which it chases, while distant objects are invisible to it though clear to us. The lower we go in the scale the more our difficulty increases. Does the sensation started by the mosaic eye of the insect compare with our own vision? If so, why have some insects both mosaic eyes and single eyes similar to ours?

Is the sense of smell which Fabre reported drew moths from miles away to a single apparently odourless moth of the opposite sex, comparable to our sense of smell?

Some animals have sense organs quite different from ours, and it is impossible for us to imagine the sensations these convey to the animal. Fishes, for instance, have lateral line organs, although in this case it has been fairly clearly established that they are "touch at a distance" receptors. Waves are set up by the tail of the fish in the water, and if there is any object near, then the waves are reflected back and affect the lateral line receptors, so giving information to the fish of the presence of objects, maybe enemies or food or obstacles in the neighbourhood.

When we go lower down the scale we find olfactory pits as rudimentary organs of olfaction, and the sense of taste not confined to the mouth but spread over the whole body, light-sensitive spots instead

of eyes, whilst the central nervous system becomes more simple and rudimentary and very sketchy in the invertebrates, and finally vanishes in animals below the flatworms. These receptors, such as the light-sensitive spot, cannot give vision, but they do give an awareness of light which is sufficient to determine the behaviour of the animal and confer on it a positive or negative phototropism according as it usually moves towards or away from the light. When we come to the cœlenterates, such as the sea-anemone, there is no central nervous system although there are still receptors. Such an animal is sensitive to meat juice in the water and starts to feed, whilst a delicate touch will also induce the feeding reaction, although a heavier touch will cause the animal to contract. Evidently there is a close relation between touch and chemical sense at this stage. There is no central nervous system so the animal cannot experience any clear sensation, and the receptors are simply to call into play by reflex mechanism the appropriate reaction, feeding or perhaps protection. Nevertheless the sea-anemone and even the lowest animals of all, the protozoa such as the amœba, lacking not only brain and nervous system, but also receptor cells, seem to show irritability and a vague pleasure or unpleasure according to their surroundings. Perhaps in the single cell which constitutes the whole protozoal animal there is some ultra-microscopic structure capable of the rudiments of sensation. That it exhibits irritability is certain. From our sharp, well-defined sensation there is a general trend downwards, although in the case of smell, many of the higher animals appear to have superior perception and definition to ours. As we go down the scale smell like the other senses deteriorates, new senses make their appearance, such as compound eyes and lateral line organs, definition becomes progressively poorer till it reaches a stage when sensation is a " blooming buzzing confusion " as it has been picturesquely described, and this becomes weaker and ultimately vanishes, and the animal becomes an automaton.

Reflex Action

In man, and indeed in all animals with a brain, the sense receptors are the approach to the mind. They record the multitudinous changes in our environment. The eyes report to the brain changes in the radiant energy of our surroundings, and taste, smell, and the common chemical sense report changes in the chemical conditions. The brain receives the information, weighs it up, and sends back by motor fibres in the nerve trunks messages to which muscles make the appropriate response. Someone asks us to wink. The ear picks up the message, sends it to the brain, and the latter despatches a message to the motor nerves surrounding the eye, and the wink is accomplished in about one-sixth or one-seventh part of a second. Now suppose someone throws a stone at our eye, the stone may be travelling at about fifty feet per second so that whilst we get into action and wink or take

other avoiding action the stone travels seven or eight feet. If then we are not aware of the approach of the stone until it is within seven feet we should expect it to hit us, as it would do if we relied on voluntary effort. What, in fact, happens is that we act involuntarily and wink or duck out of the way without the exercise of will and without the intervention of the reasoning centres of the brain, and this time the wink takes only one-twentieth part of a second, so that if the visual receptors are aware of or are irritated by the stone when it is only three feet away, there is still a good chance of avoiding it. Such involuntary action is called "reflex." Many reflexes cannot be carried out voluntarily, even though more slowly, as can the wink. The smell of food causes saliva to flow and the stomach to secrete juices. A bright light cuts down the size of the eye aperture, sunlight induces sneezing, an unexpected noise makes us jump. All these are reflex actions. If smell has not warned us that a food is unsuitable, and taste has been hoodwinked or its distress message overlooked by a brain attending to something else, reflexes occur in the stomach, nausea and vomiting take place and the unsavoury material is rejected by reflex action.

We notice that the "on-purpose" wink takes 0·15 second and the reflex wink only 0·05 second. Evidently the messages have taken different paths. Those causing the reflex wink may not have been to the brain, or if so only to its lower centres. Now invertebrate animals of cœlenterate classes have no brain or ganglia or nuclei of cells to which the sensory cells report, yet they are sensitive to chemical action. Meat juice introduced into the water surrounding a sea-anemone causes it to feed, and a touch on the tentacles causes it to contract. The skin is activated by chemical and tactile stimulation, but there is no brain or other nervous system to which the messages are transmitted. Instead, the receptor cells are connected either directly or through a simple nerve net, which is simply a trunk line of the connections, directly to the muscles, and these when brought into action cause feeding or contraction. The receptors when activated pull the trigger and the muscles operate. The presence of olfactory pits or eye spots, rudimentary organs of smell and sight, is not taken to mean that such animals can experience the sensation of smelling or seeing but only that they do certain things in the presence of light or of odorous foods which are beneficial to the animal. Such is the state of affairs for sea-anemones, corals and other animals at the tissue plane of development. Protozoa, which are the most numerous animals in the world, inasmuch as in addition to the free-living protozoa nearly all other animals carry one or perhaps vast numbers of protozoal parasites, have no receptor cells. They show irritability and move away from chemical irritants in the water, and such action must be classed as reflex, though the mechanism by which the action is initiated is vague and diffuse. It is clear that of the two main functions of sense receptors, viz. to initiate sensation and to start reflex action, the latter is the more universal and primitive. In the lowest animals

it is the only function of the receptors, whilst in the highest it is essential for the maintenance and well-being of the body. In man all the delicate receptors in the ear carry out their work of preserving balance without our being conscious of what is going on, and olfaction promotes reflexes essential to the assimilation of food and nutrition. Many of the receptors, such as those for balance, act only to promote reflex action, and do not contribute to sensation ; others may act in one way or the other at different times as circumstances dictate. Finally, in this connection whilst the light-spot in the invertebrate confers on it not the sensation of vision but a positive or negative tropism, the change from this tropism to sensation is gradual and all degrees exist between the two.

Classification of Sensations

A rough analysis of human sensation distinguishes the five senses, vision, smell, taste, hearing and touch. These are so separate and distinct in man that no confusion between them seems possible. We have already seen that the common chemical sense must be recognized as separate from olfaction. It is different in its stimulus, for whereas foods, essential oils and flowers which are typical odorivectors (odour producers) do not irritate the chemical receptors, yet irritant fumes which do irritate chemically may be lacking in true odour. There is a difference also in the places of perception, for odour is detected only in the nose, but chemical irritation anywhere where the mucous membrane is exposed. It is different also in the reactions it produces, for whereas odours bring about gentle reactions, secreting juices or at the worst nausea, chemical irritation gives violent reactions, withdrawal from the scene of irritation, watering of the eyes, coughing, choking and sneezing. As therefore the source of stimulus, the locality of the sensitive spots and the behaviour induced as well as the sensation experienced are all different, we may truly say the common chemical sense is separate and distinct from odour. That one has been developed by modification and differentiation of the other is true, but now the two are so different that it is harder to find points of resemblance than of dissimilarity. There are other senses though, where differentiation has taken place and different modalities evolved but where the differences are not so striking. Let us consider Taste. Common human experience accepts taste as a unitary sense. There is no sharp distinction between sapid and tasteless substances, both are met in good food and in poisonous matter. All taste is experienced in the mouth, no violent reactions are experienced ; we may reject matter and expel it from the mouth, but that is discrimination and not a violent reflex like coughing or sneezing, and, finally, different tastes seem to grade into each other. A closer examination shows that the grading of tastes into each other is due principally to odour, from which sensation practically all " flavour " is derived, and that if odour and temperature-tactile complications are removed, we are left with four tastes, bitter, sweet, salt, sour, which do not grade into each other

and which are partly localized, bitter definitely at the back of the tongue, and sweet at the tip and edges, but the sensitive areas of all four overlap. More detailed analysis shows that the receptors or taste-buds vary, and some are sensitive to sweet only, others to sour only and so on. Here we have different sensations, some difference in locality of the sensitive areas, receptors sensitive only to one of the tastes, and different sensations which do not grade into each other. They are in fact four different senses, but the degree of differentiation is not so great that the distinctiveness of the four is recognized without a careful analysis. Similarly, on the skin we feel touch, temperature differences and pain. All these in the crude analysis are "touch," but we know from experience that touch and pain are very different sensations although we may have a shrewd suspicion that pain is simply an overdose of touch. In fact, anatomical analysis shows that there are spots on the skin sensitive only to mechanical touch and not to pain or temperature differences, whilst other spots distributed over all the body are sensitive only to pain, and others only to temperature, whilst even the latter can be divided into two kinds, those sensitive to heat and those to cold. All are quite distinct and sensitive only to the one stimulus. They are specialized. All come from the primitive tactile-temperature fuzzy sensation, but they have become so modified, as the animal has developed, that they cannot do each other's work now. In reality, they are separate senses. Vision consists of two main kinds, black and white, which operates in poor lights and colour vision in good lights. They are actuated by different stimuli and transmitted to the brain by different mechanisms in the eye, and one can operate while the other is quiescent. The differences are clear. Whether you are prepared to call them different senses depends on how far your conception of a sense is based on common human experience and how far on critical analysis. Colour vision is dependent on the independent appreciation of three separate colours, red, green and violet, whilst blue, yellow and all other colours are compounded of these three (browns and olive greens require a darkening or addition of black). Are we prepared to classify red, green and violet as separate sensations ? Probably not, because all intermediate colours are known and grade into each other. But it would be equally true to say that all tastes between sweet and sour can be prepared by mixing. Nevertheless we are readier to concede four separate sensations in taste than three in colour vision, because it is easier to distinguish the former than the latter and because ordinary experience confirms that the back of the tongue reacts mostly to bitter and the front to sweet, whereas we cannot ascribe red to one part of the eye, violet to another, and so on.

With hearing all the tones grade into each other, and so with smell all odours do. There may be separate senses in both hearing and smell, but if so either the degree of differentiation is not great enough for us to discern it, or more likely our analytical methods have been unsuitable.

Then there are the body senses of hunger, thirst and sexual desire, all quite definite sensations and with specialized receptors. Also we have the sense of equilibrium, but this is more automatic than sensation producing.

Enough has been discussed to show that the five senses of man on careful examination show many differences and distinctions, and it is sometimes said that there are twenty or thirty separate senses. It is all a matter of how you define a unitary sense. Herrick has discussed the problem and has suggested four criteria: (1) the stimulus, (2) the sensation, (3) the sensory mechanism, and (4) the type of response. These are the considerations we have made use of in the above discussion. The sensations have been classified in various ways. Man can classify his own senses on a psychological basis, but an animal's only by its receptors. They can be divided into subjective and objective. The former have reference to the bodily individual—we feel hot or cold and we localize touch, temperature and pain in certain parts of the body, and we think of them as temporary properties of the body, so heat, cold, pain and touch are subjective sensations. On the other hand, vision, hearing and smell are objective and referred to the environment. When we smell something we do not consider it as a property of the nose but of the object we are smelling, similarly if we see or hear. Taste seems to occupy an intermediate position; we think of an object as tasting bitter but we also think of the back of our tongue as having a bitter feeling. Smell is pre-eminently objectified. The common chemical sense is more subjective than objective but, like taste, may function either way.

Another method of classification is based on the stimulus. All the senses are stimulated either by radiant energy, such as heat or light, or by chemical energy in the case of taste and the common chemical sense and it is usually agreed smell, or by mechanical energy in the case of touch. This division gives us three great classes of receptors:

Radio-receptors, viz. heat and cold organs and the eye.

Chemo-receptors, viz. smell, taste, common chemical sense and vomero-nasal organs.

Mechano-receptors, viz. touch, pressure, equilibrium organs, hearing, lateral-line organs of fishes.

Pain may be due to mechanical or to chemical reception, for the pain receptors may react to chemicals produced by abnormal body tissue condition. The same applies to hunger and thirst for they also may be stimulated by pressure or by chemical action. It is not possible to say which, and in general it is difficult to classify our sensations. Reasons for this are first, that senses are in all stages of differentiation, from a primitive sensibility, and second, that we cannot experience a pure sensation, but every perception is coloured by past experience and association. The brain gathers together the

material from all the senses and quite without our wish gives us a composite presentation. If we take steps such as closing the eyes and nose to cut out all sensations except taste, we are nearly as badly off, the memory and association centres of the brain call up all their previous evidence and the sensation is quite a composite presentation. It is said that a man who is cured of blindness as an adult and has been familiar with the handling of a cube and a sphere could not on first seeing tell by sight which was the cube and which the sphere. Such is the power of the associative centres. In the classification into radio-, chemo- and mechano-receptors we bridge the difficulty by considering not the sensation but the stimulus applied to the receptor. Even then we are in doubt as to the function of some nerve endings. There is one notable difference between the mechano-receptors and the others. In the case of light, heat, cold, smell, taste and the chemical sense the receptors are directly exposed on the surface of the body to the stimulus, but in the case of the mechano-receptors for hearing, equilibrium and pressure and pain, the receptors may be deep-seated in the body and the stimulus may act through the intervening tissue. A corollary of this is that pain, hunger and thirst should be classified with the mechano-receptors and not with the chemo-receptors.

There is another method of classification relative to the body, into exteroceptors, interoceptors and proprioceptors.

Exteroceptors are distance receptors, the eye, the ear and the nose which see, hear and smell at a distance. In this connection it is usually contended that to smell something particles of it must come into contact with the olfactory region, but this has been the subject of some argument, and in any case we usually think not of the nose being in contact with the object smelled, but as smelling at a distance. Smell is in fact the distance receptor for nutrition of lower animals.

Interoceptors are such as taste and touch and probably hunger, thirst and sexual desire which are phylogenetically primitive and their responses in man have characteristics of the primitive, vague, ill-defined and undifferentiated, contributing little more than a modification of the general background against which the more specialized sensations such as smell and taste show up in relief.

Proprioceptors are those which convey information to the central nervous system regarding the movements and posture of the body. Such are deep pressure, equilibrium and the muscle receptors in all parts of the body. The proprioceptors have a very great effect on the working of the body and without them no movement can be performed accurately. In cases where their use is lost, such as in *locomotor ataxy*, movements lack adjustment of range and force and are jerky and fumbling, and whilst attempts will be made to compensate for the loss of the proprioceptors by using the exteroceptors, the eye watching the limb and attempting to guide its movements, it is an unsatisfactory substitute. Normally the proprioceptors send

their reports from the muscles to the central nervous system which then initiates the correct responses.

Extero or distance receptors may be stimulated by radiant energy as in light or heat, or by chemical energy as in smell, or by mechanical energy as in hearing and the lateral-line organs of fishes. Similar organs to this last exist in bats and so enable them to fly with inadequate vision and yet avoid obstacles as if they flew in a good light, and it is thought that a similar sense, due to the perception of reflected air waves of very low frequency such as six per second, may enable birds like starlings, which fly in compact flocks at high speed, to avoid collision whilst wheeling and swerving. A not dissimilar method has been adapted by human ingenuity to the detection of submarines.

We have seen that taste consists of four separate sensations, sour, sweet, salt and bitter, and that as yet it has not been possible to identify the components of smell. There is, nevertheless, evidence that smell is made up of different modifications. Firstly, some individuals suffer from partial anosmia. Anosmia is the condition of being unable to smell and is most commonly due to injury to the olfactory nerve, but in cases where some substances affect the olfactory organs and others do not the suggestion is that there are at least two kinds of smell receptors, only one of which is inoperative. Some individuals find a flower like verbena odourless, others think it has a powerful odour, whilst people with apparently normal olfactory powers may be unable to smell hydrocyanic acid gas. Partial anosmia is probably very common, but most people go through life unaware of what they are missing in this respect. Other evidence is gained from fatigue. The nose is exhausted by long smelling at an oil, until after say ten minutes it can no longer smell it. Then the stimulant—the oil—is removed and another but different essential oil substituted and the nose cannot detect it, but let a quite different substance, say camphor, be held to the nose and it is perceived immediately. The inference is that of more than one kind of receptor only one kind has been exhausted. If then there are different odour receptors, how many must there be to account for the multitudinous different smells we experience. If there were only one kind of receptor there would be only one smell, two receptors, A and B, would give three sensations, A, B and A + B, whilst three would give seven odours, four fifteen, and n different receptors would give $2^n - 1$ different odours. If we postulate that we can distinguish between a thousand different odours, we require ten different receptors on the assumption that each can be active or quiescent, but that there are no grades of activity. Actually the central connections of the receptors to the brain have more to do with such distinctions than the receptors themselves. There is some similarity to a telephone system. It is not a question of which telephone instrument is used, but of the connections to it which determines the response.

Differentiation

All the highly specialized and diverse sensations we now enjoy are derived from the protozoal irritability by differentiation. A variation favourable to the species led to differentiation and new features emerged. Just as life, sensibility, mind and reflective thought are new features which have emerged in the cosmos so, but with less striking difference, have the different senses emerged. That the emergence has been gradual in every case there can be little doubt. Even of " life " we already know viruses, such as those which cause smallpox, mumps and infantile-paralysis, which grow in the presence of living matter, but can be dissolved and recrystallized and even then multiply. Would it be wrong to see in this behaviour a stage in the emergence of life, and if there are stages there is gradation and no necessity for the sudden appearance of new features.

In evolution irritability preceded sensation, and irritability with its reflex reactions had already developed in different directions before sensation appeared. The sea-anemone has sensitive cells and is more sensitive to touch on the tentacles than on the body, whilst it shows the reverse degrees of sensitiveness to meat juice. There are no areas peculiar to one kind of irritation, tactile or chemical, but gradation has started, and the cœlenterates, the phylum to which the sea-anemone belongs, have no central nervous systems so that sensation as we understand it is out of the question. The lack of differentiation in the receptors of such animals points inevitably to the conclusion that any sensations that they are capable of are *perceptions brutes* and quite undifferentiated " blooming buzzing confusions." These recepts give rise to the responses necessary for the survival of the animal, but the receptor and motor mechanism which carries out the responses forms a single receptor muscular unit. At a higher stage differentiation leads to the separation of the receptor mechanisms from the motor mechanisms. In jelly-fishes a nerve-net runs round the margin of the bell and controls and co-ordinates the animal's behaviour. Specialized sense organs occur round the bell margin embedded in the jelly between the bases of the tentacles. Some sense organs are small sacs containing a hard calcareous concretion and concerned with the maintenance of equilibrium whilst light-sensitive spots also occur. In the lowest animals the primitive sensation is tactile, but a composite tactile, which includes touch, temperature and chemical sensibility and only two responses are possible, to or away from, a positive or a negative tropism. As the animals change and become highly specialized so receptors which respond only to one type of stimulus make their appearance.

The first stage in this process is the development of a chemical sense separate from the tactile, which development is already found in the sea-anemone. Later, but still at an early stage, e.g. jelly-fish and earthworm, light-spots appear. Very probably such early light-spots are sensitive to light and heat, for we should expect lack of

differentiation, but the range of frequencies to which they are sensitive has not yet been worked out.

The differentiation of the chemical sense into taste and smell is accelerated because these senses are so useful for nutrition which is the animal's most essential requirement. Smell is the distance receptor for food and taste gives the food the final check, approving it, or disapproving, such disapproval being the forerunner of disgust.

Earthworms show taste preferences but little evidence of smell. Fishes have taste-buds over large areas of the bodies, especially some of the deep sea fishes (*Siluridæ*). If a fish is touched with a wad of cotton-wool on its side the fish turns but will not snap at it, but if the cotton-wool is soaked in meat juice it snaps at it. That this is truly a taste response is proved by cutting the branch of the 7th nerve which innervates the taste-buds of the flank, when the snapping response no longer occurs (Parker, *J. Acad. Nat. Sc.*, Philadelphia, XV, 221, 1912). As the sense organ becomes more specialized so its distribution is more confined. The taste-buds which occur over the body of fishes are restricted to the mouth and pharynx in higher animals; and in man, where differentiation has proceeded to the four separate tastes, the buds are confined to limited areas of the mouth. Taste-buds are few in birds, most occurring in the parrot. Estimated numbers of buds in different mammals are:

Bat	800
Squirrel	6,000
Hare and Man	9,000
Sheep and Marsupials	10,000
Pig and Goat	15,000
Rabbit	17,000
Ox	35,000

These numbers suggest that taste like smell is partly degraded in man, that the sense attained its maximum importance in our ancestors and since then has declined in importance simultaneously with the rise of visual ability. Only biologically useful sensibility is perpetuated. So long as an animal relies on the chemical senses for its nutrition and mating, taste and smell will develop and possibly differentiations of which we cannot know will appear. For example, the vomero-nasal organ may give to some animals a sense of olfaction unknown to us, and it is quite possible that our ancestors were, and even present-day animals are, sensible of more than four kinds of taste. When vision became highly developed in our ancestors, so that they obtained through it supremacy over other animals, the high development of the olfactory and gustatory organs became redundant. To a large extent food could be discerned and discrimination exerted by the eye. As soon as the specialized qualities of the nose and tongue were no longer essential they ceased to be used, and degradation set in from one generation to the next.

Animals without taste-buds in the skin, such as frogs, respond to

solutions of salt, alkalis, acids and bitter substances applied to the skin but not to solutions of sugar. This suggests that the taste responses in the frog have not been entirely lost over the body, or really that taste-in-the-body which was a differentiation of the common chemical sense is reverting to that sense. The behaviour of the frog in this respect suggests that the sweet taste was a later development than the sour, salt or bitter tastes, and indeed everyday experience shows that many animals are unattracted by sweets. Fishes which have had their gustatory nerve cut behave in a similar way to frogs, they respond to acids, alkalis, salts and bitters but not to nutritive substances.

To summarize, the most primitive sensory receptor is to be found in the single cell of the protozoa which exhibits irritability. The signs of irritability consist of a faster *tempo* in its movements and attempts to recede from chemical irritants in the water. There is even evidence of attempts to recede from an approaching enemy. This is no evidence of consciousness, for the whole business may be quite automatic and the animal may have no powers of control. The absence of specialized structure, and particularly of a nervous system, supports this view. On the other hand, our own experience leads us to view increased activity on irritation or the approach of danger as a response of consciousness, and a fuller understanding of the basis of perception may some day credit such lowly creatures with a form of consciousness. Then special sense cells make their appearance and the receptor effector mechanism is structurally differentiated from the rest of the protoplasm. Then, still at the stage of the cœlenterates, the receptor and effector mechanisms become separate. Up to now the only sensibility has been a general tactile-chemical-temperature response, but at this stage areas of the animal become specially sensitive to either tactile or chemical stimulation but still sensible of both. Then as the animal develops and becomes more complex different receptors sensitive to only one stimulus occur. Such early ones as light or light-and-heat sensitive spots and equilibrium devices emerge to meet the animal's economic requirements. Then the chemical sense develops into taste and smell, but still the general chemical sensibility is retained, then taste develops into four varieties, sweet, sour, salt, bitter, and the nose develops ability to perceive and distinguish very many, say thousands of, odours. Simultaneously the light and heat spot develops into an eye, perhaps mosaic in an insect or single like our own, and then colour vision comes along. Lateral-line organs appear in fishes and bats and perhaps in birds. The other part of the primitive diffuse sensibility, the tactile component, develops into touch, deep pressure, hearing and pain, but its development is slower than that of the chemical senses. As all these senses develop and become specialized they become localized. The cœlenterates are chemically sensitive over the whole skin, the fishes have taste-buds spread over large areas of their bodies, but mammals taste almost exclusively with the tongue, and smell with the small area of the

olfactory cleft. With the increase in specialization comes the difficulty of regrowing. Primitive animals if mutilated have little difficulty in growing new parts. Thus when starfishes were ruining oyster beds, as the starfish can and does open an oyster by a process of exhaustion, the starfishes were caught, chopped up and returned to the water, and the result was that the starfishes became a far greater nuisance than ever before as all the chopped portions grew into fresh starfish.

This ability to regenerate lost organs is no longer possessed by highly specialized animals, and if we lose an eye there is no hope of regeneration. Such were the three main lines of development, radio-, mechano- and chemo-reception. In the chemical senses a peak has been passed and we have fallen below the best performance our kind put up. It is a general rule in biology that powers allowed to deteriorate in a species are not recoverable, so there is little hope of our descendants enjoying the delights of high-powered olfaction and taste perception experienced by our ancestors. But the prospect is by no means dull, for as civilization progresses, higher specialization will be required of man, and there is no reason why new and unimaginable modalities of the chemical sense should not develop. It is unlikely that man will ever use the vomero-nasal organ again, but there may be in us the rudiments of much more exciting organs, seeds planted by a far-seeing Creator to bear fruit millions of years hence.

The Nervous Impulses

We have seen that the nerves are the connecting-links between the central nervous system, which is the brain and the cord on one hand and the peripheral receptors on the other. This is the case with the afferent fibres which affect the brain by carrying information to it. In the case of the efferent fibres, by which the brain gives effect to its wishes, the connection is from the brain and the cord to the muscles.

The question arises as to what sort of message the nerve fibres carry to the brain. The method of approach has been to isolate a nerve, usually the frog's sciatic nerve, with gastrocnemius muscle attached and apply an electric stimulus to it.

About 1770 Galvani, an Italian physiologist, was studying the frog's nerves. He had a dissected frog on the same table as an electrical machine and noticed that if the frog's legs were touched with a scalpel at the same time as a spark was taken from the machine the legs were violently convulsed. Later he found that lightning flashes had the same effect and also that mere suspension of a dead frog by a copper hook from an iron railing caused the leg muscles to twitch. Galvani appears to have thought that the current of electricity had its source in the dead frog, but later, Volta (1745-1827) gave the correct explanation that the electric charge had its source in the junction of two dissimilar metals. Both recognized clearly that the application of an electric current to the nerve produced muscular reactions.

Since then it has been found that when the nerve is stimulated, for example, by tension or touch, an electric current runs up it, and

also that if the stimulus is an electric charge, as in the case of Galvani and Volta, an electric current still runs up the nerve, but is not dependent on the stimulus being electric in character. The electrical stimulus applied is not the source of the current carried by the nerve. In experimental work it is easier to control the timing, frequency and strength of an electric current than it would be of, say, touch. For that reason only, is the electrical stimulus used in research, for the electric impulse which passes up the nerve would be similar if the stimulus was touch. Many important facts have come to light, and whilst they do not bridge the gap between the stimulus of a finger prick and the ensuing sensation of pain they throw a flood of light on the first steps. First, the impulse is similar in character for all the senses that have been investigated, and these include touch, deep pressure and vision. Similar diphasic electric currents have been observed in the frog's sciatic nerve, the nerve from a cat's toe-pad, and the optic nerve of an eel. It does not appear to matter what the stimulus is, whether it is radiant or mechanical energy, the message sent by the peripheral receptors to the brain is unchanged, an electric current. The nature of the sensation rests with the central system, and indeed it is clear that this must be so, since the same stimulus may arouse different sensations. Red light rays impinging on the eye cause that organ to send an electric current to that part of the brain responsible for the sensation of colour vision and we see, but the same stimulus, the red light rays, impinging on the skin cause currents to go to the temperature centre of the brain and we experience warmth. As another example ammonia excites chemical irritation but also has a true and distinct odour, whilst again the light pressure of a pin on the skin causes the sensation of touch, but heavy pressures cause pain, and even similar pressures on different parts of the body cause very different sensations.

Forbes and Gregg (*Amer. Journ. of Physiology*, **39**, 172, 1915) recorded the response in an efferent nerve caused by stimulating a sensory nerve and found it to be a typical action current. Gasser and Newcomer (*ibid.*, **57**, 1, 1921) recorded the response in the phrenic nerve which brings about the rhythmical contraction of the diaphragm, and although this latter is at the rate of one per second, found the action current in the nerve had a frequency of about seventy per second and was diphasic in character. Steinach (*Pflüger's Archiv.*, **43**, 495, 1896) found currents in the sensory nerve of the frog on tapping the skin but did not measure them. Buytendyk (*Konik Akad. v. Wetens te Amst.*, Dec. 8, 1910) stimulated the ear of a rabbit with a pistol shot and found an electric response in the auditory nerve lasting about 1/50th sec. As all the senses investigated show this uniformity of impulse, it is only logical to credit those which on account of experimental difficulty it has not been possible yet to investigate with the same properties. There can be no doubt that the function of the nerve fibres is simply to conduct electrical impulses from the sense receptors to the brain, and in the case of the efferent fibres, to transmit electrical

impulses from the brain to the muscles. The duty of the olfactory nerve is to carry electrical impulses from the olfactory hairs and cells in the yellow pigmented areas of the nasal cavities to the olfactory lobe of the brain. What brain processes cause these impulses to give the sensation of smell we can only guess at, and the problem may provide a fruitful field of research for many generations. In the same way the nerves serving the tongue and palate carry electric impulses by various routes to the brain. We can only follow the path to the first nerve junction or *synapse* where some sort of rectifying action takes place. The uniformity of impulse suggests the possibility of crossing fibres by surgical treatment, just as lines can be crossed and unfortunately sometimes are in a telephone exchange, when the subject might hear an onion or smell an enjoyable symphony concert. Whether he would want to listen to the onion for the best part of an evening, and if one sniff at the concert would be sufficient it is impossible to predict.

Adrian in "The Basis of Sensation" (Christopher's) has shown that it is possible to record the nervous impulses and so measure their frequency and in fact analyse them completely.

First, experiments were made with a frog's sciatic nerve which after removal from the body will if kept in a moist atmosphere respond to electrical stimulation for many hours, then with a cat's toe-pad, and later with the eye and optic nerve of a conger eel. In the case of the cat's toe-pad, the animal was killed by decapitation under deep chloroform anæsthesia and the circulation maintained by the surviving heart and lungs being artificially ventilated. As the electrical effects in the nerve are very small they are first magnified about 5,000 times by a wireless valve amplifier consisting of a 3-valve resistance capacity coupling amplifier with large intervalve condensers. The magnified current from the amplifier was passed to a capillary electrometer in which changes of potential cause the mercury in a capillary tube to rise or fall. The changes in height of the mercury column were photographed on a moving film through a microscope in such a way that an alternating current of constant frequency would give a regular and symmetrical curve. The general arrangement of the electrometer is shown in Fig. 11.

The preparation of the nerve and end-organ is screened in a metal box from electromagnetic disturbances and placed on the electrodes leading to the input circuit of the amplifier. One end of the muscle is fixed and to the other a thread is tied so that the muscle can be stretched by various weights. In this way a natural stimulus can be employed and the current in the nerve measured by the electrometer. It is observed that the current only passes when the end-organs are stimulated and that the frequency changes with the strength of the stimulus. No current passes unless a stimulus is applied. A heavy stimulus fires off a rapid volley of impulses, but each impulse is of the same size whatever the stimulus. Eventually a preparation of only one nerve fibre was prepared by a "tear-away" method and then

the action current was a regular diphasic current recurring at intervals of 0·03 second. The frequency, but not the strength of the impulse, varied with the stimulus. Also if the stimulus was kept constant the frequency declined due to "fatigue." Where an electric current was used as the stimulus it was possible to observe the effects of very short stimuli. If the duration was less than 0·00001 second there was no excitation of the nerve. Usually the current in the nerve reaches a maximum in 0·001 second as there is a very short initial "treppe" or warming-up effect. If, however, the current used as the stimulus is raised very slowly, it is possible to apply great intensities of stimulation without exciting the nerve. If the stimulus is raised gradually, the receptor or nerve or both adapt themselves to the changing environ-

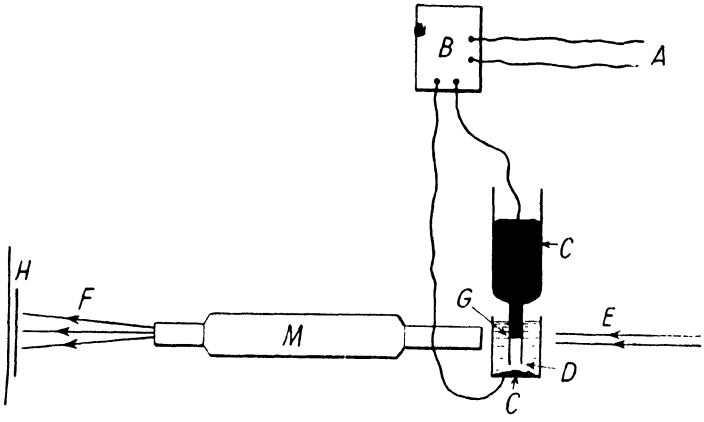


FIG. 11.—Diagrammatic arrangement of Adrian's nerve impulse recording apparatus.

A. Nerve specimen.
B. Amplifier.
C. Mercury.
D. Sulphuric acid.
E. Incident light.
F. Emergent light carrying magnified image of G.
G. Meniscus of electrometer.
H. Photographic plate with travelling guides.
M. Microscope.

ment, possibly the electrical charge or the ions, if a chemical effect is involved, leak away, but it is quite definite a sudden application of stimulus is essential for a response in the nerve. After one impulse the nerve is inactive or in a *refractory state* for a period. The *refractory period* is 0·003 second in the case of a frog's nerve at 15° C. and the nerve cannot transmit impulses at shorter intervals than this. Until the 0·003 second elapses after the transmission of one impulse the nerve is inactive, nor even then does it recover its full efficiency quickly, for after 0·02 second it has regained but 95 per cent. of its efficiency and is only fully recovered after 0·1 second. The constitution of the nerve fibre will not allow it to conduct two impulses at less than a definite time interval apart. Each impulse is a discrete event

and continuous activity is impossible. The nerve impulses correspond to a volley of bullets from a machine-gun rather than to the jet of water from a hose. Impulses travel more slowly at lower temperatures and quicker in warm than in cold blooded animals. The nerve fibres adapt themselves rapidly to continuous stimulus and the outward effect of this adaptation is fatigue. If we smell continually at a scent we can no longer smell it at all after perhaps ten minutes, but by then taking a rest the olfactory nerves recover their sensitivity in a few minutes.

It may be repeated that in all these experiments the electric response in the nerve is derived not from the electrical stimulus but from the potential energy in the fibre, and is obtained equally if a natural stimulus such as pressure or tension is used instead of electrical.

We have seen that the stimulus may be too short or weak to excite the nerve and also that the intensity of the impulse is not affected by

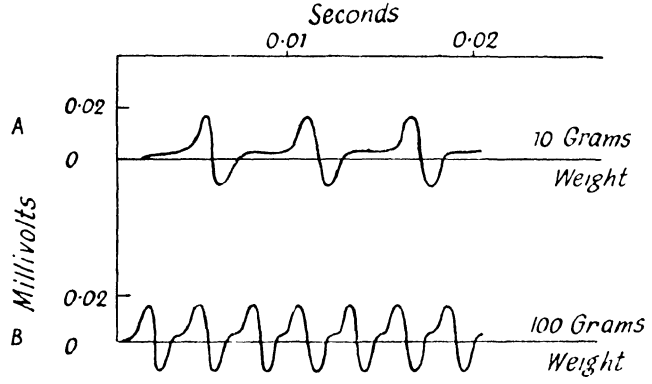


FIG. 12.—Increased stimulus B gives nerve impulses of greater frequency than A but similar amplitude. Ten seconds after application of load (after Adrian).

the stimulus although the frequency of the impulses is so affected. In fact, there is an " All or Nothing " relation between the stimulus and the activity which it produces. Within the limits imposed by the refractory period we can, however, control the total number of impulses that are started and the frequency with which they are set off. To illustrate this the two curves in Fig. 12 may be considered. The upper curve is a record of the impulses in a frog's nerve by suspending on the muscle a 10 gm. weight whilst the lower curve represents the effect of a 100 gm. weight under similar conditions. It will be seen that the E.M.F. developed by each impulse in either case is the same but the frequency is higher for a more intense stimulus.

When the electrodes leading to the amplifier are placed at different points on the nerve a diphasic curve like those shown in Fig. 12 is obtained, but if the nerve is injured so that it is permanently active under one of the electrodes then the electrometer records a monophasic current (Fig. 13). It has also been shown that the impulses

in sensory fibres are of the same type as those in motor fibres. Hence the message to the brain from the peripheral receptors and the consequential message from the brain to the muscles are both made up of a series of discrete impulses, and these impulses cannot vary in strength but do vary in frequency.

It was originally thought that pain was caused by excessive stimulation of any cutaneous receptor, but this view was abandoned when definite pain spots just like touch, heat and cold spots were identified in the skin (von Frey, *Berichte d. K. Sachs Ges. d. Wiss.*, **23,** 1896). We now believe there are special receptors and conductors for pain, but the urgency and massiveness of pain suggest that there may be some peculiarities in its collecting system. Possibly the touch and temperature conductors can signal pain by a prolonged volley of impulses. The frequencies of touch and pain impulses are about the same.

Adrian also worked with the eye and optic nerve of the conger eel. This optic nerve was estimated to contain from six thousand to ten thousand fibres and was long and slender but much smaller

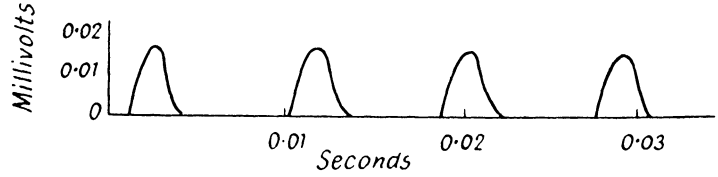


FIG. 13.—Monophasic current of impulses from injured nerve. Compares with Fig. 12 which shows diphasic current from uninjured nerve (after Adrian).

than in the case of an animal with highly developed visual powers. The eel was killed and the eye and optic nerve dissected out, and the nerve rested on electrodes leading to the amplifier. In front of the eye was an arrangement of lenses and the whole apparatus was housed in the dark, when there were no electric responses detected by the electrometer to which the amplifier was connected.

On exposing a light in front of the system of lenses there was an electrical discharge of the usual oscillatory character met with in the experiments on cutaneous sensation. It was in fact made up of action currents of the usual type and the logical inference is that the eye also sends its messages to the brain in the form of a series of discrete impulses of uniform strength. The eye showed a difference in the following respect—there was an appreciable interval between the exposure of light and the first appearance of electrical impulses in the nerve, whereas such an interval is not observed or is extremely short in cutaneous sensation. The explanation of this difference is that the mechanism of the eye is so complex with its structure of nerve cells, fibre networks and synapses of the retina, and it is a general principle in all sensation that the simpler and shorter the path through

which the message goes the quicker the perception. In this respect the eye is a very highly specialized organ and responds slowly.

The outstanding result of these experiments is that the fundamental activity, the nervous impulse, is common to the eye and to the cutaneous senses. It is a reasonable deduction that it is also the fundamental activity of the chemical senses. Indeed, work by Allen and Weinberg (*Quart. Jour. of Exper. Physiol.*, **15**, 387, 1925) has established that for each intensity of stimulus in the case of taste there is a critical frequency, and it seems clear that there is a close relation between this work and that of Adrian on the nature of the nervous impulses. This side of the matter will be examined in Chapter 5. The similarity of the nervous impulse has, however, been definitely established for touch, pressure, pain and vision. The differences are such as might be expected and can be seen in the following list:

Vision. Interval followed by burst of activity gradually decreasing in frequency (on the eye of conger eel).

Pressure. Immediate activity gradually decreasing in frequency (on one of the toe-pads on a cat's hind leg).

Touch. Sudden rapid burst of activity on contact but all over in 1/5th second, although contact maintained (cat's toe-pad).

Pain. A needle was pressed slowly on cat's toe-pad and there was a discharge of impulses which increased in frequency as the needle was driven further into the skin.

The nervous impulse is common to all the senses, and the quality of sensation aroused by it depends on the connections in the central nervous system. Change in intensity of the stimulus changes the frequency but not the intensity of the impulses. Adaptation of the receptor or the nerve to changing conditions makes rapid application of the stimulus necessary to secure a response. The response is of the "all or nothing" variety which is a universal property of the transmission of nervous impulses in nerve fibres. A very intense stimulus crowds the impulses together but does not affect the size of individual impulses.

Fechner's Law

At this stage we might reasonably look for some mathematical relation between the intensity of the stimulus and that of the sensation produced. Now here we encounter a grave difficulty, for although it is easy to measure the stimulus, whether it is tension, pressure or the concentration of sugar in water solution, or the concentration of an odorous gas in air, yet we have no absolute unit of measurement for sensation. We know our sensation of vision is more intense in a bright light than in the dusk, and that a lump of sugar in the mouth gives a more intense taste than a similar lump dissolved in a cup of tea, and that the nearer we approach to an unpleasant smell the more

intense is our sensation, but it is another matter to express these degrees of sensation quantitatively.

One method of approach is to measure the change in stimulus necessary for a change in sensation. For example, we hold a basket of apples in the hand and someone adds a small apple to it and we do not notice it, for the change in intensity of stimulus, the change in weight of the basket, is not great enough to cause any change in sensation, but if a large apple is added, we notice the difference in weight. Similar reasoning would apply to the minimum changes in concentration of sugar in water solution to cause a change in the taste sensation, or to the change of concentration of sulphuretted hydrogen in air to affect the sensation of odour.

Weber (1795-1878) first noticed that the change necessary to produce a noticeable difference was proportional to stimulus. In other words, a small weight added to a small weight produces a perceptible difference, but a small weight added to a large weight does not produce a perceptible difference, for here a larger weight is necessary.

If S is the stimulus and ΔS the increase in stimulus necessary to give a just noticeable change in sensation, then Weber's Law may be expressed

$$\frac{\Delta S}{S} = k \text{ (a constant).}$$

Fechner developed this theme. He postulated that equal increments in sensation must be proportional to that same ratio, so if ΔP is the change in sensation and C is another constant,

$$\Delta P = C\frac{\Delta S}{S}.$$

If we consider that this represents the threshold of perception, where P is just disappearing and integrate,

$$P = K \log S,$$

where K is a different constant. Expressed in words this relation indicates that sensation is proportional to the logarithm of the stimulus. The stimulus must be increased geometrically for the sensation to increase arithmetically. This relation is Fechner's Law, but Fechner called it Weber's Law, so it is referred to sometimes as one, sometimes as the other, and also as the Fechner-Weber relation. It was for long thought that the law only held for the middle ranges of intensity of sensation, but Allen has shown that in the case of taste and touch, at least, similar logarithmic relations between the critical frequency of sensation and the stimulus hold for all stimuli, but three different constants are necessary for heavy, medium and light stimulation.

Adrian has suggested that the sensation is proportional to the frequency of the nervous impulses, and if this is so the corollary is that the frequency of the impulses is proportional to the logarithm of the stimulus or

$$N_1 = k \log S.$$

Experimental work on taste and smell indicates that the stimulus, i.e. the concentration of the sapid or odorous substance, must usually be increased by about 30 per cent. to produce a perceptible difference in sensation, so that in the chemical senses $\Delta S/S$ has the comparatively high value of 0·3 whilst in vision it is much lower, 0·01, in hearing 0·1, in pressure on the skin 0·05 and in the perception of weight differences 0·025. We see then that the discrimination of intensity in the chemical senses is very crude.

It might be argued that the function of taste and smell is mainly qualitative, and that they discriminate in quality between a multitude of smells and flavours, whereas touch or pressure sensations are not concerned with varieties of sensation but mainly with degree of sensation for the preservation of bodily comfort, but this argument can scarcely be extended to hearing and certainly not to vision, which sense excels in discrimination of quality (colour) and of intensity. This susceptibility of vision to slight changes of intensity may be a relic of a highly developed phototropism in our ancestors, but by the same reasoning where is the relic of a highly developed chemotropism ? The answer, unsatisfactory to be sure, must be that the development of radio-receptors and chemo-receptors proceeded along different lines. In this connection the well-known change in quality of an odour with dilution is suggestive. Indole and civet are both repulsive when concentrated, but attractive in dilute solution, whilst some of the lower aliphatic amines are decidedly fishy in dilution but only ammoniacal when concentrated.

Reaction Time

It has already been pointed out that a reflex or involuntary wink will follow less than 0·05 second after the stimulus, but that a wink " on purpose " will take 0·15 second to develop. Insects have much shorter reaction times than mammals, of the order of 0·003 second. The reaction follows the stimulus almost immediately, which no doubt largely contributes to the difficulty of despatching flies and wasps. A man flying an aeroplane at 400 miles per hour travels 26 yards in 0·15 second while his body achieves the action his brain has ordered. An insect with a reaction time of 0·003 second would only travel 18 inches. The advantage of a short reaction time is clear but it usually accompanies a simple structure. The higher the animal, the more complex its nervous system, the longer and more interrupted the path to the brain centres, and the slower its reaction. In the same animal different senses show big differences in time of reaction, and in man these are very evident. Vision with the most complex and highly specialized receptor mechanism has a slow reaction, as was noticed in the absence of impulses in the optic nerve of the eel for a considerable period after exposure of the eye to light. This slow reaction to change of the radiant energy in the environment brings with it a long *persistence* of sensation, after the stimulus has stopped. This phenomenon has made the cinematograph possible earlier than it would have

been had the reaction time of vision been shorter, in which case " slow-motion " films run very fast would have been necessary.

By measuring the times that sensations persist after removal of the stimulus a measure of the reaction time is obtained. For the different senses of man which have been measured these are

Vision	0·013 to 0·045 second.
Audition	0·0127 to 0·0215 ,,
Touch	0·0024 to 0·0089 ,,
Taste	0·0015 to 0·0040 ,,

(Allen and Weinberg, *Quart. Jour. Exper. Physiol.*, **15,** 396, 1925).

The variations in each sense correspond to different degrees of stimulation, but it is noteworthy that touch and taste, the two most primitive and least differentiated senses, have the shortest persistence times and will therefore have shorter reaction times. The simple, primitive mechanism is responsible for smartness of response. We all experience persistence of visual images, we " see " objects for a perceptible period after closing our eyes or averting our gaze, but we never smell anything for an appreciable period after removal of the nose from the odorivector. Although it has not been measured the persistence of odour must be short like that of taste. In this connection it is of interest to note that touch on certain parts of the body behaves exceptionally ; for instance, if the inside of the ear is touched, the touch can be felt for some seconds after removal of the finger, which is quite unusual. Ordinarily the sensation of touch disappears too rapidly to be noticed. If this happened in the ear the entrance of foreign bodies to the ear would be facilitated, so the persistence of touch sensation in the ear may be a safeguard against this.

A short reaction time is associated with a short " reflex arc." This is a term used to define any system of receptor, sensory nerve, central connection, motor nerve and muscle. Thus the frog's nerve and gastrocnemius muscle is a reflex arc, whilst the nerves from tongue to brain and back from brain to tongue are another. Clearly, in addition to length, interruptions play a part, and in complex systems where two or more senses are correlated to make a single perceptual pattern, the time is also longer. Another factor determining the sensitiveness is the speed at which the impulses pass along the nerve fibres. This has been measured and typical examples are

In man	100 metres/second.
In frog	30 ,, ,,
In earthworm	15 ,, ,,

Whilst these speeds are high, that for man is equivalent to 220 miles per hour, they are not comparable with the speed at which light or electrical energy travels, and indicate that the impulse, electrical although it undoubtedly is, may have a chemical origin. Generally, impulses are slower in cold than in warm-blooded animals, and the well-known acceleration of chemical action by rise in temperature supports the above view.

Adaptation

If, enchanted by the fragrance of a rose, we smell it repeatedly, the result is not altogether satisfying, for the intensity of its odour seems to fade and after some little time we can no longer sense it at all. The change is not in the rose which is still full of perfume to a new observer, but in ourselves. The sensory apparatus has become fatigued, and needs a rest to regain its efficiency and, sure enough, if we put the rose aside for a few minutes and smell it again, we enjoy its fragrance in full intensity anew. Disagreeable smells usually fatigue us more slowly, but here also fatigue ensues eventually. The stuffiness or smokiness of a crowded room affects us unpleasantly when we enter it but after a little while we are no longer aware of it. People who work in unpleasant odours become accustomed to them. Taste also becomes fatigued, and McKenzie has recorded that Scottish cheese-tasters, aware of this, take a sip of whisky after each sample to restore the keenness of the palate. When we put on our clothes we are almost immediately unaware of them touching us, and if we want to feel any special garment we wriggle or move the part of the body in question. This lack of awareness might in the last case be due either to inattention on the part of the central nervous system, or to exhaustion or depression of the activity of the peripheral receptors. When we try to capture the smell of a rose or of violets and the sensation fades, this is not due to inattention of the central system for a strong mental effort is being made to recapture it, and it is in fact in all these cases due to adaptation of the peripheral receptors to their environment. If the perfume of a rose is constantly applied to the nose, the nose appears to conclude that the odour of the rose is the normal condition and as such unworthy of response.

Adrian has shown that if a constant stimulus, such as the light pressure of a needle on a cat's toe-pad, is applied, the nervous impulses start off at a high frequency and gradually become fewer and fewer. Similarly, in the case of the retina of the eel's eye the frequency of impulse fell when the retina was exposed to a constant illumination. Also if the stimulus be applied very gently and be increased very slowly it is possible to obtain stimuli of high intensity without exciting any impulses in the nerves. The nerves have adapted themselves, perhaps by leakage of chemical by-products, to the changing conditions of environment, and a local potential difference sufficient to excite the nerve into activity is never built up. On the other hand, if the stimulus is increased sharply or even normally, excitation of the nerve occurs as there is no time for potential differences, whether chemical or electrical, to leak away. Looked at from this point of view much of what we normally call " fatigue " is really " adaptation." The rapid adaptation of the receptors makes it difficult for us to gauge the intensity of the stimulus from the sensation evoked. This is particularly the case in the less specialized receptors, touch and taste, where adaptation is very rapid. In the more highly specialized receptors,

particularly those for vision, adaptation is slower and the sensation is more persistent and we are able to judge changes in intensity of illumination accurately. With smell we have little appreciation of intensity, just as with taste, and a 30 per cent. change in intensity of stimulus is necessary to produce a perceptible difference in intensity of sensation, but in vision adaptation is slower, judgment of intensity is better and we can detect a change of stimulus as little as 1 per cent. Receptors in the muscles (proprioceptors) also have slow rates of adaptation so that the central system is supplied with adequate information to maintain bodily poise. Likewise only a small—say 2½ per cent.—change of stimulus is necessary in a weight we hold for us to detect the difference.

The diminution in the frequency of impulses is shown diagrammatically in Fig. 14. With the light stimulus of ¾ gram adaptation

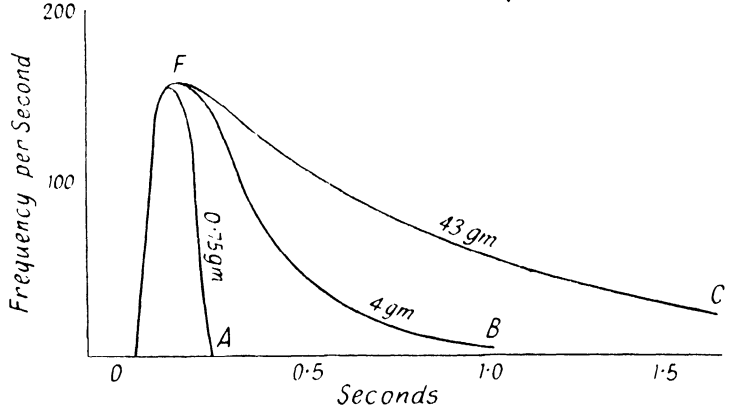


FIG. 14.—Diminution in frequency of nerve impulse is more rapid with a light stimulus A than a heavier stimulus B or C. Initial frequency F is the same for all stimuli (after Adrian).

is rapid and complete, i.e. impulses have stopped, after less than half a second, but with a medium stimulus of 4 grams adaptation is slower, and still slower with a heavy stimulus of 43 grams. We can see that in spite of the adaptation the differences in duration of the message transmit some information to the brain about the intensity of the load.

Adaptation in primitive sensation is advantageous. In lower animals, such as cœlenterates and annelids, survival depends on appropriate response to change of environment. The same is true of higher animals, but in this case other factors make the position more complex.

The invertebrate must respond quickly and appropriately to change of environment. Change is the predominant factor. The animal's receptors on stimulation by an irritant in the water or by a temperature change excite the nerves, and impulses are dispatched and the appropriate response taken by reflex or voluntary action or by an intermediate type of action. All has been done that can be

done, adaptation occurs and the nerves are no longer stimulated but now quiescent and ready for the next change. If they were kept in an excited stage whilst the stimulus lasted they would not be so readily excited by a new stimulus, and the appropriate response would not be undertaken. In primitive life each change is dealt with separately and quickly and adaptation is advantageous. In higher animals there is apparatus to correlate information from different receptors, and each change is not necessarily responded to *per se*, but only if the mental correlate of all the factors involved indicates that change is desirable.

Movement overcomes adaptation, for new receptors are brought into play. This is why we wriggle to obtain information as to the relation of our clothes to our bodies. To enjoy a sweetmeat we keep it moving by the action of lips, cheeks and tongue, for if we let it lie at rest on the tongue the sweet sensation soon disappears. The movement not only overcomes the adaptation but increases the rate of solution of the sweet in the saliva which contributes to enhanced sensation. In the case of smell we keep sniffing to gain the maximum sensation, for if we take a single inspiration and leave it at that, just breathing normally, the smell disappears. On the other hand, if we wish to reduce sensation and induce sleep we lie still and the end-receptors are speedily fatigued, and if we keep still, other receptors are not brought into action, the brain is no longer flooded with a welter of messages, consciousness fades and sleep supervenes. Or again, if we injure a limb and experience pain the first reflex action is to withdraw the member from the danger zone, but after that we keep it still to minimize the pain. In spite of our care the movement of the blood in the capillaries is quite sufficient movement to change the receptors exposed to stimulation and the pain continues. Adaptation, whilst less marked, also occurs in vision. Adrian found that the adaptation of the eel's eye was similar to that of a cat's pressure receptors but slower. It was, however, faster than the adaptation in a frog's spindle muscle. If we look at something only faintly visible in a darkened room with one eye closed and the other kept still by light pressure with the finger on the lower lid, the object becomes invisible after about 20 seconds, but if movement of the open eye is then allowed by relaxing the pressure of the finger on the lid, then the object reappears. The vision receptors had become completely adapted in 20 seconds but by allowing movement, different vision receptors in the same eye were exposed to illumination, and these not being adapted or fatigued were stimulated by the light from the object which was accordingly seen.

Whilst fatigue is due to the adaptation of the nerves and receptors to the new environment, such adaptation may have a chemical mechanism. The everyday " fatigue " is accompanied by chemical changes, for example, athletes near collapse due to supreme exertion have a sugar content below normal. Muscular fatigue is likely to be due to an accumulation of waste products.

Woodrow and Karpman (*Jour. Exp. Psych.*, **2**, 431-47, 1917) have claimed that the adaptation time for olfaction, the time for the sensation to disappear, is proportional directly to the vapour tension of the odorous material. Other things being equal we should expect the olfactory stimulus to increase with high vapour pressure and *vice versa*, and we have already seen that adaptation is more rapid after gentle stimulation than after intense stimulation.

Fatigue of synapses, the nerve junctions, appears to occur. If a decapitated mammal is kept "alive" by artificial respiration a few reflexes can be elicited through its spinal cord, e.g. when a certain area of the back is irritated by an electric current misdirected scratching movements of the hindleg occur, but with continued stimulation the reflex subsides, but a slight shifting of the electrodes will cause it to reappear. It cannot be the efferent fibres and may be the synapses which are fatigued.

Dyson (*Chemistry and Industry*, 1938, **57**, 647-51) has suggested that small quantities of a substance in producing the sensation of odour form an absorbed layer in the olfactory region, and in fatigue this layer is absorbed in the bulk of the region and the ability to detect that odour does not return until dispersal in the bulk has taken place.

In olfaction particularly, fatigue developed by one odorivector makes the nose insensitive to some different odorivectors, but not to others. There is discrimination and this will be discussed later.

To summarize, a steady stimulus does not give a steady level of sensation. First there is a short interval usually of less than 1/20th second before anything is felt and this interval is longer with highly specialized senses like vision, then there is a short warming-up and the full sensation is quickly reached, in one-tenth of a second or less, and then there is a gradual falling off in intensity of sensation due to fatigue or to adaptation of the end-receptors to the changed environment. This adaptation may be complete in half a second for light stimuli such as touch, but takes longer for heavy stimuli in which pain may also be involved. It has been found that these changes are accompanied by changes in the frequency of the electrical impulses which travel from the receptors, when they are stimulated, up the afferent nerve fibres to the central system, that in fact their frequency rises quickly to its maximum and then falls gradually. Adaptation is rapid in the case of interoceptors, touch and taste, slower with exteroceptors such as vision and slowest of all with proprioceptors. Rapid adaptation deprives the brain of information regarding the intensity of the stimulus, but slow adaptation as with the proprioceptors allows the information to be delivered. Finally, a very gradually increased stimulus gives no impulses in the nerves and no sensation. The stimulus must be sudden or adaptation occurs before sensation is experienced.

Consciousness

In attempting to bridge the gap between stimulus and sensation we have found that much information can be derived from impulse

measurements in the nerve. These measurements have been made on the frog's leg, the cat's paw and the eel's eye, and the question arises as to how far the information gained is applicable to man. It might be said that to prick the toe-pad of a decapitated cat and observe the electric impulses in its nerves is a far cry from the sensation of pain we experience if we prick a finger. We do not differ from the higher animals so much in the structure of the receptors and nerves as in the complexity of our brains. So far as the impulses have been traced, through the receptors and nerves, there is a great similarity between ourselves and the other animals, and it is only reasonable to believe that a similar mechanism is involved and that electrical impulses with similar properties are the first product of the stimulus in ourselves. If we attempt to go further, differences are immediately evident. We never experience a pure sensation, for all our thoughts and feelings are coloured by previous experience and by associations which come involuntarily to the mind. Animals, however, lack the intricate association centres possessed by us, and arguing from anatomical differences their perceptions must be much simpler and approach nearer to the pure sensation. There is in animals only a rudimentary apparatus to collect the information forthcoming from all the senses at once, to integrate it and turn it into a useful perceptual pattern of the environment. There is a greater use of the senses individually, but it is all a question of degree. The baby chick takes or makes its first peck by instinct, but that first peck makes an impression on the cortex of the chick's brain, and the second and subsequent pecks are modified by the experience gained in the first peck. Similarly, the first smell or taste of a young animal will make an impression on its brain cortex and this will modify all subsequent smells and tastes. The second taste will make another impression and so on, so that the complexity of a sensation increases rapidly as the animal goes through life and the sensation for the same stimulus will greatly change as the influence of past experience and associations affect and ultimately overwhelm and obliterate the elementary reaction to a given stimulus. We know ourselves that odours associated with unhappy experiences are unwelcome to us and that we do our best to avoid them or even avoid noticing them if we can, even although these same odours are generally considered pleasant by mankind and indeed were once appreciated by us individually. The same can happen in the reverse direction, and an unpleasant taste or smell may be welcome by its association with a happy past experience. The writer when a boy was recovering from an illness and had a meal outside on a fine bright day. One of the dishes was vegetable marrow which was badly burnt and unpalatable, but to avoid any suggestion of lack of appreciation was eaten. Since then vegetable marrow, especially if a little burnt piece can be tasted, has brought forward a vivid impression of the sunlit garden and of the happiness of returning health.

The cardinal difficulty of the study of mental appreciation is that at every step we have to argue back from our own consciousness.

Perception is a phenomenon of consciousness, and all our knowledge must be derived from human experience. Consciousness implies a conscious subject and an object of which the subject is conscious. Our sensations are facts to be reckoned with and supply all the material on which our mental activities are based. Even higher mental activities of reflection and contemplation are founded on experience forwarded by the end-receptors, what has been heard, seen, felt, tasted or smelled.

We are able to localize a sensation in our consciousness by the number of nerve fibres serving the part irritated. Sensory touch spots are few in the small of the back, and we cannot be sure whether two separate points or only one are being touched unless they are an inch or more apart. On the fingers touch spots are crowded, and we are conscious of separate touches very close together. Such sensitive spots are closer still on the tongue, so that everything in the mouth, such as the movement of a loose tooth, feels about twice as big as it really is by mental reference to finger touch.

Division of the nerve fibres to any particular area deprives that area of touch-temperature differences and pain, but not of deep pressure and deep-seated pain, as these are served by separate receptors not on the periphery.

On the other hand, observations on the effects of damage or disease to the brain show that the losses are not of temperature differences, but those of the higher integrations and of deep-seated pressure differences which help the maintenance of bodily posture.

Stimulation of the receptors of a primitive animal caused an awareness of a change in the environment—pleasant or unpleasant—and the animal responded to or away from the change. This is consciousness on the reflex plane. The next development is to consciousness on the plane of instinct. Awareness develops into attention and later to interest, whilst different sensory presentations are linked and correlated, although still very imperfectly, into perception with more meaning than on the reflex plane and such perception causes instinctive responses, the motor activity of consciousness on the plane of instinct. By further development memory and conscious association and ideation develop and we reach the plane of intelligence. We distinguish reflex from instinctive and both from intelligent responses, but there are no sharp divisions, no sudden emergence of an entirely new feature. There has been gradual growth from the elementary protozoan comfort or discomfort, and all intermediate stages exist between that crude discrimination and our own mental development.

At the level of reflex consciousness it is the primitive tactile-chemical receptors which exert the predominating influence, and at the level of instinct it is still the interoceptors which are most used, taste, touch and the chemical sense and not so much vision. Smell, however, is very important at the level of instinct. Physical pleasure or pain can hardly be said to accompany the reactions from distance receptors. A sight, however disturbing, does not set up physical pain, and the

pleasure experienced by vision is on a higher level than that experienced through taste and touch. Vision is the preponderant sense on the plane of intelligence. At the instinctive level the greatest physical pleasure is felt in the act of coitus, whilst a warm bath brings pleasure on a similar level of consciousness. As evolution advances the sharpness and clarity of consciousness increases. The first *perceptions brutes* and " blooming buzzing confusions " are separated into their components and this analysis gives clearer definition of sensations. The next development is the correlation of these clarified sensations into a whole—a perceptual pattern to which memory and mental association also contribute. Many accessory factors are involved in the formation of a perceptual pattern in a higher animal and many of them are not yet understood. There is little certainty about the conscious accompaniments of sensory phenomena in animals,

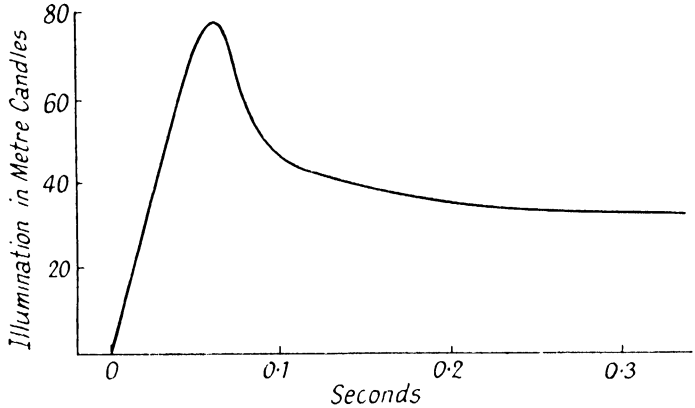


FIG. 15.—Type of curve obtained by Broca and Sulzer, showing the response to a flash of light. Sensation quickly reaches a maximum, falls off steeply at first then more slowly.

and we have to classify their senses by their receptors and not on a psychological basis as we classify our own.

It is the distance receptor, the power of vision which has given man supremacy over the animals. The erect position has been of enormous help in developing the field of vision, whilst the animal with his nose to the ground still has a limited field of vision and a highly developed sense of smell. The proficient sense of vision not only informs man of his immediate but also of his distant environment and enlarges enormously his field of consciousness. As a result he can anticipate future changes in environment, and anticipation is the source of reasoning and the higher thought processes. Without the erect posture reflective thought and intelligence as we understand them could scarcely have developed.

The close relation between the behaviour of nerve impulses and consciousness should be pointed out. Adrian suggests that other

things being equal and the attention not distracted the intensity of sensation will be proportional to the frequency of the impulses, but in view of the powerful influence of the association and memory centres of the brain, it is unlikely that we can ever experience a sensation sufficiently simple or isolated to follow such a simple proportionality. At the same time such a relation in a general sense exists. Broca and Sulzar studied the sensation caused by a flash of light, and found that, plotted against time, it gave curves which showed first a quiescent period then a sharp rise to maximum intensity, followed by a sharp and then a gradual decline, curves which duplicate all the features of those obtained by measuring the electrical impulse from the retina of the eel's eye. Fig. 15 shows the type of curve obtained by Broca and Sulzar. There is therefore a close correspondence between the electrical impulse discharge and the sensation of which we are conscious. Fig. 16, based on a similar diagram in Adrian's "The Basis of Sensation," shows how the steady stimulus changes to a gradually reduced excitatory process in the receptors and then to a discontinuous series of impulses in the nerve fibre and finally to a continuous gradually waning sensation, due to the integrating and correlating action of the synapses and central system.

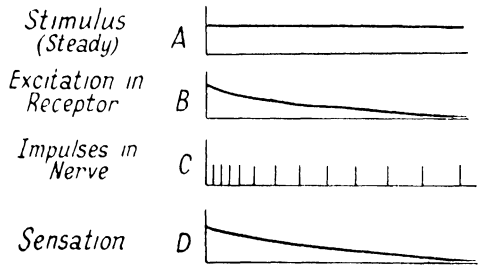


FIG. 16.—Relation between stimulus A, sensory message B and C and sensation D (after Adrian).

Integration

If we attempted to value the contents of a draper's shop by a comprehensive look round, little confidence could be placed on our conclusion. To secure a reliable estimate we first divide the stock into similar articles, count and price each kind separately and add the lot together. The process is one of differentiation followed by integration with memory associations included in the integration, represented by price in the above analogy. It is the same with our perceptions. We stand on a cliff top and admire the view, the sea crashing on rocks below, the odour of seaweed, the taste of salt in the air, the cry of the gulls and the roar of the breakers, and enjoy the wind freshening the skin. At the same time we maintain our balance, and keep a careful eye on our distance from the cliff edge. We do all this without any conscious effort of differentiation and integration, but the processes are nevertheless in operation. The final result may be no better defined than a general feeling of well-being and pleasure, but to attain this all the sense receptors have been brought into

action scanning the scene in all directions and sending hundreds of thousands of impulses racing up to the brain at 200 miles an hour. The central system has smoothed these and integrated all the impulses from the olfactory nerve to excite the sensation of seaweed odour, and the impulses from the gustatory nerves for the salt taste, from the retina for the picture, and from the ear for the sounds, as well as the touch from the exposed areas of skin. At the same time it has received messages from the equilibrium apparatus in the labyrinth, and has correlated this with the stereoscopic vision from the eyes and the position of the limbs from the proprioceptors to ensure balance and avoid undue proximity to the cliff edge. Then some higher centre has taken all these integrations and correlated the lot into a perceptual pattern of safety, well-being and pleasure. The processes of differentiation have already been examined in this chapter, but those of integration are not yet well understood. Much work has been carried out and information gained by anatomical analysis. Examination has been made of nerve paths and bands of association, and also of the effects of disease and injuries to the brain and cord. In the case of animals, mutilation experiments have been made where the removal or damage of some part of the animal's central system is effected and the changes in behaviour noted. As an example of the last, a grasshopper from which the brain is removed is much more active than a normal one, and from other sources, too, we know that one of the brain's chief functions is to inhibit undesirable or wasteful activity. The use of alcohol depresses these inhibiting instincts and results in increased activity of a type which might normally be suppressed.

The first smoothing or rectification of the nervous messages from high frequency discrete impulses to low frequency continuous currents takes place at the synapses.

Sensory nerve fibres do not pass directly into the central system as motor fibres do, but form small ganglia or swellings just before entrance to the central system. These ganglia throw out fibres which join up with others but the connection is not a continuous one. It is made through a valve or synapse which has a variable resistance. It is supposed that the rectification of the high frequency nervous impulses takes place at the synapse, where "vibration becomes sensation, and dead becomes alive." The synapses offer considerable resistance to the impulses, and if there are many in the path of an impulse then the response is slow, as in vision. In the case of olfaction the ganglia or swelling is not found, but the cell has either migrated into the brain or else is represented by the olfactory cell in the epithelium. If the latter is the case the condition is similar to that of the invertebrates, and as Parker has pointed out the olfactory epithelium may be a relic of our invertebrate ancestors, unchanged through time.

As the synapses and central system rectify the nervous impulses or integrate them into sensation, we should expect the sensation to be a close correlate of the physical conditions in the nerve, seen in

the manner suggested by Fig. 16. Mental associations will be developed over a large area of the cortex and the higher centres will integrate with these the messages from the different sense organs into one perceptual pattern to which all the senses contribute. All experience is felt against a background largely made up of immediately prior sensations and of generally neutral tone. All experience is of change. Without change there is, on account of adaptation, no sensation, and without the sensory messages the brain would be idle.

The background, against which we feel experience, is affected by the bodily tone and the messages from the proprioceptors. The sensation from smelling a rose would not be very pleasurable if we were hungry or thirsty, and in some circumstances hunger will overcome taste prejudices. Similarly, the background is liable to emotional disturbances which may completely stop the flow of ideation and appreciation. The correlate of the sensations is finally pleasure or its antithesis which is not pain but disgust. Pleasure is largely the satisfaction derived from something accomplished, posture regained, the act of coitus, distance covered, a movement understood, an escape, a kill, something eaten or drunk, but there are also pleasant tastes and smells, and if many of these are pleasant by associations with the thought of food others, like the scent of a flower, seem to give purely æsthetic enjoyment without practical or useful association. The same may be said of tickling which clearly gives pleasure to a young child. Disgust has a duty to perform. If material unsuitable for food is taken hurriedly without consulting the nose and tongue, then nausea or disgust will ensue and the body will vomit the material. Some protozoa regularly engulf alike suitable and unsuitable material particles and subsequently reject the unsuitable. Mind has evolved with structure, but in moments of crisis there still arises in the mind an urgent primitive tropism—to or away from.

The gap between pricking a finger and feeling the sensation of pain still lies before us. The rectified nervous impulses may constitute the sensation in the eyes of the materialist whilst from the other point of view the nervous impulses may exist only in thought. But we have to reckon with our sensations, and their absolute identity with nervous impulses is not readily accepted by our minds. Usually the truth is clear and simple, and that which is difficult and confused later proves to have been untrue. The likelihood is that great progress will be made in the next few centuries in developing our understanding of the growth of sensation from stimulus. The knowledge gained by investigation to the present has shown the immensity of the field before us.

Olfactory Memory

As a subject to illustrate the powers of association in the mind nothing could be better than the sense of olfaction. The experience is familiar to all of a perfume perceived quite inattentively, bringing back to the mind a vivid picture of the past. Usually, I think, it is

of some scene of our youth, for the mind seems to lose as it grows older its impressionable nature, and whilst odours and scenes may still be associated, the scenes are not recalled with the same vividness and clarity as those of youth. In my own case the smells of sweetbriar, and of the carpet of needles under pine trees take me back unfailingly to my grandfather's garden which I was last in at the age of seven, whilst the smell of strawberries takes my father back to the fields at Blairgowrie where as a boy he picked the fruit. Similarly, when he gets the smell of a moss-rose, he at once pictures an old gate behind which was a moss-rose tree, of which he got the scent each time he passed through. That gate was at Croft House, Methven, which he left when seven or eight years old. Sixty years later, the scent recalls the scene wonderfully clearly.

An odour brings back a forgotten scene to the mind as nothing else will, especially if it comes on you unawares.

Olfactory associations are very powerful and Kenneth (*Perf. Essent. Oil Record*, **19**, 15) analysed many of them. He used 63 people, of whom 29 were men and 34 women for his tests, whilst the 26 odorivectors or osmyls were as follows: amyl acetate, amyl alcohol, asafœtida, benzol, butyric acid, camphor, carbon bisulphide, cassia oil, cedarwood oil, citronella oil, clove oil, ethyl alcohol, eucalyptus oil, lavender oil, menthol, musk, origanum oil, orris root, pine oil, otto of roses, sandalwood oil, terebene, Tonka bean, ferric valerian, vanillin and xylol. This, it may be remarked, is a good representative selection, and includes all varieties from otto of roses to carbon bisulphide which is perfectly foul. Kenneth points out that whereas discrimination between odours is largely a matter of training (cf. the "chemist's nose" in Chapter 1), associations of odours with other phenomena are natural, and the reflex paths for affective reactions to olfactory stimuli are present in the human fœtus. He found that certain odours had a greater appeal to one sex than the other, thus camphor, menthol, citronella oil and ferric valerian were preferred by women, whilst cedarwood oil, pine oil, musk and Tonka bean were preferred by men. Whilst the sense of smell after puberty is generally more acute in women than men, the greater use of tobacco and alcohol by men contributes to this. However, owing to their greater acumen women found fewer pleasant smells than men. Typical reactions on smelling the osmyls were

Ethyl alcohol	(1) A desire to attend Communion.
	(2) A desire to avoid alcoholic drinks.
Musk	(1) Persons of the opposite sex.
	(2) Incense of a French cathedral.
	(3) Botany lessons.
	(4) Immoral.
Menthol	(1) Headache.
	(2) Bottle of smelling salts.

Pine oil	(1) Turpentine.
	(2) Norway.
	(3) Good.
Vanillin	(1) Tennyson (via drowsiness and the Lotus Eaters).

He divided the reactions into six groups :

Synæsthetic Reactions, such as auditory and gustatory.
Contracted Reactions, such as pine oil—turpentine, and cedarwood oil—pencil.
Expanded Reactions, such as pine oil—Norway, amyl acetate—village sweet shop, and rose oil—garden.
Indirect Reactions, such as vanillin—Tennyson.
Egocentric Reactions, such as rose—soothing, and musk—immoral.
Doubtful Reactions.

Many of the associated reactions gave very vivid mental images of home, school, etc. Odours like amyl acetate (pear drops), ethyl alcohol and vanillin evoked a larger proportion of contracted reactions, the very simple kind, than did the more subtle odours of cedarwood, pine oil and camphor. With 53 persons and 26 odorivectors the possible number of reactions was 1,378, and it is recorded that of the 1,296 associative reactions almost 30 per cent. were of the expanded type. The conclusion is that many factors are involved, such as concentration and chemical stability of the odorivectors and the health and sex of the subject.

Whilst the olfactory sense restores mental images with great clarity, the reverse process of trying to recall an odour is not easy. It is easy to recall a visual image as we have geometrical qualities and colour differences as points of reference, whilst many people recall auditory impressions such as a song or melody with great facility, but for the senses of taste and smell we have usually to call up the visual image first. In the case of food it seems almost impossible to avoid recalling the visual image. With other substances with which a person may be familiar, such as alcohol, ether and chloroform, it is possible to will the brain processes which call up the sensation of their quite different odours, although all three are water-white liquids and there are no perceptible points of reference. Possibly the mental impressions that the smell of ether is usually strong because of its volatility, and that chloroform is sickly assist in this process, but at least the associations are more remote and it requires a conscious effort to recall an odour.

Ribot found that people vary in their ability to recall perfumes and estimated that 12 per cent. could recall most perfumes at will, and 40 per cent. could not recall any by an effort of will, the balance having intermediate standards of ability in this respect.

Unlike Reactions

As an example of the different sensations within the modality of smell, which the same stimulus can set up in different subjects, may

be mentioned " Unlike Reactions of Different Individuals to Fragrance in Verbena Flowers " (Blakeslee, *Science*, **48,** 288, 1918). Two kinds of verbena were used, a pale pink which smelt like arbutus to Blakeslee but had no pronounced smell for his assistant, and a red flower which was odourless to Blakeslee but fragrant to his assistant, who thought it like a carnation in smell. It is to be noted that both workers were familiar with the odours of arbutus and carnation apart from the verbena flowers. Blakeslee repeated the tests on a number of other people. He found that 17 men preferred the pale pink and 9 men the red, whilst 9 women preferred the pale pink and 4 the red, and again confirming the superior keenness of olfaction in women, 2 women found both flowers fragrant. The tests were made with the eyes closed. Blakeslee reports that there was an amusing uniformity in the reactions of his subjects. The subject would generally say he feared he was not smelling well that day, would then blow his nose and almost at once pick out either the pink or the red and wonder how anyone could think the other fragrant.

As regards the pleasure or disgust aroused by the sensations of odour and taste, these are usually sharply defined and leave little room for doubt. A taste may, however, be complex; thus saccharin has a powerful sweet taste which in suitable dilution is unmistakably pleasant, but it also has an unpleasant after-taste. Disgusting would be too severe a term, but the same substance under one set of conditions arouses the perception of both pleasure and " unpleasure." Also the effect of dilution on such bodies as indole and civet is well known, for they are disgusting when concentrated and delightful in dilution. Another case in point is triethyl phosphine, which has a stupefying odour when concentrated but a pleasant hyacinth smell when diluted. It would be interesting to explore the sensations evoked by these substances at intermediate concentrations where pleasure merges into unpleasure, but it is more likely we should find not that they merged into each other but that they overlapped. It will be seen how difficult it is to predict the æsthetic reaction to a given substance. Not only does it depend on the intrinsic odour properties of the substance but also on its concentration and on the sex and physical properties of the subject who will smell it.

CHAPTER 4

OLFACTION

Respiration

We smell as we breathe, but normal breathing is not very conducive to good olfaction. We become dimly aware of some odorous substance in the atmosphere and instinctively we sniff and then experience the full sensation of olfaction. Ordinarily as we breathe, the air passes round the turbinates and is warmed by the vascular material of which the lower part of the nose is composed, and finds its way to the posterior nares along a fairly low road, but in order to reach the olfactory cleft and cause smell the air must take the high road through the olfactory region. In the ordinary way it does not, in bulk, pass higher than the middle turbinate, but there are always eddy currents when air passes through such an involved labyrinth as the interior of the nose, and some of these eddy currents reach the olfactory region and induce faint olfaction. The signal given, the sniff is taken and the bulk of the air drawn through the olfactory region and the sensation experienced adequately.

Paulsen in 1882 sawed through the head of a dead person near the median plane and put red litmus in different parts of the nasal cavities. He then put the two halves of the head together and blew ammonia through the nose. He then took the two halves apart and by observing in which parts the litmus had turned blue he inferred the course of the air. He found that whilst the air ascended and reached a peak in the middle of the nasal cavity from which it then fell to the posterior nares, the height of the peak was considerably lower than that of the olfactory cleft. He also found that when the air was blown in the reverse direction, i.e. from the throat to the nostrils, it took a similar but lower path, so that in neither inspiration nor expiration did the air approach the olfactory cleft. Franke in 1893, using a similar method with a current of smoke, showed that whilst the path of the air was generally low, eddy currents did exist. Kayser, 1890 (*Zeitschr. Ohrenheilk*, Bd. **20,** 96-109) adopted a more natural method in which he caused light magnesia powder to be inspired by a sleeping person and then examined the distribution of the magnesia on the nasal cavities by means of a rhinoscope. He confirmed Paulsen's conclusions. There seems no doubt that ordinarily during breathing the air reaches the olfactory region by means of eddy currents. Zwaardemaker had suggested that diffusion might be the mechanism, but this process is too slow to account for the rapid perception of odour we normally experience. Zwaardemaker also showed (*Arch. néerl. Physiol.*, **1,** 347-73, 1917) that odorous substances tend to condense moisture from the air, and the moisture condensing on the nasal cavities helps perception of odour. The

physical significance of the condensation will be considered in a later chapter.

It had earlier been suggested that olfaction only occurred when air was breathed in and not when it was breathed out, but this is not true as is easily seen by breathing in through the mouth and out through the nose when olfaction will be experienced. Owing to the lower path of the outward air odour is usually noticed during inspiration, but the many odours of food are mostly experienced through the vapours finding their way from the mouth and throat to the olfactory region during expiration.

During normal respiration through the nose the air takes the path which is most richly provided with a blood supply, and is warmed so that it reaches the lungs at a temperature of about 70° F. with a variable quantity of water vapour, but it is expired at body temperature 98·5° F. and is then saturated with water vapour. From a consideration of the temperature and humidity of the air, expired air would be expected to promote olfaction better than inspired air. It may be of interest later to note here the chemical constitution of the air by volume:

	Inspired.	*Expired.*
Oxygen	20·96 per cent.	16·02 per cent.
Nitrogen	79·00 ,,	79·00 ,,
Carbon dioxide	0·04 ,,	4·38 ,,
Water	Variable	Saturated
Inert gases	Trace	Trace

The loss in the expired air is due to absorption by the body.

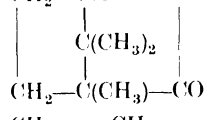
The mechanism of the sniff was investigated by Ogle (*Medico-Chirurgical Transactions*, **53,** 263-90, 1870), who considered that the action is to bring together by lateral compression the outer wall and the septum opposite to the respiratory channel, so closing the usual respiratory path and forcing the air through the olfactory channel. He instanced a case of a man suffering from double facial palsy, complete on the left side and nearly complete on the right side. This subject also complained of loss of smell, and with the left nostril he could hardly smell the strongest odours but was a little better with the right nostril. He still retained the perception of flavours, and Ogle concluded that the defect lay not in the olfactory apparatus but in the inability due to the palsy to contract the muscles for a sniff. In another case described by Ogle a woman had inflammation of the Schneiderian membrane of the nose which had thickened so that it obstructed the ingress of air through the nostrils, since the nasal septum was in contact with the middle turbinated bone. Air could, however, be expelled through the nose so the thickened membrane evidently in this case exerted a valve action. On putting odoriferous substances under the subject's nose she could not smell them, although tactile and common chemical sensibility, e.g. to smelling salts, were

normal. Also as air could be expelled through the nose she was cognizant of flavours.

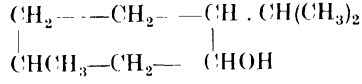
In other cases where the soft palate adheres to the posterior wall of the pharynx all communication between the mouth and the nasal cavity is cut off, and then all power of smelling through the nostrils is gone and also of perception of flavour through the posterior nares. When communication is re-established by surgery both smell and flavour return. In these cases the loss of the power of smell was due to the normal respiratory paths being obstructed. Such a state of affairs is a temporary disability that almost everyone experiences if he has a common cold or catarrhal affection. In this connection it is worthy of note that the most usual reliefs are themselves powerful odorivectors: ammonia, camphor, menthol, eucalyptus and thymol. Possibly their function is to induce a rapid flow of mucus which will soften the thickened and hardened mucus obstructing the respiratory and olfactory channels.

As long ago as 1673 in his essay on "The Great Efficacy of Effluviums," Robert Boyle pointed out that "Spirit of *Sal Armoniack*" gave effluvia that would open the nasal passages when clogged with "a great cold." There is a similarity about the chemical composition of these strong smelling reliefs we use for a cold. Their formulæ illustrate this:

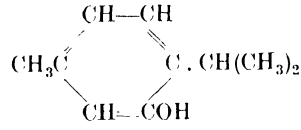
Camphor.



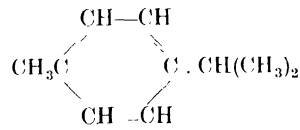
Menthol.



Thymol.



Eucalyptus is a source of Cymene which is



The common feature of two methyl groups attached to the same carbon atom $\diagdown C(CH_3)_2 \diagup$ and the presence in the structure of a third methyl group is rather striking.

The Stimulus

There is a school of thought which believes that olfaction like hearing is due to a wave motion in the atmosphere, but the general

belief is that material particles of the odorous substance must come into contact with the olfactory region to promote olfaction. The wave theory will be examined in a later chapter as it has no place here, for if olfaction is due to wave motion that is likely to be the end of the matter until the waves have been detected and measured, which has not yet happened. Let us, instead, adopt the popular view that particles of the odorant must make contact with the olfactory region. This presents no difficulty to the imagination in the case of such volatile liquids as benzene, toluene, or ether, or even with volatile solids like naphthalene and camphor. But a grain or two of a powerful odorivector like musk will scent a room for years without apparent loss of weight. Robert Boyle, in his essay on " The Strange Subtilty of Effluviums," points out that weighed amounts of ambergris, asafœtida, nutmegs, and cloves suspended in the air for days lost either nothing or only a minute fraction of their weight though they continually emitted odours, and cloves had retained their scent for thirty years. Where then do the odorous molecules which activate the nose come from ? The usual answer is that even unweighable quantities of musk contain millions of molecules, and only the relatively small number of molecules necessary to form a surface layer on a small part of the interior of the nose are necessary to cause smell, and further, that the loss in weight of the musk can be detected over a long period. To the author it seems a questionable argument, but it is the general view, so let us accept it for the time and see where it leads us.

It is clear from the way odour travels with the wind and is perceived by respiration that the stimulus is air-borne. Now if the stimulus consists of material particles these presumably cause chemical change when they come in contact with the olfactory hairs or the mucous lining of the olfactory cells. It will be remembered that the hairs pass through the lining of the cells and project beyond it. Now chemical change may proceed in the solid state and in various cases of polymerization is well known to do so. On the other hand, such behaviour is exceptional, and mostly, chemical action takes place in solution or in the melt or in the gaseous phase. The melt can be ruled out at once as such substances as naphthalene melt only at temperatures much higher than that of the body. Chemical reaction between two solids is unusual, so we are left with (1) chemical action in solution, or (2) the action of a gas on a solid, the latter being the nose. If the latter were the case and the vaporized particles, or molecules, of the odorivector formed a layer on the olfactory region, so long as that layer was present, olfaction would be experienced, but we know from experience that the smell of a scent is evanescent. Hence the layer must disappear into the bulk of the tissues, and this could come about either by chemical combination or by solution. Now it is a fact that very many odorous substances are chemically reactive but some are not. I think benzene could fairly be described as a stable substance and usually needs severe conditions to make it react, but it

has a distinctive and powerful odour. Paraffins also, which are very unreactive, are odorous. By a process of elimination we conclude that the surface film of odorivector is removed by solution. By solution in what ? Is water solubility necessary to enable the odorous molecules to penetrate the mucous lining, or do the olfactory hairs projecting through this lining render this unnecessary ? They, themselves, may have a thin mucous film over them rendering water solubility advantageous for olfaction. Then if the surface film is to dissolve in the tissues of the olfactory region it must be soluble in fatty or oily substances, or as it is expressed, it must have lipoid solubility. Another explanation of the phenomenon of evanescence which might be put forward is that the surface layer forms and excites olfaction temporarily and then adaptation rapidly sets in ; another sniff is taken, fresh receptors go into action, olfaction is resumed, and as for the surface layer it is slowly washed away by the mucus. However, the former theory leads to the view that water and lipoid solubility might both be advantageous in producing olfaction. Backman (*Physiol. Abstracts*, **2,** 479, 1917) investigated this matter and concluded that both aqueous and lipoid solubility were in fact necessary for a substance to be odorous. It will be remembered that many substances, commonly thought of as immiscible with water, such as ether and benzene, have in fact appreciable although limited solubilities. Backman instanced the homologous series of aliphatic alcohols. Methyl and ethyl alcohol are readily soluble in water but have a low solubility in fatty substances and are therefore only faintly odorous, whilst on the other hand a higher member, cetyl alcohol, although soluble in fats is insoluble in water and therefore odourless. Intermediate members such as butanol are soluble in both water and fats and have powerful odours. Such considerations must be confined to a series of similar substances, otherwise chemical differences will outweigh solubility properties. Acetone, for example, has a low lipoid solubility but a powerful odour.

If the mechanism of olfaction was accompanied by solution of the odorivector, it might be thought that to present to the nose an already prepared solution would be helpful. Such, however, is not the case, and this may be considered damaging to the solution theory. Although fishes smell the substances in solution, man requires the stimulus to be carried in the air. Weber (*Arch. Anat. Physiol.*, 1847, 342-56) was unable to recognize the smell of eau-de-Cologne when he poured a solution of it into his nostrils, but Aronsohn (1884) showed that cold water damaged the olfactory hairs and destroyed the sense of smell. He used physiological salt solution at body temperature instead of cold water and then recognized the smell of clove oil from a solution of it. Next, Veress (*Arch. ges. Physiol.*, Bd. **95,** 365-408, 1903) maintained that it was very difficult to fill the olfactory cleft with liquid, and that Aronsohn had in fact smelled the vapour of the clove oil, the solution not having penetrated to the olfactory region. He (Veress) practised on a cadaver and found a way of filling the

olfactory cleft, and he then found he experienced sensations of smell from aqueous solutions but quite different sensations from the proper odours. It will be seen that the subject has had its ups and downs, but without committing oneself one way or the other, it is a safe inference that to dissolve an odorous substance in water (or physiological salt solution) is not helpful to olfaction but quite the reverse.

The normal stimulus for olfaction then is not in solution, but is air-borne either as molecules or material particles or as pressure waves. There is some relation between solubility and odour, but then chemically reactive substances usually are soluble in a variety of solvents, and the connection is more probably between olfaction and the type of molecular arrangement which simultaneously confers reactivity and solubility.

Abnormal Stimuli

The normal olfactory stimulus is contained in the air which has been in contact with odorous matter. The solutions of odorous matter used by Veress which gave rise to unusual odours are abnormal. An electric current produces vague odour sensations and is an abnormal stimulus. Aronsohn, for example, filled the olfactory tract with physiological salt solution and passed a weak electric current and reported vague olfactory sensations. Allen and Weinberg tried to measure the critical frequency of smell by applying through long electrodes in the nostrils a rapidly interrupted current, and stated that a distinct sensation was experienced although measurements could not be made on account of sneezing. This violent reflex suggests that the action may have been on the trigeminal nerve and a chemical sense response in the case of Aronsohn as well as of Allen and Weinberg. On the other hand, since electric currents are commonly used to stimulate touch and taste receptors, there is a likelihood that they are also effective on the olfactory receptors.

A third type of abnormal stimulus is the injection of certain chemicals in the blood stream which is stated (cf. Maybee, *Canadian Chemistry and Process Industries*, **23,** 115, 1939) to give characteristic sensations of smell immediately.

A fourth type is the smell experienced by suggestion or in dreams or hallucinations. Whether the gentle odours are sensed in these circumstances I do not know, but cases of the smell of coal gas being imagined, or the smell of burning having been sensed in a dream or even awake without any good reason, may occur to the reader. In this type of abnormal stimulus the brain processes occur without adequate stimulation of the receptors.

A fifth type is the odour produced by ultra-violet light from a mercury vapour lamp. Bordier and Nogier (*Comptes Rendus*, **147,** 354-5, 1908) investigated this and failed to find ozone or oxides of nitrogen in the air through which the ultra-violet light had passed. They then substituted nitrogen and carbon dioxide successively for the air when ozone and oxides of nitrogen could not possibly be produced,

and they noticed the same odour which they attributed to free ions. Later, F. Fischer (*Ber.*, **42,** 2228-30, 1909) contended that they were wrong and that the odour was due to ozone which he detected. It is generally supposed that the odour noticed in the vicinity of electrical machines is due to the formation of ozone. It may not be generally known that ozone is extremely toxic to man.

Another phenomenon which has been thought to stimulate olfaction is that due to striking stones together. J. Piccard and A. Piccard (*Arch. sci. phys. nat.*, **25,** 425-9, 1908) investigated the peculiar odour often observed when two quartz pebbles are struck together, and came to the conclusion that it was due to the heat formed by the impact volatilizing surface impurities on the stones. Fleissner (*Z. angew. chem.*, **21,** 1845, 1908) confirmed this and by preparing artificial stones untouched by hand showed that no odour was given.

A similar case was investigated by Schwarz (*Central Min. Geol.*, **1913,** 660-5). Minerals, especially silicates, with hardness between 3·5 and 9 when rubbed give off empyreumatic odours similar to nitrogenous decomposition products. The cause was thought to be the decomposition of impurities by the heat of friction, but Schwarz found that on just warming the minerals no odour was evolved, hence the heat of friction could not have been the cause of the odour.

There is thus grave doubt as to the existence of an abnormal olfactory stimulus in these cases, but electrical phenomena are frequently stimuli to the olfactory receptors.

In this connection the application of various drugs such as cocaine and strychnine gives a brief period of hyperosmia—unusually keen olfaction—before inducing local anæsthesia.

Human Acumen

Animals with the nose close to the ground are sensible of smells we cannot detect. The sensibility appears to increase with the number of conchæ in the animal. Whilst three or four are normal for man, five and six are sometimes found, and in fact some individuals have such an acute sense of smell that they can distinguish by it the two sexes and even individuals amongst their friends, and still more remarkable they can even identify by smell the owner of clothing submitted to them. Whilst anatomical differences are responsible for such acumen, development of the sense by training is also possible. The normal individual cannot reach such heights as those specially gifted, but training will greatly improve his olfactory discrimination. A little practice with different flowers will convince the reader of this. Uncertainties at first encountered, usually to our surprise, soon disappear. Keen-scented animals are termed macrosmatic, and man ordinarily microsmatic. Doubtless our ancestors were macrosmatic, and some persons even to-day warrant this description.

Women are usually keener in their perception of smell than men, and this is rightly attributed to their greater abstinence from tobacco and alcohol. Another factor has been noted by Elsberg (*Arch. Neurol.*

Psychiat. Chicago, **37**, 223-36, 1937), namely that olfactory hyperacuity occurs just before and during the menstrual period. Apart from this Elsberg found in his determinations of the minimal identifiable odour (described later) that in healthy persons there is fairly uniform olfaction, the main differences being due to differences in the form of the nasal passages.

The sense of smell in man is enormously more acute than that of taste or the chemical sense, as is readily seen by comparing the minimum stimuli for the three senses.

Minimum Stimulus

By this is meant the quantity of matter which just, and only just, evokes the sensation. Ethyl alcohol is one of the relatively few substances which has odour, taste independent of the odour, and also is a stimulus for the common chemical sense and it affords an opportunity of comparing directly the sensibilities of the three senses. The lowest concentrations that can be smelled, tasted and chemically sensed are

0·44 per cent. wt./wt. in air for smell.
14 per cent. wt./wt. in water for taste.
25 per cent. wt./wt. in water for chemical sensation.

Hence smell is in the case of ethanol about 30 times as delicate as taste and about 60 times as delicate as the common chemical sense. The high figure of 14 per cent. as the minimum for taste may seem surprising when it is recalled that beer has only about 4 or 5 per cent. of ethanol in it, and the explanation is of course that the taste of beer is not due to the alcohol but to the flavouring materials added, euphemistically let us say hops, and also that what normally passes for taste is largely odour perceived by the nose during exhalation of air from the throat, where it picks up the warm fumes of the beverage.

Ethanol, however, is relatively weak in odour and taste. Bitter substances are the most effective stimuli for taste, and strychnine hydrochloride is one of the most effective of all, being detectable in 0·00004 per cent. solution in water, i.e. 4×10^{-5} per cent. Now let us consider a powerful odorivector, say chlorphenol. This is just perceptible when 1 mg. is dispersed in a room of 230 cu. metres volume according to Fischer and Penzoldt, and the concentration may be arrived at as follows :

22·4 litres of air weighs approx. 29 gm.
or 0·0224 cu. metres air weighs approx. 29 gm.
so 230 cu. metres air weighs approx. 30×10^4 gm.

Hence the concentration of 1 mg. chlorphenol in 230 cu. metres air is

$$\frac{1}{30 \times 10^4 \times 10^3} \text{ or } 3 \times 10^{-9} \text{ wt./wt. or } 3 \times 10^{-7} \text{ per cent. wt./wt.}$$

Hence the wt./wt. concentration of chlorphenol which can just be detected by smell is 3×10^{-7} per cent., whilst the concentration of

strychnine hydrochloride in water which can just be detected by taste is 4×10^{-5} per cent. so that the sense of smell is 100 times as sensitive as that of taste in this instance. Fischer and Penzoldt (*Sitzb. phys.-med. Soc. Erlangen*, **18,** 7-10, 1886) also investigated the power of ethyl mercaptan and found that this could be detected when 0·01 mg. was dispersed in a room of 230 cu. metres capacity, so that then the concentration was 3×10^{-9} per cent. wt./wt., which is 10,000 times more dilute than the taste threshold solution of strychnine hydrochloride.

It may be remarked here what a powerful influence the sulphur atom in the mercaptan has on its smell. Ethyl alcohol C_2H_5OH is only perceptible in air in a concentration of 0·4 per cent. wt./wt., whilst ethyl mercaptan C_2H_5SH is perceptible as $0{\cdot}3 \times 10^{-8}$ per cent. wt./wt., or one hundred million times more delicate.

The threshold concentration to which reference was made above is the minimum concentration for any particular substance which just arouses sensation. It is, I think, a most remarkable feature of olfaction that it will respond to substances so widely different in power as alcohol and mercaptan in so effortless a manner.

By taking in one case strychnine hydrochloride, nearly the most powerfully sapid substance known, and in the other case mercaptan, one of the most powerfully odorous substances, and comparing their weight/weight threshold concentrations we have deduced that odour is 10,000 times as sensitive as taste, both working under most favourable conditions. In one case the solution is in air, in the other case water, and I think this gives the most realistic picture as we need quite a considerable volume of the odorous air, say 20 c.c., to take a satisfactory sniff, and this weighs 0·026 gm., whilst in tasting a sapid liquid we can do quite well with 0·05 c.c., weighing 0·05 gm., which is of the same order as the weight of the air we need for a sniff. Therefore the weight/weight basis is the most logical for comparison.

Sometimes, however, one comes across the concentration expressed as molar, i.e. number of gram molecules in a litre of diluent (or more properly solution, but the concentrations we are discussing are so low that the difference is insignificant), and no account is taken of whether the diluent is air or water. Then our solution of mercaptan, of which 0·01 mg. is perceptible in 230 cu. metres is $\frac{0{\cdot}01}{230 \times 10^3 \times 10^3 \times 62}$ molar, or 7×10^{-13} molar. Strychnine hydrochloride is just sapid with 0·0004 gm. dissolved in 1 litre of water, and since the molecular weight of strychnine hydrochloride $C_{21}H_{22}N_2O_2 \cdot HCl \cdot 2H_2O$ is 406·7 this is about 1×10^{-6} molar. The conclusion is drawn that smell is of the order of 10^6 or 10^7 times as sensitive as taste, but this is an unreal comparison as it takes no account of the much greater volume required for a sniff than for a taste. Allowing for this difference, say 20 c.c. for smell and 0·05 c.c. for taste, we see that the relative sensitivities are about 10^4 or ten thousand to one.

In considering these relations it is useful to bear in mind that

whereas 1 litre of water weighs 1,000 gm. the same volume of air weighs 1·29 gm., so that water is about 777 times as heavy as air at normal temperature and pressure. Now " 777 " is an easy number to remember and it involves only a very small error.

The general opinion is that olfaction is due to the formation of a monomolecular layer on the olfactory region. How do we stand for the necessary number of molecules ?

Fischer and Penzoldt found that 0·01 mg. mercaptan is perceptible in 230 cu. metres of air. We know that the number of molecules in a gram molecule (the Avogadro number) is 6×10^{23}, hence the weight of one mercaptan molecule is

$$\frac{62}{6 \times 10^{23}} \text{ gm. or about } 1 \times 10^{-22} \text{ gm.}$$

or

$$1 \times 10^{-19} \text{ mg.,}$$

so that in 0·01 mg. mercaptan there are

$$1 \times 10^{17} \text{ molecules.}$$

Now this number of molecules, 1×10^{17}, were dispersed in a room of 230 cu. metres so that the number of mercaptan molecules in a 20 c.c. sniff would be

$$\frac{1 \times 10^{17} \times 20}{230 \times 10^{6}}, \text{ or say } 1 \times 10^{10} \text{ molecules mercaptan,}$$

and as the area of the olfactory region is about 1 sq. inch there would be linearly 10^5, i.e. a hundred thousand molecules per inch.

This is of the same order as the number of molecules per linear inch in a gas. Here we have 6×10^{23} molecules in 22·4 litres at N.T.P., or say 10^{24} molecules in 37 litres.

Taking the cube root we find there are

$$10^8 \text{ molecules linearly in 33·3 cm.}$$

or

$$8 \times 10^6 \text{ molecules linearly per inch.}$$

It will be seen, therefore, that a most powerful odorivector which has a very small minimum stimulus of only 1 molecule in 5×10^{10} molecules of air, would provide enough molecules even at such a great dilution to give a reasonable concentration of molecules on the olfactory epithelium, provided that all the odoriferous molecules in the 20 c.c. sniff were adsorbed as a surface layer by the olfactory epithelium. Unless some such selective mechanism as adsorption takes place it is difficult to imagine how one molecule of mercaptan in fifty thousand million molecules of air can make its presence felt. If the widely held theory of surface adsorption followed by solution is correct, then if a subject inspired air containing sufficient mercaptan (or other odorivector) to make it just odorous, and then exhaled the air down the nose, that air should have been deprived of most of its mercaptan and if collected and retested should no longer be odorous. In such a way it might be possible to test if there is a loss of odorivector, which loss is an essential feature of the solution theory. If the expired air

were still odorous then it would seem to be contrary to the " solution of odorivector in the lipoid tissues " theory.

Bach (*Gesundheits Ing.*, **60,** 222-5, 1937) describes a method after Henning of determining threshold values of odorous substances by evaporating a known quantity into a known volume of air and repeatedly diluting with an equal volume of pure air. A diagrammatic sketch of the apparatus used is given in Fig. 17. The gas in the second jar has one-half the concentration of that in the first, in the third

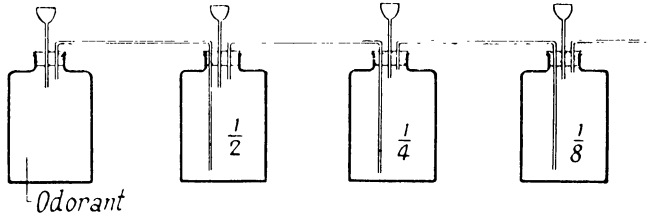


FIG. 17.—Dilution osmoscope.

one-quarter, in the seventh one sixty-fourth and so on. In this way by repeated dilution the following threshold values quoted by Bach were determined. The concentration is expressed in milligrams of substance per cubic metre of air and in the last column as weight/weight concentration, remembering that 1 cu. metre of air weighs 1250 gr. at usual room temperatures. The concentration is that which was barely odorous—the threshold value.

Odorivector.	Mg./cu. metre of Air	Concentration of Odorivector in Air wt /wt per cent.
Diethyl ether	0·75-1	7×10^{-5}
Chlorphenol	0·004	3×10^{-7}
Mercaptan	0·00004	3×10^{-9}
Synthetic musk	0·000005	4×10^{-10}
Natural musk	0·007	6×10^{-7}
Pyridine	0·04	3×10^{-6}
Skatol	0·0000004	3×10^{-11}
Butyric acid	0·001	8×10^{-8}
Iodoform	0·006	5×10^{-7}
Phenol	1·2	1×10^{-4}
Vanillin	0·0000002	2×10^{-11}

A hall 500 metres long by 100 metres wide and 50 metres high would be made unpleasant by one milligram of skatol. It will be noted that this dispersion is 100 times greater than that used by Fischer and Penzoldt in 1887 with mercaptan. It will be seen that the concentration of the odorant Pentalarm referred to in Chapter 1, where it was stated that " only three-fourths of a pound is required to odorize 1,000,000 cu. feet of gas so that a mixture of $\frac{1}{2}$ to 1 per cent. of the odorized gas in the air may be readily detected," is much higher than the

concentrations of minimum stimuli we have been considering, and the concentration of Pentalarm quoted corresponds to 0·06 mg. per cu. metre and is about one thousand times greater than the threshold stimulus for ethyl mercaptan. This is a deliberate provision on the part of the makers to ensure that any escaping gas which has been odorized with Pentalarm is readily detected. Such would not be the case if the threshold concentration was used. It may be noted that Katz and Talbert (*Chemical Abstracts*, **25,** 547, 1931) found the threshold value of trinitro tertiary butyl xylene (synthetic musk) to be 0·00005 part per million vol./vol., i.e. 5×10^{-8} per cent. wt./wt., one hundred times higher than that given in the table on page 80.

Passy (*Comp. rend. Soc. Biol. Paris*, **44,** 84-8, 239-43, 1892) made many measurements of the minimum stimuli and defined the "specific smell strength" of a substance as the reciprocal of the smallest amount of that substance in grams per litre which can be detected by odour. Passy also took the precaution of using several individuals for his tests.

Huyer, for a thesis at Utrecht in 1917 (*Physiol. Abstracts*, **3,** 109, 1918), made measurements in Zwaardemaker's apparatus and showed that the perceptible minima of aniline, *o*-, *m*- and *p*-toluidines, and xylidine ranged between 0·49 and $0·06 \times 10^{-6}$ gm. mol. per litre of air.

Elsberg (*Bull. neurol. Inst. N.Y.*, **4,** 544-5, 1936) noted that the threshold is lower when both nostrils are used than when only one is used. He was using his Blast Injection Method.

As regards the effect of temperature on threshold values, Morimura (*Tohoku J. Exp. Med.*, **22,** 417-18, 1934) made experiments with propionic acid, acetic acid, camphor, naphthalene and chloroform in a Hoffman and Kohlrausch olfactometer and decided that the lowest threshold values were between 25° and 30° C., and that an increase in temperature of 5° raised the threshold appreciably. This result is a little surprising. Woerdeman (*Arch. néerl. Physiol.*, **19,** 88-93, 1934) made experiments with students as subjects and showed that a perfume aroused a more intense sensation if warm than cold.

Man is microsmatic, yet how wonderful his sense of smell which detects quantities far beyond the limits of balances, microscopes, or other laboratory paraphernalia, with the possible exception of the spectroscope.

Examination of the literature shows that many discrepancies exist in "minimum stimulus" determinations, and this is not surprising when we consider the differences in olfactory sensitiveness between individuals, the prevalence of partial anosmia, the difficulties of measurement and, possibly most difficult of all, how to decide when a stimulus does become perceptible. The matter should be investigated with a group of substances similar to those used by Kenneth in his investigations of olfactory association, and with as many individual subjects as possible.

Nevertheless, the existing literature gives a positive impression of the extreme attenuation at which odorous substances are perceptible, and shows clearly that the sense of smell is much more sensitive than

that of taste or the chemical sense. Normal conceptions of weight and concentration are unsuitable for the minimum stimuli. They are equally well estimated in number of molecules as in grams.

Fatigue

Happiness is ephemeral. That which is just out of reach is the summit of desire. We strain every nerve and succeed in our quest. Happiness is ours—for the moment. The positive emotion of happiness fades to a neutral condition of content. To regain happiness something new is required, not necessarily on a higher level for we may fall far and by rising a little regain happiness, though we have much less to be pleased with than before the fall. Change is necessary, only change rouses the emotions. So with sensation, a steady stimulus yields only a brief nerve impulse and then nothing. Change is necessary to bring other receptors into play or to restore the nerves from their state of fatigue.

We smell a flower. The scent is enchanting but elusive. We draw nearer and smell harder, but the enchantment fades and soon we can no longer sense the perfume at all. After a short rest our sense of smell returns. This is a perfect example of the results of

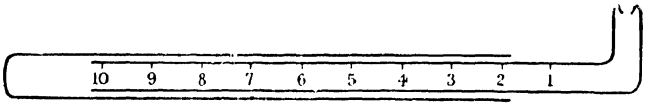


FIG. 18.—Zwaardemaker's olfactometer (graduated in olfacties).

Adaptation already discussed in relation to the nerve, the receptors and the stimulus. Fatigue is the result of Adaptation. Adaptation is the cause of Fatigue. If the stimulus is permanent the adaptation is also lasting and fatigue continues, so that sensibility to that particular stimulus is lost. An illustration of this obtains in the factory worker who becomes so accustomed to the unpleasant smell associated with his work, that he can no longer smell it. Fortunately for the rest of us most factory workers do not have an environment which causes the body to put on its sheath of adaptation. Delicacy is retained by avoiding persistent over-stimulation.

The first point to note about olfactory fatigue is that it ensues rapidly. Aronsohn in 1884 tested nine people and found that the smells of oil of lemon and oil of orange lasted from 2·5 to 11 minutes, averaging 3 minutes, and that a 0·2 per cent. solution of coumarin in water lasted for 1·7 to 2·3 minutes, so it is clear that a strong stimulus completely exhausts the receptors in two or three minutes. Aronsohn also noted that recovery from fatigue took place in about the same time (1 to 3 minutes).

The second point to note about olfactory fatigue is that it is gradual. The sensitiveness is gradually lost, so that as the time of exposure to

the olfactory stimulus increases, the minimum stimulus also increases, the threshold concentration advances. Zwaardemaker ("Die Physiologie des Geruchs," 1895) measured this with his olfactometer shown in Fig. 18. He found that concentrated solutions raise the minimum stimulus and bring fatigue and exhaustion more quickly than dilute solutions. With volatile substances such as benzene the effect was very rapid, the minimum stimulus increasing six-fold in 10 seconds, but with less-volatile rubber a similar increase required a full minute.

The third point about olfactory fatigue is that it is selective. A temporary anosmia or fatigue can rapidly be produced for a particular odour without the power to perceive other odours being appreciably affected. Aronsohn noted that fatigue, produced by smelling ammonium sulphide continuously, leaves the nose unresponsive to sulphuretted hydrogen, hydrochloric acid and bromine, but sensitive to ethereal oils. This example is not altogether satisfactory, as bromine and hydrochloric acid at any rate are irritants to the common chemical sense, and as Parker has noted there may be a differential effect between the olfactory endings and the trigeminal nerves. The writer has experimented with flowers, and has noted that after exhausting the nose with the smell of white clover, a bloom of red clover smells rather like turpentine, but that if the nose is first exhausted by smelling red clover then white clover has no smell. The inference is that red clover has an odorous constituent, missing in white clover, and the observation may be of interest if subsequently confirmed by other investigators and not due to personal idiosyncrasy.

Selective fatigue, discriminating between odours, implies the existence of more than one type or modality of odour. Just as there are four fundamental tastes, there may be several fundamental smells. How many there are could be determined by some modification of Allen and Weinberg's experiments on the critical frequency of taste.

Zwaardemaker has divided all smells into nine classes. It would be expected that substances in the same class would cause fatigue not only for themselves but for each other, but would not cause fatigue for substances in other classes. This, however, has not always proved to be so. Nagel took vanillin and coumarin which are both in the same class and subdivision of Zwaardemaker's classification. He exhausted his nose for vanillin and then smelled a mixture of the two and could smell only coumarin. The opposite method of classifying odours by the fatigue results has also not proved profitable. The point is important, as if it were found possible to classify odorivectors according to their mutual effects on fatigue, it would be a strong argument for the existence of different fundamental odour senses. It is not a very promising line of attack at present, as even with taste, where the four fundamentals are well defined, a stimulus for one taste usually has an influence on the other tastes in that their sensitivity is either enhanced or depressed, so with odour if different *component* types exist, it is almost certain that gross fatigue of one component, would cause abnormalities in the other components. The

most promising approach appears to be by critical frequency measurements, if the practical difficulties can be overcome.

In connection with the application of the critical frequency method to different sensations Kravkov (*Acta. ophthal. Kbm.*, **17,** 426-42, 1939) has found that if olfactory stimuli are applied to a subject whilst the critical flicker frequency for vision is being measured for different monochromatic lights during dark adaptation, the critical flicker frequency is changed. It is diminished for green rays and increased for red rays by the application of oil of bergamot, camphor and geraniol. Indole had no effect. The surprising conclusion is that the critical flicker frequency is diminished or the persistency increased or the sensitivity reduced. In other words, smelling camphor reduces our sensitivity to green but increases it to red. Whilst we know that the olfactory and visual centres are associated, such a conclusion could hardly have been anticipated.

The observation of Woodrow and Karpman (*Jour. Exp. Psych.*, **2,** 431-47, 1917) that the adaptation time for olfaction, i.e. the time needed for the olfactory sensation to wane completely, is proportional to the vapour tension of the odorous material, should also be remembered.

Elsberg has reported (*Bull. neurol. Inst. N.Y.*, **4,** 479-500, 1935) that the duration of olfactory fatigue varies with the time during which the odour acts on the receptors. Also when both nostrils are used the fatigue duration is longer than when one nostril has been blocked. Stimulation of the receptors on one side of the nose affects the efficiency of the receptors on the other side. This is a point which will be discussed later under the heading " Induction " in the chapter on " Gustation," as it is a common quality.

Masking

It has long been known that two substances odorous singly may be inodorous together. Zwaardemaker used his double olfactometer in which one of the two substances was introduced to either nostril to measure the ratio of quantities required for neutralization. By this method all possibility of chemical reaction between the two substances was removed, and also it shows that since different receptors are involved the neutralization must have a central origin. Pairs of neutralizing odorous bodies recorded by Zwaardemaker in " Die Physiologie des Geruchs," 1895, were

Cedarwood and rubber.
Wax and rubber.
Wax and balsam of Tolu.
Paraffin and rubber.
Rubber and balsam of Tolu.

Aronsohn had previously noted that the smell of camphor was neutralized by the smell of Cologne water or of oil of juniper.

Backman (*Verslag. Akad. Wetenschappen Amst.*, **25,** 971-84, 1917) investigated the olfactory properties of benzene, toluene, xylene, pseudo-cumene and durene, and found that although when using very small quantities the olfactory effect of mixtures was additive, yet with higher concentrations and certain definite proportions of two or more members, compensation effects of practically no odour could be obtained. In cases of very similar odours, such as benzene and toluene, this effect was less noticeable.

Various patents have been issued which describe devices for masking unpleasant flavours of medicines, etc. One of these by Michael (Australian Patent 20,127) suggests that to mask the odour of castor oil it should be boiled, then saccharin and vanillin added and, after cooling, oil of lemon and oil of peppermint added. There may be some masking in this, but it looks more like a case of overwhelming the smell of castor oil with strong odorivectors. In another case Shuger (U.S. Patent 2,103,830) has suggested masking the odour of materials containing pungent volatile substances by adding a fragrant compound such as ethyl acetate, benzyl acetate or geraniol.

Dyson (*Perf. Essent. Oil Record*, **28,** 13), whose theory is that the fundamental source of osmic sensation lies in the internal vibrations of the molecules, believes that when pairs of odours compensate they do so by simple interference, as their dominant vibrational frequencies are near each other and interfere during perception.

Dilution

The great change in odour which sometimes occurs on dilution has been noted in several places. Jasmine owes its delightful scent to a trace of indole, but indole when concentrated has a disgusting smell.

Many of the aldehydes used in perfumery are obnoxious, but a trace added to a perfume may lift it quite above the ordinary level. Civet and ambergris, both of which are animal products, are unpleasant in themselves, but are widely used in expensive perfumes. Another instance already noted is triethyl-phosphine with a hyacinth odour in dilution, but suffocating when concentrated.

Different Responses

Just as the odour of a substance may change with its concentration, so one substance may evoke quite different responses in different individuals. Spikenard, mentioned as a perfume in the Old Testament, is still greatly appreciated in the East but is detested by most Europeans. Different responses to musk are common, as noted by Kenneth. Blakeslee's investigation of unlike reactions to verbena flowers has already been mentioned. Mustard gas is described as like garlic or horse-radish, which have quite different odours, and is even odourless to some people, as is also hydrocyanic acid.

Drugs

Foerster (*Chemical Abstracts*, **5,** 3848, 1911) has noted that the olfactory nerves are temporarily rendered more sensitive by the action of cocaine in the first stages, and by the administration of strychnine. Zwaardemaker had also noted that cocaine gave a short period of hyperosmia followed by local anæsthesia. Gymnemic acid is said to have been used to give complete anosmia, after which different olfactory sensations returned at different times, but gymnemic acid is usually considered to abolish certain taste sensations rather than odour. The return of different sensations after local anæsthesia will be considered in the chapter on the " Common Chemical Sense."

Measurement of Odour

If we smell solutions of different concentrations of an odorivector we call tell without difficulty if one is stronger than the other by about 30 per cent. By this is meant that a difference would be detected between 10 and 13 per cent. solutions or between 20 and 26 per cent. solutions. Trained observers can reduce this figure, and Dyson has given 15 to 18 per cent. as the minimum increase necessary for perceptible olfactory difference. To estimate odour by sniffing at a bottle of the odorant is difficult. The perfumer does not smell at a bottle of scent, but rubs a little of it on the back of his hand and allows the alcohol to evaporate before smelling it.

Rosenthal (*Parfümer*, **2,** 33-4, 1928) recommends that to test essential oils and extracts for odour about 0·1 c.c. should be diluted with alcohol and spread on filter paper. In another paper (*Riechstoffind.*, **1927,** 142-3, 151, 161) he suggests as a method for determining if one perfume has a more powerful odour than another and if so how much more powerful, that a 0·88 per cent. solution of the perfume should be made in diethyl phthalate and progressively diluted until the odour of the perfume is no longer distinguishable.

Maybee (*Canadian Chemistry and Process Industries*, **23,** 115, 1939) suggests that strong odours are best compared by the unaided nose from blotters or beakers, but that odours of weak solutions are conveniently measured for intensity with the nose extended by a tube which goes right into the flask.

The " Blast Injection Test " (*Arch. Neurol. Psychiat. Chicago*, **37,** 223-36, 1937) has been used by Elsberg in his work on the physiology of smell. A cylinder of compressed air, a test bottle of the odorous material and nose pieces are used. A measured volume of the odorous substance is injected into the nasal passage under a known pressure with voluntary cessation of breathing.

Elsberg defined the smallest amount of air containing an odour that could be identified as the Minimal Identifiable Odour (M.I.O.).

Another method developed by Elsberg was the " Stream Injection Method," in which air containing the odorant is injected in a steady

stream while the subject breathes through the mouth. This method proved useful in studying olfactory fatigue.

In *Bull. Neurol. Inst.*, **4**, 5-31, 1935, Elsberg had previously defined the smallest volume necessary for the identification of an odour by the Blast Injection method as the Olfactory Coefficient of the substance. For a number of substances investigated this ranged from 5 c.c. to 30 c.c. Low boiling-points and high volatility gave low coefficients as a rule. Later the term M.I.O. appears to have replaced olfactory coefficient.

Adler and Finley (*Arch. Neurol. Psychiat. Chicago*, **40**, 147-50, 1938) carried out clinical work with Elsberg's method and reported that the olfactory function could be quantitatively assessed by his method of the M.I.O.

A similar method for determining threshold odours was described by Hofmann and Kohlrausch (*Biochem. Z.*, **156**, 287-94, 1925). They blew different mixtures of an odorous substance and air into the nose of the subject until the threshold for odour was reached.

The *Camera Inodorata* was invented by Zwaardemaker and later used by Komuro (*Arch. néerland. Physiol.*, **6**, 20-4, 1921). It consisted of a large box with glass walls and aluminium top and bottom into which the head was thrust through a slide. It was made quite inodorous by the discharge from a mercury vapour lamp, when the minimum stimulus was found to be about 25 per cent. less than outside in the atmosphere, since the nose becomes more sensitive when all other odours are eliminated. The box was provided with an olfactometer and a ventilation device.

The name *camera inodorata* was given by analogy to the *camera obscura* used in measurements of light. It is described in *Perf. Essent. Oil Rec.*, **12**, 243-4, 1921.

The most famous of all odour-measuring devices is Zwaardemaker's Olfactometer ("Die Physiologie des Geruchs." 1895). It is illustrated in Fig. 18 and consists of two tubes, one sliding in the other, and the inner of which is shaped to fit into the nostril. The odorous material to be tested is carried on the inner surface of the outer tube. When the inner tube completely covers the inner surface of the outer tube the odour cannot be detected, but when the inner tube is partly withdrawn then air which has been in contact with the inner wall of the outer tube is drawn through the inner tube into the nose. The inner tube is accordingly withdrawn until the odour is just perceptible, and the distance it has been withdrawn denotes one *olfactie* or unit of odour stimulus. Then withdrawing the inner tube, which is graduated, to twice, thrice, etc., this length gives stimulations of two, three, etc., olfacties. A graded series of measured stimuli can be obtained, and also by using different outer tubes internally coated with different odorivectors these latter may be compared. Zwaardemaker at the same time designed and used a double olfactometer which simply consisted of two single olfactometers, one for each nostril, arranged on a suitable stand for holding them in position.

The term "olfacty" is also now in use to denote the number of molecules per cubic centimetre which can just be detected, i.e. at the odour threshold. The olfacties of some common substances are

Ethyl alcohol	3×10^{13}
Benzene	4×10^{11}
Cresol	5×10^{10}
Pyridine	3×10^{9}
Iodoform	4×10^{8}
Skatol	$1{\cdot}7 \times 10^{7}$

van Dam (*Arch. néerland Physiol.*, **1,** 660-7, 1917) used a modification of Zwaardemaker's olfactometer. He dispensed with the outer tube and instead inserted a rod of the odorous material into the "inner" tube, and the length of rod necessary to give threshold stimulation of odour was noted. In the case of liquids he mixed these with melted paraffin in definite proportions and cast rods from the mixtures. A similar apparatus was used by him in absorption experiments to which reference will be made later. It may just be mentioned here that he used a rod of, say, gold and exposed it to the vapour of an odorous material and then measured the olfactory power of the gold rod due to the adsorbed layer of odorant.

The other well-known odour-measuring device is the Fair and Wells Osmoscope. This was arranged for control of water supplies, but is suitable for the measurement of any delicate odours such as minimum stimuli. It is described in *Water Works Eng.*, **87,** 1051-5, 1934, and in *Chemical Abstracts*, **28,** 549, 1934. It consists of four main parts: (1) a cylindrical odour tube with an open bottom, the top being perforated by a single hole and with banks of holes along the sides; (2) a cylindrical tube fitting snugly over the odour tube; (3) a cylindrical air tube open at the bottom, sliding snugly over the sleeve and carrying banks of holes along the sides; (4) a nose-piece capping the odour tube. The principle on which it works is that the number of times an odorous material must be diluted with an equal quantity of air to reach the threshold value is determined. This is termed the *p*O value, and the lower the *p*O value the better the water sample, or if an odorant is being tested a high *p*O value indicates a powerful odorant. The principle of using dilution to measure the odour value was also adopted by Henning and reviewed by Bach (*Gesundheits Ing.*, **60,** 222-5, 1937) and is illustrated in Fig. 17. An improved type of dilution odour meter has been described recently by Fair and Wells in U.S. Patent 2,136,844.

Allison and Katz (*Jour. Ind. Eng. Chem.*, **11,** 336-8, 1919) used a method in which a controlled volume of air was passed over the odorous substance, of which the loss in weight was noted and the air was suitably diluted by means of Venturi-type flow meters.

One other measuring device which should be mentioned is that of Fournie (*Perf. Essent. Oil Rec.*, **8,** 278, 1917). It consisted of two concentric glass tubes closed at one end and fitting one over the other

with a little friction. The outer tube is provided with a vertical series of round holes of uniform size and the inner tube has both a vertical and a spiral series. An odourless paper on which a number of drops of the substance to be tested is inserted and the apparatus closed. After a suitable time by rotating the outer tube various holes in the inner tube are brought into register with those in the outer tube. The number of holes necessarily communicating to give the odour is the reciprocal of the power of the odour. It is in principle the same as Zwaardemaker's olfactometer. Such devices as have been described can be used not only to compare the strengths of odorants but also their persistency. Some odorants volatilize quickly, others are more or less permanent. Opposites in this respect are diethyl ether and musk. Persistency is a valuable property in perfumes, so its measurement has attracted some attention. Luque (*IX Congr. intern. quim. pura. aplicada.*, **4,** 549-58, 1934) has defined the Specific Tenacity of odoriferous substances as the number of hours × 100 during which 1 gram. of 1 per cent. solution of the substance in absolute alcohol retains its odour when placed in a glass tube kept at 40° C., the tube containing a plug of absorbent felt 2 cm. thick, and a current of air being passed through the tube.

Wagenaar (*Chem. Weekblad.*, **35,** 618-21, 1938) has used an olfactometer to judge ability of persons to detect odours. He dissolved the odorant in alcohol as 1 per cent. solution and impregnated pumice with it. The olfactometer consisted of a tube of 3·5 cm. diameter and 25 cm. long and was graduated into 10 divisions. The tube was fitted with an adjustable carrier to hold a small cube of the pumice saturated with the alcoholic solution of the odorant, and this carrier was moved along the tube from the far end towards the nose until the smell was detected. He measured how far off the nose the pumice could be to give (*a*) a detectable odour, (*b*) an identifiable odour. The odorants used were benzaldehyde, camphor, clove oil, mustard oil, geranium oil, oil of peppermint and vanillin. Out of a possible score of 70 marks he awarded over 55 to more than half of a large group of people tested. He noted women were better than men and tobacco chewers worst of all.

Tasman (*ibid.*, **35,** 707, 1938) criticized Wagenaar's work adversely. From experience on testing 300 persons in Utrecht he found that only those breathing equally through both nostrils gave reliable results. The instrument sponsored by the Dutch military authorities is recommended by Tasman as being more reliable. Wagenaar later replied to these criticisms.

Chemical Change in the Body

Whilst the chemical senses are activated by touching or being close to substances usually of a chemically reactive nature, the nature of the chemical reactions which these cause in the receptive tissues is not known. Such a chemical change doubtless takes place first in

the receptors, possibly it is something in the nature of ionization or orientation of amino acids, but owing to the rapidity with which the receptors regain their sensitivity it is probably a reversible change. The stimulus has induced an impulse which passes up the nerve and doubtless causes chemical changes in the central nervous system. This mechanism is, however, not confined to the chemical senses, as in vision photo-chemical changes are known to take place. The difference is that in the chemical senses, an additional chemical component (as distinct from energy) from outside is supposed to enter into the reaction. In the case of smell at least, the minimum stimuli are very small, and there is room for argument as to whether the stimulus is vibratory, chemical or solvent. This is not meant to exclude the possibility of any two or even all three mechanisms being involved.

The effect of olfactory and gustatory stimulation on the flow of saliva was studied by Grisogani (*Atti. accad. Lincei.* (6), **1,** 602-4, 1925). He found that the parotid secretion in man was under the influence of such stimulation. Normally it shows periodic oscillation in which salivary flow stops and recommences. Sour and bitter tastes increased the flow. Ammonia vapour had no effect, but odorants like oils of mint, cloves, lavender and rosemary showed a stimulating action on the secretion, whilst unpleasant odorants, such as iodoform, carbon bisulphide, toluene and capryl alcohol showed a depressing effect. In fact the effects vary with the subject, and are enhancing or depressing according as the odours are pleasing or displeasing. With mixed odours, one pleasing the other displeasing, the latter prevails and the salivary flow is depressed. Nature's safety first. The absence of effect of the chemical irritant, ammonia, is noteworthy.

Niccolini (*Boll. soc. ital. biol. sper.*, **10,** 429-31, 1935) has found that the thiocyanate content which is a normal constituent of the nasal mucus of men, carnivores and herbivores is increased by true non-irritant odours but is depressed by irritating chemicals. Thiocyanic acid is also a normal constituent of saliva, and Niccolini found (*Arch. ital. sci. farmacol.*, **4,** 77-115) that stimulation of the olfactory nerve increased the secretion of thiocyanic acid and decreased the amount of aqueous secretion, but stimulation of the trigeminal nerve endings conversely decreased the thiocyanic acid secretion but increased the aqueous secretion. The secretion of thiocyanic acid is under nervous regulation. He could find no relation between the amounts of thiocyanic acid in the nasal orifices and in the urine.

It has long been known that the continued inhalation of turpentine causes the urine to smell of violets, and when we come to examine the composition of the odorous principles of violets we shall see that this is not such a long jump chemically as it is olfactorily. The disagreeable odour of fermented or stale urine is, according to Dehn and Hartman (*Jour. Amer. Chem. Soc.*, **36,** 2136-46, 1913), due to a neutral ill-smelling substance—urinod C_6H_8O, possibly β-cyclohexene 1-one, which occurs in urine in conjugated form and is set free on fermentation. It is very toxic.

Nunneley (*Medico-chirurgical Trans.*, **53,** 35, 1870), in carrying out experiments on the action of diuretics, reported that 5-10 drops of English Oil of Juniper taken every few hours, besides making the urine clear and free from albumen, also gave it a strongly aromatic odour occasionally recalling the smell of violets.

Anosmia

Anosmia means inability to smell. It may be partial or complete, congenital or acquired, and may be temporary or permanent.

Partial anosmia is not uncommon and is usually due to a cold, catarrhal conditions or adenoids, all of which obstruct the passage of air through the nose. Even if permanent, partial anosmia is not crippling, and it is quite possible to go through life unaware of the deficiency. The writer has seen cases of middle-aged men who, on being asked to smell samples of war gases on instructional courses, have discovered their inability to do so, without apparently having previously known that their sense of smell was defective. Partial anosmia may be likened to colour blindness but is not so serious in our way of living.

Temporary anosmia is produced by fatigue or continued stimulation, or by drugs such as cocaine.

Congenital anosmia may be partial or complete. Glaser (*Science*, **48,** 647, 1918) thought that it showed some resemblance to a sex-linked inheritance. He investigated the case of a Russian Jew from Kiev, who was unable to distinguish odours in the usual way although irritants affected him. One brother was similar and a second brother had only a slight capacity for detecting odours. Two sisters were normal. His mother and his maternal grandfather were also anosmic. The locality appeared to inbreed the defect. The particular family was characterized by stammering, hernia, thumb nearly twice the normal width, excessive sex interest and good mentality.

Anosmia may be due to (1) a defect or disease in the olfactory nerve, or (2) a defect in the accessory apparatus which restricts breathing through the nose, or (3) a defect in the central nervous system.

Early in the nineteenth century there was some dispute as to whether the olfactory or the trigeminal nerve was responsible for the sense of smell. Eschricht in 1825 pointed out that people with a degenerated or without an olfactory nerve were anosmic, and Bishop (*Proc. Roy. Soc. London*, **3,** 205-6, 1833) showed that a person with paralysis of the trigeminal nerve could still have full olfactory powers. Later, of a litter of five pups, four had the olfactory nerves cut and these were unable to find their mother's nipples although the fifth, as a control, was normal. Many other experiments showed conclusively that smell was served by the first cranial nerve.

Ogle (*Medico-Chirurgical Trans.*, **53,** 263-90, 1870) adduced cases illustrating the physiology and pathology of the sense of smell. He first gave three cases where the smell was lost due to the rupture

of the olfactory nerves as they passed from the bulb through the holes in the ethmoid bone. The cases were as follows :

(1) B had fallen from a horse twenty-seven years previously and struck the left posterior part of the head heavily on the ground. It is, however, well known that a blow at the back of the head is more likely to cause injury to the frontal part which rests directly on the floor of the skull and is not cushioned by cerebro-spinal fluid. B was, after his accident, liable to headaches and had completely lost the sense of smell. The strongest odours under his nose produced no sensation whatever, although the tactile sensibility of his nostrils was normal, and snuff occasioned sneezing and tickling. He stated that he had also lost the sense of taste as he could not distinguish one meat from another, whilst boiled onions, boiled apples and boiled turnips all appeared the same to him. His palate could not distinguish the aroma of wines, although he could distinguish them a little by roughness or sweetness. He could also recognize sweet, salt, bitter and acid tastes. He disliked any new article of diet. Clearly the subject's sense of taste and common chemical sense were intact, but his sense of smell and with it the perception of flavour had been lost.

(2) A man was knocked down by a cab. All injuries passed off but there was a total loss of smell. He could not perceive the strongest odours, e.g. asafœtida. He had also lost the perception of flavour, port seeming like sugar and claret like vinegar. Tactile sensibility was normal.

(3) C. L. knocked on the head in a drunken row at Christmas 1868, suffered from strange sensations in the head, nose bleeding and complete loss of smell. He eventually became insane.

In all three cases the sense of smell was lost as the result of a severe blow, and there is little doubt that the loss was due to rupture of the olfactory nerve. The loss of taste in the popular sense, including aroma or flavour perception, was included, but true taste derived from the gustatory nerves was unimpaired. Disease or injury may split the compound sensation of flavour into its two components. In the three cases above smell was lost but taste remained. In other cases where smell remains and true taste alone is lost the patient is almost regardless of his changed condition.

Ogle instanced other cases when the sense of smell was lost or partly lost by obstructions in the nose, and these were mentioned earlier in this chapter under the heading " Respiration." In these cases flavour was usually unimpaired as the odorous vapours were able to enter the nasal passages from the throat.

In the third type of case the damage is central, as in the following case :

A patient, E. D., suffered from partial aphasia and agraphia and loss of smell. He was nearly insensible to smell but ammonia affected

him. This patient recovered from his aphasia and the sense of smell returned.

Other cases have shown the frequent coincidence of aphasia (inability to read and speak well-understood words, whilst agraphia is inability to write similar words) with anosmia. In most cases of aphasia a brain lesion exists close to the Silvian fissure, and to the floor of this fissure there can be traced the external root of the olfactory bulb. Aphasia is usually due to inflammation involving the superficial layers of the brain.

Ogle therefore showed three classes of cases where loss of smell was due to (1) injury to the olfactory nerve following a blow, (2) obstruction of the breathing passages, (3) a lesion in the brain close to the olfactory bulb.

Pigment

Ogle also investigated and reported in the same paper as that quoted above the connection between albinism and anosmia. A case was recorded in the *American Journal of Medical Science*, 1852, of a boy in Kentucky. He was the son of two black slaves and was normal until his twelfth year, when white patches appeared near the left eye and gradually spread over the body, so that in ten years' time apart from his woolly hair he looked like a very fair European. When the boy lost colour he began also to lose the sense of smell, and when all the colour had gone he was quite anosmic.

It has already been noted that the olfactory region is yellow to brown in colour, and Ogle concluded that the mysterious disease had destroyed the pigment here as well, and olfaction was therefore impossible. The pigment in macrosmatic animals is darker than in man. In man it is light yellow, in the cat deep yellow-brown, and in the fox reddish-brown, whilst the Bowman glands secrete a pigmented fluid, although in man the Bowman glands are purely mucous in character (*Physiol. Abstracts*, **17**, 88, 1932). Further, dark-skinned man has more pigment even in the eye and brain than fair men. Arabs of the Great Desert are said to smell a fire 30 miles off. The African negro can distinguish the traces of a white man from those of a negro. Olfactory sense is feeble in children, who taste well but have little appreciation of flavour, and in all young animals nasal pigmentation is much less intense than in adults.

The case of the Himalayan rabbit, which only gains pigment at weaning time, was instanced in Chapter 1, as also was the peculiar liability of white animals to poisoning. There is reason to think that truly white animals are anosmic but there are few really white. The white whales of Spitzbergen are instanced by Ogle and said to have no sense of smell.

The way in which dark clothes absorb odours more readily than light ones seems as if it may have a bearing on this point. Other senses than smell may be affected by albinism. Darwin pointed out

that cats with a pure white skin and blue eyes are almost invariably deaf, but not so if there is a single blotch of colour.

Ogle concluded that sight, smell and hearing all require the presence of pigment for the full performance of their functions, and that in each the pigment is not contained within the nerve structures themselves but lies external to these and in immediate contiguity to their ultimate elements. The pigment is more probably connected with the reception than the transmission of sensory impulses. Since in sight and hearing the sensory impression is known to result from waves in the ether or air " one cannot but suspect that the same may be true in the remaining sense and that the undulatory theory of smell, deriving also, as it does, support from some other facts may perhaps after all be the true one."

Ogle's suggestion is a remarkable anticipation of much of the best modern thought. His connection of pigment with olfaction seems to have received little attention recently, but he certainly made out a strong case in connecting the two.

The Chinese phrase quoted by Kenneth in his " Osmics," and conveying the idea of a gross lack of discrimination, may serve to conclude these remarks on anosmia—" p'u pien shang chuh "—or inability to distinguish a fragrance from a stink.

CHAPTER 5

GUSTATION

The Four Tastes

The multitude of "tastes" we commonly experience are due not only to gustatory sensations but also to tactile, heat and cold, and above all, olfactory sensations. The tongue is bountifully supplied not only with taste receptors but also with touch, heat and cold receptors. If the nose is held we find how much of "taste" was really odour, and boiled turnips and apples and onions are practically the same. Ham and lamb are indistinguishable, port is like sugar, claret like weak vinegar. Most of the discrimination attributed to the palate is really performed by the olfactory membranes. The ethereal odour of fruits is often designated as taste. On the other hand the "odour" of chloroform is largely due to stimulation of the sweet taste receptors. Just as one odour can mask another, so in the case of tastes, the syrups of orange, cinnamon and sarsaparilla will disguise a salty taste and raspberry and cocoa will disguise a bitter taste.

The salty and sour tastes seem to be simpler than the sweet or bitter. Taste is a higher differentiation of the common chemical sense, and the elaborate taste receptors show that it is a much later development than the common chemical sense which has free nerve endings. Above the fishes, taste is confined to the mouth. In man it is confined to the dorsal surface of the tongue, the soft palate, the epiglottis and the beginning of the gullet, but in children taste-buds are spread over wider areas of the mouth. As evolution has proceeded taste has been more and more restricted to one locality, and a similar state of affairs is seen in the growth of man from the fœtus, for with increasing age the receptors disappear from all but very localized areas. In children, but not in adults, the centre of the tongue and the inner surfaces of the cheeks are taste-sensitive. As we are descended from sea-inhabiting invertebrates we should expect the salt taste to be the most primitive, followed by acid taste, which would function chiefly as a warning. These two tastes are more concerned with environment and safety than with food. Later when bitter and sweet tastes made their appearance they were concerned with nutrition. We know well that salt and acid tastes are stimulated by special groups of substances, viz. salts and acids, but bitter and sweet tastes are more widespread. Possibly for this reason, or perhaps there may have been confusion between salt and sour tastes on the one hand and chemical irritants on the other, there was in the nineteenth century a reluctance to recognize more than two tastes—sweet and bitter. However, Schiff (*Leçons sur la Physiologie de la Digestion*, **1**, 414, 1867) showed that a solution of acid too weak to affect the general mucous surface would evoke a sour taste in the mouth. A similar observation regarding salt solutions was made by von Vintschgau (*Physiologie*

des Geschmackssinns. Hermann Handb. Physiol., Bd. 3, Theil 2, 145-224, 1880).

For some time now it has been generally agreed that there are four main tastes, sweet, sour, salt, bitter, and this view has received striking confirmation from the experiments of Allen and Weinberg, to be discussed later in this chapter.

The Sour Stimulus

The sour substances we commonly encounter all contain acids. There is acetic acid in vinegar, citric acid in oranges and lemons, malic acid in apples, and fatty acids in sour milk. The stimulus for the sour taste is an acid. Whilst practically all acids are sour they may also have other tastes, for example, citric acid is sweet as well as sour, and picric acid is bitter as well as sour. A very weak acid like carbolic acid or phenol is not distinctively sour, but as such a body is a weaker acid than carbonic acid it is hardly an acid in the general sense. With this reservation a sour taste is a common property of acids. The feature common to all acids is to ionize in aqueous solution into an anion and a cation which latter is always the hydrogen ion. The higher the concentration of hydrogen ions in a pure solution the stronger is its acid character and the more sour the taste. Strong acids are very highly ionized, that is, most of the molecules have dissociated into ions, but not all of them.

$$HCl \rightarrow H^+ + Cl^-.$$

In dilute solutions the degree of dissociation is greater than in concentrated solutions, although the absolute concentration of H^+ ions will be greater in the concentrated than in the dilute solution. Often, however, the degree of dissociation increases so rapidly on dilution that a dilution with an equal volume of water will not seriously reduce the concentration of hydrogen ions. Weak acids are not highly ionized, and their solutions contain a relatively large number of undissociated molecules. The dissociation is expressed

$$CH_3COOH \rightarrow CH_3COO^- + H^+$$

but only a small proportion of the CH_3COOH molecules are dissociated. The sour taste is generally proportional to the concentration of hydrogen ions. A strong acid such as hydrochloric acid in dilute solution is practically completely ionized, so that the taste must be due either to the H^+ or Cl^- ions. Kahlenberg (*J. Phys. Chem.*, **4**, 33, 1900) showed that hydrochloric acid still tastes sour at N/800 concentration whilst at this concentration sodium chloride, which is also practically completely ionized

$$NaCl \rightarrow Na^+ + Cl^-,$$

is tasteless. Hence the taste of the acid is not due to the chlorine ions and must be due to the hydrogen ions. Further, the addition of a salt such as sodium acetate to an acetic acid solution reduces the hydrogen ion concentration and also causes the acid solution to taste

less sour (Richards, *Am. Chem. Jour.*, **20,** 121, 1898). Kahlenberg also noted an anomaly of weak acids. Hydrochloric acid which can just be tasted in N/800 has four or five times the concentration of H^+ ions found in N/200 acetic acid which being a weak acid is much less dissociated. Nevertheless N/200 acetic acid just possesses a sour taste.

Acetic acid can be tasted when its hydrogen ion concentration is only one-quarter that of just sapid hydrochloric acid.

Harvey (*Jour. Am. Chem. Soc.*, **42,** 712-14, 1920) prepared buffer solutions of acetic acid and sodium acetate and compared with several observers the tastes of these solutions with hydrochloric acid solutions. His results showed that the sour taste depends on both the H^+ ion concentration and the total free acid.

Paul (*Z. Elektrochem.*, **28,** 435-46, 1922) showed that acids of nearly the same dissociation constant which would have similar concentrations of H^+ ions such as acetyllactic and tartaric acids could have very different tastes. Likewise, isohydric solutions of different acids could have different tastes, and he concluded that the sour taste was due partly to the H^+ ion but also to the undissociated acid. He also thought that the vapour pressure of the acid exerted an influence.

Liljestrand (*Arch néerland Physiol.*, **7,** 532-7, 1922) made experiments with buffer solutions. First, he showed that with pure acids the threshold concentrations for the sour taste corresponded to *p*H 3·4-3·5 for mineral acids and to *p*H 3·7-3·9 for organic acids, such as acetic, lactic, citric and butyric acids. If a buffer solution was made the ionization would be depressed so that to keep the same *p*H 3·9 more acid had to be added, and such a solution containing more acid and some buffer salt tasted more sour than pure acid of similar *p*H value. In fact, a buffer mixture of acetic acid and sodium acetate just gives a sour taste at *p*H 5·6, which represents a much lower H^+ ion concentration than *p*H 3·9 which is the threshold concentration of pure acid. By using large quantities of buffer salts it was possible to make solutions of nearly neutral *p*H value which nevertheless had a sour taste. As was to be expected the pure acids gave the sour taste immediately, the buffer solutions more slowly as ionization had to proceed on the tongue, possibly following absorption or neutralization by the tongue of the already free H^+ ions. Liljestrand concluded that the sour taste is not due to any definite *p*H value but rather to the titration capacity of the solution.

Ostwald and Kuhn (*Kolloid-Z.*, **29,** 266-71, 1921) investigated the problem from the colloidal aspect, and suggested that whilst the sour taste was qualitatively determined by the H^+ ion concentration it was regulated quantitatively by the swelling of the colloidal tissues of the tongue and mouth, and the swelling was not directly determined by H^+ ion concentration. They also found that solutions of acids containing buffer salts were more sour than solutions of the pure acids of similar *p*H value.

Rosenbaum (*Arch. ges. Physiol* (*Pflügers*), **208,** 730-1, 1925) ascribed the strong sour tastes of solutions of weak acids which were poor in

H^+ ions to a peculiar ability of such weak acids readily to penetrate the organs of taste.

Bacharach (*Z. Biol.*, **84,** 335-46, 1926) found the threshold concentrations for different buffered solutions. Some of these were

Na_2HPO_4	and	NaH_2PO_4	*p*H 6·4
K_2HPO_4	,,	NaH_2PO_4	,, 6·2
CH_3COOH	,,	CH_3COONa	,, 5·9
CH_3COOH	,,	CH_3COOK	,, 5·6
CH_3COOH	,,	$(CH_3COO)_2Mg$	,, 5·3

He concluded that the sour taste arises at different *p*H values, and depends on both the concentration of H^+ ions and the total concentration of the solution.

Baráth and Vandorfy (*Biochem. Z.*, **176,** 473-7, 1926) made a comparison of the tastes of equimolar solutions of acetic and hydrochloric acids. The more dissociated acid was the stronger, but at very great dilutions, less than 0·01 N., the acetic acid might give a stronger taste than the hydrochloric acid.

The subject was also investigated by Dietzel (*Kolloid-Z.*, **40,** 240-8, 1926), who concluded that the sour taste was not quantitatively proportional to the strength of the acid, although the two run more or less parallel. Other factors, such as surface tension, vapour pressure and swelling of the tissues by the acid, came into play.

Berlatzky and Guevara (*Comp. rend. soc. biol.*, **98,** 176-7, 1928) confirmed that the threshold of sour taste for different acids corresponded to different *p*H values, and that the anion as well as the H^+ ion played a part in determining the taste.

Taylor (*Jour. Gen. Physiol.*, **11,** 207-19, 1928) measured the threshold concentrations and the *p*H values at those concentrations of nine different organic acids. He assumed that a given degree of sourness was due to a definite H^+ ion concentration within the taste-bud. This was a new departure, and offered a chance of reconciling the logical view that taste and H^+ ion concentration would be proportional, with the anomalous experimental results obtained. The relative concentration of undissociated acid also inside the taste-bud may then be calculated from the dissociation constants of the acids. The ratio

$$\frac{\text{undissociated acid outside taste-bud}}{\text{undissociated acid inside taste-bud}}$$

is the relative gradient necessary to cause penetration of the acid into the tissues. Polar groups such as —OH, —Cl, and —Br introduced into an acid reduce its ability to penetrate the tissues. In a later paper Taylor, Farthing and Berman (*Protoplasma*, **10,** 84-97, 1930) showed that the addition of a polar grouping such as —OH, $\rangle C{=}C\langle$, $\rangle C{=}O$, —COOH or NH_2 to an organic acid made its penetration to the receptor from 20-500 times more difficult, but that the lengthening of the carbon chain in the acid by the introduction of

additional methylene groups had the reverse effect. These results pointed to the tissue which absorbed the acids being fatty rather than protein.

Cragg (*Trans. Roy. Soc. Canada*, 1937 (111), **31,** III, 131-40) has reported that at the threshold for the sour taste the *p*H value of the following acids is between 4·2 and 4·6 : hydrochloric, sulphuric, nitric, monochloracetic, acetic, formic and tartaric acids. Further, the addition of 3 per cent. sugar or of saccharine, equal in sweetness to this, causes no change in the *p*H value of hydrochloric acid but reduces its sourness by 15 per cent.

Kenrick (*ibid.*, III (3), **25,** 227-8, 1931) found that the proportion of buffer salt (phosphate) necessary to bring different acids to a *p*H value of 5 was proportional to the sourness of the various acids alone. A strong acid like hydrochloric would require much more buffer salt to reduce its hydrogen ion concentration to *p*H 5 than would a weak and relatively undissociated organic acid. Kenrick found also that the threshold concentrations for sour taste were lowered, i.e. the sensitivity to sour taste was enhanced by the presence of bitter or astringent substances such as quinine and tannin. He also noted that sourness was an immediate sensation connected with the taste-buds, and did not depend on the action of saliva secretions.

The evidence is that the sour taste is mainly but not entirely dependent on the hydrogen ion. The anion and the undissociated molecules also play a part. Mineral acids, such as nitric and hydrochloric, cannot be distinguished from each other by taste, and in these cases it appears to be a simple question of the hydrogen ion concentration controlling the sour taste, but organic acids like acetic, tartaric and citric acids have distinctive tastes and are more sour than they should be if it was simply a question of hydrogen-ion concentration. The anomalous sourness of these weak organic acids may be due to the undissociated molecules, which act as a reserve and dissociate to give fresh ions as fast as they are used up, but if this is the case it is not clear why acetic acid and hydrochloric acids should not be equally sour *in equal molar concentrations*, as the initial degree of ionization would not appear to be very important if the undissociated molecules could ionize as required to give replacement ions. In fact hydrochloric acid is much more sour than an equimolar solution of acetic acid, except at great dilutions. It has also been suggested that penetration of the tongue surface may be a factor, but penetration can be observed by using natural indicators, and it is a slow process whilst taste is a quick reaction. As acetic acid is a much better solvent for fatty substances than the mineral acids this may have some bearing on the point. Water solubility alone is necessary to give the sour taste, but if it is accompanied by lipoid solubility more general access to the receptors is possible with correspondingly more acute sensation. In the case of citric acid it is possible that the sweet taste enhances the sour sensation.

The Salt Stimulus

The typical salt taste is that of common salt, sodium chloride. Also the chlorides of potassium, ammonium and calcium all taste similar to sodium chloride. Hence one would say the anion Cl^- and not the cation, Na^+, K^+, NH_4^+ or Ca^{++} was responsible for the taste. Kahlenberg (*Bull. Univ. Wisconsin*, Sci. ser. **2**, 1-31, 1898) showed that whilst sodium chloride solution was distinctly saline at 0·04 molar, a similar solution of sodium acetate was not saline, hence the saline taste must be due to the Cl^- ion and not to the Na^+ ions, but in this connection it must not be forgotten that the sodium chloride would be more completely dissociated than the sodium acetate, and that the concentration of Na^+ ions in the sodium chloride solution would be greater than in the sodium acetate solution. Now sodium bromide and sodium iodide are also salty, but potassium iodide is bitter as well as salty. However, it is clear that the Cl^-, Br^- and I^- ions often give a saline taste. The sulphates and nitrates of sodium and potassium are also salty. Whilst the anion, Cl^-, Br^-, SO_4^{--} or NO_3^- seems to be effective in producing the saline taste, yet the cation also has an effect, otherwise all chlorides would taste the same. Similarly, the cation has a specific effect since all salts of sodium do not taste the same.

Gayda, Turin (*Arch. fisiol.*, **10**, 175-92, 1912), concluded that the taste of salts was a function of both the anion and cation, but that potassium salts were exceptional, as their salty taste was more pronounced than predicted by rule.

On the other hand, Stooff (*Die Umschau.*, **24**, 228-9, 1920), who investigated the taste of drinking water, reported that the K^+ ion was the most difficult to detect by taste whilst iron was the easiest cation to detect. Sodium was detected before potassium, magnesium before calcium, and iron before manganese. The ammonium ion was easily distinguished in the presence of others. Of the anions the hydroxyl ion OH^- is the first to be noticed, and this is followed in order by NO_3^-, Cl^-, HCO_3^- and SO_4^{--}. Potash, KOH, was noted before soda, NaOH, which was rather strange as the Na^+ ion was usually detected before the K^+ ion. Iron and manganese salts were detectable in a concentration of 1 in 50,000, and other salts and hydroxides required higher concentrations. Free carbon-dioxide in quantities over 100 mg. per litre had such a strong influence on the taste that small quantities of salts were not noticed when this was present. Stooff also reported that ethyl alcohol was recognized at a dilution of 1 in 50,000 but this must have been by odour and not by taste, as relatively high concentrations, about 13 per cent. of ethyl alcohol, can only just be tasted. He also noted that water did not have the same taste in all parts of the mouth, and it is well known that if a substance has two tastes say sweet and bitter, then it tastes sweet at the tip of the tongue and bitter at the back of the tongue.

Kionka and Strätz (*Arch. exptl. Path. Pharm.*, **95**, 241-57, 1922)

compared normal solutions of eighteen different salts and divided them into three groups.

(1) Those with a dominating salty taste, viz. :
NaCl, KCl, NH_4Cl, LiCl, RbCl, NaBr, NH_4Br, LiBr, NaI, LiI.
(2) Those with both salty and bitter tastes, viz. :
KBr, NH_4I.
(3) Those with a dominating bitter taste, viz. :
CsCl, RbBr, CsBr, KI, RbI, CsI.

With the exception of caesium chloride, the chlorides were all salty. Of the six iodides, three were bitter, two salty, and one intermediate. The four salts with the highest molecular weight, RbI, CsI, KI, RbBr, were decidedly bitter. The eight salts with the lowest molecular weight had a predominant salty taste with the exception again of caesium chloride. They concluded that the taste of a salt depends on the cation, Na^+, K^+, Rb^+ or Cs^+, etc., which determines the intensity, and upon the anion, Cl^-, Br^-, I^-, etc., which gives the character.

Maybee (*Canadian Chemistry and Process Industries*, **23**, 115, 1939) notes that compounds of lithium and sodium are salty, of potassium are salty and bitter, and of rubidium are very bitter. Likewise chlorides, thiocyanates and acetates are usually salty, bromides slightly bitter and iodides definitely bitter. It will be seen, therefore, that there is a general rule that the low molecular weight salts are salty whilst the high molecular weight salts are bitter. Very probably in all cases more than one set of receptors are acted on, even a dominating salty compound having some effect on the sour, sweet, and particularly the bitter receptors, and with increase in molecular weight the dominant note shifts from the salt to the bitter receptors. The main salt taste appears to be due to the free anions. The possibility of the unionized material playing a part cannot be ruled out.

Richter and MacLean (*Am. J. Physiol.*, **126**, 1-6, 1939) worked on fifty-three human adults and found that salt solution could be distinguished from distilled water at a concentration of 0·016 per cent. and sometimes as low as 0·007 per cent., and that the saline taste could be recognized at 0·087 per cent. and sometimes at 0·02 per cent. Richter (*Endocrinology*, **24**, 367-71, 1939) showed that the salt taste threshold of twenty normal rats averaged 0·055 per cent., about the same as in man, but that the removal of the adrenals from eight rats reduced their salt taste threshold to 0·003 per cent., i.e. the sensitivity was increased nearly twenty-fold. The adrenalectomized rats showed a craving for salt even when offered in amounts unlikely to have any beneficial effect, and this appeared to be due to chemical changes in the taste mechanism in the oral cavity which resulted in an enhanced salt discrimination.

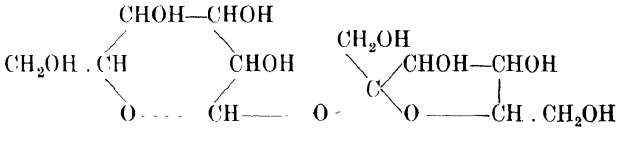
The salt taste, together with the bitter is diminished by rise in temperature, i.e. a cold salt solution tastes more salty than when warm. The acid and sweet tastes are, conversely, enhanced by rise in temperature (Goudriaan, *Arch. néerl. de Physiol.*, **15**, 253-82, 1930).

The Sweet Stimulus

Whereas the sour taste is produced by a well-defined class of similar substances, the acids, and the saline taste by the salts, the sweet taste is produced by a variety of organic compounds which as a rule are not ionized. The sweet taste is a later development than the salt and sour and is concerned with nutrition. Perhaps the sweet substances most commonly met are sugar, glycerine and saccharine. The first two of these have certain resemblances—they are both polyhydric alcohols with the following formulæ :

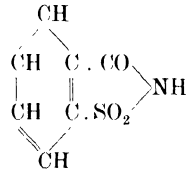
Glycerol $CH_2OH . CHOH . CH_2OH.$

Sugar (sucrose) is glucose fructoside or fructose glucoside



The repetition of the $—CH_2OH$ group will be noted and is indeed significant, but if we now consider saccharine it is quite different.

Saccharin (*o*-sulphobenzimide)



It will be seen that it contains the aromatic benzene nucleus, yet often this same nucleus imparts a bitter taste, for whilst

Glycol	$CH_2OH . CH_2OH$	is sweet.
Styrol	$C_6H_5 . CHOH . CH_2OH$	is bitter.

Many naturally occurring glucosides are bitter and these frequently contain the benzene nucleus, but on removal of the nucleus by hydrolysis give the sweet sugar.

Whilst the sugars are absorbed by the body and form a valuable food yet saccharin passes through the body unchanged.

Other stimuli for sweet taste are lead acetate (sugar of lead) and the salts of beryllium (glucinum). In the latter case the sweet taste is shared by different salts of beryllium, all of which are ionized, and it is the Be^{++} ion which is responsible for the sweet taste. It is said that extremely dilute solutions of caustic soda and caustic potash taste sweetish (cf. Druce, *Chemist and Druggist*, **111,** 755, 1929). α-Amino acids are a group of organic substances with a sweetish taste. Cohn, in his book, " Die organischen Geschmacksstoffe," drew certain conclusions as to sweetness. He noted, for example, that a multiplicity of hydroxyl groups gave sweetness, and these and α-amino acid groups and such like he termed " sapophoric " groups and noticed that they

frequently occurred in pairs. Cohn also pointed out that many substances had an after-taste. Saccharin, although intensely sweet, has a noticeable and persistent bitter after-taste. Oertly and Myers (*Jour. Amer. Chem. Soc.*, **41**, 855, 1919) took Cohn's work further. Considerable success had at this time been achieved by de Witt's theory of dyeing. This postulated the necessity of two different kinds of group in the same molecule to form a dyestuff, a chromophore and an auxochrome. By analogy Oertly and Myers postulated that to be sweet a substance must contain a "glucophore" and an "auxoglue." The significance of Cohn's observation that his sapophoric groups very frequently occurred in pairs will now be seen. Six glucophores were pointed out by Oertly and Myers, viz.:

(1) —CO—CHOH—(H) The group —CO—CHOH— must be combined with at least one hydrogen atom to become a glucophore.

(2) $CH_2OH \cdot CHOH—$ (3) $COOH \cdot CHNH_2—$ (4) $—CH_2ONO_2$

(5) $—C\begin{matrix}H_{3-x}\\Cl_x\end{matrix}$ (6) $C\begin{matrix}H_{3-x}\\Cl_x\end{matrix}—C\begin{matrix}H_{2-y}\\Cl_y\end{matrix}$

Where Cl stands for any halogen.

The nine auxoglues found were

(1) H— (2) $CH_3—$ (3) $C_2H_5—$ (4) $CH_3CH_2CH_2—$ (5) $(CH_3)_2CH—$
(6) $CH_2OH—$ (7) $CH_3CHOH—$ (8) $CH_2OH \cdot CH_2—$ (9) $C_nH_{2n+1}O_n—$

of normal polyhydric alcohols, the simplest of which is

$$CH_2OH \cdot CHOH—.$$

In order to have a sweet taste a substance must contain a glucophore and an auxoglue. Typical cases were

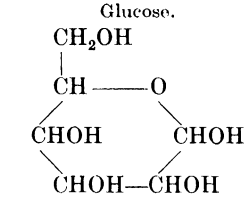
	Glucophore.	Auxoglue.
Glycol . . .	$CH_2OH—CHOH—$	H—
Glycerol . . .	$CH_2OH—CHOH—$	$CH_2OH—$
Glucose . . .	—CO—CHOH—	$CH_2OH—$
Glycine . . .	$COOH \cdot CHNH_2—$	H—
Chloroform . .	$—CCl_3$	H—
Ethyl nitrate . .	$—CHONO_2$	$CH_3—$

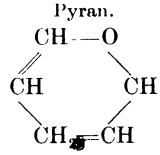
Whilst this theory brings some order into the mass of empirical knowledge it is not comprehensive and must be regarded only as a beginning. It makes no explanation of the sweetness of saccharin or of dulcin *p*—$HO \cdot C_6H_4 \cdot NHCONH_2$.

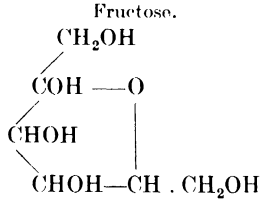
Sucrose, $C_{12}H_{22}O_{11}$, obtained from the sugar cane, average content 13 per cent., or the sugar beet, average content 16 per cent., is the natural sweetening agent. On treatment with certain enzymes or with dilute acids it is hydrolyzed—

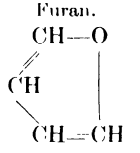
$$\underset{\text{Sucrose.}}{C_{12}H_{22}O_{11}} + H_2O \rightarrow \underset{\substack{\text{Glucose or}\\\text{dextrose.}}}{C_6H_{12}O_6} + \underset{\substack{\text{Fructose or}\\\text{lævulose.}}}{C_6H_{12}O_6}$$

Now sucrose is dextro-rotatory to polarized light whilst dextrose is also dextro-rotatory but levulose is lævo-rotatory, and as it is more strongly so than dextrose is dextro-rotatory the mixture of glucose and fructose obtained from sucrose is lævo-rotatory, whilst the original sucrose was dextro-rotatory. Accordingly sugar is said to be "inverted" on hydrolysis and the resultant mixture is "invert sugar," whilst the enzyme causing the hydrolysis is *invertase*. The structure of glucose and fructose is interesting for the former has a six-atom ring and is a derivative of pyrane, whilst fructose probably has a five-atom ring and is a derivative of furan.









There are many sugars but not all are equally sweet. As long ago as 1906 Becker and Herzog (*Z. physiol. Chem.*, **52,** 496-505) measured the sweetness of some of them, and found that the sweetness decreased in the following order :

sucrose, levulose, lactose, dextrose, maltose, galactose.

In this series lactose and dextrose were about equal.

More recently Biester, Wood and Wahlin (*Am. Jour. Physiol.*, **73,** 387-96, 1925) have issued a quantitative report. Taking sucrose as the standard with a sweetness of 100 units, other sugars have the following values :

Fructose . . .	173	Rhamnose . .	32
Glucose . . .	74	Galactose . .	32
Xylose . . .	40	Raffinose . .	23
Maltose . . .	32	Lactose . .	16

These values are for equal weights. Now the molecular weights of sucrose, $C_{12}H_{22}O_{11}$, glucose, $C_6H_{12}O_6$, and fructose, $C_6H_{12}O_6$, are respectively 342, 180 and 180, so on hydrolysis

$$1 \text{ kilo sucrose} \rightarrow \frac{180}{342} \text{ kilo glucose} + \frac{180}{342} \text{ kilo fructose},$$

and taking the respective sweetness values from the above table we have

Sucrose.		Glucose.		Fructose.
100 sweet units →	$\frac{180}{342}$ ×	74 sweet units +	$\frac{180}{342}$ ×	173 sweet units
or 100 sweet units →		39 sweet units +		91 sweet units
or 100 sweet units →		130 sweet units.		

This increase in sweetness on the inversion of sucrose actually takes place and Biester, Wood and Wahlin measured the sweetness of invert sugar to be 127·4.

Willaman (*Z. ver. deut. Zuckerind.*, 1927, 365-7) confirmed that the sweetness of levulose was 173 compared with sucrose 100. This figure agreed with that given above and was determined by measuring the lowest concentration detectably sweet to a number of subjects. Earlier work which had involved remembering the sweetness of one solution when tasting the next had led to a lower figure of 108, but the later figure of 173 is clearly more reliable.

Renner (*Confectionery Production*, **5**, 1939, 255-6) has pointed out that the relative sweetness of cane sugar, glucose and fructose changes with dilution. He estimated that the sweetness of glucose to cane sugar (100) was 53 at a concentration of 8 per cent. but was 88 at 35 per cent. concentration.

Carr, Beck and Krantz (*Jour. Amer. Chem. Soc.*, **58**, 1394-5, 1936) measured the degree of sweetness of various sugars by noting the minimum concentration which would just produce a sweet taste within a half to one minute. In the following table the sweetness is shown together with the number of carbon atoms and hydroxyl groups in the molecule and the molecular weight.

	Sweetness.	C Atoms.	OH Groups.	Mol. wt.
Sucrose	100	12	8	342
Ethylene glycol	130	2	2	62
Glycerol	108	3	3	92
dl-erythritol	238	4	4	122
Penta erythritol	110	5	4	136
l-arabitol	100	5	5	152
d-mannitol	57	6	6	182
dl-sorbitol	54	6	6	182
i-dulcitol	74	6	6	182
Inositol	50	6	6	180

No relation between the number of carbon atoms, hydroxyl groups, or the molecular arrangement or spatial configuration and the sweet taste has been observed in these compounds.

As regards measurement of sweetness, the threshold method has been most used lately, and as has been indicated this depends on the minimum concentration of the substance which can just be tasted. The sweetness is the inverse of this concentration, and for convenience the sweetness figures are usually adjusted to sucrose = 100.

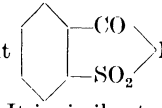
Another method which has been used is Pauli's method (*Biochem. Z.*, **125,** 97-105, 1921, and *Die Umschau*, **24,** 592, 1920), and as this has the advantage of enabling the observer to compare concentrated solutions it will be briefly described. A standard solution of 2 per cent. sucrose is usually used. Then two solutions of the substance to be tested are prepared, one weaker and one stronger than the standard, and then about seven intermediate strengths differing by equal quantities are made up. The observer makes several tests by tasting the series and noting which is weaker or stronger than the standard, and then the series is turned round and more tests made to ensure freedom from chance. This method has the disadvantage of involving remembering sweetness, but by taking many solutions and using several testers, blindfolded, it has given good results. Some of these will be given a little later.

Meanwhile it is necessary to draw attention to the artificial sweeteners saccharin and dulcin at this stage. Whilst sugar is our natural sweetening agent, saccharin finds a place in the diet of diabetics who cannot tolerate sugar, and in war-time in the diet of the general population if sugar is scarce. Saccharin was discovered in 1879 by Remsen and Fahlberg in America. They made it by oxidizing *o*-toluene sulphonamide—



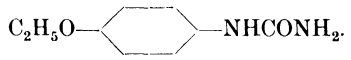
o-toluene sulphonamide. Saccharin.

Fahlberg noted that his bread tasted sweet when eating his supper, traced the taste to his hands and returning to the laboratory identified the sweet substance there. Pure saccharin is about 700 times as sweet as sugar, but the commercial product may be only half as sweet. It is only soluble with difficulty in water, one part in 400 parts of boiling water, but the slight solubility at body temperature is sufficient to give the taste sensation.

The sodium salt 

is readily soluble and is known as " crystallose." It is similar to saccharin itself in sweetness.

Dulcin or " sucrol " is *p*-ethoxyphenyl urea



In Germany interest in this product was shown in 1916 (*Chem. Ztg.*, **40,** 853-5), and it was stated to be harmless to animals and man and to have no bitter after-taste which saccharin possesses. Its sweetness was given as 200 times that of sucrose, so it is considerably less sweet than saccharin.

Paul (*Z. Nahr. Genussm.*, **43,** 137-49, 1922) used Pauli's method to determine the sweetness of saccharin and dulcin. He found that the sweetness was not constant but decreased with increasing concentration of the solution. Thus saccharin may vary between 200 and 700 and dulcin between 70 and 350. Paul also observed (*Elektrochem.*, **27,** 539-46, 1921) that the degree of sweetness of saccharin is increased out of all proportion by the addition of dulcin. Normally the sweetness of mixtures was the sum of the sweetness of the components but saccharin and dulcin gave an anomalously high figure.

Heiduschka and Komm (*Z. angew. Chem.*, **38,** 291-4, 1925) used Pauli's method, and determined the sweetness as "degree of sweetness" compared with an equal weight of sucrose taken as unity, and also as the molecular degree of sweetness compared with an equimolar solution of sucrose. Some of their results were

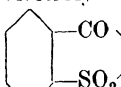
	Degree of Sweetness.	Molecular Degree of Sweetness.
Glycine . .	0·64	0·14
Sarcosine . .	0·62	0·16
dl-alanine . .	0·92	0·24
d-alanine . .	0·73	0·19

Heiduschka, Komm and Simeons (*ibid.*, **38,** 941-5, 1925), using a similar method, investigated the change in sweetness on dilution. They found that the degree of sweetness increases with decreasing dilution (the sugar solutions of course being correspondingly diluted) and that below 5 per cent. there is often a rapid increase. Figures given for two of the amino acids are

	Degree of Sweetness.	Molecular Degree of Sweetness.
2½ per cent. solution glycine . . .	1·19	0·26
5 ,, ,, ,, . .	1·03	0·22
7½ ,, ,, ,, . . .	0·85	0·18
10 ,, ,, ,, . . .	0·77	0·17
15 ,, ,, ,, . . .	0·64	0·14
(cf. above table)		
20 ,, solution glycine . . .	0·55	0·12
25 ,, ,, ,, . . .	0·46	0·10
2½ ,, ,, *dl*-alanine . .	1·70	0·44
5 ,, ,, ,, . .	1·28	0·33
7½ ,, ,, ,, . .	1·06	0·27
10 ,, ,, ,, . .	0·93	0·24

Emil Fischer (*Untersuchungen über Aminosäuren*, 1906) had shown that many α-amino acids have a sweet taste.

Taufel and Wagner (*Ber.*, **58B**, 909-12, 1925) pointed out that as saccharin was sweet and its sodium salt which was a strong

electrolyte was also sweet, the sweet taste was due to the anion  . However, if the dissociation was depressed by the addition of sodium sulphate, sodium acetate, or dilute hydrochloric acid the sweetness was not affected within experimental error (25 per cent.). Dulcin was found to be a very weak base, and its sweetness was considered to be due to the free molecule. They thought the increase in sweetness on mixing solutions of saccharin and dulcin was due simply to the greater dilution each substance then enjoyed so behaving with enhanced sweetness, and was not due to any kind of salt formation.

Täufel and Klemm (*Z. Nahr. Genussm.*, **50,** 264-73, 1925) showed that if alcohol was added to aqueous solutions of saccharin it considerably increased the sweetness.

Gilman and Hewlett (*Iowa State College Jour. Sci.*, **4,** No. 1, 27-33, 1929) compared the sweetness of dulcin, saccharin and some furane derivatives with 2 per cent. sucrose solution. The following are amongst the figures they gave

Sucrose . .	100 (standard)	Furonitrile . .	100
Dulcin . .	265	Furylacrylonitrile	200
Saccharin . .	675	Furfuraldoxime .	2·5

In a similar connection Gilman and Dickey (*Jour. Am. Chem. Soc.*, **52,** 2010-3, 1930) showed that syn-5-benzyl-2-furfuraldoxime was 700 times sweeter than sugar and slightly sweeter than saccharin.

Oddo and Perotti (*Gazz. chim. ital.*, **67,** 543-52, 1937) tried to clear up the point of the anomalously high sweetness of saccharin and dulcin mixtures. Since dulcin is a substituted urea they tried adding (1) urea, (2) thiourea to saccharin solutions. They obtained similar enhancement of the sweetness, so it appears to be a property of the urea grouping. In addition urea shared with dulcin the property of masking the bitter after-taste of saccharin, but thiourea increased this disagreeable feature.

Owing to its intense sweetening power saccharin is often diluted with a less powerful sweetener. Kreidl, for example, in Austrian Patent 122,657 (1930), suggests the dilution of saccharin with glycine, the resulting powder being useful for spreading over confectionery.

Recently Blanksma and Van der Weyden (*Rec. trav. chim.*, **59,** 629-32, 1940) have described a body :

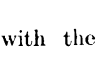
4-nitro-2-aminophenyl propyl ether

$$4\,.\,2\,.\,O_2N\,.\,NH_2C_6H_3OC_3H_7$$

which they say is 3,300 times as sweet as 1 per cent. sucrose and therefore the sweetest substance known. It is about five times as sweet as saccharin.

Some substances have two quite noticeable tastes, sweet at the tip of the tongue and bitter at the back of the mouth. Such a one is " Bittersweet," and the property is due to a glucoside called Dulcamarin found in it. Similarly, certain salts like Epsom salts are simultaneously salt at the tip and bitter at the back of the tongue.

The Bitter Stimulus

Like the sweet taste and unlike the salt and sour, the bitter taste is found in a variety of compounds. We have already seen that whereas sodium chloride is typically saline, caesium chloride is bitter, and that iodides, e.g. potassium iodide, are often bitter. As the molecular weight increases there is a gradual change in the salts, from saline to bitter taste. Cohn pointed out that a similar relation between sweet and bitter existed for many organic substances, as the lower members of a homologous series will be sweet but the higher members bitter. Magnesium and ammonium salts are often bitter, e.g. magnesium sulphate, which is Epsom salts. The bitter taste is due to the Mg^{++} ion and it is of interest to remember that magnesium is the next member of the group of which beryllium (sweet salts) is the first member. Calcium, the next member of the same group, also gives bitter salts. Other well-known bitter substances are picric acid (*πικρός*, bitter) and the alkaloids. In picric acid the bitter taste overwhelms the sour taste. Picric acid contains three $-NO_2$ groups, and it seems to be established that the presence of three such groups in a molecule confers the bitter taste, whilst two may do so. Henry (*Compt. rend.*, **121,** 213, 1895) showed that bitterness was frequently associated with the group  As an example of the change from sweet to bitter on ascending a homologous series we may take the betaines of amino acids. Kuhn and Giral (*Z. physiol. Chem.*, **231,** 208-9, 1935) showed that whereas valerobetaine and caprobetaine had transient sweet tastes, the betaine of aminopentadecylic acid was bitter. One outstanding feature of the bitter taste is that it is so much more sensitive than the others.

Parker and Stabler (*Amer. Jour. Physiol.*, **32,** 230-40, 1913) showed that quinine hydrochloride $C_{20}H_{24}O_2N_2 . HCl . 2H_2O$ could be tasted in a solution as dilute as 0·00004 molar, i.e. 0·0016 per cent., so that if 5 c.c. is used as the test portion this only contains 0·00008 gm.

Scholl and Munch (*Jour. Amer. pharm. Ass.*, **26,** 127-9, 1937) gave comparative figures for the bitterness of different substances as follows:

Brucine . .	1000-1250 (dimethoxystrychnine)
Strychnine . .	320
Quinine . .	100
Aloin . .	33
Theobromine .	5

Gertz (*Skand. Arch. Physiol.*, **44,** 129-42, 1923) has reported that

the minimum detectable concentrations of caffeine and theobromine are respectively 0·006 and 0·004 per cent. From this estimate, and taking into account the comparative figures for bitterness of quinine and theobromine, one would expect the threshold value of quinine hydrochloride to be 0·004 per cent. × 5/100 or 0·0002 per cent., which is about eight times more dilute than the threshold concentration of 0·0016 per cent. determined by Parker and Stabler. Such discrepancies are frequently found, and are to be expected in determinations where the personal equation enters so strongly.

Minimum Stimuli

The threshold values for the four tastes have mostly been given already but are grouped here for comparison.

Sour taste is detectable in N/800 HCl or 0·0045 per cent. HCl.

Salt taste is detectable in 0·055 per cent. NaCl.

Sweet taste is detectable in 0·7 per cent. sucrose or about 0·001 per cent. saccharin.

Bitter taste is detectable in 0·0001 per cent. brucine.

These figures are conservative. For example, Gley and Richet (*Compt. rend. Soc. Biol.*, **37,** 237-9, 1885) reported that strychnine hydrochloride could be tasted in 0·00006 per cent. solution. In any case the bitter taste of strychnine and brucine is clearly detectable in much greater dilutions than the other tastes.

It may be noted that Howell ("Text-book of Physiology," 8th edition, 1922, p. 295) gives the following as the threshold values :

Sour . . .	0·007	per cent.	HCl.
Salt . . .	0·25	,,	NaCl.
Sweet . . .	0·5	,,	Sugar.
Bitter . . .	0·00005	,,	Quinine

His figure for the bitter taste agrees well with Gley and Richet's early figure, the salt taste is high in view of Richter's recent work, whilst the sour and sweet threshold figures agree well with the most recent determinations.

If the sweet stimulus used is sugar the order of sensitivity, highest first, is in each case

Bitter, Sour, Salt, Sweet,

but if the new synthetic sweeteners like saccharin are included, and there is no reason why they should not be, then the order is

Bitter, Sweet, Sour, Salt.

Baryscheva (*Arch. sci. biol. U.S.S.R.*, **40,** No. 3, 139-41, 1936) pointed out that fluctuations in the threshold of the taste sensation can occur in anyone owing to various factors acting on the nervous system. Sensitivity may be enhanced or depressed. With repeated practice a very keen sensitivity can be developed, probably because of the fixation of attention on these sensations. Taking into account

not only the differences between individuals, but also the temporary differences in one individual, it is not surprising that discrepancies are found when comparing threshold values.

Abnormal Stimuli

For many years now it has been conceded generally that there are four primary tastes. It has been claimed that it is possible to make any known taste by suitable mixtures of sweet, salt, sour and bitter substances. For example, von Skramlik (*Physiol. Abstracts*, **6,** 622, 1922) indicated that tastes could be imitated by mixtures of sodium chloride, quinine, tartaric acid and glucose. Most mixtures had three of the four primary tastes as constituents. Baryscheva (*Arch. ges. Physiol.* (*Pflügers*), **215,** 103-5, 1926) also claimed that the taste of any substance may be imitated by using mixtures of solutions of sodium chloride, sucrose, oxalic acid and quinine hydrochloride. The most striking confirmation of the existence of four primary tastes has come from Allen and Weinberg (*Quart. Jour. Exper. Physiol.*, **15,** 387, 1925) who found four critical frequencies of gustation for each electrical stimulus, and were able to link these four frequencies up with the four primary tastes in ways to be described.

Many tastes will occur to the reader which are not readily assigned to any one of the four groups. Meat, for example, the taste of which is also found in glutamic acid salts, is not noticeably sweet, sour, salt, or bitter. In fact, most of its " taste " is odour, and anosmic people cannot distinguish between meats by taste.

The alkalis caustic soda, caustic potash and sodium carbonate have a distinctive taste, sometimes thought to be due to the hydroxyl ion. Such substances can be detected in solutions as dilute as 0·01 per cent. It has been suggested that the alkaline taste is a complex of other tastes and touch, and also that it is due to the alkalis acting chemically on the tongue and producing odorous substances. Neither of these suggestions is very convincing as our experience tells us that alkalis have a distinctive taste. The writer suggests that the alkaline " taste " is a modality not of taste but of the common chemical sense, and it may be noted that alkalis are chemically irritating to other parts of the body as well as the tongue. It would be interesting to compare the threshold values of alkaline solutions on the centre of the dorsal surface of the tongue and on the inside surfaces of the cheeks where there are no taste-buds in adults with the threshold value on the tip of the tongue which is plentifully supplied with taste-buds.

Borax again has an astringent taste not easy to place as sour, sweet, saline or bitter.

A " metallic " taste is excited by solutions of salts of the heavy metals such as silver and mercury. It is stated that silver nitrate can be detected at 0·003 per cent. and mercuric chloride at similar concentrations. The taste is ascribed to the Ag^{+} and Hg^{++} ions, but here again it has been ascribed variously to a mixture of other tastes and to olfaction.

Distilled water has an unusual taste due to the lack of carbon dioxide which occurs in most waters. True insipidity is not necessarily associated with distilled water. The saliva is the liquid standard by which we judge all other tastes and that has not been distilled. Distilled water has a taste like a very dilute solution of alkali.

Hydrogen peroxide has a peculiar taste, and Renqvist (*Skand. Arch. Physiol.*, **42,** 272-80, 1922) considers it to be due to chemical action on the tongue.

Paprika, pepper and ginger, have hot tastes whilst peppermint and menthol have cold tastes, and Stary (*Arch. Exptl. Path. Pharm.*, **105,** 76-87, 1925) considers that these tastes are due to stimulation of the heat and cold sensitive spots on the tongue. In any case such substances as pepper are in the author's view clearly irritants of the chemical sense and will be considered in the next chapter, although in addition to their pungency pepper and ginger have a sweet taste too which adds to their attractiveness.

It has long been known that the passage of an electric current through the tongue evokes a sour taste, partly on account of electrolysis of the saliva producing H^+ ions and partly due to direct stimulation of the receptors by the electric current, just as the nerves of a frog's leg can be so stimulated. This direct stimulation involves not only the sour receptors but also the saline, sweet and bitter receptors.

F. Pasteur (*Compt. Rend. Soc. Biol. Paris,* **121,** 332-4, 1934) reported that a metallic taste is developed when a constant current is passed through a subject with the electrodes on the mandible.

Bujas and Chweitzer (*ibid.*, **126,** 1106-9, 1937) reported that whilst an alternating electric current applied to the tongue with low frequency and intensity gives a sour taste, if the frequency and intensity are increased then a bitter taste is evoked.

Taste Blindness

Just as differences are found between the odour-perceptive powers of different individuals so in taste such differences occur.

As there are four primary taste sensations it might be expected that some individuals would be deficient in one or more of these, but no such cases have been reported. No person is known, for example, to be sensitive to sour, salt and sweet, but insensitive to bitter substances. True, taste may be completely lost by damage to the nervous system, but no destruction of one taste leaving the others unimpaired has been noted. Work on the critical frequency of taste shows that all four tastes are very intimately connected and that any one taste affects the three others, and it may be that differentiation of the four tastes into different senses has not yet proceeded far enough for complete separation to take place.

Nevertheless taste deficiencies are found, and particularly towards synthetics. Whilst dulcin is *p*-ethoxyphenyl urea

$$p\text{-}HOC_6H_4NHCO\,.\,NH_2$$

and is very sweet, the substance *p*-ethoxyphenyl thiourea

$$p\text{-}HOC_6H_4NH \cdot CS \cdot NH_2$$

is bitter, and has been used for investigation of taste deficiencies or taste blindness as it is called. To most people this substance *p*-ethoxyphenyl thiourea is bitter, but some cannot taste it. Snyder (*Science*, **74,** 151-2, 1931) investigated this point and found that 68·5 per cent. of the individuals tested could taste it but 31·5 per cent. could not. When neither parent can taste it, none of the children can taste it either. The deficiency is not sex linked or sex influenced, but it is inherited by offspring according to Mendel's Laws. Fox (*Proc. Natl. Acad. Sci.*, **18,** 115-20, 1932) found that the similar bodies phenyl thiocarbamide, $C_6H_5NHCS \cdot NH_2$, sym-diphenyl thiocarbamide, $C_6H_5NHCS \cdot NHC_6H_5$, and asym-diphenyl thiocarbamide,

$$(C_6H_5)_2N \cdot CS \cdot NH_2,$$

were bitter to some people and tasteless to others. The property was independent of age, race, sex and the *p*H value of the saliva, but was thought to have some relation to the solubility of the substance in the saliva of the person examined. Levine and Anderson (*Science*, **75,** 497, 1932) showed that the percentage of individuals who fail to taste *p*-ethoxyphenyl carbamide is much less among the American Indians than among the white population, only 6 per cent. against 40 per cent.

Blakeslee (*Proc. Natl. Acad. Sci.*, **18,** 120-30, 1932) examined 103 families for taste deficiency towards phenyl thiocarbamide. He concluded that it was due to differences in the taste threshold and was not a real deficiency. As, however, the threshold value is sometimes so high that a concentrated aqueous solution, and even the dry powder, cannot be tasted when placed on the tongue, it is for all practical purposes a deficiency. The experiments showed clearly that the inability was inherited, and also that the ability to taste phenyl thiocarbamide did not run parallel with general acuteness of taste.

Physiological

The number of taste-buds in man may be greater than has been thought. Mochizuki (*Folia. anat. japon.*, **18,** 337-69, 1939, and *Physiol. Abstracts*, AIII, 206, 1940) investigated the foliate papillæ of the tongues of 115 Japanese. There were usually 5 or 6 foliate papillæ at either side, but the total number of taste-buds in the foliate papillæ varied greatly in different individuals from 322 to 2,957, and was usually between 1,300 and 1,400. One single papilla may carry between 13 and 441 taste-buds, usually between 50 and 100. There were no differences between men and women, but the total number of taste-buds was found to decrease with age.

A similar observation respecting age was made by Allara (*Arch. ital. Anat. Embriol.*, **42,** 506-64, 1939), who found that the gustatory papillæ reach their full development at puberty and remain in this

state till the age of 45 when regressive changes occur and atrophy sets in. Recently Richter and Campbell (*Am. J. Physiol.*, **128,** 291-7, 1940) found that the sugar-taste threshold of 58 children averaged 0·68 per cent., whilst that of 52 elderly individuals averaged 1·23 per cent.

The number of papillæ can be counted and the small filiform papillæ are known not to carry taste-buds, whilst the foliate, fungiform, and circumvallate papillæ carry buds in large numbers. The question has been raised whether all the buds in a single papilla are for one of the four primary tastes, say sweet, all those in another papilla for sour and so on. Early workers reached the conclusion that some papillæ had buds sensitive to several tastes but others only responded to a single taste. Thus Kiesow (*Arch. ital. Biol.*, **30,** 377-98, 1898) mapped 39 identifiable fungiform papillæ on one tongue and applied to them with a fine brush solutions of hydrochloric acid, sodium chloride, quinine sulphate and sugar. He found four of the 39 were insensitive to all tastes, but the others responded as follows :

	Acid	Salt	Quinine	Sugar.
Sensitive	18	18	13	26
Insensitive	17	17	22	9

Of those which were sensitive three papillæ were exclusively sensitive to acid, three to salt and seven to sugar. None were exclusively sensitive to bitter, possibly as the front of the tongue was used for experiment. Whilst these results largely confirmed earlier work, recent work on induction has illustrated the difficulties of mapping sensitive spots, whilst work on the critical frequency of gustation has shown how each taste is affected by the others. It is true that Lasarev, in his theory put forward in 1922, accepted the idea of papillæ being exclusively sensitive to one taste, but even he allowed for some papillæ being sensitive to other tastes as well, and there appears to be nothing damaging to his theory in the idea of each papilla being sensitive to more than one taste. The experimental difficulties encountered by Kiesow and other early workers in painting individual papillæ must have been considerable. The weight of evidence favours the view that papillæ are not generally exclusively sensitive to one taste. According to their position on the tongue they will be more sensitive to one taste, bitter if at the back of the tongue for example, but still sensitive to all the tastes.

The relation between taste and the circulation of blood in the tongue was investigated by von Skramlik (*Z. exp. Med.*, **12,** 50-4, 1921). He found that the application of a 20 per cent. solution of glucose to a frog's tongue stopped temporarily the flow of the blood in the capillaries, and the stronger the solution the more effective it was. Quinine in 25 per cent. solution produced just the opposite effect—an increased flow of blood and twitching of the tongue muscles. The effect of quinine was opposite to that of sugar and immediately

overcame it. Dilute 4 per cent. solutions of salt gave a brief acceleration of flow, but more concentrated 10 per cent. solutions stopped the flow. This effect also was immediately overcome by quinine. Weak (0·5 per cent.) tartaric acid solutions increased the blood flow. These observations are very suggestive and appear to have a close correlation with fatigue which would perhaps repay investigation.

Grisogani (*Atti. accad. Lincei.* (6), **1,** 602-4, 1925) investigated the effect of gustatory stimuli on salivary flow. Ordinarily the salivary flow shows periodic oscillation, first flowing then stopping then flowing again and so on. Grisogani found that the flow was more abundant and the crests of the waves of flow higher under gustatory stimulus.

It has been reported by Simons (*Pharm. Weekblad.*, **74,** 315-21, 1927) that an early symptom of arsenic medication is a change in the sense of taste.

Cocaine will abolish taste and the buccal sensations are abolished in the following order : pain, bitter, sweet, saline, sour, and touch, which is an indication of the extent of differentiation the four tastes have undergone. Eucaine-B especially reduces the bitter taste, whilst Stovaine and Gymnemic acid abolish sweet and greatly reduce bitter without greatly affecting salt and sour. Gymnemic acid is obtained from the leaves of the asclepiad *Gymnema sylvestre.*

Work has been carried out on dogs to determine the effect on taste of changes in the mineral balance. Timofeev and Kroll-Lifshits (*Chem. Zentr.*, 1936, II, 1566) took the salivary secretion of the parotid gland as an indication of taste. They found that sodium and ammonium chlorides fed to the dogs depressed their taste sensitivity, but disodium hydrogen phosphate enhanced the sensitivity to acids, but depressed it for salts. If the dogs were exercised for long periods their taste became duller, but not if they were first fed with disodium hydrogen phosphate, in which latter case work had little effect on their thresholds.

In the case of man, sensitivity of taste is found under conditions of repose and freedom from distractions. To enjoy the flavours of food or drink the body must be normal and healthy. Constant use of tobacco particularly dulls the sense of taste.

Temperature

The effect of temperature on taste is of interest, for if taste were purely chemical we should expect it to be enhanced by high and depressed by low temperatures. Olfaction is known to be largely influenced by temperature, and the odour of a substance becomes much more noticeable on warming. Meats and vegetables have more flavour when hot than cold. Several times the normal quantity of flavouring essences must be added to iced food. Iced coffee and Ovaltine have but a fraction of the flavour they have when warm. Food and drink can normally be taken with comfort as hot as 55° C.

Komuro (*Arch. néerl. Physiol.*, **5,** 572-9, 1921) measured the limit of

taste with acid, salt, sugar and quinine, and found that the sensitiveness just about doubled on raising the temperature from 10° to 20° C. and that it was fairly steady from 20° to 30° C. and then fell off from 30° to 40° C. Accordingly any hypothesis that taste is purely chemical fails, but chemical action may still play a large part in it.

Goudriaan (*ibid.*, **15,** 253-82, 1930) reported that an increase in temperature increased the sensations of sweet and sour, but decreased those of salt and bitter. In the case of mixtures sweet prevails over sour, but salt and bitter prevail over sweet.

Critical Frequency

We know that a visual image persists for an appreciable time, say one-twentieth of a second, after the stimulus is removed or the gaze averted. A similar phenomenon occurs in the case of taste but the response is much smarter, and the duration of the taste sensation is much shorter. Let us say for the sake of argument that it is one-hundredth part of a second, then if we apply an instantaneous taste stimulus to the tongue fifty times a second we shall experience an intermittent taste—non-taste series of sensations, and so if we increase the frequency of the applied instantaneous stimuli to 60, 70, 80 and 90 per second. Now if we increase the frequency to 100 per second, each new stimulus will come in just as the sensation from the previous stimulus fades and we shall experience a continuous sensation. This frequency will be known as the critical frequency of gustation, and if it is 100 per second, then the persistency of the taste sensation will be 1/100 second, and similarly, if the critical frequency of gustation is N per second, then the persistency of the taste sensation is 1/N second. Clearly it would be difficult in practice to apply a sweet or bitter substance to the tongue 100 times a second, but it has long been known that an electric current applied to the tongue induces a sour taste, and an electric current is easily controllable as to frequency. Allen and Weinberg (*Quart. Jour. Exper. Physiol.*, **15,** 385-420, 1925) made use of this and set out to find the critical frequency for the sour taste, having little hope of finding suitable stimuli for the other tastes. A current from a storage cell was applied through a potentiometer to control the voltage and a make-and-break device to control the frequency to two electrodes between which the tongue was placed. The intensity of stimulation was first fixed by adjusting the potentiometer, and the limits between which readings were taken were 0·16 and 0·70 volt, as at lower potentials no sensation was experienced, and at higher, muscular twitching was induced. Having set the stimulus, then the speed of the make-and-break apparatus was adjusted until the interrupted sensation just fused into a continuous sensation. Care was taken not to fatigue the tongue. When a large number of measurements were obtained for different voltages, and were plotted, frequency against voltage, it was found that all the readings fell on four well-defined curves, as shown in Fig. 19. The

curves are similar in character, gently sloping upward at low voltages with a decided increase of slope and rapid convergence towards a point at high potentials. As the potential increases, the critical frequency is reduced, or in other words, the duration of the sensation is increased. The fact that there were four curves is strong evidence of the existence of four fundamental tastes all of which are stimulated by the electric current. This shows that they are not independent. There were many more points on one of the curves than on the others, and as the

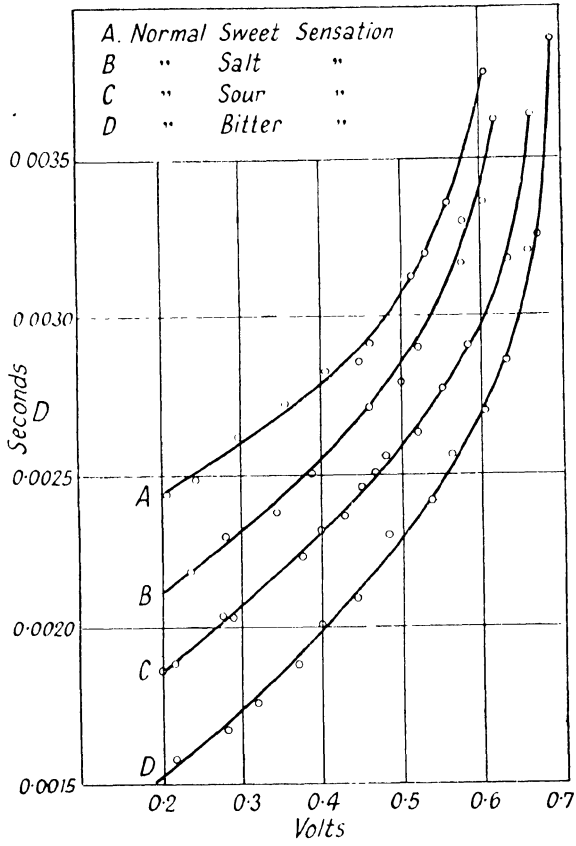


FIG. 19.—Normal gustatory sensation (after Allen and Wemberg).

predominant taste sensation on passing the current is sour, this curve was taken to be that for the sour taste. Now gymnemic acid is known to anæsthetize the sweet taste and partly the bitter, and therefore the tongue was rinsed with a one-half per cent. solution of gymnemic acid, and critical frequency measurements taken again. This time there were only three curves, sweet being absent, and one of the three,

bitter, was very short. In this way the identity of each of the four curves was determined and was as follows (Fig. 19) :

A	Sweet.	C	Sour.
B	Salt.	D	Bitter.

Typical durations (inverse of critical frequency) were as follows :

Voltage.	Duration in Seconds.			
	Sweet	Salt.	Sour.	Bitter.
0·20	0·0024	0·0020	0·0018	0·0015
0·40	0·0028	0·0025	0·0023	0·0020
0·60	0·0037	0·0034	0·0030	0·0027

It will be seen that the average duration of the taste sensation is about one-four hundredth part of a second, and that taste is thus much smarter in reaction than sight or hearing. Bitter is smarter than the other tastes and is known from minimum stimulus measurements to be the most sensitive taste. The sensitivity of the four tastes is in the order bitter, sour, salt, sweet, and this is the same order as that in which the tastes group themselves in increasing order of critical frequency. This, however, leaves out of account synthetic sweeteners like saccharin and dulcin.

Now the taste on electrical stimulation is due to electrolysis of the saliva with formation of ions, and in electrolysis the significant factor is the quantity (coulomb) of electricity, obtained by multiplying the current by the time. According to Ohm's Law

$$i = V/r,$$

where i is the current through the tongue,
V is the potential difference,
r is the resistance of the tongue between the electrodes and may be considered constant.

Where D is the duration and Q the quantity of the stimulus

$$Q = iD$$

$$= \frac{1}{r} . VD = A . VD,$$

where A is the constant $1/r$.

Taking logarithms

$$\log Q = \log (VD) + \log A,$$

and as V and D are experimentally measured, Q, the measure of the stimulus, can be found.

When the results were examined it was found that the following relation held :

$$1/D = -k \log Q + C,$$
$$\text{or} \quad = -k \log (VD) + k \log A,$$

where k and $\log A$ are constants.

The similarity of this to Fechner's Law will be noted. The equation fits the results, and when $1/D$ is plotted against $\log Q$, the " curves "

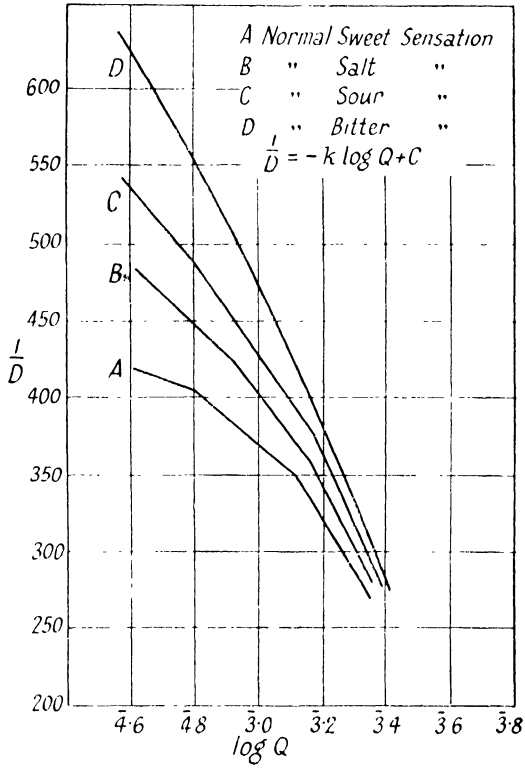


FIG. 20.—Normal gustatory sensation (after Allen and Weinberg).

are straight lines with two abrupt changes of slope, as shown in Fig. 20. The convergence of all four curves to a point at a high intensity of stimulation is again well marked. The three branches of each curve are to be noted. Previously it had been thought that Fechner's Law, that the sensation is proportional to the log of the stimulus, only held for the middle range of intensities, but it is now clear that it holds throughout, but that different constants obtain for very low and very

high degrees of stimulation. Similar relations have been obtained for other sensations and may be compared :

Taste $1/D = -k \log Q + C$
Vision $1/D = k \log I + C$ where I is the intensity of illumination.
Audition $D = k \log P + C$ where P is the air pressure.
Touch $D = -k \log P + C$ where P is the pressure.

We may say that the persistence of the sensation varies either directly or inversely as the logarithm of the intensity of stimulation. The changes of slope indicate that at some definite intensity of stimulation there is a definite change in the sensitivity of the receptors. Whilst the equations fit the observed results, the physiological significance of the changes from $1/D$ in vision and taste to D in audition and touch, and from k in vision and audition to $-k$ in taste and touch is not understood. As the four possible arrangements are taken up with these four senses, it will be doubly interesting to see what equation prevails for smell, when the critical frequency measurements can be made.

The values of D, the duration, for the different senses are

Vision . . .	0·013 to 0·045	second.
Audition . .	0·0127 to 0·0215	,,
Touch . . .	0·0024 to 0·0089	,,
Taste . . .	0·0015 to 0·0040	,,

Fatigue

The sense of taste is particularly liable to fatigue. If a toffee is kept still in the mouth the sweet sensation disappears and the result is unsatisfactory, so we keep on moving the toffee round with the tongue, increasing the rate of solution and bringing fresh taste-buds into action. Similarly, two successive dishes with the same flavour are not served in a meal. In their experiments Allen and Weinberg took care that the electric current was only passed through the tongue for two or three seconds at a time, and that intervals of 20 minutes or so were allowed between observations to enable the tongue to recover from fatigue. They also made measurements in cases where the tongue was deliberately fatigued to observe the results. Generally, the effect of fatigue is to increase the duration of sensation, or in other words, reduce the critical frequency and the sensitivity. In the fatigue experiments the same side of the tongue as that on which the electrodes were set was stimulated by solutions of (1) bisulphate of quinine, (2) acetic acid, (3) sodium chloride, and (4) sugar for the bitter, sour, salt and sweet tastes respectively. First a one-eighth per cent. solution of bisulphate of quinine at the mouth temperature was applied for 45 seconds and the mouth quickly rinsed with water at the same temperature, and a measurement of the critical frequency taken. It was found that the duration for all four tastes was increased, i.e. all were fatigued and working at reduced sensitivity. This illustrates clearly the inter-dependence of the four tastes and explains

how such a large variety of taste sensations are known. It was to be expected that application of a quinine salt to the tongue would fatigue the bitter taste receptors and reduce their sensitivity, but it could not have been predicted that it would also fatigue the sour, salt and sweet taste receptors. The quantitative effect may be seen from these figures, all taken at a potential of 0·40 volt.

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0028	0·0025	0·0023	0·0020
Fatigued with quinine bisulphate	0·0029	0·0027	0·0024	0·0022

These differences are well outside experimental error, and indeed, Allen and Weinberg in their original paper give their results to another significant figure.

Next, fatigue of the sour receptors was attempted with a 1·5 per cent. solution of acetic acid, applied as before. This proved to depress the salt, sour, and bitter receptors, which suffered from fatigue, but to enhance the sensitivity of the sweet sensation. Comparative figures for the duration of sensation, all with a potential of 0·40 volt, are

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0028	0·0025	0·0023	0·0020
Fatigued with acetic acid. .	0·0026	0·0027	0·0025	0·0021

The duration for salt, sour, and bitter is increased, i.e. the receptors have been fatigued by the acetic acid, but the opposite is the case for the sweet receptors. This is the physical interpretation of the well-known experience that sweets taste sweeter after taking something sour. The experience is not " psychological " in the sense that it does not conform to known physical laws. It is not commonly realized though that fatigue with a sour substance makes the subject less sensitive to salts and bitters.

Next, fatigue of the salt receptors with 10 per cent. sodium chloride solution was attempted. Again bitter, sour, and salt sensations were depressed owing to fatigue, but sweet was enhanced. Over the range 0·52 to 0·65 volt sweet sensitivity was anomalously and very greatly enhanced. The reason for this is not known. Durations of sensation were as follows, at a potential of 0·40 volt :

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0028	0·0025	0·0023	0·0020
Fatigued with sodium chloride .	0·0028	0·0026	0·0024	0·0021

and at a potential of 0·60 volt, which was in the range of anomalous sweet enhancement :

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0037	0·0034	0·0030	0·0027
Fatigued with sodium chloride .	0·0024	0·0036	0·0030	0·0028

The salt receptors, as would be expected, are most severely fatigued by the salt solution, but the sour and bitter receptors are also fatigued. The extreme enhancement of the sweet receptors was quite unpredictable. The addition of a pinch of salt to coffee would depress the bitter taste and enhance the sweetness, but it is certainly not usual to add salt to tea where the same considerations might apply.

Finally a 5 per cent. solution of sugar was used to fatigue the sweet receptors. There was a high degree of depression of the sweet sensation and some depression of salt and sour (bitter not recorded). Using 0·40 volt potential, the duration times were

	Duration in Seconds.		
	Sweet	Salt	Sour.
Normal	0·0028	0·0025	0·0023
Fatigued with 5 per cent. sugar .	0·0031	0·0026	0·0024

Hence fatigue with 5 per cent. sugar solution depressed sweet, salt and sour receptors.

Surprisingly, "fatigue," with a much more concentrated sugar solution, 20 per cent., resulted in enhancement in sensitiveness of all four receptor systems. With a potential of 0·40 volt the duration times were

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter
Normal	0·0028	0·0025	0·0023	0·0020
"*Fatigued*" with 20 per cent. sugar	0·0027	0·0024	0·0023	0·0018

Hence the effect of a stimulus upon the gustatory receptors depends upon its concentration, low concentrations causing depression of sensitiveness and high concentrations, enhancement. According to Allen and Weinberg, both depression and enhancement reflexes are caused in all these cases, and it is just a question of which is the greater of the two. The results of the fatigue are summarized in the following

table. It should be remembered that an increase in duration indicates fatigue or depression and *vice versa :*

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0028	0·0025	0·0023	0·0020
Fatigued with 0·125 per cent. quinine bisulphate . .	0·0029	0·0027	0·0024	0·0022
Fatigued with 1·5 per cent. acetic acid	0·0026	0·0027	0·0025	0·0021
Fatigued with 10 per cent. sodium chloride . . .	0 0028	0·0026	0·0024	0·0021
Fatigued with 5 per cent. sugar.	0·0031	0·0026	0·0024	—
Fatigued with 20 per cent. sugar	0·0027	0·0024	0·0023	0·0018

All at 0·10 volt potential.

Induction

Usually, if receptors are subjected to a stimulus they become fatigued. (Such a case as a concentrated solution (20 per cent.) of sugar enhancing the sensitiveness of the sweet receptors is unusual.) But the effect on neighbouring receptors is quite the opposite for they are usually made more sensitive. If the tip of a finger is lightly touched, that finger-tip becomes fatigued and less sensitive to touch, but the tip of the finger next to it becomes, by some reflex action, more sensitive. The first finger before becoming exhausted passes through the central system a message to its neighbour to be on the *qui vive*. Similarly, if the upper lip be lightly stroked with a brush, the sensitivity of the lower lip to touch is temporarily enhanced. This phenomenon is known as induction. On account of it, it is impossible to stimulate any receptor without affecting those near to it. Consequently when an attempt is made to count the hot, cold, and touch-sensitive spots on, say, the tongue, it is found that the counts vary, and when the spots are mapped no consistency can be gained, due to the simultaneous effects of fatigue and induction.

A similar effect is found in the sense of vision (Allen, *Jour. Op. Soc. Amer.*, **7**, 583, 913, 1923). For when one eye was stimulated with bright light, the three primary sensations, red, green and violet, in the other eye were enhanced in sensitiveness.

Having investigated the effect of fatigue on taste by first applying a taste stimulus to the side of the tongue to which the electrical stimuli were also applied, Allen and Weinberg then applied the taste stimulus to the opposite side of the tongue to which the electrical stimuli were applied and so investigated the effect of induction.

The left side of the tongue, i.e. the opposite side to that in the electrodes, was stimulated as before with 1·5 per cent. acetic acid, and it was found that the sensitivity of all receptors on the right side was enhanced. When a 20 per cent. solution of sodium chloride was used, again all receptors on the opposite side were made more sensitive.

When the left side of the tongue was stimulated with 0·125 per cent. quinine bisulphate, a paradoxical result was obtained, as all the receptors on the right side were depressed in sensitivity. The reason for this is not clear, but abnormalities in the bitter receptors had also been noted when the sour and salt stimulants were used. Durations of sensation were as follows, all at 0·40 volt potential :

	Duration in Seconds.			
	Sweet.	Salt.	Sour.	Bitter.
Normal	0·0028	0·0025	0·0023	0·0020
0·125 per cent. quinine bisulphate	0·0029	0·0026	0·0024	0·0021
1·5 per cent. acetic acid . .	0·0026	0·0023	0·0022	—
20 per cent. sodium chloride .	0·0026	0·0024	0·0022	0·0019

From the table it will be seen that a bitter stimulus applied to the left side of the tongue has fatigued all the taste receptors on the right side of the tongue, but that sour and salt stimuli applied to the left side of the tongue has enhanced by induction the right side of the tongue.

Whilst all these results appear to have a general pattern running through them, that stimulus of receptors fatigues those receptors but enhances the sensitivity of adjacent receptors, there are some results which invite further investigation, notably the anomalous enhancement of the sweet sensation by a certain range of salt stimuli applied at the same side of the tongue, and the paradoxical depression of all receptors by a bitter stimulus applied at the opposite side of the tongue. These results are bound to raise again the question whether there is only one type of end-organ which is responsive to all taste stimuli, the different sensations being due to different degrees of stimulation, or whether there are four independent or partly independent gustatory end-organs. The balance of the evidence at present points to the existence of four different types of receptors specific to sour, salt, sweet, and bitter, and these receptors being connected through nerves and synapses, so that activity in one induces activity on a small scale in others adjacent to it. Some people have taste deficiencies, or at least greatly elevated thresholds of sensation, for certain substances, such as phenyl thiourea, which supports the view that the taste mechanism is made up of component parts, one of which may be missing in some persons.

Theories

In considering theories of taste we may bear in mind the following points :

(1) Actual contact of the sapid substance with the tongue or surrounding surfaces is necessary. We cannot taste at a distance.
(2) The receptors—the taste-buds—are exposed on the surface, or are connected to the surface of the tongue by canals—the gustatory pores.

(3) The typical stimuli are concentrated aqueous solutions in contrast with the lipoid soluble substances which act as stimuli to olfaction.
(4) Taste " fatigue " occurs on continued stimulus.
(5) Taste enhancement occurs by contrast or " induction," for example, distilled water has a sweet taste immediately after we have experienced a sour taste.
(6) There are four well-established primary tastes.
(7) There is an optimum temperature of 20° to 40° C. for taste.

Renqvist (*Skand. Arch. Physiol.*, **38,** 97-201, 1918) regarded the taste surfaces as a colloidal solution, in which the protoplasmic sensory particles and their components were suspended in the liquor or solution to be tasted. Then taste sensation would be due to adsorption, on the sensory particles, of the substance in the solution, and equal degrees of sensation would correspond to adsorption of equal amounts. On this basis it would be expected that valency would be important, and it was found that the concentration of chlorides of divalent elements like barium and calcium was less than that of the chlorides of monovalent elements like sodium to give equal sensation, whilst the concentration of the chloride of aluminium (trivalent) necessary was still less. The phenomena of taste differences between isomers is partly explained if the mechanism of taste involves adsorption, for it is well known that adsorption involves three dimensional arrangement, for example, when a monomolecular layer of a fatty acid floats on water, with all the carboxylic groups anchored in the water, and the long carbon chains rearing upwards from the surface. Such a theory of adsorption from a solution also goes some way to accounting for the many taste phenomena which appear to be due to ions. The adsorption potentials at the interfacial surface of a polar liquid and an oil were said to be due to accumulations of oppositely charged ions on the two sides of the interfacial surface by Ehrensvärd and Sillén (*Nature*, **141,** 788-9, 1938), who further suggested that such adsorption potentials probably play a part in taste and smell perception.

Lasarev (*J. Russ. Phys.-Chem. Soc. Phys. Sec.*, **54,** 106-9, 1922) put forward a chemical theory. The papillæ are separately sensitive (this is open to question) to sweet, sour, salt and bitter stimuli, although some sweet substances may affect the sour, salt and bitter papillæ so giving *nuances* of taste. Each papilla is supposed to contain a taste-sensitive substance which reacts chemically with, and is decomposed by, the appropriate sweet, sour, etc., stimulus to which it is sensitive. The decomposition product is then said to ionize and to excite the nerve terminals in the papilla.

Hahn (*Physiol. Abstracts*, **22,** 212, 1937) made experiments on adaptation in taste, and presented evidence to show that taste is due to a monomolecular chemical reaction between the sapid substance and an unknown chemical substance situated as a substrate on the surface of the tongue.

Michael, who introduced the idea of "brightness" of taste and smell, notes that a taste may be "brighter" than any odour could be. With Limmer (*Arch. ges. Physiol.* (*Pflüger's*), **233,** 645-51, 1933) he attempted to correlate the sensitivity of the tongue to sapid substances with the heats of solution of the sapid substances. The tongue is sensitive to temperature differences of 1° or 2°. Since potassium nitrate and sodium bromide have very different heats of solution, it is possible by this means to distinguish a mixture of 5 KNO_3 95 NaBr from pure NaBr.

It will be seen that the three lines of attack are (1) adsorption, (2) chemical, (3) heat of solution. There is no reason why (3) should not be combined with (1) or (2) as a separate factor. That taste is primarily stimulated by a chemical reaction seems probable, and that ionization plays a part is certain. It is equally certain that it is not entirely chemical or stereo-isomers could hardly have different tastes as they do have in many cases. Possibly molecular vibration (cf. Dyson's correlation of the Raman effect with odour) is the initial stimulus, but that it is followed by chemical action or adsorption or chemical orientation on the tongue is most likely.

CHAPTER 6

THE COMMON CHEMICAL SENSE

Function

The recognition of chemical sensibility, distinct from smell and taste, as a separate sense is due to Parker. Sensibility to chemical irritants had long been known, but it was only when Parker correlated the existing information and carried out a great deal of new work, particularly on fishes, to show how separate and distinct a sense it is, that it came to be recognized as a separate sense. This work is dealt with later in this chapter, but it would not be fitting to start otherwise than by acknowledging the debt the subject owes to Parker.

Chemical sensibility is primitive. The lowly protozoa *Paramecium* takes an avoiding reaction on the approach of chemical irritants in the water it inhabits. The sea-anemones contract on chemical irritation, the jelly-fishes, the flatworms, the earthworms all show a negative tropism to chemicals and get away from them as fast as possible. The legs of the lobster are covered with tens of thousands of sensory bristles, many of them chemically sensitive. In the vertebrates, the fishes and amphibia have chemical receptors spread over large areas of the skin. The function of these receptors is to notify the approach of danger, and is not connected with nutrition for which the differentiations, smell and taste, cater.

As animals leave the water as they evolve and take to the land, their skin becomes more horny and the chemical sensibility is restricted to small areas. In man the mouth and nasal cavities, the eyes, anus and reproductive openings are all sensible to chemical action. In fact any part where the mucous membrane is exposed or semi-exposed is vulnerable. A cut or scratch on the hand is similarly sensitive. The same restriction of the receptors to relatively small areas applies to the mammals and birds, and it is only when we descend to the amphibia that an enormous increase in the vulnerable areas is found. As the function of the sense is to warn of the approach of danger, and as aquatic animals are clearly more likely to be injured by chemical irritants in the water than are land animals, the necessity for the much more widespread system of receptors in amphibia and fishes is evident.

The Stimulus

For aquatic animals the stimulus is a chemical irritant in the water. Such might be the salt in sea-water to a fresh-water animal, or conversely, the absence of salt in fresh-water to a sea fish which strayed into a river mouth, or the poisonous discharges of certain inimical plants and animals, or the chemical pollution of areas of

the sea by volcanic disturbances. The coming of the Industrial Age must have thrown a heavy extra load on the chemical receptors of the fishes. For man the stimulus is normally an irritant, pungent, lachrymatory or suffocating vapour in the air, but it may also be a solid or a liquid. The solid may be dispersed in the air as a smoke, and the liquid may cause irritation in the form of a finely dispersed mist in the air or, alternatively, if it should make contact in bulk with the body. Examples frequently encountered are the action of onion vapours making the eyes water, pepper inducing sneezing, acid fumes causing smarting, ammonia causing distress to the eyes and sneezing, and chlorine attacking the eyes and causing choking. The receptors are the free nerve endings of the trigeminal—the fifth cranial—nerve.

A dog which has had the olfactory nerve severed is still sensitive to ammonia and irritants. People who are anosmic as a result of damage to the olfactory nerve, or to the central system, still use smelling salts and snuff and smoke tobacco, and are just as liable to irritation by ammonia or pepper as normal subjects. Chemical sensation is independent of the normal olfactory system. It is not so delicate as smell or taste. For example a very dilute solution of hydrochloric acid which will not irritate the mucous membrane will still evoke a sour taste in the mouth, and Parker and Stabler (*Amer. Jour. Physiol.*, **32,** 230-40, 1913) reported that whereas a 3 molar (13·8 per cent.) solution of ethyl alcohol will stimulate taste, a 5 to 10 molar (23 to 46 per cent.) solution is necessary to stimulate man's irritant receptors. The disparity between the sensitivity of smell and the chemical sense is, of course, much greater.

Katz and Talbert (*Chemical Abstracts*, **25,** 547, 1931) measured the intensities of stimulation of 55 different substances for odour, eye irritation, and nasal irritation. They found that trinitro tertiary butylxylene (artificial musk) was the most powerful as an odour and was observable at 0·00005 part per million, whilst chloracetophenone was the most powerful eye irritant, observable at 0·0083 part per million, and was also the most powerful nasal irritant, observable at 0·021 part per million. It is interesting to note that the eye is two or three times as sensitive as the irritant receptors in the nose, but is nevertheless 160 times less sensitive than the olfactory apparatus in the nose.

Two methods of stating concentration are in common use :

(1) In parts per million vol./vol., i.e. in c.c./cu. metre.
(2) In mgm./cu. metre.

The second system takes account of the molecular weight of the substance. To convert parts per million into mgm./cu. metre it is necessary to multiply by molec. wt./22·4, since 22·4 c.c. of a gas weighs M mgm. where M is the molec. wt.

In the case of chloracetophenone M is 154·5, so that

$$0{\cdot}0083 \text{ p.p.m.} = \frac{0{\cdot}0083 \times 154{\cdot}5}{22{\cdot}4} = 0{\cdot}058 \text{ mgm./cu. metre,}$$

and $$0{\cdot}021 \text{ p.p.m.} = \frac{0{\cdot}021 \times 154{\cdot}5}{22{\cdot}4} = 0{\cdot}15 \text{ mgm./cu. metre.}$$

Reactions

A great difference is apparent between the reactions to common chemical stimuli and olfactory stimuli. The reactions to the latter are usually gentle, a sniff to enhance the pleasure of a perfume, and at most a recoil from a fœtor, but the responses to irritant stimuli are vigorous. First, there is an attempt to avoid the stimulus on the lines developed by the paramecium, then tears may stream from the eyes and vision may be temporarily lost, or sneezing or choking may ensue so that the subject or victim is temporarily incapacitated.

A Separate Sense

We customarily speak of the smell of an onion or of ammonia, and whilst it is true that both have true odour, we include in the term "smell" the chemical irritation. Really, it is quite a separate effect, since people who have damaged their olfactory nerve and are quite anosmic to true smells like essential oils, perfumes, and food flavours, are still normally cognizant of ammonia, chlorine, and such irritants. The free nerve endings of the trigeminal nerve are affected by chemical irritants and are independent of the olfactory and gustatory nerves. Parker showed that when a piece of meat was held close to the flank of a catfish, *Amiurus*, it would turn round and snap at it, since the flank is covered with taste-buds, but that if one of these fishes has the nerves serving the taste organs and the lateral line organs cut, it no longer snaps at the bait. Such a fish is, however, sensitive to sour, saline, and alkaline solutions, but not to sweet. As the only receptors left in order are the free nerve terminals, it must be these which are operative.

In the same way this type of nerve ending is the only one that occurs in parts of the skin of the dogfish, *Mustelus*, which is very sensitive to acids and alkalis, less so to salts and bitters, and not at all to sugar solution.

It is well known that a frog's foot, which contains no taste organs, can be stimulated by very dilute acid solutions. These experiments clearly show the distinctiveness of the chemical sense from taste.

Whilst our own experience tells us that the sensations we experience, when the mucous surfaces are irritated, are different from smell, taste, and touch, there is a little more resemblance to the sense of pain. Experiments have therefore been carried out on animals to show if the common chemical sense is separate from that of pain. In one case the tail of a lancetfish, *Amphioxus*, was subjected to twenty applications in rapid succession of a 0·025 molar solution of nitric acid and then did not respond to further applications of this acid.

The chemical receptors were fatigued but not the touch receptors, since the fish reacted when its fatigued tail was touched with a light brush. In another case a fish had its tail stroked with a brush thirty times, and then, when it was fatigued to touch and did not respond to further strokes, it still did respond to stimulation of the skin with weak acid.

In another case Sheldon (*Jour. Comp. Neurol. Psychol.*, **19,** 273-311, 1909) treated the surface of a dogfish with a 2 per cent. solution of cocaine, and found that, whilst this anæsthetized the fish to touch in 10 to 20 minutes, chemical sensitivity continued much longer, although it was eventually abolished. Crozier (*ibid.*, **26,** 1-8, 1916) used ½ per cent. cocaine on a frog's foot and found that after a time the frog no longer reacted to pinching but did so to a dilute solution of formic acid.

It is clear that the chemical sense is distinct from smell, taste, touch, and pain, and has a separate set of receptors. These receptors are the free nerve endings of spinal and cranial nerves, and are comparable in distinctiveness with heat, cold, or pain receptors, but are more localized.

Classification of Stimuli

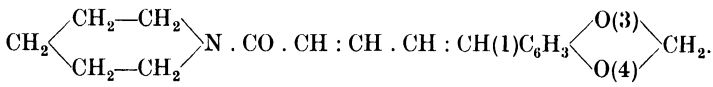
A variety of substances irritate the chemical sense receptors. The different sensations we experience from such substances attacking the eyes, or the nose or the throat, strongly suggest that there are different modalities of the chemical sense just as there are of the gustatory sense. The chemical irritants are characterized firstly, as one might expect, by their chemical reactivity, and secondly, by the relatively large quantities required to promote sensation. This last factor points to the action being primarily chemical and not due to molecular vibrations as is thought to be the case with smell. Certain broad differences as between lachrymatory substances and nasal irritants are at once apparent, and in order to simplify the treatment of the subject, I propose to divide the irritants into classes on the basis of the sensations they arouse, and examine the members of the classes for common or diverse features.

Pungent Spices

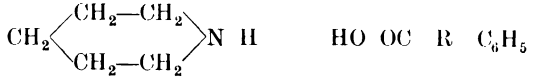
These act by irritation of the inner oral and nasal surfaces. They cause mucus to flow from the nose and induce sneezing, both of which are reflex actions designed to remove the irritating substance from the nose. Such are pimento, mace, nutmeg, vanilla, cinnamon, ginger, cassia and pepper.

The best known of such substances is pepper. The appreciation of this spice with food rests on two factors: (1) its pleasant sweetish taste, and (2) its irritant action on the common chemical sense receptors in the mouth. If pepper is dissipated in the air it attacks the common chemical sense receptors in the nose, and these are much more sensitive than those in the mouth.

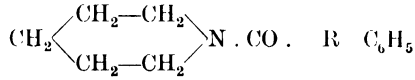
Pepper is the fruit of *Piper nigrum* and *Piper longum*, and is ordinarily ground before use. Its active constituent is piperine, which is the piperidide of piperic acid and is an alkaloid with this constitution:



Staudinger and Schneider (*Ber.*, **56B**, 699-711, 1923) showed that crystallized piperine when bitten into had only a slightly sharp taste, but an alcoholic solution gave such an intensely sharp sensation that it overwhelmed the pleasant taste of pepper. The reason for the crystals only having a slight taste is their relative insolubility in the saliva. When piperine was ground with twenty times its own weight of flour for six hours the product had only a faint peppery taste, but if the grinding was continued for ten days, then the product had the same sharpness as pepper. Hence piperine is the chief active agent of pepper, and the peppery taste experienced in the mouth depends on the degree of dispersion of the piperine, and the finer the dispersion the more readily it can react with colloidal structures on the tongue and in the mouth. Investigation has shown that the constitution of piperine may be varied considerably without affecting the peppery taste provided that the amide union of the piperidine nucleus with an aliphatic-aromatic acid is retained. The formation of this union may be represented:



Piperidine. Aliphatic-aromatic acid.



Pepper-like substance.

where R represents an aliphatic chain which may be saturated, or unsaturated as in the case of natural pepper, and where the C_6H_5 group may be substituted.

Staudinger and Schneider found that amongst synthetics the peppery "taste" was most pronounced in derivatives of δ-phenylvaleric acid which is

$$C_6H_5CH_2CH_2CH_2CH_2COOH.$$

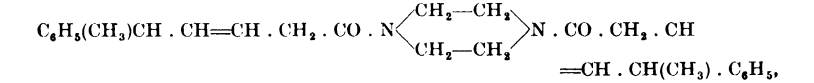
In piperic acid the chain length is similar to δ-phenylvaleric acid, but there are two points of unsaturation, whilst in addition the benzene nucleus is also substituted.

Now piperidine, which is a base, will combine to form a salt with piperic acid, and this salt does not taste sharp, but it is only when water is eliminated to form the amide that the sharp taste appears. Hence the amide union is essential.

Other substances of similar constitution were shown to have a pepper "taste," e.g. β-cinnamenyl acrylic piperidide, as a 2·5 per cent. mixture in flour was as sharp as natural pepper, which contains 5 to 10 per cent. piperine. This shows that the methylene-dioxy group is not essential to the pepper taste, and as dihydropiperine and tetrahydropiperine have equally strong pepper tastes, the unsaturation is not essential.

Rheinboldt (*Ber.*, **56B**, 1228-9, 1923) confirmed that purified piperine had only a slight taste but that its alcoholic solution was very sharp.

Riccomanni (*Atti. accad. Lincei* (V), **33**, 145-8, 1924) reported that the presence of a piperidine nucleus in the molecule was not necessary to give the pepper "taste," since the compound 1 . 4-di-δ-phenyl-Δ^{β}-pentenoyl piperazine,



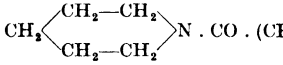
had a pungent aromatic taste, and mixed as a 2 per cent. dispersion in flour gave a taste similar to that of pepper. Also styryl methyl ketone gave a sharp taste as a 1 per cent. dispersion in flour. This ketone has a relatively simple constitution,

$$C_6H_5CH : CH . CO . CH_3.$$

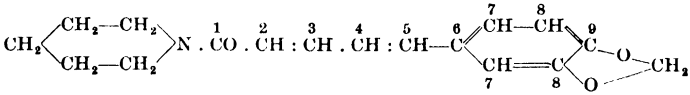
Asano and Kanematsu investigated the pungency of the piperidides of the fatty acids with 8 to 14 carbon atoms (*Jour. Pharm. Soc. Japan*, **531**, 375-80, 1926). They found as follows :

C_8	caprylic acid piperidide	Weakly pungent.
C_9	pelargonic acid piperidide	Violently pungent.
C_{10}	capric ,, ,,	Distinctly pungent.
C_{11}	undecylic ,, ,,	Weakly pungent.
C_{12}	lauric ,, ,,	Not pungent.
C_{14}	myristic ,, ,,	Tasteless.

The constitution of the violently pungent compound, pelargonic piperidide, is

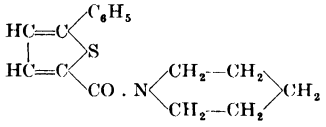


so evidently the benzene nucleus is not necessary to give pungency in this type of compound. Of course, the more the constitution of the "piperine" is altered the less the product has the true taste of pepper as distinct from its pungency. It is interesting to note that there are nine carbon atoms in the pelargonic chain attached to the piperidine residue in the violently pungent material, and there are also nine atoms in the unbroken carbon chain similarly placed in the piperine molecule :



and also nine in Riccomanni's piperazine derivative.

Substances like pepper must be partly soluble to cause irritation. Steinkopf and Gording (*Biochem. Z.*, **292**, 368-70, 1937) showed that 2 phenylthiophen-5 carboxy piperidide

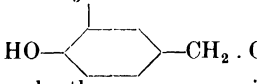


is tasteless in crystalline form, but in dilute alcoholic solution has a sharp peppery taste and burns the tongue.

It will be seen that substances with very different constitutions may be peppery, but that usual constituents of peppers are a piperidine nucleus joined by an amide linkage, to a nine-carbon chain acid.

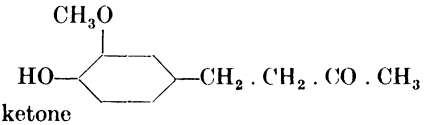
Another substance which is of particular interest from our familiarity with it and which may be classed with pepper is ginger. It has a similar hot, spicy taste and irritates the interior surfaces of the mouth. It is true that we do not usually associate sneezing with ginger, but I think it is similar to, although milder than, pepper. Ginger has a more marked and sweeter true taste than pepper, but also it excites a burning irritant sensation which belongs to the common chemical sense. Like pepper it is pungent.

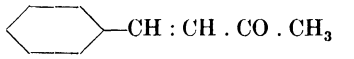
Lapworth, Pearson and Royle, and Lapworth and Wykes (*Jour. Chem. Soc.*, **111**, 777-98, 1917) investigated the active principles of African ginger, this being the most pungent kind in use. The ketone zingerone, $C_{11}H_{14}O_3$, was isolated and found to have the constitution 3-methoxy-4-hydroxy-phenylethyl methyl ketone or

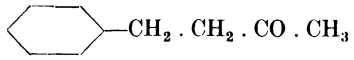


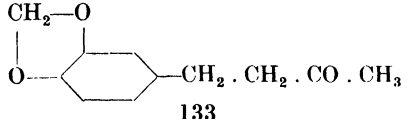
They considered that the phenolic group and the >CO group in suitable relation to each other were responsible for the pungency.

Nomura and Nozawa (*Sci. Rep. Tohôku. Imp. Univ.*, **7**, 79-92, 1918, and *Chemical Abstracts*, **13**, 118, 1919) made various phenolic ketones resembling zingerone and tasted them to find what factors determined the pungency of the product. Some of their results are as follows :

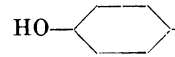
Zingerone  Pungent.

Styryl methyl ketone  Pungent.

Phenylethyl methyl ketone  Pungent.

3,4-methylene-dioxyphenylethyl methyl ketone  Pungent.

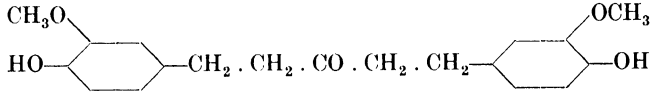
p-hydroxyphenylethyl methyl ketone



Pungent.

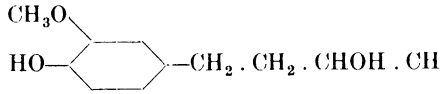
It is clear that considerable variations in structure are possible without affecting the pungency.

Later in 1925 Nomura and Hotta (*Sci. Repts. Tohôku. Imp. Univ.*, **14,** 119-25, and *Chemical Abstracts*, **19,** 2943, 1925) synthesized di-(4-hydroxy-3-methoxyphenylethyl) ketone



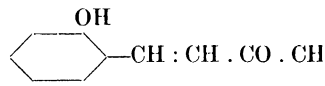
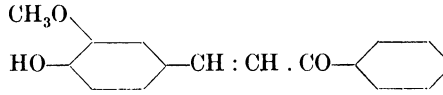
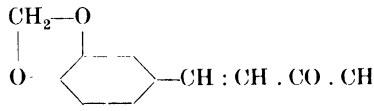
and found that it is almost tasteless in the solid state, but a little pungent in alcoholic solution. This is rather surprising as the characteristic feature—the 4-hydroxy-3-methoxyphenylethyl group—of zingerone is duplicated. It is, however, often found that two components are necessary to give sensation, and that one of the components is a light radicle, as we saw in the glucophore and auxoglue theory, and as we shall also find in the Toxophor-Auxotox theory.

It was also shown that when zingerone was reduced to the secondary alcohol 4-hydroxy-3-methoxy-phenylethyl methyl carbinol

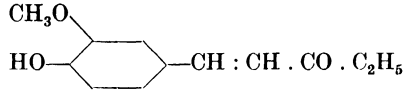


this was also pungent, so that the presence of the >CO group in the side chain was not absolutely essential for the pungency, although the secondary alcohols were not so pleasant as the ketones.

Pearson (*Pharm. Jour.*, **103,** 78-80, 1919) measured the dilutions in which pungency was still perceptible in a series of compounds similar in constitution to the above. Some of his results were as follows :

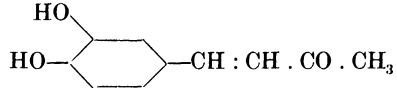
	Perceptible at
2-hydroxystyryl methyl ketone 	1 in 100,000
4-hydroxy-3-methoxystyryl phenyl ketone 	1 in 30,000
3,4 dioxymethylenestyryl methyl ketone 	1 in 30,000

4-hydroxy-3-methoxystyryl ethyl ketone



1 in 10,000

3,4 dihydroxystyryl methyl ketone



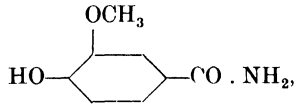
1 in 500

It is not easy to see what are the essential factors, but this much at least is clear. Whereas the peppers are characterized by a piperidine nucleus linked to a 9-carbon acid, the gingers are characterized by a phenolic nucleus linked to the β-carbon atom of a ketone.

The pungency of amides as a " taste " phenomenon has attracted some attention. Jones and Pyman (*Jour. Chem. Soc.*, **127**, 2588-98, 1925) prepared and examined the pungency of a large number of amides, most of them derivatives of vanillylamide to which they assigned an arbitrary pungency value of 100 with which the others could be compared. Some of their results are given below :

Amide.	Pungency.
vanillylamide	100
Δ^{ω}-undecenovanillylamide	>100
benzovanillylamide	0·5
phenylacetovanillylamide	0
β-phenylpropiovanillylamide	40
γ-phenylbutyrovanillylamide	40
δ-phenylvalerovanillylamide	40
cinnamovanillylamide	0·5
chloroacetovanillylamide	3
trichloroacetovanillylamide	3
bromoacetovanillylamide	3
iodoacetovanillylamide	3

The constitution of vanillylamide is



and it may be noted that it has the same phenolic nucleus as zingerone. The results of the research led the authors to believe that the shape of the molecule as a whole rather than the nature of the side chain was the important factor

Giacalone and Collesano (*Gazz. chim. ital.*, **65**, 129-31, 1935) found that some simple amides of heavily halogenated acids were pungent, for example, tribromacetamide and iodoacetamide. They also examined the *p*H values of the amides, and concluded that where it was on the acid side the amide had a burning, pungent or bitter taste.

The Chemical Senses

Mitter and Ray (*Jour. Indian Chem. Soc.*, **14,** 421-4, 1937) examined the pungency of acylated isobutylamides, and concluded that the maximum pungency was obtained with acids of 7 to 9 carbon atoms and that unsaturation also increased pungency. These conclusions fall into line with the observations on pepper structure. Some of their products and degrees of pungency assigned to them are given below :

Isobutylamide of	2-heptenoic acid	Strongly pungent.
,, ,,	2-nonenoic acid	,, ,,
,, ,,	heptoic acid.	Pungent.
,, ,,	benzoic acid	Very pungent.
,, ,,	hexoic acid	Less ,,
,, ,,	2-hexenoic acid	,, ,,
,, ,,	3-decylenic acid	,, ,,

The structure of the first member of the above table is

$$CH_3 . (CH_2)_3 . CH : CH . CO . NH . CH_2 . CH\begin{matrix}CH_3\\CH_3\end{matrix}$$

Lachrymatories

In addition to the relatively mild pungency of pepper and ginger, many other substances are distressingly pungent. The action on the internal surfaces of the nasal orifices as a rule coincides with lachrymatory action on the eyes. It will therefore be convenient to discuss such substances in that connection.

The most familiar is ammonia, which causes sneezing and lachrymation. In high concentrations, for example 20 per cent. in aqueous solution, it causes very painful burns on the skin, and particularly on the eyes, resulting in temporary blindness. With suitable treatment there is full recovery of the sight and no permanent damage.

Chloracetone is a substance used as a lachrymatory and was first employed in warfare in March 1915. It was known as " Tonite " by the French, and " A-Stoff " by the Germans. Its chemical constitution is $ClCH_2 . CO . CH_3$. The lowest concentration producing irritation of the eyes is 18 mgm. per cu. metre of air, whilst the limit of insupportability is 100 mgm. per cu. metre. Such a concentration as 18 mgm. per cu. metre of air is $\frac{0{\cdot}018 \times 100}{1293}$ per cent. wt./wt. or 0·0014 per cent. wt./wt., since 1 cu. metre of air weighs 1293 grams. It will be seen that it is more comparable in sensitivity with taste than with smell.

Bromacetone, $Br\,CH_2 . CO . CH_3$, is more aggressive than chloracetone. It was first used in warfare in July 1915, and is detectable in 1 mgm. per cu. metre.

Ethyl iodoacetate, $CH_2I . COO\,C_2H_5$, was first used in warfare in December 1915, and is noticeable at a dilution of 1·4 mgm./cu. metre.

Two other lachrymatories being studied towards the end of the 1914-1918 war were

Bromobenzyl cyanide, $C_6H_5 . CH\ BrCN$,
and Chloroacetophenone, $C_6H_5 . CO . CH_2Cl$,

both of which were detectable at 0·3 mgm. per cu. metre, whilst the limit of insupportability for the latter, chloroacetophenone, is as low as 4·5 mgm. per cu. metre.

So far as lachrymatory properties are concerned these increase with the weight of the halogen; thus bromacetone is 18 times more powerful than chloracetone and benzyl iodide is twice as powerful as benzyl bromide. Whilst one halogen atom often confers lachrymatory properties, more than one tends to reduce these properties but to increase the asphyxiant action. Thus monochloromethyl chloroformate, $ClCOO . CH_2Cl$, is predominantly lachrymatory, but trichloromethyl chloroformate, $ClCOO . CCl_3$, has practically no lachrymatory action but is an asphyxiant. The position of a single halogen atom also has an influence, for in the β-position the lachrymatory action is more noticeable than in the α-position, for example, ethyl β-chloropropionate, $ClCH_2 . CH_2 . COO\,C_2H_5$, is more powerful than ethyl α-chloropropionate, $CH_3CHCl . COO\,C_2H_5$, and similarly, β-chloroethyl methyl ketone, $ClCH_2 . CH_2 . CO . CH_3$, is a more powerful lachrymatory than α-chloroethyl methyl ketone, $CH_3 . CHCl . CO . CH_3$. This feature is due to the greater reactivity of the halogen in the β-position than in the α. In such substances as the above the ketonic oxygen is the most strongly polar,

$$Cl\ CH_2CH_2 . C\overset{-}{O} . CH_3,$$

and by Lapworth's theory of alternating polarities, the carbon atom to which it is attached is polarized positively,

$$Cl\ CH_2CH_2 \overset{+}{C}O\ CH_3,$$

and the other carbon atoms are therefore polarized as follows:

$$Cl\ \overset{|}{C}H_2CH_2 \overset{+}{C}O\ CH_3,$$

so that the chlorine atom is attached to a positively charged carbon, and is itself polarized negatively,

$$\overset{-}{Cl}\ \overset{+}{C}H_2CH_2 \overset{+}{C}O\ CH_3.$$

But in the case of the α-chloroketone, we have

$$CH_3\ \overset{+}{C}HCl\ \overset{+}{C}O\ CH_3,$$

the chlorine attached to a negatively polarized carbon and is therefore positively polarized. This is an unnatural condition for a halogen which normally is negative as in the typical reaction

$$\overset{+}{H} + \overset{-}{Cl} \rightarrow HCl.$$

Hence the chlorine in the β-chlorketone is reactive and the substance more lachrymatory than the α-chlorketone where the chlorine is unreactive.

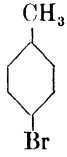
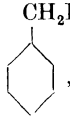
Similarly, we have reactive chlorine in ethyl β-chlorpropionate,

$$C_2H_5O \cdot \overset{+}{C}O \cdot CH_2\overset{+}{C}H_2\overset{-}{Cl},$$

but unreactive chlorine in ethyl α-chlorpropionate,

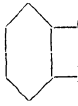
$$C_2H_5O \cdot \overset{+}{C}O \cdot CH\overset{+}{C}l \cdot CH_3.$$

In the aromatic series the chlorine in a side chain is reactive, but chlorine in the nucleus is unreactive.

Hence bromotoluene,  , is not lachrymatory, but benzyl bromide,  , is so.

The introduction of a nitro group into the molecule has been found to increase lachrymatory properties, for example, benzyl chloride

 —CH_2Cl is lachrymatory and detectable at 77 mgm./cu. metres,

but  —CH_2Cl, *o*-nitrobenzyl chloride, is much more lachrymatory and detectable at 1·8 mgm./cu. metres.

Whereas more than one halogen will reduce the lachrymatory action, the presence of several nitro groups appears to increase it.

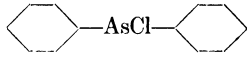
Symmetrical compounds are usually more lachrymatory than unsymmetrical. Thus sym-dichloromethyl ether, $Cl\,CH_2 \cdot O \cdot CH_2Cl$, is a much stronger lachrymatory than asym-dichloromethyl ether, $CH_3 \cdot O \cdot CHCl_2$.

Another class of lachrymatories, although not so powerful as those mentioned above, are the volatile acid anhydrides such as acetic and butyric anhydrides. These appear to be hydrolysed to the acids with the formation of heat in the eye.

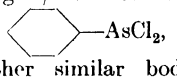
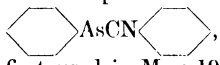
Amongst the intensely active lachrymatories used in warfare, the presence of a halogen or a cyanide group, which is chemically similar to a halogen, is a common feature and, further, the lachrymatory properties depend on its reactivity which is determined by its position in the molecule. In addition symmetry of molecular structure enhances the lachrymatory power.

Sternutatories

Whilst many of the lachrymatory gases also cause sneezing, there are others, known as the sternutatories, which affect the nose rather than the eyes. An example is diphenyl chloroarsine (Clark I.)

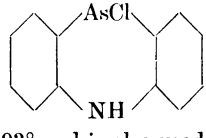


It was first used in September 1917 by the Germans, and as it passed the respirator filters then in use it proved a great surprise to the Allies. Diphenyl chloroarsine is a solid (m.pt. 41° C.) and soluble to the extent of 0·2 per cent. in water. The minimum concentration which irritates the nasal surfaces is 0·1 mgm./cu. metre, whilst the limit of insupportability is 1 to 2 mgm./cu. metre for 1 minute.

Phenyl dichlorarsine,  , has also been used, but is not so powerful. Another similar body is diphenylcyanoarsine,  , which is also a solid (m.pt. 31° C.) and was first used in May 1918. It is said that a concentration of 0·01 mgm. or even 0·005 mgm. per cu. metre can be detected by odour, whilst the limit of insupportability is 0·25 mgm. per cu. metre for 1 to 2 minutes, and in this respect it is unsurpassed by any of the war gases.

Both diphenylchlorarsine (Clark I) and diphenylcyanoarsine (Clark II) are solids and have such low vapour pressures that they have to be diffused in the air as a smoke consisting of very fine particles. Hence the need for special precautions in the filter of a gas respirator, since such solid particles are not adsorbed by the active carbon which is the main filtering agent. It will be realized, too, that such a class of substances has a special action on the chemical receptors which is unlike and distinct from the action of vapours and finely dispersed liquids.

Since 1915 certain heterocyclic arsines have been prepared as sternutatories. Such are

Adamsite  or 10 chloro-5 . 10-dihydrophenarsazine.

This substance melts at 193° and is also used as an " arsenical smoke." Its lower limit of irritation is 0·1 mgm. per cu. metre and its limit of insupportability is 0·4 mgm. per cu. metre.

Similar bodies in which the chlorine atom is replaced by a bromine atom or by a cyanide group have also been made and have similar physiological action.

Suffocants

The suffocants are a class of lung irritant gases which irritate the receptors on the respiratory tract. The best known is chlorine.

It was used in warfare, April 1915, and is the only element used for this purpose excepting its near relation bromine, which was used only on a small scale. Compared with the lachrymatories and the arsenical smokes, quite high concentrations of chlorine are required, 10 mgm. per cu. metre for detection, and 100 mgm. per cu. metre as the limit of insupportability.

It is extremely painful to breathe even a dilute mixture of chlorine and violent coughing is the immediate reaction.

Phosgene, $COCl_2$, is a dangerous suffocant, especially as it has little irritating action on the mucous membranes and the respiratory tract. It has a smell of musty hay. The writer has noticed that low-lying fields in misty weather smell like phosgene. It can be breathed without a great deal of discomfort, and therein lies its danger, for some hours later the damage to the lungs reveals itself. It can be detected in 5 mgm. per cu. metre, and the lower limit of insupportability is 20 mgm. per cu. metre.

Diphosgene or trichlormethyl chloroformate, $Cl\,COO\,.\,CCl_3$, was known by the Germans as "Perstoff." It is similar to phosgene in toxicity. It is to be noted that it is much less irritant than the lachrymatory monochlormethyl chloroformate.

Other suffocants are

Chloropicrin	CCl_3NO_2	Detectable at 2 mgm. per cu. metre, and lachrymatory as well as suffocant.
Dichlormethyl ether	$CH_2Cl\,.\,O\,.\,CH_2Cl$	(French Cici.)
Dibromomethyl ether	$CH_2Br\,.\,O\,.\,CH_2Br$	(French Bibi.)
Thiophosgene	$CSCl_2$	

Skin Irritants

In addition to the lachrymatories, the irritant arsenical smokes and the suffocants, there are the skin irritants or "orticants." Where the irritation is gross so that blisters form, the irritation is called "vesicant."

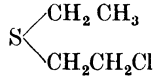
Phenyl carbylamine chloride,  —$N:CCl_2$, was first used in May 1917 by the Germans to disguise the smell of mustard gas, since it (phenyl carbylamine chloride) has an odour of onions. It is a strong irritant, detectable in 3 mgm. per cu. metre.

Mustard gas, dichlorodiethyl sulphide, $CH_2Cl\,.\,CH_2\,.\,S\,.\,CH_2\,.\,CH_2Cl$, was the most used of all the irritants. It was used by the Germans in July 1917, and it was several months before the Allies had it in production. Curiously the substance has been known since 1822 (Despretz, *Ann. chim. phys.* (2), **21**, 428, 1822). It has a strong vesicant action, and inflammation may not appear till 24 hours after exposure. Fair people are more sensitive than dark. Irritation may be caused by 0·2 mgm. per cu. metre, but without visible lesions. Erythema of

the skin is produced with an application of 0·12 mgm. per sq. cm. of skin, and blisters with four times this quantity.

The corresponding dibromide is similar but not so aggressive. The corresponding dichlorodiethyl selenide (Bell and Gibson, *J. Chem. Soc.*, **127**, 1877, 1925), has a similar vesicant action.

The rather similar compounds, ethyl β-chlorethyl sulphide,



and the $\alpha\alpha'$-dichlordiethyl sulphide,

$$CH_3 . CHCl . S . CHCl . CH_3,$$

are weak in toxicity.

Many such compounds have been made, and the following points have emerged:

(1) The sulphur atom is necessary to give the skin-penetrative power, since the oxygen analogue, $\beta\beta'$-dichlordiethyl ether, is relatively harmless.

(2) The chlorine atoms must be at the end of the chain, and in addition none must appear in the α-position for $\alpha\beta\beta'$-trichlordiethyl sulphide, $CH_2Cl . CHCl . S . CH_2 . CH_2Cl$, is also relatively harmless.

Despite its name, "Mustard Gas," $\beta\beta'$-dichlordiethyl sulphide has no connection with natural mustard. It may be noted here, though, that when powdered black mustard seeds (*Sinapis nigra*) are distilled with water, a natural oil of mustard is obtained, and the principal constituent of this is allyl isothiocyanate, $CH_2{=}CHCH_2N{=}CS$. Pure "natural" mustard oil also has a pungent odour and causes blisters on the skin. Sec-butyl mustard oil,  , also occurs naturally in scurvy grass (*cochlearia officinalis*). The conjunction of sulphur in the structure of natural mustard oil with its aggressive action on the skin may be noted.

Other skin irritants are sym-dichloroacetone, $CH_2Cl . CO . CH_2Cl$, which has an "orticant" action on the skin as well as being lachrymatory, and Lewisite, which is chlorovinyl dichloroarsine,

$$ClCH{=}CHAsCl_2.$$

This substance is detectable at 0·8 mgm./cu. metre, and has a limit of insupportability of 48 mgm./cu. metre. Both Lewisite and mustard gas are liquid under ordinary conditions. The odour of Lewisite (geraniums or nasturtium leaves) is said to be not detectable below 14 mgm. per cu. metre, so that in this specific substance chemical irritation is more sensitive than odour. As we have seen, the most powerful odours are much more powerful than the most powerful chemical irritants, but there is no reason why in any one case the chemical action should not be more powerful than the odour.

Liquid Stimuli

We have considered the lachrymatories, the arsenical smokes, the suffocants, and the skin irritants, all of which are chemically reactive, and to which our receptors are so sensitive that they will detect quantities perhaps as low as 0·1 mgm. per cu. metre. These substances have been synthesized because they give to the last degree the aggressive chemical irritation. We have classified them largely by the sensations they have given to the eyes, to the nose, or the throat, or the skin. There are, however, a multitude of other substances which affect the common chemical receptors on the exposed mucous surface but to a less degree and in a more diffuse manner. Such substances as benzene and acetone, are chemically stable, particularly the former, and have no marked lachrymatory, sternutatory, suffocant, vesicant or orticant action, but if they are applied as a drop of liquid to the eye or the interior nasal surfaces, or to a cut on the finger, they are extremely painful. The common chemical sense registers its protest at the presence of an unsuitable substance in contact with the body. Salt solutions or even cold water in the nose call forth unpleasant sensations. Dilute acids are readily noticed on the mucous surfaces, and so are dilute alkalis. These are all manifestations of the original common chemical sense. The war gases have been developed as most powerful stimulants of the differentiations of the common chemical sense to act on the eye, nose, throat or skin. The spices like pepper and ginger I regard, too, as stimulating another differentiation of the chemical sense.

Differentiations

The different types of chemical stimuli we have encountered may now be noted.

(1) General Liquid Stimuli. Common to all the mucous surfaces, and stimulated by any liquid (e.g. alcohol, benzene or cold water) other than isotonic salt solution. Certain other substances, such as sugars, may be dissolved in the isotonic salt solution without causing chemical sensation.
(2) Alkaline Taste Stimuli caused by alkalis in the mouth and not a true taste (e.g. aqueous caustic soda or sodium carbonate).
(3) Spicy Taste Stimuli again restricted to the mouth but a chemical irritation and not a taste (e.g. pepper, ginger).
(4) Lachrymatories specifically attacking the eyes (e.g. chloracetone).
(5) Solid Stimulants such as the arsenical smokes which particularly attack the nasal orifices.
(6) Suffocants such as chlorine and phosgene which attack the respiratory tracts.
(7) Skin Irritants such as mustard gas and Lewisite, and, in a much less degree, certain perfumes such as benzylidene acetone, a sweet pea perfume suitable for applying to fabrics but not to the skin.

Many substances belong to more than one of these classes. Ammonia, for example, first attacks the interior of the nasal cavities, but with continued exposure also attacks the eyes, and is both sternutatory and lachrymatory. Pepper also has a spicy taste and under suitable conditions attacks the nose. Chloracetophenone attacks eyes and nose, and is both a lachrymatory and a sternutatory. This, however, in no way invalidates the classification as there is no reason why one substance should not affect different modalities of one sense. In taste we have "bitter-sweets" affecting two well-defined differentiations, and such a substance as ethanol affects not only different modalities of one sense but even different senses, common chemical, taste and smell.

The classification of the stimulants of the common chemical sense into seven groups has been attempted on a physiological basis. We can be fairly sure of differences in our sensations and naturally class all lachrymatories together, notwithstanding the manifest differences in physical properties and chemical structure of the substances so grouped together. Other classifications which suggest themselves are

(1) Solid, Liquid, and Gaseous Irritants. Such a classification would not be without significance, but I believe this factor of the physical state to be secondary in importance.

(2) Insoluble, fat-soluble, water-soluble, and fat-and-water soluble may have more significance than (1) since the prelude to chemical reaction is often solution.

(3) A classification based on chemical structure, but we have already seen that very slight differences in structure of such a substance as mustard gas make great differences in the aggressive action of the substance, so that *a priori* such a scheme does not appear very promising. Nevertheless the many relations between structure and irritant power which have already been discovered are beginning to show the skeleton on which such a classification will no doubt eventually be built.

Theories

The facts which any theory of the mechanism of the common chemical sense should cover must include the following :

(1) The receptors are the free nerve endings of the cranial and spinal nerves, particularly the trigeminal nerve.

(2) The location of the receptors is ordinarily confined to those surfaces where the mucous membrane is exposed, but if a substance has skin-penetrative properties, it may act as a stimulus on any part of the body.

(3) Fatigue such as is encountered with olfaction and gustation is not so common with the common chemical sense. It is true that people who habitually work in an atmosphere of ammonia eventually are unaware of it, but there is little evidence of rapid fatigue with concentrations normally met. Fatigue may occur more readily at threshold concentrations.

(4) The stimulus may be solid, liquid, or gaseous. It may be inorganic, such as chlorine or arsenic trichloride, or organic. Frequently it contains an element not functioning at its maximum valency, e.g. trivalent nitrogen in ammonia and piperine, and divalent sulphur in mustard gas.

(5) The common chemical sense is more closely allied to pain than are smell and taste. Over-stimulation of the common chemical sense receptors invariably brings pain, probably a survival of its primitive ancestry.

(6) The sense has developed along different lines so that differentiations are in process of emergence. The spicy taste, eyes watering, and nasal irritation are all quite distinctly separate sensations.

No complete theories seem to have been advanced for this sense as they have so abundantly for olfaction and to a less extent for gustation. In particular, whether the action of the stimulus is chemical or vibratory, and whether the stimuli need to be water- or fat-soluble, do not seem to have been decided. Inasmuch as the stimuli are usually chemically active, and often carry an element working at a lower valency than its maximum, and as the surfaces which are attacked are freely exposed, this suggestion is made. The stimulating substance first forms a monomolecular layer, on the irritated surface, of an addition compound by means of the auxiliary valencies of the unsaturated element in the stimulant, finding groups with which they can combine and reach their maximum valency in the eye or the nose. The inference is that solubility does not take place in the bulk, but that the layer of addition product is removed from the scene of action by being washed away with the rapid flow of mucus in the nose, or by lachrymation in the eye, or by coughing or sneezing. All the usual reactions are such as to help in removing the stimulant. If the stimulus is so concentrated and persistent that the reflexes do not remove the layers of combined irritant from the irritated surfaces, then gross pathological changes take place as the surfaces cannot " breathe " and pain ensues.

Whilst the mechanism by which the irritants stimulate sensation has been neglected, a great deal of work has been directed towards establishing relations between chemical constitution and physical properties on the one hand and aggressive action on the other. They do not yet form more than a framework for a theory, but the main points may be put down as follows :

(1) The vapour pressure of stimulants may vary between wide limits. At 20° C. bromobenzyl cyanide has a vapour pressure of only 0·012 mm. mercury, but that of phosgene is 1173 mm. mercury—about 100,000 times as great.

(2) The boiling-point of stimulants may vary between wide limits, e.g. chlorine boils at −33·5° C. and chloracetophenone at 245° C. Similarly, with the melting-point, for with the two substances

just mentioned, the melting-points are −102° C. and 58° C. respectively.

(3) The aggressive substance may be inorganic, e.g. ammonia, chlorine, arsenic trichloride, or organic, e.g. mustard gas, chloracetone.

(4) Most of the severe organic irritants contain halogen. Heavy halogens in organic compounds have greater lachrymatory action than light ones, e.g. bromacetone is more lachrymatory than chloracetone.

(5) More than one halogen atom diminishes the lachrymatory action but increases the asphyxiant action, e.g. monochlormethyl chloroformate is primarily lachrymatory but trichlormethyl chloroformate is primarily asphyxiant.

(6) In the aliphatic series the halogen atom is more active in the β-position than in the α-position, e.g. ethyl β-chlorpropionate is a more powerful lachrymatory than ethyl α-chlorpropionate.

(7) In the aromatic series the halogen in the side chain is more active than in the nucleus, e.g. benzyl bromide is lachrymatory but not bromtoluene.

(8) Sulphur imparts skin-penetrative power, e.g. dichlordiethyl sulphide is vesicant but not dichlordiethyl ether.

(9) The molecule frequently contains an element working at less than its maximum valency, e.g. trivalent arsenic is a more powerful agent than pentavalent arsenic.

(10) In the aromatic arsines, one substituent aromatic group is more powerful than two or three, e.g. phenyl dichlorarsine is more aggressive than triphenyl arsine. The phenyl group is more powerful than its homologues tolyl, etc.

(11) The addition of a nitro-group increases aggressiveness, e.g. *o*-nitro benzyl chloride is fifty times as powerful a lachrymatory as benzyl chloride.

(12) An $\diagup$NOH group increases the irritant action on the skin.

(13) The cyanide group —CN behaves very similarly to a halogen.

(14) Unsaturation usually increases aggressiveness, e.g. acrolein is a strong irritant but propionaldehyde is harmless.

(15) Symmetrical molecules usually have greater aggressiveness than unsymmetrical, e.g. sym-dichloracetone is much more irritant than asym-dichloracetone.

Analogous to de Witt's theory of chromophores and auxochromes in the construction of dyestuff molecules, a theory of toxophors and auxotoxes has been put forward, first by Ehrlich (*Deut. med. Wochschr.*, 1898, p. 1052) and later by Nekrassov (*Khimija Otravliajuscikh Vescesto*, Leningrad, 1929). According to Nekrassov, to be a powerful irritant a substance must contain both a toxophor and an auxotox. Toxophor groups are :

$$\diagup CO, \quad S\diagup, \quad \diagup C=C\diagdown, \quad -NO_2, \quad -NC, \quad -As\diagdown$$

and so on, whilst the auxotoxes are halogens, oxygen, $—NH_2$, benzyl, phenyl, methyl, etc., radicles.

Whilst it is a start, it is clear that such a theory embraces a multitude of products and many of them are not particularly irritant. Also an increase in the number of active groups frequently leads to a decrease in the aggressiveness, whilst Nekrassov's theory would lead one to expect the reverse. Indeed, in the case of dyestuffs, several chromophore groups usually impart increasing depth of colour.

CHAPTER 7

CHEMICAL SENSIBILITY IN LOWER ANIMALS

Animal Classification

Now that we have examined some of the properties of the chemical senses in humans, it will be of interest to compare the development of these senses in the animal kingdom. Starting with the simplest forms of animal life, we shall find that there is a gradual development of chemical sensibility and simultaneously a restriction of the sensitive areas. Low forms of life have large areas of vague diffuse sensibility; whereas higher forms have only small areas of the body which are sensitive, but the sensations experienced are better defined and keener. No sudden emergence of the chemical senses as a new feature is found, and in fact the emergence is so slow and gradual that the difficulty is to fix a point in the scale at which each sense begins to operate.

All animal life is based on protoplasm, the jelly-like substance of protein character but as yet of unknown chemical constitution. In the larger animals the protoplasm is divided by partitions into cells, otherwise the ratio $\frac{\text{volume}}{\text{area}}$ would become too great for the economy of the animal. The simplest form of life known is that of the filter-passing viruses, which are complex proteins which can be recrystallized, but will grow on living matter although not apart from it. Then come the flagellates, from which both plants and animals evolved. The flagellates swim by lashing flagella and are plant-animals. Some photo-synthesize, a typically plant performance. The lowest form of life which is indisputably animal, is the protozoan; then come the porifera or sponges, the cœlenterates and so on. The main groups with which we are concerned in connection with the development of the chemical senses are

(1) Protozoa, e.g. amœba and paramecium.
(2) Sponges.
(3) Cœlenterates, e.g. corals, sea-anemones, jelly-fishes.
(4) Platyhelminthes or flatworms, e.g. planaria.
(5) Mollusca, e.g. snails, oysters, octopuses.
(6) Annelids, e.g. earthworms.
(7) Crustaceans, e.g. lobsters, shrimps, barnacles.
(8) Arachnids, e.g. spiders, scorpions, ticks.
(9) Insects, e.g. moths, beetles.

All the above are invertebrates—all the following are vertebrates:

(10) Fishes, e.g. sharks, rays, cod.
(11) Amphibians, e.g. frogs, toads, newts.
(12) Reptiles, e.g. snakes.
(13) Birds, e.g. hens.
(14) Mammals, e.g. hedgehog, squirrels, dogs, apes, man.

The Chemical Senses

It is estimated that about one million species of animals are known, and that of these three-quarters of a million are arthropoda, which are characterized by jointed legs and include the crustaceans, arachnids, and insects. The mammals characterized by the growth of hair and the presence of mammary glands for feeding the young, account for perhaps 5 per cent. of all the known species. As regards the relative number of animals (not number of species of animals) the protozoa head the list, for as noted earlier, most other animals carry one or perhaps many protozoan parasites.

Protozoa

The protozoa are not divided into cells, or to put it another way, they consist of only a single cell. They abound in fresh and salt water and in sand, and as parasites in animals. A typical variety is the *amœba*, a microscopic inhabitant of fresh-water ponds. He has no head or tail, and no visible structural arrangements for the detection of taste or smell. There are no receptors, nerves or brain to be seen, and if the animal is cut into two, both parts grow to complete animals. Nevertheless, in spite of its lack of structural features, amœba are able to distinguish inert particles from the minute plants and animals on which they feed. They reject unsuitable food and go away from light. This behaviour suggests that there must be some mechanism in the apparently gelatinous particle of protoplasm which causes reflex action. The *paramecium* is another protozoan pond inhabitant, but is covered with fine cilia which rotate and draw a stream of water towards the animal. If the water drawn by the paramecium's cilia contains a chemical then the animal takes an avoiding reaction just as it does if it bumps into an obstacle. Clearly at this stage the chemical environment determines the behaviour, although we can see no mechanism for the reception of stimuli or for sensation or reflex action.

So that as far as we know the most primitive receptor mechanism is bound up with the effector mechanism in the protoplasm of the protozoa. The evidence lies not in the structure of the animal, but in its behaviour which denotes primitive pleasure or unpleasure.

Sponges

The sponges or *Porifera* are multi-cellular, but the cells are all of one type. Sponges when growing resemble raw liver in appearance and are slimy. They have muscle but no nervous tissue. The surrounding water is drawn into the sponge through the countless pores, and ejected as a stream through holes at the top of the sponge, food being filtered out during this process. Sponges show chemical reaction, for when an irritant substance is present in the water the sponge contracts so that the size of the orifices through which the water is taken in is reduced. As there are no sense cells to receive stimuli, and no nerve cells to transmit the stimuli, it appears that the muscle cells must be stimulated directly to cause the contraction.

Cœlenterates

Jelly-fishes, corals, and sea-anemones are marine, and the hydra is a fresh-water cœlenterate. These animals represent the "tissue" stage of development, and have two kinds of cells, flat epithelial cells on the surface in addition to the main sustentacular cells. Stimuli are received by the surface cells and are picked up from them by a "nerve net." The nerve cells are connected with each other to form a nerve net or ring round the animal, the nerves being more concentrated near the mouth. These transmit the impulses to muscle cells which contract or to gland cells which secrete. There is no brain or central nervous system, so that sensation as we understand it cannot exist, but nevertheless the animal by its reflex actions gives the appearance of experiencing pleasure or unpleasure. If meat juice is added to the water of an aquarium containing sea-anemones, they are soon beautifully expanded (Pollock, *Jour. Linn. Soc. London, Zoöl.*, **16,** 474, 1883). If meat juice is discharged on the tentacles of a sea-anemone the gullet opens, whilst if the pedal edge of the column is touched the whole animal contracts. Evidently we have here the beginning of a differentiation of the primitive tactile-chemical sense into two differentiations, tactile and chemical. Also it is to be noted that the sensibility of the surface of the sea-anemone shows preference to touch in one part, and to chemical irritation in another.

The hydra, when feeding, remains attached to the bottom of the pond it inhabits, and has tentacles trailing in the water. When a small worm or other suitable article of diet comes within range, it is riddled with a shower of these poisonous tentacles and engulfed. Now, if one of the tentacles of a hydra is touched, the whole animal contracts. Chemical irritants in the water have the same effect. The animal has the rudiments of a nervous system, but it is very inefficient, and like that of the sea-anemone, apparently designed simply for reflex reaction. The hydra is an animal usually about half an inch across with tentacles about three times that length.

A more complex member of the cœlenterate group is the jelly-fish, *Gonionemus*, which is about one inch long with two-inch tentacles, and is a free-swimming animal and better equipped than the sedentary hydra, which can only move by somersaulting. In this jelly-fish a nerve network runs beneath the ectoderm of the bell surface, and is concentrated round the edge of the bell in a "nerve-ring." This nerve-ring controls the behaviour of the animal. Such jelly-fishes also have rudimentary light spots and also balancing organs. Such primitive organs do not indicate that the animals can see and at this stage there is simply a phototropism.

The most significant features from our point of view in the cœlenterates are (1) the beginning of specialization of different areas of the skin to tactile and chemical stimuli, (2) the structural differentiation of the receptor mechanism from the rest of the protoplasm.

Platyhelminthes

The flatworms comprise such animals as the planaria or turbellarian worms, which are about a half-inch long and are found under stones in streams, and the parasitical tapeworms and flukes. The parasites have no need to search for their food and they are devoid of sense organs, but the free-living flatworms such as the planaria show a marked advance over the cœlenterates. They possess bilateral symmetry compared with the cœlenterates radial symmetry, and they consist of three layers of cells instead of two, which allows greater complexity of structure and brings them to the " organ " level of development.

We find in the flatworms the first development of a central nervous system, and one end of the animal is a definite head with eyes and other sense organs. In the head there is a concentration of nervous tissue into a bi-lobed brain, and from this run two strand-like concentrations of nerve cells with various connections called a " nerve-ladder " which allow free passage for nervous impulses. Different sensory cells are used to receive touch, temperature, and chemical stimulation, but we cannot say which are which. Planaria respond rapidly by means of their chemical senses to the presence of food by turning or moving towards it. A piece of raw meat placed in a stream attracts these worms, or such as are downstream from it. The significant feature in the flatworms is the presence of a central nervous system. In addition to the receptors activating muscles by reflex action, they send messages to the brain probably enabling the animal to experience sensation, although doubtless of a diffuse and undifferentiated character—a " blooming buzzing confusion."

Mollusca

This group of soft-bodied animals includes snails, slugs, and oysters, normally inhabiting shells for protection, and squids, on the other hand, in which the shell is vestigial, and where the animal relies on its speed for safety. The development of the nervous system also varies between wide limits. The clam which lives with its anterior end buried in the mud has no head, for in such a position a head would be useless, but the squid has a head and highly developed brain. Taking the group as a whole the nervous system consists of a ring of nervous tissue round the œsophagus with two pairs of longitudinal nerve cords going to the foot and mantle. The sensory receptors are located on tentacles. In the clam there are yellow epithelial cells, thought to be sensitive to chemicals in the water. Yellow pigmented cells are found in the olfactory regions of the mammals including man. The squids, which are the largest animals among invertebrates, have well-developed chemical sense organs sometimes stated to be olfactory.

Amongst the gastropods a Roman vineyard snail will take no notice of suitable food under glass, but as soon as it is uncovered it is quickly found, suggesting that smell is the operative sense.

Amongst the bivalves, the scallop seems to scent the approach of its enemy, the starfish, and swims away on the latter's approach.

Up to this stage it has not been possible to assign taste or smell to the simpler invertebrates. All we can say is that they are sensitive to chemicals and to food in considerable dilution. The way the sea-anemones expand when nutrient juice is added to the water they are in, and the way the planaria drive upstream for food, are suggestive of olfaction. It is impossible to say where taste and smell emerge from the common chemical sensibility, and as the emergence is gradual any attempt to define such a level would be arbitrary, and would depend on the definition. In the squid with its highly developed brain and nervous system, the possibilities of experiencing sensation and different kinds of sensation are greater than in those invertebrates we have yet considered, for example, it has image-perceiving eyes. The main classes of the molluscs are (1) the gastropods, e.g. snails, slugs, limpets, whelks, (2) the bivalves, e.g. clam, oyster, scallop, (3) the cephalopods, e.g. squids and octopuses.

Annelids

The earthworm is a typical annelid. The sense cells are not highly concentrated at the anterior end, but occur in the segments which constitute the body. There are no eyes, but light sensitive spots are placed at both ends. The earthworm is unaffected by sound, but shows taste preferences, preferring carrot leaves to celery, and celery to cabbage, and it is thought that taste cells occur in the mouth. The sense of smell, so far as it can be distinguished from the chemical sense, is very feeble. It is probably at about this stage of development that differentiation of the common chemical sense into smell and taste begins to be noticeable. It may be noted that the speed of the impulses in the nerves of the earthworm is only about 5 feet per second, and is of the order of a hundred times slower than in man.

Crustaceans

This is a class of the phylum of *arthropoda*, or jointed-leg animals. It includes crayfish, lobsters, shrimps, crabs, and barnacles. The style of architecture is a soft body, heavily armoured, and with joints in the armour to give facility of movement. It may be contrasted with that of the vertebrates which have the soft body built on the bony skeleton. Whilst man's supremacy points to the skeleton architecture being the most adaptable and generally superior, so far as numbers are concerned the armoured family of arthropods win easily. The segmented plan of the annelids is modified and improved in the arthropods. The cellular and cuticular layers of the body wall have been modified to form a variety of sense organs greater than found in other invertebrates. These include image-forming eyes as some insects have been seen trying to extract nectar from flowers on a wall-paper, hearing organs, balancing organs, and on the antennæ, receptors

to touch and chemical stimuli. Also the body surface is covered with sensory bristles assumed to be sensitive to touch and with other receptors for chemical stimulus. The lobster is a highly developed crustacean and has its antennæ, and even its walking legs, covered with tens of thousands of receptors for touch and the chemical senses.

The shrimp is also a crustacean, and Spiegel has shown that it is much more attracted by the water-soluble constituents of a fish muscle meal than by the ether-soluble. This suggests that the chemical sense of the shrimp is more comparable to our own taste or chemical perception than to our sense of olfaction which is much more stimulated by the ether extract than by the water extract.

Arachnids

The arachnids constitute another class of the arthropoda and include scorpions, spiders, mites and ticks, and crane-flies (daddy-longlegs). They have no antennæ but an abundance of sensory bristles or hairs which cover the body, particularly the appendages. In the spider there is a pair of pedipalps, which are leg-like appendages that are chemically sensitive, before the mouth. In the scorpions the pedipalps are used to seize prey.

Insects

This is the largest class of arthropods. It is the only group of animals likely to challenge man's dominance of the Earth. The bees make honey for us, but the insect kingdom is generally inimical. Its members spoil our fruits, eat the crops, and bring disease to us. The minute *phylloxera* destroys our vineyards, locusts ravage our crops, flies and gnats sting and infect our cattle and sheep, mosquitoes carry malaria, tsetse flies bring sleeping sickness, and lice bring typhus. The fertilization of plant life must also be set on the credit side. Insects, too, have developed a social life. The termite ants have workers and soldiers—the latter naturally armoured in front only, for them to conquer or to die. Other ants keep slaves, whilst whole colonies of ants will engage in organized pitched battles. In view of their importance, it is not surprising that great attention has been paid to their habits, and it has proved surprising to find that in many cases they are endowed with chemical sensibility of a far higher order than our own. So remarkable did Fabre find this sensibility in moths that he considered it a separate vibrational sense. Noting that powerful odorants like naphthalene and lavender did not prevent a moth from detecting from a distance the odour of one of the opposite sex he wrote : " A clap of thunder does not diminish a feeble jet of light, the sun will not muffle a faint sound," and with the vibratory theory in mind, " For emission, substitute undulation, and the problem of the Great Peacock moth is solved. Without any material emanation, a luminous point shakes the ether with its vibrations and fills with light a sphere of indefinite magnitude. So, or in some such manner, must the warning

effluvium of the mother Oak Eggar operate. The moth does not emit molecules; but something about it vibrates, causing waves capable of propagation to distances incompatible with an actual diffusion of matter. From this point of view smell would have two domains—that of particles dissolved in the air and that of electric waves. The former domain alone is known to us. . . . The second category of odour, far superior in its action through space, escapes us completely, because we lack the essential sensory equipment."

Without going all the way with Fabre it seems clear that insects do have a sensibility we are denied. Insects are the first invertebrates to have separate organs for smell and taste. Whereas in gastropods, crustaceans and so on, we speak of one unified chemical sense, in insects we can often distinguish between smell and taste. There are insects of so many stages of development that this differentiation is to be thought of as taking place in the class of insects rather than as an improvement all insects possess over lower invertebrates.

Aquatic insects are, as would be expected, more sensible to taste. Bauer (*Z. vergl. Physiol.*, **26,** 107-20, 1938) examined the water-beetles, *Dytiscus*, and found that they could distinguish between sucrose and hydrochloric acid, between quinine hydrochloride and sodium chloride, between sucrose and sodium chloride, but not between sucrose and glucose, hydrochloric and tartaric acids, and quinine and aloin. Evidently they can distinguish salts, sours, sweets and bitters as groups, but not the different substances in a group. The threshold concentrations were

	per cent.
Sucrose	3
Hydrochloric acid	0·00015
Sodium chloride	0·06
Quinine hydrochloride	0·000005

which are similar to those of man. The olfactory organs according to Bauer took no part in the perception of taste.

The likes and dislikes of an insect in respect of smell may be changed. Thorpe (*Proc. Roy. Soc.*, *B***126,** 370-97, 1938) conditioned *Nemeritis* so that it became tolerant towards cedarwood-oil which is normally repellent to it.

There are various ways of investigating the olfactory powers of insects and of locating the position of the receptors. Various parts of the insects may be removed (mutilation) or anæsthetized with cocaine-hydrochloride solution, or painted over with a varnish. Abbott investigated the olfactory powers of the beetles, *necrophorus americanus* and *necrophorus orbicollis*, by using such methods. He used pyridine, skatole, isosafrole and the essential oils of almond, clove, and bergamot as odorants. He found that mutilation or covering with shellac increased the reaction time but did not prevent the response. The olfactory organs were widespread, occurring on the antennæ as well as on the bases of the wings and legs. The beetle,

necrophorus americanus, could detect a 0·00009 per cent. solution of skatole.

The exploits of the *bolboceras gallicus*, a little round black beetle with a pale velvety abdomen, in sinking vertical shafts apparently directly by olfaction to the truffles on which it feeds, have already been mentioned in Chapter 1.

The sense of smell is ceaselessly employed by the social insects. A bee entering a strange hive brings with it the odour of another hive and is at once put to death. Ants in one formicary get along well, but will not tolerate an intruder. Now, if their olfactory organs on the antennæ are cut off they fall upon occupants of their own formicary with the greatest fury. It seems clear that they recognize their comrades by the sense of smell (Forel). It was Forel who first showed that olfaction was mostly lost if the feelers were cut off. There are eleven joints in the feeler of the bee and v. Frisch showed that if seven of them were cut off the bee could still perceive odours, but if eight were removed it was anosmic. Evidently the olfactory receptors lie in the last eight joints.

The method by which the sensitivity of olfaction of bees is worked out is as follows :

Sugar water is placed in a small box and after the bees have found it and are making trips to and from the hive, it is substituted by one like it, also containing sugar water but sprinkled inside with a flower extract. After the bees have made sufficient trips to this new box to get used to the scent, several new unscented boxes are placed beside a new scented one, and when the bees return they go in the scented one, evidently associating the presence of the sugar water with the scent. When trained to one odour, for example, rose, they will not go to another such as lavender. v. Frisch trained bees to a particular odour and showed they could distinguish oil of orange peel from forty-three other ethereal oils. It is thought that there is a strong resemblance between olfaction in the bee and in man. Substances of which we find the odours similar, appear also to puzzle the bees.

Bees are very fond of nectar which has a different odour from the general odour of the flower. It may be taste which attracts them in this case.

Battel-Reepen (*Biol. Centralblatt.*, **5,** 20, 1900) stated that where buckwheat was grown the bees worked only until 10 a.m., as it is only in the early hours of the morning the nectar is produced, although the flowers bloom and disseminate their perfume throughout the day.

Flowers are indispensable to anthophilous insects and *vice versa.* Possibly the odour of flowers is a result of their adaptation towards the insects, and again it is clear that the insects have adapted themselves to the flowers. Primitive forms of insects are not attracted to flowers, as their kind came into the world before flowering plants existed. The question arises, how are bees and other insects attracted to the flowers. Is it by sight or smell ? Lubbock and Forel have

given the verdict to colour, whilst Plateau (1907) thinks they are guided entirely by smell. The Peckhams noticed that wasps went to red nasturtiums and left yellow alone, although both smell the same to us, but that does not mean much as many of the scents which motivate insects cannot be detected by us. Lovell observed that bees always chose the most brilliantly coloured flowers even though they had been fed on honey from a grey box. Plateau (1876) describes an observation by Vallete who saw a day sphinx (*macroglossa stellatarum*) try its beak upon flowers painted on tapestry. Flowers from which the petals have been removed remain unvisited by bees, until certain bees hunting for nectar discover the new source. On the other hand, bees work hard among the greenish flowers of ivy, the currant and the willows, whilst they disdain the beautiful big flowers of the *Pelargonium zonale*, but Pérez has shown that bees will visit this flower if honey is inserted in it. Kerner has seen the convolvulus sphinx proceed directly to the flowers of honeysuckle a hundred yards away, and which could not be seen from the starting point. The experiments of Werry (1904) bear on this subject. She exposed various flowers, etc., about five metres from a beehive in a bare field where there were no other flowers to distract the bee's attention. The results were as follows :

		Visited by
Expt. 1	Natural flowers (coreopsis) uncovered . . .	32 bees
	Similar flowers covered by leaves . . .	7 ,,
Expt. 2	Highly coloured flowers with only slight odours (dahlias)	35 ,,
	Very odoriferous, but only slightly coloured flowers (reseda)	6 ,,
Expt. 3	Natural flowers.	32 ,,
	Natural flowers under glass	12 ,,
	Honey	0 ,,
Expt. 4	Natural flowers.	25 ,,
	Artificial flowers	20 ,,
	Natural flowers covered by leaves . . .	7 ,,

Darwin had observed that bumblebees show a preference for a white flower, then purple, then golden.

The conclusion is that both odour and sight play a part. In a multitude of flowers where the air is heavy with perfume, sight may play the chief role, but when the flowers are scarce and have to be found at a distance, scent is called into play.

Insects do not visit all flowers indifferently. Most go to diverse plants, but some limit themselves to a very small number of flowers, e.g. the moth, *micropteryx calthella*, keeps to the buttercup, and flowers like it (*Ranunculus repens* and *Ranunculus acris*).

Some insects are attracted to flowers which have vile and filthy smells in our estimation. Such flowers are *Aristolochia sipho*, which (to us) smells like urine, *Aristolochia labiosa*, which smells like spoiled

fish, and the Serpent Arum, *Arum dracunculus*, which smells like a decomposed cadaver.

Other insects feed on excrement and putrefying flesh, and in some cases the plant seems to have adapted itself to give a similar smell to attract the insects which may carry pollen, or in other cases may feed the plant.

Bouvier quoted a case where 463 *coleoptera* were found on five flowers of *Arum dracunculus*, and of these 377 belonged to a species, *Saprinus nitidulus*, which ordinarily feeds on cadavers. In the case of sarcophagous and stercoral insects the odour is the principal attraction and is perceived from afar. It is only reasonable to suppose that flowers with agreeable odours similarly attract insects from afar.

Fabre reported that the necrophori (carrion beetles) in quest of a breeding ground will travel great distances to find the corpses of small animals, informed by such odours as offend us. He exposed a dead mole in the sunlight, and as soon as it was swollen with the gases of putrefaction, and the fur commenced to fall from the greenish skin, a host of insects arrived, *Silphidæ*, *dermestes*, horn-beetles, and *necrophori*, of which no specimen could be found in the garden before the bait was exposed. From far away the sense of smell had warned them. Fabre also describes how insects invaded a serpent arum flower. The wide lanceolated blade of a vinous purple is twisted at the base into a purse the size of an egg. For two days the flower exhales a horrible stench of putrid flesh—odious, intolerable. Hordes of insects, such as dissect the corpses of frogs, adders, hedgehogs, etc., are informed by the odour of the flower and travel to it. They fall upon the great leaf whose vivid purple gives it the appearance of a strip of putrid flesh, and intoxicated, so Fabre says, by the delicious corpse-like odour, they roll down and are engulfed in the capsule. In a few hours this is full of delirious insects swarming and rolling, seething and boiling, clicking and squeaking. Most perish, they do not wish to escape, the lure is irresistible. They are not prisoners, not ovipositing, not feeding. Apparently they are just enjoying usually at the cost of their lives, the supreme enjoyment of an odour. Such behaviour indicates not only that in these insects the sense of odour is highly developed, but that they probably possess a modality of olfaction unknown to man.

Insects appear to use the sense of odour to guide them to their homes, although in many cases, as is to be expected, vision also is used. A wasp that can see its burrow alights exactly at it, but if it is carrying a heavy load and has to walk instead of fly, it requires a long search to find its home. Insects acquire an intimate knowledge of the topography near their homes. A pebble moved from its place upsets them, although they are not inconvenienced by the felling of a tree in the vicinity.

Ants find their way along their roads by olfaction. If they are deprived of their antennæ they cannot keep to even well-worn routes. To draw a finger across their trail upsets whole unmutilated ants.

Forel found that opaque varnish applied to the eyes of ants embarrassed them, but they still found their way, but that without their antennæ even with the full use of their eyes, they were quite lost.

Bethe set bees at liberty 3 or 4 kilometres away from their home and most returned.

Amongst the lepidoptera, some male moths show a marvellous ability to find a distant female. This is the sense which Fabre was inclined to think might be stimulated by a ray, but Fabre himself later showed that the males also sought out places on which the female had previously rested, and also showed that if the female was in a closed compartment the males were not attracted, but if the compartment was not quite closed so that ingress and egress of air was possible, then the males were attracted. All this points to the effluvium, whether molecules or rays, being air-borne, and not etheric as Fabre was inclined to think. Some instances of this peculiar ability of the male moths may be given.

Standfuss placed a newly hatched female Emperor moth (*Saturnia pavonia*) at his window in the heart of a town, and within $6\frac{1}{2}$ hours caught 127 males attracted to her.

Mell marked some male Chinese moths (*Actias selene*) and released them from a railway train, to seek out the female in a gauze cage on the verandah of his house. From a distance of $2\frac{1}{2}$ miles, 40 per cent. of the marked males returned to his house, and from 7 miles, 26 per cent. were successful.

Fabre imprisoned a Great Peacock or Emperor moth under a gauze cover one morning while it was still damp with the moisture of metamorphosis. About 9 p.m. the same night the male Great Peacocks seemed to take possession of the house. Great night moths were flying round the gauze cover, about forty male moths all eager to do homage to the female. For the next eight nights, as soon as it was dark, the butterflies came between 8 and 10 p.m. The weather was stormy, the darkness profound, and the house surrounded by bushes and shrubs, but nevertheless the butterflies arrived undamaged. They appeared to fly to the house with certainty, but arrived there, they were uncertain as to the precise location of the attractive object. The final discovery was left to a vague and hesitating search. It was as if they located the house by a sense such as sight, but when they arrived near the female the sense of scent was brought into play. To investigate the nature of the sense Fabre cut the antennæ off 8 moths and released 6 of them the next day, the other 2 having died. The next evening 25 moths arrived, but only one of these was without antennæ, i.e. one of the 6 released. Next day he loosed 16 without antennæ, and of the 14 arrivals the next night, none were without antennæ. This points to the antennæ being the seat of the receptors concerned in the attraction. However, to make sure he removed a little of the hair from the centre of the corselet of 14 other moths, leaving the antennæ intact, and the hair being removed simply as a method of identification. The next night 20 arrived, but of these

only 2 were tonsured. The total number of moths which came in the eight nights that the lure lasted was 150. The position of the cage was changed each night, and the female could be imprisoned in a drawer out of sight without making any difference, whilst if the cage was surrounded by naphthalene this also made no difference. If, however, the female was imprisoned in a drawer and all the chinks were stopped up, this baffled the males. The Emperor moths were rare in the district, and must have come from some distance. The female moth appears odourless to us. All the evidence points to a very acute sense of smell being the directing factor—possibly a variety unknown to us. Fabre later worked with the Lesser Peacock (*Attacus pavonia minor*) because it more conveniently mated in daytime. However, the first male moth " arrived as noon struck, we were sitting down to table—' aha '—I cried—' this is precisely the pilgrim we are waiting for. Fold your napkin and come and see what happens. We will dine later.' " According to Fabre these moths came when the *bise* was blowing from the north, and they must also have come from the north. How, then, could they be warned by a flow of odoriferous atoms in a direction contrary to that of the aerial torrent ? The observation seems to be at variance with most of the evidence. If confirmed it would throw doubt on any theory of material particles or even sound waves warning the moths.

Fabre later showed that if a female moth, this time the Oak Eggar or Banded Monk—was placed under a glass, the males paid no attention to her, but went straight to a twig on which the female had previously perched at the other side of the room. He also filled a dozen saucers with naphthalene, lavender oil, petroleum, sodium sulphide, and tobacco, the concentrated odours of a gas-works, a smoking-room, a petroleum well, and a chemical factory as he described it, but these had no embarrassing effect on the moths, which found the female without difficulty. He found, too, that if the female had been on cardboard, flannel, dust, sand, or a porous object, then the object attracted the males, but metals, marble, and glass quickly lost their efficacy.

Fabre concluded, " To call the moths of the countryside to the wedding feast, to warn them at a distance and to guide them, the nubile female emits an odour of extreme subtlety imperceptible to our own olfactory sense organs." The points arising from these experiments which show that the information was gained by olfaction or an allied sense are

(1) The signal was received at considerable distances.
(2) It was received in the dark, and beyond screens of trees.
(3) Difficulty in the final location of the exact place was characteristic of smell or sound rather than vision.
(4) Substances on which the lure had rested took on the attractive property.
(5) If such substances were porous they were more efficient.

(6) Hiding the lure in a slightly open drawer did not affect its efficacy, but if all the chinks were stopped up the lure lost its power, as it also did under glass.
(7) Loss of the antennæ incapacitated the males.

Features which are difficult to marry with the odour theory are

(1) In a strong wind the moths flew downwind, but the odour could hardly have been carried upwind.
(2) One moth which had been deprived of its antennæ returned. There are probably some, but relatively few, receptors disposed on other parts of the body.

The first objection is difficult to overcome. It really requires confirmation. Fabre himself saw a difficulty in the sensitiveness of the males, but we know from many sources of the exquisite delicacy of olfaction, and I do not think this objection would hold to-day. The evidence that the olfactory sense is the medium used to pick up the signals is overwhelming. It may be, indeed it probably is, not quite the same olfaction as we know. It may be about as different from ours as a bitter taste is from a sweet taste ; both are tastes, and the main difference is in the central connections and the resultant sensation.

It is chemical sense which guides the female lepidoptera to lay their eggs on the leaves of plants which are later suitable to be devoured by the caterpillar.

Similarly, the ichneumon flies lay their eggs in the larvæ of other insects and have to bore shafts direct to the prospective hosts, guided apparently by smell.

The attractions of flowers for bees and of the female for the male moths are cases of positive chemotropism. The vinegar fly (*drosophila ampelophila*) reacts positively to alcohol, acids and ethers of fermenting fruit and flies straight to such guides, but if the terminal segment of one antenna is removed it takes a manœuvring method. The ant exhibits a negative chemotropism as it flees from essence of cloves. Hydrotropism directs water-bugs and water-beetles from far away to water, and this appears to be another modality of the chemical sense. A " tropism " suggests an elementary or instinctive reaction lower than sensation. Here again all degrees between a primitive tropism and full sensation exist.

Most of the sensorial impressions of insects are received by means of hairs connected with nerve cells. These hairs are principally concentrated on the antennæ but in a less degree occur over the body. They are also concentrated on the palpi of the mouth apparatus. The hairs on the antennæ receive smell and sound, whilst taste is located in the mouth. Touch is general, and the eyes supply vision. The sensorial equipment of a highly developed insect bears marked resemblances to our own.

In insects and many other arthropods there are three body regions, head, thorax, and abdomen. The head of an insect is all in one piece although the embryo head consists of six segments—a characteristic

of the arthropods, and the segments, although fused, can be seen in the adult. On the grasshopper, for example, there are two compound eyes on the first head segment, long-jointed sensory antennæ on the second, upper lip on the third, jaw on the fourth, accessory jaws with jointed sensory palp on the fifth, and on the sixth a lower lip with a sensory palp on each side. The nervous system runs along the front and is concentrated, as in the lobster, in two main ganglia. The brain which lies between the eyes has no centres for co-ordinating muscular activity. After removal of the brain a grasshopper can still jump, fly or walk, and as it then responds to the slightest stimuli by violent action it is clear that its brain normally exerts an inhibiting effect. As in lower invertebrates the brain serves chiefly as a sensory relay between receptors and muscles.

It will be seen that the insects are abundantly supplied with sense organs. Their taste threshold in some cases approximates to our

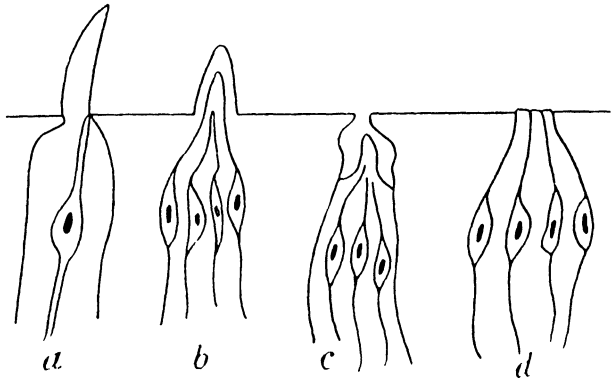


Fig. 21.—Insect receptors.

own, the bees have similar olfactory perception, and the moths a much keener olfactory sense. The prolific distribution of receptor cells, considered together with the behaviour of the insects, renders it likely that they possess in addition modalities of the chemical sense unknown to us. Fig. 21 illustrates the main types of receptors found in insects.

(*a*) Bristles sensitive to touch.
(*b*) Small slender bristles, not movable, which have thin permeable walls and are receptors for chemical stimuli.
(*c*) Pits sensitive to chemical stimuli.
(*d*) Plates which may be sensitive to chemical stimuli.

Fishes

The lancetfish, *Amphioxus*, and the cyclostomes, such as *Petromyzon*, occupy an intermediate position between the invertebrates and the true fishes. The *Amphioxus* in particular represents a stage between the invertebrates and the vertebrates. It has a *notochord* instead of a vertebral column, and it may be mentioned that the

notochord is found in early human embryos. *Amphioxus* is a small two-inch-long semi-transparent animal found in shallow marine waters. It is of particular interest to us as it is " monorhine." It, and the cyclostomes share this feature, has only one nasal orifice. Animals which have two nasal orifices, like ourselves, the mammals and the higher fishes, are " amphirhine." The *Amphioxus* and *Petromyzon* are monorhine, and have only one nasal aperture which is median and dorsal. Fig. 22 indicates the position of the nasal aperture on the *Petromyzon*. Fishes with naked gills, like the sharks and rays, have the olfactory pits paired, and on the ventral side of the snout. They are associated with the respiratory passages, and this is more marked in the higher lung fishes where there are features corresponding to our nares and choana. In highly specialized bony fishes the olfactory pits may be some distance from the mouth, and quite independent of respiration.

Jagodowski (*Anat. Anz.*, **19,** 257-67, 1901) showed that the pike has long flagella, similar to our olfactory hairs.

Whereas olfaction is confined in fishes to the two (or in some cases, one) olfactory pits, taste is widespread. The taste nerve serves the flanks and barbels of the fishes as well as the region of the mouth.

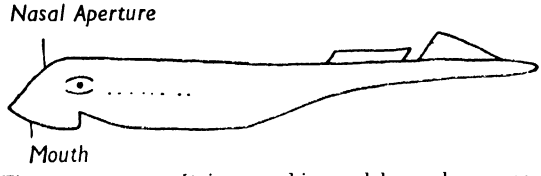


FIG. 22.—The petromyzon. It is monorhine and has only one nasal aperture which is median and dorsal in position.

Many fishes, such as the cod, have the skin and pectoral fins richly supplied with taste receptors, which may reach enormous numbers in deep-sea fishes. Taste receptors do not occur in the skin above the class of fishes but are confined to the mouth. Common chemical sense receptors are also scattered over the surfaces of fishes, and indeed of higher animals. But although endowed with the primitive chemical sense and its differentiations, taste and smell, fishes are not able to correlate the impressions they receive separately from these senses into a perceptual pattern. The dogfish seeks its food by smell, and if the olfactory bulb is severed, it ceases to feed spontaneously, even though hungry and able to see food. It seems that the olfactory sense starts a train of reactions culminating in feeding, and the fish, if deprived of its olfactory equipment, cannot initiate this sequence of reactions at a later stage.

The olfactory organs of fishes are stimulated by solutions and not by air or gases or vapours. This led some of the early workers to consider that the sense concerned was taste rather than smell. It is true that not many of the strong odorants man is familiar with are readily soluble in water. Aronsohn in 1884 had shown that goldfish

would not eat ant pupæ, of which they were normally fond, if the pupæ had been sprinkled with clove oil. This and many similar experiments were not conclusive as the effect might have been due to common chemical irritation and not to olfaction, but in 1910 Parker (*Jour. Expt. Zoöl.*, **8,** 535-42) cleared up the point. Two wads of cheese cloth, one containing earthworms and one empty, were hung in an aquarium containing five catfishes (*Amiurus*). Although the positions of the wads were occasionally interchanged, that containing the worms was seized 11 times by the fishes in an hour, and the other wad not at all. Next the olfactory tract was removed from five catfishes and these fishes did not seize either wad. Next the external taste organs were cut from five other catfishes but their olfactory tracts were left intact, and these fish seized the wad containing the worms 34 times in an hour. The experiments were repeated, and the conclusion reached that the olfactory organs of the catfish sense food at distances greater than those at which taste can act, or it may truly be said that catfishes scent their food.

In other experiments the anterior nares were stitched up instead of removing the olfactory tract. Later, Parker (*Bull. U.S. Bureau Fisheries*, **33,** 61-8, 1914) showed that when only one nostril was plugged the fishes turn persistently towards the side of the open nostril. In measurements on the dogfish the following results were obtained by Parker :

State of Fishes.	Turning Movements.	
	To Left.	To Right.
Normal	50	50
Left nostril occluded .	11	89
Right ,, ,, .	87	13
Both nostrils open again .	44	56

This shows that dogfishes seek their food by olfaction and turn to the side with the greatest odour.

Taste-buds are plentiful on the flanks of many fishes, and if a piece of meat or a wad of cotton-wool soaked in meat juice is held close to a catfish it will turn and snap at it. If the branch of the gustatory nerve which innervates the taste-buds of the flank is cut the fish will no longer do so, but is still stimulated by sour, alkaline, and salt solutions, the free nerve endings of the spinal nerves being the receptors. Sheldon (*Jour. Comp. Neurol. Psychol.*, **19,** 273-311, 1909) found that the whole outer surface of the dogfish, *Mustelus*, was very sensitive to acids and alkalis but less so to salt and bitter substances, and not sensitive at all to sugar solutions. The general conclusion is that fishes have senses of olfaction confined to the olfactory pits, of taste near the mouth and flanks, whilst they are sensitive to chemicals of a mildly irritating type over the whole body surface.

Amphibia

Living amphibians are without scales, such as fishes and reptiles possess, and they usually have lungs. They have toed appendages instead of fins.

Copeland (*Jour. An. Behaviour*, **3,** 260-73, 1913) has shown that the spotted newt (*Diemyctylus viridescens*) has similar olfactory powers to the fishes, and Risser (*Jour. Exp. Zoöl.*, **16,** 617-52, 1914) made similar observations on tadpoles. It has long been known that a frog's foot can be stimulated by weak solutions of acid, and there is in amphibians the same general sensitiveness of the skin to chemicals. Taste-buds in amphibia are not found on the body surface but are numerous in the mouth and pharynx.

Bruni (*Boll. soc. ital. biol. sper.*, **8,** 1332-4, 1933) showed that the sensory organs of the frog's palate and tongue were of taste. Sapid substances, such as acetic acid, quinine hydrochloride and sucrose, produce changes in the cytoplasm of certain cells of the palate of the live frog when examined microscopically.

Reptiles

Comparatively little work has been carried out on the chemical sensibility of reptiles.

There are only few taste-buds in snakes and alligators, but there are more in tortoises. So far as general chemical sensibility is concerned they might be expected to occupy a position intermediate between the amphibians, which are chemically sensitive over the whole body, and mammals where the chemical sensitivity is confined to small areas.

Birds

Birds, like humans, rely chiefly on the sense of vision, and in their flight may also be guided by some sense analogous to the lateral-line in fishes. Their chemical senses do not appear to be highly developed. White is a more usual colour in birds than in other animals, and the absence of pigment which we associate with anosmia does not seem to embarrass them. It has been suggested that the bird of prey senses the fallen mule from the height of the clouds by olfaction, but there is good reason to think this is more a matter of vision than smell. The common sight of a thrush listening with head cocked for worms moving under the lawn suggests at once that it is not gifted olfactorily. In birds taste-buds are fewest. The trigeminal nerve shows great development in ducks and geese, as presumably aquatic birds are more likely to come in contact with irritants.

The question of taste in hens was studied by Engelmann (*Z. vergl. Physiol.*, **24,** 451-62, 1937). He found that there was no qualitative discrimination between sodium chloride and hydrochloric acid, or between hydrochloric and acetic acids, or glycerol and magnesium chloride. In each case the bird prefers the more dilute solution

irrespective of which substance it contains. Magnesium chloride was preferred to acids and sodium chloride. It seems that the sense of taste is very rudimentary and in fact resembles more a common chemical sense in the mouth than a true taste.

Mammals

It is a matter of frequent observation that many of the mammals have a much keener sense of smell than man. Among the *carnivora* the dog, the cat, and the fox, and among the *herbivora* the sheep and the rabbit are all very macrosmatic. The *cetacea*, whales and porpoises, are supposed to be anosmic, or at least some of them are. There is a correspondence between the amount and intensity of the nasal pigmentation and the acuteness of smell. In the macrosmatic animals the pigmentation extends over a larger area, and is darker than in man, whilst in addition the Bowman glands secrete a pigmented fluid, brown in the dog, sienna in the rabbit, and nearly black in the sheep. In animals the Bowman glands keep the olfactory region constantly covered with a layer of pigmented fluid, but in man their place is taken by ordinary mucous glands.

Fabre records the case of a *rabassier* or truffle-hunter who relied on his dog which " goes forward, scents the wind, stops, questions the soil and scratches the earth a few times." The rabassier digs at the point indicated, and if the spade has gone astray the dog sniffs at the bottom of the hole and guides the digger. The rabassier knows where the edible truffles are likely to be and adds his knowledge of discrimination to the dog's keenness of scent, but if left to itself the dog unearths large and small, fresh and putrid, odorous and (to us) inodorous, fragrant and offensive hypogenous fungi, some of which, to us, had no appreciable scent beyond a vague fungoid flavour more or less common to all, whilst others smelled of cabbage or turnip or even fœtid. The dog, however, paid no attention to nearby toadstools and mushrooms apparently with the same fungoid odour. Clearly, such powers of perception are vastly superior to ours, but these pale into insignificance beside the performance of the *Bolboceras gallicus*, which not only sank vertical shafts without trial exploration to the truffle, but also confined itself to one particular species.

Whilst the olfactory keenness of many animals far surpasses our own, it is amongst the insects that olfactory sensitiveness reaches its peak.

As has already been noted, the olfactory sense is often absent in young mammals whose diet is exclusively maternal milk, and only develops at weaning time when it can be helpful to the animal. In the case of man, olfaction is supposed to reach its peak at, and soon after, puberty, and to decline after the age of forty-five. An interesting investigation of the change in size of the olfactory bulb of the white rat with age was made by C. G. Smith (*J. Comp. Neurol.*, **61**, 477-508, 1935). He found that the olfactory bulb and centre at first grew, but

after the first year atrophied progressively. The vomero-nasal centre, however, remained unchanged, and we have to remember that some form of olfaction may be sensed by the animal through its vomero-nasal apparatus.

Electrical phenomena have been noted in the olfactory bulb of a rabbit during olfactory sensation.

Although the sense of smell is so much keener in many mammals than in man, the sense of taste appears to be fairly equally keen in man and the higher animals.

Richter and Campbell (*Amer. J. Physiol.*, **128,** 291-7, 1940) compared the taste thresholds in rats and man for sucrose. The rats recognized the difference between distilled water and sucrose solution in average concentrations of 0·5 per cent. Young adult humans detected a difference at 0·17 per cent., and recognized the sweet taste at 0·41 per cent., so that the sense of taste is keener in man than in the rat. It may be noted that these determinations of the threshold concentration of sucrose for man are lower than hitherto accepted. The same authors (*Science*, **91,** 507-8, 1940) showed rats exhibit a preference for alcoholic solutions between 1·8 and 6·0 per cent. concentration to water.

Coming to the primates, Fisher, Ford and Huxley (*Nature*, **144,** 750, 1939) taste-tested the chimpanzees with solutions of phenyl thiocarbamide sweetened with sugar, and showed that for the former substance the proportion of tasters to non-tasters is about the same in chimpanzees as in man.

In the case of the common chemical sense the higher animals show reactions similar to those of man.

CHAPTER 8

CLASSIFICATION OF ODOURS

General

In Chapter 6 we attempted to classify the common chemical sense stimuli into seven classes, chiefly on a physiological basis. Taste has for long been divided into the four primary classes, and it has been claimed by different workers that all tastes can be made artificially by mixing the four primary tastes. When we consider odours, however, the position is more difficult. We cannot readily classify odours as we have done the common chemical stimuli by the physiological reactions, for the reactions to odorants are usually mild and undefined, a sniff, a drawing away, or perhaps, in extreme cases, disgust and nausea. In the case of taste, sweet and bitter are so commonly experienced, and so distinctive and well known even to a child that the work of classification is already half-done.

There are no similarly well-known types of odours to which we ascribe words corresponding to " sweet " and " bitter." The best we can do is " flowery," " fruity " or " foul," and so on. Endeavours to classify the odours have not been very successful. The number of types of odour seems large, and different judges do not agree as to the distinctions. Probably in respect of the appreciation of a large variety of odours man's sense of smell transcends that of the animals although in ability to trail prey and mates, the animal's endowment is superior to ours. Many attempts have been made to classify the odours. The best-known classifications are those of Rimmel, Zwaardemaker, and Henning, and these will be examined first.

Rimmel's Classification

This is based on the empirical likenesses of the pleasant odours which it divides into eighteen classes. It is empirical but it is useful. It carries out the first arrangement of the multitudinous odorants into some form of order. It is not perfect, as some odours, such as methyl salicylate or oil of wintergreen, do not find a proper place in the scheme. Eighteen classes seems rather a large number, but it was the smallest Rimmel found practicable. Each class has a name, e.g. " Fruit," a typical member, e.g. " pear," and other members, e.g. apple, quince, etc. The full list of Rimmel's eighteen classes is given below :

Class.	*Typical odour.*	*Odours in same class.*
(1) Rose	Rose	Geranium, Sweetbriar, Rosewood.
(2) Jasmine	Jasmine	Lily-of-the-Valley.
(3) Orange flower	Orange flower	Acacia, Syringa, Orange-leaves.
(4) Tuberose	Tuberose	Lily, Narcissus, Jonquil, Hyacinth.
(5) Violet	Violet	Orris-root, Cassie, Mignonette.
(6) Balsamic	Vanilla	Benzoin, Storax, Tonka-bean, Heliotrope, Balsams of Peru and Tolu.
(7) Spice	Cinnamon	Cassia, Nutmeg, Mace, Pimento.

Class.	*Typical odour.*	*Odour in same class.*
(8) Clove	Clove	Carnation, Clove-pink.
(9) Camphor	Camphor	Patchouli, Rosemary.
(10) Sandal	Sandalwood	Vetivert, Cedarwood.
(11) Citrine	Lemon	Bergamot, Orange.
(12) Lavender	Lavender	Spike Lavender, Thyme, Marjoram.
(13) Mint	Peppermint	Spearmint, Balm, Rue, Sage.
(14) Aniseed	Aniseed	Carraway, Dill, Coriander, Fennel.
(15) Almond	Bitter almonds	Laurel, Peach kernels, Mirabane.
(16) Musk	Musk	Civet
(17) Ambergris	Ambergris	Oak Moss.
(18) Fruit	Pear	Apple, Pineapple, Quince.

The limitations of this system are clear. First, it does not include food odours on the one hand, nor repulsive odours on the other. Secondly, some of the classes invite grouping together, e.g. classes 1 to 4 and possibly 5 could be grouped as " flowery," whilst 16 and 17, musk and ambergris, could be similarly grouped. However, the classification was intended for the perfume manufacturer rather than as a systematic classification of odours on a physiological or constitutional basis.

Zwaardemaker's Classification

In 1895 (" Die Physiologie des Geruchs ") Zwaardemaker put forward a systematic classification of odours in nine general classes each of which may contain two or more sub-divisions. These were

Class.	*Sub-divisions.*
(1) Ethereal	(*a*) Fruits, (*b*) Beeswax, (*c*) Ethers.
(2) Aromatic	(*a*) Camphor, (*b*) Cloves, (*c*) Lavender, (*d*) Lemon, (*e*) Bitter almonds.
(3) Balsamic or Fragrant	(*a*) Flowers, (*b*) Violet, (*c*) Vanilla and coumarin.
(4) Ambrosial	(*a*) Amber, (*b*) Musk.
(5) Alliaceous	(*a*) Sulphuretted hydrogen, (*b*) Arsine, (*c*) Chlorine.
(6) Empyreumatic	(*a*) Roast coffee, (*b*) Benzene.
(7) Caprilic	(*a*) Cheese, (*b*) Rancid fat.
(8) Repulsive	(*a*) Deadly nightshade, (*b*) Bed-bug.
(9) Nauseating or Fœtid	(*a*) Carrion, (*b*) Fæces.

Such a system is clearly associative and subjective. What is repulsive to one person may not be so to another. Nevertheless it represents a distinct advance, as many odours can be reasonably assigned to one of the nine groups. In connection with Zwaardemaker's classification it has been suggested that in the olfactory apparatus there are nine groups of cells, one corresponding to each primary smell, and these cells are spatially arranged and partial anosmia is then due to a deficiency in one or more of these nine classes of cells. It has been shown that when total loss of smell is temporarily produced by anæsthesia, the ability to smell burning or empyreumatic smells (class 6) returns first, whilst class 8, repulsive smells, is the last to recover.

If it is correct that those odorants in one class act on a particular set of receptors, and those in another class act on a different set, then some interesting fatigue phenomena should be evident. If the olfactory apparatus is fatigued by a substance in class 1, it would be

expected that it would be fatigued for any substance in the same class, but not for a substance in a different class, since this latter would act on a fresh lot of receptors. Zwaardemaker (*Arch. néerl. Physiol.*, **6**, 336-54, 1922) found that certain natural groups of odorants were given by experiments on sensorial fatigue and that these mostly corresponded to the sub-classes of the system of Linné. This system of Linné was an early arrangement on which Zwaardemaker based his own arrangement which was a considerable extension of Linné's. Hence the sensorial fatigue gave natural groups corresponding to some extent to the sub-classes in Zwaardemaker's own classification.

Ohma (*Arch. néerl. Physiol.*, **6**, 567-91, 1922) investigated the question of fatigue for the odours which formed the second class of the Linné-Zwaardemaker system. This consists of the Aromatic odours which are divided into five classes as follows : camphor, cloves, lavender, lemon and bitter almonds. Ohma succeeded in producing a perfect fatigue with the members of any one sub-class, which was greater than the fatigue for a member of another sub-class. Thus camphor, eucalyptol and eugenol produced perfect fatigue for each other and therefore are rightly classed and sub-classed together. These substances produced only partial fatigue for citral and safrol which belong to the same main class but to a different sub-class. The fatigue experiments were carried out near the physiological threshold concentration. A striking objection to Zwaardemaker's arrangement is that chloroform and iodoform are found along with fruity odours in the first class. This certainly seems an artificial arrangement.

Henning's Olfactory Prism

In his book " Der Geruch " (Leipzig, 1916) Henning put forward a new classification. He abandoned the old arrangement, and after careful analysis suggested that odours should be classified into these six groups :

(1) Spicy, e.g. cloves, fennel, anise.
(2) Flowery, e.g. heliotrope, coumarin, geranium.
(3) Fruity, e.g. oil of orange, oil of bergamot, citronellal.
(4) Resinous or balsamic, e.g. turpentine, eucalyptus oil, Canada balsam.
(5) Burnt, e.g. pyridine, tar.
(6) Foul, e.g. sulphuretted hydrogen, carbon bisulphide.

The classes were not absolutely separate but were joined by intermediate odours which merged the classes into each other. He pictured the arrangement as an Olfactory Prism, as shown in Fig. 23, each of the six odours occupying a corner of the prism, and all odours, fundamental or intermediate, find places on the surface of the prism. It will be seen that an odour could be a fundamental odour occupying a corner, could be along an edge when it would have two components, on a triangular surface with three components or on a square surface

with four components. It appears to be impossible for it to have five or six components, and also impossible for it to have three and not four components, on a square side of the prism. Thus a substance could not be fruity, flowery, and spicy without also being resinous. Whilst these arguments show that the prism will not represent all odours, it has to be remembered that the prism itself is only a method of illustration and has no physical significance *per se*. Consequently these objections to the prism do not apply to the arrangement devised by Henning. Henning also showed that certain chemical groupings were associated with his six classes. It was not so much a question of which group was present as of its position and relation to the rest of the molecule. These arrangements were

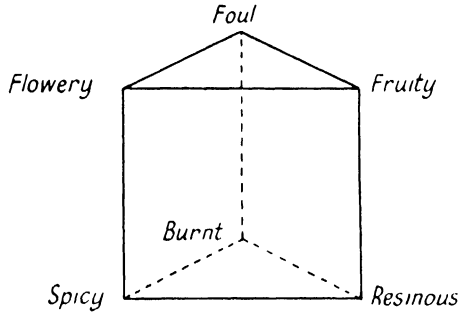
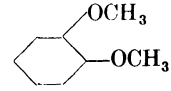


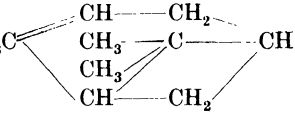
FIG. 23.—Henning's olfactory prism.

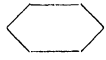
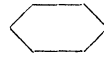
(1) Spicy. The para arrangement in the benzene ring, two osmophoric groups being in the 1 : 4 position thus :  , e.g. anisaldehyde CH_3O—  —CHO.

(2) Flowery. The ortho or 1 : 2 arrangement is the dominant influence here, thus :  , e.g. veratrol  .

(3) Fruity. Here the groups are forked —  , as in citral :

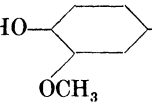
$$CHO\,.\,CH : C(CH_3)\,.\,CH_2\,.\,CH_2\,.\,CH : C\begin{matrix}CH_3\\CH_3\end{matrix}$$

(4) Resinous. The osmophoric groups are within the ring thus :  , e.g. pinene 

(5) Burnt. A smooth ring typifies the burnt odours thus :  , e.g. pyridine  .

(6) Foul. The odours are typified by the arrangement $S\begin{matrix}R\\R\end{matrix}$, e.g. sulphuretted hydrogen, $S\begin{matrix}H\\H\end{matrix}$, and mercaptan, $S\begin{matrix}H\\C_2H_5\end{matrix}$.

In this scheme intermediate odours are evinced by substances which have characteristics of more than one class, e.g.

vanillin, 

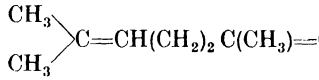
has both ortho and para groups and is flowery and spicy.

Parry's Alcohol Classification

Parry (*Perf. Essent. Oil Rec.*, **7**, 129-34, 1916) pointed out that no scientific classification of odours existed but that some generalizations could be made. Closed chain hydrocarbons were more aromatic than open chain, and in the closed chain the orientation of the groups had a definite influence on the odour. Whilst this was well known Parry went further and divided the alcohol odours into six main classes, as follows :

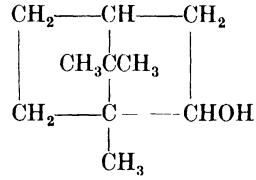
(1) Fruity odours of higher fatty alcohols. (In the author's experience such as stearyl alcohol, a C_{18} saturated alcohol, and oleyl alcohol, a C_{18} unsaturated alcohol, are more " waxy " than " fruity " in odour.)

(2) Soft, rose-like, and similar odours of the di-olefinic alcohols of the geraniol type. Geraniol,



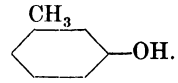
(3) Soft, heavier odours of the cyclo-substituted aliphatic alcohols, e.g. phenylethyl alcohol, $C_6H_5CH_2CH_2OH$, a constituent of rose perfume.

(4) Sharp odours of the terpene alcohols, e.g. borneol, a secondary alcohol obtained by the reduction of camphor with this formula :



(5) Heavy oriental odours of the sesquiterpene alcohols, e.g. eudesmol, $C_{15}H_{25}OH$ or 1-methylene-5-methyl-8-isopropyl-8-hydroxy-dekahydronaphthalene from eucalyptus oil (Ruzicka and Capato, *Liebig's Annalen der Chemie*, **453**, 62, 1927), and nerolidol from orange flowers, 2, 6, 10-trimethyl-$\Delta^{2,\ 6,\ 11}$, dodekatriene-10-ol,

$$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CH(CH_2)_2 \cdot CCH_3(OH) \cdot CH{=}CH_2.$$

(6) Phenolic odours, e.g. cresol, 

Parry also suggested the classification of esters either by keeping the acid radicle constant and changing the alcoholic radicle or the converse, but this is more or less self-evident.

Crocker and Henderson's Arrangement

Four kinds of smell nerves were postulated, corresponding to (1) Fragrant, (2) Acid, (3) Burnt, (4) Caprylic odours. This last represents the disagreeable and putrid odours. Any given odour may contain all four of these fundamental odours, and their relative degrees of stimulation fix the individuality of the odour. If the maximum intensity that any of the fundamental odours can attain is 8, then all the numbers from 0000 to 8888 represent different odours. Thus the rose smell is represented by 6423.

Fragrant	.	.	Stimulated	to	a degree	of 6
Acid	.	.	,,	,,	,,	4
Burnt	.	.	,,	,,	,,	2
Caprylic	.	.	,,	,,	,,	3

Boring, in 1928, studied this method and found good reproducibility. The importance of the method is clear, as it would enable an odour to be reproduced anywhere at any time simply by its code number. Boring decided that between two and four thousand different odours can be distinguished by most people.

Various

Amongst other classifications suggested, the following may be mentioned. Heyninx divided odours into the following classes: acrid, rotten, fœtid, burning, spicy, vanilla or ethereal, and garlicky. He based his division to some extent on the spectrum analyses of the odorants. The division he arrived at seems to bear some resemblance to Zwaardemaker's.

Erb (*Osteopathic Digest*, **3**, 2, 4, 1927) used this classification.

(1) Infra odours which by their strength and pungency produce distracting sensations (probably common chemical reactions).
(2) Fragrant odours.
(3) Empyreumatic odours.
(4) Caprylic odours.
(5) Acid or sour odours.
(6) Ultra-odours, feeble non-registering smells.

The perfumers use Piesse's "Gamut of Odours," and Cerbeland's extension of Rimmel's classification.

In 1924 von Skramlik (*Naturwissenschaften*, **12**, 813-24), after investigating the action on the olfactory apparatus of gaseous mixtures

containing 2, 3 and 4 components, came to the conclusion that every classification of odours is wholly arbitrary and that on the existing knowledge the only basis for characterizing an odour was the particular chemical compound itself.

Whilst it is clear that no perfect classification of odours has yet been devised, there is no reason to regard the existing classifications as valueless. If they did nothing else they do at least sort out the vast gamut of odours into groups suitable for investigation. In addition the fatigue results show that Zwaardemaker's classification is fundamentally sound, whilst Henning's offers an approach to the problem of the relation between chemical constitution and odour.

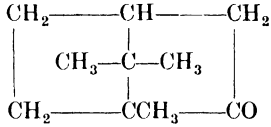
CHAPTER 9

CHEMICAL CONSTITUTION AND ODOUR

General

Early investigators hoped to find a precise and full relation between the chemical constitution and odour of substances, so that by examining the constitution of a hitherto unknown substance it would be possible to predict its odour and also so that it would be possible to synthesize bodies with any required odour. Such hopes have not been fulfilled for, on the one hand, it has been found that stereoisomers, substances which are mirror-images of each other, may have different odours, whilst, on the other hand, substances with similar odours may have widely different constitutions. For example, the following substances have similar camphoraceous odours:

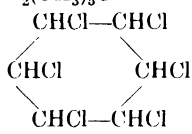
Camphor



Hexachlorethane $CCl_3—CCl_3$

Pentamethyl ethyl alcohol $C_2(CH_3)_5OH$

Benzene hexachloride



Tetrachlornaphthalene $C_{10}H_4Cl_4$

Artificial camphor (from turpentine) $C_{10}H_{16} . HCl$

Durene $C_6H_2(CH_3)_4$;

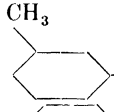
and the following smell of bitter almonds

Hydrocyanic acid HCN

Nitrobenzene $C_6H_5 . NO_2$

Benzaldehyde $C_6H_5 . CHO$.

Again, *sym*-trichlorphenol smells like iodoform. Conversely, *o*-chlorphenol in dilute solution has a powerful odour like that of iodoform, but *m*- and *p*-chlorphenol are much less pronounced and more like the unsubstituted phenol.

Whereas *m*-tolyl thiocarbimide,  , is pungent, its isomer *p*-tolyl thiocarbimide,  , has a sweet anise odour.

Consequently, the view has prevailed that odour is not dependent on chemical constitution, but on the physical differences brought

about by the arrangement of the constituent groups, which physical differences are reflected in the molecular vibrations of the substance.

The pendulum has swung too far, and the close relation that exists between chemical constitution and odour is forgotten. There are very many groups of substances of similar constitution possessing similar odours. The effect on the odour of the introduction of a new group into a substance may often be predicted. It may well be that with greater knowledge which will be gained in the next few decades, the whole subject will rationalize itself, and to-day's anomalies and inconsistencies will fall perfectly into place in the complete pattern.

The Elements

It is only logical to consider the elements and their odour before studying the complex organic compounds. If we neglect the existence of isotopes, there are ninety-two elements possible, of which at least ninety are well-established, and of which thirty occur free in nature. These thirty are hydrogen, helium, neon, oxygen, nitrogen, argon, krypton, xenon, radon, mercury, sulphur, bismuth, cadmium, zinc, tellurium, antimony, arsenic, silver, gold, copper, nickel, cobalt, iron, palladium, carbon, platinum, ruthenium, rhodium, iridium, and osmium.

Under normal conditions—i.e. at atmospheric pressure and temperature—none of these is odorous. If heated so as to vaporize, arsenic smells of garlic, but the others are without characteristic odour. Of the other elements, which do not occur naturally uncombined, the most noteworthy from the olfactory standpoint are the halogens, fluorine, chlorine, bromine and iodine vapour. All four are extremely poisonous and have strong irritant action, but in addition to this they are truly odorous. All belong to the same group in the Periodic Classification and their atoms have seven electrons in their outer rings. It should be noted, however, that it is not atomic chlorine and bromine that we ordinarily smell, but the diatomic molecules, Cl_2, Br_2, where the electronic rings have fused. We have no knowledge of what atomic chlorine or bromine would smell like. Fluorine, F_2, has an intensely irritating smell recalling hypochlorous acid, HOCl, or nitrogen peroxide, NO_2. When very dilute it is not unpleasant.

Chlorine, Cl_2, has a well-known irritating smell.

Bromine, Br_2, is similar to chlorine but sweeter and heavier in odour.

Iodine vapour, I_2, has a slight smell recalling that of chlorine.

The halogens do dissociate into single atoms at high temperatures. Bromine at 800° C. dissociates to the extent of 0·16 per cent. and at 1280° C. to 18 per cent. Iodine shows more tendency to dissociate, and at 850° C. 8 per cent. has dissociated to monatomic iodine and at 1460° C. as much as 73 per cent. is monatomic, but it is not until a temperature as high as 480° C. is reached that measurable dissociation commences. Clearly, such temperatures are quite impossible in the nose, so that we can only smell the halogens in their diatomic state.

The atomicity of the molecule is important; for, whereas oxygen, O_2, is odourless, yet ozone, O_3, has a characteristic smell, frequently

observed near electrical machines. It is therefore quite possible that elementary chlorine or bromine would have an odour different from the common diatomic gases.

Of the other elements, phosphorus has a strong garlicky odour. It is only yellow phosphorus which has this odour for its allotropic modification, red phosphorus, is odourless. Here, again, the difference in odours is due to the numbers of atoms in the molecule. Yellow phosphorus is P_4, and red phosphorus P_n, where n is a much greater number than 4. This difference in atomic packing in the molecules of red and yellow phosphorus is reflected in their specific gravities.

Yellow phosphorus, P_4, is 1·83-1·85.
Red ,, P_n, is 2·05-2·39.

It may be noted, too, that another allotropic modification, black phosphorus, obtained by subjecting yellow phosphorus to great pressure, has a still higher specific gravity, 2·60-2·65, which suggests a molecular constitution of P_{n+}, and this form also is odourless.

It is clear that in addition to the type of atom present, the number and arrangement of atoms in a molecule influence the odour. The modern tendency is to go too far in this direction and discount the effect of the chemical nature of the substance. It should not be forgotten that no substance, not containing chlorine, smells quite like chlorine.

Oxygen and nitrogen as O_2 and N_2 respectively, occupy a special position since they are the main constituents of air and normally fill the olfactory cavity. They represent the condition to which all other substances are referred as regards smell. The fact that we cannot smell oxygen or nitrogen may not be due to the same cause as our inability to smell, say, hydrogen and carbon monoxide. We truly say that the last two are odourless, but all we can justifiably say of oxygen and nitrogen is that since we normally live in them they cannot excite the olfactory nerve. Their odourless nature is subjective—not objective. The fact that ozone, O_3, has a characteristic smell, supports this view.

Hence there are no elements which in their atomic state are known to excite olfaction, but there are seven elements which in a diatomic or polyatomic state *do* cause olfaction. These are fluorine, chlorine, bromine, iodine, oxygen (as ozone), phosphorus and arsenic. It may be noted that there are only two kinds of smell represented here, for the halogens all smell more or less alike, whilst phosphorus and arsenic are described as garlicky, and ozone reminds some of chlorine and others of garlic. It appears that such simple molecules as those containing only one kind of atom can produce only two different odours, halogen or garlic. The writer suggests that attempts to classify the odours into a small number of fundamental odours should take this into account, and further, that two of the fundamental odours are "halogen" and "garlic." Further than this, although strongly ozonized air is unpleasant and toxic, in minute quantities the odour is pleasant and refreshing. Hence even in a fundamental single odour we find the phenomenon of change of human reaction with dilution.

The Chemical Senses

It may be noted that of the seven odorous elements, four, the halogens, are in Group 7 of the Periodic Classification, and two, phosphorus and arsenic, are in Group 5, with the seventh, oxygen, in Group 6. Evidently there is some parallelism between odour and ability to function in a high state of valency.

The Electrochemical Series

It is possible to arrange the elements in a series according to the potential difference between the element and a solution of its salt; the higher this potential difference, the higher the position of the element. Such a series of the more common elements, omitting completely the inert gases and rare earth elements, is as follows:

These metals liberate hydrogen from acids	Cæsium	METALS
	Rubidium	
	Potassium	
	Sodium	
	Lithium	
	Barium	
	Strontium	
	Calcium	
	Magnesium	
	Aluminium	
	Chromium	
	Manganese	
	Zinc	
	Cadmium	
	Iron	
	Cobalt	
	Nickel	
	Tin	
	Lead	
	Hydrogen	
	Antimony	
	Bismuth	
	Arsenic	
	Copper	
	Mercury	
	Silver	
	Palladium	
	Platinum	
	Gold	
	Iridium	
	Rhodium	
	Osmium	
	Silicon	NON-METALS
	Carbon	
	Boron	
	Nitrogen	
	Selenium	
	Phosphorus	
	Sulphur	
	Iodine	
	Bromine	
	Chlorine	
	Oxygen	
	Fluorine	

A highly placed metal will displace a lower metal from its salts—e.g. zinc or iron will deposit copper from copper sulphate solution. The series is therefore no artificial arrangement, but has a general and well-recognized significance. It is at once remarkable that six of the seven odorous elements occupy six of the last seven places in the table, only arsenic occupying a higher place.

Further than this, if we consider not odorous elements but odorous compounds, then compounds of sulphur and selenium usually have vile smells, whilst compounds of nitrogen and carbon embrace every kind of odour. It is clear that an electronegative or non-metallic character is allied closely with odorant properties. Even amongst the metals the lowest of them, osmium, takes its name from the Greek ὀσμη (*osme*) = a smell, on account of the penetrating smell of its compounds such as the tetroxide OsO_4. Elements high in the table, in particular, all those above hydrogen, are quite unassociated with odour.

Niccolini (*Arch. ital. sci. farmacol.*, **6**, 241-78, 1937) has pointed out that all the elements of the first two groups of the periodic system are "olfactory-negative," and in binary compounds, at least, suppress the possibility of developing odours. These elements are lithium, sodium, potassium, rubidium, cæsium, copper, silver, gold, beryllium, magnesium, calcium, strontium, barium, zinc, cadmium, mercury, and radium. Reference to the electrochemical table shows that these elements include the first nine in the table. As regards hydrogen, which is usually placed in the first group, Niccolini stated that it had a slight olfactory-positive effect, but this was so slight that it was readily overcome by the effect of other atoms combined

with it. One reason for the olfactory-positive effect of hydrogen is the volatility of its compounds. Other workers, however, consider that hydrogen has an olfactory-negative effect.

Inorganic Compounds

The odorous inorganic compounds are mostly those concerned with the non-metallic elements. Water is odourless, since it is normally present as moisture in the olfactory region and is the standard, along with air, to which other substances are referred for odour. Let us, however, substitute the oxygen by sulphur, and we have hydrogen sulphide, a very bad egg olfactorily. If we consider hydrogen selenide, H_2Se, the odour is even more objectionable. One volume of sulphuretted hydrogen in ten million volumes of air is detectable. Whereas carbonyl chloride, $COCl_2$, or phosgene, has a faint smell of musty hay, thiocarbonyl chloride, $CSCl_2$, or thiophosgene, has a powerful fœtid smell. Carbon dioxide is odourless but carbon disulphide has a strong odour, objectionable in the commercial product but aromatic and not unpleasant when very pure. In combination with oxygen, sulphur gives the acid, stinging sulphur dioxide, which affects the trigeminal nerves more than the olfactory, but which nevertheless also has a true smell. Hydrogen persulphide, H_2S_2, has a pungent irritating smell, whereas hydrogen peroxide, H_2O_2, is odourless. Sulphur chloride, S_2Cl_2, is pungent, and as it is decomposed by water to sulphur dioxide, hydrochloric acid and sulphur, such decomposition probably takes place in the nose. Whilst sulphur alone has no smell, it is clear that in combination it is a powerful odoriferous agent. That elementary sulphur has no smell is probably due to the high atomicity of its molecules, similar in this respect to red phosphorus. The influence of the sulphur atom is readily seen in the following table, where the odours of some common inorganic oxygen and sulphur analogues are compared.

Oxygen Compound and Odour.		*Sulphur Compound and Odour.*	
H_2O	Odourless.	H_2S	Rotten eggs.
$COCl_2$	Faint musty hay	$CSCl_2$	Fœtid.
CO_2	Odourless	CS_2	Strong aromatic.
H_2O_2	Odourless	H_2S_2	Pungent irritating.

Among the nitrogen compounds, ammonia, NH_3, has a well-known odour, and has the lowest molecular weight of all odorants. Nitrous oxide, N_2O—laughing gas—has a faint, pleasant smell. The smell of nitric oxide, NO, does not appear to have been observed as it oxidizes in the nose to nitrogen peroxide, NO_2, the smell of whose brown fumes is well known. There appears to be no reason why nitric oxide could not be breathed in an atmosphere of nitrogen for a sufficient length of time to determine its odour. Hydroxylamine, NH_2OH, is odourless, monochloramine, NH_2Cl, has a penetrating odour, and hydrazoic acid, N_3H, also has a penetrating and also unpleasant odour.

The halogens have characteristic smells, and in combination with hydrogen the strong acids, HF, HCl, HBr, HI, are primarily irritants,

and odour can be detected only in great dilutions, for otherwise the irritant swamps the olfactory effect. In combination with oxygen matters are different, for chlorine monoxide, Cl_2O, has an odour rather like that of chlorine, whilst chlorine peroxide, ClO_2, has an unpleasant odour which causes headache. Hypochlorous acid, HOCl, smells of its anhydride, Cl_2O, whilst hypoiodous acid, HOI, smells of iodoform or saffron when dilute, but in concentrated solution it smells of iodine. Bleaching powder, Ca(OCl)Cl, has a peculiar smell not quite like that of chlorine, and which may be due to chlorine monoxide.

There are a few carbon compounds usually considered as inorganic. Carbon monoxide and carbon dioxide are both odourless. Cyanogen, C_2N_2, has a faint smell of peaches. Methane, CH_4, and ethane, C_2H_6, are nearly odourless; ethylene, C_2H_4, has an ethereal smell; and acetylene, C_2H_2, has an unpleasant garlicky smell. Hydrocyanic acid, HCN, is usually said to smell of bitter almonds, and to the author certainly does so, but its olfactory effect seems to vary considerably. It has been investigated by Meyer (*Gasmaske*, **7**, 112, 1935), who reported that liquid, or strong aqueous solutions of hydrocyanic acid have a penetrating pungent odour and cause a harsh scratching sensation in the throat, whereas dilute solutions have a "dull" smell. The odour is said by Meyer to be quite different from that of bitter almonds. From 5 to 10 per cent. of people cannot smell it at all in low concentrations, and in all cases it rapidly paralyzes the olfactory and gustatory nerves so that it cannot be perceived after a few seconds. Other workers have reported that it is quite different from nitrobenzene and benzaldehyde, to which it is often likened. Whilst it is not the sort of stuff everybody cares to make extended observations with, the fragmentary evidence available suggests that it has unusually diverse effects on different subjects.

Many silicon and germanium compounds are organic in character. Silicon fluoride, SiF_4, is intensely pungent, likewise are titanic chloride, $TiCl_4$, and stannic chloride, $SnCl_4$, but largely owing to the hydrogen halide formed by hydrolysis.

Compounds of phosphorus, arsenic, antimony, and bismuth frequently exhibit odours of garlic. Phosphine, PH_3, is exceptional, and smells of decayed fish.

Hydrocarbons

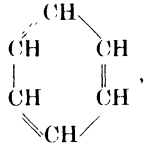
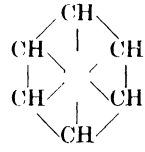
The simplest of all organic bodies are the hydrocarbons, containing as they do only the two elements, carbon and hydrogen, and yet comprising members with very different odours. The simplest group is the methane series, the saturated fatty hydrocarbons with formula C_nH_{2n+2}. The odours of some of these are:

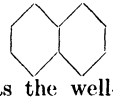
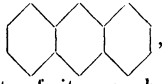
Methane	CH_4	Odourless.
Ethane	C_2H_6	Practically odourless.
Propane	C_3H_8	Practically odourless in concentrations below inflammable limits.
Butane	C_4H_{10}	

Pentane	C_5H_{12}	Indistinct.
Hexane	C_6H_{14}	Easily noticeable.
Heptane	C_7H_{16}	,, ,,
Octane	C_8H_{18}	Powerful petrol odour.
Nonane	C_9H_{20}	,, ,, ,,
Decane	$C_{10}H_{22}$	,, ,, ,,

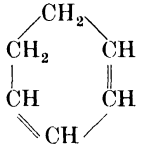
As we go higher the odour falls off owing to the lower volatility of the higher members. The fact that these saturated hydrocarbons have strong odours upsets a lot of theories of odour. One of the first points to strike the student of the relation between odour and constitution is that unsaturation or the presence of residual valencies is a powerful contributing factor to odour, and there is no doubt that this is so. Consequently it has been made the corner-stone of diverse theories of odour, e.g. Durrans stated, " I believe that such unsatisfied residual valencies are the prime cause of a chemical substance having an odour." Saturated paraffins would then be the last substances to have odour, but in fact most of the paraffins with appreciable volatility are odorous. Unsaturation in the paraffin increases the odour although it does not initiate it. Whilst ethane, C_2H_6, is practically odourless, ethylene, $CH_2{=}CH_2$, has an ethereal odour, and acetylene, $CH{\equiv}CH$, which has a triple bond, has an even more marked odour and is garlicky. Branched chain and straight chain isomeric hydrocarbons usually have similar smells, and amongst the higher members the position of a double bond—i.e. whether it is at the end or near the middle of the molecule—does not materially affect the odour.

In the aromatic series where the hydrocarbons are cyclic we find that much more powerful odours are present.

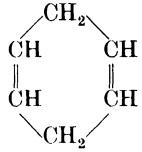
Benzene,  , or possibly 

has a well-known powerful odour, and is similar to most home dry-cleaning or spot-removing liquids. Its homologues, toluene, $C_6H_5CH_3$, xylene, $C_6H_4(CH_3)_2$, mesitylene, $C_6H_3(CH_3)_3$, ethylbenzene, $C_6H_5C_2H_5$, have odours of a similar character to that of benzene, but with sufficient individuality to be readily recognized. All are characteristically different from the paraffins, hexane, octane, etc. Naphthalene, which has the double ring structure,  , contributes a good deal of the smell to coal gas, and has the well-known odour of moth-balls of which it is often a constituent. Anthracene, with a triple ring structure,  , has a considerably less powerful smell on account of its much lower volatility. The powerful odour of

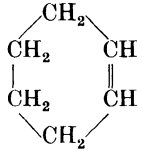
benzene compared with the paraffin hexane is due to its ring structure as well as to the unsaturation, for benzene can be hydrogenated by a roundabout method to $\Delta^{1,3}$ dihydrobenzene, which has only two double



$\Delta^{1,3}$ dihydrobenzene.

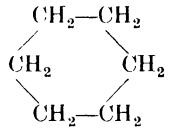


$\Delta^{1,4}$ dihydrobenzene.



Tetrahydrobenzene.

bonds compared with the three in benzene, and yet its odour is distinctly stronger and more pungent than that of benzene itself. An isomeric $\Delta^{1,4}$ dihydrobenzene is also known, and this has a less pungent odour than its $\Delta^{1,3}$ isomer, and is more comparable in odour with the tetrahydrobenzene. Further hydrogenation to tetrahydrobenzene reduces the odour slightly compared with $\Delta^{1,3}$ dihydrobenzene, but it is still pungent, whilst complete reduction to cyclohexane reduces the odour

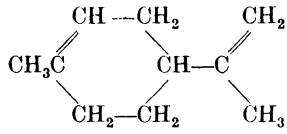


Cyclohexane.

again so that it is now comparable with that of the original benzene in intensity, but blander and more fatty in character. In the case of the naphthalene nucleus hydrogenation reduces the odour, both tetrahydronaphthalene (tetralin), $C_{10}H_{12}$, and decahydronaphthalene (decalin), $C_{10}H_{18}$, having a much milder odour than naphthalene itself.

The diversity of smells which come from such a simple order as the hydrocarbons illustrates the complexity of the relation between odour and constitution and warns us at an early stage that no simple empirical relation is to be found. The following table illustrates this :

Methane	CH_4	Odourless.
Ethane	$CH_3 . CH_3$	Nearly odourless.
Ethylene	$CH_2{=}CH_2$	Ethereal.
Acetylene	$CH{\equiv}CH$	Garlicky.
Nonane	$CH_3(CH_2)_7CH_3$	Strong gasoline odour.
Benzene	C_6H_6	Odour of dry-cleaning agent.
Naphthalene	$C_{10}H_8$	Odour of moth-balls.
Diphenylmethane	$(C_6H_5)_2CH_2$	Odour of geraniums when dilute. Also said to resemble oranges.

Limonene  Agreeable lemon-like odour.

Factors of general importance which emerge from this brief consideration are

(1) In a homologous series, e.g. saturated paraffins, the lower members may be odourless ; the odour will rise to a maximum and fall off in the higher members, due to low volatility.
(2) The molecular arrangement is important, e.g. ring or open-chain.
(3) Unsaturation is not primarily responsible for odour, but is a factor which enhances it.

Alcohols and Phenols

With a few exceptions, such as carbon tetrachloride and hexachlorethane, all organic bodies contain hydrogen as well as carbon. It will therefore be logical to consider next those which, in addition to these, contain only a hydroxyl group. In the aliphatic series we have the alcohols, and in the aromatic series we have alcohols, if the —OH group is in the side chain, and phenols if it is in the benzene nucleus. The simplest fatty alcohols are

Methanol	CH_3OH.	Ethanol	C_2H_5OH
Propanol	C_3H_7OH.	Butanol	C_4H_9OH

and so on. The first members have a rather sweet, spirituous smell, which gradually rises in intensity to nonyl alcohol, $C_9H_{19}OH$, which is an oily liquid, by which time it has also acquired a disagreeable element. Higher alcohols in this series have less and less odour as their volatility decreases. Stearyl alcohol, $C_{18}H_{37}OH$, and cetyl alcohol, $C_{16}H_{33}OH$, are waxes with only faint odours.

Unsaturation in the alcohols makes the odour rougher and irritating. Whereas isopropanol is quite pleasant in odour, and in fact is largely used as the basis of cheap eau-de-Cologne, the corresponding unsaturated body, allyl alcohol, $CH_2{=}CH.CH_2OH$, is a liquid of irritating odour. Propargyl alcohol, $CH{\equiv}C.CH_2OH$, which is more unsaturated than allyl alcohol, is, however, a liquid of agreeable odour. Oleyl alcohol has a double bond in the middle of the molecule,

$$CH_3 . (CH_2)_7 . CH : CH . (CH_2)_7 . CH_2OH$$

and has an ethereal waxy odour. It is only when the double bond is near to the hydroxyl group that it exerts much effect on the odour. Allyl alcohol where the double bond is Δ^2 (i.e. between the second and third carbon atoms), is irritating, but oleyl alcohol, where it is Δ^9, is ethereal. A tertiary carbon atom in an alcohol may impart a camphoraceous odour, but only if it is close to the hydroxyl group.

Two alcohols belonging to the open-chain terpene type which have interesting odours are

Geraniol, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2OH,$

which occurs naturally in roses, lemon-grass and geraniums. It resembles roses in odour when diluted, and is one of the main constituents of attar of roses.

Linalol, $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C : CH . CH_2 . CH_2 . C(CH_3)OH . CH : CH_2,$

which occurs in lavender and bergamot, and is fragrant.

The presence of two or more hydroxyl groups appears to have an anti-osmophoric effect. Glycols, glycerol and sugars are odourless. The reason may be that such bodies are ideally water-soluble, but are not lipoid-soluble. They provide a perfect example of the fact that odour and taste are not usually found well developed in one substance. All have a sweet taste, and all are inodorous.

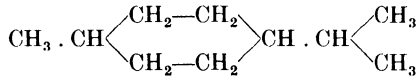
In the aromatic series, the alcohols where the hydroxyl group is in the side chain, have pleasant odours which are not so strong or piercing as the aliphatic. Benzyl alcohol, $C_6H_5 . CH_2OH$, has only a faint odour and is to be found in ylang-ylang, tuberose absolute, and other perfume ingredients Phenylethyl alcohol,

$$C_6H_5 . CH_2 . CH_2OH,$$

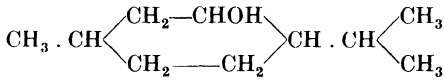
is an essential, although not the main, constituent of the rose perfume. It is, however, the main water-soluble constituent.

Cinnamyl alcohol, $C_6H_5 . CH : CH . CH_2OH$, has a weak but pleasant odour, and is sometimes added to hyacinth perfumes. It is clear that the double bond, although close to the hydroxyl group, does not have the same intensifying irritating effect in the aromatic alcohols as in the fatty series, nor does a tertiary carbon atom induce a camphoraceous odour in the aromatic series. The influence of the phenyl group is so great that it overwhelms these other influences.

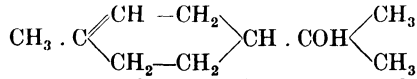
Some of the alcohols of the hydrobenzene series, particularly those of the terpene class, are interesting. The parent hydrocarbon of these is menthane :



and menthol is menthanol-3

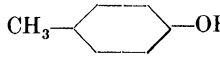


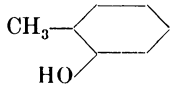
and has a characteristic peppermint-like odour. Terpineol, which has an odour resembling that of lilac, has a similar constitution :

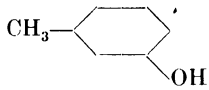


It is found in many essential oils, e.g. bergamot, neroli, and petitgrain.

Owing to the constitutional analogy of the phenols to the alcohols it is logical to consider them in this group. Both have the formula ROH, but in the fatty series $R=C_2H_5$ or similar, whilst in the aromatic series where $R=C_6H_5$ or similar, we have the phenols. The odour of phenol is familiar to all from its association with carbolic soap and disinfectants. Substitution in the benzene nucleus by methyl groups reduces the sharp acid character of the odour. and the cresols, $CH_3C_6H_4OH$, and the xylenols, $(CH_3)_2C_6H_3OH$, are less irritant and softer in odour than phenol. Of the three cresols the

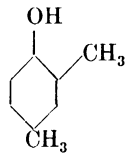
p-cresol,  has the strongest odour,

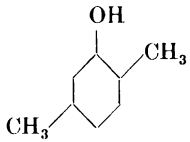
o-cresol,  has an intermediate odour,

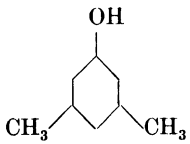
m-cresol,  which is the one most frequently met, has the weakest odour.

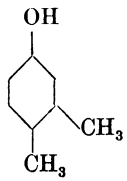
Comparison of the isomeric xylenols enables one to detect odour differences.

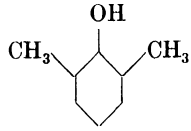
Examination of five of the isomeric xylenols has given the following results :

2-4 xylen-1-ol,  Faint odour.

2-5 xylen-1-ol  Mild cresolic odour.

3-5 xylen-1-ol  Strong cresolic odour.

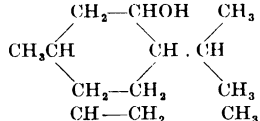
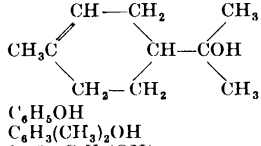
3-4 xylen-1-ol  Dull musty odour.

2-6 xylen-1-ol  Oil of wintergreen odour.

Examination of these results suggests that substitution *meta* to the hydroxyl group induces a cresolic odour, but that *para* substitution has the opposite effect. It is curious that in the cresols themselves the *meta* cresol is less odorous than the *ortho* and *p*-cresols.

The introduction of two or more hydroxyl groups has the same effect in this series as in the aliphatic, for resorcinol, hydroquinone, and catechol, the three isomeric dihydroxybenzenes, are all odourless.

The diverse olfactory effects which the hydroxyl bodies give are exemplified in the following table :

Ethanol	C_2H_5OH	Sweet spirituous odour.
Nonanol	$C_9H_{19}OH$	Strong disagreeable odour.
Cetyl alcohol	$C_{16}H_{33}OH$	Faint ethereal waxy odour.
Allyl alcohol	$CH_2 : CH\ CH_2OH$	Irritating odour.
Propargyl alcohol	$CH \equiv C\ .\ CH_2OH$	Agreeable odour.
Oleyl alcohol	$CH_3(CH_2)_7CH : CH(CH_2)_7CH_2OH$	Faint waxy odour.
Glycol	$CH_2OH\ CH_2OH$	Odourless.
Glycerol	$CH_2OH\ .\ CHOH\ .\ CH_2OH$	Odourless.
Benzyl alcohol	$C_6H_5CH_2OH$	Faint aromatic odour.
Phenylethyl alcohol	$C_6H_5CH_2CH_2OH$	Constituent of rose perfume.
Cinnamyl alcohol	$C_6H_5CH : CH\ CH_2OH$	Weak, pleasant hyacinth odour.
Menthol		Peppermint odour.
Terpineol		Lilac odour.
Phenol	C_6H_5OH	Carbolic, disinfectant odour.
Xylenol	$C_6H_3(CH_3)_2OH$	Similar, less sharp.
Resorcinol	$1\ .\ 3\ .\ C_6H_4(OH)_2$	Odourless.

Ethers

Ethers may be considered as hydroxy compounds in which the hydrogen atom of the hydroxyl group is replaced by an alkyl or aryl or alkaryl group.

The commonest of these bodies is diethyl ether, $C_2H_5OC_2H_5$, the "ether" used as an anæsthetic. It is excessively volatile, and has a sweet spirituous odour. Of the higher ethers those of heptyl alcohol have very interesting odours. They were investigated by Roger and Dvolaitskaya (*Manufacturing Perfumer*, **2**, 36, 1937) who considered that the heptyl radicle introduced a fatty green fruit effect or the odour of a crushed green stalk of which the ether grouping increased the ethereal fruity character. When heptyl alcohol is linked with alcohols of the fatty series from methyl alcohol to lauryl alcohol, the resulting ethers from heptyl methyl ether to heptyl lauryl ether

diminish in odour as the molecular weight increases. Typical ethers were :

Heptyl hexyl ether	$C_7H_{15}OC_6H_{13}$	Odour like bluebell stalks.
,, heptyl ether	$C_7H_{15}OC_7H_{15}$	Odour like wet wool.
,, undecyl ether	$C_7H_{15}OC_{11}H_{23}$	Fugitive odour of fatty aldehydes.
,, phenyl ether	$C_7H_{15}OC_6H_5$	Odour of opoponax.

Highly odorous products were also obtained by making the heptyl ethers of geraniol and linaloöl and of benzyl, phenylethyl, and cinnamyl alcohols. In the phenyl and cresyl ethers of heptyl alcohol, the phenol character predominated over the heptyl. Herold (*Seifensieder Ztg.*, **67**, 426, 460, 1940) has pointed out that aliphatic ethers have less odour than the corresponding alcohols, but that phenolic and naphtholic ethers have more odour and more pleasant odours than the corresponding phenols and naphthols.

In the aromatic series we have the aliphatic aromatic ethers like anisole, $C_6H_5 . O . CH_3$, and phenetole, $C_6H_5 . O . C_2H_5$, both of which have characteristic odours, the former fragrant but overpowering, the latter a little sharper. Then there are the true aromatic ethers, such as diphenyl oxide, $C_6H_5 . O . C_6H_5$, which has a musty odour, but on dilution develops a smell of geraniums, and is in fact used in " artificial geranium crystals " and in scented soap.

The ether group is only a weak osmophore and is easily overpowered by other features of the molecule, such as the benzene ring, tertiary carbon atom, and other groups yet to be discussed. Some of the ethers with their odours are compared in the following table :

Diethyl ether	$C_2H_5OC_2H_5$	Sweet spirituous.
Heptyl hexyl ether	$C_7H_{15}OC_6H_{13}$	Bluebell stalks.
Anisole	$CH_3OC_6H_5$	Fragrant overpowering.
Phenetole	$C_2H_5OC_6H_5$	Fragrant aromatic.
Heptyl phenyl ether	$C_7H_{15}OC_6H_5$	Opoponax.
Diphenyl ether	$C_6H_5OC_6H_5$	Geraniums when dilute.

We shall find very similar types of odours but much more intense in the esters.

Carboxylic Acids

The lower aliphatic acids have strong odours. Formic acid, H . COOH, is so irritating and pungent that it cannot be sniffed to detect any true odour. Acetic acid, $CH_3 . COOH$, has a penetrating odour which, when it is diluted, resembles vinegar, of which it is the essential constituent. Both normal butyric, $CH_3 . CH_2 . CH_2 . COOH$, and isobutyric acids, $\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!\!CH . COOH$, have disagreeable odours, and the objectionable odour of perspiration is due to these substances. Acids of this series higher than nonylic acid, are solid waxy substances at room temperatures and without odour, e.g. palmitic acid, $C_{15}H_{31}COOH$, stearic acid, $C_{17}H_{35}COOH$. It is likely that the powerful odours of the middle members, butyric, valeric, and caproic acids are due to their solubility in both water and fats. When the water

solubility vanishes in the higher members, then they are odourless. The effect of unsaturation is to make the odour of acids more acrid. Acrylic acid, $CH_2 : CH . COOH$, has a more pungent odour than acetic acid but similar in character. Crotonic acid,

$$CH_3 . CH : CH . COOH,$$

has an acrid butyric odour. Higher up the series the odour diminishes and disappears at the C_{11} unsaturated acids, so that oleic acid, $CH_3 . (CH_2)_7 . CH : CH . (CH_2)_7COOH$, is odourless. Propiolic acid, $CH{\equiv}C . COOH$, which has an acetylene linkage, resembles acrylic acid in odour.

The presence of a hydroxyl group in a carboxylic acid reduces the odour. Thus whilst propionic acid, $CH_3 . CH_2 . COOH$, has a strong penetrating odour, lactic acid, $CH_3 . CHOH . COOH$, is odourless. The faint acid odour of sour milk is not due to lactic acid, which is present but odourless, but to traces of volatile fatty acids. Dicarboxylic acids, oxalic, COOH—COOH, malonic,

$$COOH . CH_2 . COOH,$$

and so on up to sebacic acid, $COOH . (CH_2)_8 . COOH$, are odourless, as are also tricarboxylic acids, such as tricarballylic acid,

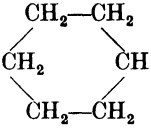
$$CH_2COOH . CH\ COOH . CH_2COOH,$$

and citric acid, $CH_2COOH . C(OH)COOH . CH_2COOH$.

We have seen that the effect of a hydroxyl group in a carboxylic acid is to depress its odour. Rothstein (*Bull. soc. chim.*, **51,** 691-6, 1932) investigated the odours of some alkoxy acids, substances containing both ether and acid groups with the general formula, $ROCH_2COOH$, where R=heptyl, sec-octyl, phenylethyl, etc., and found that the acids had odours resembling the alcohols from which they were derived, so that in this case evidently the acid group is overwhelmed.

The aromatic-aliphatic acids are not strong odorants. Phenyl acetic acid, $C_6H_5CH_2COOH$, has an odour resembling a weak tincture of civet which makes it useful in the perfume industry. The aromatic carboxylic acids, e.g. benzoic, $C_6H_5 . COOH$, and cinnamic acids, $C_6H_5CH : CH\ COOH$, are odourless. The influence of the phenyl group is very powerful in this negative fashion, for formic and acrylic acids are both powerful odorants, yet their phenyl derivatives, which are benzoic and cinnamic acids respectively, are odourless. Whilst unsaturation makes the aliphatic acids more acrid, unsaturation in the side chain of aromatic acids has no effect.

Whereas the aromatic acids are odourless, the reduced aromatic acids have strong unpleasant odours, thus

hexahydrobenzoic acid 

has a rancid odour similar to that of capric acid, $C_9H_{19}COOH$.

The odours of some of the acids are tabulated for comparison below.

Formic acid	$H . COOH$	Pungent, irritating.
Acetic acid	$CH_3 . COOH$	Penetrating. Vinegar when dilute.
Butyric acid	$CH_3(CH_2)_2 . COOH$	Disagreeable. Perspiration.
Isobutyric acid	$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CH . COOH$	More disagreeable.
Palmitic acid	$C_{15}H_{31} . COOH$	Odourless.
Acrylic acid	$CH_2 : CH . COOH$	More pungent than acetic.
Crotonic acid	$CH_3 . CH : CH . COOH$	Acrid butyric.
Oleic acid	$CH_3 . (CH_2)_7 . CH : CH . (CH_2)_7 . COOH$	Odourless.
Propiolic acid	$CH \equiv C . COOH$	Acrylic.
Lactic acid	$CH_3 . CHOH . COOH$	Odourless.
Succinic acid	$COOH . (CH_2)_2 . COOH$	Odourless.
Tricarballylic acid	$COOH . CH_2 . CH\,COOH . CH_2COOH$	Odourless.
Phenylacetic acid	$C_6H_5 . CH_2 . COOH$	Weak civet.
Benzoic acid	$C_6H_5 . COOH$	Odourless.
Hexahydrobenzoic acid	$C_6H_{11} . COOH$	Rancid.

Esters

Structurally, the esters bear the same relation to the acids as the ethers do to the alcohols.

C_2H_5OH	Alcohol.	$CH_3 . COOH$	Acid.
$C_2H_5OC_2H_5$	Ether.	$CH_3 . COOC_2H_5$	Ester.

Olfactorily, however, there is a difference, for whereas the ethers have odours clearly derived from the alcohols, and in many cases less intense, the esters exhibit a much wider, stronger and more interesting range of odours than the acids. The flavours and odours of fruits and flowers are chiefly due to the presence of esters. The esterification of the fatty carboxylic acids regularly gives a pleasant fragrant smell, and the esters are largely used in the preparation of artificial fruit essence. The following examples may be noted :

Propyl acetate	$C_3H_7 . O . CO . CH_3$	Like pears.
Amyl acetate	$C_5H_{11}O . CO . CH_3$	Like Jargonelle pears (and the toffee pear-drops).
Isoamyl acetate	$(CH_3)_2CH . CH_2 . CH_2 . O . CO . CH_3$	Like pears.
Ethyl butyrate	$C_2H_5 . O . CO . C_3H_7$	Like pineapples.
Isoamyl isovalerate	$(CH_3)_2CH . C_2H_4 . O . CO . C_4H_9$	Like apples.

The higher esters have no odour owing to their insolubility. Beeswax, for example, which when refined is odourless, is melissyl palmitate,

$$C_{30}H_{61} . O . CO . C_{15}H_{31},$$

and spermaceti is cetyl palmitate, $C_{16}H_{33} . O . CO . C_{15}H_{31}$. The heptyl esters have been investigated from the olfactory standpoint by Roger and Dvolaitskaya (*Recherches*, **1**, 79-82, 1937, and *Manufacturing Perfumer*, **2**, 215). They found the heptyl esters had the same fruity, fatty and green odours as the heptyl ethers, but the esters had more persistent odours than the rather fugitive ethers.

The persistency did not, as might have been expected, vary in the same direction as the boiling-points, for the high boiling heptyl esters of heptylic, nonylic and caprylic acids were less persistent than the formate and acetate. The odours of some of the heptyl esters were

Heptyl formate	$C_7H_{15} . O . CO . H$	Fruity.
,, acetate	$C_7H_{15} . O . CO . CH_3$	Fruity.
,, isobutyrate	$C_7H_{15} . O . CO . C_3H_7$	Cyclamen-camomile.
,, caproate	$C_7H_{15} . O . CO . C_5H_{11}$	Bruised green leaves.
,, undecylate	$C_7H_{15} . O . CO . C_{10}H_{21}$	Smoke, ink.
,, salicylate	$C_7H_{15} . O . CO . C_6H_4OH$	Steel.
,, geranate	$C_7H_{15}O . CO . C_9H_{15}$	Hawthorn, mimosa.

The esters of dibasic and tribasic acids have very similar odours to those of the monobasic acids but less intense. Ethyl malonate, $C_2H_5 . O . CO . CH_2 . CO . O . C_2H_5$, and the ethyl esters of succinic, glutaric, adipic, pimelic, suberic and sebacic acids are all fragrant and fruity. So are the mono-esters of the dibasic acids, e.g. ethyl hydrogen adipate, $COOH . (CH_2)_4 . COOC_2H_5$, and the esters of tribasic acids such as citric are similar. Each ester has a distinctive smell, and if they are used frequently, familiarity soon enables the chemist to recognize the ester by its odour. Esters of dihydric and polyhydric alcohols have weak odours.

Esters of some of the weak inorganic acids are similar in odour, e.g. ethyl borate has a sweet smell similar to that of ethyl adipate, whilst isopropyl borate is sweet and rather sickly.

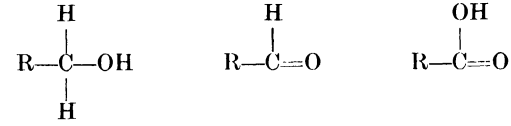
The introduction of a benzene nucleus gives a heavier, richer note to the odour of esters, e.g. benzyl acetate, $C_6H_5 . CH_2 . O . CO . CH_3$, is used in synthetic jasmine. If the phenyl group occurs in the acidic part of the molecule a fragrant body still results, e.g. methyl benzoate is known as Niobe Oil and is used for making artificial ylang-ylang perfumes. Methyl salicylate, $CH_3O . CO . C_6H_4OH$, is the main constituent of oil of wintergreen. Amyl salicylate is the basis of clover and orchid perfumes. Isobutyl cinnamate has a soft sweet odour, and is used in face-powders.

The uniformity of type of odour is more marked in esters than in most groups. The fragrance of esters leads to their use in fruit essences and perfumes. Typical odours are

Methyl acetate	$CH_3OCO\,CH_3$	Fragrant.
Ethyl acetate	$C_2H_5OCO\,CH_3$	,,
Propyl acetate	$C_3H_7OCO\,CH_3$	Pears.
Amyl acetate	$C_5H_{11}OCO\,CH_3$	Pear-drops.
Ethyl butyrate	$C_2H_5OCO\,C_3H_7$	Pineapple.
Heptyl acetate	$C_7H_{15}OCO\,CH_3$	Fruity.
,, isobutyrate	$C_7H_{15}OCO\,C_3H_7$	Cyclamen-camomile.
,, caproate	$C_7H_{15}OCO\,C_5H_{11}$	Bruised green leaves.
,, geranate	$C_7H_{15}OCO\,C_9H_{15}$	Hawthorn, mimosa.
Octyl acetate	$C_8H_{17}OCO\,CH_3$	Oranges.
Diethyl adipate	$C_2H_5OCO\,(CH_2)_4 . OCOC_2H_5$	Fruity.
Ethyl hydrogen adipate	$C_2H_5OCO\,(CH_2)_4COOH$	,,
Triethyl citrate	$(C_2H_5OCOCH_2)_2C(OH)COOC_2H_5$	,,
Melissyl palmitate	$C_{30}H_{61}OCO\,C_{15}H_{31}$	Odourless.
Benzyl acetate	$C_6H_5CH_2OCO\,CH_3$	Jasmine.
Methyl salicylate	$CH_3OCO\,C_6H_4OH$	Oil of wintergreen.
Amyl salicylate	$C_5H_{11}OCO\,C_6H_4OH$	Clover.

Aldehydes

The aldehydes are intermediate in structural characteristics between the alcohols and acids :



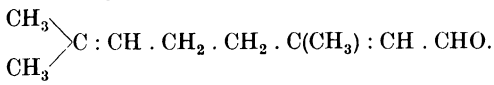
Alcohol. Aldehyde. Acid.

They are more reactive than the alcohols owing to the presence of the doubly bound oxygen, and as they are more volatile than the acids they might be expected to have interesting odours and indeed they have. Knowledge of their olfactory properties was forwarded by Gildermeister, Schimmel and Wallach more than thirty years ago.

Formaldehyde, $O{=}CH_2$, is the simplest member and the pungent odour of its 40 per cent. solution known as formalin is well known. It is very prone to polymerization forming polymers known as paraformaldehyde, probably $(CH_2O)_3$ and polyoxymethylenes. These, as would be expected, have a much less intense "formalin" odour. It is a general rule whether with elements or compounds that polymerization reduces and finally destroys odour. Acetaldehyde, $O : CH . CH_3$, is the next member, and has a sharp disagreeable odour. Like formaldehyde, it polymerizes readily and gives paraldehyde, which is odorous, and metaldehyde, which has a refreshing tonic odour. Propaldehyde, $C_2H_5 . CHO$, and butaldehyde, $C_3H_7 . CHO$, are liquids with suffocating odours. As the series of fatty aldehydes is ascended the odour gradually changes from pungent to pleasant. Methyl heptin carbonate, a derivative of the C_7 aldehyde, and the C_7 and C_9 aldehydes, are used in perfumery. Still higher the odour is depressed, as is usual in a homologous series and stearaldehyde has only a feeble, waxy aroma.

The effect of unsaturation in the lower members is to increase the acrid irritating note of aldehydes. Acraldehyde, $CH_2 : CH . CHO$, is the simplest unsaturated aldehyde, and is unbearably irritating. The disagreeable smell observed when a tallow candle is extinguished is due to acraldehyde, or acrolein as it is also called. Crotonaldehyde, $CH_3 . CH : CH . CHO$, is similar. The aldehyde with the acetylene linkage, propiolaldehyde, $CH{\equiv}C . CHO$, also has an intensely irritating odour.

An aldehyde with an open-chain terpene structure is geranial, or citral (2 : 6-dimethyl-$\Delta^{2:6}$-octadien-8-al),



It has an agreeable lemon odour and is obtained from lemon-grass oil. It is useful as a source of ionone. It is also found in oil of orange-rind and oil of citron. It may be noted that although this substance

contains two points of unsaturation, apart from the aldehydic group itself, it has no irritating effect. The skeleton of the aldehyde determines its general olfactory character and unsaturation just modifies this.

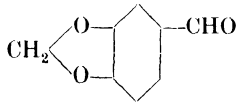
Introduction of a hydroxyl group into an aldehyde usually suppresses the odour, e.g. glycollic aldehyde, CH_2OH . CHO, is odourless. Amongst the dialdehydes, glyoxal, CHO . CHO, is the simplest and is also odourless.

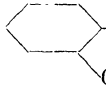
In the aromatic series benzaldehyde, C_6H_5 . CHO, is the main constituent of bitter-almond oil, and has the well-known bitter-almond smell. It may be noted here that the smell of nitrobenzene resembles benzaldehyde but is much cruder. Nitrobenzene was at one time used as an adulterant for benzaldehyde, but owing to its toxicity was objectionable.

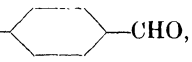
Cinnamaldehyde, C_6H_5 CH : CH . CHO, is the chief constituent of oil of cinnamon and has a pleasant, spicy odour. A derivative of this which was prepared by Bogert and Powell (*J. Amer. Chem. Soc.*, **53,** 2747, 1931) was 2-ethylhydrocinnamic aldehyde,

$$C_6H_5 . CH_2 . CH(C_2H_5) . CHO,$$

which had an agreeable but not very strong odour. Piperonal, known commercially as heliotropine, has the odour of heliotrope or of cherry-pie ; its constitution is

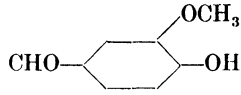


Phenylethyl aldehyde, $C_6H_5 . CH_2 . CHO$, has a hyacinth odour, and phenylpropyl aldehyde (hydrocinnamic aldehyde) suggests both hyacinths and cinnamon. Whereas the introduction of a hydroxyl group into an aromatic aldehyde reduces the intensity of the odour, the etherification of the hydroxyl group restores it. Thus salicyl-aldehyde,  , which occurs in oil made from meadow-sweet, *Spiræa Ulmaria*, has a delicate floral odour which is used for fancy bouquets and perfumes, but anisic aldehyde,

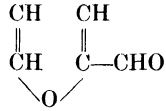


has a heavier odour and is used for lilac, mimosa, and wallflower perfumes. Anisic aldehyde is known commercially as Aubepine, and is essential for artificial hawthorn perfumes. This is not a very good comparison, for, as we shall see later, the orientation of the groups in the benzene ring has a powerful influence on the odour.

Vanillin, the aromatic principle of vanilla, contains both hydroxyl and an ether group,



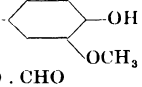
In the heterocyclic series, furfural or furfuraldehyde,



which has an odour of new bread, may be mentioned.

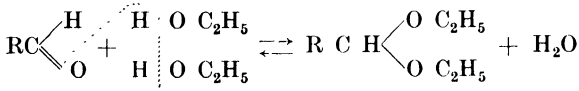
In the naphthalene series, α- and β-naphthaldehydes have similar odours to each other.

The odours of some aldehydes are grouped below for comparison :

Formaldehyde	H . CHO	Pungent formalin.
Paraformaldehyde	$(CH_2O)_n$	Mild formalin.
Acetaldehyde	CH_3CHO	Pungent.
Acrolein	$CH_2 : CH\ CHO$	Irritating. Snuffed candle.
Propiolaldehyde	$CH_2{\equiv}C$. CHO	Irritating.
Stearaldehyde	$C_{17}H_{35}CHO$	Faint waxy.
Geranial (citral)	$(CH_3)_2C : CH\ C_2H_4C(CH_3) : CH$. CHO	Lemon.
Glycollic aldehyde	CH_2OH . CHO	Odourless
Benzaldehyde	C_6H_5CHO	Bitter almonds.
Cinnamic aldehyde	$C_6H_5CH : CH\ CHO$	Cinnamon.
Piperonal	$CH_2O_2C_6H_3CHO$	Heliotrope.
Phenylethyl aldehyde	$C_6H_5CH_2CHO$	Hyacinth.
Salicylaldehyde	o-$HO\ C_6H_4CHO$	Spiræa.
Aubepine	p-$CH_3O\ C_6H_4CHO$	Hawthorn.
Vanillin		Vanilla.
Furfural	C_4H_3O . CHO	New bread.

Acetals

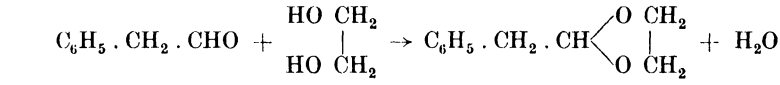
Acetals are the products of aldehydes combining with two equivalents of an alcohol, water being eliminated thus



The action is reversible, for water will partially hydrolyze an acetal back to the aldehyde and alcohol. It will be seen that the characteristic feature is the presence of two ether groups attached to the same carbon atom. The acetals are usually liquids of aromatic odour, and were not considered highly osmophoric by Durrans. British Patent 346,115 (I.G. Farbenindustrie) claims that although known cyclic acetals from dihydric alcohols such as glycol and aliphatic aldehydes or benzaldehyde have only a faint or disagreeable odour, yet if the dihydric alcohols are condensed with araliphatic aldehydes

such as phenylacetaldehyde, then cyclic acetals with strong agreeable odours result. For example :

Phenylacetaldehyde and glycol

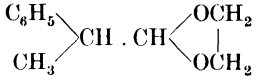


and this acetal has an odour of roses.

Similarly, if phenylacetaldehyde is condensed with

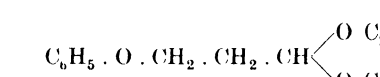
αβ-dihydroxypropane $CH_2OH . CHOH . CH_3$	the acetal smells of fresh roses.
αβ-dihydroxybutane $CH_2OH . CHOH . C_2H_5$	,, ,, hyacinths.
αγ-dihydroxybutane $CH_2OH . CH_2 . CHOH . CH_3$	,, ,, ,,
2 : 4 dihydroxy-4-methylpentane $CH_3 . CHOH . CH_2 . C(OH)CH_3 . CH_3$	,, ,, mignonette.

Similarly, if glycol was condensed with 1-oxo-2 phenyl-2-methylethane (hydratropic aldehyde), the product had an odour of mushrooms.



Shoruigin and Korshak (*Ber.*, **68B,** 838-44, 1935) investigated the odours of some ethers of hydroxyaldehydes and their acetals, and noted the following :

Phenyl ether of β-hydroxy-propionaldehyde diethyl acetal



had a refreshing odour of water-melons. Curiously, all three tolyl ethers had only faint flowery odours, whilst the α- and β-naphthyl ethers were almost odourless. The benzyl ether was rose-like, and the isoamyl ether was like burnt tobacco.

U.S. Patent 2,184,526 (du Pont de Nemours & Co.) describes the use of a hemiacetal of *p*-isopropyl α-methyl hydrocinnamaldehyde in perfumes.

It will be seen that the acetals can have a very wide range of odours.

Ketones

Ketones contain the carbonyl group $\rangle C{=}O$ in union with two carbon atoms. The general formulæ are

Aldehyde  , Ketone  . The lower fatty ketones such as

Acetone	$CH_3 . CO . CH_3$.	Methyl ethyl ketone	$CH_3 . CO . C_2H_5$.
Propione	$C_2H_5 . CO . C_2H_5$.	Butyrone	$C_3H_7 . CO . C_3H_7$.

are pleasant-smelling liquids.

It was noticed by v. Braun and Kröper (*Ber.*, **62B,** 2880-5,

1929) that ethyl octyl ketone, $C_2H_5 . CO . C_8H_{17}$, did not possess nearly to the same degree as methyl nonyl ketone,

$$CH_3 . CO . C_9H_{19},$$

the characteristic rue-like odour of the latter. They therefore prepared a series of isomeric ketones :

Methyl nonyl ketone . .	$C_9H_{19} . CO . CH_3$.
Ethyl octyl ,, . .	$C_8H_{17} . CO . C_2H_5$.
Propyl heptyl ,, . .	$C_7H_{15} . CO . C_3H_7$.
Butyl hexyl ,, . .	$C_6H_{13} . CO . C_4H_9$.
Diamyl ketone . . .	$C_5H_{11} . CO . C_5H_{11}$.

They found that as the table was descended the rue-like odour diminished progressively and was replaced by a fruity odour which increased progressively. Evidently the heaviest radicle in the ketone largely determines its odour.

Acetophenone, $C_6H_5 . CO . CH_3$, or hypnone, is fragrant, as is also benzophenone, $C_6H_5 . CO . C_6H_5$, a completely aromatic ketone.

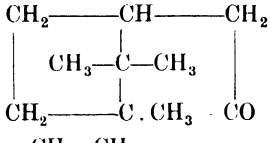
The diketones have also pleasant odours. Biacetyl,

$$CH_3 . CO . CO . CH_3,$$

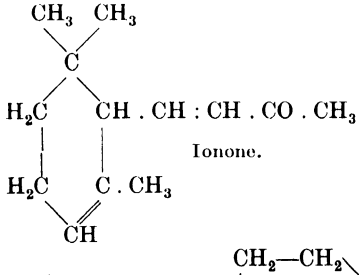
has a sweetish odour, and is responsible for the pleasant odour of fresh butter. Biacetyl is a 1 : 2 diketone, acetylacetone,

$$CH_3 . CO . CH_2 . CO . CH_3,$$

a 1 : 3 diketone, and acetonylacetone, $CH_3 . CO . CH_2 . CH_2 . CO . CH_3$, a 1 : 4 diketone. All have agreeable odours.



In the aliphatic ketones the presence of a tertiary carbon atom is likely to give a camphoraceous odour. Camphor itself is a ketone, and it may be noted that it contains two tertiary carbon atoms.

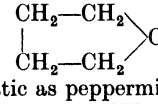


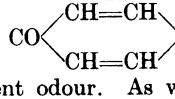
Ionone.

Ionone—artificial violet—is also a ketone with the structure shown, which is isomeric with that of irone, the true violet essential oil.

Muscone, the essential olfactory component of musk, is also a ketone.

Substances with the carbonyl group in the ring also have pleasant odours.

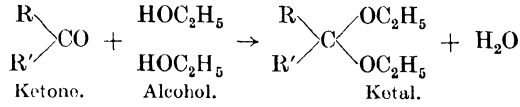
Cyclopentanone,  , is reminiscent of, but not nearly so characteristic as peppermint. Cyclohexanone is similar.

Benzoquinone,  , an unsaturated cyclic diketone, has a pungent odour. As was noted in Chapter 6 zingerone, the essential constituent of ginger, is a ketone.

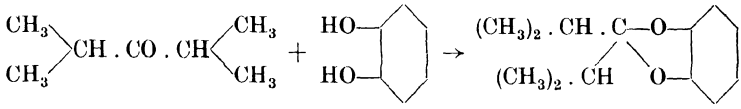
The ketones, then, are characterized by a generally pleasant odour. Under the influence of a tertiary carbon atom the odour becomes camphoraceous. In other circumstances intense violet or musk odours will be produced, and these will be examined later.

Ketals

Ketals bear the same relation to ketones as acetals do to aldehydes.



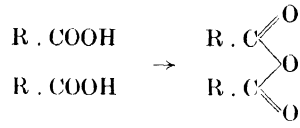
U.S. Patent, 2,169,984 (Weissenborn) describes how perfumes with odours similar to jasmine, honey, and rose may be made with ketals having six to nine carbons in the ketone residue. For example, di-isopropyl ketone may be combined with catechol.

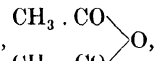


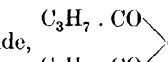
Similarly, methyl amyl ketone or di-isobutyl ketone could be used.

Anhydrides

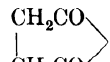
Anhydrides are formed by the loss of one molecule of water from two molecules of a monobasic acid or from one molecule of a dibasic acid.

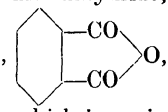


The lower fatty acid anhydrides such as acetic anhydride, 

and butyric anhydride, 

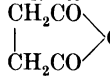
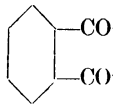
, have powerful, pungent odours and lachrymatory properties. They combine with water in the eye to form the respective acids. Their action is more on the common chemical than the olfactory receptors. Higher in this series stearic anhydride, $(C_{17}H_{35} . CO)_2O$, is odourless, conforming to the general rule that the odour of high molecular weight compounds falls off.

Well-known anhydrides of dibasic acids are succinic anhydride, 

, in the fatty series, and phthalic anhydride, 

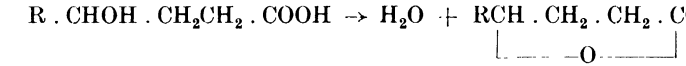
, in the aromatic series, both having suffocating odours, which is again

more chemical irritation than true olfaction. Odours of acid anhydrides are grouped for comparison : —

Acetic anhydride	$(CH_3CO)_2O$	Pungent. Lachrymatory.
Butyric anhydride	$(C_3H_7CO)_2O$	Disagreeable. Pungent. Lachrymatory.
Stearic anhydride	$(C_{17}H_{35}CO)_2O$	Odourless.
Succinic anhydride		Suffocating.
Phthalic anhydride		Suffocating.

Lactones

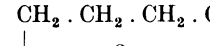
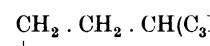
The γ-hydroxy acids readily lose water with the formation of lactones.



This change is an internal esterification. Consequently we might expect that the lactones would have similar fragrant odours to the esters, which group we have already considered. γ-, δ-, and ϵ-lactones which have rings containing one oxygen, and four, five, and six carbon atoms, respectively, are known as these are stable configurations, but α- and β-lactones are normally not formed. In the case of the γ-hydroxy acids the tendency to lactone formation is so strong that some such acids are known only in the lactone form or in solution.

In addition, lactones with very large rings are known, and will be considered in the section on macrocyclic compounds, where they are important on account of their musk odour.

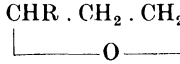
As the lactones are a group of compounds with characteristic odours they have attracted a good deal of attention. Rothstein (*Bull. soc. chim.* (5), **2**, 80-90, 1935) has prepared a series of α-substituted γ-butyrolactones, and investigated their odours. These are as follows :

γ-butyrolactone		Faint aromatic.
α-propyl γ-butyrolactone		Cumin odour with trace of anise.
α-butyl γ-butyrolactone	Cumin—anise, trace of ambergris.	
α-isoamyl γ-butyrolactone	Angelica seed—ambergris.	
α-hexyl γ-butyrolactone	Ambergris—apricot leaves.	
α-heptyl γ-butyrolactone	Peach—fresh musk.	
α-octyl γ-butyrolactone	Peach odour more marked.	

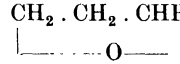
α-nonyl γ-butyrolactone	As previous but weaker. Note odour of cocoa flowers.
α-decyl γ-butyrolactone	Fresh unctuous odour, musk, cocoa.
α-undecyl γ-butyrolactone	Musk—cocoa.
α-dodecyl γ-butyrolactone	Musk—cocoa but fainter.
α-geranyl γ-butyrolactone	Musk—fresh peach odour.
α-citronellyl γ-butyrolactone	Musk—pear—peach.
α-rhodinyl γ-butyrolactone	Mellow musk—peach.
α-phenyl γ-butyrolactone	Balsamic.
α-benzyl γ-butyrolactone	Tolu balsam.

In the straight chain substituents the heptyl, octyl, and nonyl butyrolactones have a peach odour which is decidedly musk-like. The musk odour is maintained by the next three members which in addition have an odour of coconut oil, and this becomes predominant in an attractive flowery note.

In another paper Rothstein (*Bull. soc. chim.* (5), **2**, 1936-44, 1935) investigated the effect of substituting in the γ-position instead of the α-position.



γ-substituted γ-butyrolactone.



α-substituted γ-butyrolactone.

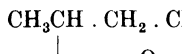
His findings were :

γ-amyl γ-butyrolactone	$C_5H_{11}CH \cdot CH_2 \cdot CH_2 \cdot CO$ | ——O—— |	Cocoa with trace aniseed.
γ-isoamyl γ-butyrolactone	Peach.	
γ-heptyl γ-butyrolactone	Strong peach odour.	
γ-octyl γ-butyrolactone	Peach slightly musk.	

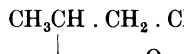
Evidently in a homologous series three consecutive members have the same fundamental odour modified by slight *nuances*. From C_{11} to C_{15} the γ-substituted butyrolactones had a musk odour like their α-isomers. The α-substituted lactones had generally stronger odours than the γ-substituted lactones. It should be noted that *all* the lactones used were γ-lactones, but that some were substituted in the α- and some in the γ-position.

Rothstein also concluded that a branched chain lactone had practically the same odour as its straight chain isomer but in addition a fresh green leaf note.

v. Braun, Anton and May (*Ber.*, **70B**, 1250-3, 1937) investigated the odour of some α-substituted γ-valerolactones. γ-valerolactone is simply γ-methyl-γ-butyrolactone.



γ-valerolactone.

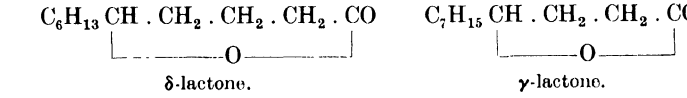


α-substituted γ-valerolactone.

It was found that as the substituent group R in the α-position of the valerolactone was increased in weight the odour became stronger,

thus α-propyl valerolactone had a stronger odour than α-ethyl valerolactone, and this was stronger than α-methyl valerolactone. The maximum odour was obtained when the substituent group was hexyl; α-heptyl γ-valerolactone had only a faint odour and the octyl and decyl valerolactones were odourless. On the other hand, 3-7-dimethyloctyl valerolactone, which is isomeric with decyl valerolactone, had a quite perceptible odour. Branching of the chain extended the odour higher in the series. Cyclohexyl valerolactone was odourless, the cyclization having an unexpected effect.

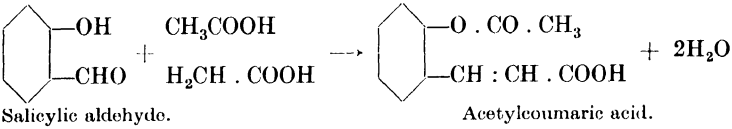
Stoll and Bolli (*Helv. chim. acta.*, **21,** 1547-53, 1938) compared a δ-lactone from 5-hydroxyundecylic acid with the γ-lactone,



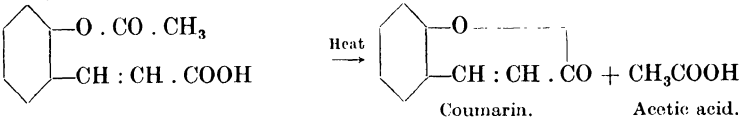
δ-lactone. γ-lactone.

and found that the increased size of the ring increased the intensity of the odour but that the pleasant grassy odour of the γ-lactones was missing in the δ-lactones. It was possible that the greater odour intensity was due to the greater volatility of the δ-lactones. Lactones obtained by methods which would give mixtures of stereoisomers had a coarser and more penetrating odour than those made by more straightforward methods.

In the aromatic series the best known lactone is coumarin. This is obtained from salicylic aldehyde by Sir William Perkin's synthesis.

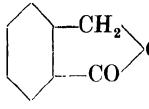


Salicylic aldehyde. Acetylcoumaric acid.



Coumarin. Acetic acid.

Coumarin has a pleasant odour of new mown hay. It occurs in vernal grass and in the common woodruff as well as in oil of lavender. Tonka beans, the seed of *Dipteryx odorata*, smell of new mown hay, due to their coumarin content. Dihydrocoumarin has only a faint odour of coumarin. It has been pointed out by Angeli and Polverini (*Gazz. chim. ital.*, **61,** 276-80) that amongst the substituted coumarins only those have odour which are readily oxidized, and they ask if this is a clue to the mechanism of olfaction.

Whereas coumarin is a δ-lactone, there is one common representative of the aromatic γ-lactones to be found in phthalide or *o*-hydroxymethylbenzoic lactone,  , which has a characteristic odour.

The *a priori* inference that as the lactones are internal esters we should find fragrant and fruity odours has been borne out. The odours of some of the lactones are grouped below for comparison.

γ-butyrolactone	$CH_2 . CH_2 . CH_2 . CO$ $\quad\quad\quad

and ethylene dichloride, $CH_2Cl \cdot CH_2Cl$, similar agreeable ethereal odours are found. Chloroform, or trichlormethane, has a well-known ethereal odour and sweet taste and is one of the unusual cases where taste contributes to odour. Iodoform, CHI_3, is supposed to smell like saffron. The completely substituted body carbon tetrachloride, CCl_4, has a not unpleasant ethereal smell, often noticed in chemical fire extinguishers in which it is used.

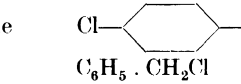
The effect of unsaturation is surprising, for whereas the propyl halides, $CH_3 \cdot CH_2 \cdot CH_2 \cdot Cl$, etc., have ethereal odours, the corresponding allyl halides, $CH_2 : CH \cdot CH_2Cl$, etc., have leek odours.

In the aromatic series the introduction of a halogen into the benzene nucleus increases the odour of the hydrocarbon. Chlorbenzene has an aromatic odour, not unpleasant in dilution, but sickly when concentrated or even when inhaled dilute for long. *p*-dichlorbenzene,  , has an odour reminiscent of both camphor and naphthalene, and is in fact used to combat the clothes moth. The presence of a hydroxyl group as well as the halogen assists the odour. In the fatty series ethylene chlorhydrin, $CH_2OH \cdot CH_2Cl$, has a more powerful odour than either ethylene dichloride,

$$CH_2Cl \cdot CH_2Cl,$$

or glycol, $CH_2OH \cdot CH_2OH$, which is odourless. In the aromatic series chlorphenol is a very much more powerful odorant than either chlorbenzene, dichlorbenzene or phenol, and was used by Fischer and Penzoldt in their work on minimum stimuli.

There is a difference in the olfactory effect of substitution in the nucleus and the side chain. Whilst chlorbenzene, $C_6H_5 \cdot Cl$, has a quite mild odour, benzyl chloride, $C_6H_5 \cdot CH_2Cl$, benzal chloride, $C_6H_5 \cdot CHCl_2$, and benzotrichloride, $C_6H_5 \cdot CCl_3$, have stupefying odours. Odours of some of the halides are grouped below for comparison.

Methyl chloride	CH_3Cl	Ethereal.
Methylene chloride	CH_2Cl_2	,,
Chloroform	$CHCl_3$	Sweet, ethereal.
Iodoform	CHI_3	Saffron.
Chlorbenzene	$C_6H_5 \cdot Cl$	Mild.
p-dichlorbenzene		Camphor—naphthalene.
Benzyl chloride	$C_6H_5 \cdot CH_2Cl$	Stupefying.
Hexachlorethane	C_2Cl_6	Camphoraceous.

Amines

In the amines we encounter for the first time the effect of introducing nitrogen into the molecule. We shall find that in place of the " vegetable " smells of fruits, flowers, balsams and so on which we have encountered in the compounds of carbon, hydrogen and oxygen,

the introduction of nitrogen introduces a new note in "animal" odours. The amines are simply substituted ammonias :

NH_3	$R . NH_2$	$RR' . NH$	$RR'R'' . N$
Ammonia.	Primary amine.	Secondary amine.	Tertiary amine.

and one, two or three of the hydrogen atoms in ammonia may be substituted by other groups giving, respectively, primary, secondary, and tertiary amines.

The simple amines, like methylamine, CH_3NH_2, have, in dilution, a fishy smell like boiled lobsters, but when concentrated, the odour is more ammoniacal. The secondary and tertiary amines have the "fishy" smell more developed, and trimethylamine, $(CH_3)_3N$, is the odoriferous constituent of herring brine. The higher amines, owing to increased molecular weight and lowered volatility, become odourless. The tertiary amines have the property of forming quaternary ammonium bases, e.g. tetramethylammonium hydroxide, $N(CH_3)_4 . OH$, which are strong bases comparable with caustic soda, and these compounds are odourless. It is often found that nitrogen compounds in which the nitrogen is quinquevalent are odourless, but where the nitrogen is at less than its maximum valency as it is trivalent in the amines, the compounds are odorous.

The presence of an oxygen linkage greatly reduces the odour, e.g. triethanolamine, $\begin{matrix} HOC_2H_4 \\ HOC_2H_4 \\ HOC_2H_4 \end{matrix}\!\!>\!N$, has only a faint oily odour compared with the intense fishy smell of triethylamine.

It may be noted that just as the introduction of an amino group into an acid reduces the acidity, so it reduces the odour. Thus

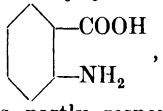
Methylamine	CH_3NH_2	is fishy, and
Acetic acid	CH_3COOH	is pungent, but
Glycine	$NH_2 . CH_2 . COOH$	is odourless.

Similarly, aminopropionic, aminovaleric, and aminocaproic acids are odourless, whether the amino group is in the α-position on the carbon holding the carboxylic group or whether it is ut the ω-position at the end of the chain. This illustrates how odour and chemical reactivity often run parallel.

In the aromatic series substitution of an amino group in the side chain gives amines of ammoniacal odour, e.g. benzylamine,

$$C_6H_5 . CH_2 . NH_2.$$

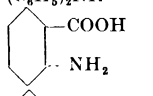
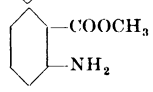
Substitution in the nucleus has, as usual, a different effect, and aniline, $C_6H_5 . NH_2$, has a rather feeble odour of gas-lime. The secondary amine diphenylamine, $C_6H_5 . NH . C_6H_5$, has an agreeable floral note.

Whilst anthranilic acid, 

, is odourless, its methyl ester, methyl anthranilate, is partly responsible for the odour of

orange-blossom and jasmine, and when diluted with alcohol resembles these flowers in odour.

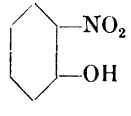
Odours of some of the amines are grouped below for comparison.

Methylamine	$CH_3 . NH_2$	Ammonia, boiled lobsters.
Trimethylamine	$(CH_3)_3 . N$	Herring brine.
Triethanolamine	$(C_2H_4OH)_3N$	Oily, slightly fishy.
Tetraethylammonium hydroxide	$(C_2H_5)_4N . OH$	Odourless.
Aminovaleric acid	$NH_2 . (CH_2)_4COOH$	Odourless.
Cadaverine	$NH_2 . (CH_2)_5NH_2$	Decaying flesh.
Benzylamine	$C_6H_5 . CH_2 . NH_2$	Ammoniacal.
Aniline	$C_6H_5 . NH_2$	Gas-lime.
Diphenylamine	$(C_6H_5)_2NH$	Floral.
Anthranilic acid		Odourless.
Methyl anthranilate		Orange-blossom, jasmine.

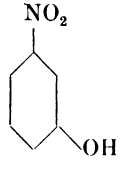
Nitrogen Compounds

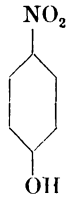
The amines are nitrogen compounds, but have been dealt with separately, as they are an important class and have characteristic odours. For similar reasons heterocyclic nitrogen compounds will be considered later. The other main nitrogen compounds will now be reviewed. The alkyl nitrates are esters of nitric acid, and in this respect comparable with the halides, but they have a much more dominant ester-olfactory tone. Methyl nitrate, $CH_3 . O . NO_2$, and ethyl nitrate, $C_2H_5 . O . NO_2$, have the oxygen ester linkage and the pleasant odour associated with it. The corresponding esters of nitrous acid, methyl nitrite, $CH_3 . O . NO$, and ethyl nitrite, $C_2H_5 . O . NO$, have powerful oppressive odours, but when dilute the latter resembles apples.

The nitroparaffins, $R . NO_2$, have not the oxygen linkage. They are comparable with the halides considered as substituted hydrocarbons. Nitromethane, $CH_3 . NO_2$, and nitroethane, $C_2H_5 . NO_2$, have pleasant odours, and β-nitrohexane, $CH_3 . (CH_2)_3 . CH(NO_2) . CH_3$, resembles aniseed in odour. In the aromatic series nitrobenzene, $C_6H_5 . NO_2$, has the bitter-almond odour of benzaldehyde but coarser. The influence of the entry of the hydroxyl group to nitrobenzene is interesting, for

ortho nitrophenol 

has a strong characteristic odour, but

m-nitrophenol 

and *p*-nitrophenol  are nearly odourless.

2, 4, 6, trinitro-tertiary butylxylene is artificial musk and possibly the strongest odorant known. Trinitro-tert butyl toluenes have also been used as artificial musks.

Amides with the general formula R . CO . NH_2 have the acid and basic characteristics nicely balanced. They are chemically inert and odourless. Acetamide, CH_3 . CO . NH_2, usually smells of " mice," but is odourless when pure.

Nitriles or cyanides have the general formula R . CN, e.g. acetonitrile is identical with methyl cyanide, CH_3 . CN, and has an odour which is agreeable but a little reminiscent of hydrocyanic acid. Butyronitrile, C_3H_7CN, has a definite bitter-almond odour. The higher nitriles and dinitriles, such as sebacic nitrile, $CN(CH_2)_8CN$, have sweet nutty odours, nevertheless rather unpleasant in character. In the aromatic series benzonitrile or phenyl cyanide, C_6H_5 . CN, has the bitter-almonds odour.

Whereas in the nitriles which have the bitter-almond nutty odour of light to medium intensity we have the linkage R—C≡N, in the isocyanides or carbylamines we have the linkage R—N=C. The carbon functions as a divalent element, and once again this appearance of an element functioning below its full valency coincides with the appearance of a powerful odour. The carbylamines, e.g. ethyl carbylamine, C_2H_5 . N=C, have offensive nauseating odours. Phenyl carbylamine, C_6H_5 . N=C, is similar in odour.

Phenylhydrazine, C_6H_5 . NH . NH_2, has a pleasant aromatic odour. The odours of some of the alkyl substituted hydrazines were reported by Westphal (*Ber.*, **74B**, 759-76, 1941). In the trialkylhydrazines, R_2N . NHR, e.g. trioctylhydrazine, the lower members have pleasant odours reminiscent of fresh grass, but the higher members are almost odourless. The tetra-alkylhydrazines, R_2N . NR_2, also have pleasant odours.

Phenylhydroxylamine, C_6H_5 . NH . OH, is an irritant, and phenylazoimide, $C_6H_5N\langle^{N}_{N}\|$, has an unpleasant penetrating odour. Diazomethane, $CH_2\langle^{N}_{N}\|$, and azobenzene, C_6H_5 . N : N . C_6H_5, are both odourless.

The odours of some typical nitrogen compounds are given in the following table :

Methyl nitrate	$CH_3 . O . NO_2$	Pleasant ester.
Methyl nitrite	$CH_3 . O . NO$	Powerful, oppressive.
Nitromethane	$CH_3 . NO_2$	Pleasant.
β-nitrohexane	$CH_3 . (CH_2)_3 . CH(NO_2) . CH_3$	Aniseed.
Nitrobenzene	$C_6H_5 . NO_2$	Coarse, bitter almonds.
Acetamide	$CH_3 . CO . NH_2$	"Mice" usually, odourless if pure.
Methyl cyanide	$CH_3 . CN$	Agreeable, reminiscent of prussic acid.
Sebacic dinitrile	$CN(CH_2)_8CN$	Unpleasant, nutty.
Ethyl carbylamine	$C_2H_5N : C$	Offensive, nauseating.
Phenylhydrazine	$C_6H_5 . NH . NH_2$	Pleasant, aromatic.
Diazomethane	$CH_2 \begin{matrix} N \\ \| \\ N \end{matrix}$	Odourless.
Tetraethyl tetrazine	$(C_2H_5)_2N . N : N . N(C_2H_5)_2$	Alliaceous.

Sulphur Compounds

We have just seen that the nitrogen compounds show a variety of odours which on balance are unpleasant and are often of an "animal" character. The sulphur compounds we shall find also afford a range of odours, many of which are offensive. It might be expected that both elementary sulphur and nitrogen would be odorous, but, as we have already noted, nitrogen is a component of the atmosphere and always present in our olfactory clefts so that it could not excite the sensation of odour, whilst sulphur is polymerized, and polymeric molecules rarely exhibit odour.

Sulphur occurs combined in onions, garlic, horse-radish and mustard.

The simplest organic sulphur compounds are the alkyl sulphides. Thus allyl disulphide,

$$CH_2 : CH . CH_2 . S . S . CH_2 . CH : CH_2,$$

is the principal constituent of oil of garlic obtained from *Allium sativum* from which the name "allyl" and the adjective "alliaceous" are derived.

The odour and taste of mustard seeds are due to allyl mustard oil or allyl isothiocyanate, $CH_2 : CH . CH_2 . N : CS$. It does not exist as such in the seeds but is formed from a glucoside, potassium myronate, when the seeds are pulverized and left in contact with water. A similar ester, ethyl isothiocyanate, $C_2H_5 . N : CS$, also has the characteristic odour of mustard, but its isomer ethyl thiocyanate, $C_2H_5 . S . CN$, resembles onions in odour. This affords a good instance of the difference in odour, due to apparently slight structural differences.

$C_2H_5 . N : C : S.$
Ethyl isothiocyanate
Mustard.

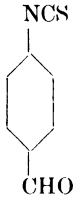
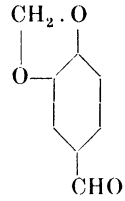
$C_2H_5 . S . C : N.$
Ethyl thiocyanate
Onions.

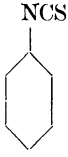
Ethyl sulphite, $O{=}S\begin{matrix} OC_2H_5 \\ OC_2H_5 \end{matrix}$, is another type of ester of a weak inorganic acid, and this ester has an odour of peppermint. The corresponding ester, $(C_2H_5O)_2SO_2$, diethyl sulphate, of sulphuric acid

has a heavy, sweet, ethereal odour. The acid ester, $C_2H_5O \cdot SO_2 \cdot OH$, is faintly fruity.

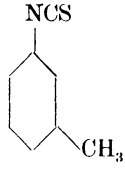
Whereas the sulphides or thio-ethers, such as oil of garlic, have the general formula $\begin{matrix} R \\ R' \end{matrix}\!\!>\!S$, another group of substances with the formula $\begin{matrix} R \\ H \end{matrix}\!\!>\!S$ have the name "mercaptans." They have a most powerful and offensive odour, similar in character to garlic but stronger in every way. A mixture of the amyl mercaptans, $C_5H_{11} \cdot SH$, is used as an odorant under the name Pentalarm, and was discussed in Chapter 1. All the other mercaptans, such as ethyl mercaptan, $C_2H_5 \cdot SH$, have very similar odours. Dyson has pointed out (*Perf. Essent. Oil. Rec.*, **28,** 13, 1937) that the alkyl mercaptans have nearly indistinguishable powerful clinging odours, and that a corresponding characteristic is a line in the Raman spectrum with a shift frequency of 2,567 to 2,580. This subject of Raman spectra will be dealt with more fully in a later chapter.

It will be remembered that mustard gas is a sulphur body, a thio-ether, $\beta\beta'$-dichlordiethyl sulphide, $Cl\,CH_2 \cdot CH_2 \cdot S \cdot CH_2 \cdot CH_2\,Cl$.

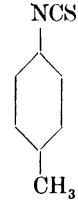
In the aromatic series phenyl isothiocyanate, $C_6H_5 \cdot N : CS$, has the pungent and characteristic odour of the mustard oils. Its *p*-aldehyde,  , *p*-thiocarbimide benzaldehyde, has a strong odour resembling that of heliotropine,  . If a methyl group is substituted in the *meta* position of phenyl thiocarbimide the pungency is maintained, but if the substitution is made in the *para* position then a sweet aniseed odour results :



Phenyl thiocarbimide, pungent.

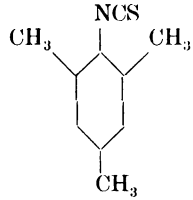


m-tolyl thiocarbimide, pungent.

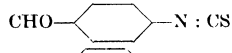
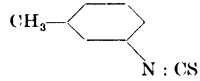


p-tolyl thiocarbimide, sweet anise.

whilst if three methyl groups are introduced in the *ortho* and *para*

positions as in  , mesityl thiocarbimide, then the product has an agreeable floral odour like spiræa (Dyson, *Chemistry and Industry*, **57**, 647-51, 1938).

The odours of some of the sulphur compounds are grouped below for comparison :

Allyl sulphide	$(CH_2 : CH . CH_2)_2S$	Garlic.
Allyl isothiocyanate	$CH_2 : CH . CH_2 . N : CS$	Mustard.
Ethyl isothiocyanate	$C_2H_5 . N : CS$	Mustard.
Ethyl thiocyanate	$C_2H_5 . S . C : N$	Onions.
Ethyl sulphite	$(C_2H_5O)_2 . SO$	Peppermint.
Diethyl sulphate	$(C_2H_5O)_2 . SO_2$	Heavy, sweet ethereal.
Amyl mercaptan	$C_5H_{11} . SH$	Powerful, unpleasant.
Mustard gas	$(ClCH_2 . CH_2)_2S$	Horse-radish.
Phenyl thiocarbimide	$C_6H_5N : CS$	Mustard.
p-thiocarbimide benzaldehyde		Cherry-pie.
m-tolyl thiocarbimide		Pungent.
p-tolyl thiocarbimide		Sweet anise.

Heterocyclic Compounds

The ring compounds we have considered up to now have been :

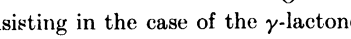
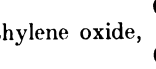
(*a*) Benzene derivatives, which have generally aromatic odours.

(*b*) Naphthalene and anthracene derivatives with characteristic odours.

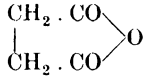
(*c*) Reduced benzene derivatives such as cyclohexane, which have usually aliphatic odours.

(*d*) Cyclopentane derivatives with odours similar to (*c*).

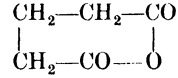
In all four cases the ring is composed solely of carbon atoms, although other atoms and groups are of course attached to the ring atoms. There are, however, many heterocyclic substances in which oxygen, nitrogen or sulphur atoms enter into the ring.

Considering first those with oxygen in the ring, we recall the lactones which have the general formula  and which certainly have a ring consisting in the case of the γ-lactones of four carbon and one oxygen atoms. The lactones, however, are really internal esters and have been dealt with separately. The simplest heterocyclic compound is ethylene oxide,  , which has a sweetish, ethereal smell.

The anhydrides of succinic and glutaric acids come in this category. Both have suffocating odours.

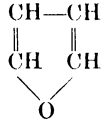


Succinic anhydride.

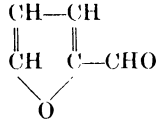


Glutaric anhydride.

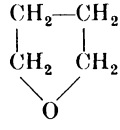
These substances, however, are aliphatic, and their ring structure is accidental. A new type is exemplified in furan which has a characteristic, not unpleasant odour. Its aldehyde, furfural, is unpleasant when concentrated, but when dilute has a pleasant odour of bran and new bread, in which indeed it is present.



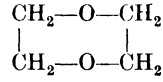
Furan.



Furfural.

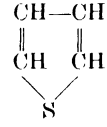


Tetrahydrofurane.

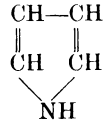
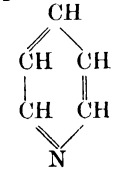


Dioxan.

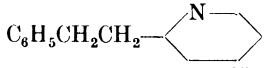
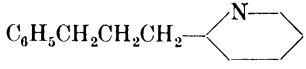
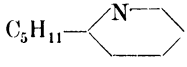
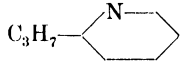
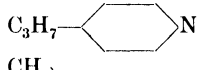
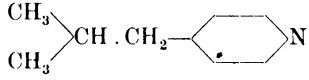
Tetrahydrofurane has a sweet ethereal smell like dioxan but more powerful. It is often found that reduction of unsaturated ring compounds gives products with aliphatic odours. Thus cyclohexane smells like the paraffins, piperidine is ammoniacal, whereas its unsaturated analogue pyridine is rank. Similarly, α-propyl pyridine is flowery but α-propyl piperidine is the noxious coniine.

Next, considering the sulphur compounds we have thiophen which is the sulphur analogue of furane, with the formula,  .

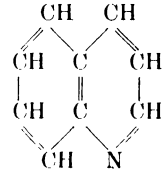
Our knowledge of the sulphur compounds, and especially the fact that in this case the sulphur atom is operating at a valency of two, whereas it is capable of operating at six, would lead us to expect a foul offensive odour in thiophen. Actually it has only a faint neutral sort of smell. Such is the influence of the ring arrangement.

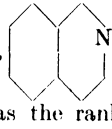
The nitrogen analogue pyrrole,  , has an odour like chloroform. Pyridine has a larger ring,  , equivalent to that of benzene, but with the nitrogen atom replacing one —CH group, and it has a rank, unpleasant odour. The pyridine of commerce owes much of its odour to α-picoline or methyl pyridine, which is usually present in large quantities.

Hexahydropyridine or piperidine has a quite different odour, now ammoniacal and pungent. Some derivatives of pyridine have been prepared and examined by Sandulesco and Sabetay (cf. *Manufacturing Perfumer*, **2**, 31, 1937), and considering the unpleasant odour of pyridine itself, it comes rather as a surprise to find that they have often beautiful floral perfumes. Some of these were as follows :

α-phenylethyl pyridine		Rose.
α-phenylpropyl pyridine		Rose
α-amyl pyridine		Flowery.
α-propyl pyridine		Flowery.
γ-propyl pyridine		Violets.
γ-isobutyl pyridine		Heliotrope.

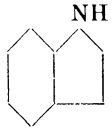
Quinoline is a double ring compound, benzene and pyridine rings being fused together, and has an odour like aniseed but with a more aromatic note.



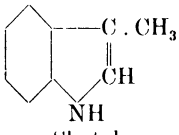
Its isomer, isoquinoline,  , has a similar odour.

Decahydroquinoline has the rank penetrating odour of coniine, the hemlock poison.

In a similar way a substance with fused benzene and pyrrole rings exists and is known as indole.

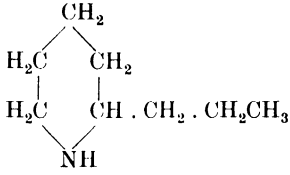


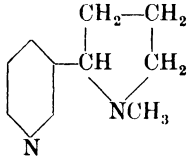
Indole resembles α-naphthylamine in odour, and is unpleasant when pure or in concentrated solution, but in small quantities it is present in oils of jasmine, neroli, etc., and occurs in orange and lemon flowers. Methyl indole or skatole has an objectionable fæcal odour.



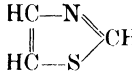
Skatole

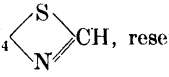
Of the alkaloids, some, like morphine, are odourless, but coniine and nicotine have very strong odours. Coniine, which is α-propyl piperidine, has this constitution and has a stupefying odour.



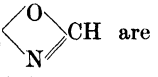


Nicotine is a derivative of pyridine substituted with a N-methyl pyrrolidine nucleus. It has a rank, offensive tobacco odour.

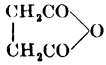
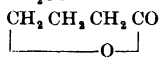
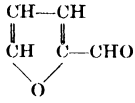
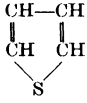
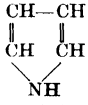
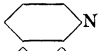
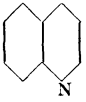
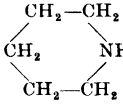
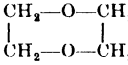
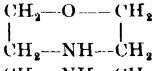
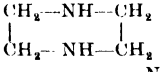
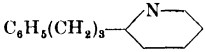
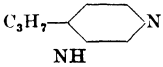
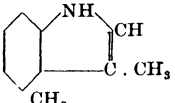
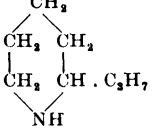
Thiazole,  , which has both nitrogen and sulphur in the ring, resembles pyridine in odour, whilst

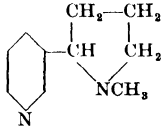
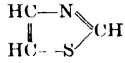
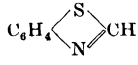
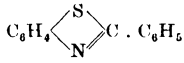
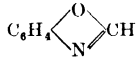
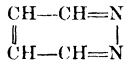
Benzothiazole,  , resembles quinoline.

Bogert and Stull (*Am. Perfumer*, **20,** 453, 1925) have examined some substituted benzothiazoles. First, they point out that incompletely oxidized organic sulphur compounds, which are sufficiently volatile to have any odour at all, usually have an unpleasant one, but exceptions to the rule are found in 2-phenyl benzothiazole, 2-*p*-tolyl benzothiazole and 2-furyl benzothiazole, all three of which possess a tea-rose or geranium odour. Later Bogert (*American Perfumer*, **32,** 51, 1936) found that 2-α-pyrrylbenzothiazole and 2-methyl 6-bromobenzothiazole shared this odour. Some analogous benzoselenazoles also shared this tea-rose odour. This is a most surprising observation, as selenium and tellurium compounds are usually more offensive than sulphur compounds, and to find an organic selenium compound smelling of tea-roses is quite a pleasant shock. The 2-methyl-6-bromo-benzothiazole recalls Dyson's finding that the entry of a halogen imparts a soft anise odour to the otherwise pungent mustard oils. Bogert found eight closely related compounds with the tea-rose smell, and concluded that there was a connection between the odour and the architectural type of the molecule, and that the structure played a more important role than the elements concerned. This observation will be found very much to the point when we consider the macrocylic compounds in which the musk odour persists, whether the compound is unsaturated as in civetone or saturated as in muskone, or whether it is a ketone, lactone, imine, carbonate, malonate, oxalate, sebacate, etc.

Some of the benzoxazoles, oxygen analogues of the benzothiazoles with the typical formula  are said to have a tobacco odour. The odours of some of the heterocyclic compounds are grouped below for comparison.

Ethylene oxide		Sweet, ethereal.
Ethylene imine		Ammoniacal.

Succinic anhydride		Suffocating.
Butyrolactone		Faintly aromatic.
Furfural		New bread.
Thiophen		Faint, neutral.
Pyrrol		Chloroform.
Pyridine		Rank, unpleasant.
Quinoline		Aromatic, aniseed.
Piperidine		Ammoniacal, pungent.
Dioxan		Faint, sweet, ethereal.
Morpholine		Faint, ammoniacal.
Piperazine		Bitter odour like dandelions, slightly ammoniacal.
α-phenylpropyl pyridine		Rose.
γ-propyl pyridine		Violets.
Indole		α-naphthylamine when concentrated, but jasmine when dilute.
Skatole		Fæcal.
Coniine		Stupefying.

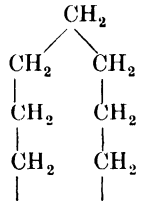
Nicotine		Rank, tobacco.
Thiazole		Pyridine.
Benzothiazole		Quinoline.
2-phenyl benzothiazole		Tea-rose.
Benzoxazole		Tobacco.
Pyridazine		Pyridine.

The close relation of pyridine, with its rank, unpleasant odour, to γ-propyl pyridine, with its odour of violets, and the not very distant propyl piperidine or coniine, with its stupefying odour, prompts the reflection that the rank offensive and the delicious are balanced on a knife-edge. A slight tilt and the pleasurable becomes disgusting. The same thing is seen in indole, repugnant when concentrated, but charming in jasmine and orange-blossom when dilute, and the same again in the substituted benzothiazoles and benzoselenoazoles, delightful in themselves but so closely related to the most offensive compounds. I think this borderline where pleasure changes to disgust varies a little in individuals. Some enjoy a " high " bird, or ripe cheese, others find them disgusting. Some with hyper-acute olfaction find the pineapple disgusting, though to most it is delicious.

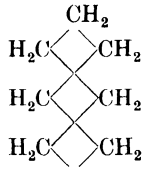
Macrocyclic Compounds

For many years it was recognized that compounds with rings of 5, 6 or 7 carbon atoms could readily be formed, but larger and smaller rings were difficult to make owing to the strain, as explained in Baeyer's theory. In the last twenty years many compounds of different types, esters, lactones, anhydrides, ketones, formals, etc., with large rings, containing up to about twenty atoms, have been formed. On Baeyer's strain theory the existence of such compounds would be improbable, and it has been suggested that these large rings are stable because all the ring atoms form a twisted ring. Angeli (*Gazz. chim. ital.*, **60,** 939-46, 1930) has suggested that in these large rings lateral nodes are

formed due to twisting of the polymethylene chains which form most of the rings, thus :



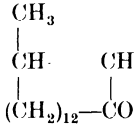
Normal ring arrangement (part only shown).



Twisted ring arrangement (part only shown).

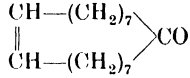
Angeli also suggests that the points of intersection would form nodes which would function in the same way as osmophoric groups close to the carbonyl group. However that may be, the conception of the large rings, with twists in the ring is helpful at the present stage.

Ruzicka (*Helv. chim. Acta.*, **9**, 230, 716, 1008, 1926) found that the essential principle of musk was a ketone, muscone, which he synthesized,



3-methyl cyclopentadecanone or 1-methyl cyclopentadecan-3-one.

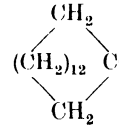
The essential principle of civet was found by Ruzicka to be



civetone or Δ^9-cycloheptadecen-1-one.

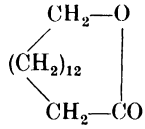
Two bodies which have since been synthesized and marketed owing to their musk-like odours are

Exaltone or cyclopentadecanone



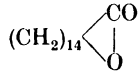
and

Exaltolide or pentadecanolactone



Kerschbaum (*Ber*, **60**, 902, 1927) also isolated two lactones, both of which possessed a fine musk fragrance, from angelica root oil, and these were

Exaltolide the 16-atom ring lactone



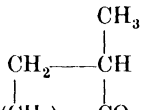
and

Δ^7 hexadecanolactone, an unsaturated 17-atom ring lactone

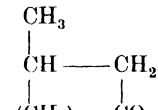


(musk-seed oil).

Ruzicka and Stoll (*Helv. chim. Acta.*, **11,** 1159, 1928) gave a synthetic method for making the exaltone, which they also found in angelica root oil, and which they referred to as the lactone of pentadecan-15-ol-1-acid. It was shown that on saponifying the lactone to the free hydroxy-acid the odour was lost, so that the odour is evidently bound up with the macrocyclic structure. Ruzicka and Stoll (*ibid.*, 670-86, 1928) attempted to prepare cyclic ketones similar to muscone but with the methyl group in different positions, relative to the carbonyl group, to see if this affected the odour. The odour of 1-methyl-cyclopentadecan-2-one, for example, was similar to, but less intense than, that of muscone.

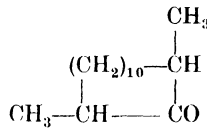


1-methyl-cyclopentadecan-2-one.



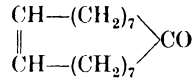
Muscone.

whilst 1-3 dimethylcyclotridecan-2-one

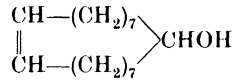


did not have a musk odour.

The effect of reducing the ketone structure had previously been investigated by Ruzicka, Schinz and Seidel (*Helv. chim. Acta*, **10,** 695, 1927) who showed that the alcohol corresponding to civetone has only a faint odour.



Civetone, strong odour of civet.



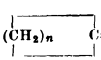
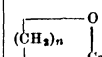
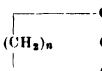
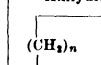
Secondary alcohol from civetone. Faint odour.

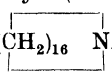
The influence of ring size on the odour of macrocyclic ketones, lactones, carbonates and anhydrides was investigated by Hill and Carothers (*Journ. Am. Chem. Soc.*, **55,** 5039-43, 1933). They showed that 5- and 6-atom rings often had odours of bitter almonds and menthol, but that the odours were rather vague till a 9-atom ring was reached :

9-12	atom rings	gave	camphor or mint odours.
13	,, ,,	,,	woody or cedar-like odours.
14-15-16	,, ,,	,,	musk odours.
17-18	,, ,,	,,	civet odours.
Beyond 18-19	,, ,,	odour	practically disappears.

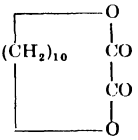
The following table, taken from Hill and Carother's paper, exemplifies these odour changes :

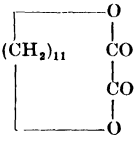
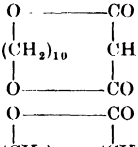
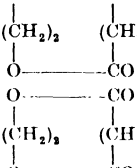
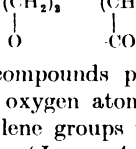
ODOURS OF CYCLIC COMPOUNDS

Total atoms in ring (carbon and oxygen).	Ketone. 	Lactone. 	Carbonate. 	Anhydride 
5	Bitter almonds, menthol	Fruity	Faint	Nil
6	,, ,,	Faint	,,	,,
7	Transitional	Faint spicy, floral	—	Faint pungent
8	,,	—	—	—
9	Camphoraceous	—	Minty, empyreumatic	—
10	,,	—	Minty, less empyreumatic	Spicy
11	,,	—	Earthy, camphoraceous	,,
12	,,	—	,,	,,
13	Cedarwood, then musk, especially dilute	—	Cedar, faint rose and camphor	—
14	Musk	Musk	Musk, camphoraceous	Aromatic
15	Pine musk	Musk and ambergris	Musk	Musk
16	Transition	Musk	Musk	—
17	Civet	Civet	Musk	—
18	Faint civet	Faint	—	—
19	Faint	—	—	Musk
21	—	—	Faint	—

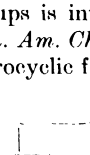
It seems clear that the musk odour reaches a maximum at 15 to 16 atoms in the ring. Tetradecamethylene carbonate (17 atoms) was very like exaltolide, the 16-atom lactone. The common structural feature in all the above compounds is the carbonyl group, but Ruzicka, Salomon and Meyer (*Helv. chim. Acta.*, **17**, 882, 1934) showed that the cyclic imine,  , also had a musk-like odour, so that evidently the carbonyl group is not essential. The odour of the imines, whilst very fine, is too weak for practical purposes, and the anhydrides polymerize too readily to be useful. The lactones, then the ketones, have the finest and most useful odours.

Macrocyclic esters were also shown by Hill and Carothers to have musk-like odours, e.g. :

Decamethylene oxalate (14-atom ring)  Fresh, musk-like odour.

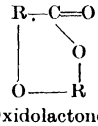
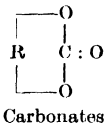
Undecamethylene oxalate (15-atom ring)		Musk odour.
Decamethylene malonate (15-atom ring)		Faint musk.
Ethylene sebacate (14-atom ring)		Musk-like.
Ethylene undecanedioate (15-atom ring)		Musk-like.

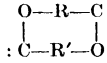
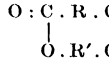
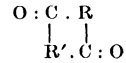
Of these, the first two compounds possess two adjacent carbonyl groups, to which annular oxygen atoms are attached, whilst in the others one or more methylene groups is interposed between the two carbonyls. In a later paper (*Journ. Am. Chem. Soc.*, **57**, 925-8, 1935), the same authors showed that macrocyclic formals had similar odours, thus,

tetradecamethylene formal,  (17-atom ring)

has a musk-like odour.

In a review of the causes of musk odour Stoll (*Manufacturing Perfumer*, **1**, 107-8, 1937) examines eight classes of compounds

I	II	III	IV
			
Lactones.	Ketones.	Oxidolactones.	Carbonates.

V	VI	VII	VIII
			
Dilactones.	Dicarboxylic esters.	Diketones.	Imines.

and reaches the following conclusions :

(1) For the musk odour the basic ring structure must contain at least 14 and less than 19 members and at least one carbonyl $\rangle C : O$ or imino $\rangle NH$ group (cf. I, II, III, IV, VIII).

(2) A second carbonyl group as in VII completely destroys the odour. (Author's note—but does not have this effect in VI.)

(3) Substitution of one ring member by a heterocyclic atom increases the intensity of the odour and displaces it in the direction of ambergris (cf. I).

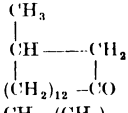
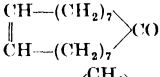
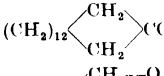
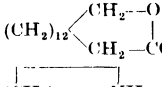
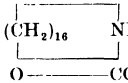
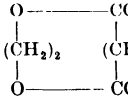
(4) Two or more heterocyclic atoms reduce the odour and make the tonality coarser (III, IV).

(5) If the ring contains 2 oxygen and 2 carbonyl groups there is a faintly sweetish odour, remotely like musk, but the odour is stronger than in the diketones VII. (Author's note—this applies to V, hardly to VI.)

Stoll concludes that by far the best musk odour is given by the 16-membered lactone of 15-hydroxypentadecanoic acid, exaltolide.

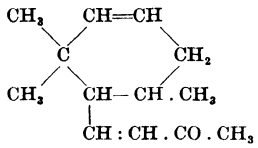
The study of the macrocyclic compounds has shown how the general architectural design of the molecule determines the odour. Differences of arrangement in a small part of the large molecule make minor differences in odour, but do not change the general character of the odour. It is only in small-molecule compounds, where the reactive group, such as $>CO$ carbonyl, —CHO aldehyde, —COOH acid, or $—OC_2H_5$ ether, constitutes a large part of the molecule that the reactive group appears to determine the odour. When the group is small relative to a large molecule it exerts only a minor influence. We have already noted that some of the benzothiazoles and benzoselenazoles have floral and attractive perfumes, and I believe the same explanation to hold in this case also, viz. that the " anti-social " tendencies of the unoxidized sulphur and selenium atoms are overwhelmed by the pleasant tendencies of the large molecule, in which they find themselves. Let us remember, then, that it is the general architectural design of the molecule that determines its odour, and that it is only in small molecules that any one group can exert a determining influence.

The odours of a few of the macrocyclic compounds are grouped below for comparison.

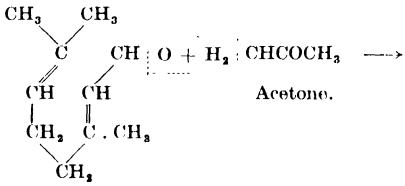
Muscone		15-ring ketone	Musk.
Civetone		17-ring ketone	Civet.
Exaltone		15-ring ketone	Musk.
Exaltolide		16-ring lactone	Musk.
Hexadecamethylene imine		17-ring imine	Musk.
Ethylene sebacate		14-ring ester	Musk-like.

Ionones

The active principle of violets is irone,

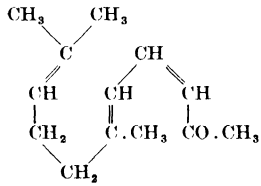


It occurs only in microscopic quantities and its extraction is difficult. Tiemann and Kruger (*Ber.*, **26,** 2675, 1893) isolated irone from orris root, the dried rhizomes of *Iris florentina*. They attempted to synthesize it from citral and acetone, but instead of getting irone they got α- and β-ionones.

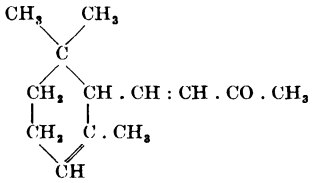


Citral or geranial.

Acetone.

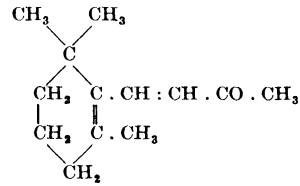


Pseudo ionone.



α-ionone.

and

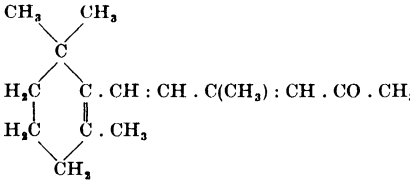


β-ionone.

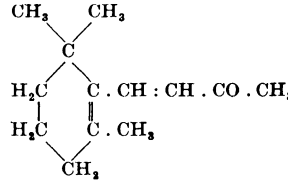
It will be seen that the ionones differ from each other and from irone only in the position of the double bonds. Recent evidence has, however, been brought forward to show that irone probably has a seven-atom ring. Whereas α-ionone has a sweet odour similar to orris root, β-ionone is nearer to true violet. Practically all violet perfumes are now made from ionone, to which may be added a trace of violet-leaf oil which contains 2 : 6 nonadienal,

$$CH_3 . CH_2 . CH : CH . CH_2 . CH_2 . CH : CH\ CHO$$

(Ruzicka and Schinz, *Helv. chim. Acta.*, **17,** 1592, 1934). It was shown by Karrer and Morf (*ibid.*, 3-7, 1934) that β-euionone had a finer and more practical scent than β-ionone. β-euionone is 2-methyl-4-(1′1′3′ trimethyl-2′-cyclohexen-2′-yl) butadienyl methyl ketone. The constitution of this substance is compared with that of β-ionone below. It will be seen that it has a longer side chain.



β-ouionone.



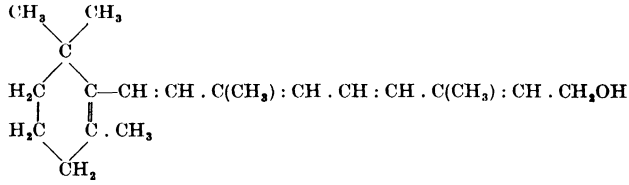
β-ionone.

The position of the double bond in the ring seems to be unimportant, but unsaturation in the side chain is essential, and, according to Durrans, the violet odour is only obtained when the acetone side chain is next to a ring methyl group. Other substances than the ionones, such as γ-propyl pyridine, may have a violet odour.

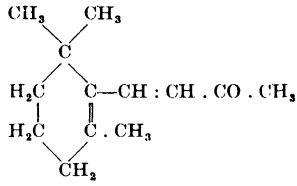
Vitamines

The relation between the ionones and vitamin A has been noted by several observers (cf. Herold, *Seifensieder Ztg.*, **65**, 848-9, 1938). It is bound to raise the question, whether essential accessories to diet have pleasant tastes and odours, to ensure that they will not be neglected. Such perceptions might not reach the threshold of consciousness. The structural formulæ of vitamin A and β-ionone are as follows :

Vitamin A



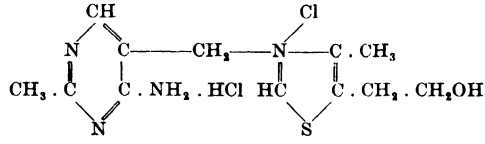
β-ionone



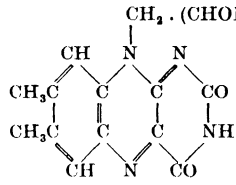
It will be seen that vitamin A has one β-ionone ring. β-carotin has two such rings.

The formulæ of some of the other vitamins are interesting and bear a general architectural resemblance to some of the heterocyclic odorous compounds we have examined. They are

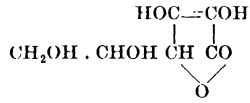
Vitamin B (antineurin) (Williams, *Jour. Amer. Chem. Soc.*, **58**, 1063-4, 1936)



Vitamin B_2 or G (lactoflavine)



Vitamin C (ascorbic acid)



Vitamin D (calciferol) and vitamin E (α-tocopherol) are sterols with complex structures. Karrer and Morf (*Helv. Chim. Acta.*, **17**, 3-7, 1934) point out that, although substances may be similar in structure to vitamin A in the possession of a β-ionone ring and an unsaturated side chain, none of them is a substitute for it in animal growth. α- and β-carotenes, however, change to vitamin A in the body, so that they are physiologically active.

All that can be said at present is that the molecular designs, where known, of vitamins bear striking resemblance to those of some pleasant and powerful odorants. We have already seen how the search for food and its ingestion and the nutrition of the body are controlled by odour, and as it is to-day established that certain vitamins present in very small quantities in food are essential for bodily health, it is only natural that vitamins should have an olfactory attraction. It may be that the vitamins are themselves odorous or that they are always associated by natural design with odorous constituents. The attractive odours of the citrus fruits, lemon, lime and orange, rich in vitamin C come to mind. The danger of throwing out these vital elements, when man "refines" food, as in the polishing of rice and the preparation of the white loaf, is now recognized.

Mixed Compounds

Whilst the vast majority of the organic substances are composed of carbon, hydrogen, oxygen, sulphur, nitrogen, and the halogens, many other elements will combine with alkyl groups. The compounds of arsenic and phosphorus have received a lot of attention, from the point of view of chemical aggressive action in warfare, and many of them have already been considered in Chapter 6. In the second division of the carbon group of the periodic classification we have, besides carbon, silicon, germanium, tin, and lead, and all these elements show a marked tendency to form organic compounds.

Silicon tetraethyl (silicononane), $Si(C_2H_5)_4$, resembles light petroleum in odour, whilst the similar alcohol, $Si(C_2H_5)_3 . C_2H_4OH$, silicononyl alcohol, has a camphoraceous odour. Silicoheptane, $(C_2H_5)_3 . SiH$, has a petroleum-like odour similar to triethylmethane, $(C_2H_5)_3 . CH$. Tin tetraethyl and lead tetraethyl of petrol fame are liquids with pleasant odours.

The elements phosphorus, arsenic, antimony, and bismuth in Group 5 also show a tendency to form organic compounds. The phosphines, PRH_2, PRR'H and PRR'R'', are analogous to the primary, secondary and tertiary amines respectively, and have penetrating, stupefying odours, although triethyl phosphine, $P(C_2H_5)_3$, in dilution, has an odour of hyacinths. The arsenic derivatives containing alkyl groups are known as cacodyl, meaning ill-smelling, compounds. Trimethylarsine, $As(CH_3)_3$, for example, has a repulsive odour, and cacodyl oxide, $As(CH_3)_2OAs(CH_3)_2$, has a most objectionable odour, as has cacodyl, $As_2(CH_3)_4$, itself. The variation of odour with constitution in these organo-metallic compounds is well illustrated by a series of three compounds made by Malinovskii (*Jour. Gen. Chem. U.S.S.R.*, **10,** 1918-22, 1940).

$(Cl\ CH_2CH_2O)_3As$	Odourless.
$(Cl\ CH_2CH_2O)_2As\ Cl$	Slight pungent odour.
$Cl\ CH_2CH_2O\ As\ Cl_2$	Pungent odour.

Selenium and tellurium, in Group 6, form compounds analogous to those of sulphur but with even more offensive smells. If, however, the selenium or tellurium atom is in a ring as in selenophene, analogous to thiophen, or in the benzene selenazoles, the odour may not be offensive. The odours of some of these mixed compounds are grouped below for comparison.

Silicononane	$Si(C_2H_5)_4$	Light petroleum.
Silicononyl alcohol	$Si(C_2H_5)_3 . C_2H_4OH$	Camphor.
Tin tetraethyl	$Sn(C_2H_5)_4$	Pleasant.
Trimethylphosphine	$P(CH_3)_3$	Repulsive.
Cacodyl	$As_2(CH_3)_4$	Repulsive.

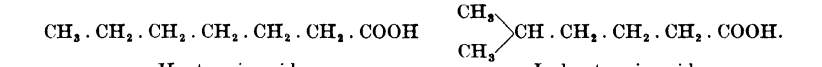
The general inference is that whilst the members of Group 4, viz. silicon, germanium, tin and lead behave respectably, those of Group 5 introduce an objectionable note. We note, again, that where atoms function below their maximum valency, objectionable odours result. Phosphorus, for example, has a full valency of five, but is only trivalent in the phosphines.

Isomerism

There are degrees of difference between isomers. Cyanides or nitriles, R . C=N, are isomeric with the carbylamines or isonitriles, R . N : C, but as there are great differences in chemical reactivity and physical properties between the two classes of compounds, it is not a matter for surprise that the odours are very different, the nitriles having the bitter-almonds odour, and the isonitriles the powerful revolting carbylamine odour.

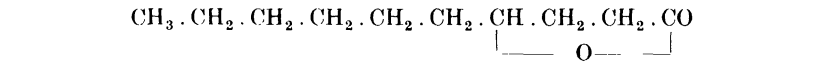
In other cases of isomerism the differences in structure have little effect on the chemical reactivity and the physical properties, and in such cases it is more surprising to find considerable odour differences between isomers with otherwise very similar properties.

The odours of the esters of heptanoic (œnanthic) and isoheptanoic (5-methyl-hexanoic) acids provide a case in point. These acids have constitutions as shown :

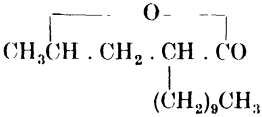


Heptanoic acid. Isoheptanoic acid.

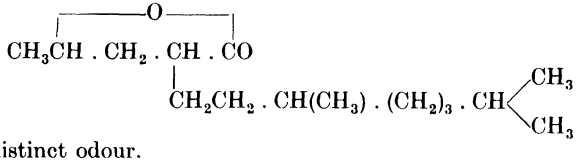
Rothstein (*Bull. Soc. chim.*, **53**, 1106, 1933) made and compared the esters of both acids with benzyl alcohol, hydrocinnamyl alcohol, hydratropyl alcohol and geraniol, as well as some others. The isoheptanoates were found to possess finer and more pleasant odours than the heptanoates. True, there was no marked change in odour, but it seems remarkable that such a slight and chemically unimportant change in the molecule should have any influence at all on the odour. Similarly, Stoll and Bolli (*Helv. Chim. Acta.*, **21**, 1547-53, 1938) found that in the γ-decalactones



branching of the side chain made the odour more sweet and flowery. v. Braun, Anton and May (*Ber.*, **70B**, 1250-3, 1937) found that decyl-

valerolactone  was odourless, but

3 : 7 dimethyloctylvalerolactone

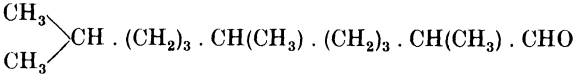


had a distinct odour.

Another illustration of the effect of branching on the odours of isomers is provided by



the straight chain aldehyde which has a very faint fatty odour, not very pleasant, and Norhexahydrofarnesal



(2 . 6 . 10-trimethyl undecylaldehyde), which is isomeric with myristaldehyde, but has an unusually pleasant and strong refreshing floral odour. (v. Braun and Anton, *Ber.*, **62B**, 1489-91, 1929.) Similarly, 2 . 6 dimethylheptyl aldehyde has a stronger and more pleasant odour than nonyl aldehyde.

So much for chain-branching. Now let us consider balance. We have already noted that whereas methyl nonyl ketone, $C_9H_{19} . CO . CH_3$,

has an odour of rue, and is indeed the chief constituent of oil of rue, yet its isomer, ethyl octyl ketone, $C_8H_{17} . CO . C_2H_5$, has a much less intense odour of rue and a more fruity note, whilst diamyl ketone, $C_5H_{11} . CO . C_5H_{11}$, is essentially fruity. All three are isomeric but lack of balance in the molecules gives individuality to the odour. Rothstein (*Bull. soc. chim.*, **51,** 838-45, 1932) made some alkoxy esters of the general formula

$$R . O . CH_2 . COOR'$$

where R was methyl, ethyl, isopropyl and isobutyl, and R′ was benzyl, phenylethyl, phenylpropyl, etc. In passing from the methoxyacetates to the isobutoxyacetates odour lost its intensity and tenacity. Thus :

phenylethyl ethoxyacetate $C_2H_5 . O . CH_2 . CO . O . C_2H_4 . C_6H_5$,
and
benzyl isopropoxyacetate $(CH_3)_2CH . O . CH_2 . CO . O . CH_2 . C_6H_5$

are isomeric, but whilst the former has a pot-pourri odour the latter has only a very feeble scent. Similarly :

phenylethyl methoxyacetate $CH_3 . O . CH_2 . CO . O . C_2H_4 . C_6H_5$,
and benzyl ethoxyacetate $C_2H_5 . O . CH_2 . CO . O . CH_2 . C_6H_5$

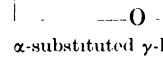
are isomeric but smell, respectively, of rose and jasmine. Further, Rothstein showed that the series of compounds

$$R . O . CH_2 . CO . O . R' \qquad [R = \text{Alkyl},\ R' = \text{Aralkyl}]$$

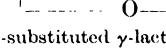
all had more marked and characteristic odours than their isomers

$$R' . O . CH_2 . CO . O . R.$$

Rothstein (*Bull. soc. chim.* (5), **2,** 1936-44, 1935) also compared α-substituted and γ-substituted γ-lactones,



α-substituted γ-lactone.



γ-substituted γ-lactones.

and found that whilst both series were similar in possessing from C_{11} to C_{15} odours of musk and peach yet the α-substituted lactones had stronger and more lasting odours.

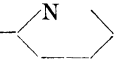
Whilst it has been shown that there may be differences of odour between isomers of very similar constitution, it must not be forgotten that isomers of similar constitution, forgetting those of gross differences such as nitriles and isonitriles, nitro compounds and nitrites, are more likely to show odour resemblances than are substances which are not isomeric. Such stress is sometimes laid on the odour differences of similar isomers, which differences are superficially illogical, that one is apt to forget that the chemical resemblances between isomers often carry with them similarities in odour. What is meant may be clear in the following list of bodies prepared by v. Braun and

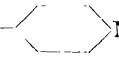
Gossel (*Ber.*, **57B**, 373-82, 1924) in an attempt to find to what characteristics of molecular construction the rose smell of citronellol is due.

I.	$(CH_3)_2C : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CH_2OH$	Citronellol.
II.	$CH_2 : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CH_2OH$	No similarity.
III.	$CH_2 : CH . CH_2 . CH_2 . CH(CH_3) . CH(CH_3) . CH_2OH$	,, ,,
IV.	$CH_2 : CH . CH_2 . CH(CH_3) . CH(CH_3) . CH(CH_3) . CH_2OH$	,, ,,
V.	$CH_3CH : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CH_2OH$	Some similarity to I.
VI.	$CH_3CH : CH . CH_2 . CH_2 . CH(CH_3) . CH(CH_3) . CH_2OH$	More similarity to I.
VII.	$CH_3CH : CH . CH_2 . CH(CH_3) . CH(CH_3) . CH_2 . CH_2OH$	Most similarity to I.
VIII.	$(CH_3)_2C : CH . CH_2 . CH_2 . CH(CH_3) . CH(CH_3) . CH_2OH$	Resembles closely.

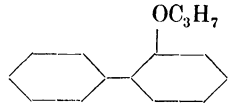
Now of these compounds IV, VI and VII are isomeric with I. In addition, VI and VII have structural similarity in respect of the methyl groups close to the double bond, and they resemble citronellol in odour, although IV, which has not the same molecular characteristics, does not resemble citronellol in odour. It may be noted that VI and VII which are isomeric with citronellol resemble it more closely than V which, although it is structurally similar, is not isomeric. Hence our conclusion, molecular architecture has the dominant influence, isomerism has less influence. It should perhaps be noted here that v. Braun concluded that the chief factor in molecular construction to give the citronellol perfume was the presence of the complex $(CH_3)_2C=C\diagup$, at a definite distance from the primary alcohol group.

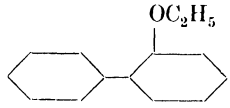
In the heterocyclic series we have already seen that

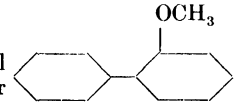
α-propyl pyridine $CH_3CH_2CH_2$—  has a floral odour,

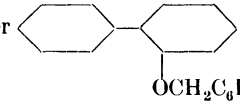
but γ-propyl pyridine $CH_3CH_2CH_2$—  smells of violets.

It is in the aromatic series that the differences in odours of isomers are most surprising. One often finds that a change in the place of substitution will completely change the odour. As an example the biphenylyl ethers may be quoted. They were studied by Brewster and Putman (*Jour. Amer. Chem. Soc.*, **61**, 3083-5, 1940). They found that the *ortho* ethers had the following odours :

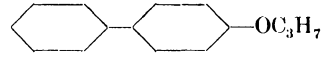
2-biphenylyl propyl ether  Faint, aromatic.

2- ,, ethyl ether  Faint, sweet, floral.

2-biphenylyl methyl ether  Faint, fruity, aromatic.

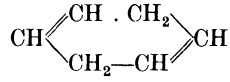
2- ,, benzyl ether  Pleasant, nut-like at 100° C.

but that the corresponding *para* ethers :

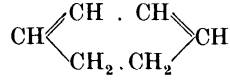
4-biphenylyl propyl ether 

etc., were all odourless. Here, then, the simple change from *ortho* to *para* position of a substituent group completely destroys the odour of a whole series of compounds. The explanation usually given to such phenomena as this is that the presence of the substituent groups close to each other is necessary. In this case the substituent groups are a phenyl group and the ether group, considered as substituents in the benzene nucleus. Such an explanation recalls the necessity for the methyl groups to be near the point of unsaturation in the citronellol series. I prefer, however, to regard it as a special case of the general rule that the odour depends on the general configuration or architectural style of the molecule as a whole. It is clear that the substitution of a side-chain in the 2- or *ortho*-position is going to have a very different effect on the shape of the diphenyl molecule from substitution in the 4- or *para*-position. We shall also find that substitution in the 3- or *meta*-position often has a very different effect from substituting in *ortho*- and *para*-positions. This is frequently explained on polarity considerations which will be reviewed later, but it might be made clear at this stage that if the shape of the molecule is responsible for the odour, there is no *a priori* reason to expect the shape of a *meta*-substituted compound to be intermediate between the shapes of *ortho*- and *para*-substituted compounds.

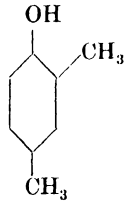
In the benzene ring the saturation of two of the carbon atoms, which are *ortho* to each other gives a stronger odour than similar saturation, with hydrogen in both cases, of carbon atoms *para* to each other. Thus, as we have already seen, in the section on Hydrocarbons :

1 : 4 dihydrobenzene 

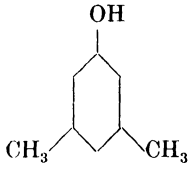
has a weaker odour than

1 : 2 dihydrobenzene (or $\Delta^{1\cdot3}$ dihydrobenzene) 

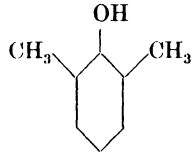
The weakness of odour of the *para*-substituted xylenol, 2 : 4-xylen-1-ol, compared with the strong phenolic odour of the *meta*-substituted 3 : 5-xylen-1-ol has also been noted



2 : 4 xylen-1-ol, weak odour.



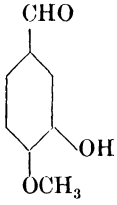
3 : 5 xylen-1-ol, strong phenol odour.



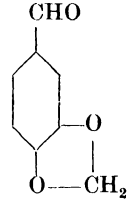
2 : 6 xylen-1-ol, wintergreen odour.

Among the trisubstituted benzenes many well-known perfume substances possess the 1 : 3 : 4 arrangement, e.g. :

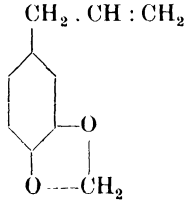
vanillin



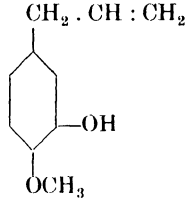
piperonal (heliotropin)



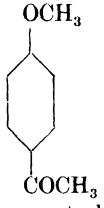
safrole



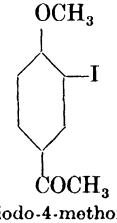
eugenol (oil of cloves)



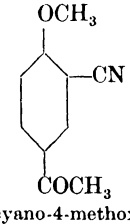
The 1 : 3 : 4 arrangement has accordingly been called the ideal configuration, but Bogert and Curtin (*Jour. Amer. Chem. Soc.*, **45**, 2161-7, 1923) showed that this arrangement did not in itself give a perfume. They started with *p*-methoxyacetophenone which has a fine floral odour, and made derivatives with additional osmophoric groups in position 3, but all were practically odourless.



4-methoxyacetophenone, fine floral odour.



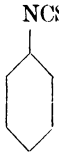
3-iodo-4-methoxy-acetophenone, nearly odourless.



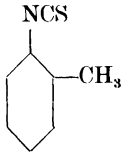
3-cyano-4-methoxy-acetophenone, nearly odourless.

A trisubstituted benzene containing three osmophoric groups in 1 : 3 : 4 configuration is therefore not a perfume on that account, even though its physical constants, such as boiling-point and solubilities, may be favourable.

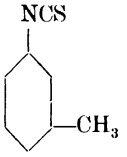
The effect of position isomerism in the benzene ring on the odour of the products has been examined by Dyson in an extensive series of researches mostly published in different volumes of the *Perfumery and Essential Oil Record*. He has taken as his starting point phenyl mustard oil which has a pungent odour. He found (*Perf. Essent. Oil. Rec.*, **17**, 20-2, 1926) that whilst the introduction of a single *o*- or *m*-group causes little or no modification in the aromatic nature of the odour, a single group in the *p*-position causes an aniseed-like odour, which is almost independent of the chemical nature of the substituent group :



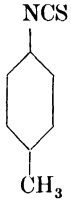
Phenyl thiocarbimide, strongly pungent.



o-tolyl thiocarbimide, strongly pungent.

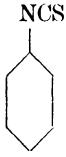


m-tolyl thiocarbimide, very strongly pungent.

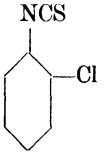


p-tolyl thiocarbimide, sweet aniseed.

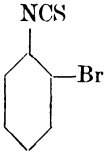
In *Perf. Essent. Oil Rec.*, **19**, 88-91, 171-4, 341-2, 1928, he extended the investigation to the influence of the halogen substituents. Whereas *o*-chlorphenyl thiocarbimide and the corresponding *meta* body had a very keen mustard oil odour, the *o*- and *m*-bromophenyl thiocarbimides had a less apparent odour of the same nature, and the *o*- and *m*-iodophenyl thiocarbimides had almost no odour, yet all three *para* phenyl-mustard oils had powerful anise scents.



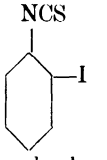
Pungent.



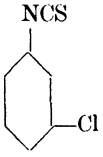
Pungent.



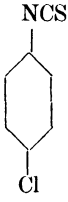
Less pungent.



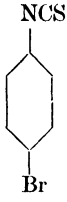
Nearly odourless.



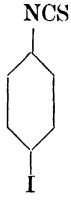
Strongly pungent.



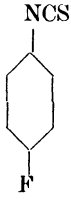
Sweet anise.



Sweet anise.

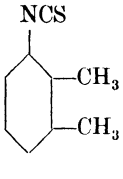


Very sweet anise.

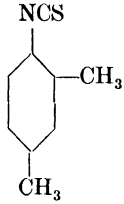


Anise-mustard oil.

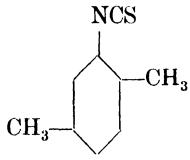
The fluoro-compound provides a mixture of anise and mustard oil as the fluorine influence is evidently weaker than that of chlorine. In fact the sweetness of odour reaches a maximum in the *p*-iodophenyl mustard oil. The influence of the introduction of two methyl groups may be seen from the following (*Perf. Essent. Oil Rec.*, **22**, 278, 1931):



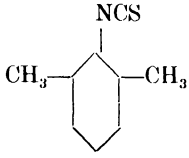
2 : 3 xylyl thiocarbimide, pungent.



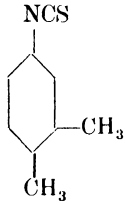
2 : 4 xylyl thiocarbimide, delicate anise.



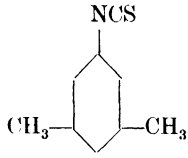
2 : 5 xylyl thiocarbimide, pungent.



2 : 6 xylyl thiocarbimide, delicate spiræa.

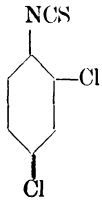


3 : 4 xylyl thiocarbimide, harsh, with anise note.

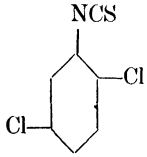


3 : 5 xylyl thiocarbimide, pungent.

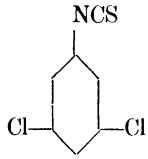
Similarly, with the dichlorphenyl thiocarbimides:



2 : 4 dichlorphenyl thiocarbimide, sweet anise.

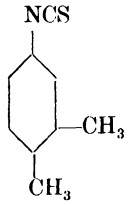


2 : 5 dichlorphenyl thiocarbimide, pungent.



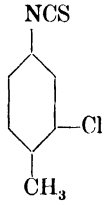
3 : 5 dichlorphenyl thiocarbimide, pungent.

It is clear that substitution in the *para*-position gives a soft anise note which will overwhelm the pungent note due to the *meta*- or *ortho*-substitution, so that the resultant odour is anise when the groups are similar. The effect of a chlorine substituent is, however, more powerful than a methyl group, for in the following series:



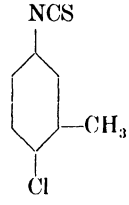
3 : 4 xylyl thiocarbimide.

A.



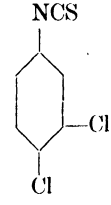
4-methyl 3-chloro-phenyl thiocarbimide.

B.



3-methyl 4-chloro-phenyl thiocarbimide.

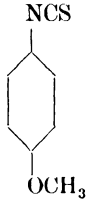
C.

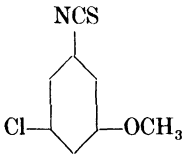


3 : 4 dichlor-phenyl thiocarbimide.

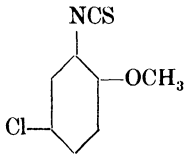
D.

B and D, which have *meta*-Cl, are more pungent than A and C, which have *meta*-CH_3, and B, where the softening anise note is due to CH_3, is more pungent than D, where the *para*-Cl exerts a more powerful softening anise note. For the same reason C is less pungent than A. There is an anise note alongside the pungency in all four, but it is most marked in C and D, where the Cl is in the *para*-position.

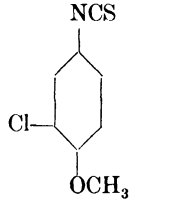
The introduction of a methoxy group gave a very pronounced anise odour,  , *p*-methoxyphenyl mustard oil; but all four di-methoxyphenyl mustard oils and the 3 : 4 : 5 trimethoxyphenyl mustard oil were practically odourless. Compounds containing both methoxy and chlorine groups had interesting odours :



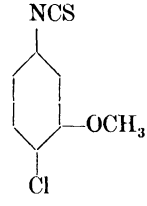
3-methoxy 5-chlor phenyl thiocarbimide, geranium, slightly pungent.



2-methoxy 5-chlor phenyl thiocarbimide, faint floral, no anise.



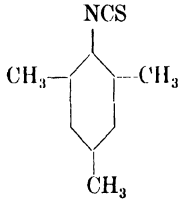
3-chlor 4-methoxy phenyl thiocarbimide, nearly odourless, faint pleasant.



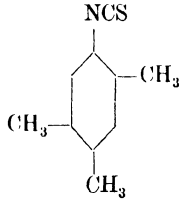
3-methoxy 4-chlorphenyl thiocarbimide, anise, spiræa.

The effect of substituting in more than three positions in the benzene

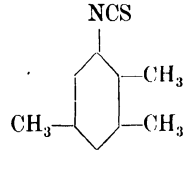
ring may be seen in the following examples (Dyson, *Perf. Essent. Oil Rec.*, **19**, 3-5, 1928):



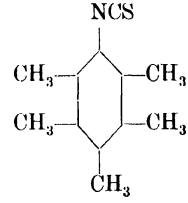
Mesityl thiocarbimide, very floral.



ψ-cumidyl thiocarbimide, anise with faint note of pungency.



2 : 3 : 5 trimethyl phenyl thiocarbimide, pungent.



Pentamethyl phenyl thiocarbimide, very faint floral odour.

Dyson (*Perf. Essent. Oil Rec.*, **19**, 171-4, 1928) enunciated three rules regarding substitution in the phenyl mustard oils.

(1) The effect is dependent on the orientation of the groups, *para* giving anise, *meta* giving pungent, and *ortho* groups having an effect mainly on the floral character of the odour.

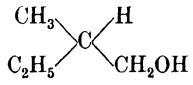
(2) The nature of the odour depends more on the position than on the nature of the substituent group.

(3) Where methyl and chlorine occur together in the same mustard oil, chlorine is more strongly effective than methyl.

Similar rules may be seen to apply to a large number of aromatic substances. The conclusions drawn regarding the basis of odour by Dyson from his observations will be examined in a later chapter.

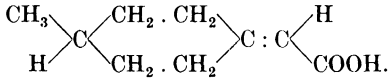
Stereoisomerism

The mirror-images of molecules of most substances are identical with the molecules themselves, but in some compounds, owing to molecular asymmetry, the mirror-image of the molecule cannot be turned or twisted to coincide with the original molecule. We then have left- and right-hand molecules, and, according as they divert polarized light to the right or left, they are known as *d*- or *l*-forms. A mixture of the two in which the two influences cancel each other and which therefore does not turn polarized light is the *dl*- or racemic form. If this compensation is effected internally in a molecule then that is known as the meso-form. Usually this asymmetry is caused by the presence of an asymmetric carbon atom, i.e. one attached to four different groups. Such a substance is secondary amyl alcohol:



Asymmetric nitrogen, sulphur and other atoms may also cause stereoisomerism. Another structural arrangement which gives optically active stereoisomers, but which contains no asymmetric carbon atom,

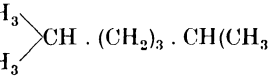
is that known as *Dissymnétrie moléculaire*, as in 1-methyl cyclohexylidene-4-acetic acid :



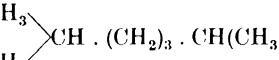
Such mirror-images, or stereoisomers, of a substance do not, as a rule, differ in chemical properties, and it is a matter of some difficulty to resolve a *dl*-mixture into its *d*- and *l*-components.

Surely here, we should say, the odours of stereoisomers would be identical and if not, well, there can be little relation between odour and chemical constitution. Nevertheless, differences in odour and, indeed, other physiological properties have been detected between stereoisomers. Usually the differences are of slight degree. If, however, we think of odour as determined by molecular architecture why should we expect identical responses from mirror-images ? We are ourselves left- and right-handed. We cannot write so easily with one hand as the other, nor kick a ball so well with one foot. Often we cannot see so well with one eye as the other, or hear equally well with both ears. A left-handed golf club would not be so useful to a right-handed person as would a right-handed club. Why therefore should it be surprising that a left-handed substance has a different effect from an otherwise similar but right-handed substance on our olfactory apparatus ? In fact such differences exist.

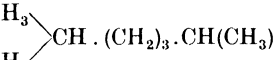
v. Braun and Kaiser (*Ber.*, **56B**, 2268-74, 1923) made three pairs of optical isomers, and concluded that stereoisomerism could affect odour.

dl-3·7-dimethyl octanol, 

had a right pleasant odour, but the *d*-active form had a more refreshing and somewhat more penetrating odour.

dl-3·7-dimethyl octanal, 

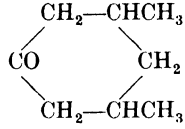
had a more pleasant and intense odour than the *d*-form and was reminiscent of citronellal, whilst the *d*-form nearly resembles citral.

dl-4·8-dimethyl nonanol, 

was more intense and less smooth than the *d*-form, but both were reminiscent of geranium leaves.

Later, v. Braun and Teuffert (*Ber.*, **58B**, 2210-15, 1925) showed that active *m*-methylcyclohexyl ethylene oxide had a stronger odour than the inactive form. v. Braun and Haensel (*Ber.*, **59B**, 1999-2011, 1926) found that $1^{cis}\ 3^{trans}$ dimethyl-5-cyclohexanone had a suggestion

of mint in its odours, but that the 1^{cis} 3^{cis} stereoisomer was reminiscent of cineole and thujone,



1·3 . dimethyl-5-cyclohexanone.

Subsequently v. Braun and Anton (*Ber.*, **60B**, 2438-46, 1927) were able to isolate the *d*- and *l*-forms from the *dl*-form of the above ketone, and found that they showed distinguishable differences in odour, as also did the alcohols to which they could be reduced, the *d*-alcohol having a fresher and stronger odour than its antipode. v. Braun concluded that as all these isomers were made from the same starting material (3-5 xylen-1-ol) and with the same reagents, they afford incontrovertible proof that the olfactory apparatus can distinguish the finest differences in spatial arrangement.

Singh and Lal (*Nature*, **144**, 910-11, 1939) examined the active forms of some bisaminomethylene camphors, and found that the *l*-form had always the most intense odour, followed by the *dl*- and the *d*-forms.

Conclusions

Before drawing conclusions from the evidence presented in this chapter, it may be of interest to note some of the conclusions arrived at by different investigators. Many have already been quoted, e.g. Stoll on musk odour, Hill and Carothers on macrocyclic compounds, von Braun on stereoisomerism, and Dyson on substitution in the benzene ring. Some of the others are

Rupe and Majewski (*Ber.*, **33**, 3401, 1900) suggested that the odour of substances was due to osmophoric groups. This theory has been applied in one form or another to dyestuffs, taste and toxicity. There is no doubt that certain groups, such as methoxy, carbonyl and so on, do exert a positive influence, whilst the hydroxyl group exerts an opposite effect in suppressing odours. The point at issue is whether such an influence is primary or secondary. I believe it is secondary to molecular architecture.

Marchand (*Deut. Perf. Ztg.*, **1**, 223-4, 243-5, 287-8, 1915) concluded that perfumes are compounds which contain oxygen in the form of a bridge atom. Esters, lactones and ethers contain an oxygen linkage, but not ketones, aldehydes or ionones. Marchand also concluded that two such oxygen atoms in a molecule reduced the odour. Glycols, resorcinol, and macrocyclic dilactones are almost inodorous, but esters of dicarboxylic acids are quite strongly odorous. Marchand also concluded that all perfume effects are dependent on free valencies.

Prins (*Perf. Essent. Oil Rec.*, **8**, 222-3, 1917) considered it more correct to regard all groups as osmophoric, differing only in strength. The odour of benzene derivatives is therefore similar, because the

substituting groups cannot entirely overcome the influence of the osmophoric benzene ring. Prins considered that if an alteration to part of an aromatic substance had a great influence on the chemical character of the strongest osmophoric group, a considerable change in the odour would result. But we have seen that considerable changes in odour result without correspondingly important changes in reactivity, e.g. the change from pungent to anise on *para*-substitution of the phenyl mustard oils. Prins also concluded that if two changes were made in the constitution of a compound, then that which has the strongest influence on the most powerful osmophoric group will have the greatest influence on the odour.

Pirrone (*Rivista ital. essenze profumi*, **11,** 2-5, 1929) concluded that there are two osmophoric groups in odorous compounds, the stronger creating the type of odour and the weaker controlling the variety. The rest of the molecule also has an influence. Analogy of chemical constitution often carries similarity of odours, e.g. furan resembles benzene, and furylacrolein is like cinnamon, whilst nitrothiophen and nitrobenzene are very similar. Many compounds of similar odour have greatly different constitutions, e.g. tertiary trichlorobutyl alcohol and bornyl acetate, and again many compounds have a camphor odour. Other conclusions he reached were that the entrance of a methyl group in the aromatic series does not modify the fundamental odour, that lengthening of a side-chain changes the odour and that in esters, to increase the molecular weight of the alcoholic radicle is to decrease the odour, whilst unsaturated bonds in a molecule have a strong influence on odour, and their position is important.

von Hornbostel (*Arch. ges. Physiol.* (*Pflügers*), **227,** 517-38, 1931) made the following points :

(*a*) Odour intensity [1] increases with an increase in the number of carbon atoms in any homologous series.

(*b*) The introduction of a double or triple bond, or of a halogen carbonyl, nitro, or hydroxyl group or the closure of a ring decreases the intensity.

(*c*) The odour increases if several hydroxyl, carbonyl, nitro, phenyl or similar groups are present in adjacent positions in the molecule.

(*d*) the " cis " form is more intense in odour than the " trans."

Dyson (*Chemistry and Industry*, **57,** 647-51, 1938) has concluded that the connection between chemical constitution and odour is indirect and that large osmic differences often cannot be attributed to changes in chemical constitution, but are due to physical differences engendered by orientation of the constituent groups.

We have accumulated in this chapter a great deal of evidence bearing on the relation between chemical constitution and odour. After a precise examination of it I have selected the following general principles. They are open to criticism, but the subject is in an early

[1] *Helligkeit.* " Lightness " or " brightness " better than " intensity." Qualitative rather than quantitative.

stage of development, and if they are criticized and replaced by a better lot they will have served their purpose.

(1) Compounds of different constitutions may have similar odours, e.g. camphor, silicononyl alcohol, durene.
(2) Compounds of very similar constitution may have different odours. If, however, the constitutional differences are slight, odour differences are generally correspondingly slight.
(3) No element which occurs free in nature is odorous under normal conditions, but elementary arsenic is odorous if heated and vaporized.
(4) Seven of the elements are odorous, viz. fluorine, chlorine, bromine, iodine, phosphorus, arsenic, oxygen (as ozone).
(5) Polymerization reduces or destroys odour whether in elements, e.g. red phosphorus, or in compounds, e.g. glycols.
(6) The elements give only two kinds of smell—" halogen " and " garlic "—which are possibly fundamental or pure odours.
(7) Ability to function in a high state of valency is productive of odour. (The halogens are in Group 7, oxygen in Group 6, and phosphorus and arsenic in Group 5 of the Periodic Classification.)
(8) Electronegative or non-metallic character is allied closely with odorant properties. Elements at the bottom of the electrochemical series are odour-producing.
(9) Electropositive elements suppress odour formation. (Those in Groups 1 and 2 or at the top of the electrochemical series.)
(10) Sulphur, selenium and tellurium compounds often have vile smells whilst their oxygen analogues are odourless.
(11) Compounds of phosphorus, bismuth and arsenic often have garlicky odours.
(12) Unsaturation enhances odour but does not initiate it. (The paraffins are odorous.)
(13) In the paraffins, straight and branched-chain isomers have similar odours, and the position of the double bond (if any) is unimportant.
(14) In a homologous series the odour will rise to a maximum as we ascend the series and will then fall off owing to decreased volatility.
(15) Unsaturation often introduces an irritant note to the odour, particularly if close to a polar group, e.g. aliphatic aldehydes and acids.
(16) A tertiary carbon atom will frequently induce a camphoraceous odour.
(17) The osmophoric influence of the phenyl group is strong. It overcomes that of alkyl ether groups and also of the amino group.
(18) The introduction of a hydroxyl group frequently depresses or abolishes odour, e.g. aliphatic acids.

(19) Aromatic acids are usually odourless, whereas most aliphatic acids are odorous.

(20) Fully reduced aromatic bodies have odours similar to those of fatty substances, e.g. cyclohexane, hexahydrobenzoic acid.

(21) Fully reduced heterocyclic bodies also develop aliphatic odours, e.g. piperidine.

(22) Esters have fragrant fruity odours. This includes esters of weak inorganic acids such as boric.

(23) Strong odour is often found accompanied by volatility and chemical reactivity, e.g. aldehydes. Chemical reactivity and unsaturation run parallel to odour.

(24) Esters of diacids have good odours, but those of dihydric alcohols have weak odours.

(25) Ketones generally have pleasant odours.

(26) Whereas introduction of a hydroxyl group frequently destroys odour, the etherification of this group usually restores the odour.

(27) Lactones have fragrant ester-like odours.

(28) The alkyl halides have sweet smells, which become heavier in type as we pass from chlorine to bromine and to iodine. Two or three halogen atoms have an additive olfactory effect.

(29) When a halogen is already a substituent, a hydroxyl group behaves abnormally and increases the odour.

(30) The odour of amines is more ammoniacal when concentrated than when dilute, and the fishy odour is stronger in dilute than in concentrated solutions.

(31) Nitrogen compounds frequently have an "animal" odour. Compounds not containing nitrogen do not ordinarily have an "animal" odour.

(32) An oxygen linkage is frequently associated with a pleasant odour, e.g. esters, lactones, nitrates.

(33) Many nitriles have a bitter-almonds odour.

(34) Compounds in which an element functions at a valency lower than its maximum usually have offensive odours, e.g. hydrogen sulphide and the isonitriles.

(35) Many sulphur compounds, particularly where the sulphur is divalent, have offensive odours, e.g. mercaptans.

(36) Sulphur and nitrogen and oxygen atoms in a ring do not play their usual olfactory role. Their influence is subordinate to that of the ring, e.g. thiophen, furan.

(37) If a heterocyclic body is completely reduced, the sulphur or nitrogen or oxygen atoms regain their normal olfactory effect.

(38) Whereas unsaturation is often a contributory factor to odour, ring unsaturation appears to have a negative olfactory action.

(39) The main factor in determining odour is the architectural type of the molecule.

(40) The osmophoric groups play a part subordinate to that of the architectural style. In small molecules this part is greater than in large molecules.

(41) The olfactorily offensive and delicious are often closely related.

(42) Some substances change their odour on dilution, e.g. indole, amines.

(43) In ring compounds, the number of ring members often determines the odour :

5-6	members	give	bitter almonds and menthol odour.
6-9	,,	,,	transitional odour.
9-12	,,	,,	camphor or mint odours.
13	,,	,,	woody or cedar odours.
14-16	,,	,,	musk and peach odours.
17-18	,,	,,	civet odours.

More than 18 give faint or no odour.

The odour of compounds with rings from 9-20 members is largely independent of the substituent groups.

(44) For a musk odour in macrocyclic compounds the basic ring structure must be between 14 and 19 atoms, and at least one carbonyl or imine group is necessary. Musk odours are not confined to macrocyclic compounds.

(45) One heterocyclic atom increases the odour of macrocyclic compounds, two reduce it.

(46) In the ionones, the position of the double bond in the ring is unimportant, but unsaturation in the side-chain is essential for the violet odour.

(47) Arsenic compounds are usually garlicky or ill-smelling (cacodyl), but not if the arsenic is a heterocyclic member of a ring.

(48) In a mixed ether-ester compound, the ester group has a dominant olfactory effect.

(49) Branching of a chain usually enhances the odour.

(50) There is no relation between the odours of isomers with important structural differences.

(51) Structurally similar isomers usually have similar odours. As the difference in molecular structure or architectural style of isomers increases, so do odour differences.

(52) The position of a side-chain influences the odour. The nearer the side-chain to a polar group, the stronger the odour, e.g. α-substituted lactones have stronger odours than γ-substituted.

(53) Position isomerism in the benzene ring has a marked influence on odour, e.g. *o*-biphenylyl ethers are odorous, *para* are odourless.

(54) The 1 . 3 . 4 arrangement in the benzene ring usually leads to a pleasant odour, but not if the substituent groups are heavy.

(55) *Para*-substitution often introduces a soft anise note.

(56) *Meta*-substitution usually enhances the power and pungency of an odour.

(57) *Ortho*-substitution often gives a floral odour.

(58) With equal substituents the *para* influence overwhelms the *meta* (or *ortho*)—if both are present.

(59) Where methyl and chlorine occur as substituents in a benzene ring the latter has the greater influence.

(60) The odour of a substituted aromatic compound depends more on the position than on the nature of the substituent groups.

(61) Stereoisomers may have different odours. The differences are not usually very great.

(62) Finally, the general conclusion is that odour is determined by the architectural arrangement of the molecule. Osmophoric groups (*sic*) have a secondary influence, only in so far as they modify the general arrangement. The great difficulty is, of course, the subjective nature of odour classification. Once this difficulty is removed and it is possible to define exactly the quality of an odour, then logic and precision will reduce chaos to order, and the relation between odour and chemical constitution will be disclosed to us with mathematical exactness.

CHAPTER 10

TASTE AND CONSTITUTION

General

In the preceding chapter it was necessary to study odour in relation to the constitution, the latter being known. In the case of taste we have the advantage of being able to study constitution in relation to taste. The reason is that whilst odours are ill-defined and subjective in character, the tastes are few and well-defined. The first point we realize is that sapid substances are a different class altogether from odorants. The very substances which have the strongest tastes, such as polyhydric alcohols, sugars, amides, imides, salts and many mineral acids, are odourless.

The salt taste and the sour taste are associated with salts and acids respectively. They have been dealt with in Chapter 5, where it was shown that both anion and cation have an influence on the taste of salts, and that the sour taste is primarily due to hydrogen ions, but is modified by the solubility characteristics of the substances. Sweet and bitter tastes are not confined to such well-defined classes of substances as the salts and acids. In fact, sweet and bitter tastes are found in nearly every chemical class, a phenomenon common to smell and colour. In most cases there are slight differences in taste between sweet members of different classes. First, we will examine the kinds of compounds found in the salt, sour, sweet and bitter groups and then later investigate the influence on the taste of various groups into the molecule and the influence of structural differences.

Salty Compounds

We have seen in Chapter 5 that the salt taste is typical of such salts as sodium chloride, ammonium chloride, potassium chloride and so on, but that high molecular weight salts, such as potassium iodide and cæsium chloride, are bitter. As the molecular weight of the salt rises there is a gradual change from salty to bitter taste. It was also shown that the salt taste was due mainly to the ions and that both anions and cations played a part, otherwise all chlorides or all sodium salts would taste the same, which is not the case. The relation between salt taste and chemical construction is therefore simple. An ionized salt of low molecular weight is necessary and usually gives a salty taste. Exceptions are the salts of beryllium, which are sweet, as are also some salts of lead. Salts of magnesium and ammonium are usually bitter.

Frequently the salty taste is associated with another taste, partic-

ularly in the case of salts of organic acids. The following examples are taken from Cohn's " Die Organischen Geschmacksstoffe " :

Salty-bitter. Ammonium chloride, cæsium halides, rubidium halides, barium chloride, potassium nitrate, sodium and potassium sulphates, potassium tartrate.

Salty. Ammonium bicarbonate, rubidium fluoride, lithium chloride.

Salty and astringent. Zinc chloride.

Salty and alkaline. Potassium bicarbonate, potassium bromide.

Salty then bitter. Tetramethyl antimonium iodide.

Salty-metallic. Mercuric formate.

Whilst the salt taste is often associated with the bitter and sour tastes, it is not often found associated with a sweet taste, although lithium acetate is described as sweetish, then salty.

Sour Compounds

As we saw in Chapter 5 the sour taste is a property common to acids and depends on the presence of hydrogen ions, which are formed when acids ionize in water. Whilst no exact relation between the hydrogen-ion concentration and the degree of sourness could be found, there was certainly a parallelism between the two. Stronger acids had more sour tastes than weaker ones. As some acids, particularly organic, had greater solvent properties in the lipoid tissues these acids had a more sour taste than appeared to be warranted by their hydrogen-ion concentration. Nevertheless the relation between the sour taste and chemical constitution is simple. It depends on the presence of free hydrogen ions, and that in turn is a common feature of acids. The sour taste is also often associated with another taste, and the following are a few of the many examples given by Cohn :

Sweet-sourish. Ammonia alum.

Sour. Acids, potassium dihydrogen phosphate, KH_2PO_4, and other acid salts.

Sourish. Bromacetyl salicylic acid.

Sweet and sour. Salicylic acid, methyl aspartic acid.

Sourish-sweet. *m*-aminobenzoic acid.

Sour and bitter. Citraconic acid, potassium hydrogen oxalate, protocatechuic acid.

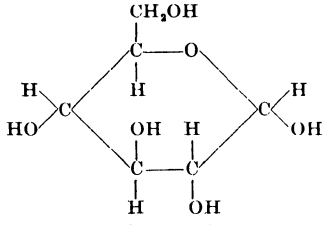
Sour then bitter. Camphoric acid, 2 : 4 : 6 pyridine tricarboxylic acid.

It will be noted that even in these compounds of sour mixed with other tastes, the acid character prevails. Not all acids are sour though, α-amino acids which chemically are nearly neutral, are often sweet.

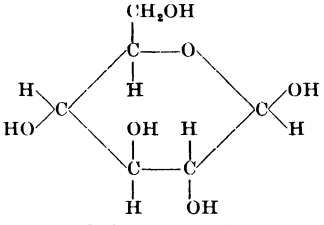
Sweet Compounds

The sweet taste is found in most chemical classes. Amongst the inorganic compounds we have the formate, acetate, propionate and isovalerianate of lead as well as the beryllium salts. In the organic

series the dihydric alcohols and sugars, typical of which are the two glucoses

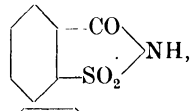


α-glucose (cis)



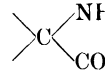
β-glucose (trans).

which are equally sweet, both 74 per cent. of the sweetness of sucrose. Of the synthetics,

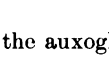


and dulcin, C_2H_5O—  —$NHCONH_2$,

are the best known. Erythritan and polygalitol, which are the 1 : 4 and 1 : 5 anhydrides of erythritol and mannitol, respectively, also possess a sweet taste, although the former has a bitter taste in high concentrations and the latter an astringency in high dilution (Carr, Beck and Krantz, *J. Am. Chem. Soc.*, **58**, 1394-5, 1936).

The α-amino acids, as noted by Fischer, are sweet, although leucine, $(CH_3)_2CH \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, which occurs in animal fluids in the pancreas, spleen, and glands, is only faintly sweet. These α-amino acids all contain Cohn's "dulcigen" group  , Cohn, in fact, introduced the idea of sapophoric groups, and was followed by Oertly and Myers whose theory required the presence of a glucophore and an auxoglue (Chapter 5), e.g. α-aminobutyric acid,

$$CH_3 \cdot CH_2 \cdot CHNH_2 \cdot COOH,$$

contains the glucophore, —  , and the auxogluc, C_2H_5, and is sweet, whereas aspartic acid, $COOH\ CH_2 \cdot CHNH_2 \cdot COOH$, contains the same glucophore but has no auxogluc ; instead, the glucophore is attached to an acid radicle, $COOH\ CH_2$—, and the acid tastes sour. The sweet taste is often associated with the bitter taste, and less frequently with the salt and sour tastes. It is particularly noteworthy that as we ascend a homologous series the taste will change gradually from sweet to bitter. Some of the sweet and sweet-mixed taste substances listed by Cohn are given below :

Sweet. Glycol, glycerine, glycine, sugar, phloroglucinol, saccharin, dulcin.

Sweetish. *r*-dimethyl tartrate.
Tasteless then sweet. Sodium naphthionate.
Sweet and bitter. Glyceraldehyde, *p*-chlorsaccharin, *d*-valin.
Sweet then bitter. Urotropin, aloin, *p*-methylsaccharin, β-amino-isovalerianic acid.
Sweet then disagreeably bitter. *m*-chlorphenyl alanin.
Sweetish and bitter. Guaiacol ester of isovalerianic acid.
Sweetish then bitter. Magnesium benzoate, butyramide.
Sweet then bitterish. Methyl glyceraldehyde.
Sweetish then bitterish. Ethyl butyrate.

Bitter Compounds

We have already seen that the bitter taste is common to many classes of compounds. The most bitter substances of all are the alkaloids, brucine and strychnine. Nitro-compounds, such as picric acid, are often bitter, especially if there are three or sometimes two nitro groups present. In the inorganic series, the magnesium salts are bitter, and the heavy salts containing cæsium, rubidium as cation, or iodide as anion, are also bitter. The wide variety of bitter compounds may be seen from the following examples taken from Cohn :

Bitter. Picric acid, phenyl urea, glucose triacetate, strychnine.
Bitter then sweet. *o*-benzoyl benzoic acid, *p*-aminoazobenzene sulphonic acid, *l*-leucyl-*d*-tryptophan, phenolphthalein, sodium-α-naphthoyl *o*-benzoate.
Bitter and sweetish. Tetrachlorethyl ether, 2 : 3-dichlorhexan.
Bitterish and sweet. Hexenylglycerin.
Bitterish then sweetish. Sodium ethyl sulphonate.
Bittersweet, pungent. Nitrostyrol.

Alkyl Groups

The influence of the entry of an alkyl group on the taste of a substance is often readily seen. It may simply alter the taste slightly, as in the case when we go from one to the next member of a homologous series, or it may cause a sudden change in, or even abolish, the taste.

The alkylation of the amide or amine group frequently produces a sweet taste.

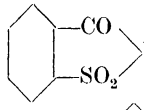
Urea, $CO(NH_2)_2$, is bitter, but *a*-dimethylurea, $CO(NH_2)(N(CH_3)_2)$, and *a*-diethylurea, $CO(NH_2)(N(C_2H_5)_2)$, are both sweet.

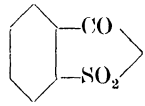
γ-aminobutyric acid, $NH_2CH_2(CH_2)_2COOH$, is not sweet, but γ-methyl-aminobutyric acid, $CH_3NH \cdot CH_2(CH_2)_2COOH$, is sweetish ; formamide, $H \cdot CO \cdot NH_2$, is bitter, but methylformamide, $H \cdot CO \cdot NHCH_3$, is sweetish.

de Graaf (*Diss.*, Leiden, 1930), found that malonamide was tasteless, but that if an alkyl group was introduced into one of the amino groups, a sweet substance resulted, in agreement with Cohn's rule.

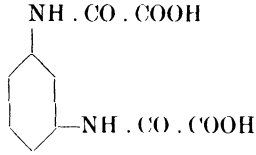
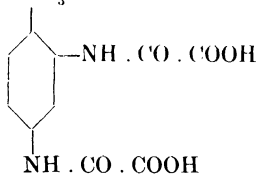
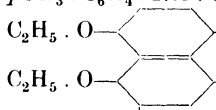
Similarly, Tierie (*Rec. trav. chim.*, **52**, 357-65, 1933) found that 5-methyl semi-oxamazide was sweeter than semi-oxamazide itself.

Alkylation of an acid imide group abolishes the sweet taste, e.g. :

Saccharin,  , is sweet, but

N-methylsaccharin,  , is tasteless.

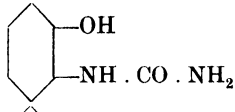
Entry of an alkyl group in the carbon chain frequently changes the taste. Owing to the complicated effects of isomerism, no general rule can be formulated. Insipid and sweet bodies may become bitter, or bitter and tasteless substances may become sweet.

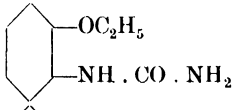
Benzonitrile	$C_6H_5 . CN$	is pungent, but
p-tolunitrile	$p\text{-}CH_3 . C_6H_4 . CN$	is sweet ;
m-phenylene dioxamic acid,		is tasteless, but
m-tolyl dioxamic acid,		is sweet ;
Phenyl urea	$C_6H_5NH . CO . NH_2$,	is bitter, but
p-tolyl urea	$pCH_3 . C_6H_4 . NH . CO . NH_2$	is sweet ;
Sucrol	$C_2H_5 . O-$  $-NH . CO . NH_2$	is sweet, but
2-ethoxytolyl 5-carbamide	$C_2H_5 . O-$ $-NH . CO . NH_2$	is not sweet.

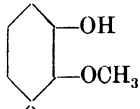
Alkylation of a hydroxyl group converting it into an ether group frequently destroys the sweet taste due to the hydroxyl groups. This is just the opposite effect from what we found in considering odour, where the introduction of a hydroxyl group usually destroyed odour but the etherification of the hydroxyl group restored it.

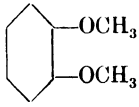
Glycol, $CH_2OH . CH_2OH$, is sweet, but

Glycol monomethyl ether is not sweet ;

o-hydroxyphenyl urea  is sweet, but

o-ethoxyphenyl urea  is tasteless ;

Guaiacol  is sweet, but

Veratrol  is not sweet.

Hence when the entering alkyl group is attached to a nitrogen atom as in amides and amines it frequently introduces a sweet taste, but not when it replaces the hydrogen of an imide group. When the alkyl group is attached to a carbon atom the result is impossible to foresee, anything may happen. When the alkyl group is attached to an oxygen atom, as when it replaces the hydrogen atom in a hydroxyl group, then there is usually a reduction in the sweet taste. This emphasizes the observation that a hydroxyl group is olfactory-negative but gustatory-positive.

The Phenyl Group

We remember that the osmophoric influence of the benzene nucleus was very strong and that it overcame the influence of many of the groups introduced into it. It imparted a bitter-almonds odour to many substances, and the odours of aromatic substances are collectively different from those of the fatty compounds. We might therefore be prepared for a sudden change in taste due to the introduction of the phenyl group. In fact, if a phenyl group enters a molecule by replacement of a hydrogen or alkyl group a sudden change is started to bitter or tastelessness. The phenyl group seems to have an effect opposite to that of alkyl groups, and unlike the latter it has the same effect irrespective of whether it is joined to carbon, oxygen or nitrogen. Examples are

Glycol	$CH_2OH . CH_2OH$	is sweet, but
Phenylglycol	$C_6H_5CHOH . CH_2OH$	is bitter.
Glycine	$CH_2NH_2 . COOH$	is sweet, but
Phenylglycine	$C_6H_5CHNH_2 . COOH$	is tasteless.
Glycerin	$CH_2OH . CHOH . CH_2OH$	is sweet, but
Phenoxypropanediol	$C_6H_5OCH_2 . CHOH . CH_2OH$	is bitter, and
Phenylglycerin	$C_6H_5CHOH . CHOH . CH_2OH$	is also bitter.

Methylformamide	$H . CO . NHCH_3$	is sweet, but
Formanilide	$H . CO . NHC_6H_5$	is bitter.
a-diethylurea	$(C_2H_5)_2N . CO . NH_2$	is sweet, but
Diethyldiphenylurea	$(C_2H_5)_2N . CO . N(C_6H_5)_2$	is bitter.

Often when tastelessness is the result of introducing a phenyl group, it results from the insolubility in water of the aromatic compound, and if an alcoholic solution is made of the water-insoluble compound it is found to have a bitter taste. It must be remembered, too, that the introduction of a phenyl group enormously increases the molecular weight of most compounds, and an increase in weight, as we have seen with the salts, is often productive of a bitter taste.

The Hydroxyl Group

The hydroxyl group is often responsible for taste. The first two of Oertly and Myers' six glucophores, viz. :

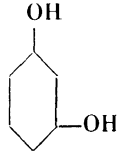
$$—CO—CHOH—(H) \qquad \text{and} \qquad CH_2OH . CHOH—$$

contained hydroxyl groups. Also three of their nine auxoglucs, viz. :

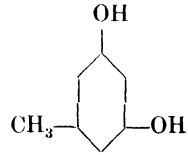
$$CH_2OH—, \quad CH_3 . CHOH— \quad \text{and} \quad CH_2OH . CH_2—$$

embraced the hydroxyl group. Assuming that the six glucophores are equally distributed in sweet compounds, and that so are the nine auxoglucs, the chances on this theory of any sweet substance containing a hydroxyl group are $\frac{30}{54}$ or, colloquially, 5 to 4 on. The glycols, glycerines and sugars spring to mind as groups where the sweet taste is intimately connected with the presence of hydroxyl groups. Other substances which are sweet and hydroxylic are

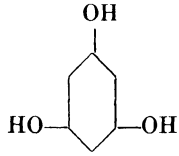
Resorcinol



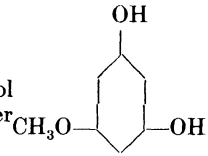
Orcinol



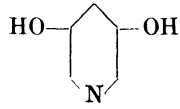
Phloroglucinol



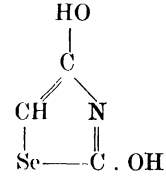
Phloroglucinol methyl ether



Dihydroxy-pyridine



and Dioxyselenazole



The monohydric alcohols also have sweet tastes. That of ethyl alcohol is rather feebly weak. Some of the unsaturated alcohols were

investigated by Murahashi (*Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **34,** 155-72, 1938, and *Chemical Abstracts*, **32,** 3756, 1938). He found

1-octen-3-ol $CH_2:CH-CHOH-CH_3(CH_2)_4$

2-octen-2-ol $CH_3 . C(OH) : CH . (CH_2)_4CH_3$ and

3-methyl-2-hepten-4-ol $CH_3 . CH : C(CH_3) . CH(OH) . (CH_2)_2 . CH_3$

all had a sweet taste, but that

6-methyl 1-hepten-3 ol $CH_2:CH-CHOH-CH_3-CH . (CH_2)_2$ (CH_3 branch)

had no sweet taste.

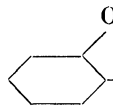
He concluded that sweetness is associated with the structure R . CH(OH) . C : CH—, where R is a normal aliphatic chain. The effect of chain branching in depriving the alcohol of its sweet taste is remarkable.

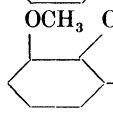
The Alkoxy Group

We have already seen that in the case of odour the change from hydroxyl to methoxy enhances the effect, but that in the case of taste, the reverse effect obtains. When, however, the methoxy group is considered *per se* and not in relation to the hydroxyl group, it frequently is found to have a tendency to turn tasteless and bitter substances to sweet, particularly in the aromatic series. Examples are

Benzonitrile	$C_6H_5 . CN$	not sweet, but
Anisonitrile	p-$CH_3O . C_6H_4 . CN$	sweet.
Phenyl urea	$C_6H_5NH . CO . NH_2$	bitter, but
p-methoxyphenyl urea	p-$CH_3O . C_6H_4 . NH . CO . NH_2$	sweet.
Phenol	C_6H_5OH	only sweetish, but
Guaiacol	o-$CH_3O . C_6H_4 . OH$	sweet.

There are exceptions to the rule that the influence of the methoxy group is to make the taste of aromatic substances sweeter. Such are

Salicylic acid  is sweet, but

Guaiacol carboxylic acid  is bitter, and

α-naphthoylbenzoic acid is bitter then sweet, but
α-methoxynaphthoylbenzoic acid is just bitter.

Regarding the action of the ethoxy group there is no certainty. It is true that dulcin or *p*-ethoxyphenyl urea,

$$p\text{-}C_2H_5O \cdot C_6H_4 \cdot NH \cdot CO \cdot NH_2,$$

is sweeter than its methoxy analogue, but on the other hand, whereas

Anisonitrile	$p\text{-}CH_3O \cdot C_6H_4 \cdot CN$	is sweet,
p-ethoxybenzonitrile	$p\text{-}C_2H_5O \cdot C_6H_4 \cdot CN$	has no sweet taste.

Saccharin is sweet but *p*-ethoxysaccharin is not sweet.

Esters

Esters and lactones have attractive floral and fruity odours. What kind of tastes do they have ? Those, such as ethyl and propyl butyrates, which have fruity odours have sweet tastes. The introduction of a halogen moves the taste towards bitter, for chlorethyl butyrate, $C_3H_7COO\ C_2H_4\ Cl$, has a sharp and bitter taste.

Methyl isovalerianate, $CH_3O \cdot CO \cdot CH_2 \cdot CH(CH_3)_2$, has a taste reminiscent of bananas but, in addition, slightly pungent.

Taste falls off as molecular weight increases, e.g. octyl isovalerianate, $C_8H_{17}O \cdot CO \cdot CH_2 \cdot CH(CH_3)_2$, has only a very feeble taste.

Unsaturation often brings pungency, e.g. although ethyl nitrite, $C_2H_5O\ NO$, is sweetish, allyl nitrite, $CH_2 : CH \cdot CH_2 \cdot O\ NO$, is bitter and unpleasantly pungent.

Esters of hydrochloric acid, i.e. the chlorparaffins, are usually sweet, and so are the esters of xanthic acid. Most esters of resorcinol and orcinol are also sweet. Esters of aromatic acids, of sulphonic acids, the lactones and the urethanes are usually bitter. Esters of polybasic acids, particularly derivatives of malonic ester, taste bitter. Practically any relation may exist between the tastes of the alcohol and the ester from it. For example :

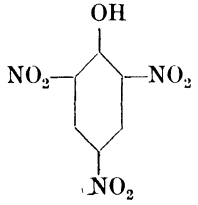
Ester.	Taste of Ester.	Taste of Alcohol.
Ethyl nitrite	Sweet	Indifferent (slightly sweet).
Butyl nitrate	,,	Indifferent.
Ethyl borate	Bitter	Indifferent (slightly sweet).
Diethyl adipate	,,	,, ,,
Resorcinol diacetate	Sweet	Sweet.
Hexamethylene glycol diacetate	Bitter	Bitter.
Diphenyl tartrate	Indifferent	Sweetish
Benzoyl guaiacol	,,	Sweet.
Dibenzoyl salicin	,,	Bitter.
Glucose triacetate	Bitter	Sweet.
2-chlorethyl benzoate	,,	,,

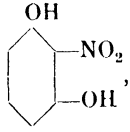
Many of the esters of inorganic acids are sweet, and many esters, containing powerful sweet influences in the shape of resorcinol, etc.,

groups, are sweet, but on the whole most of the esters of organic acids are bitter. The usual taste movement on esterification is away from sweet and towards bitter.

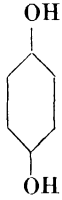
The Nitro Group

One nitro group may confer a sweet taste, e.g. nitrobenzene is sweet, but, in general, a nitro group weakens the sweet taste, gives a bitter after-taste to it or completely substitutes it by a bitter taste. Even where one nitro group gives a sweet taste, the introduction of another will bring bitterness, e.g. *m*-dinitrobenzene is bitter. Three nitro groups invariably cause a bitter taste as in picric acid

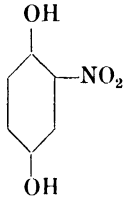


Whilst resorcinol is sweet, 2-nitro resorcinol, 

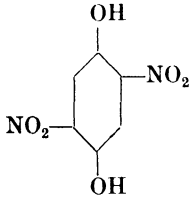
, is only faintly sweet. Similarly,

hydroquinone 

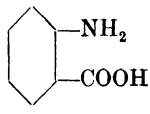
is sweet, but

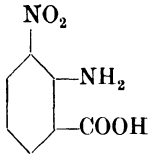
nitrohydroquinone 

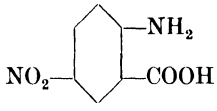
is only faintly sweet, and

2,5-dinitrohydroquinone 

is not sweet.

Anthranilic acid  is sweet, but neither

3-nitro-2-aminobenzoic acid  nor

5-nitro-2-aminobenzoic acid  are so.

Phenylalanin $C_6H_5 . CH_2 . CH(NH_2) . COOH$ is sweet.
p-nitrophenylalanin $p\text{-}NO_2 . C_6H_4 . CH_2 . CH(NH_2) . COOH$ is bitter-sweet.

It is a general rule that substances with three or more nitro groups taste bitter, and that substances with two nitro groups, with few exceptions, taste bitter.

The nitroparaffins, such as nitroethane, $C_2H_5NO_2$, nitropentane, $C_5H_{11}NO_2$, etc., taste sweet. Unsaturated nitro bodies, such as nitro-allyl, $CH_2 : CH . CH_2NO_2$, are pungent and bitter. The chlornitro-paraffins, such as 1, 1-chlornitroethane, $CH_3—CHCl . NO_2$, and 1-2-chlornitroethane, $CH_2Cl . CH_2NO_2$, are also pungent. Branching of the chain also alters the taste, e.g. tert. nitrohexane,

$$(C_2H_5)_2 . C(NO_2) . CH_3,$$

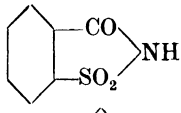
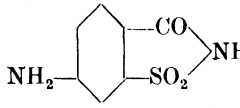
is caustic and burning, whilst its straight chain isomer, *n*-nitrohexane, is sweetish. The dinitroparaffins, such as 1, 1 dinitroethane and 1, 1 dinitropropane, are not bitter, but have peculiar characteristic sweet tastes.

The Amino Group

The entry of an amino group into a tasteless or bitter substance frequently invests that substance with a sweet taste. If the substance is already sweet before the entry of the amino group, then the sweet taste persists. The following examples may be noted :

Benzonitrile	C_6H_5CN	not sweet, but
m-aminobenzonitrile	$m\text{-}NH_2C_6H_4CN$	sweet.
Sulfonal	$(CH_3)_2 . C(SO_2—C_2H_5)_2$	bitter, but
Aminosulfonal chlorhydrate	$HCl . NH_2CH_2 . C(CH_3)(SO_2 . C_2H_5)_2$	bitter-sweet.

The following are instances where the sweet taste already present persists on the entry of the amino group :

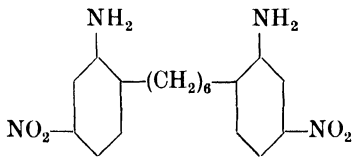
Saccharin		sweet, and
p-aminosaccharin		also sweet.
Sucrol	$NH_2 . CO . NH-C_6H_4-OC_2H_5$	sweet, and
Aminosucrol	$NH_2 . CO . NH-C_6H_3(NH_2)-OC_2H_5$	also sweet.
Nitrobenzene	$C_6H_5NO_2$	sweet, and
m-nitraniline	$m\text{-}NH_2 . C_6H_4NO_2$	also sweet.

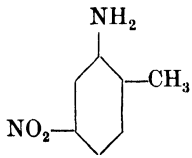
The amino acids furnish a good example of the sweet influence of the amino group, for whilst acetic, propionic, etc., acids are intensely sour the corresponding α-amino acids, glycine, NH_2CH_2COOH, and alanine, $CH_3 . CH(NH_2) . COOH$, are sweet. In the β- and γ-amino acids the sweet taste is largely lost. β-alanin, $NH_2 . C_2H_4 . COOH$, is very slightly sweet or nearly tasteless as is also β-amino isovalerianic acid, $(CH_3)_2C(NH_2)CH_2 . COOH$. γ-aminobutyric acid is not sweet,

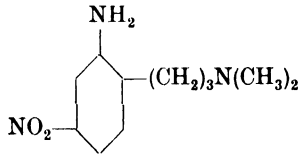
$$NH_2(CH_2)_3COOH.$$

The free bases, such as methylamine, heptylamine, etc., are bitter as of course are the alkaloids. In the case of the free bases branching of the chain usually introduces a pungent note.

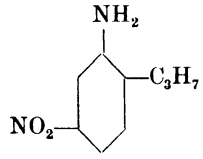
The taste variation in some nitroaromatic amines was investigated by v. Braun and Rawicz (*Ber.*, **49,** 799-809, 1916). They found the following :

 Tasteless.

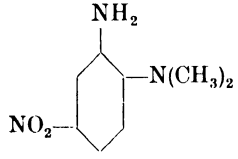
 Sweet.



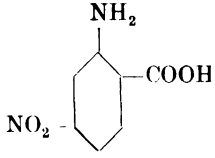
Very bitter.



Sweet.



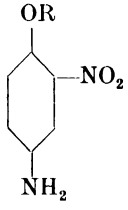
Tasteless.



Sweet.

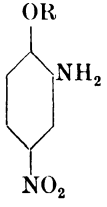
Another series of aromatic nitroamines, studied more recently by Blanksma and van der Weyden (*Rec. trav. chim.*, **59,** 629-32, 1940), has given interesting results. In the following compounds which they made R is an alkyl radicle, methyl, ethyl or propyl.

The 2-nitro-4 aminophenyl alkyl ethers,



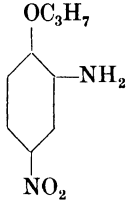
were all tasteless,

but the 4-nitro-2-aminophenyl alkyl ethers,



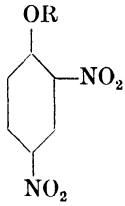
were sweet,

and in this series where R = propyl, the compound



4-nitro-2-aminophenyl propyl ether proved to be 3,300 times sweeter than 1 per cent. sucrose, about six times sweeter than saccharin, and to date the sweetest known substance. If, however, the NH_2 group of this compound is acetylated, the sweetness is lost.

The corresponding dinitrophenyl alkyl ethers



were all bitter.

It appears that the sweet taste develops in a molecule when the amino group neutralizes the acidity of the molecule. If the amino groups are in such excess that the product is strongly basic then bitterness is the outcome.

Amides

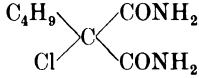
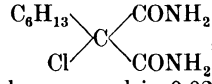
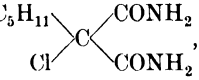
Just as in α-amino acids where the basic NH_2 group neutralizes by its proximity, the acid —COOH group and a sweet taste results, so in amide formation the carboxylic group is neutralized by chemical combination with an amino group and once again a sweet taste often results, as will be seen. At the same time some of the simplest amides are bitter, e.g. :

formamide, H . CO NH_2, and acetamide, $CH_3CO\ NH_2$, are both bitter, but methylformamide, H . CO NH CH_3, is sweet, as are also *n*-butyramide, C_3H_7 . CO NH_2, which, however, has a bitter after-taste, and glycollic acid amide, CH_2OH . CO NH_2.

The sweet influence of the hydroxyl group or of the butyl chain tips the balance to sweet. The opposite effect is seen in the case of nitrocyanacetamide,  CH . CO NH_2, which is sour, due to the dominant influence of the acid groups.

Like acetamide, diacetamide, $NH(CO\ .\ CH_3)_2$, is bitter, and triacetamide, $N(COCH_3)_3$, has an aromatic taste. Of the dibasic acids the amides, such as oxamide, $CONH_2\ .\ CONH_2$, and adipamide, $CONH_2\ .\ (CH_2)_4\ .\ CONH_2$, are tasteless, but the half amides, oxamic acid, $CONH_2\ .\ COOH$, and adipamic acid, $CONH_2\ .\ (CH_2)_4\ .\ COOH$, are very sour.

The alkyl chlormalonamides were investigated by Dox and Houston (*J. Am. Chem. Soc.*, **46**, 1278-81, 1924). The derivatives made had the general formula  . When R was methyl, ethyl and

propyl, the substances had decidedly sweet tastes. The butyl derivative  was bitter-sweet, and in the branched chain derivatives where R was isopropyl, isobutyl or isoamyl, bitterness prevailed and masked the sweetness. The maximum sweetness was reached with the hexyl derivative,  , which is one of the sweetest aliphatic substances known, and in 0·02 per cent. solution is as sweet as 6 per cent. sugar. Later Dox and Jones (*J. Am. Chem. Soc.*, **50,** 2033-6, 1928) reported that amyl chloromalonamide,  , had an intensely sweet taste and that a 0·005 per cent. aqueous solution was as sweet as 2 per cent. sugar. The isoamyl derivative was, however, bitter.

Hydrazides

The hydrazides are similar to the amides and to the ureas in structure.

$R . CO . NH_2$	$R . CO . NH . NH_2$	$RNH . CO . NH_2$
Amide.	Hydrazide.	Urea.

de Graaf (*Diss.*, Leiden, 1930), found that the hydrazides of malonic and of alkylmalonic acids (but not of oxalic acid) had intensely sweet tastes. Methyl, ethyl, propyl and isopropyl malonic dihydrazides, e.g. $C_3H_7 . CH(CONH . NH_2)_2$ were sweet, but butyl and benzyl malonic hydrazides, e.g. $C_6H_5CH_2 . CH(CO . NH . NH_2)_2$, were bitter. The presence of a free hydrazide group is necessary for the sweet taste, which is much diminished on acetylation, although the diacetyl derivative of carbodihydrazide, $CO(NH . NH . CO . CH_3)_2$ was sweet, and in fact was the only sweet acetyl derivative found. If the hydrazides were condensed with aldehydes or ketones the product was bitter :



It is a general rule (Cohn) that the groups



impart a bitter or burning taste.

It was found that the introduction of a third hydrazine group into malonic dihydrazide gave a tasteless substance,

$$NH_2NH \cdot CH \cdot (CO \cdot NH \cdot NH_2)_2.$$

The hydroxyl group opposes the hydrazide group thus :

Succinic dihydrazide	$\begin{matrix} CH_2 \cdot CO \cdot NH \cdot NH_2 \\ \vert \\ CH_2 \cdot CO \cdot NH \cdot NH_2 \end{matrix}$	Very sweet.
Malic dihydrazide	$\begin{matrix} CHOH \cdot CO \cdot NH \cdot NH_2 \\ \vert \\ CH_2 \cdot CO \cdot NH \cdot NH_2 \end{matrix}$	Sweet.
Tartaric dihydrazide	$\begin{matrix} CHOH \cdot CO \cdot NH \cdot NH_2 \\ \vert \\ CHOH \cdot CO \cdot NH \cdot NH_2 \end{matrix}$	Slightly sweet.
Mucic dihydrazide	$\begin{matrix} CHOH \cdot CHOH \cdot CO \cdot NH \cdot NH_2 \\ \vert \\ CHOH \cdot CHOH \cdot CO \cdot NH \cdot NH_2 \end{matrix}$	Not sweet.

In connection with the condensation of a dihydrazide with an aldehyde or ketone to give a bitter substance Blanksma and de Graaf (*Rec. trav. chim.*, **57**, 3-12, 1938) associate the group —CO . NH . N : C< with a bitter taste in all substances which are appreciably soluble in water.

Blanksma and Bakels (*Rec. trav. chim.*, **58**, 497-513, 1939) show that the presence of one —CO . NH . NH_2 group is insufficient to cause a sweet taste and that two located near to each other are necessary. Some dihydrazides do not have the sweet taste. The introduction of a phenyl group into the molecule favours a bitter taste.

Ureas

The ureas are an important group from the taste aspect. Dulcin is a substituted urea.

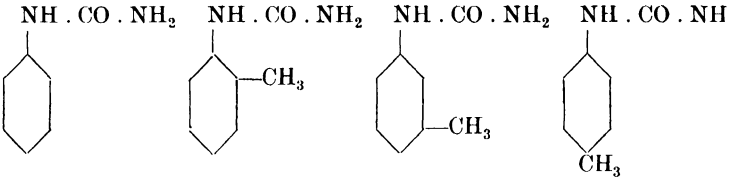
Urea itself, the diamide of carbonic acid, $CO\langle^{NH_2}_{NH_2}$, is bitter and cooling. Asymmetry seems to favour a sweet taste, for whilst

s-dimethylurea $CO\langle^{NHCH_3}_{NHCH_3}$ is rather bitter,

a-dimethylurea $CO\langle^{NH_2}_{N(CH_3)_2}$ is very sweet,

whilst the corresponding *a*-diethylurea is also sweet. Complete substitution with the isoamyl group gives tetra isoamylurea, $(C_5H_{11})_2N \cdot CO \cdot N(C_5H_{11})_2$, which is bitter.

In the aromatic series phenyl urea, $C_6H_5 \cdot NH \cdot CO \cdot NH_2$, is bitter, but the tolyl ureas show surprising differences in their tastes.



Phenyl urea, bitter. | *o*-tolyl urea, tasteless. | *m*-tolyl urea, bitter. | *p*-tolyl urea, sweetish.

The alkoxy phenyl ureas to which class dulcin, *p*-ethoxyphenyl urea, belongs are very sweet.

Some α-aryl β-alkyl ureas were made by Boehmer (*Rec. trav. chim.*, **55,** 379-91, 1936). They were of the type α-phenyl β-ethyl urea, C_6H_5NH . CO . NH C_2H_5, and when sufficiently soluble to give a taste proved, as expected, to be bitter.

Nitrogen Compounds

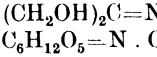
Those that are basic are bitter, the acid ones are sour or bitter, but the neutral nitrogen compounds are often sweet, e.g. α-amino acids, hydrazides and ureas.

The oximes also are sweet, e.g.

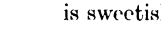
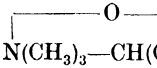
dihydroxyaceton-oxime $(CH_2OH)_2C{=}N\,OH$ and
glucose oxime $C_6H_{12}O_5{=}N$. OH.

Betaines are bitter as a class although there are exceptions.

The simplest betaine  is sweetish, as is

α-homobetain  but

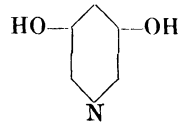
trimethyl-α-aminobutyrobetain is bitter.

Kuhn and Giral (*Z. physiol. Chem.*, **231,** 208-9, 1935) showed that the betaine of ω-aminopentadecylic acid,  , is bitter but that the homologous betaine of ω-aminoheptadecylic acid was tasteless,  . Both the free amino acids are tasteless, but their methyl esters are bitter and tasteless, respectively. As with odour, taste disappears when a homologous series is ascended.

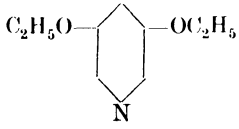
The quaternary ammonium compounds, such as methyl triethyl ammonium hydroxide, $(C_2H_5)_3CH_3$. N . OH, are bitter. In fact, alkalinity and the bitter taste seem to go hand in hand.

Of the heterocyclic compounds pyridine and its derivatives are generally burning and bitter, although the sweet influence of the

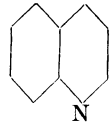
hydroxyl group is seen in 3 . 5 dihydroxypyridine,



which is sweet. The corresponding diethoxy compound,



is not sweet, but burning. Quinoline,



and its derivatives are also bitter.

The carbylamines where the carbon is divalent, such as methyl carbylamine, CH_3NC, and ethyl carbylamine, C_2H_5NC, are very bitter.

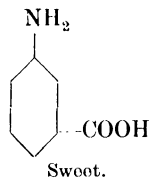
The $—NH_2$ group functions like the —OH group in introducing a sweet taste, so that amides, amino acids, ureas and hydrazides are generally sweet.

Basic nitrogen compounds are always bitter. Other nitrogen compounds are frequently bitter.

The Halogens

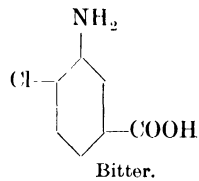
In the aromatic series the influence of the halogen is to make the substance bitter. A sweet substance may be converted to bitter. Iodine has the greatest influence and fluorine the least. Once again we note the parallelism of the bitter taste and high molecular weight. The bitter influence of the halogen may be seen in the following compounds :

m-aminobenzoic acid



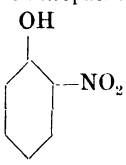
Sweet.

4-chlor *m*-aminobenzoic acid



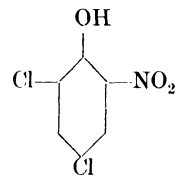
Bitter.

o-nitrophenol



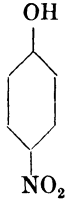
Sweet.

4-6 dichlor 2-nitrophenol



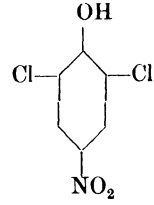
Bitter.

p-nitrophenol



Sweet.

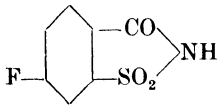
2-6 dichlor 4-nitrophenol



Bitter.

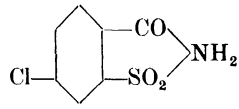
In the saccharin group the influence of the halogen is very clearly seen. The substituted saccharins have the following tastes :

p-fluorsaccharin



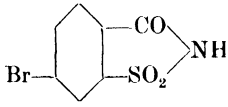
Sweet, bitter after-taste.

p-chlorsaccharin



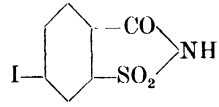
Sweet and bitter, bitter rather more marked.

p-bromsaccharin



Very sweet, then extremely bitter.

p-iodosaccharin



Slightly bitter, no sweet taste whatever.

The increasing anti-sweet and bitter influence with increasing molecular weight is clearly seen in the above examples.

In the aliphatic series, the heavily halogenated compounds are often sweet. The sweet taste of chloroform is well known, and similar compounds are

1, 1, 2, 2 tetrachlorethane	$CHCl_2 . CHCl_2$	Sweet.
1, 1, 2, 3 tetrachlorpropane	$CHCl_2 . CHCl . CH_2Cl$	,,
pentachlorethane	$CCl_3 . CHCl_2$	,,
1, 1, 2, 2 tetrachlorethyl ether	$CHCl_2 . O . CHCl_2$	,,

Chloral, chloral hydrate and other chloral derivatives are bitter.

Hence there are two quite different effects from the halogen substitution.

Substitution in the aliphatic hydrocarbons usually gives a sweet taste, but in the aromatic series it gives a bitter taste. The degree of bittering is greatest with iodine and least with fluorine.

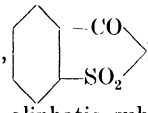
The influence of the halogen substituents in acid amides was investigated by Giacalone and Collesano (*Gazz. chim. ital.*, **65**, 129-31, 1935). They made the amides of different halogenated acids, noted

the taste, the solubility in water and the *p*H value of 1 per cent. aqueous solutions. They arrived at the following results :

Substance.	Taste.	Solubility in Water.	*p*H of 1 per cent. Aqueous Solution.
Acetamide $CH_3 . CO . NH_2$	Cool with slight bitter after effect	Very	6·9
Monochloracetamide $CH_2Cl . CO . NH_2$	Almost tasteless	10 per cent.	7·2
Dichloracetamide $CHCl_2 . CO . NH_2$	Sweetish	7 ,,	7·3
Trichloracetamide $CCl_3 . CO . NH_2$	Sweet	1·3 ,,	7·2
Monobromacetamide $CH_2Br . CO . NH_2$	Burning	16 ,,	6·7
Dibromacetamide $CHBr_2 . CO . NH_2$	Slightly sweet with astringent after taste	1·9 ,,	7·2
Tribromacetamide $CBr_3 . CO . NH_2$	At first sweet, then pungent	1·6 ,,	7·1
Monoiodoacetamide $CH_2I . CO . NH_2$	Pungent	—	7·0

Those amides where the *p*H value was on the acid side had a burning pungent taste. The *p*H value reached a maximum for the dihalogenated compounds. Increase in the number of chlorines or bromines, i.e. increase in the negative character of the molecule increases the sweetness.

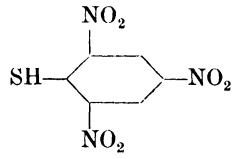
Sulphur Compounds

Sulphur compounds usually have offensive odours unless either the sulphur atom is fully oxidized or it is a member of a heterocyclic ring, when its influence is subordinate to, or even overwhelmed by that of the ring. What then is the taste of these compounds ? First comes to mind the case of saccharin,  , which has sulphur as a heterocyclic ring atom. In aliphatic substances, however, the sulphur usually induces a bitter taste. Here we have an analogous influence of the ring system in taste as in odour. Aliphatic sulphur compounds have unpleasant odours and bitter tastes, but cyclic sulphur compounds may be sweet smelling, as in the benzothiazoles, and sweet tasting, as in saccharin and many of its derivatives.

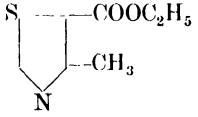
In the mercaptans we have

β-methylaminoethyl mercaptan $CH_3NH . CH_2 . CH_2 . SH$ bitter, rough taste,

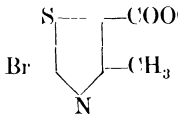
and in the thiophenols,

thiopicric acid 

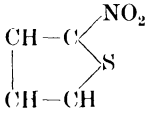
Cohn states that all mercaptans, thiophenols, thioethers, disulphides, thioamides, thioureas, and nitrobenzene and nitronaphthalene sulphonic acids taste bitter, and that the following sulphur compounds are sweet—thiazole carboxylic esters, xanthic esters, the saccharin group and some sulphonic esters of phenyl triazines. Examples are

4 methylthiazol-5 carboxylic ester  which is

sharp and sweetish ; the 2-chlor, 2-brom- and 2-iodo 4 methylthiazole-5

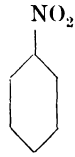
carboxylic esters  which are sweet and

sharp ; methyl ester of xanthic acid, C_2H_5O . CS . SCH_3, which is sweet ;

nitrothiophen,  , which is very sweet.

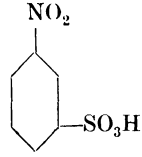
As regards substitution in the benzene ring, if the starting substance is not sweet it is impossible to predict the result, but if it is sweet then the introduction of a sulphur grouping often damages the taste and makes it bitter, thus :

Nitrobenzol



Sweet.

m-nitrobenzene sulphonic acid

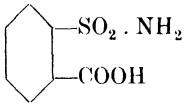


Bitter.

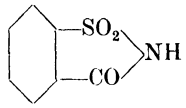
It is clear that the majority of sulphur compounds are bitter, but that if the sulphur atom is a member of a heterocyclic ring, there is no such tendency to bitterness, and, in fact, the saccharins which are intensely sweet contain heterocyclic sulphur. It will be seen later that if the ring containing the sulphur is broken the saccharins are no longer sweet.

Saccharin

Discovered as long ago as 1879 by Remsen and Fahlberg (*Ber.*, **12,** 470) saccharin was until comparatively recently the sweetest substance known, and to-day is pre-eminent as a substitute for sugar. It is made from the *o*-sulphonamide of benzoic acid which readily loses water to give saccharin. This amide has no sweet taste :

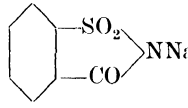


Not sweet.



Intensely sweet.

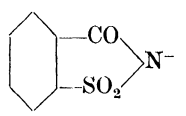
Saccharin is only slightly soluble in water, but if a few drops of the cold aqueous solution be added to a glass of water the latter then tastes like the sweetest syrup. The salts of saccharin are sweet, e.g. :

Sodium salt " crystallose " 

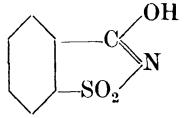
intensely sweet.

Ammonium salt—sweeter even than saccharin.
Methylamine, potassium, barium, mercury and cadmium salts—all sweet.
Lithium salt—sweet and fresh.
Strontium salt—fresh then sweet.
Calcium salt—warming, then sweet.
Copper salt—very astringent—hardly any sweet taste.
Lead salt—sweet with metallic after-taste.
Nickel salt, $(C_7H_4SO_3N)_2Ni$—slightly sweet.
Nickel ammonium salt, $(C_7H_4SO_3N)_2Ni \cdot H_2O \cdot 4\ NH_3$—sweet.
Quinine salt—first sweet, then bitter.

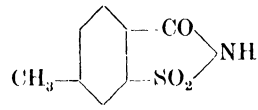
As the sweetness persists through most of its salts it is reasonable to think that the sweet taste is due to the influence of the anion



This is borne out by the lack of sweetness in pseudo-saccharin

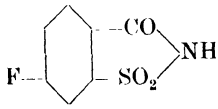


The influence of a methyl group *para* to the carbonyl group is to reduce the sweet taste and to give a bitter after-taste.

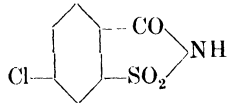
p-methyl saccharin or *p*-tolylsulfimide 

has an intensely sweet taste (just less than half that of saccharin) followed by a decidedly bitter taste after the sweet taste has disappeared.

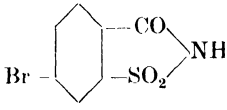
The influence of a halogen has already been discussed but is noted here for convenience :



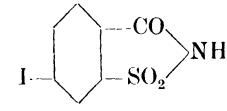
Sweet, like saccharin.



Sweet and bitter, latter slightly more marked.

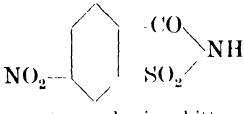


First sweet, then bitter.

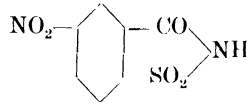


Slightly bitter, no sweet taste whatever.

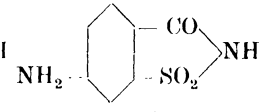
A *para*-nitro group gives an intensely bitter taste like that of quinine and so does a *meta*-nitro group, whilst a *para*-amino group gives an intensely sweet substance :



p-nitrosaccharin, bitter like quinine.

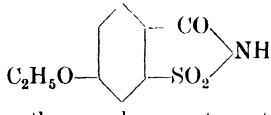


m-nitrosaccharin, bitter like quinine

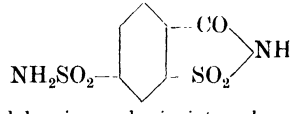


p-aminosaccharin, intensely sweet.

Also may be noted :

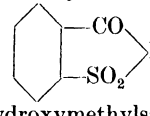


p-ethoxysaccharin, not sweet.

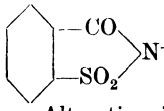


p-sulphaminosaccharin, intensely sweet.

Evidently considerable alterations can be made in the constitution of saccharin without destroying the sweet taste, provided the substitution is in the benzene ring, and that no very strongly negative groups like $—NO_2$ are introduced.

If, however, we consider substitution of the hydrogen in the imide group we find that few liberties may be taken. All the following are tasteless, N-methylsaccharin,  N-ethylsaccharin, N-bromethylsaccharin, N-hydroxymethylsaccharin and N-phenylsaccharin. Presumably this substitution in the imide group interferes

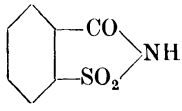
with the ionization of the product, so that the sweet saccharin ion



cannot be formed.

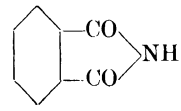
Alteration in the heterocyclic ring also interferes with the taste (cf. Holleman, *Rec. trav. chim.*, **42,** 839-45, 1923).

Saccharin.



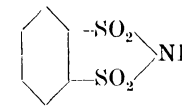
Sweet.

Phthalimide



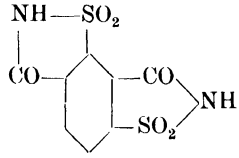
Tasteless.

Benzene disulphimide

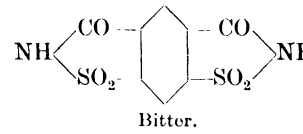


Sweet taste with strong, bitter after-taste

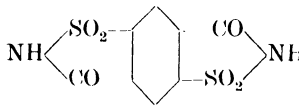
Even duplication of the heterocyclic arrangement destroys the taste. Wischin (*Ber.*, **23,** 3,113, 1890) and, later, Holleman made substances with the following constitutions :



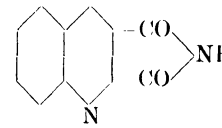
Very bitter.



Bitter.

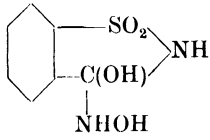


Feebly bitter.



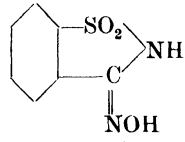
Quinolenic acid, sour.

Modification of the carbonyl group of saccharin destroys the sweet taste with the formation of a tasteless substance if the new group is $\rangle$C RR′ or $\rangle$C(OH)R where R = alkyl, etc., and with the formation of a bitter substance if the new group is $\rangle$CS or $\rangle$C=NR. According to this rule, hydroxylamino saccharin



should be tasteless, but it has actually a sweetish burning taste and affords a rare exception to the rule (Mannessier-Mameli, *Gazz. chim. ital.*, **65,** 77-84, 1935).

Saccharin-oxime



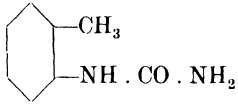
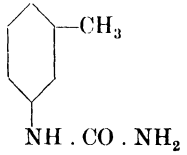
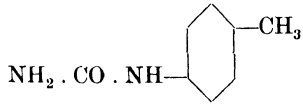
has only an insipid taste.

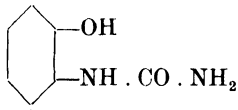
Magidson and Gorbatschow (*Ber.*, **56B**, 1810-17, 1923) pointed out that none of the theories of structure and taste explains the sweetness of saccharin. This sweetness increases with dilution. Between the concentrations of 0·00324 N and 0·00001013 N the ratio $\frac{\text{sweetness}}{\text{dissociation}}$ varies only from 4,781 to 9,059, i.e. 2-fold, whilst the ratio $\frac{\text{sweetness}}{\text{molecular concn.}}$ varies from 58,640 to 6,663,000, i.e. 113-fold. It is clear, therefore, that the sweetness is due to the anion and not to the undissociated substances. Further proof of this is provided by the diminution in sweetness on addition of ionizable sodium salts to solutions of crystallose, for these would depress the ionization. Also, substitution of alkyl groups in the imide group would give an unionizable compound, and such substitution products, e.g. N-methyl saccharin, are in fact not sweet at first, but develop a slight sweet taste when kept in the mouth for several minutes, as a result of hydrolysis, i.e. regeneration of the original saccharin.

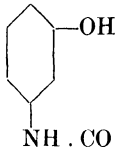
Physically, saccharin is a white crystalline substance which sinters slightly at 220° C. and melts at 228-9° C. In vacuum it will sublime without decomposition. At room temperature it is only 0·43 per cent. soluble in water, and is about 3 per cent. soluble in alcohol and 5 per cent. in acetic acid.

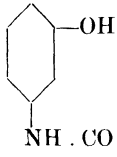
Dulcin

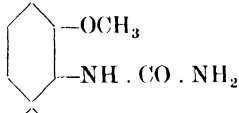
Whereas saccharin in high dilution is about 675 times as sweet as sugar, dulcin is about 200 times as sweet as sugar. Dulcin dissolves to about 0·12 per cent. in water at room temperature and more readily in alcohol. It melts at 172° C. It was discovered in 1883 by Berlinerblau (*J. für. Prakt. Chemie.*, **30**, 103). The tastes of some related compounds are as follows :

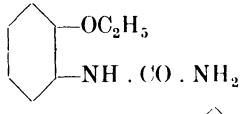
Urea	$NH_2 . CO . NH_2$	Bitter.
a-dimethylurea	$NH_2 . CO . N(CH_3)_2$	Sweet.
Phenylurea	$C_6H_5 . NH . CO . NH_2$	Bitter.
o-tolylurea		Tasteless.
m-tolylurea		Bitter.
p-tolylurea		Sweetish.

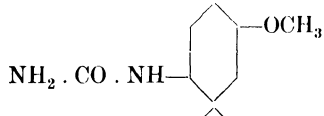
o-hydroxyphenylurea  Very sweet.

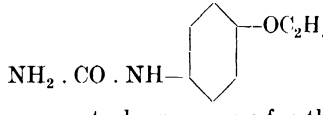
m-hydroxyphenylurea  Sweet and pungent.

m-hydroxycarbanilide  Tasteless.

o-anisylurea  Tasteless.

o-ethoxyphenylurea  Tasteless.

p-anisylurea  Very sweet.

Dulcin  Very sweet.

The ether linkage appears to be necessary for the sweet taste, as does also the carbonyl group in the urea, for

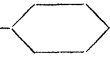
p-ethoxyphenyl thiourea, *p*-$C_2H_5O \cdot C_6H_4 \cdot NH \cdot CS \cdot NH_2$, is bitter.

The similar compound

p-phenetylsemicarbazide, C_2H_5O—  —$NH \cdot NH \cdot CO \cdot NH_2$,

was found by Cohn to be tasteless.

The most similar compound to dulcin is

p-anisyl urea, CH_3O—  —$NH \cdot CO \cdot NH_2$.

This is sweet, as noted above, but according to Boedecker and Rosenbusch (*Ber. pharm. Ges.*, **30,** 25-8, 1920) only one-fourteenth part as sweet as dulcin itself.

It is often found that doubling of a substituted benzene nucleus inhibits the development of physiological effect, and this fact is known

as Sternberg's rule. An illustration of it was put forward by Speckan (*Ber. pharm. Ges.*, **32,** 83-107, 1922), who showed that ethylenedioxyphenyl urea, $C_2H_4(OC_6H_4 . NH . CO NH_2)_2$, was tasteless.

We have seen that a halogen substituted in the nucleus, e.g. in *m*-aminobenzoic acid or in saccharin, induces a bitter taste, but not as a rule in an aliphatic compound or in a side chain. Accordingly we should expect that β-bromodulcin,



would still be sweet, and Speckan confirmed that it is so. He also showed that the replacement of the ethoxy group by an acid group destroyed the taste. Thus :

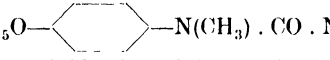
p-carbethoxy phenylcarbamide, $C_2H_5O . CO—C_6H_4—NH . CO . NH_2$,

is tasteless, and

p-benzoyl oxyphenylcarbamide, $C_6H_5O . CO—C_6H_4—NH . CO . NH_2$,

has a transitory acid taste, finally becoming faintly sweet.

Bergmann, Camacho and Dreyer (*Ber. pharm. Ges.*, **32,** 249-58, 1922) set out to prepare dulcin derivatives with greater solubility and equal sweetness. They found that methyl phenetyl urea,



was 220 times more soluble than dulcin and was equally sweet but less pleasant. The general rule that alkylation of an amino group brings sweetness will be remembered, but I think it is rather surprising that a compound with the structure of methyl phenetyl carbamide should be so much more soluble than dulcin.

They also found that N-hydroxyethyl-N-phenetyl urea,

$$C_2H_5O . C_6H_4 . N(CH_2CH_2OH) . CO . NH_2,$$

was easily soluble and was also sweeter, although less pleasing, than dulcin.

The corresponding dihydroxypropyl phenetyl urea,

$$C_2H_5O . C_6H_4 . N(CH_2CHOHCH_2OH) . CO . NH_2,$$

was readily soluble but was not sweet. N-phenetyl-N-carbethoxy methyl urea, $C_2H_5O . C_6H_4 . N(CH_2 . CO . OC_2H_5) . CO . NH_2$, had a slight solubility in water but was not sweet but faintly bitter.

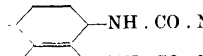
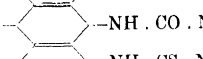
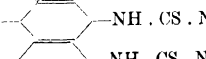
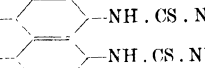
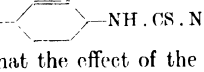
The following four bodies were found to be difficultly soluble and to have no distinctly sweet taste.

N-phenetyl-N′-allyl urea	$C_2H_5O . C_6H_4 . NH . CO . NH . CH_2CH=CH_2$.
N-phenetyl-N′-methyl urea	$C_2H_5O . C_6H_4 . NH . CO . NHCH_3$.
N-phenetyl-N-methyl-N′-methyl urea	$C_2H_5O . C_6H_4 . N(CH_3) . CO . NHCH_3$.
N-phenetyl-N-methyl-N′-allyl urea	$C_2H_5O . C_6H_4 . N(CH_3) . CO . NH . CH_2CH=CH_2$.

Thoms (*Deut. Zuckerind.*, **49,** 1056, 1924) also showed that the replacement of one of the hydrogen atoms in the amino group of

dulcin by an alkyl group reduced the sweetness. Similarly, the introduction of a second carbamide group *ortho* to the first causes loss of sweetness. Thoms concluded that for the production of flavour the presence of one or more sapophoric groups was not enough, for these groups must occupy a definitely related position. Such a statement is easily seen to be true not only with taste, but with odour, toxicity, colour and every other physical property.

Lange and Reed (*J. Am. Chem. Soc.*, **48**, 1069-74, 1926) made a series of substances similar to dulcin but with two phenyl groups. These were

p-phenoxy phenyl urea		Tasteless.
p-phenoxycarbanilide		Tasteless.
p-phenoxy phenyl thiourea		Slightly bitter.
p-phenoxy thiocarbanilide		Slightly bitter.
p-*p'* diphenoxy thiocarbanilide		Tasteless.

The results show that the effect of the phenoxy group is to decrease both the sweet and the bitter taste, since phenetyl urea is sweet but phenyl urea and phenyl thiourea and phenetyl thiourea are bitter.

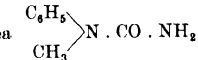
Lorang (*Rec. trav. chim.*, **47**, 179-90, 1928) reviewed the relations between taste and constitution in dulcin derivatives and arrived at the following conclusions :

(1) Small changes in the ethoxy group to methoxy, hydroxy, methyl, hydroxyethoxy, HO C_2H_4O—, and β-bromethoxy, Br C_2H_4O—, leave the sweet taste more or less unaltered. Larger groups, such as propoxy, butoxy, phenoxy or hydroxy phenoxy, HO C_6H_4O—, cause the sweet taste to disappear.

(2) Substitution in the *ortho* or *meta* positions of the phenyl group by chlorine, bromine, nitro, nitroso or carbamide groups causes the sweet taste to disappear. Substitution in these positions by the amino group leaves a slightly sweet product.

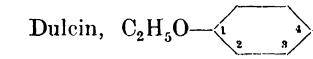
(3) The sweet taste modified by an after-taste remains when the hydrogen of the N atom attached to the phenyl group is substituted by methyl, hydroxyethyl, etc. When the hydrogen of the terminal N atom is substituted by alkyl, or when both N atoms have their hydrogen replaced by alkyl then the sweet taste is lost.

Thate (*Rec. trav. chim.*, **48**, 116-20, 1929) pointed out that many asymmetrical ureas have a sweet taste, e.g. dulcin, *a*-dimethylurea, and to investigate this point he made the following phenylureas :

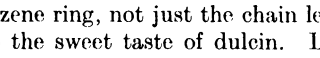
α-methyl α-phenyl urea		Sweet.
4-methyl phenyl urea		Quite sweet.
α-methyl α-4 methyl phenyl urea		Very sweet.

and found that generally the methyl group intensified the sweetness since phenyl urea, $C_6H_5NH \cdot CO \cdot NH_2$, is bitter, not sweet.

Wertheim (*J. Am. Chem. Soc.*, **56,** 735-6, 1934) showed that δ-ethoxybutyl urea, $C_2H_5O \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2NH \cdot CO \cdot NH_2$, was faintly bitter. This substance, like dulcin, has four carbon atoms in a line between the oxygen and nitrogen linkages.

Dulcin, 

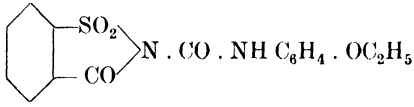
so that the benzene ring, not just the chain length, pays an important contribution to the sweet taste of dulcin. Later, Wertheim (*J. Am. Chem. Soc.*, **57,** 545-6, 1935) showed that

p-ethoxybenzyl urea, 

is practically tasteless, and that the corresponding *meta* and *ortho* bodies were also practically tasteless, but the last (*ortho*) was slightly bitter in solution.

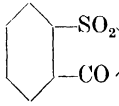
Alberti (*Gazz. chim. ital.*, **69,** 150-62, 1939) confirmed that substitution in the terminal $—NH_2$ of dulcin gave a tasteless product.

Since saccharin and dulcin are two of the sweetest substances known, it might be thought that a compound embodying the essential features of both substances would be exceptionally sweet. Finzi and Colonna (*Atti. accad. Lincei Classi. sci. fis. mat. nat.*, **26,** 19-24, 1937) showed that



saccharin-2-*p*-ethoxyformanilide.

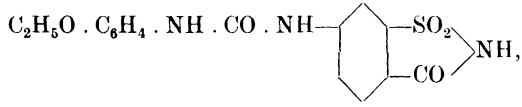
which clearly contains the principles of



Saccharin and dulcin

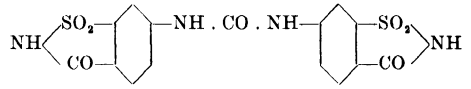
is without a sweet taste.

Similarly, saccharin-6-dulcin,



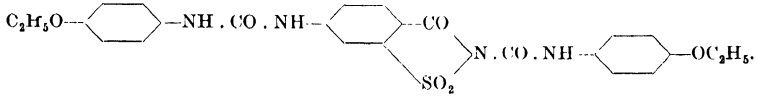
although soluble was not sweet, confirming the general rule that substitution in the terminal $—NH_2$ of the urea group causes loss of sweetness. In addition, unsymmetrical ureas are often sweet but symmetrical ureas are not, and sweetness in unsymmetrical ureas is usually lost if substitution in the second amino group is carried out.

Other products shown to be not sweet are

sym. 6, 6′ disaccharin urea, 

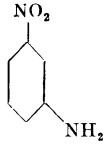
and

didulcin saccharin,

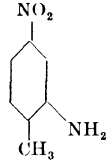


Homologues

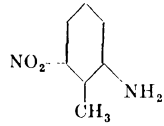
A priori we should expect that homologues with similar chemical and physical properties would have like tastes. Generally, in fact, there is a resemblance and uniformity, but small differences occur from one member to the next, and as these differences are often cumulative the taste differences in a series may be very great. Often the homologue of a substance introduces a new note in the taste, thus, whilst saccharin is only sweet, methylsaccharin has a bitter after-taste. Of the homologues of *m*-nitraniline, which itself is sweet, only 4-nitro 2-toluidine is sweet, for 6-nitro-2 toluidin and 2-nitro-4-toluidin are nearly tasteless.



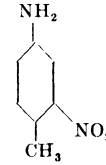
Sweet.



Sweet



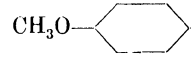
Tasteless.

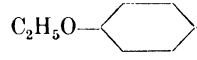


Very slightly bitter.

Whereas phenylurea, $C_6H_5NH \cdot CO \cdot NH_2$, is bitter,
p-tolyl urea, $4\text{-}CH_3C_6H_4NH \cdot CO \cdot NH_2$, is sweet.

Here an increase in molecular weight is accompanied by a change from bitter to sweet, but the reverse can also apply, for whereas

p-anisonitrile,  is sweet,

p-ethoxybenzonitrile,  is bitter.

Indeed this latter change from sweet to bitter on ascending a series is more usual than the opposite.

In general, there is a close resemblance in taste between near homologues, e.g. methyl, ethyl, isopropyl and isobutyl chlorides are all sweet. Resorcinol, $C_6H_4(OH)_2$, and orcinol, $CH_3 \cdot C_6H_3(OH)_2$, are both sweet. Ethylene, trimethylene and tetramethylene glycols are

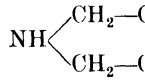
all sweet. Phloroglucinol, $C_6H_3(OH)_3$, and methyl phloroglucinol, $CH_3 . C_6H_2(OH)_3$, are both sweet.

Lead formate, acetate, propionate and isovalerianate are all sweet. Glycine, alanine, α-aminobutyric acid, α-aminoisobutyric acid, α-aminovaleric acid and α-aminocaproic acid are all sweet.

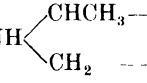
a-Dimethyl urea and *a*-diethyl urea are both sweet.

So are dulcin and *p*-anisylurea.

Amongst the bitter substances we have trinitrobenzene and trinitrotoluene, trinitrophenol and trinitro *m*-cresol, ethyl and propyl borates, piperazine,

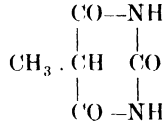


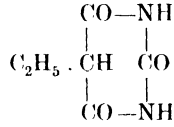
and dimethyl piperazine,



formamide, acetamide and propionamide. All the above are bitter.

In the sours, most acids are sour, e.g. methyl and ethyl barbituric acids





Piperine, methyl piperine and ethyl piperine have similar peppery tastes.

Furukawa (*J. Tokyo Chem. Soc.*, **39,** 584-660, 809-45, 1918, and *Chemical Abstracts*, **13,** 768, 1918) showed that in the alicyclic series the lower aldehydes and alcohols have cooling or warming tastes, e.g. cyclohexanol, but that the higher homologues are astringent.

Isomerism

Isomers do not necessarily have similar tastes. The influences are irregular. There may be no connection between the tastes of isomers that are considerably different in constitution, but nearly-related isomers might be expected to have similar tastes. Some examples will illustrate the taste differences which in fact exist between isomers of very similar constitution :

2 . 3 dibrompropylene	$CH_2{=}C\,Br\,CH_2Br$	Sweetish.
1 . 3 dibrompropylene	$CHBr{=}CH\,CHBr$	Pungent.
n-octyl alcohol	$CH_3(CH_2)_6CH_2OH$	Sweetish.
Methyl heptyl carbinol	$CH_3(CH_2)_5 . CH(CH_3)OH$	Bitter.
Butyl nitrate	$CH_3(CH_2)_3NO_2$	Sweetish.
Isobutyl nitrate	$(CH_3)_2CHCH_2NO_2$	Sweetish and pungent.

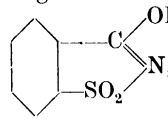
Chain branching is often associated with a tendency towards pungency.

The α-aminocarboxylic acids are collectively sweet, but β- and γ-amino acids only exceptionally are sweet, e.g. :

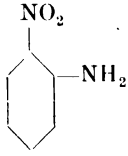
	α-alanine	$CH_3 . CHNH_2 . COOH$	is sweet.
but	β-alanine	$CH_2NH_2 . CH_2 . COOH$	is not sweet.
	leucine	$(CH_3)_2CH . CH_2 . CH(NH_2)COOH$	is sweet,
but	isoleucine	$\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CH . CH(NH_2)COOH$	is bitter.

This last illustrates the effect of chain branching and not of removing the amino group from the influence of the carboxylic group.

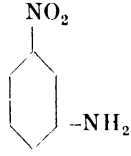
It will be remembered that in the ureas only the unsymmetrical have sweet tastes, their symmetrical isomers being tasteless or bitter.

Also in the saccharin series, pseudosaccharin,  , which is isomeric with saccharin, is not sweet.

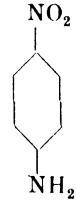
In the aromatic series we find enormous taste differences resulting from the orientation of the substituent groups in the ring. Of the three nitranilines only one, the meta, is sweet :



Not sweet.

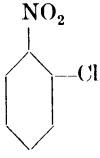


Sweet.

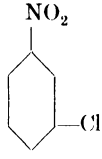


Almost tasteless.

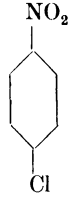
whilst in the chlornitrobenzenes only one—again the meta—is tasteless.



Sweet.

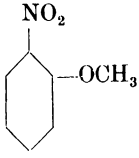


Tasteless.

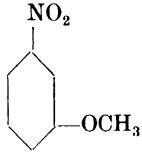


Sweet.

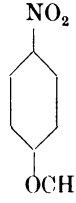
In other cases all three isomers may have similar tastes, e.g. the nitranisoles



Very sweet.

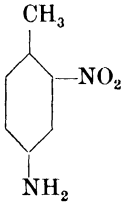


Very sweet.

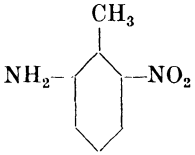


Very sweet.

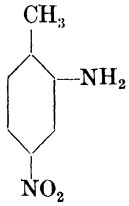
Since *m*-nitraniline is sweet we might expect that the nitro-toluidines in which the amino and nitro groups are still *meta* to each other would also be sweet, but we actually find 2 nitro-4 toluidin and 6 nitro-2 toluidin and 4 nitro-2 toluidin :



Very Slightly bitter.



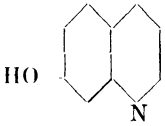
Tasteless.

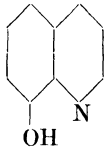


Sweet.

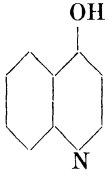
It is clear that whatever generalities may be found in the relation of taste to orientation will not be superficial.

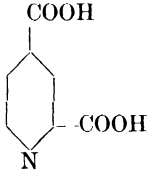
A similar state of affairs obtains in the heterocyclic series, for whilst

7-hydroxyquinoline  is tasteless,

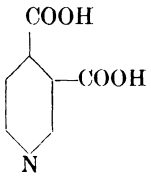
8-hydroxyquinoline  is pungent and bitter,

whilst

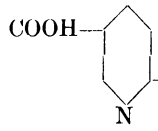
4-hydroxyquinoline  is also bitter.

Pyridine-2-4-dicarboxylic acid  is bitter,

but

pyridine-3-4-dicarboxylic acid  is sour,

whilst

pyridine-2-5-dicarboxylic acid  has three tastes, sweet, bitter and sour.

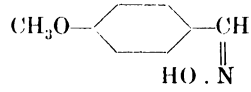
Stereoisomerism

We saw that the odours of stereoisomers could be different although not usually greatly different. The physiological effects of stereoisomers on the organism is known often to be different, e.g. *l*-adrenaline increases the blood pressure much more strongly than *d*-adrenaline. Similarly, considerable differences exist between *d*- and *l*-cocaine and *d*- and *l*-nicotine. Consequently it should not be a matter for surprise that stereoisomers exhibit different tastes.

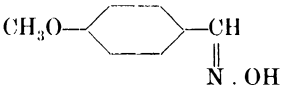
The earliest to be found was asparagine (Piutti, *Compt. rend.*, **103,** 134-7, 1886), which is often present in sprouting seeds and is

aminosuccinamic acid, $C_2H_3(NH_2)\begin{matrix}CONH_2\\COOH\end{matrix}$

The dextro-rotatory variety is sweet but the lævo- is tasteless. *d*-Valin, $(CH_3)_2CH \cdot CH(NH_2) \cdot COOH$, is sweet, but *l*-valin is not. The case of the valins is important since they both have the glucophore, $—CH(NH_2)COOH$, and the auxogluc, $(CH_3)_2CH—$, but as one is sweet and the other insipid it is clear that spatial arrangement is just as important as the presence of any particular groups. As would be expected the racemic mixture *dl*-valin is sweet.

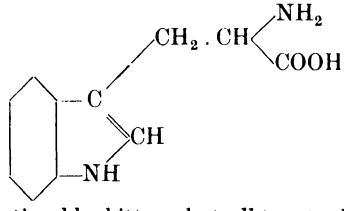
α-anisaldoxime (anti)  is intensely sweet

but

β-anisaldoxime (syn)  is tasteless.

d-Leucin is decidedly sweet but *l*-leucin is faintly bitter.

A curious example is quoted by Cohn :

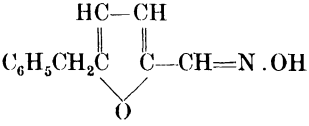
d-tryptophan (indole alanine)  is nearly tasteless,

l-tryptophane is noticeably bitter, but *dl*-tryptophane is sweet, and yet the *dl*-variety is a mixture of the *d*- and the *l*-varieties. The

observations appear to have been made with synthetic racemate and with naturally occurring active *d*- and *l*-varieties. Possibly a more detailed examination would disclose the reason for the anomaly. If not, the significance of the observation may be immense.

According to Gilman and Dickey (*J. Am. Chem. Soc.*, **52,** 2010-13, 1930)

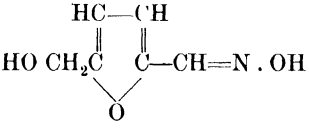
syn-5-benzyl-2 furfuraldoxime



is 700 times sweeter than sugar, i.e. about as sweet as, or a little sweeter than saccharin, but the corresponding anti-body is only 100 times sweeter than sugar.

Both the syn and anti oximes of

5-hydroxymethyl-2-furfural



are without a sweet taste, which is surprising as the substitution of a phenyl group for a hydroxyl has given a sweet taste. The syn and anti oximes of furfural itself are as sweet as each other.

Tseng and Chu (*J. Chinese Chem. Soc.*, **1,** 188-98, 1913, and *Chemical Abstracts*, **28,** 669, 1934) found that *dl*-glutamates were not always like the *d*-compounds.

Sodium-*d*-glutamate, $NaOCO \cdot CH(NH_2) \cdot (CH_2)_2 \cdot COONa$, has an intense meat-like taste.

Tyrosine, $p\text{-}HO \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2)COOH$, has been examined by Kaneko (*J. Chem. Soc. Japan*, **59,** 433-9, 1938, and *Chemical Abstracts*, **32,** 9062, 1938), who indicates that all its dextro-rotatory derivatives have a sweet taste, whilst the lævo or naturally occurring derivatives have a bitter disagreeable taste. He states that taste is not related directly to positive or negative optical rotation but to the stereostructure of the compound. In other words, optical activity and taste are both the result of certain molecular configurations.

Taste of Perfumes

We have already seen that many perfume substances have bitter or unpleasant tastes. Thus the lactones which have such pleasant odours have bitter tastes. Esters on the whole are bitter though some of them with fruity odours have sweet tastes. We have seen also that changes which tend to increase odour depress smell and *vice versa*. For example, the introduction of hydroxyl groups depresses odour but induces a sweet taste, whilst the etherification of these hydroxyl groups increases or restores odour but reduces the taste.

Generally, too, oil-soluble or ether-soluble substances have stronger odours than water-soluble bodies, but the reverse is the case with taste.

Many of the aldehydes and ketones we have already seen to be strongly odorous, and many have pleasant smells and are used in perfumery. It is then a matter of interest to see if in this case also the taste is unpleasant. Furukawa (*J. Tokyo Chem. Soc.*, **41,** 706-28, 1920, and *Chemical Abstracts*, **15,** 1145, 1921) investigated this matter. The precaution of keeping the nose shut during the tasting tests was taken, since otherwise the odour would have interfered with the taste perception. He found that the following aldehydes had sweet tastes—anisaldehyde, cinnamaldehyde, heliotropin, salicylaldehyde, *p*-hydroxybenzaldehyde, peryllaldehyde and furfural, whereas the following had no sweet taste—benzaldehyde, vanillin, citral, citronellal, acetaldehyde and formaldehyde. The following ketones had no sweet taste—zingerone, menthone, camphor, ionone, methylheptenone and acetone. No ketone with a sweet taste was discovered and yet the ketones have pleasant odours. In semicarbazones only a reduced sweet taste existed and phenylhydrazones had no sweet taste. Oximes are sometimes sweet. Kodama pointed out that acetophenone oxime was sweet. Japanese Patent 35,332 (Furukawa, 1920) describes a new perfume peryllartine (α-anti-perylla aldoxime) which is 2,000 times sweeter than sugar, and about three times as sweet as saccharin. Perilla aldehyde, $C_9H_{13}CHO$, constitutes about 50 per cent. of the oil from *perylla nankinensis*.

It is very curious that although α-anti-perilla aldoxime is 2,000 times as sweet as sugar, its syn-isomer is tasteless (Gilman and Dickey, *J. Am. Chem. Soc.*, **52,** 2011, 1930).

Conclusions

Before drawing conclusions from the evidence we have collected, it will be well to note the conclusions at which various workers have already arrived.

Cohn ("Die organischen Geschmacksstoffe," 117-23, 1914) attributed taste largely to the presence of sapophore groups. Starting from the observation that polyhydroxy bodies and α-amino acids are sweet whereas highly nitrated bodies are bitter and so on, he finds certain sapophore groups which give to their families definite tastes. Sapophore groups are

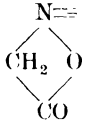
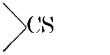
$(OH)_x$	Sweet.
$\begin{matrix} & & NH_2 \\ & \diagup & \\ > C & & \\ & \diagdown & \\ & & COOH \end{matrix}$	Sweet (dulcigen).
$\begin{matrix} & CO \\ ortho & \\ & COOH \end{matrix}$	Sweet-bitter.

$(NO_2)_x$	Bitter.
$(NO_2)_xNH \cdot NO_2$	Bitter.
NO_2 SO_3H	Bitter.

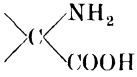
In addition many substances containing the following groups are sweet :

$=N—O \cdot CH_2 \cdot COOH$	Oximacetic acids.
	Azides.
$=N—OH$	Oximes.
$—CN$	Nitriles.

The following groups are usually accompanied by a bitter taste :

$N=$	Tertiary base.
$=N=$	Ammonium base.
	Betaine.
$—SH$	Mercaptan.
$—S—$	Sulphide.
$—S—S—$	Disulphide.
	Thioamides and thioureas.

In each class there are usually exceptions.

The group  is "dulcigen."

Groups —SH, —S—, —S—S— and =N— are "amarogen," and groups —COOH and $—SO_3H$, which give a sour taste, are "acidogen."

Cohn also pointed out that often with increase of molecular weight as we ascend a homologous series the taste of the members gradually changes from sweet to bitter. The lowest members of a series may be sweet, the next sweetish, then, although the sweet taste remains, a separate bitter taste appears, and finally the higher members are purely bitter. In this connection the glycols are instructive :

Ethylene glycol	Sweet.
Trimethylene glycol	Sweet.
Propylene glycol (1, 2)	Sweetish.
Tetramethylene glycol	Less sweet.
Hexamethylene glycol	Bitter.

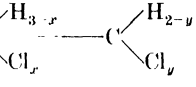
Cohn recognizes that two other factors have a bearing on this property. One is that as we ascend a series, the solubility decreases and finally, when the products become insoluble, they are therefore tasteless, and the second is that the sapophoric taste-inducing group

has a bulk which is important in a low member, but in the high members with the large molecules the proportion of sapophoric group in the molecule becomes more unfavourable.

It is convenient to note here the glucophore and auxogluc groups of Oertly and Myers, although we have already discussed them in Chapter 5. It will be remembered that to give a sweet taste, the presence of a glucophore and an auxogluc was necessary. The six glucophores were

(1) —CO—CHOH—(H)
(2) CH_2OH . CHOH—
(3) COOH . $CHNH_2$—
(4) —CH_2O NO_2

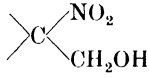
(5) 

(6) 

(Cl — Halogen)

and the nine auxogluc were

(1) H—
(2) CH_3—
(3) C_2H_5—
(4) $CH_3CH_2CH_2$—
(5) $(CH_3)_2CH$—
(6) CH_2OH—
(7) CH_3 . CHOH—
(8) CH_2OH . CH_2—
(9) $C_nH_{2n+1}O_n$—

Henry (*Compt. rend.*, **121,** 213, 1895) had shown that bitterness was frequently associated with the group  , and Fischer had shown that many of the α-amino acids had a sweet taste.

Renqvist (*Skand. Arch. Physiol.*, **40,** 117-24, 1920), who worked on esters and acids, concluded that with increasing molecular weight there was a decreasing taste, and also that the variation of taste amongst isomers was irregular.

Barral and Ranc (*Rev. sci.*, **56,** 712-23, 1918) stated that there was no general law by which the taste of any compound could be predicted, but that there were certain generalities. These were: (1) The introduction of a radicle especially if aromatic destroys sweet taste giving a bitter one, and the heavier the radicle, the more marked is this effect. (2) Introduction of halogen into the aliphatic hydrocarbons gives a sweet taste. (3) Addition of a hydroxyl group to an amino body gives a sweet taste. (4) The entry of the methoxy group into an aromatic molecule changes bitterness to sweetness. (5) Polyhydroxy compounds are sweet. (6) Poly-nitrated compounds are usually bitter. (7) Taste is affected by variation of the constitution of the molecule.

Kodama (*J. Tokyo Chem. Soc.*, **41,** 495-534, 1920, and *Chemical Abstracts*, **14,** 2805, 1920) pointed out that as :

(1) Optical isomers have different tastes ;
(2) Substitutions always affect the taste ;
(3) All the compounds containing either Cohn's sapophore groups or Oertly and Myer's glucophores contain vibratory hydrogen ;
(4) The taste of electrolytes is due to the sum of the tastes of the molecular electrolyte, the anions, the cations and complex ions,

therefore the taste of organic substances is due to electronic vibrations of the sapophoric element.

Holleman (*Rec. trav. chim.*, **42,** 839-45, 1923) summarized the knowledge regarding saccharins as follows :

(1) The alkali and alkaline earth salts of saccharin are sweet, whilst the heavy metal salts are astringent.
(2) The sweet taste is lost if the sulphimide ring is opened or if the imide hydrogen is replaced.
(3) Substitution in the benzene nucleus reduces the sweet and introduces a bitter taste.
(4) In the *para* position the effect of the halogen increases with its atomic weight.

Finzi and Colonna (*Gazz. chim. ital.*, **68,** 132-42, 1938), after a critical survey of the relations between chemical constitution and taste, conclude that it is impossible to derive any law for aromatic compounds, and that sweet taste depends not on any single factor, such as a sapophore group, but on the entire chemical complex of the particular compound studied.

I think it is a fair statement that many relations between taste and constitution are known which always stand firm, and that many more usual relations (with exceptions) have been identified, but that the evidence has not yet been built up into a logical unification. No doubt it will come in the future.

Just as we concluded the previous chapter with a list of relations between odour and constitution, so now I have studied the evidence and append here a list of the general relations between taste and constitution.

(1) The sour taste is characteristic of acids and acid salts. The primary cause is the hydrogen ion.
(2) The degree of sourness runs parallel with the hydrogen-ion concentration, but is anomalously high when the acid has lipoid-solvent properties.
(3) Not all acids are sour. A bitter or sweet taste may overwhelm the sourness, e.g. picric acid is bitter and salicylic acid is sweet. Nearly all acids containing the group —COOH are sour.

(4) The saline taste is characteristic of salts. They ionize in the saliva.

(5) The anion, the cation, complex ions and the undissociated salt all contribute to the taste.

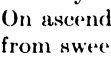
(6) Salts of low and medium molecular weight are salty in taste, but heavy salts such as iodides or salts of cæsium are bitter. Heavy cation and heavy anion certainly give bitterness, but if one ion is heavy and the other light the result cannot be predicted.

(7) Beryllium salts and some lead salts are sweet. Magnesium and ammonium salts are bitter. Salts of heavy metals such as mercury usually have a metallic taste.

(8) Substances may have more than one taste, e.g. *p*-chlorsaccharin is sweet and bitter and pyridine 2 . 5 dicarboxylic acid is sweet, bitter and sour.

(9) Unlike the salt and sour tastes, the sweet and bitter are not confined to single chemical groups but are found in practically every class.

(10) Polyhydroxy compounds are usually sweet, e.g. glycols, sugars (Cohn's sapophore, $(OH)_x$).

(11) α-amino acids are usually sweet (Cohn's dulcigen group ). β- and γ-amino acids are not usually sweet, particularly the latter. The closer together the amino and carboxylic groups the greater the sweetness.

(12) On ascending a homologous series the taste frequently changes from sweet to bitter.

(13) The influence of any particular group is less in a large molecule than in a small one.

(14) On ascending a homologous series taste eventually disappears, simultaneously with solubility.

(15) The presence of three nitro groups in a molecule gives a bitter taste. Two nitro groups usually give a bitter taste. One nitro-group often gives a sweet taste, e.g. nitrobenzene.

(16) Alkylation of an amine group usually gives a sweet taste.

(17) Alkylation of an amide group often gives a sweet taste, e.g. *a*-dimethylurea.

(18) Alkylation of an imide group destroys sweetness, e.g. N-methyl saccharin is tasteless.

(19) Etherification of a hydroxyl group often abolishes a sweet taste, e.g. glycol monomethyl ether is not sweet.

(20) Many of the changes which increase odour, decrease taste and *vice versa*. Lipoid-solubility is primarily important for odour, water-solubility for taste. Strongly sapid substances are often odourless.

(21) Alkylation of the benzene ring often gives a sweet taste, e.g. *p*-tolunitrile is sweet but not benzonitrile.

(22) The entry of a phenyl group usually causes a bitter taste, irrespective of whether it is attached to carbon, oxygen or nitrogen. This may partly be due to the increase in molecular weight so caused.

(23) Chain branching reducesthe sweet taste and introduces a bitter or a burning pungent taste.

(24) Introduction of a methoxy group frequently gives a sweet taste, e.g. anisonitrile.

(25) Esters with fruity odours usually have sweet tastes, e.g. ethyl butyrate. Esters of inorganic acids are mostly sweet.

(26) Esters of aromatic acids, sulphinic acids, as well as lactones and urethanes are bitter.

(27) Esters of resorcinol and allied substances are usually sweet, but no general relation exists between the taste of an alcohol and the ester derived from it.

(28) Unsaturation often brings pungency, e.g. allyl nitrite, probably an instance of the common chemical effect overpowering the taste.

(29) Nitroparaffins are sweet, but unsaturation and chain branching give pungency and a caustic taste.

(30) The amino group often brings a sweet taste, especially if the positive effect of the amine group is balanced by the proximity of a negative group, such as carboxyl or nitro.

(31) Acylation of the amino group reduces or destroys the sweet taste.

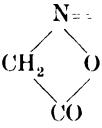
(32) Free bases are bitter, particularly alkaloids and tertiary ammonium bases (Cohn's groups $N=$ and $=N=$).

(33) The simplest amides are bitter. Amides of dibasic acids are tasteless. Many amides are sweet.

(34) Dihydrazides, where the two hydrazide groups are close together, have sweet tastes (oxalic exceptional), but not where far apart.

(35) For ureas to have a sweet taste it is necessary for one of the NH_2 groups to be unsubstituted, hence symmetrical ureas are not sweet.

(36) Neutral nitrogen compounds are often sweet, e.g. α-amino acids, dihydrazides, ureas, oximes (usually sweet).

(37) Betaines are bitter (Cohn's sapophore ).

(38) In the aliphatic series heavily halogenated bodies are often sweet, e.g. chloroform.

(39) In the aromatic series, a halogen in the nucleus introduces a bitter note. The bitter effect is least with fluorine and greatest with iodine.

(40) Sulphur in aliphatic compounds induces a bitter taste. Mercaptans, sulphides, disulphides, thioamides, and thioureas are bitter (Cohn's groups —SH, —S—, —S—S—, —CS—). The sulphonic acids, $—SO_3H$, are sour or bitter.

(41) The effect of a sulphur atom as a ring member is quite different. The ring functions as a whole, e.g. saccharin has heterocyclic sulphur.

(42) The effect of a sulphur-containing group substituted in the benzene ring is to reduce the sweet taste and throw it towards bitter.

(43) The sweetness of saccharin is due to the anion. Its alkali and alkaline earth salts are sweet, but saccharin salts of heavy metals are astringent.

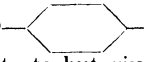
(44) The sweet taste of saccharin is lost if the sulphimide ring is opened or if the imide hydrogen is replaced.

(45) Substitution in the benzene ring of saccharin reduces the sweet and gives a bitter taste.

(46) *p*-alkoxy phenyl ureas are sweet, e.g. dulcin. If the terminal NH_2 group is substituted taste is lost (cf. 35).

(47) Doubling of the phenyl group inhibits the taste effect in both saccharin and dulcin (cf. 22).

(48) Small changes in the ethoxy group of dulcin to methoxy, hydroxy, chlorethoxy, etc., leave the sweet taste still there, but larger groups like propoxy and acid groups destroy the sweet taste.

(49) Substitution of the hydrogen on the already substituted nitrogen, C_2H_5O—  —$\underline{N}H \cdot CO \cdot NH_2$ (underlined), leaves the sweet taste but gives a bitter after-taste.

(50) Some aldehydes are sweet, but no ketones. Semicarbazones of sweet aldehydes are less sweet, and phenylhydrazones are not sweet. Oximes often are sweet.

(51) Certain sapophore groups are often associated with sweet tastes and others with bitter tastes. The most important are

sweet: $(OH)_n$, $—CH(NH_2)COOH$, $—C\begin{matrix}H_{3-n}\\Cl_n\end{matrix}$, $—CH_2ONO_2$.

bitter: $(NO_2)_{>2}$, $\equiv N$, $=N\equiv$, —SH, —S—, —S—S—, —CS—.

(52) Not only the groups present, but also their arrangement determine taste.

(53) Homologues usually have similar tastes if close to each other in a series, e.g. formamide, acetamide, propionamide, all bitter.

(54) Isomers with considerably different constitutions have no taste relationship.

(55) Close isomers may have different tastes, e.g. leucine sweet, isoleucine sweet and pungent, but there is usually some resemblance.

(56) Substitution in the benzene nucleus gives isomers with unpredictable tastes. Often *ortho* and *para* are similar but different from *meta*.

(57) Stereoisomers may have different tastes. The dextro rotatory isomer usually has the sweeter taste, e.g. *d*-valin sweet, *l*-valin tasteless.

(58) Taste depends not only on the groups present but also on their arrangement in space.

CHAPTER 11

PHYSICAL PROPERTIES OF ODOROUS MATERIALS

Vapour Pressure

The molecules in a liquid are not all moving at the same speed, and some of the faster ones are constantly breaking away from the surface of the liquid. If the liquid is exposed to the atmosphere these molecules pervade the room, and if we leave a dish of ether exposed we can soon smell it all over the room, and the ether gradually evaporates. In a similar way the pool of rain-water in the road evaporates. Whereas the change solid → liquid takes place only at the melting-point, the change liquid → gas can take place at any temperature and so can the change solid → gas, for molecules are constantly escaping from the surface of a solid just as from a liquid. If now the air over the liquid is confined by a flask, molecules of the liquid escape from the surface and fly about the interior of the flask, and after a time there are so many in the space above the liquid that some of them are flying back into the liquid. As more and more escape from the liquid into the gas the number of those re-entering increases and finally equals the number leaving. Then equilibrium is reached, and the number of molecules in the space over the liquid is constant. These molecules by their constant collisions with the walls of the container exert a pressure, and this pressure is known as the Vapour Pressure or Vapour Tension. Clearly it will increase as the temperature increases, for this speeds up the molecules which therefore have better chances of escaping. Apart from temperature changes the vapour pressure is constant for any given substance. We know that such substances as ether which are volatile evaporate readily, and these have high vapour pressures, whilst others, such as medium paraffin (similar to medicinal paraffin), are not volatile, and do not evaporate quickly, and such substances have low vapour pressures. The vapour pressure is usually expressed in millimetres of mercury. Regnault's apparatus for measuring the vapour pressure consists of two mercury barometer tubes (Fig. 24), A and B. A functions normally, but into B is inserted a little of the substance, say water, whose vapour pressure is being determined, and it floats on top of the mercury. The pressure exerted by the vapour from this water depresses the mercury in tube B, and the difference in levels between the mercury in tubes A and B is measured in millimetres and is the vapour pressure of the substance in mm. Hg. It has to be appreciated that solids such as ice, as well as liquids, have quite measurable vapour pressures. When the vapour pressure of a liquid becomes, by raising the temperature, equal to the atmospheric pressure, which is about 760 mm. Hg., then the liquid boils. The important point is that at room

temperatures, far below its boiling-point, a substance may have a measurable and often a high vapour pressure.

The vapour pressure of water at different temperatures is as follows :

10° C.	9·2 mm. Hg.	60° C.	149·4 mm. Hg.
20° C.	17·5 ,, ,,	70° C.	233·7 ,, ,,
30° C.	31·8 ,, ,,	80° C.	355·1 ,, ,,
40° C.	55·3 ,, ,,	90° C.	525·8 ,, ,,
50° C.	92·5 ,, ,,	100° C.	760·0 ,, ,,

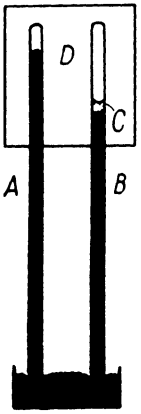


FIG. 24.—Regnault's apparatus for measuring vapour pressure of a liquid.

A. Normal barometer.
B. Barometer-tube with substance C floating on top of the mercury.
C. The substance whose vapour pressure is being measured.
D. Thermostatic water bath.

A correction for expansion must be made to the height of the mercury column at 0° C.

The vapour pressure of ice is as follows :

−90° C.	0·00007 mm. Hg.	−40° C.	0·096 mm. Hg.
−80° C.	0·0004 ,, ,,	−30° C.	0·29 ,, ,,
−70° C.	0·0019 ,, ,,	−20° C.	0·78 ,, ,,
−60° C.	0·0081 ,, ,,	−10° C.	1·95 ,, ,,
−50° C.	0·029 ,, ,,	0° C.	4·58 ,, ,,

Now if we postulate that in order to smell a substance, molecules or particles of it must come into contact with the olfactory hairs, then we see the importance of vapour pressure in relation to odour. Those substances with high vapour pressures provide large numbers of molecules in the atmosphere around them, whereas those with low vapour pressures leave the atmosphere poor in their molecules. *A priori* we should expect substances with high vapour pressures to be readily observable by smell and those with low vapour pressures to be poor in smell. First of all we notice that warming and so increasing the vapour pressure of a body increases its strength of odour, too. Next we note that substances with high vapour pressures such as ether, chloroform and petrol, have stronger odours than less volatile liquids like heavy paraffin and glycerine. Similarly, volatile solids like camphor and naphthalene have stronger odours than less volatile

solids such as iron and glass. The vapour pressure of camphor even at −20° C. is still 0·007 mm. Hg. It is usually agreed that to be odorous a substance must have a perceptible vapour pressure. Newton exposed a grain or two of musk and found that after several years it had not altered appreciably in weight, although throughout that time it had filled the room with its scent. Here, then, appears a contradiction as if there is no loss in weight, no molecules have escaped, and the odour could not have been due to the contact of the molecules with man's olfactory apparatus. Later work has shown, however, that under such conditions there is a definite, although small, loss in weight of the musk. Dyson has laid it down that to be odorous a substance must have a perceptible vapour pressure (*Chem. and Industry*, **57**, 647-51, 1938).

The vapour pressures at 20° C. of a large number of odorous substances—mostly perfumery ingredients—have been determined by Crocker and Henderson and published in the *American Perfumer* for October 1935. So that the significance of their results may be appreciated, it may be noted that the vapour pressure of some common substances at 20° C. is as follows :

Mercury	0·0012 mm. Hg.
Iodine	0·20 ,, ,,
Acetic acid	11·7 ,, ,,
Water	17·5 ,, ,,
Ethyl alcohol	43·9 ,, ,,
Carbon tetrachloride	91·0 ,, ,,
Chloroform	159·6 ,, ,,
Acetone	184·8 ,, ,,
Carbon disulphide	297·5 ,, ,,
Ether	442·0 ,, ,,

Crocker and Henderson divided the substances into three classes of high, medium and low volatility. In each class were several groups, each group having a range of from 1 to 0·56 from highest to lowest member in the group so that a drop of 4 groups is equivalent to a reduction of volatility to 1/10th and one of 8 groups to a reduction to 1/100th. Some examples were

High Volatility

Group A, V.P. 1·0 to 3·1 (1·0-1·8 and 1·8-3·1) mm. Hg.	cineol, *p*-dichlorbenzene, *d*-limonene, phenol, ethyl heptoate.
Group B, V.P. 0·56 to 1·0 mm. Hg.	benzyl cyanide, naphthalene, acetophenone, aniline, benzaldehyde.
Group C, V.P. 0·31 to 0·56 mm. Hg.	guaiacol, camphor, menthol, citronellal, *m*-cresol, methyl heptine carbonate, nitrobenzene, thujone.
Group D, V.P. 0·18 to 0·31 mm. Hg.	bornyl acetate, bergamot oil, pulegone, methyl salicylate, linalyl acetate.
Group E, V.P. 0·10 to 0·18 mm. Hg.	decanoic aldehyde, methyl nonyl ketone, benzyl alcohol, phenyl ethyl acetate, safrole, thymol.

Medium Volatility

Group F. V.P. 0·056 to 0·10 mm. Hg.	anethole, borneol, geranyl acetate, carvacrol, piperonal, catechol, citral.
Group G, V.P. 0·031 to 0·056 mm. Hg.	undecanoic aldehyde, diphenyl ether, anisic aldehyde, citronellol, indole, terpineol, jasmone, diphenyl.
Group H, V.P. 0·018 to 0·031 mm. Hg.	methyl ionone, cinnamyl acetate, ionone, isoeugenol, perilla alcohol, geraniol, lauric aldehyde, phenylacetic acid, skatole.
Group I, V.P. 0·010 to 0·018 mm. Hg.	hydroxycitronellal, myristic aldehyde, isoamyl salicylate, ethyl cinnamate.

Low Volatility

Group J, V.P. 0·0056 to 0·010 mm. Hg.	cinnamyl alcohol, anisic alcohol, β-naphthyl ethyl ether, coumarin, *p*-dichlorphenol, dibenzyl.
Group K, V.P. 0·0031 to 0·0056 mm. Hg.	ethyl myristate, nerolidol, naphthyl methyl ketone, parsley oil, clary sage oil, patchouli oil, ethyl citrate, vanillin, *o*-hydroxydiphenyl.
Group L, V.P. 0·0018 to 0·0031 mm. Hg.	benzophenone, ethyl sebacate, cinnamic acid, diphenylamine.
Group M, V.P. 0·0010 to 0·0018 mm. Hg.	benzyl phenyl acetate, dibutyl phthalate, benzyl salicylate, farnesol, *p*-cresyl phenyl acetate, muscone, Tolu balsam, vetivert oil.
Group N, V.P. 0·00056 to 0·0010 mm. Hg.	benzyl cinnamate, Musk ambrette, civetone, musk xylol, β-naphthyl salicylate.

It may be noted that whilst a hydroxyl group entering a molecule usually reduces its odour, it also decreases the volatility, e.g. diphenyl is ten times as volatile as *ortho* hydroxydiphenyl, and citronellal is thirty times as volatile as hydroxycitronellal. It will be seen that the vapour pressure of some of the constituents of N group is about 5,000 times less than in A group, and yet civetone and musk xylol in N group are two of the most powerful odorants known. Of course, even with low vapour pressures, there may be enormous numbers of molecules, perhaps sufficient to provide a monomolecular layer on the olfactory epithelium. On the other hand, the evidence suggests that vapour pressure is a very secondary consideration indeed in odour production.

It will be remembered that Woodrow and Karpman (*Jour. Exp. Psych.*, **2**, 431-47, 1937) claimed that the fatigue time—the time needed for the olfactory sensation to wane completely—was directly proportional to the vapour pressure of the odorant. This observation certainly suggests that olfaction is governed by the number of molecules which can make contact with the olfactory apparatus.

An interesting adaptation of the relations between smell and vapour pressure was introduced by Tammann and Oelsen (*Z. anorg. allgem. chem.*, **172**, 407-13, 1928). In order to determine the vapour pressure of an odorous substance at low temperatures where it would not ordinarily be measurable the following method is used. Its vapour pressure is measured at a higher temperature, and a fixed volume v_1 of air saturated with its vapour at that temperature is diluted with a volume v_2 of pure air until the odour is just disappearing, i.e. the odour threshold is reached. Then at a lower temperature it is found that the fixed volume v_1 need only be diluted by a volume v_3 (v_3 being

less than v_2) to reach the threshold. Then the vapour pressure at the lower temperature is given by the expression:

$$\text{V.P.}_2 = \frac{\text{V.P.}_1 \times (v_1 + v_2)}{(v_1 + v_2)}.$$

Tammann and Oelsen found that the vapour pressure for camphor was

at $-40°$ C. $(0{\cdot}842 \pm 0{\cdot}133) \times 10^{-3}$ mm. Hg.
at $-18{\cdot}5°$ C. $(7{\cdot}30 \pm 0{\cdot}36) \times 10^{-3}$ mm. Hg.

The threshold values for seven different persons varied from

$$6 \text{ to } 13 \times 10^{-9} \text{ g./c.c.}$$

For butyric acid, the vapour pressure

at $-78°$ C. was $(1{\cdot}13 \pm 0{\cdot}20) \times 10^{-5}$ mm. Hg.
at $-22°$ C. was $(3{\cdot}74 \pm 0{\cdot}37) \times 10^{-2}$ mm. Hg.

and the threshold values for this substance for different people varied from $0{\cdot}9$ to $1{\cdot}2 \times 10^{-10}$ g./c.c.

The temperature at which a substance could be detected by odour was also determined. For a given substance the variation was $1{\cdot}7°$ C. and for seven persons the deviation from the mean temperature was $1{\cdot}2°$ C.

The effect of the variation in vapour pressure with temperature of such a relatively non-volatile but powerful odorant as skatole is shown in the following measurements made by Chamuleau and Noyons (*Acta. Brevia. néerland Physiol. Pharmacol. Microbiol.*, **2**, 94-5, 1932, and *Chemical Abstracts*, **26**, 5806, 1932).

Temperature.	*V.P. of skatole.*
44° C.	0·027 mm. Hg.
40° C.	0·018 ,, ,,
37° C.	0·013 ,, ,,
34° C.	0·009 ,, ,,
20° C. (by interpolation)	0·002 ,, ,,

This last interpolated figure, incidentally, is ten times lower than that of Crocker and Henderson.

It has been stated that substances which have a very low vapour pressure and hence cannot be perceived normally by smell, will nevertheless excite the sensation of odour if dissolved in isotonic salt solution and irrigated through the nose, so that the molecules come into contact with the olfactory apparatus.

Solubility

According to Parker all the adequate stimuli of the chemical receptors are substances in solution. Both taste and smell appear to be actuated by solutions. As we ascend a homologous series molecular weight increases and solubility and volatility fall off. Simultaneously taste and odour disappear. Whereas water solubility appears to be sufficient to stimulate taste as in the sugars and salts, in the case of odour lipoid solubility appears necessary too.

As noted earlier, Backman (*J. phys. path. gen.*, **17**, 1-4, 1917) suggested that to be odorous a substance must be soluble both in water and in lipoids. The olfactory region is covered with a watery mucous layer which the odorant molecules must pass through, and after that then the molecules must dissolve in the lipoid matter which constitutes the olfactory cells. Such a theory takes no account of the possibility of the olfactory hairs projecting right through the watery mucous layer, in which case solubility in water would appear not to be essential. Backman pointed out that in a homologous series the lower members were often water-soluble but not lipoid-soluble, the middle members were both lipoid-soluble and water-soluble, and the higher members were lipoid-soluble but insoluble in water, and therefore the middle members were the most strongly odorous. Thus methanol and ethanol are practically insoluble in lipoids, and have only feeble odours, but butanol is soluble in both water and lipoids and is strongly odorous, whilst cetyl alcohol, although lipoid-soluble, is water-insoluble and therefore odourless.

It is clear that if the olfactory hairs project through the watery mucous layer, insolubility in water should be no deterrent to a substance exhibiting odour. The fact that high molecular weight substances, such as cetyl alcohol, are practically odourless may be due to the lack of volatility rather than lack of water-solubility. It is certainly true that many highly odorous substances are commonly thought to be insoluble in water, e.g. benzene and toluene, but a large number of these odorants are, in fact, soluble to a slight extent in water.

The solubilities at room temperature of some typical odorants are given below :

Odorant.	*Parts soluble in 100 parts of*		
	Water.	*Alcohol.*	*Ether.*
Benzene	0·082	Inf.	Inf.
Toluene	0·047	,,	,,
Xylene	Insol.	Very sol.	Very sol.
Naphthalene	0·003	4·18	Very sol.
Musk xylene (trinitro tert. butyl xylene)	Insol.	Slightly sol.	Soluble.
Benzaldehyde	0·33	Inf.	Inf.
Nitrobenzene	0·19	Soluble	Soluble
Phenol	6·7	189	Very sol.
Camphor	0·1	100	173
α-ionone	Slightly sol.	Inf.	Inf.
β-ionone	,,	,,	,,
Irone	,,	Very sol.	Very sol.
Iodoform	0·01	1·3	13·6
Vanillin	Slightly sol.	Very sol.	Very sol
Eugenol	,,	Inf.	Inf.
Skatole	0·05	Very sol.	Soluble
Indole	Slightly sol.	,,	Very sol.
Ethyl alcohol	Inf.	—	Inf.
Butyl alcohol	7·9	Inf.	Inf.
Amyl alcohol	2·7	,,	,,
Cetyl alcohol (odourless)	Insol.	10·2	Soluble.
Butyric acid	5·6	Inf.	Inf.
Trimethylamine	Very sol.	Very sol.	Soluble.
Ethyl mercaptan	1·5	Soluble	Soluble.

For comparison the solubilities of some sapid but odourless compounds are given below :

Glycol	Inf.	Inf.	7·9
Glycerine	,,	,,	Insol.
Glycine	25·3	Insol.	Insol.
Glucose	83	1·9	Insol.
Quinine	0·057	166	22·2
Saccharin	0·43	3·1	Slightly sol.
Strychnine	0·016	0·9	0·018
Sodium chloride	36	Slightly sol.	Insol.
Oxalic acid	9·5	23·7	16·9

It is clear that odorous materials are generally more soluble in ether than in water, and that sapid inodorous materials are more soluble in water than ether. Ether solubility may be taken as an indication of lipoid solubility. The balance of evidence suggests that water solubility is not essential for odour.

It might also be argued that lipoid solubility is unnecessary, as the stimulation of the olfactory nerve might result simply from the bombardment of the sensory region by the odorant molecules. A reply to this which has been put forward by Dyson is that solution in the lipoid terminals of the osmic cells is necessary to remove the adsorbed layer of molecules, for otherwise odour would be persistent and not evanescent as we know it to be. Still, as stated earlier, it might be that the watery mucus washes away the adsorbed layer.

Another point to which attention may be drawn, is that since the olfactory apparatus is proteid in structure and not fatty it may be that protein solubility and not fat (or lipoid) solubility is important. In support of this suggestion it may be noted that most fats are odourless and it would be expected that they would be *par excellence* odorants if fat solubility was of prime importance. It is true that such proteins as silk, gelatine and albumen are practically odourless, but they are highly polymerized and when broken down into their component parts such as amines, amino-acids and so on, these are highly odorous. Also some natural proteins, such as occur in salmine from salmon roe, are odorous.

In this connection Kremer (*Arch. néerl. Physiol.*, **1**, 715-61, 1917) compared the amounts of a given odorant taken up by water and a saturated solution of lecithin in Ringer solution respectively. Now lecithin is a protein and an important constituent of brain matter, egg-yolk, etc. Kremer found that strong odorants like pyridine, citral and guaiacol were taken up in greater amount by the lecithin solution than by water. Other protein solutions such as ox-brain press juice and extract gave results similar to lecithin. It is clear that at least some powerful odorants are more soluble in protein solutions than in water.

We might conclude this discussion on the solubility of odorous substances by the reflection that water solubility is not essential for odour but is probably helpful, as it enables a much higher concentration of the odorous molecules to penetrate the mucus and make contact

with the olfactory cells. If, however, they cannot pass the mucus layer owing to water insolubility they can still initiate odour by their action on the olfactory hairs which project right through the mucus.

Solubility in protein or fats may be essential. Certainly many odorous substances do possess such a solubility, but it is equally possible that it is chemical reactivity which is essential, so that the odorous molecules may react with the olfactory apparatus. The evanescence of olfaction may be due to the removal of the adsorbed (monomolecular ?) layer of odorant on the olfactory region by solution in the bulk tissues, or it may alternatively be due to removal of this layer by the washing action of the mucus. If the latter is the case solubility in fats or proteids, or even solubility of any sort, might not be an essential property of odorous substances, provided they were chemically reactive. I am aware that the paraffins are rather a difficulty in this argument as they are not reactive but are odorous. On the other hand, in the vast majority of organic compounds, odour and reactivity run parallel. In regard to the evidence offered by Backman it may be noted that those substances which are water-soluble and lipoid-soluble are invariably chemically reactive. It may be that odour and solubility are both dependent on chemical reactivity and that the primary relation is between odour and reactivity.

Infra-Red Absorption

Since light waves of different lengths are unequally deviated when passing through a transparent prism, ordinary white light is split up into a spectrum. The visible portion of the spectrum extends from

Violet wave-length 3930×10^{-10} metres
to Red ,, 7594×10^{-10} metres

The spectrum, however, extends beyond these limits although we cannot see it. Herschel in 1800 showed that a thermometer with a blackened bulb when placed some distance beyond the red end of the visible spectrum, indicated a rise in temperature. This portion of the spectrum is termed the infra-red. A glass prism is not suitable for examination of the infra-red spectrum as glass absorbs infra-red rays but prisms of other substances such as sylvine are more suitable in this respect. If instead of white light, yellow sodium light is used from a flame made yellow with a sodium salt, and so containing particles of incandescent sodium, then the spectrum consists of two yellow lines of wave-lengths 5,896 and 5,890 tenth-metres (10^{-10} metres). If the light from a mercury vapour lamp is used, the light is almost entirely due to a brilliant green line 5,461 tenth-metres. Such light is approximately monochromatic. Now a substance which emits waves of definite periods when heated, will selectively absorb waves of the same periods when cool (Kirchhoff's Law). Thus, if white light from a very hot source, such as an arc, is made to traverse a cooler source of light, such as a lamp flame burning with sodium

light, then the spectrum of the white light contains two black bands corresponding to the position of the sodium lines 5,896 and 5,890. This absorption spectrum is typical of sodium, and other substances have similar well-defined spectra specific to themselves. Such absorption spectra are also found in the infra-red spectrum and can be determined by photography. Faraday first, and Tyndall later, observed that odorous substances strongly absorb infra-red radiation. The phenomenon was at one time attributed to the presence of moisture, but it has been shown latterly that dry odorous substances do absorb infra-red rays. The underlying principle is that just as absorption bands in the visible spectrum determine colour, similarly, absorption bands in the infra-red (or the ultra-violet) may determine odour.

In referring to wave-lengths of infra-red light the symbol μ is usually adopted :

$$1\mu = 10{,}000 \text{ tenth-metres} = 10^{-6} \text{ metres} = \tfrac{1}{1000} \text{ millimetre.}$$

(Similarly, sodium light $= 0{\cdot}59\mu = \frac{1}{1700}$ mm.)

Hydrogen selenide has an intensely objectionable odour, and has absorption lines in the infra-red at 4·05 to 4·58μ and 8·0 to 10·3μ.

The infra-red absorption bands of phenyl mustard oil are three lines near 4·8μ. A very large number of substances show absorption bands in the infra-red spectrum, and some of them are odorous and some are not.

Paraffin and carbon disulphide, both of which are odorous, are transparent throughout the whole range of the infra-red spectrum and show no absorption lines. Carbon dioxide and aqueous vapour which are not odorous, exercise selective absorption on waves of lengths 2·8μ, 4·3μ and 5·9μ, but as these two substances are normally present in our nasal orifices we could not expect to be able to smell them.

If, as is now widely maintained, the perception of odour depends on the intramolecular vibrations of an odorant, then we should expect such odorants to exhibit absorption bands. The existence of an absorption band indicates that the substance has an intramolecular vibration of the same frequency as that of the light absorbed, since the absorption depends on interference between the vibrations of the molecule and of the light. Pending determination of the range of frequencies which are perceptible to the osmic apparatus, there is no reason apparent why such absorption bands should be more noticeable in the infra-red spectrum than in the visible or the ultra-violet spectrum. The visible spectrum extends for only about one octave, whereas the infra-red spectrum covers six octaves, so there is presumably more chance of any given substance having absorption bands in the infra-red than in the visible spectrum. It may be remembered that pigment is always associated with the olfactory apparatus, and this may be connected with the absorption and modification of molecular vibrations.

In an investigation of the subject Grijns (*Proc. Acad. Sci. Amsterdam*, **21**, 476-8, 1919) failed to correlate smell intensity with the capacity for absorbing radiant heat.

Ultra-violet Absorption

The portion of the spectrum extending beyond the violet is termed the ultra-violet. It consists of radiant energy of higher frequencies and shorter wave-lengths than visible light. It can be investigated by photography, as such " light " has a high actinic value. Glass absorbs ultra-violet light so a glass prism is not used, but quartz is a suitable medium. The range of wave-lengths usually dealt with is from 3,930 to 1,000 tenth-metres, i.e. 0·39 to 0·10μ. Just as in the case of the infra-red rays, when a beam of ultra-violet light is directed through a chamber containing the substance under examination before entering the prism, then black absorption bands appear in the white (to photographic plate) spectrum.

Heyninx investigated this subject, and pointed out that odorous substances which gave ultra-violet absorption bands consisted of molecules vibrating with a period equal to that of the ultra-violet light they absorbed. Hence, he argued, actual contact of the odorous substance and the olfactory apparatus might be unnecessary, as the olfactory hairs could be stimulated by the waves formed by the intra-molecular vibrations. Differences in kinds of odour would then be due to different frequencies of vibrations, which could be determined from the ultra-violet absorption bands. However, in the table drawn up by Heyninx it can be seen that water and hydrogen cyanide have precisely the same absorption bands, but we know prussic acid has an odour whereas water has not, and even admitting that we could not detect the odour of water since it is a normal constituent of our olfactory equipment, still we can say positively that hydrogen cyanide has a different odour from water. Yet if odour is conditioned by molecular vibration and this latter can be measured in terms of absorption bands, then water and hydrogen cyanide should have similar odours. Other pairs of substances with similar absorption bands but dissimilar odours were

(*a*) acetone-methylnonic acid and butyric acid,
and (*b*) iodoform and cinnamic aldehyde.

Practically all substances give ultra-violet absorption bands, e.g. benzene, toluene and xylene and hydroquinone, pyrocatechol and phenol. The last three examined in hexane solution have very similar absorption spectra, but very dissimilar odours.

In this case as in the case of the infra-red spectra, the primary relation may be between absorption and chemical reactivity. Indeed, Ramart-Lucas, Naik and Mehta (*J. Indian Chem. Soc.*, **15**, 421-5, 1938, and *Chemical Abstracts*, **33**, 534, 1939), working on the substituted amides of malonic acid, found that there was a relation

between the chemical activity and the absorption in the ultra-violet spectrum.

The strongest lines in the spectra arise from the most probable electron transitions in the atom. It may be noted in the *International Critical Tables* that the seven odorous elements, oxygen, phosphorus, arsenic, fluorine, chlorine, bromine and iodine, although they show ultra-violet absorption band have no very strong lines, or *raies ultimes* as they are called. Practically all other elements possess such lines.

v. Hornbostel (*Pflüger's Arch.*, **227**, 517-38, 1931) has suggested that the degrees of odour " brightness " correspond to the optical absorption bands, and that the " olfactory spectrum " corresponds to shorter wave-lengths than the visible spectrum.

Considering all the evidence it appears that there can be no quantitative relationship between ultra-violet absorption and odour.

Ultra-violet Irradiation

An interesting phenomenon in a similar connection was recorded by Zwaardemaker and Hogewind (*Proc. Acad. Sci. Amsterdam*, **21**, 131-7, 1918). It concerned the spontaneous transformation to a colloidal state of solutions of odorous compounds when exposed to ultra-violet light. Solutions of odorous materials such as eugenol, safrol, etc., were made in glycerine or paraffin or water, and it was found that after exposure they exhibited a Tyndall effect, i.e. a beam of light passing through the solution is scattered by the particles of solute and so becomes opalescent. The following solutions are arranged according to their degree of transformation into suspensoids.

Solutions in water. Eugenol, cresol, guaiacol, geraniol, cumidine and thymol.

Solutions in glycerine. Eugenol, safrol, creosote, nitrobenzene, cresol, and apiol.

Solutions in paraffin. Aniline, eugenol and cumidine.

When an aqueous solution of eugenol (1 in 1,200) was heated beyond 40° C. the opalescence decreased but returned on cooling. Similarly, the opalescence was not so noticeable on hot as on cold days. Sunlight and radium emanation also brought about the change from solution to suspension. The particles in suspension were negatively charged. The change to the suspensoid state was more marked with odorants of high molecular weight than with low.

We have already noted in Chapter 4 an observation that odour was produced when air was irradiated with ultra-violet light and that this was attributed to free ions, although later the odour was ascribed to the formation of ozone.

The time required to destroy odours by irradiation with ultra-violet light has been studied by Tempelaar (*Thesis, Utrecht*, 1913). In each case the time required to reduce the odour from 2 olfacties to 1 olfacty on Zwaardemaker's olfactometer was noted. It will be

remembered that 1 olfacty represents the normal threshold stimulus, and that 2 olfacties represent twice the concentration of molecules that gives 1 olfacty. The times required for the light from a quartz mercury vapour lamp to cause such a reduction in the odour of different substances were as follows :

Valeric acid	0 min. 10 sec.	Vanillin	2 min.
Trimethylamine	0 ,, 30 ,,	Eugenol	3 ,,
Methyl nonyl ketone (rue)	0 ,, 35 ,,	Coumarin	3 ,, 30 sec.
		Cresol	5 ,,
Pyridine	0 ,, 45 ,,	Chloroform	6 ,,
Safrol	0 ,, 50 ,,	Anethole	6 ,, 30 sec.
Skatole	0 ,, 50 ,,	Linalyl acetate	7 ,,
Aniline	1 ,, 40 ,,		

Michael (*Biochem. Z.*, **233,** 470-7, 1931) showed that when odorous substances were irradiated with ultra-violet light their odour changed, and this change in odour is due to slight chemical decomposition. The concept of " brightness " of smell was introduced to express the strength or volatility of the odour. The change in " brightness " of an odour depended on the degree and duration of the irradiation. A typical exposure was for 2 to 4 hours with a mercury vapour lamp, which was equivalent to about a good day's sunshine.

Aliphatic ketones, e.g. acetone, and mixed alkyl-aryl ketones, e.g. acetophenone, became " brighter " in smell on irradiation, but aromatic ketones, e.g. benzophenone, became " duller." Esters such as ethyl acetate and octyl acetate, as well as aromatic hydrocarbons, also became duller in smell on irradiation. It may be noted here that Michael (*Biochem. Z.*, **255,** 351-77, 1932) subsequently introduced the idea of " brightness " of taste, and showed that it ran parallel with the heat of solution of the substance, e.g. with dicarboxylic acids, the brightness of taste increased as the carboxylic groups were brought closer together, and in unsaturated acids the cis form is brighter in taste than the trans form.

Müller (*J. Prakt. Chem.*, **154,** 209-18, 1940) investigated the luminescence or fluorescence of essential oils when exposed to ultra-violet light. He examined 252 compounds representative of most types of odorant substances (alcohols, aldehydes, ketones, esters, lactones, etc.) and found that

160	showed a more or less violet luminescence.	
37	,, bright violet	,,
22	,, pale greenish	,,
10	,, bright green	,,
10	,, bright yellow-green	,,

Refractive Index

It is surprising how many strong odorants have refractive indices in the neighbourhood of 1·5. Some examples are

Benzene	1·502	Toluene	1·498
Xylene	1·500	Naphthalene	1·582
Benzaldehyde	1·546	Nitrobenzene	1·553
Phenol	1·542	Camphor	1·532
α-ionone	1·498	β-ionone	1·520
Irone	1·501	Eugenol	1·542

Of course not all odorants have this property, e.g. iodoform has a value of 1·800 and butyric acid one of 1·399. Likewise non-odorous bodies may have a refractive index of 1·5, e.g. glycine has a value of 1·495. It is, however, remarkable how many odorants do have a refractive index close to 1·5. In *Perf. Essent. Oil Rec.*, **28**, 1937, 96-9, there is given a list of 101 perfumery chemicals. Of these hydroxy-citronellal has the lowest refractive index, 1·4495, and cinnamic aldehyde has the highest 1·6211, which is quite a narrow range for so many diverse substances.

The Raman Effect

In 1928 Raman showed that when monochromatic light, e.g. the green light from a mercury vapour lamp, was scattered by a pure substance, the scattered light was no longer homogeneous, but when

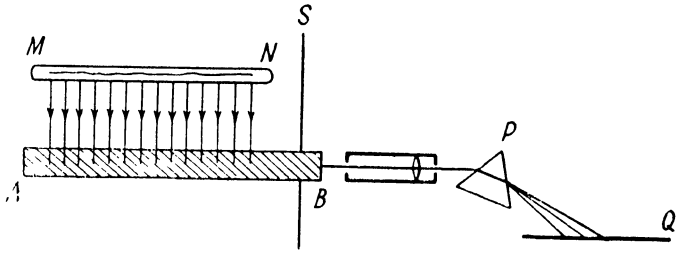


FIG. 25.—The Raman effect.

MN. Source of light.
AB. Quartz tube filled with liquid under examination.
S. Metal screen.
P. Prism.
Q. Sensitive plate.

examined with a spectrometer was found to consist of light of both longer and shorter wave-lengths than the monochromatic light used. The difference in wave-length is the Raman shift. The differences in wave-length of light are independent of the wave-length of the light used. The Raman spectrum is characteristic of any pure compound. It is related to the infra-red absorption spectrum. If, for example, green mercury lamp light of wave-length 4,358 tenth-metres falls on benzene some light of wave-length 5,000 tenth-metres is reflected. The shift is thought to be due to a resonance effect, derived from the energy of the molecules of the scattering substance. This is evidently a method of gaining information respecting the molecular vibrations.

The principle is shown in the diagram, Fig. 25. The substance (liquid) under examination is contained in the closed tube AB, and is irradiated with monochromatic light from a lamp MN. Only light which has been scattered by the substance in the tube AB is able to pass through the metal screen S. This light is then analysed with a spectrometer and found to consist of various light waves of different lengths as well as the incident monochromatic light.

According to Dyson, whose theory we shall examine in the next chapter, only substances possessing Raman shifts between 1,400 and 3,500 are odorous. The Raman effect is characterized by the following regularities:

(1) The Raman spectrum of a pure liquid is a series of lines, not just a single line, and must therefore represent not just a single modification of the original light but a series of such modifications.
(2) The Raman spectrum of a given pure substance is constant, but the spectrum is unique, i.e. no two substances have exactly similar Raman effects.
(3) The Raman shift (difference in wave-lengths of incident and emergent lights) is independent of the incident wave-length.

It is clear then that the Raman shift is a measure of the intramolecular vibrations of a substance, and since the odour is commonly supposed also to be dependent on the intramolecular vibrations we might expect to find a close relation between Raman shift and odour. Dyson has shown very convincingly that there is such a relation. Thus the alkyl mercaptans R—SH are a homologous series with powerful, objectionable odours, and the odours of the first members of the series are very similar to each other. Comparison of the Raman spectra of methyl, ethyl, propyl, butyl and amyl mercaptans shows that they all have a Raman shift of 2,567 to 2,580. No other compounds have this shift, and no other compounds have the mercaptan odour and presumably the mercaptan molecular vibrations. We could, therefore, say that the osmic frequency of 2,580 is that of the mercaptan, just as we associate the visual vibration of 4,358 tenth-metres with green (blue ?).

When the Raman spectra of the paraffin hydrocarbons are examined methane has a very simple spectrum with a shift at 2,800, and the spectrum becomes more and more complex as we pass from ethane to propane, octane, decane and dodecane. Still the 2,800 shift persists. Pure octane, nonane, decane and dodecane have powerful and similar odours. As we go further up the series the Raman spectra are similar but odour falls off due to the decreasing volatility of the higher compounds. If we compare the olefines with the paraffins we find a new shift in the 1,600 to 1,800 region, which explains the characteristic difference in odour between the paraffins and the olefines. Likewise the acetylenes have a line in the 2,100 region.

If, as is usually the case, the Raman spectrum of a substance consists of a series of shifts in the region 1,400 to 3,500, then the smell is not a simple odour but the resultant perception of the simultaneous sensation of several different odours. By examination of the Raman spectra it might be possible to show which substances have pure, simple or fundamental smells.

Aldehydes and ketones are found to have Raman shift lines in the region of 1,700. An interesting point is that stereoisomers have different Raman spectra, and, as we have discussed, often have different odours. Thus the Raman lines for

cis 2-pentene are 1,248, 1,266, 1,375, 1,658.
trans 2-pentene are 1,298, 1,313, 1,378, 1,674.

It is supposed that Raman shifts below 1,400 and above 3,500 are not perceptible to man. For those that are, the correlation of Raman shift and odour is as follows :

Raman Shift.	*Type of Odour.*	*Raman Shift.*	*Type of Odour.*
1,500	—	2,500	Mercaptan and allied odours.
1,600	Imines.	2,600	—
1,700	Aldehydes, ketones.	2,700	Ether types.
1,800	Esters, terpene aldehydes.	2,800	Higher aliphatic hydrocarbons.
1,900	Acyl chlorides.		
2,000	—	2,900	—
2,100	Acetylenes.	3,000	Aromatic hydrocarbons.
2,200	—	3,100	—
2,300	Chlorinated aromatic hydrocarbons.	3,200	Heterocyclic and amine bases.
2,400	—	3,300	Pyridine, pyrrole.
		3,400	—

It is evident that there is a much closer relation between odour and the Raman effect than between odour and infra-red or ultra-violet absorption. Exceptions will probably be found. Glycerine, for example, is odourless but it has a vapour pressure and some lipoid solubility, and according to Saksena (*Proc. Indian Acad. Sci.*, **10A**, 333-40, 1939, and *Chemical Abstracts*, **34**, 3173, 1940) it has lines in its Raman spectrum at 466, 2,880, 2,955, 3,202, which should presumably excite olfaction.

For further particulars of the relation between odour and the Raman effect Dyson's original papers should be consulted. They are

Perf. Essent. Oil Rec., **28**, 13. 1937.
Chemistry and Industry, **57**, 647-51, 1938.

Spray Electricity

Zwaardemaker and Hogewind (*Proc. Acad. Sci. Amsterdam*, **22**, 429-37, 1920) found that the spray formed by extruding water from a fine jet is not electrically charged, but if the water contains an odorant in solution even in small quantities, then the spray carries a strong positive charge. This the authors pointed out afforded a means of detecting odorous molecules other than by the sense of smell. In a

later paper Zwaardemaker and Zeehuisen (*Proc. Acad. Sci. Amsterdam*, **23**, 658-62) showed that although pure water and solutions of most inorganic salts give no charge there are a few salts which impart a slight negative charge to the spray, probably on account of the anions being in excess on the surface of the drops.

Zwaardemaker (*Vers. Akad. Wetenschappen Amst.*, **25**, 3-10, 1916) showed that when a disk well insulated with amber and paraffin is held very close to the atomizer it does not become charged but that it does as it is moved away, reaching a maximum charge and then diminishing. The formation of the static electricity is due primarily to the reduction in surface tension of the water caused by the odorant, but molecular weight and solubility of the odorant also play a part. These are the same properties, viz. reduction in surface tension of solvent, molecular weight and solubility as determine the " specific smell-strength." This latter is defined as the smallest amount of substance in grams per litre which can be detected by odour. Zwaardemaker found that when the " log smell-strength " was plotted against molecular weight in the case of the fatty alcohols, he got a curve similar in shape to that obtained by plotting the optimum distance of the plate from the atomizer against the molecular weight. Hence " smell-strength " and the distance of the plate from the atomizer to obtain the maximum charge showed a close parallelism. When the same curves were plotted for the fatty acids the " smell-strength " showed a maximum for valeric acid, the C_5 acid, and the " central distance of the plate " showed a maximum for caproic, the C_6 acid.

The quantity of the electric charge per c.c. of saturated solution has been worked out for various substances by Zwaardemaker, Backman and Huyer, separately. The following are taken from a list compiled by Zwaardemaker in *International Critical Tables*, **1**, 359, 1926.

Odorant.	*Spray electricity per c.c. of saturated solution.* 10^{-10} *coulombs.*
Aniline	0·4
Scatol	1·0
Trinitroisobutyl toluene (artificial musk)	1
Toluene	5·1
Nitrobenzene	9·6
Phenol	15·2
Camphor	20·3
Heliotropin	52
Citral	360

If the concentration of the odorant is reduced, i.e. instead of a saturated solution using a half-saturated solution the quantity of the charge is also reduced by rather more than one-half.

Backman (*Verslag. Akad. Wetenschappen Amsterdam*, **25**, 971-84, 1917) atomized saturated aqueous solutions of benzene, toluene, xylene,

pseudocumene and durene against an aluminium plate. He found that the charge produced decreased from benzene to durene, but that with equimolecular solutions it was nearly the same for benzene, toluene, pseudocumene and durene but anomalously high for xylene. If we compare this with the perceptibility of these substances by smell, we find that the perceptibility increases regularly from benzene to pseudocumene, but durene has a fainter odour. Evidently there is no very close parallelism.

Zwaardemaker (*Arch. néerl. Physiol.*, **1**, 347-73, 1917) was able to make a stable fog by atomizing a 2 per cent. sodium chloride solution, but if an odorous substance was added to the salt solution then the fog was much less stable and soon disappeared. In the former case when no odorant was used the positively and negatively charged particles must have been present in equal quantities, since excess of neither remained when the fog was dissipated. In the latter case when an odorant was present the vapour imparted a strong positive charge to an isolated metal disk or glass tube inserted into it. It was suggested, therefore, that the fog contained large positively and small negatively charged particles, and that the latter dispersed more easily on account of their small size and higher speed. Whilst all odorous substances exhibit the spray charge phenomenon, not all substances which exhibit the charge are odorous. It is clear that anything which facilitates condensation of watery vapour containing an odorant in the olfactory regions will promote perception of the odorant. Hence the odorants which generally reduce surface tension promote conditions in the nose under which they will best be perceived.

Diffusion

Under natural conditions the detection of odour depends largely on the diffusion of the odorous particles through the atmosphere, and this is greatly aided by wind, as odour travels with the wind. Those substances which diffuse most rapidly will be the first to be perceived. Backman, in his 1917 paper, just quoted, reported the measurement of the rates of diffusion of benzene and its homologues. Through 40 cm. of air at 19° C. benzene and toluene required 75 seconds to diffuse and xylene and pseudocumene required 60 seconds. These speeds may be compared with those determined by Zwaardemaker for eugenol, camphor and ether.

Benzene	0·53 cm. per sec.	Eugenol	1·3 cm. per sec.
Toluene	0·53 ,, ,,	Camphor	2·1 ,, ,,
Xylene	0·67 ,, ,,	Ether	4·4 ,, ,,
Pseudocumene	0·67 ,, ,,		

Diamagnetism

Zwaardemaker and Hogewind (*Arch. néerl. Physiol.*, **4**, 224-32, 1920) failed to find any relation between magnetism and odour. In any homologous series when the number of atoms in the molecule

were plotted as abscissæ and the values of diamagnetism found were plotted as ordinates, a practically slight line resulted. If magnetism and odour had run parallel the curve would have risen to a peak at about C_{10} and then fallen to zero.

Dilution

Odours often change in quality as well as strength on dilution. Many substances used in perfumes are not fragrant in a pure state or in a concentrated solution. Indole is present in jasmine, but pure indole has a disgusting smell. Civet and ambergris, two of the most important fixatives, are disagreeable when pure. The C_7 aldehyde heptanal has a penetrating aromatic odour, but a trace of it will lend distinction to a perfume. Further, the odour of a dilute solution may be more powerful than that of a more concentrated solution. The explanation sometimes given of the change of odour is that there are two different odours, jasmine and fæcal in the case of indole, and the latter has a higher threshold value than the former, so that in great dilution only the jasmine odour is perceptible.

Adsorption

It is a common experience to find that a substance or material has acquired an unwanted odour. Working overalls and laboratory coats are particularly liable to this, and the clothes of a person working in proximity to an odorous material such as an amine are soon redolent of it. Tobacco is another case in point. It picks up and walks away with any wandering flavour or smell. In peace-time, tobacco ships usually carry nothing else and are specially cleaned and fumigated before the tobacco is loaded. Ogle in 1870 mentioned that dark substances absorb odours much more readily than do light ones, and that in dissecting rooms dark clothes acquire the cadaveric odour sooner and are less readily deprived of it than light ones. He noted that Dr. Stark of Edinburgh found black the most powerful absorbent of odours, then blue, green, red, yellow and white.

Activated carbon such as cokernut charcoal will adsorb enormous quantities of odorous substances. It will take up at least half its own weight of benzene. It will readily adsorb chloroform and similar substances. It picks up ammonia well, but gases like hydrogen, nitrogen, oxygen, carbon monoxide and carbon dioxide, it will only adsorb in very small quantities. As gases which excite smell are usually adsorbed well by carbon and other surface agents it is not unlikely that adsorption in the olfactory apparatus precedes the sensation of smell.

Kaolin, $Al_2O_3 . 2SiO_2 . 2H_2O$, when pure, is odourless, but when moistened with water or alkali, the odour of clay is noticeable. Clay can adsorb gases and odours owing to its colloidal nature and consequent large surface. Clay will retain adsorbed odours indefinitely. Talc is similar, and its strong adsorptive power for odours renders it

useful in perfumery (Rohland, *Deut. Parf. Ztg.*, **1**, 266-9, 1915). Such substances will also pick up tastes and on shaking a solution of iron saccharate with colloidal clay, the sweet taste passes to the clay.

van Dam (*Physiol. Abstracts*, **2**, 480, 1917) determined the adsorption of odoriferous liquids such as ionone, eugenol, citronyl acetate, acetophenone, nitrobenzene, etc., on rods of platinum, gold, zinc, glass and paraffin wax. A drop of the odoriferous liquid was placed in a flask and the rod inserted through the stopper of the flask. The rod was withdrawn from the odoriferous air in the flask after one minute and then tested for strength of odour in an olfactometer. He found that the degrees of adsorption varied, paraffin wax often being the best adsorbent.

Zwaardemaker (*Proc. Acad. Sci. Amsterdam*, **23**, 654-7, 1921) pointed out that adsorption of odorous molecules on solid surfaces may take place in three ways: (1) through the condensed layer of moisture usually present on all surfaces, (2) by direct adsorption to the clean solid surface from which the moisture film has been removed, (3) by direct attraction of charged particles by an oppositely (electrically) charged surface. Cases of the first type are given below. After exposure of the surface to a continuous stream of odoriferous air for five minutes, the adsorbed odorant was perceptible by smell for the time indicated. Clearly the longer the duration the odour persists, the greater the adsorptive power.

Odorant.	*Adsorbing Surfaces.*	*Duration of Odour.*
Pyridine	Aluminium, glass, gold, lead, nickel, silver	Not more than a few seconds.
,,	Copper, zinc and porcelain	A few minutes.
,,	Iron and steel	½ to 1 hour.
Valerianic acid	Copper, gold, iron, lead, nickel, porcelain, steel, zinc	Not more than a few seconds.
,, ,,	Aluminium, silver, tin	A few minutes.
,, ,,	Glass	½ hour.
Skatole	Porcelain	Hardly at all.
,,	Glass	1½ hours.
,,	Metals	1 to 20 days.
Ionone	Glass, porcelain, silver	Not more than a few seconds.
,,	Lead, nickel, iron, copper, aluminium	1 to 4 days.

It is clear that there are marked preferences. A fuller list of such phenomena is given by Zwaardemaker in *International Critical Tables*, **1**, 359, 1926.

Cases of adsorption of the second type, not due to moisture film, were demonstrated on surfaces of amber, sulphur and paraffin wax. Some remarkable instances were found where one adsorbed odorant would be driven out of a surface by another odorant. For example, eugenol or xylidine would drive out allyl alcohol. The reverse action could not be brought about.

CHAPTER 12

THEORIES OF ODOUR

Province of Odour Theories

In the perception of odour there are three well-defined processes. First, the olfactory region is stimulated, secondly, the stimulation passes by way of the olfactory nerve to the brain, and thirdly, brain processes take place which result in odour sensation. The third stage is still practically a closed book to us. The second has been clarified by the work of Ogle and Adrian. The former showed that the olfactory region must be accessible to a stream of air during respiration, and that obstruction of the air passages, or damage to the olfactory nerve would prevent olfaction. Adrian demonstrated that the sensory nerves carry their messages from the receptor cells to the brain as a series of discrete electrical impulses and that, failing fresh stimulation, the sensation falls off due to adaptation. It is true that this has not been demonstrated in the case of odour, but it has been so clearly proved in the case of the other senses which have a similar nerve system to the olfactory apparatus that there can be no reasonable doubt under this heading. If the third stage, the final brain processes, is a mystery to us, the second, that of the transmission of the stimulus from the receptor to the brain, is established fact. The first stage has reached an intermediate stage of development.

We know that the normal stimulus is air which has been in contact with an odoriferous substance. The province in which the theories abound is the relation of the chemical and physical properties of the odorants to their odour and the means by which they excite the olfactory region. In particular, the question which has caused the greatest controversy is whether particles of the odorant must come in contact with the olfactory apparatus, or whether the message can be passed from the odorant to the nose by waves. Again, if the odorant must make contact with the olfactory region, is its action on the receptors chemical or vibratory ?

Master-theories

Theories abound. To theorize calls for less patience and time than to experiment. Above all, experimentation involves hard work with a good deal of repetition and frequent disappointments. Some of the greatest names in the study of olfaction, such as Zwaardemaker, v. Braun and Ruzicka, constantly recur in the experimental data, but only rarely are they to be found in the ranks of the theorists. In practically every case the truth is found by laborious experiment, seldom by evolving a theory and then proving or disproving it. Mendel's laws of heredity do seem to have been the result of theorizing

followed by experimentation—a hunch that came off, but only once in a blue moon will success attend such a process.

Despite the multiplicity of theories they may be reasonably divided into three groups which we may call the Master-Theories. These are

(1) The corpuscular theory which regards the stimulation of the olfactory region as due to particles of the odorant flying about in the air and making contact with the nasal orifices. The action on the olfactory region is regarded as chemical.
(2) Similar to (1) in requiring actual contact of particles of the odorant with the olfactory region, but regarding the stimulation as due to vibratory rather than chemical action.
(3) The wave-theory which regards the odorant as emitting waves which affect the olfactory organ, just as light waves affect the eye.

Probably the best arrangement will be to consider the known facts which the theories of olfaction must fit, then to review the principal theories, and finally to review the evidence for and against these theories.

Olfactory Facts

To be useful a theory must first comply with the known facts, then it may be possible to predict the behaviour of new substances from the theory, and if these predictions are later proved in fact, the theory has been useful. It will probably not be permanent. New discoveries will show its limitations and it may be found to have covered only special cases.

However, the first essential is compliance with existing facts, and in the case of olfaction these facts may be stated as follows :

(1) All normal people can smell.
(2) People suffering from brain lesions, injured olfactory nerve or obstructed nasal passages may be anosmic.
(3) Cases of preferential anosmia, i.e. ability to sense certain smells and not others are not well-established. Such cases occur, but little is known of them.
(4) Some substances are odorous, others are not.
(5) We can smell at a distance. If we smell the roses in a garden we do not ordinarily consider part of the roses as being in contact with the nose (although corpuscles may in fact be so).
(6) Substances of different chemical constitution may have similar odours.
(7) Substances of similar constitution usually have similar odours, e.g. in a homologous series. Nevertheless, isomers and even stereoisomers may have different odours.
(8) Substances of high molecular weight are usually inodorous and often non-volatile and insoluble.

(9) The quality as well as the strength of odour may change on dilution.
(10) The sense of smell is rapidly fatigued.
(11) Fatigue for one odour will not affect the perception of other dissimilar odours, but will interfere with the perception of similar odours.
(12) Two or more odorous substances may cancel each other out. This compensation will mean that two odorous substances smelt together will be inodorous.
(13) Odour travels down-wind.
(14) Many animals have a keener sense of olfaction than man. Insects have such extraordinary keenness of smell that it may be a different modality of the chemical sense from that known to us.

Ogle

In 1870 Ogle wrote (*Medico. Chirur. Trans.*, **53**, 263-90) :

" As in the eye and the ear the sensory impression is known to result not from the contact of material particles given off by the object seen or heard, but from waves or undulations of the ether or the air, one cannot but suspect that the same may be true in the remaining sense, and that the undulatory theory of smell, deriving also, as it does, support from some other facts, may, perhaps after all be the true one." Ogle attached considerable importance to the presence of pigment, and showed that macrosmatic animals have darker pigment and larger areas of the inner nasal surfaces pigmented than man. How, he asked, could the olfactory pigment affect the reception of olfactory impressions ? Possibly, he suggested, it might serve to absorb the vibrations of odour and to convert them to vibrations of heat which would affect the contiguous cells in which the olfactory nerves end. The pigment cells, he pointed out, were not in the nerve structures themselves but were adjacent thereto. Pigment was essential to sight, hearing and smell, and the first two were known to be stimulated by waves, therefore the last was also probably so stimulated. As regards hearing, cats with pure white fur and blue eyes were almost invariably deaf, but not if there was a single blotch of colour.

Again, " The pigment which is so constant in the olfactory region is there to absorb the odorous emanations. The darker the tint of the pigment and the wider its extension, the greater will the absorption be. Hence the keen scent of black or coloured animals or men." Here, then, at an early date we have a clearly defined undulatory theory of smell. It is the prototype of a whole series of similar theories put forward in the next seventy years. It offers no ready explanation of fatigue phenomena or of change of quality of odour on dilution, and the fact that odour travels down-wind would seem to invalidate an ether-wave theory, but not an air-wave theory, for, of course, sound also travels down-wind.

Woker

In 1906 Woker (*J. Physical Chem.*, **10**, 455-73) classified odours and drew the following conclusions :

Saturated compounds rarely produce odour, and then only in the case of very volatile substances. Volatility is increased, especially by loading a carbon atom with identical groups. Substances containing at least one tertiary carbon atom often have a camphoraceous odour, if at least two of the substituents of the tertiary carbon atom are identical. In these cases it is unimportant whether the compound is saturated or unsaturated, but in the latter case three of the substituent groups on the tertiary carbon atom must be the same. Other things being equal, the odour increases as the degree of saturation diminishes. A triple (acetylenic) linkage gives a more intense odour than a double (ethylenic) linkage. The presence of more than one point of unsaturation increases the odour.

It will be seen that Woker's theory was chemical, and that outstanding importance was attributed to unsaturation. It was the forerunner of many later theories, notably that of Durrans.

Fabre

In " Social Life in the Insect World " Fabre considers the miraculous way in which the male butterfly is attracted over great distances by the female. He attributes the attraction to odour, and concludes that odour must be transmitted as waves and not as material particles. He writes, " For emission substitute undulation and the problem of the Great Peacock is explained. Without any material emanation a luminous point shakes the ether with its vibrations and fills with light a sphere of indefinite magnitude. So, or in some such manner, must the warning effluvium of the mother Oak Eggar operate. The moth does not emit molecules, but something about it vibrates causing waves capable of propagation to distances incompatible with an actual diffusion of matter. From this point of view smell would have two domains—that of particles dissolved in the air and that of etheric waves. The former domain alone is known to us. . . . The second category of odour, far superior in its action through space, escapes us completely, because we lack the essential sensory equipment." It will be seen that whilst Fabre elaborates a theory of odour waves for moths and insects he is content to accept the conventional theory of material particles for man. His reference to " etheric vibrations " is not compatible with his own experimental results. He showed that if ingress and egress of air was excluded as in the case of a closed drawer, odour could not pass. Of course, it might be argued equally well that light could not pass into a closed drawer, but there is so much other evidence that odour is air-borne that we may safely leave the ether out of it.

Heyninx

Heyninx (*Thesis*, Utrecht, 1917) argued that odorous vapours were composed of molecules vibrating with a period equal to that of the ultra-violet light they absorbed, so that actual contact of the odorous molecules with the olfactory hairs might not be necessary. The differences between odours were due to differences in the frequency of vibration. No explanation was offered as to how the olfactory hairs reacted to these ethereal waves. Such a theory clearly accounts for the compensation of odour, as the vibrations from two odorants could cancel each other by interference so that there would be no resultant odour, as in the case of benzene and rubber. However, as McKenzie pointed out in " Aromatics and the Soul " (Heinemann, 1923), the ultra-violet light and odour associations put forward by Heyninx showed irregularities. Iodoform and cinnamic aldehyde had practically the same absorption bands but different odours, whilst acetone-methylnonic and butyric acids have precisely the same absorption bands and yet exhale totally different odours, and again hydrocyanic acid and water had similar bands. In addition infra-red absorption bands have been connected with odour. Probably the significance is that chemically reactive molecules have vibratory groups, and such molecules are also odorous. There is probably no special significance in the vibrations occurring in the ultra-violet spectrum.

Marchand

Of the four theories we have just considered, those of Ogle, Fabre and Heyninx were all concerned with vibrations, and postulated that odour might arise without actual contact of the odorous molecules with the olfactory region. Fabre's theory, it is true, was restricted to insects, and he excluded man from it. Now we come to another theory of the type of Woker's. Marchand (*Deut. Parf. Ztg.*, **1**, 223-4, 243-5, 287-8, 1915) said clearly that all perfume effects are dependent on free valencies. It is certainly true that unsaturation enhances odour. Other workers have not failed to connect the two. Nevertheless, it is difficult to reconcile the odour of the paraffins which are saturated, e.g. hexane, heptane, octane, with the view that odour depends on unsaturation. Marchand pointed out that many strongly odorous bodies contain doubly-bound oxygen, e.g. aldehydes, ketones and acids, but that the presence of two such groups in a molecule lowers the perfume effect or may destroy it entirely.

Henning

In his book " Der Geruch " (Leipzig, 1916) Henning abandons the view that particular odours are associated with special groups and gives more importance to the arrangement of the groups in the molecule. The structures are significant, not so much in themselves but because of the positions they occupy. One of these structures may be the cause of odour if it occupies an appropriate place in, say, the

benzene nucleus. In a general way it was possible to indicate the type of chemical constitution corresponding to the six different types of odour. These types were

Spicy, with osmophoric groups in the *para* position as in anisaldehyde.
Flowery, with the groups in *meta* or *ortho* positions as in tuberon.
Fruity, where the groups are forked as in citral.
Resinous, where the groups are within the ring as in pinene.
Burnt, where the ring is smooth as in pyridine.
Foul, where the ring is fragmentary as in cacodyl.

Intermediate odours are due to a combination of two groupings, e.g. vanillin has both *ortho* and *para* arrangements and is spicy and flowery. This theory is limited to the chemical and structural aspect.

Backman

Backman (*J. phys. path. gen.*, **17**, 1-4, 1917, and *Physiol. Abstracts*, **2**, 479, 1917) put forward a theory that the molecules of the odorous substances must come into contact with the olfactory region and then must dissolve, first in the watery mucus and later in the lipoid tissues. Hence to be odorous a substance must be soluble in both water and oils, and so the middle members of a homologous series, such as butanol and amyl alcohol were strongly odorous. The early members like ethanol were not readily oil-soluble and consequently had feeble odours, whilst the higher members like stearyl alcohol were insoluble in water and inodorous. We have already examined the solubility of odorants, and whilst all appear to be soluble in oils, some are definitely insoluble in water. It may be argued that such substances may be slightly soluble in water, but not sufficiently to be detectably so. Still if we start making our facts fit the theories we shall end in disaster.

Teudt

Teudt concluded that odour was due not to material particles of volatile substances but to oscillations of valence electrons within the molecules of each substance (*Prometheus*, **30**, 201-4, 209-11, 1919, and *Chemical Abstracts*, **14**, 1685, 1920, and *Physiological Abstracts*, **4**, 484, 1920). The source of odour lay not within the atom but within the molecule between those atoms which contained the valency electrons. Odours were caused by the vibration of these electrons. The electronic vibrations of the sensory nerves, and consequently the odorous effects, were increased by resonance when odoriferous particles with similar intramolecular vibrational frequencies were inhaled. Air might also by resonance increase the olfactory effect. Metallic atoms readily detach electrons and are therefore not suited for the production of odour. The connection between odour-formation and the electro-negative character of the elements has already been pointed

out in connection with the Electrochemical Series in Chapter 9. Teudt showed a remarkable anticipation of the modern theories. His conclusions were derived from theoretical considerations rather than from exact knowledge of the intramolecular vibrations which was not then available, but his conclusions are very similar to those now accepted.

Durrans

Durrans first made an exhaustive study of the relation between odour and chemical constitution. This was reported in *Perf. Essent. Oil Rec.*, **10**, 104-34, 1919. Later, in the same journal (**11**, 391-3, 1920), he put forward a Residual Affinity Odour Theory. He pointed out that molecules of odorous compounds frequently showed the possession of free residual affinity, e.g. the ease with which they formed double or addition compounds. This property was not confined to odorous molecules. Durrans suggested that probably the chemical reaction that takes place in the nose and gives rise to the sense of odour is an addition reaction, except in the case of sternutatory and similar substances, where the action is destructive. The probable sequence of events was (1) the odorous molecules reach the nostrils, (2) they dissolve in the aqueous mucous layer, (3) they pass in part to the lipoid layer, the amount passing depending on the partition coefficient of the substance in oil-water, (4) an addition reaction takes place in the fat-layer, (5) the addition reaction causes a change of energy which produces the stimulus for the nerves.

The particular odour would depend on the velocity and the kind and the number of addition reactions taking place. The essential feature is the common inherent characteristic of odorous molecules of possessing residual affinity, quite apart from questions of solubility or physiological action. " If the various osmophores and sources of odour be examined, it will be noticed that there is always a possibility of residual affinities or unsatisfied partial valencies existing. It will suffice to mention the oxygen atom, the benzene ring and multiple bonding. . . . I believe that such unsatisfied residual valencies are the prime cause of a substance having an odour." Dyson has criticized this statement of Durrans on the ground that the saturated paraffins should be odourless, but in fact those with appreciable volatility are odorous—some strongly—therefore residual affinity *per se* cannot be the primary cause of their odour. The paraffins are the stumbling-block of many theories. Chemical reactivity and odour run parallel in so many cases. It would be interesting to see if there were any diminution of odour with progressive purification of some individuals from the paraffin series.

Heller

Heller (*Am. Perfumer*, **14**, 365-6, 1920) put forward the theory that the odorous molecules first came into contact with the olfactory

mucous membranes in which the nerve ends are embedded. They then exerted a direct chemical action on the neuron. This theory in itself does not embrace any new features, but Heller pointed out that Teudt's theory of resonance implied that the odoriferous molecules remained unchanged and that the sensation of odour should therefore be experienced when the air is exhaled as well as when inhaled, and therefore since this was not the case the odorous molecules must suffer chemical change as his (Heller's) theory allowed for. This view of Heller's is open to criticism. In the first place, if the odorous air is drawn in through the mouth and expelled through the nose the sensation of odour is perceived. So far this is in accord with Heller's views, but we have seen in an earlier chapter that the exhaled air takes a lower path than the inhaled air during breathing and is therefore less likely to come into contact with the olfactory region. In addition, during inhalation the olfactory nerves are subjected to a strong stimulus and are partially fatigued, so that the weaker stimulus of the exhaled air would be unlikely to produce a noticeable effect. It seems to the writer that the simplest method of proving whether the odorous molecules are changed during olfaction, would be to inspire a volume of faintly odorous air and collect the expired air. Then after a suitable interval of a few minutes for normal breathing, to breathe in the collected air and collect it on expiration again. By repeating this process a number of times it should be possible to decide if the odorous molecules are unchanged or are lost during olfaction. If they proved to be lost the question of whether this was due to chemical action or adsorption would still remain.

Tschirch

Tschirch (*Chem. Zentr.*, **3**, 190-1, 1921) put forward the theory that the odour of a substance depends on its solubility in air and also on its partition coefficient between air and the lipoid plasma of the olfactory cells. Hence to be odorous a substance must be soluble in lipoids and in air. The idea of solubility in air is used by Tschirch in a different sense from having a vapour pressure or being volatile. Tschirch further suggested that the sensation of smell was probably due to the formation of a loose compound of the odoriferous substance with the plasma of the olfactory cell. It was therefore a chemical stimulus.

Zwaardemaker

According to Zwaardemaker (*Arch. néerland Physiol.*, **6**, 336-54, 1922) the intensity of odour depends on (1) the volatility, (2) diffusibility, (3) ease of absorption on the surface of the watery membranes, and (4) ease of solution in the lipoid tissues. We have already seen how volatility affects the odour, and that many odorous substances have very low vapour pressures. Zwaardemaker considered that gases of low diffusibility best served the purposes of olfaction, as

otherwise the odorous material would be quickly lost. Substances which lower the surface tension of water collect in the surface layer of condensation, so if odorous air condenses in the nose those substances which lower the surface tension of the watery mucus will be readily adsorbed by it as a surface layer. Most odorants do lower the surface tension of water when dissolved in it.

In this connection Zwaardemaker and Zeehuisen (*Proc. K. Akad. Wetensch. Amst.*, **22**, 175-8, 1919) had found that spray electricity disappears at about the same point as odour, i.e. if a solution of an odorant was diluted until its spray was no longer detectably electrified, then at the same point the odour was no longer detectable. Spray electricity is thought to be due to the reduction of surface tension caused by the odorant.

Finally comes solution in the lipoids of the epithelial cells. First comes volatility to ensure that molecules may make contact with the nose, then low diffusibility so that the molecules are not quickly lost, then absorption on the watery mucous surface and, finally, solution in the olfactory cells. Zwaardemaker pointed out that the molecular weight of an odorant could not be less than 17 (ammonia) nor larger than 300 (alkaloids). However, some authorities ascribe a faint odour to methane which has a molecular weight of 16. Zwaardemaker considered that odour was dependent on the presence of odoriphores, special chemical groups, each of which was responsible for a special odour. The quality of the odour would, however, change and become more aromatic on ascending a homologous series. Some of the odoriphores were

Group 1. Ethereal odours. Ether linkages.
Group 2. Aromatics. Benzene nucleus with a side chain. In the case of odours of citral the long aliphatic chain with evenly distributed weight was the odoriphore.
Group 3. Balsamic. Benzene nucleus with lateral chain often containing another odoriphore group such as aldehyde, ketone or ester.
Group 4. Ambrosial. Odoriphores unknown.
Group 5. Alliaceous. Various odoriphores containing sulphur and arsenic.
Group 6. Empyreumatic. Typical phenol grouping.
Group 7. Caprilic.
Group 8. Repulsive. Pyridine nucleus.
Group 9. Nauseating. Pyrrol nucleus.

The action of the odoriphore in exciting olfaction might, it was suggested, be based on one of the following :

(1) Relative movements of the odoriphore groupings in the molecule.
(2) Electron movements.
(3) The static arrangement between the groupings in the molecules.
(4) The characteristics of the groups.

Zwaardemaker covers all the points then known. To summarize his theory, a substance to be odorous must

(1) Possess odoriphoric groups.
(2) Be volatile.
(3) Be not too readily diffusible (this presumably for sustained but not for temporary effect).
(4) Lower the surface tension of water so that it is readily adsorbed as a surface layer in the watery mucus.
(5) Dissolve in the lipoids.

Ungerer and Stoddard

These two workers (*Ungerer's Bull.*, **3,** No. 1, 7-10, 1922, and *Chemical Abstracts*, **16,** 2384, 1922) put forward a vibrational theory of odour. The cause of odour is the intramolecular vibrations which affect the olfactory nerves. These vibrations are too delicate to detect by instruments. Each pure substance has its characteristic frequency of vibration and hence a characteristic smell, provided that the frequency is not outside the range of olfactory sensitivity, for the vibrations may be too short or too long to be detected by the olfactory apparatus, just as the ultra-violet and infra-red rays are not perceptible to the eye. It is thought that unsaturation in the chemical sense would give rise to these molecular vibrations, and the fact that many odorous substances are unsaturated supports the theory. Often when a substance is isolated in a state of high purity it no longer possesses its characteristic odour, and yet the minute quantity of impurity which is removed is found to have only an indifferent odour. The profound effect of this small quantity of relatively inodorous impurity on the bulk of substance was thought by Ungerer and Stoddard to be due to its effect on the vibration, the resultant vibration of the two substances having a more intense action on the olfactory nerve than the vibration of either separately. Similarly, the addition of an infinitesimal amount of some substances such as musk, ambergris, and certain aldehydes may have a profound effect on a perfume and may give it a distinctive note. This also is thought to be due to it so affecting the molecular vibrations of the bulk perfume constituents that there is perfect co-ordination of the two sets of vibrations with a resultant pleasing olfactory effect.

Delange

Delange (*Bull. Soc. chim.*, **31,** 589-630, 1922) supported the view that unsaturation or residual valency is the cause of odour. In non-odorous compounds the valencies are usually neutralized.

Missenden

Missenden (*Perf. Essent. Oil Rec.*, **17,** 62-4, 1926) considered that odour was determined by three factors, intensity, quality and olfactory sense.

The first requirement is that the odorous molecules shall come into contact with the nasal membranes, and the number which do so determines the intensity of the odour. Then the odorous molecules react chemically with the lipoid tissues, and the nature of the chemical reaction determines the quality of the odour. Anything which causes violent or rapid reactions with the lipoid surfaces is pungent or unpleasant, and if there is no reaction there is no odour. In between these two extremes all varieties of odour are found. It is suggested that it might be possible to classify odorants on the basis of their reaction velocity with the lipoids, provided a suitable standard lipoid could be prepared. If the quantity of substance is great but the chemical reaction slow then the odour is weak but characteristic. If, on the other hand, the quantity of substance is small (low volatility) but the chemical reaction considerable there is only a little olfactory sensation, but if both quantity and velocity of reaction are great the olfactory effect may be overpowering.

Nicol

In a paper in *Perf. Essent. Oil Rec.*, **17,** 176-8, 1926, Nicol discusses the significance of the sinuses or air spaces in the nasal bones. These vary in size in different individuals and are not usually symmetrical in the same person. The sinuses are in connection with the nasal orifices, and Nicol suggests that they play a part in olfactory fatigue. The sphenoidal and frontal sinuses do not attain their full development until after puberty. No general theory of olfaction is put forward but it is thought desirable to note the suggestion regarding the sinuses, which do not figure in most theories of odour.

Pirrone

The theory put forward by Pirrone (*Rivista. ital. essenzi. profumi.*, **11,** 2-5, 1929) that odour depends on the presence of two osmophoric groups, the stronger creating the type of odour and the other the variety, has been discussed in an earlier chapter. It is purely chemical.

Niccolini

Niccolini (*Boll. soc. ital. biol. sper.* **8,** 424-6, 1933) suggests that odour depends on three factors, (1) volatility, (2) solubility in the nasal mucosa, and (3) oxidizability. Here is a new feature, viz. to be odorous a substance must be oxidizable. We immediately think of the paraffins again. Tests made by Niccolini on 75 substances of the fatty acid series showed that

18 were oxidizable in one minute and of these 16 or 88 per cent. were odorous, but

57 required much longer to oxidize and of these only 35 per cent. were odorous.

No doubt there is a parallelism between odour, chemical reactivity and oxidizability. It could scarcely be put higher than that.

The observations of Angeli and Polverini (*Gazz. chim. ital.*, **61,** 276-80, 1931) that only those coumarin derivatives which were easily oxidized had strong odours may be recalled in this connection.

Krisch

This worker did not put forward a complete odour theory, but he made an observation which he considered contradicted the corpuscular theory of odour, and hence concluded that smelling like hearing and seeing is caused by vibrations. The observation reported in " Die Naturwissenschafte," from *Liepziger Neueste Nachrichten*, 20th January 1934 (and quoted by Maybee, *Can. Chem. Proc. Ind.*, **23,** 115, 1939), was that an oak beauty butterfly perceived substances at a dilution in which no molecule of the substance would come in contact with its body, hence the insect smelled a substance which did not come in contact with its sensory organs.

Müller

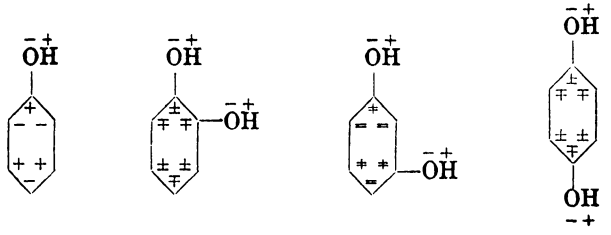
A " dipole " theory of odour was advanced by Müller (*Perf. Essent. Oil Rec.*, **27,** 202, 1936). The principle is that variety in odour is due to difference in dipole moment. Certain dipole-free compounds such as benzene, hexane, etc., have smell, but such substances are said to have similar smells.

If the electric centre (analogous to the centre of gravity) of the positive charges in a molecule does not coincide with the electric centre of the negative charges, then the molecule like a magnet has poles and an electric moment. The dipole moment is most noticeable when the molecules are sufficiently far apart not to interfere unduly with each other. Thus substances like indole and farnesol only develop their pleasant odours in high dilution. Müller requires that the molecules make contact with the nose where an irritation is set up by contact with the molecular field of the osmoceptor substance in the nose. The irritation affects the olfactory nerves. The molecules which have caused the irritation have been neutralized and prevent further olfaction unless time is given for their removal, hence we have olfactory fatigue.

Non-polar bodies such as benzene, carbon tetrachloride and hexane are said all to have very similar smells and are called " Pseudo-aromatics." In the case of unsaturated hydrocarbons such as olefines and acetylenes, an induced dipole is set up and variations in odour manifest themselves.

The dipole moments of benzaldehyde, nitrobenzene and benzonitrile are similar but not quite the same, and there are slight odour differences.

The polarity of the four following phenols



Phenol. Catechol. Resorcinol. Hydroquinone.

would suggest that phenol and resorcinol would be odorous and catechol and hydroquinone odourless. This is true except that resorcinol has only a faint smell, and this is attributed by Müller to association of the molecules (polymerization). The lack of smell of glycols is attributed to the same cause. If the hydroxyl group in a dihydric alcohol or phenol is replaced by an ether group then association is reduced and odour is enhanced.

Generally, where the polarities oppose each other the odour is not so strong as where they augment each other thus



Catechol monomethyl ether is odorous.

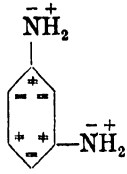
Resorcinol monomethyl ether is strongly odorous.

In a homologous series the olfactory effect increases with the chain length up to a maximum of about C_8 but vanishes at about C_{14}. It is stated by Müller that in addition to questions of low volatility the inodorous nature of the higher members of a series is due to the dipole moment becoming insignificant.

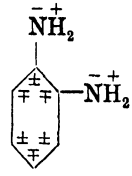
There are some difficulties in the way of Müller's theory, chief of which are (1) the strong odour of non-polar bodies like paraffins and benzene, (2) the number of times that " association " has to come to the rescue as an explanation of lack of odour where odour would be expected.

There is, of course, no doubt that when the polarities exercised by two polar groups in a molecule reinforce each other, as with

similar groups in the meta position, e.g. *m*-phenylene diamine (1) the chemical reactivity is enhanced, whereas when the polarities oppose each other, as in *o*-phenylene diamine, (2) the reactivity is reduced.

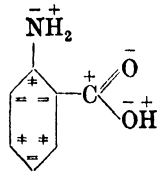


(1)

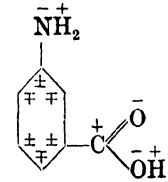


(2)

Similarly, with oppositely polar groups, the *ortho*—and *para*—arrangements mean reinforced polarities and greater chemical reactivity, whereas the *meta* position means opposing polarities and



Anthranilic acid.



m-Aminobenzoic acid.

reduced chemical activity.

Here again there is a parallelism between polarity, chemical reactivity and odour. It may be doubted if it is safe to take Müller's theory much beyond that.

Dyson

It will have been noted that in many theories the conditions volatility, solubility and intramolecular vibrations have been postulated as the fundamental requirements of odour. Not all have always made their appearance, and other properties have often been associated with one or two of these three main properties. It was Dyson (*Perf. Essen. Oil Rec.*, **28**, 13, 1937, and *Chemistry and Industry*, **57**, 647-51, 1938) who rationalized all this into a "scientific basis of odour." The requirements for a substance to be odorous are, according to Dyson :

(1) It must have an appreciable vapour pressure so that the odorous molecules may make contact with the olfactory region.

(2) It must be soluble in the lipoid matter of the olfactory region.
(3) It must have intramolecular vibrations of such a period that it has Raman shifts between 1,400 and 3,500 (see table in previous chapter).

A substance like steel or glass may have the appropriate Raman shift, but if it has no appreciable vapour pressure then it cannot be perceived by the nose. Similarly, if it is insoluble in fats it will not produce sensation.

The essential new factor in the Dyson theory is the correlation of definite odour with definite frequencies of Raman shift. Thus the mercaptans have powerful clinging odours and the lower alkyl mercaptans have nearly indistinguishable odours. The corresponding characteristic is a line in the Raman spectrum with a shift frequency which only varies between 2,567 and 2,580 from methyl mercaptan to amyl mercaptan. No other compound (than a mercaptan) has such a Raman shift, and no other compound has therefore similar intramolecular vibrations or similar odour. The paraffins which have been the stumbling block of so many theories have a Raman shift of about 3,000. This is about the only theory which accounts satisfactorily for the odour of the saturated paraffins. Hence, says Dyson, the osmic frequency of 2,580 is that of the mercaptan odour, just as the light wave of 4,358 tenth-metres is "green" (blue ?). In a homologous series like the paraffins the early members have simple Raman spectra and only slight odours, but the higher members have more complex spectra and more pronounced odours. There is no falling off in complexity of the Raman spectra in the higher members of a series, and their lack of odour is ascribed to non-volatility or lipoid insolubility.

If we compare the olefines with the paraffins there is a new set of lines, 1,600 to 1,800 in the Raman spectra, and this is taken to explain the odour differences between paraffins and olefines. It may be noted that in most cases the odour of a substance is due to many different intramolecular vibrations which in turn cause many bands in the Raman spectrum, so that the odour sensed is a mixture of odours and not one pure or fundamental odour. Clearly the method is applicable to determine which are the fundamental odours.

Another difficulty to earlier theorists which this theory overbridges is the resemblance of the odour of benzene to that of hexane. It is found that both have fairly similar Raman spectra. Aldehydes and ketones have shifts of 1,700, esters of 1,800, acetylenes of 2,100, ethers of 2,700, heterocyclic bases of 3,200 and so on.

The theory explains

(1) Why some substances have odour and others not since, apart from volatility and solubility questions, some have Raman

shifts in the detectable range of 1,400 to 3,500 but others have not. Higher and lower frequencies of vibration are not detectable by smell.

(2) Why stereoisomers may have different odours, e.g. *d*- and *l*-pinene have different shifts and cis and trans bodies often have different Raman shifts ; those of

cis 2 pentene are 1,248, 1,266, 1,375, 1,658
and of trans 2 pentene are 1,298, 1,313, 1,378, 1,674.

(3) Why, although similarly constituted compounds often have similar odours, and although regular changes in the intensity and quality of odour are often observed in a homologous series, some substances of entirely different constitution have similar odours. The answer is, of course, that constitutionally similar substances may have different Raman shifts and different odours, and conversely, constitutionally dissimilar bodies may have similar Raman shifts and similar odours. The odour of the substance depends not so much on its chemical structure as on its molecular mechanics.

(4) Why the quality of odour of a substance may change on dilution. Because it has two odours, corresponding to two Raman shifts, and one of these odours has a lower threshold value than the other.

(5) Why fatigue for a particular odour may be induced without the perception of other odours being impaired. The brain is not stimulated by a recurrent noise such as the ticking of a clock, but is stimulated by a new stimulus like the striking of a clock. In view of Adrian's work we may say that the receptors dealing with a particular vibrational frequency send their impulses along the olfactory nerve at a continually reduced frequency, so that soon these impulses stop. However, let a fresh odorant be introduced then presumably other receptors are brought into play and these are not fatigued.

(6) Why pairs of odours acting together may cancel each other. This is attributed to interference. Two dominant frequencies near each other may interfere during perception.

(7) Why one odorivector, such as musk present in small amount, may enhance the quality and power of a perfume. This may be attributed to resonance between the vibrations of the two substances.

Summary

For purposes of comparison it is convenient to contain the salient features of all these theories in a table. This is now given.

Author.	Date.	General Class.	Salient Features.
Ogle	1870	Vibrational	Vibrations affected nasal pigment, which gave out heat which excited the olfactory cells.
Woker	1906	Chemical	Unsaturation main cause of odour, but not essential if substance very volatile.
Fabre	1911	Vibrational	Limited to insects. Not known by man. Human olfaction due to material particles.
Marchand	1915	Chemical	Unsaturation (including $\diagdown$C=O). Two points of unsaturation reduces odour.
Henning	1916	Chemical	Osmophore groups are important, but their relative position determines the type of odour.
Heyninx	1917	Vibrational	Vibrations causing absorption in the ultra-violet band also caused odour.
Backman	1917	Chemical	Water solubility and lipoid solubility essential.
Teudt	1919	Vibrational	Electronic vibrations of sensory nerves increased by resonance with similar vibrations of odorants.
Durrans	1920	Chemical	Residual affinity. Addition reaction on the olfactory epithelium.
Heller	1920	Chemical	Direct chemical action on nerve-ending.
Ruzicka	1920	Chemical	Osmophore and osmoceptor.
Tschirch	1921	Chemical	Substance must be soluble in air. Loose compound formed with plasma of the olfactory cell.
Zwaardemaker	1922	Chemical-vibrational	Possess odoriphore, be volatile, lower surface tension, lipoid soluble. Odoriphore depends on vibrations in molecule.
Ungerer and Stoddard	1922	Vibrational	Intramolecular vibrations within definite frequency range. Unsaturation helpful. Interference and resonance effects.
Delange	1922	Chemical	Unsaturation.
Missenden	1926	Chemical	Intensity depends on number of molecules making contact with nose. Quality depends on nature of reaction between odorous molecules and lipoid tissues.
Nicol	1926	—	Function of sinuses.
Pirrone	1929	Chemical	Two osmophore groups, one determines type of odour, the other the variety.
Niccolini	1933	Chemical	Volatility. Solubility in nasal mucosa. Oxidizability.
Krisch	1934	Vibrational	Insects.
Müller	1936	Physical	Odorous substances are dipolar. Irritate the molecular fields of the osmoceptor in nose.
Dyson	1937	Vibrational	Volatility. Lipoid solubility. Raman shift between 1,400 and 3,500.

Each theory has been put forward sincerely and represents the conclusions of the author after much work and meditation. Probably

all contain some of the truth, but none all of the truth. Taken together they may embrace most of the truth. Analysis of the theories reveals that they embrace the following main factors :

Volatility. The substance must be volatile, so that its molecules can make contact with the nasal orifices. There is some opinion that this is not necessary with insects, but it is generally agreed that it is so with man.

Solubility. General agreement. that lipoid solubility is essential. Water solubility helpful. " Air solubility " of Tschirch is equivalent to volatility. The odorant reduces the surface tension of its solvent.

Reactivity. Many consider unsaturation or residual affinity essential, but it is not so as some paraffins are odorous. General agreement that it is very helpful. Odorants may react directly, possibly to form addition compounds with olfactory cells. Relation established between oxidizability and odour. General principle that reactivity and odour run parallel inescapable, hence olfaction probably includes a chemical reaction. Osmophore groups identified and their positions important.

Vibrations. Intramolecular vibrations as cause of odour is a common factor, largely due to failure to tie-up constitution and odour. Vibrations may affect pigment. Vibrations suggested in infra-red and ultra-violet spectra. Most quantitative accord found with Raman shifts. Vibrations may cause resonance or interference with vibrations of sensory surfaces. Vibrations of two odorants may compensate by interference or enhance by resonance.

This analysis suggests that odour perception may involve several processes in the nose, some physical some chemical. This is quite likely. We know that in vision the physical properties (wave-length) of the stimulus determine the resultant sensation, but we also know that chemical processes in the retina take place. In vision the chemicals are present in the body, the physical vibrating stimulus comes from outside. Perhaps in olfaction the physical vibratory system is present in the olfactory epithelium and the chemicals come from outside, i.e. from the odorants.

Molecular Limits

There is one point which seems to require a little further treatment before leaving this subject. Most workers agree that actual contact of molecules or corpuscles of the odorant with the nasal orifices is necessary. We have seen (Chapter 4) that the minimum stimuli require the presence of perhaps 10^8 or 10^9 molecules in the nose, and these, of course, will be rapidly dissipated in the atmosphere.

Yet the odorant appears not to change in weight in many cases. How, then, lies the balance ?

As long ago as 1904 Berthelot (*Compt. rend.*, **138,** 1249-51) stated that the odour of iodoform was perceptible when 1 gram of the substance lost one-billionth of a gram in an hour, and that in 100 years the loss of weight from 1 gram under his experimental conditions would be less than 1 mgm. In musk he found the loss of weight associated with a perceptible odour was possibly 1,000 times smaller.

If we take musk as being muscone, 3-methylcyclopentadecanone, it has a molecular weight of 238. Hence 238 grams contain

$$6 \times 10^{23} \text{ molecules (Avogadro number)}$$

so 1 gram muscone contains $\frac{6 \times 10^{23}}{238}$ molecules.

Suppose that it loses weight at the rate of $\frac{1}{1000}$ mgm. in 100 years, i.e. approximately 1 per cent. of its initial weight in a million years,

then it loses $\frac{6 \times 10^{23}}{238 \times 10^{6}}$ molecules in 100 years,

or $\frac{6 \times 10^{23}}{238 \times 10^{8} \times 365 \times 1{,}440 \times 60}$ molecules in 1 second,

or about 8×10^{5} molecules in 1 second.

Hence 1 gram of muscone can throw off molecules at the rate of a million a second, and lose only 1 per cent. of its weight in a million years. Now the point is that the number of molecules thrown off in a minute approaches that required for olfaction. In fact numbers of about 10^5 and 10^6 have been estimated by some workers (*vide International Critical Tables*) as sufficient to cause odour. Therefore the almost unmeasurable loss in weight is still adequate to find the number of molecules necessary for the process of olfaction.

CHAPTER 13

PERFUMES AND ESSENCES

Essential Oils

The scent of flowers is due to the presence of minute quantities of highly odorous oils. These oils are present in the petals of roses, violets and jasmine, in the leaves of verbenas and pelargoniums, and in the roots of vetivert and iris. In addition, similar sweet-smelling oils are present in the rinds of citrus fruits, oranges, lemons, bergamot, and in the wood of the trees in the case of sandalwood and cedarwood. Usually they occur free, but sometimes in the combined form as glucosides. The odorous oils can be separated by various means, and are known as essential oils, since they contain the essence of the flower or fruit. Some of the essential oils are, oil of aniseed, oil of bergamot, oil of caraway, oil of celery, oil of eucalyptus, oil of ginger, oil of laurel, oil of lavender, oil of lemon, oil of lemon-grass, oil of myrrh, oil of oranges, oil of parsley, oil of peppermint, oil of pineneedles, oil of rosemary, oil of spearmint, oil of thyme, oil of valerian, oil of wintergreen and so on. They are as a rule insoluble in water. The yield is not usually high, for example, a ton of roses will yield about 2 lb. of attar of roses (oil of roses, otto of roses). In some cases the yield is much higher, e.g. oil of patchouli may be obtained in yield equal to 4 per cent. of the leaves from which it is made, and up to 20 per cent. oil of cloves may be yielded by the dried flower buds of the *Eugenia caryophyllata*. The oils are, however, so powerful that only small quantities are required in a large bulk of diluent when they are used as perfumes or flavouring materials.

The main methods of separating the essential oil from the flowers, etc., are (1) expression, (2) distillation, (3) enfleurage, (4) extraction, (5) adsorption. A short description of each of these methods follows.

Expression

This method is used for fruit rinds rich in oil, such as those of the orange, lemon, lime and bergamot. The whole fruit is washed and then crushed between rollers, sprayed with water and the oil extracted by means of a centrifuge. It may be noted that the town of Bergamo, from which the fruit takes its name, gives us the adjective " bergamask " (" of or pertaining to Bergamo, whose natives are clownish in manner and dialect "—" Chambers' Twentieth Century Dictionary "). Oil of bergamot is an essential constituent of eau-de-Cologne.

Distillation

This method is cheap and greatly used. The blossoms, e.g. roses, are distilled with water, and the essential oil " steam-distils " with

the water vapour and then separates as an upper layer in the distillate. The bottom aqueous layer will also be odorous and may be used as a toilet water. Disadvantages of the method are: (1) the high temperature may decompose some of the odorous constituents, and to avoid this, distillation *in vacuo* at lower temperatures may be used, (2) the water-soluble constituents are lost. The method is used in Bulgaria for making the bulk of the world's otto of roses.

Enfleurage

Enfleurage consists in the solution and possibly adsorption of the odorous constituents of flowers in fat. The fat is composed of beef suet and lard and a little preservative. It is spread on glass plates in wooden frames and then petals are laid on the fat and the frames piled on each other. The petals are removed and replaced until the fat is saturated with the oil. As the hydrolysis of any glucosides which may be present into glucose and the free essential oil continues during enfleurage, good yields are obtained. The odorous fat or "pomade" is extracted repeatedly with alcohol to obtain alcoholic extracts of the essential oil, and the fat then left is known as *corps épuisés* and is used for making scented soaps. In the south of France, particularly at Grasse, which is the centre of the perfume industry, jasmine pomade is made in this way from the flowers of *Jasminum grandiflorum*.

Extraction

The flowers are placed on tiers of perforated plates through which a solvent such as petrol-ether runs over them. The solvent is then distilled and used again. The residue from the distillation contains the essential oil. In other cases, often with roses and violets, the petals will be macerated with melted fat and the essential oil extracted from the fat with alcohol. If olive oil is used as a solvent then the odorous products are known as *huiles antiques*. Olive oil was used before alcohol became common, by the Romans and Greeks.

Adsorption

A method in which air or an indifferent gas is passed over the flowers and then through active carbon or silica gel is described in British Patent 255,346. The carbon removes the odorous constituents from the air, and when the carbon contains so much adsorbed material that it no longer completely exhausts the incoming air then the process is stopped and the odorous material steamed out of the carbon. British Patent 292,668 states that better yields are obtained if the air or gas is pre-dried. British Patent 292,667 suggests the use of low boiling solvents, such as ethyl chloride, to extract the oil from the active carbon so that no higher temperature than 25° or 30° C. is necessary to distil off the solvent. The method is useful where flowers are decomposed by normal distillation methods.

U.S. Patent 1,786,630 (Reid) describes a similar process in which activated charcoal is used to adsorb odours in the manufacture of perfumes.

French Patent 809,275 (Madaus & Co.) describes a process in which fresh plants or their parts are rasped or ground with activated carbon, kaolin, clay or colloidal silica.

The principle is the same in all cases, the water-insoluble odorous oils are readily adsorbed by any activated surface material.

Concrete, Absolute, Isolate

After the process of enfleurage, the wax is extracted with alcohol, and on removal of the alcohol there remains a semi-solid mixture of essential oil and fatty waxy material which the alcohol has dissolved out of the lard and beef suet. This semi-solid mixture is known as a *concrete* or a *floral concrete.*

If the concrete is re-extracted with alcohol most of the wax is left behind, and when the alcoholic extract is distilled then the residue is nearly pure essential oil, and this is known as a *floral absolute.* Floral absolutes are commonly made from the rose, orange-flower, narcissus and jonquil.

An *isolate* is a pure substance separated from natural products. It is in many cases indistinguishable from the same chemical substance made synthetically. Sometimes, however, natural products are optically active whereas the synthetic product is the optically inactive racemate.

Attar of Roses

The *Rosa damascena* is the main source of Attar of Roses. Most of it comes from Bulgaria and some from the South of France. It is obtained usually by distilling rose petals with water, the oil separating from the watery distillate. The latter is rose-water. The oil is also made by enfleurage. It is a pale yellow and gels at 20° owing to its natural wax content. Only about 30 to 40 oz. of oil is obtained from a ton of roses.

The main chemical constituents are

Geraniol. $(CH_3)_2C{=}CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3) : CH\ CH_2OH$

Citronellol. $(CH_3)_2C : CH \cdot CH_2 \cdot CH_2 \cdot CH(CH_3) \cdot CH_2CH_2OH$

Nerol. Nerol is a stereoisomer of geraniol,

and their esters.

Bulgarian rose otto contains 40 to 55 per cent. citronellol.

The true perfume of the rose is not completely represented by the oil so obtained, since the natural rose perfume is contributed to by water-soluble substances which are lost in the rose-water. The chief of these has been identified as phenyl ethyl alcohol. It is not recovered from the rose-water but is synthesized and added to the rose-oil. The synthetic phenyl ethyl alcohol is identical with that lost in the rose-water.

Synthetic otto of roses has now largely replaced the natural as it costs only about one-quarter as much. It is composed of geraniol, nerol, citronellol, phenyl ethyl alcohol, and in addition a high grade synthetic otto will contain not less than 10 per cent. of the natural otto. Rose geranium oil is also often added. This is obtained by distilling rose petals and pelargonium leaves in water. Geranium oil is made similarly from the pelargonium leaves alone in Reunion and South France.

Some interesting early work on the chemical requirements for the rose odour was carried out by Austerweil and Cochin (*Compt. rend.*, **150,** 1693-5, 1910). They started with citronellol and made the following :

Citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2CH_2OH$. Rose odour.
1-methyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2CH(CH_3)OH$. Rose odour.
1-1-dimethyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2.C(CH_3)_2OH$. Rose odour.
1-ethyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2.CH(C_2H_5)OH$. Faint rose odour.
1-1-diethyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2.C(C_2H_5)_2OH$. Less pronounced rose odour.
1-propyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2.CH(C_3H_7)OH$. Rose odour less distinct.
1-butyl citronellol	$(CH_3)_2C:CH.CH_2.CH_2.CH(CH_3).CH_2.CH(C_4H_9)OH$. Rose odour less distinct.

They concluded firstly, that the odour of roses was associated with the presence of a group $—CH_2.CRR'OH$, and secondly, that an ethylenic linkage was essential. They found also that the corresponding 1-phenyl citronellol had a strong rose odour. The rose odour was lost on oxidation of the alcohol group. The formula used by Austerweil and Cochin for citronellol was

$$\begin{matrix} CH_2 \\ \diagdown \\ \quad C \\ \diagup \\ CH_3 \end{matrix} .CH_2.CH_2.CH_2.CH(CH_3).CH_2.CH_2OH.$$

To-day citronellol is thought to be a mixture of this and the corresponding

$$\begin{matrix} CH_3 \\ \diagdown \\ \quad C \\ \diagup \\ CH_3 \end{matrix} :CH.CH_2.CH_2.CH(CH_3).CH_2CH_2OH.$$

As already discussed in Chapter 9, v. Braun and Gossel (*Ber.*, **57B**, 373-82, 1924) arrived at the conclusion that the chief factor in the rose odour was the complex $(CH_3)_2C : C\langle$ at a definite distance from the primary alcohol group.

Oil of Neroli

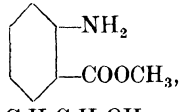
Oil of neroli is made by distillation of orange flowers *Citrus aurantium*. The best quality is distilled from the flowers of the bitter orange in France, and is known as oil of neroli, Bigarade, whilst that made from flowers of the sweet orange is oil of neroli, Portugal. Oil of neroli contains as its odorous constituents :

Linalol $(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3)OH . CH{=}CH_2$.

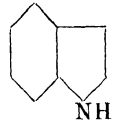
Geraniol $(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2OH$.

Nerol Stereo-isomeric with geraniol,

and their esters, and, in addition,

methyl anthranilate, 

phenyl ethyl alcohol, $C_6H_5C_2H_4OH$,

and indol, 

Oil of neroli contains about 51 to 58 per cent. of alcohols estimated as linaloöl, about 25 per cent. of esters as linalyl acetate, and about 3 per cent. of methyl anthranilate. The orange flowers from which oil of neroli is made are gathered chiefly in the South of France from the end of April to the end of May. The early flowers yield only 0·05 per cent. oil, but the later flowers yield about 0·1 per cent., i.e. about a gram of oil from a kilo of flowers.

Just as citronellol is the essential constituent of rose-oil so linaloöl is of orange-blossom. Their similarity in structure may be noted :

Citronellol $(CH_3)_2C : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CH_2OH$.
Linaloöl $(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3)OH . CH : CH_2$

Oil of neroli is used in making eau-de-Cologne.

Oil of Lavender

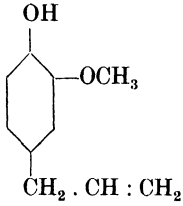
The flower spikes of *Lavandula vera* are distilled. English lavender is superior to French although it has a lower ester value. Curiously,

French lavender is evaluated on its ester content, the higher the better. The main odorous constituents are linaloöl and geraniol, both of which are found also in orange-blossom oil (neroli) and their acetates, butyrates, valerianates and caproates.

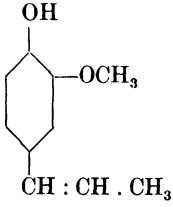
English lavender oil contains only 7 to 10 per cent. of esters as linalyl acetate, whereas French oils will contain 25 to 44 per cent. according to the district from which they come. It is not surprising, therefore, that the two oils have different odours. Linalyl acetate is the chief ester ingredient of lavender oil but has a bergamot odour when pure. The odour of lavender oil is therefore not due to any one ester but is a composite of many odorous influences.

Oil of Cloves

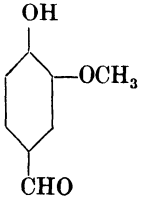
The dried flower-buds of the evergreen clove tree *Eugenia caryophyllata* is the source of oil of cloves and yields 14 to 20 per cent. The chief constituent, about 88 per cent., is

eugenol  or *p*-allyl guaiacol.

Alcoholic potash converts eugenol into

isoeugenol 

and on oxidation this gives

vanillin 

which is identical with the vanillin obtained from the vanilla fruit. The method is used for the technical preparation of vanillin. Zanzibar, the East Indies and Straits Settlements are the chief sources of cloves.

Ylang-ylang Oil

Ylang-ylang (flower of flowers) oil is obtained by distilling the flowers of *Cananga odorata*. Inferior qualities are known as cananga oil. The best ylang-ylang comes from the Philippines, and it is made also in Reunion and Java, but in the last country the quality is low and the product is known as cananga oil.

The blossoms are gathered and distilled within a few hours. The yield varies considerably, and if an attempt is made to obtain a high yield by distilling out all the oil the quality is poor. To obtain the finest ylang-ylang only two-thirds of the oil must be collected, then, of course, the receiver can be changed, and the last third collected as an inferior oil.

The oil contains a large number of constituents. It is considered that some of the high boiling products, such as benzyl benzoate, in themselves practically inodorous, fix the odour of the more volatile constituents. Linaloöl, probably geraniol, and the sesquiterpene, cadinene, are present, together with pinene, *p*-cresol methyl ether, sometimes eugenol or isoeugenol, and various esters.

Table of Essential Oils

Brief details of some of the essential oils are included in the following table, designed to show how the diverse odours and flavours we commonly meet are derived from the vegetable world.

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Allspice (Pimento)	Fruit of *Pimenta officinalis*, W. Indies	Eugenol, cineol	Odour recalls nutmeg, pepper and cinnamon. Used in bay rum.
Angelica	Root or seed of *Angelica Archangelica*, Saxony	Exaltolide and Δ^7 hexadeceno-lactone	Musky odour. Used for liqueurs.
Angostura bark	Bark of *Galipea cusparia*, Venezuela	Cadinene	Used for liqueurs.
Asafœtida	Gum resin of *Ferula narthex*, Afghanistan	Terpenes, foul sulphur compounds, diallyl sulphide	Foul-smelling.
Balsam of Peru	Oleo-resinous exudation of *Myroxylon Balsamum β-Pereiræ*, San Salvador	Benzyl benzoate, benzyl cinnamate	The resin itself is more commonly used than the oil from it.
Balsam of Tolu	Exudation of *Myroxylon Balsamum gennimum*, New Granada, Venezuela	Benzyl benzoate, benzyl cinnamate, farnesol	Hyacinth odour.
Bay	Leaves of *Pimenta acris*, W. Indies	Eugenol and its methyl ether, pinene, myrcene	Used in preparation of bay rum.
Bergamot	Peel of Bergamot, *Citrus aurantium Bergamot*, Calabria	Linalyl acetate, 40 per cent., linaloöl, limonene, bisabolene, pinene	Perfumes.

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Bitter almonds	Kernels of bitter almond, *Prunus amygdalis*, all parts of the world	Benzaldehyde, hydrocyanic acid	
Camphor	Twigs of *Cinnamomum Camphora*, Formosa	Camphor, terpenes	Household and medical uses. Also a source of synthetic safrol for art. oil of sassafras.
Cananga			Inferior grade of ylang-ylang (*q.v.*).
Caraway	Seeds of *Carum carui*, Holland, etc.	*l*-carvone, carveol, *d*-limonene	Medicine. Perfumes. Used in soaps of Brown Windsor type.
Carrot seed	Seed of carrot *Daucus carota*	Pinene	
Cassia	Leaves and twigs of *Cinnamomum cassia*, China	Cinnamic aldehyde, 80 to 90 per cent.	Spice and perfumery. Used in Brown Windsor type soap.
Cedar wood	Pencil shavings of cedar wood, *Juniperus virginiana*, Florida	Cedrene, cedrol, cedrenol	Oil used for fine soap and perfumes. Powdered wood used for incense.
Celery seed	Common celery seed, *Apium graveolens*	Selinene, sedanolide (tetrahydrobutyl phthalide)	
Chamomile	Flowers of *Anthemis nobilis*, Germany	Esters of angelic and tiglic acids	Medicine.
Cinnamon	Bark and leaves of *Cinnamomum Zeylanicum*, Ceylon, E. Indies	Bark oil—cinnamic aldehyde ; leaf oil —eugenol	Similar to oil of cassia but more delicate in odour. Used for dentifrices and also in Oriental type perfumes.
Citronella	Citronella grass, several varieties, Ceylon, Java	Geraniol, citronellal, camphene	Cheap perfumery.
Clary sage	Leaves and twigs of *Salvia sclarea*, Dalmatia	Pinene, cineol, linaloöl	Odour recalls ambergris. Used as a fixative.
Cloves	Dried flower-buds of *Eugenia caryophyllata*, E. Indies, Zanzibar	Eugenol, 80 per cent.	Source of vanillin (via isoeugenol). Also used for dentifrices and soaps.
Coriander	Fruit of *Coriandrum sativum*, many parts of the world	Linaloöl, pinene	
Cubebs	Dried fruits of *Piper cubeba*, Singapore	*dl*-Limonene, pinene, cadinene	Used in medicine.
Dill	Fruit of *Anethum graveolens*, Europe, India	Carvone, limonene	Used as a carminative.
Elemi	Exudation of *Canarium luzonicum*, Philippines	Phellandrene, *d*-limonene	

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Eucalyptus	Leaves of *Eucalyptus globulus*, Australia, etc.	Cineol, pinene	Used medicinally.
Fennel	Fruit of *Fœniculum vulgare*, Mediterranean countries	Anethol; 60 per cent., fenchone	Anethole is a source of Aubepine or anisaldehyde.
Frankincense	Exudation of *Boswellia Carterii* and *B. serrata*, India	Pinene, Camphene, *dl*-limonene	Balsamic odour.
Gardenia	Flowers of *Gardenia grandiflora*	Benzyl acetate, linaloöl, methyl anthranilate	
Garlic	Entire plant, *Allium sativum*	Diallyl disulphide	Flavours.
Geranium	Leaves of varieties of *Pelargonium*, France, Algeria, etc.	Geraniol, Citronellol	Used for floral bouquets.
Ginger	Rhizome of *Zingiber officinale*, Asia, W. Indies	Zingiberene, Zingerone, Camphene, Cineol, Borneol, citral	Flavour.
Jasmine	Flowers of *Jasminum grandiflorum*, Asia chiefly	Jasmone, indole, Methyl anthranilate	Perfume.
Lavender	Flowers of *Lavandula vera*, England, France	Cineol, limonene, linalyl acetate, linaloöl, geraniol and esters	Perfumery.
Lemon	Peel of lemon, *Citrus limonum*, Mediterranean countries	*d*-limonene, 90 per cent.; citral	
Lemon-grass	Lemon-grass, Varieties of *Cymbopogon*, E. Indies	Citral, 80 per cent.	Source of citral from which ionone is made for violet perfumes.
Limes	Fruit of *Citrus medica acida*, W. Indies	Citral, limonene	
Linaloe	Wood and fruit of *Bursera Delpechiana*, Mexico	Linaloöl	Soft sweet odour. Used for perfumes and soaps.
Mignonette	Flowers of mignonette, *Reseda odorata*		Yield only 0·002 per cent. Powerful odour. Floral extract generally used instead of oil.
Musk-seed	Seeds of *Hibiscus abelmoschus*, Java	Farnesol, Δ^7 hexadecenolactone	Known also as oil of ambrette seeds. Musky odour.
Mustard	Seeds of *Brassica nigra*	Allyl thiocarbimide	
Myrrh	Oleo-resin secreted in the bark of various *Commiphora*, Arabia, Somaliland	Cuminic aldehyde, bisabolene, pinene, *dl*-limonene, eugenol, *m*-cresol	
Myrtle	Leaves of *Myrtus communis*, Mediterranean countries	Pinene, cineol, camphene	

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Nepeta	Catmint, *Nepeta cataria*, Sicily	Menthol and its caprylic and valeric esters	
Neroli	Orange-flowers, *Citrus aurantium*, France	Nerol, geraniol, linaloöl, Phenyl ethyl alcohol methyl anthranilate	Perfumes. Used for eau-de-Cologne.
Opoponax	Exudation of varieties of *Commiphora*, Arabia, Somaliland	Bisabolene	Similar to oil of myrrh.
Orange	Peel of orange, *Citrus aurantium*, Mediterranean countries	*d*-limonene, 90 per cent.; decylic aldehyde	
Orris-root	Iris rhizomes, varieties of *Iris*, Italy	Irone, aldehydes	Odour develops after roots are dried. Powdered roots used in violet powder. Pure oil used in highest quality violet perfumes; as a fixative for ionone in cheaper qualities.
Parsley	All parts of common parsley, *Petroselinum salivum*, France, Germany	Pinene, apiol	
Parsnip	Chiefly parsnip seed, *Pastinaca sativa*	Octyl butyrate, octyl propionate	
Patchouli	Dried leaves of *Pogostemon patchouli*, Singapore, Java	Terpenes, eugenol	Used for face powder and perfumes. Thick liquid with powerful and persistent odour. Good fixative.
Pennyroyal	Leaves of *Mentha pulegium*, Europe	Pulegone, 85 per cent.	
Pepper	Unripe berries of *Piper nigrum*	Piperine, *dl*-limonene	
Peppermint	Flowering tops of mint herb, *Mentha piperita*, England, America, Japan	Menthol, 50 per cent. menthyl acetate, menthone, cadinene, *l*-limonene	Flavouring sweetmeats and dentifrices.
Perilla	Leaves of *Perilla nankinensis*, Japan	Perillic aldehyde	Peculiar hay-like odour. Used in perfumes.
Petitgrain	Leaves and young shoots of orange, *Citrus aurantium*, Paraguay	Pinene, geraniol, linaloöl, Methyl anthranilate	Used for making eau-de-Cologne.
Roses	Flowers of *Rosa damascena*, Bulgaria, France	Citronellol, 30 per cent., geraniol, 40 per cent., phenylethyl alcohol, nerol	Perfumes.
Rose-geranium	Mixture of roses and pelargonium leaves, France		

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Rosemary	Flowering tops of *Rosmarina officinalis*, S. Europe	Camphor, borneol, pinene, cineol	Used in cheap perfumes, soaps and hair-washes.
Rue	Herb, *Ruta graveolens*, France	Methyl nonyl ketone, methyl heptyl ketone	
Sandalwood	Wood or roots of *Santalum album*, India		Used as a fixative for Oriental type perfumes. Also used in soaps and face powders.
Sassafras	Bark and roots of *Sassafras officinale*, N. America	Safrol, 80 per cent., Pinene	Used in soap perfumery.
Shaddock	Grape-fruit, *Citrus decumana*, W. Indies	Limonene	
Spearmint	Herb, *Mentha viridis*, America chiefly	*l*-carvone, phellandrene, limonene and esters	Used for flavouring sweetmeats.
Spikenard	Root of *Nardostachys jatamansi*, India	Sesquiterpenes	Valued in the East as a perfume. Disliked by Western people as a rule. Largely replaced by oil of valerian.
Star Aniseed (Badiane)	Fruit of *Illicium verum*, China	Pinene, anethol, phellandrene	Flavouring.
Storax	Oleo-resin from bark of *Liquidamber orientale*, Asia Minor	Phenyl ethylene (oil of styrol)	
Sweet Basil	Herb, *Oceum basilicum*, Europe, Algeria	Ocimene, cineol, pinene	Used in mignonette perfumes, etc.
Tansy	Herb, *Tanacetum vulgare*, England, France, America	Thujone, borneol	
Tea	Leaves of tea plant, *Thea chinensis*, China		Yield only 0·006 per cent.
Thyme	Herb, *Thymus vulgaris*, France, Spain	Borneol, thymol, carvacrol, bornyl acetate	Used medicinally. Also in soap.
Tropæolum	Leaves of nasturtium, *Tropæolum majus*	Benzyl thiocarbimide, 80 per cent. (benzyl mustard oil)	
Tuberose	Flowers of *Polianthes tuberosa*, France	Methyl anthranilate, methyl benzoate	Made by enfleurage
Turpentine	Pine-wood exudations, Europe, India	Pinene, limonene	Ordinary turpentine is a solution of resins, e.g. colophony in the oil of turpentine. Source of terpineol.
Valerian	Roots of *Valeriana officinalis*, Europe, Japan	Borneol, bornyl acetate, camphene isovalerianic esters	Used in medicine, also as a soap perfume.

Oil of—	Distilled or Extracted from—	Chief Odorous Components.	Remarks.
Verbena	Herb, *Lippia citriodora*, France, etc.	Citral	Perfumes. Lemongrass oil also consists chiefly of citral and is often called verbena.
Vetivert	Roots of Khas-khas grass, *Vetiveria zizanioides*, India	Sesquiterpenes, esters	Heavy liquid used as a fixative. Perfume suggests myrrh.
Wallflower	Wallflowers, *Cheiranthus cheiri*	Nerol, geraniol, indol, methyl anthranilate	Yield only 0·06 per cent.
Wintergreen	Originally from leaves of *Gaultheria procumbens*, later bark of sweet birch. *Betula lenta.*	99 per cent. methyl salicylate	Used for flavouring dentifrices, etc.
Ylang-ylang	Flowers of *Cananga odorata*, Philippines	Benzyl benzoate, alcohols, esters	Over 30 components already isolated. Used for fine perfumes.

Resins

We have already noted the oils obtained from balsam of Peru, balsam of Tolu, frankincense and storax. The resins themselves are more important than the oils made from them. Balsams of Peru and Tolu are exudations caused by wounding the bark of certain trees. The exuding resin is purified by boiling with water, the resin separating as a bottom layer. The resin is formed by oxidation of the essential oil in the tree, the oxidation being facilitated by wounding the bark, although in some cases the exudations occur naturally.

Balsam of Peru has a sweet odour due to its ester content of benzyl and cinnamic acids. Balsam of Tolu has a hyacinth odour.

Benzoin, or " Gum Benjamin," is a similar body collected from trees of the species *Styrax*. Like the balsams of Peru and Tolu it is a useful fixative.

Storax or styrax from the tree *Liquidamber orientalis* is similar. It has a sweet odour due to its esters of cinnamic acid.

Frankincense or olibanum is a very fragrant gum resin from varieties of *Boswellia* grown in Somaliland and Arabia. It is used as incense and also as a fixative for oriental-type perfumes.

Opoponax is a fragrant resin and is exuded by the *Commiphora erythraea*. Myrrh is similar. Labdanum is very like ambergris in odour, and is obtained from some varieties of rock roses in Cyprus and Crete.

Oak moss resin is different in nature. It is not an exudation but is a lichen which grows on the oak.

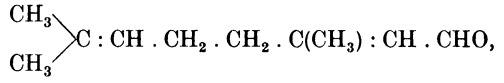
Frequently tinctures of the resins are made by extraction with alcohol. If the latter is then removed the residue is known as a "resinodor," but the alcoholic tincture is more usually employed.

The importance of these resins lies mainly in their use as fixatives.

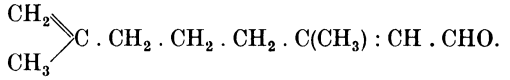
Odorous Constituents of Oils and Resins

The odorous components of essential oils are not unfamiliar to us. They are chiefly esters, alcohols, aldehydes, ketones and hydrocarbons. The hydrocarbons and, indeed, many of the other compounds, by reason of their derivation from them, have a peculiar architectural structure and are known as terpenes. There are cyclic, dicyclic and open-chain terpenes, all having the empirical formula $C_{10}H_{16}$, and then there are the sesquiterpenes, $C_{15}H_{24}$.

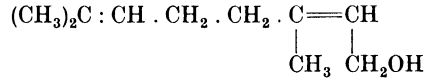
The open-chain terpenes include citral, citronellal, citronellol, geraniol, nerol, linaloöl, myrcene and ocimene and will be considered first. It will be seen that they are an important class. Citral occurs in oils of lemon, lemon-grass, limes, verbena and ginger. It is cheaply obtained from lemon-grass and has a pleasant lemon odour. It is a mixture of geranial and neral which are cis- and trans- forms of the compound,



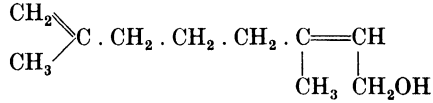
probably mixed in the natural oils with their isomer,



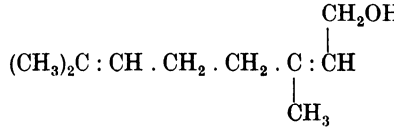
Geraniol, which occurs in oils of citronella, geranium, lavender, neroli, petitgrain, rose and wallflower, is the alcohol corresponding to geranial, and nerol, which is found in oils of neroli, roses and wallflower, is its stereo-isomer. Geraniol therefore is a mixture of

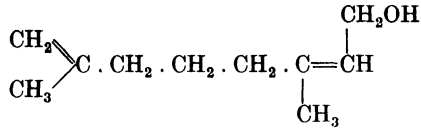


and



whilst nerol is a mixture of



and 

Citronellol occurs in oils of geranium, rose, and rose geranium and is the reduced form of geraniol and is

$$(CH_3)_2C : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CH_2OH$$

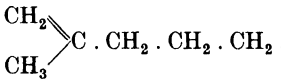
and its isomer. Citronellal which occurs in oil of citronella is the corresponding aldehyde,

$$(CH_3)_2C : CH . CH_2 . CH_2 . CH(CH_3) . CH_2 . CHO.$$

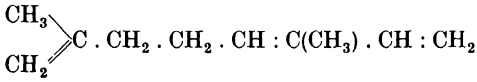
On hydration it gives hydroxycitronellal, which has an odour of lime flowers and is useful for muguet perfume.

Linaloöl, which is found in many oils including those of bergamot, clary sage, coriander, gardenia, lavender, linaloe, neroli and petitgrain, is a mixture of two isomeric tertiary alcohols,

$$(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3)OH . CH : CH_2$$

and 

Ocimene, found in sweet basil oil, is



and myrcene, found in bay oil, is

$$(CH_3)_2C : CH . CH_2 . CH_2 . C(: CH_2) . CH : CH_2.$$

Tagetone, which is responsible for the odour of marigolds, is a ketone of similar structure,

$$(CH_3)_2CH . CH_2 . CO . CH_2 . C(: CH_2) . CH : CH_2.$$

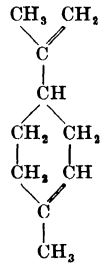
The similarity in molecular structure between these various open-chain terpenes is very striking.

The monocyclic terpenes form another group of important odorous constituents of essential oils. These are described below.

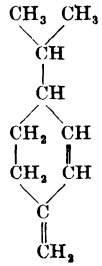
d-limonene is found in oils of caraway, dill, elemi, orange, bergamot, lavender, lime, shaddock, spearmint and turpentine, whilst *l*-limonene is found in oils of peppermint and pine-needles. The racemic *dl*-limonene, also known as dipentene, is found in oils of cubebs, frankincense, myrrh, pepper and others.

Phellandrene is found in oils of elemi, spearmint and star aniseed.

The structures of limonene and phellandrene, both $C_{10}H_{16}$ are shown below



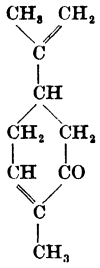
Limonene.



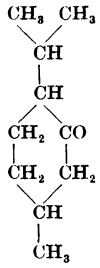
Phellandrene.

Four ketones with similar molecular skeletons are carvone, menthone, pulegone and thujone.

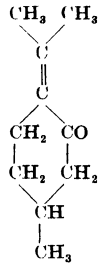
Carvone is found in oils of caraway, dill and spearmint, menthone in peppermint, pulegone in pennyroyal and thujone in tansy. Their structures may be compared :



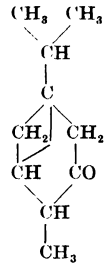
Carvone.



Menthone.



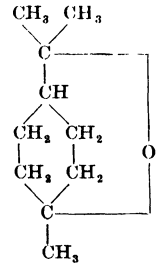
Pulegone.



Thujone.

Menthol is found in nepeta and peppermint and carveol in caraway. They are the alcohols formed by reducing menthone and carvone respectively.

Cineol, found in many oils, including allspice, clary sage, eucalyptus, ginger, lavender, myrtle, rosemary and sweet basil, has a rather different constitution

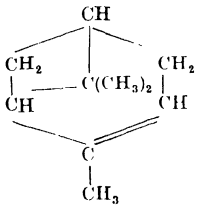


In the dicyclic terpenes we have pinene, camphor, camphene, borneol and fenchone.

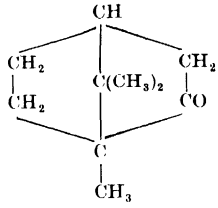
Pinene is found in many oils, including bay, bergamot, carrot, clary sage, coriander, cubebs, eucalyptus, frankincense, myrrh, myrtle, parsley, petitgrain, rosemary, sassafras, star-aniseed, sweet basil and turpentine.

Camphor is, of course, the main constituent of oil of camphor, and is also found in oil of rosemary.

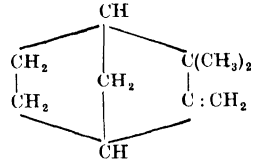
Camphene occurs in citronella, frankincense, ginger, myrtle and valerian, borneol in ginger, rosemary, tansy, thyme and valerian, and fenchone in fennel.



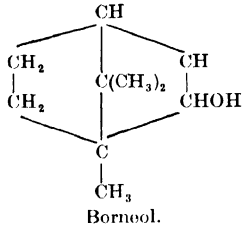
Pinene.



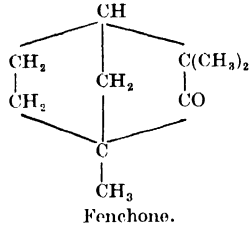
Camphor.



Camphene.



Borneol.



Fenchone.

Whereas the terpenes, both open chain like geraniol and cyclic like limonene and camphor, are derived from hydrocarbons with the empirical formula $C_{10}H_{16}$, a similar series of compounds known as the sesquiterpenes is derived from hydrocarbons $C_{15}H_{24}$.

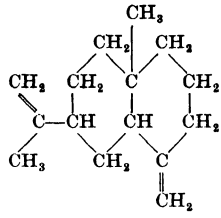
Of the open-chain sesquiterpenes, farnesol is the most common. It is met with in oils of musk-seed and balsam of Tolu and has this constitution,

$$(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2 . CH_2 . C(CH_3) : CH . CH_2OH.$$

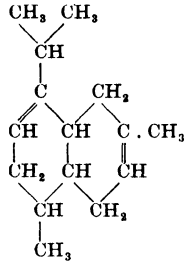
A number of interesting odorants are found in the cyclic sesquiterpenes.

Selinene occurs in oil of celery.

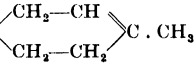
Bisabolene is found in oils of myrrh, opoponax and bergamot, cadinene in Angostura bark, cubebs and peppermint, zingiberene in ginger. Their constitutions are

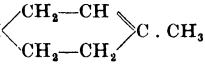


Selinene.

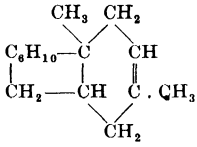


Cadinene.

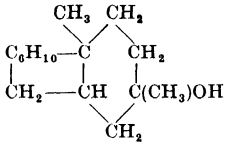
Bisabolene $(CH_3)_2C : CH . CH_2 . CH_2 . C(CH_3) : C$  $C . CH_3$

Zingiberene $(CH_3)_2C : CH . CH : CH . CH(CH_3) . CH$  $C . CH_3$

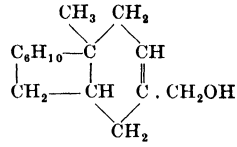
Cedrene, cedrol and cedrenol are the odorous constituents of cedarwood oil which has a soft woody odour suggesting orris. Their constitutions are (cf. *Manufacturing Perfumer*, **2**, 107, 1937)



Cedrene, $C_{15}H_{24}$.



Cedrol, $C_{15}H_{26}O$.



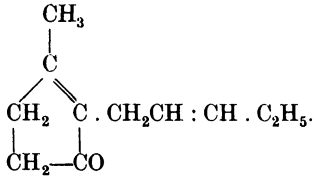
Cedrenol, $C_{15}H_{24}O$.

The general structural similarity of many of these compounds lends confirmation to the view that odour is primarily determined by the molecular architecture, and that in large molecules the substitution of so-called osmophoric groups has only a secondary influence.

Of the other cyclic constituents of these essential oils, the violet principles ionone and irone have been dealt with in Chapter 9. Some others may be briefly discussed here.

Of the macrocyclic compounds, exaltolide and Δ^7 hexadecenolactone, are both found in angelica oil and the latter also in musk-seed oil. Their constitution was considered in Chapter 9.

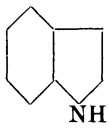
Jasmone, the ketone which occurs naturally in oil of jasmine, is a pentanone derivative



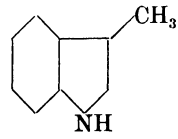
The reduced compound 3-methyl-2-amyl cyclopentanone was synthesized by Treff and Werner (*Ber.*, **66B**, 1521-7, 1933), who showed

that it was identical with Staudinger and Ruzicka's pyrethrone, and later by Issagulyanz (*Riechstoff-Ind. Kosmetik.*, **11**, 84-6, 1936). The isomeric 3-methyl-2 isoamylcyclopentanone was found to have a stronger odour.

Indole, found in oils of neroli, jasmine and wallflowers has, when pure, a powerful and disagreeable odour, fæcal in character. Its methyl analogue skatole is the odorous principle of fæces and is found in civet the animal perfume fixative.



Indole.

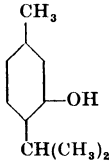


Skatole.

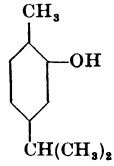
Some phenols with their characteristic odour appear in the essential oils, notably eugenol, thymol, carvacrol and *m*-cresol.

Eugenol is found in allspice, bay, cinnamon-leaf, myrrh, patchouli, and particularly in cloves.

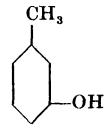
Thymol occurs in oil of thyme as does also carvacrol, whilst *m*-cresol is found in myrrh and *p*-cresol in ylang-ylang.



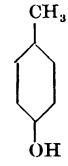
Thymol.



Carvacrol.



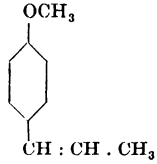
m-cresol.



p-cresol.

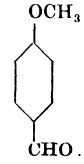
The aromatic ethers found in the essential oils include anethole, apiol, and safrol.

Anethole occurs in oils of fennel and star-aniseed. It is used as a source of " Aubepine " or anisic aldehyde from which most hawthorn perfumes are prepared.



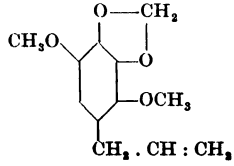
Anethole.

Oxidation

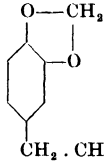


Aubepine.

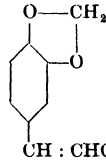
Apiol occurs in oil of parsley. It has the constitution



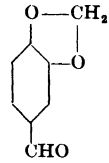
Safrol occurs in oils of sassafras and camphor, and it is important, as by treatment with caustic alkali it is converted to isosafrol, and this on oxidation yields piperonal, known commercially as heliotropin, with a cherry-pie odour.



Safrol.



Isosafrol.

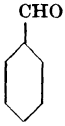


Heliotropin.

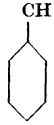
The ketones are well represented in the terpenes, with pulegone, thujone, etc., but in addition the aliphatic ketones, methyl nonyl ketone and methyl heptyl ketone, are found in oil of rue.

The aldehydes in the open-chain terpenes such as citral and citronellal have been discussed, as have aubepine and heliotropin.

Benzaldehyde is found in oil of bitter almonds, cinnamic aldehyde in cassia and cinnamon bark, decylic aldehyde in orange peel, cuminic aldehyde in oils of cumin and myrrh, and perillic aldehyde in oil of perilla.

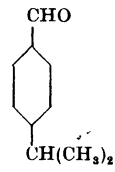


Benzaldehyde.

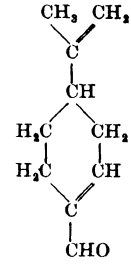


Cinnamic aldehyde.

Decylic aldehyde.



Cuminic aldehyde.



Perillic aldehyde.

It will be seen that perillic aldehyde is closely related to limonene, and should perhaps have been classed with the terpenes. It will be remembered that the oxime of this body is intensely sweet. It will be noted that decylic aldehyde occurs in oil of orange. The fatty aldehydes from C_7-C_{13} are now used extensively in perfumery. They are expensive, but a trace of one of them will often lift a perfume out of the rut.

The esters are vitally important perfumes. Usually when alcohols such as geraniol and linaloöl are present in an oil their esters are also present. Some of the most common are

Methyl salicylate, which practically composes oil of wintergreen.

Octyl butyrate and octyl propionate in parsnip. (Note the occurrence of propionates in aphrodisiacs.)

Bornyl acetate is found in oils of thyme and valerian.

Methyl benzoate in tuberose, the isovalerianic esters in oil of valerian, menthyl acetate in peppermint.

Benzyl benzoate occurs in balsams of Peru and Tolu, and in ylang-ylang, and benzyl cinnamate in the two balsams.

Linalyl acetate is found in bergamot and lavender, benzyl acetate in gardenia.

Methyl anthranilate is widely distributed in small quantities, notably in oils of gardenia, jasmine, neroli, petitgrain, tuberose and wallflower.

The esters of angelic and tiglic acids, stereo-isomers with the formula $CH_3 . CH : C(CH_3) . COOH$, are found in camomile oil, and geranyl tiglate also in geranium oil. Many esters are prepared synthetically for use as perfumes or flavouring essences, e.g. geranyl propionate, used for scenting brilliantine, isoamyl isovalerate, used as apple oil, ethyl butyrate, as a pineapple flavour, isoamyl acetate, known as artificial oil of pear.

Geranyl acetate is found naturally in oils of palmarosa, lemon-grass, geranium, neroli, lavender, etc., and is also made from geraniol on a commercial scale for use in rose and ylang-ylang perfumes.

Some interesting esters that have found employment in perfumery of recent years are derived from the parent substance Heptine, $CH_3(CH_2)_4C \vdots CH$, which it will be seen is amyl acetylene. The ester known as methyl heptin carbonate, $CH_3(CH_2)_4C \vdots C . COOCH_3$, has a strong sharp penetrating disagreeable odour, but when diluted possesses a fine and persistent fragrance of violets.

Of the other components of the essential oils mention may be made of the following :

Diallyl disulphide, $(C_3H_5)_2S_2$, occurs in oil of garlic.

Benzyl thiocarbimide, $C_6H_5 . NCS$, is found in tropæolum oil.

Allyl thiocarbimide, $C_3H_5 . NCS$, is the essential constituent of oil of mustard.

Phenyl ethyl alcohol is an essential constituent of rose oil. Most of it is usually lost in the rose-water and has to be added to the attar to give the latter the best perfume.

Phenyl ethylene, $C_6H_5CH : CH_2$, is found in storax.

Complex hydrocarbons have also been identified in oils, e.g. Marcelet (*J. pharm. chim.*, **24**, 213-25, 1936) found hydrocarbons with the formulæ $C_{23}H_{42}$, $C_{28}H_{50}$ and $C_{36}H_{68}$ in olive oil, $C_{15}H_{30}$ and $C_{19}H_{38}$ in pea-nut oils. These hydrocarbons had acrid nauseating odours.

Many of the odoriferous constituents of the essential oils are relatively rare, and apart from their natural occurrence are unknown. Doubtless many still wait to be discovered and identified.

Variation in Odour of Natural Products

Frequently, different varieties of a plant will be used for the preparation of the essential oil. It is not surprising that oils with different odours then result, but the degree of difference is unexpected.

Parry ("The Chemistry of Essential Oils," **1**, 466, 1921—4th edition revised) quotes Umney and Holmes as having classified the odours of different varieties of pelargonium. Some of these are

Variety.	*Odour.*
Pelargonium graveolens (usual variety)	Rose and rue, slight peppermint.
,, attar of rose	Strong rose.
,, little gem	Peppermint. No rose.
,, zonale	Diphenyl ether.
,, crispum minimum	Strawberry.
,, citriodorum	Lemon.
,, exstipulatum	Pennyroyal.

The next cause of variation lies in the selection of parts of the plant to be used for distillation. The odour may vary in different parts of the plant. In the pelargonium it is strong in the leaves, progressively weaker down the stalk, and absent in the flower. In *allium ursinum* the leaves smell of garlic but the flowers of lilies. The flowers of mignonette, *Reseda odorata*, yield an oil with a powerful floral odour, but the roots yield an oil with an unpleasant smell of radishes. When flowers are purchased by weight twigs will often be included, and their presence will modify the odour of the resultant oil. A third point is that the flowers should be fresh as, if not, the oil will have an inferior odour. Again, the period of the year at which the flowers are picked has an influence—usually when they are most plentiful they give better quality oil and in better yield. If the coriander fruit is used before it is ripe, the oil has an unpleasant bug-like odour in addition to its coriander odour. Similarly, the locality in which the flowers are grown affects the odour, e.g. English and French lavenders. Difference in altitude, even in the same locality, at which the flowers are grown affects odour and the yield.

Most important of all is the method of distillation. Over-heating must be avoided, and the best quality is only obtained if the last fraction is kept separate. In making ylang-ylang only 60 per cent. of the possible oil should be collected for the finest product, and the remainder collected separately. Where precautions of this nature are not taken the odour is adversely affected and the product has to be sold as inferior cananga oil.

With some flowers the perfume materials are too sensitive to withstand the heat treatment of distillation and then enfleurage or extraction must be adopted.

Dill and caraway oils both consist nearly entirely of limonene and carvone but have very different odours. The ratio of the constituents is probably responsible.

Animal Perfumes

Relatively few animal products are used in perfumes. Ambergris, civet and musk are important as they are excellent fixatives, and a little of one of them added to a perfume will greatly improve it. Castor is another similar substance but not used so extensively. These will now be considered separately.

Ambergris

Ambergris is formed from undigested remnants of squids and octopuses in the intestines of the spermaceti whale, *Physeter catodon*. It is sometimes found in the whale, and sometimes floating on the sea or on the sand by the coasts of Brazil, Madagascar, China, India and the Bahamas Isles, from which last source comes most of that reaching Britain. In appearance it is solid fatty inflammable material, grey or marbled with black. Its name suggests its description, " like grey amber." It is valuable, and according to *Manufacturing Perfumer*, **1**, 195, 1937, the following prices were paid :

£1,532 for a lump of 39 lb.
£958 ,, ,, 30 ,,
£2,200 ,, ,, 64 ,,

this being the largest piece found for years.

The lumps of ambergris which are found vary from a few grams to 100 lb. in weight. On account of its value it is a great " find," but not all " finds " are the right stuff. Often they prove to be ships' refuse, soap or ill-smelling animal fats. A collection of such mistaken " finds " is to be seen in the Technological Museum at Sydney.

True ambergris has an unpleasant sweet earthy smell. It melts at 62° C. and volatilizes to a white vapour at 100° C. Specific gravity 0·8 to 0·9. A crystalline substance, " ambrein," can be extracted from it with alcohol. Ambergris is a fine fixative, and its alcoholic solution is used for giving a floral character to perfumes. It is also used in the East as a cooking flavour. It is less liable to adulteration than musk, and its genuineness is tested by its solubility in hot alcohol, and uniform fatty consistency on penetration with a hot wire. It is soluble in ether and oils.

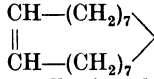
According to *Perf. Ess. Oil Rec.*, **28**, 23, 1937, four components may be noted in the odour : (1) a light sea odour, (2) an indole odour of the fæcal type, (3) a moist incense odour, (4) a musky note. The musky odour is said to be derived from the cephalopods on which the whale feeds, and depends on the size of the cachalot from which the ambergris is derived.

Civet

Civet is a glandular secretion of the African civet-cats, members of the *viverridæ*. The *viverra civetta*, the main source of civet, is about 3 to 4 feet long, of which about one-third is tail, and 10 to 12 inches high. The animal is nocturnal and carnivorous. The cat has a deep pouch near the genital organs into which a fatty yellow substance is discharged. The cats are kept captive, particularly in Abyssinia, although they never become tame. The civet is spooned out of the pouch twice a week, the male yielding more than the female. Teasing the animals is supposed to increase the yield of civet.

Fresh civet resembles butter in appearance but hardens and darkens on exposure to air. Its odour is partly musky but also disgustingly

fæcal, and is remarkable in that highly diluted alcoholic solutions have a sweet odour. It is usually packed in ox-horns holding up to 2 lb., and is liable to be adulterated with petroleum jelly, butter, banana pulp, etc. Genuine civet is almost completely soluble in petrol ether.

The essential constituent of civet is the unsaturated ketone, civetone,  , and as we have already seen the civet odour is usually found in macrocyclic compounds containing 17 or 18 ring atoms.

Musk

Whilst the musk odour is associated with various plants and animals, genuine musk comes from the musk deer, *Moschus moschiferus*. This is a solitary shy nocturnal inhabitant of the birch, juniper, and rhododendron thickets of the Himalayas. It is a small animal, only 20 inches high at the shoulder and has long grey-brown hair. The male carries a sac about the size of an orange in front of the abdomen, and this fills with a dark-brown substance in consistency not unlike moist ginger-bread. The deer is caught by trapping and the sac removed and dried, either in the sun, on a hot stone, or by oil immersion. It is known in this state as " musk in the pod." The best variety is Tonquin " Blue-Skin." If removed from the pod the musk is said to be " grained." Musk has long been considered a soporific. More recently it is considered to have a hormone-like action in stimulating male sex activity. Sano (*J. Pharm. Soc. Japan.*, **56,** 913-14, and *Chemical Abstracts*, **32,** 8519, 1938) showed that when painted on the comb of a capon it stimulated growth in the same way as one of the known sex-hormones.

It is largely used as a fixative for vegetable perfumes which it strengthens and renders more permanent. It has, however, a strong odour itself, and whilst some like and others dislike it alone, a trace will greatly improve a perfume to which it is added. It is liable to be adulterated, but if genuine is one-half soluble in water and one-third soluble in alcohol. Adulteration is detected by microscopical examination.

Muscone, the ketone to which it owes its odour, has already been described. It will be remembered that it is 3-methyl-cyclopentadecan-1-one. It comprises from $\frac{1}{2}$ to 2 per cent. of natural musk.

Other animals in which similar musk secretions are found are the musquash or musk-rat, *Fiber zibethicus*, a North American aquatic animal, in which both sexes have the secretion ; the musk-duck, *Biziura lobata*, of West Australia ; the musk shrew ; the musk beetle ; and some alligators. In the case of the musk-ox, *Ovibos moschatus*, the musky odour is noticeable at a distance, but is not due to a gland secretion.

In the vegetable kingdom various plants exhale a musky odour. The musk mallow, *Malva moschata*, grows wild. The garden musk, *Mimulus moschatus*, once popular, now appears odourless. Probably the odour was confined to a variety which has died out or perhaps human perception has lost its power of perception of that particular odour.

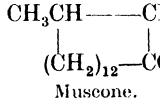
Oil of musk seed is obtained from the seeds of *Hibiscus abelmoschus*, which yield up to 1 per cent. of oil. It is also known as ambrette seed oil, and contains the macrocyclic compound Δ^7 hexadecenolactone as well as farnesol.

Angelica oil, which has a musk fragrance, also yielded a macrocyclic body, the lactone of pentadecan-15-ol-1-acid (exaltolide) as well as Δ^7 hexadecenolactone.

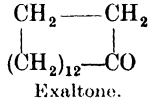
Dyson (*Perf. Essent. Oil Rec.*, **20**, 75-8, 1929) has pointed out that odour in the musk range is not confined to many-membered ketone rings, but that it is given also by various musk substitutes, mostly nitro derivatives of butyl toluene and butyl xylene, and that it seems clear that the olfactory vibrations associated with the musk odour are engendered by two entirely different types of molecules, a nitrated alkyl-substituted benzene nucleus and a many-membered ketone ring. With the later knowledge we have to-day it is still true to say that the musk odour is due to macrocyclic compounds of 15 to 17 ring members on the one hand and to nitrated alkyl-benzenes on the other.

Synthetic Musk

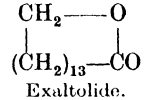
We noted earlier that synthetic perfumes were identical with the natural products, and this is true in the case of musk, for muscone has been synthesized, and exaltone and exaltolide are on the market. Their constitutions are



Muscone.



Exaltone.



Exaltolide.

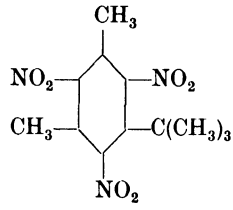
Apart from these substances which are practically the natural products made synthetically, there are the other substances known as synthetic musk or artificial musk which form the group of nitrated alkyl benzenes. These make no pretension to be similar to natural musk in anything except odour. They have the musk odour much more strongly developed than natural musk, but not so fine. Their attraction lay in their much greater cheapness.

The first successful attempt to imitate the musk odour seems to have been made by Schnaufer and Hupfeld of Frankfort in 1888. They prepared various alkyl benzenes, notably :

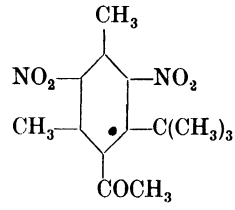
from toluene — methylisopropyl benzene
methylisobutyl benzene
methylisoamyl benzene
and from xylene the dimethyl homologues.

These bodies were then nitrated, yielding the artificial musks.

The best known and most successful artificial musk was " Musc Baur," E.P. 4,963 of 1889. Baur prepared his xylene musk from *m*-xylene and butyl bromide in the presence of aluminium chloride and then nitrated. The product after crystallization from 90 per cent. alcohol separated as yellowish-white needles possessing a strong smell of musk. It was insoluble in water, but soluble in organic solvents and even in very dilute solutions had a strong odour of musk. The artificial musk was trinitro tertiary butyl xylene.



The corresponding mono and dinitro derivatives have no musk odour, so that it is necessary to carry the nitration to completion. Whilst " xylene musk " of the constitution given above is the most common form of artificial musk in commerce, the first artificial musk made by Baur was apparently a toluene musk.

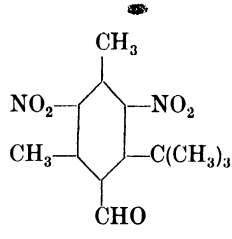


" Ketone musk " was also prepared by Baur, and, according to Barbier (*Helv. Chim. Acta.*, **11,** 152, 1928), this had the constitution :

It is noteworthy that in the " xylene musk " or " toluene musk," three nitro groups were necessary, but in the " ketone musk " only two are required. Evidently the acetyl group, CH_3CO—, reinforces the action of the nitro groups. It was possible to vary the substituent acetyl group to propionyl, butyryl or valeryl and to change the toluene to xylene without losing the musk odour.

Other artificial musks are

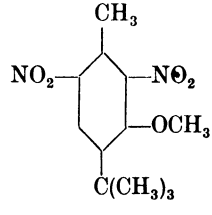
" Aldehyde musk "



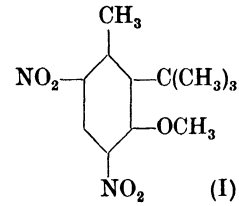
dinitro-tert-butyl xylyl aldehyde

and " cyanide musk," which is the corresponding dinitro-tert-butyl xylyl cyanide.

" Musc ambrette," which is usually regarded as the finest of the artificial musks, is 2 . 4 dinitro-6-tert-butyl-*m*-tolyl methyl ether. Here also only two nitro groups are to be found and the ether grouping must exercise an osmophoric influence.



When Baur first made ambrette musc he regarded it as a trinitro derivative. This was corrected in a communication to Barbier which the latter noted in *Helv. Chim. Acta.*, **11**, 152, 1928. Barbier assigned the formula (I) to ambrette musk, and this was accepted by de Capeller and by Ruzicka, and it was only corrected by Zeide and Dubinin (*J. Gen. Chem. U.S.S.R.*, **2**, 455-71, 1932, and *Chemical Abstracts*, **27**, 961,1933). Instead of being

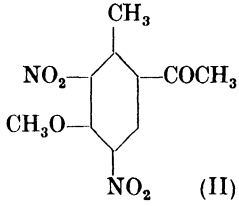


(I)

1 . 2 . 3 . 4 . 6 $C_6H(CH_3)(C(CH_3)_3)(OCH_3)(NO_2)_2$

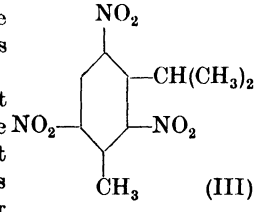
it was really 1 . 3 . 4 . 2 . 6 $C_6H(CH_3)(OCH_3)(C(CH_3)_3)(NO_2)_2$.

It will be clear that the tertiary butyl radicle plays an important role in the artificial musks, and the isobutyl or tertiary butyl group has been thought essential for a good musk odour. Barbier (*Helv. Chim. Acta.*, **11**, 152, 1928) made the substance (II) which has a general resemblance to ketone musk but has no butyl group in it, and he claimed that it had a peculiar clinging odour of the same general note as the nitro-musks but less agreeable.

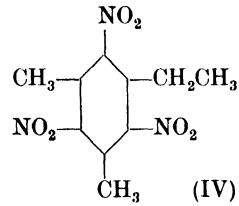


(II)

de Capeller (*ibid.*, 166, 1928) pointed out that a tertiary carbon atom seemed to be necessary for a good musk odour, and that if it was replaced by a secondary group as a trinitro isopropyl toluene the (III) odour is feeble. The corresponding body with a tertiary butyl group instead of a secondary propyl group is toluene nitro-musk and has a strong odour. If this change was carried further and a normal group substituted for the secondary group then the product, such as trinitro ethyl xylene, had no odour (IV).

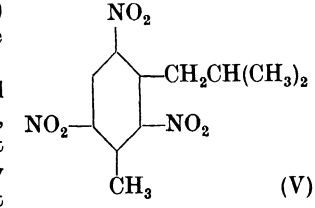


(III)



(IV)

Knoevenagel (*Ann.*, **289**, 165-6, 1896) had shown that trinitro isobutyl toluene was odorous (V).

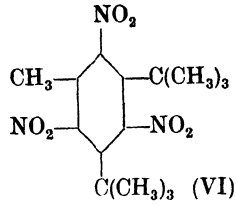


(V)

It is clear that the tertiary butyl group is present in the best nitro-musks, and that efforts to dispense with it entail a sacrifice in the power and quality of the odour. We might therefore expect a body similar in general design to those discussed but containing two tertiary butyl groups to be a musk odorant *par excellence*. However, de Capeller (*Helv. Chim. Acta.*, **11**, 169, 1928) prepared the body (VI)

and found that it only smelt faintly of musk.

Work was carried out by Hanai (*Bull. Inst. Phys.-Chem. Research* (Tokyo), **10**, 354-65, and *Chemical Abstracts*, **26**, 1631, 1932) to settle the point about the necessity of a butyl group. The following compounds were made :

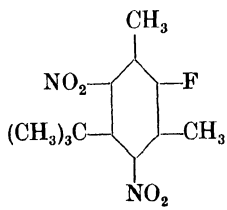


(VI)

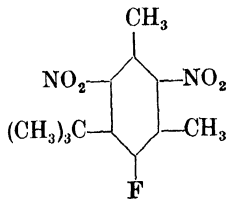
Dinitro acetyl *o*-ethyl anisole.	Odourless.
Dinitro tert.-butyl *o*-ethyl anisole.	Odour like ambrette musk but far weaker.
Dinitro tert.-butyl anisole.	Strong odour like ambrette musk.
Dinitro tert.-butyl *n*-propyl anisole.	Odour like ambrette musk.
Dinitro tert.-butyl isoamyl anisole.	Weak odour like ambrette musk and additional bad smell.
Trinitro α-methyl β-naphthol methyl ether.	Odourless.
Trinitro tert.-butyl α-methyl β-naphthol methyl ether.	Disagreeable odour.

The conclusion is that the tertiary or isobutyl group and the methyl group are closely related to odour in the nitro-musks.

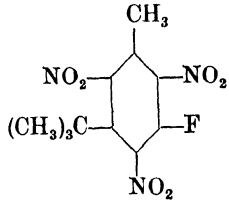
If therefore one tertiary butyl, one methyl and two nitro groups are necessary, it leaves only two places in the benzene nucleus to fill. Often if the musk is a xylene derivative one of these places will be taken by another methyl group. Even so, by substituting a halogen in the toluene musks it is possible to obtain different nuances of odour. Alternatively, cymene (isopropyl methyl benzene) may be used instead of toluene or xylene as the starting-point. French Patent 710,295 (Givaudan et Cie, 1931) described the introduction of an isobutyl or tertiary butyl radicle into cymene followed by nitration. An attempt to make the musk more volatile by the introduction of fluorine into the radicle is described by Darzens and Lévy (*Comp. Rend.*, **199**, 959-62, 1934). They made the following compounds :



2 . fluoro-3-methyl 4-6 dinitro-5-tert. butyl toluene.



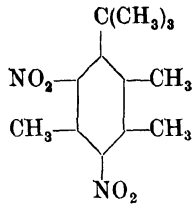
2-6 dinitro-3-methyl 4-fluoro-5-tert. butyl toluene.



2 . 4 . 6 trinitro 3-fluoro-5-tert. butyl toluene.

In spite of their greater volatility their odour was little if any stronger than that of Baur's musk.

The use of 4 . 6 dinitro 2 . 3 . 5 trimethyl 1-tert. butyl benzene (VII) as an artificial musk forms the subject-matter of U.S. Patent 2,072,293 (Carpenter, 1937).



(VII)

A commercial artificial musk is often a mixture of two or more compounds. Acetanilide is the main adulterant.

Castor

This is a secretion of the beaver, *Castor fiber*, and collects in two abdominal sacs in both sexes. It is a white, creamy liquid when fresh, but on drying changes to a dark brown fatty solid. It has a powerful resinous odour, which is affected by the diet of the animal. The two main varieties come from Canada and Russia. It finds employment as a fixative in heavy oriental type perfumes.

Fixatives

Since most of the odorous materials which go to make a scent are volatile, the perfume would normally be evanescent. It is, in use, required to be reasonably permanent, and this permanence is gained by the addition to the perfume of a fixative, a relatively non-volatile constituent which retains or fixes the odour of the other components.

The best fixatives are musk, civet and ambergris. Castor is also used for heavy perfumes. Such fixatives are themselves odorous, and contribute their own odour which, in dilution, may be very attractive as well as fixing the odour of the other materials. Musk and ambergris are of course expensive, and they are often replaced by materials from the vegetable world, such as preparations of gums and oleo-resins. Other vegetable fixatives are found in the essential oils, e.g. patchouli, sandalwood, vetivert, clary sage. Vanillin is used as a fixative, and its own perfume adds sweetness. Oak moss resin, which is a lichen growing on oak and other trees, has an odour recalling musk and lavender and is also used as a fixative. Tinctures of these fixatives are usually made by extraction in alcohol.

There has been considerable discussion as to the mechanism of fixation. Many have suggested that the addition of a little musk reduces the vapour pressures of the odorous components. It is, however, clear from a consideration of the small quantities of fixative involved and from Dalton's Law of Partial Pressures that no such simple physical explanation can hold. The writer believes that the molecules of the odorous material are adsorbed on the molecules of the fixative or else are very loosely combined by means of residual valences with the fixative. Both explanations are really the same, and in support it may be remembered that odorants are particularly susceptible to adsorption. The fixative plays the role of anchor to the fly-away odorant molecules.

In practice a perfume fixative will often itself be compounded from many products, musk ketone, ambrette musk, clary-sage oil, benzyl cinnamate, benzoin, resins of Tolu and Peru, etc.

Scent

Perfumery is an ancient art. The Egyptians used sweet-smelling substances for embalming and for incense. The Greeks and Romans made perfumes with a base of olive oil. Later the discovery of alcohol provided a more suitable medium for scents. The æsthetic side of perfumery is not susceptible at present to scientific measurement. Perfumes delight us, but some of their constituents may separately disgust us.

The compounding of perfumes is a complicated business. They are made from mixtures of natural oil, and synthetic chemicals and isolates of natural materials, together with certain animal derivatives used as fixatives. The addition of the synthetics may be necessary in order to obtain the perfume of the natural flower, for there may be components in the flower which have been lost in the floral extract or essential oil. The essential oils from flowers or the floral extracts are used in the highest quality perfumes, but synthetic bodies, or more plentiful but fairly similar natural bodies, will be used for moderately-priced articles. True violet extracts are costly, but ionone made from citral, which is cheap and obtained in quantity from grasses, is a good substitute. It is not a true synthetic, but a compromise, as natural citral is the starting-point. Similarly, vanillin is made from eugenol of oil of cloves. There is, of course, no difference between the vanillin so made and that found in vanilla beans. The vanilla beans are the unripe fruits of climbing orchids. In Mexico the birds and insects fertilize the plants, but in other parts fertilization must be done by hand. The dried fruits will sometimes exude crystals of vanillin.

The natural perfumes are usually complex mixtures, e.g. ylang-ylang contains at least thirty components. Consequently the artificial perfume, which is usually much simpler, will not catch quite the right note of the natural perfume. It is therefore not uncommon for synthetic products to form the bulk of a perfume and for a small quantity of the natural oil or extract to be added, as even a minute amount may give the perfume a distinction it otherwise lacks. Consequently, also, the perfumer mixes many constituents in his effort to reproduce the natural odour. Even using good materials a synthetic oil of rose may well cost only one-quarter of the price of virgin .otto.

Many of the natural products are adulterated, skilfully, so that detection is difficult, and often with sound natural odorants which are cheaper and more plentiful. The delicacy of odour may be lost if this adulteration is not guarded against. Also if alcohol is used as a base the fusel oil must be removed or it will coarsen the odour. On

the other hand, a trace of fusel oil may improve the odour of eau-de-Cologne. Isopropyl alcohol is sometimes used instead of ethyl alcohol, as it is cheaper, but it has not such a pleasant odour itself and is more toxic. It is especially used for cheap eau-de-Cologne.

A few natural bodies, such as coumarin, formerly obtained from the seeds of *Dipteryx odorata*, are now completely replaced by synthetic products. The constituents, other than the essential oils and floral extracts, of some of the more frequently met perfumes, are indicated below :

Rose. Geraniol, nerol, citronellol, phenyl ethyl alcohol.
Jasmine. Benzyl acetate, tolyl acetate, benzyl propionate, methyl anthranilate, indole, phenyl ethyl alcohol.
Orange flowers. Geraniol, indol, methyl anthranilate.
Hawthorn. Anisaldehyde, acetophenone, citronellol.
Clover. Amyl salicylate, linalyl acetate.
Muguet (lily of the valley). Hydroxy citronellal.
Orchid. Amyl salicylate.
Hyacinth. Phenylacetaldehyde, cinnamic alcohol, balsam of Tolu.
Geranium. Diphenyl ether, diphenyl methane.
Violets. α- and β-ionones, methyl ionone, euionone, irone, violet leaf oil, oil of orris-root.
New mown hay. Coumarin, terpinyl cinnamate, acetophenone, perillic aldehyde.
Heliotrope. Piperonal.
Carnation. Eugenol, isoeugenol.
Jonquil. Phenylacetaldehyde.
Verbena. Citral, lemon-grass oil.
Sweet pea. Anisaldehyde.
Lilac. Terpineol, benzyl acetate, hydroxycitronellal.
Mignonette. Oil of sweet basil.
Lemon. Citral.
Tuberose. Benzyl acetate, phenyl propyl alcohol, benzyl salicylate.
Bergamot. Lilanyl acetate.
Ylang-ylang. Methyl benzoate, methyl anthranilate.
Fancy bouquets. Salicylic aldehyde.

For scenting soaps the following are extensively used :

Safrol, oil of sassafras, terpineol (lilac), benzaldehyde, cinnamic alcohol, cananga oil, caraway oil, cassia oil, cedar-wood oil, oil of cloves, oil of linaloe, oil of rosemary, sandalwood oil, oil of thyme, oil of valerian.

For scenting face powders and creams :

Lilanyl cinnamate, phenylethyl cinnamate, oil of patchouli, sandalwood oil.

For flavouring dentifrices the following are used :

Methyl salicylate, oil of cinnamon, oil of cloves, oil of peppermint.

For hairwashes :

Oil of pimento (bay rum), oil of bay, oil of rosemary, ionone (violet), terpineol (lilac). (*Note.*—Rum was originally used in bay rum but industrial alcohol is now used.)

After a perfume has been made it is necessary to mature it for it to develop its full odour, just as wines and spirits are matured. Slow esterification processes take place during the maturing time.

Care is used in compounding perfumes that one component does not overwhelm the others. If we smell a wild rose and admire the delicacy of its perfume and then smell clover at the same time, the clover quite overwhelms the wild rose. Then if we add meadow-sweet we find this quite overwhelms the odour of the clover. Meadow-sweet has as its odorous principles the powerful salicyl aldehyde and vanillin.

In some cases the natural source of an odour is not available. There are neither floral extracts nor essential oils, but by skilful blending the odour is reproduced without any of the constituents being derived from the plant in question. Such cases are : carnation, hawthorn, heliotrope, lilac, lilies, orchids, trefoil and new mown hay.

As an indication of the composition of some scents the following may be noted :

Eau-de-Cologne

Alcohol	1,000 ml.
Oil of lemon	5 ,,
,, neroli	4 ,,
,, bergamot	3 ,,
,, rosemary	2 ,,

this mixture being diluted with rose-water or orange-flower water to the necessary strength. In cheaper varieties isopropyl alcohol would be used instead of ethanol, and citral and synthetic products from it largely substituted for the essential oils. The essentials of eau-de-Cologne are oils of the citrus group and either lavender or rosemary.

Lavender Water

Alcohol	1,000 ml.
Oil of lavender	20 ,,
,, bergamot	15 ,,
Tincture of musk	5 ,,

and diluted with water to the required strength.

Hawthorn

Alcohol	1,000 ml.
Anisaldehyde	10 ,,
Citronellol	10 ,,
Phenyl ethyl alcohol	1 ,,

Red Clover (Trèfle incarnat)

Alcohol	1,000 ml.
Bergamot oil	10 ,,
Ylang-ylang	10 ,,
Linalyl acetate	10 ,,
Amyl salicylate	5 ,,
Coumarin	5 ,,
Vanillin	2 ,,
Oil of vetivert	1 ,,

Carnation

Alcohol	1,000 ml.
Eugenol	20 ,,
Isoeugenol	10 ,,
Citronellol	10 ,,
Phenyl ethyl ketone	10 ml.
Musk ketone	3 ,,
Resin	3 ,,

Honeysuckle

Alcohol	1,000 ml.
Hydroxy citronellal	10 ,,
Cinnamyl alcohol	6 ,,
Phenyl ethyl alcohol	6 ,,
α-ionone	5 ,,
Terpineol	3 ,,
Piperonal	3 ,,
Musk ketone	2 ,,

Brilliantine. Violet perfume

Cotton-seed oil	1,000 ml.
Ionone	3 ,,
Cananga oil (terpeneless)	2 ,,
Chlorophyll (green)	0·5 gm.

These compounding formulæ are intended only to illustrate the process by which the floral oils and extracts are combined with synthetics to give back the original odour of the flower, and in some cases to produce the odours of flowers which do not readily yield oils by distillation, extraction or enfleurage.

CHAPTER 14

FLAVOUR AND FOOD

Flavour Factors

Flavour is a complex sensation. It comprises taste, odour, roughness or smoothness, hotness or coldness, and pungency or blandness. The factor which has the greatest influence is odour. If odour is lacking then the food loses its flavour and becomes chiefly bitter, sweet, sour or saline. It has already been noted in Chapter 4 that people suffering from loss of smell lose also what they call their "sense of taste," but which is really the odour component of the flavour. Taste remains, but only the ghost of flavour. Meats taste the same, wines merely slightly sweet or sour. I think it is legitimate to include "roughness or smoothness" as a flavour factor. Roughness may quite destroy the appreciation of an otherwise attractive food. One recalls lumpy porridge or a gritty chocolate. Hotness may be sensed either as the result of applying food at a high temperature, say 50° to 60° C., to the mouth or by tasting ginger or another "hot" spice. Similarly, coldness may be due to a change in temperature or to tasting peppermint, which has a cooling taste.

Owing to the greater volatility of the odorous components, warm or hot food and beverages have more flavour than cold. After eating or drinking cold food or liquids the sensation of flavour is experienced chiefly on breathing out, after the odorous constituents have been warmed in the mouth and throat and are consequently more volatile and more easily detected by the nose.

Apart from the æsthetic enjoyment derived from flavour in food, the flavour performs useful biological work in stimulating the flow of salivary and digestive juices. We all know how the mouth waters on perceiving the smell of a delicacy, and how the appetite sharpens when we smell the breakfast bacon. Smell starts a series of reflex processes in motion. Certain fishes will not feed unless they can smell the food, even though they are hungry (or at least starved) and suitable food is where they can see it. The appearance of the pigment (at the same time as the sense of smell, we believe) in young animals at weaning time also illustrates the importance of smell in the selection of food.

Water

The first requirement of our alimentary system is water, and we rightly attach importance to its purity. It should be odourless and tasteless. A stale odour is often the accompaniment of bacterial infection.

The concentration of dissolved carbon dioxide in water affects its taste. Distilled water has no carbon dioxide and is flat and insipid.

It may be said to have an alkaline taste. The water in our nasal passages contains carbon dioxide in solution, and this water is the standard to which we refer other substances for odour. It is therefore correct to regard distilled water as sapid, and incorrect to apply the adjective insipid to it, although I think that in colloquial use the word (insipid) is used more to indicate an alkaline taste than a complete absence of taste. These remarks apply equally whether the alkaline taste is considered as a true taste or as a manifestation of the common chemical sense. Hard water, which contains more carbon dioxide, has a distinct taste.

The evaluation of the quality of water from the standpoint of freedom from odour by the Fair and Wells Dilution Osmoscope has already been discussed, as has also the occurrence of unwanted tastes and odours in drinking water due, as a rule, to the growth of organisms. It will be remembered that the general methods of purification are filtration, adsorption and chlorination. Adsorption on charcoal has been found very useful. The objectionable taste of the water in swimming-baths is due to chlorination. In order for the chlorine to be able to render harmless the germs and viruses likely to be introduced into the water, it must be of so high a concentration as to be objectionable. River water is often contaminated with sewage residues and unfit for drinking. Consequently, since swimming involves drinking, willy-nilly, it is preferable to swim in a public swimming-bath rather than in a river, and best of all, of course, in the sea. Chlorination in very mild doses of drinking water has itself caused taste troubles, since in contact with traces of phenolic bodies it forms foul-tasting compounds. The trouble has occurred through leading drinking water through internally tarred pipes, or collecting water that has passed over tarred roads, although this is not done nowadays. Barral and Ranc (*J. Psychol.*, **17**, 16-30, 1920, and *Physiol. Abstracts*, **5**, 286) draw attention to the dangers of traces of phenol in water which has been chlorinated.

The cause of an earthy taste in water is generally the presence of the common ray-fungus *Actinomyces*, which comes from the soil. The taste is persistent but can be removed by adsorption on carbon, clay, chalk, etc. Such water may also give an earthy taint to the flesh of fish inhabiting it.

Beverages (Other than Alcoholic)

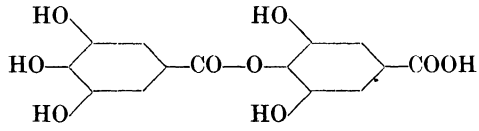
New milk has only a mild sweet taste and faint odour. The smell of sour milk is not due to lactic acid, which is odourless, but to the presence of small quantities of volatile fatty acids, e.g. butyric. Cows' milk contains about 12 per cent. solids, 3·1 per cent. protein, 3·4 per cent. fat, 4·8 per cent. carbohydrates and 0·7 per cent. minerals.

The food given to the cows has a considerable influence on the flavour of milk. The betaines in sugar beet residues may give it an unpleasant taste (cf. Chapter 1), whilst another source of trouble is

vetch seeds, which contain bitter principles which impart their taste and odour to the milk. Experiments have been made to see if this danger can be avoided by steam distilling the vetch grains to remove the bitter principles, but without much success.

Tea was originally used medicinally as a nerve stimulant. It appears to have been used in China for at least 4,500 years. Its use in Europe dates from 1517. It consists of the leaves of *Thea chinensis* and *Thea assamica*, which are dried and then fermented until they have a fragrant odour. An essential oil has been extracted from tea and is pale yellow with an intense penetrating odour of tea. This is quite a separate body from tea-seed oil obtained from the seeds, an oil which has for some purposes replaced olive oil. The tea may be flavoured by the addition of fragrant flowers. Those of the navel orange are sometimes used, and owe their effect largely to the trace of indole which they introduce. It has in fact been suggested that the quantity of such orange flowers present could be determined by the amount of indole present, and that the aroma of the tea could be related to its indole content.

About 45 to 50 per cent. of ordinary tea is water-soluble. When it is infused for drinking the aim should be to dissolve as much as possible of the aromatic essential oil and the caffeine which give the pleasant flavour and stimulating effect, without dissolving the tannin, which has an astringent taste and renders tea which has been standing some time objectionable. Most of the caffeine and essential oil are dissolved out in five minutes so that the optimum pleasant effects are then obtained, and to leave the liquor in contact with the tea-leaves longer impairs the quality of the beverage. Normally tea contains about 3 per cent. caffeine and 13 per cent. tannin. The tannin, which is remarkable for its astringent taste and peculiar odour, is a phenol derivative with the constitution



The milk which is usually added to tea has the good property of precipitating the tannin, so minimizing its astringent taste and deleterious effects.

In other countries different flavours are appreciated. In the East a weak infusion without milk or sugar is favoured ; in Russia lemon-juice is added ; in Germany rum and cinnamon, and in Spain lemon-verbena.

The odorous principles of oil of tea which are responsible for the aroma of the beverage have been the subject of intensive research in Japan. A very large number of compounds have been identified, particularly alcohols, e.g. butyl, isoamyl, hexyl, octyl, benzyl, and phenyl ethyl alcohols and geraniol.

Coffee consists of seeds from the berries of the evergreen shrub *Caffea arabica*, indigenous to Abyssinia and Arabia. After being dried, roasted and ground they give when infused with water the delightful beverage—coffee. The seeds or beans are dried and then roasted in order to destroy the tough fibrous nature of the bean and also to develop the aroma. If under-roasted the flavour is not fully developed, but if taken too far an unpleasant empyreumatic odour appears which makes the subsequent infusion nauseous. During roasting there is a loss in weight of about 16 per cent., of which about half is moisture, but the other half consists of volatile products from the fats and sugars as well as some caffeine. This loss is serious, as the pleasantly flavoured oils of the coffee are largely lost during roasting instead of appearing in the final infusion. It is clear why the flavour of the beverage—infused coffee—is only a shadow of the exquisite aroma of roasting coffee. In order to minimize the loss of essential oil, the beans should not be ground until required for infusion.

Cocoa has a less sophisticated odour than tea or coffee. As a food it is more valuable, since it contains 40 per cent. carbohydrate, 27 per cent. fat and 18 per cent. protein. The cocoa beans are about the size of haricot beans, and there are about 30 in a fruit, which is similar in shape to a fat cucumber. The beans are fermented, as this changes their taste from bitter to an agreeable aromatic flavour. Such fermented beans are suitable for chocolate making. Unfermented beans are too bitter for chocolate, and if used for cocoa, a large quantity of sugar must be added. After fermentation the beans are normally dried and roasted. This brings out the flavour, but as in coffee roasting some of the volatile oil is lost.

Theobromine or dimethylxanthine is the alkaloid in cocoa (caffeine is trimethyl xanthine). About half of the husked bean is composed of cocoa-butter, a fat with a pleasant taste and chocolate odour which consists chiefly of the glycerides of stearic, palmitic, oleic and arachidic acids.

Lemonade should have not only the pleasant taste of the citric acid and the health-giving ascorbic acid but should also have the pleasant aroma of the essential oils in the rind. Accordingly it is usual when preparing it to add shavings from the outside rind and to boil. If the heating is confined to a short, brisk boiling, the vitamin C will not be destroyed, but it will not sustain a long simmering.

Alcoholic Beverages

Alcohol cannot be tasted in low concentrations, and even in fairly high concentrations it has only a rather faint sweet taste. Neither is its odour remarkable; it is not pronounced, just pleasant and spirituous or ethereal. It is therefore surprising that alcohol should be such an indispensable constituent of so many of our drinks. It will be said that the stimulating and intoxicating effect is the attraction, but there are few people who would be attracted by a pure aqueous

solution of absolute alcohol. It is true that cases have been known of chemical workers with ready access to the absolute spirit, adding a few drops to their afternoon tea, but even this practice is so rare as to constitute a curiosity. In spite of the lack of attractiveness of pure water/alcohol mixtures, most people find non-alcoholic drinks, however pleasantly flavoured with esters, very much inferior to alcoholic beer, wines, spirits and liqueurs. The odour of the alcohol, perceived mostly after the vapours have been warmed in the throat, enhances and blends with the odours of the esters, giving an attractive *ensemble*. As is well known, raw spirits contain fusel oil which consists chiefly of isoamyl and active amyl alcohols as well as small quantities of many other alcohols, such as propyl and isobutyl. These alcohols have disagreeable odours and impair the flavour of the beverage which, since they are very harmful to the body, is just as well. Consequently the spirits are kept for long periods, during which these alcohols are converted into harmless and pleasantly odorous esters.

Beer is made by the fermentation of barley. First, barley is sprouted and the sprouted barley is heated to a temperature destroying the organism which carries the enzyme, but which does not kill the enzyme itself. The product, malt, is mashed with more barley which it ferments. The alcohol content of beer is usually less than 5 per cent. which is tasteless, although the vapours are odorous. Flavouring is necessary, and hops are used. The hop plant belongs to the nettle family. Foreign hops have not such a delicate aroma as English, and of the latter Worcester hops are milder than Kentish and are preferred for some beers. If the hops are added and boiled with the wort in making beer, much of the essential oil which contains the odorous constituents of the hop steam-distils off and is lost. Accordingly it is now more usual to extract the oil from the hops separately and add the oil either to the finished beer or at a late stage of its manufacture. The essential oil of hops contains myrcene, linaloöl and linalyl isononoate. Many attempts have been made to concentrate beer so that it could be transported cheaply and then watered down, but these have been unsuccessful as they have resulted in loss of aroma and destruction of the palate or flavour of the beer.

Wines, prepared by fermentation of grape-juice contain more alcohol, but not usually above 10 per cent., except in fortified wines where distilled alcohol is added to the wine. Light wines, such as sauternes, hocks, clarets and burgundies, are not fortified but ports and sherries may be so. In these cases the alcohol content is high enough to have a distinct taste effect, whilst naturally the odour effect is enhanced. However, the bouquet of the wine is determined principally by the esters it contains. These vary according to the district from which the wine comes, the year, according as the crop is good or poor, and the age, since esterification will have proceeded during maturing. The best length of maturing time varies with the wine, perhaps 40 years for port and 12 to 15 years for champagnes. The temperature at

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which the wine matures should be between 53° and 58° F. Champagne is often chilled before drinking, but if the temperature is taken below 50° F. much of its fragrant bouquet and pleasant vinous flavour is lost. If wine is too warm the odour of the alcohol interferes unduly with that of the esters and the fineness of the bouquet is lost.

Wine will readily take up other odours, and it is necessary to exclude these from places of storage. The relation between the *p*H value and the taste of wine was investigated by Crisci (*Ann. chim. applicata*, **20**, 566-83, 1930). A low *p*H value gave the wine a sour taste, but other factors exerted an influence, notably the undissociated organic acids and the presence of sugar, glycerol, alcohol and tannin. Crisci pointed out that if a wine is diluted with water its *p*H value may not be greatly affected, but the taste will change. Glucose may be added to " improve " wines.

Brandy is the distillate obtained from fermented grape-juice. It is colourless when new but takes its yellow-brown colour and some tannin from the oak casks in which it is stored. Inferior or new brandy has a fiery taste and earthy bouquet, but if aged and matured it has a sweet, mellow ethereal flavour. The bouquet is due to esters, mainly ethyl pelargonate, but also acetic, butyric and valeric esters, as well as traces of terpenes. Liqueur brandy, which should be in the region of fifty years old, is drunk from thin convex glasses, so that the warmth of the hand increases the volatility and the vaporous particles are partly restricted from escaping by the narrow lip of the glass, so that the warm odorous vapours which collect in the glass may be inhaled.

Rum is distilled from the sugar cane, and its flavour is due to esters of high molecular weight acids.

Whisky is distilled from fermented barley. Gin is similar to whisky but flavoured with juniper.

Liqueurs are prepared by adding various flavouring ingredients to spirit and distilling, and in some cases essential oils may afterwards be added to the distillate.

Caraway seeds provide the flavour of kümmel ; peppermint, balm and cinnamon that of crême de menthe ; cloves, nutmegs, cinnamon, balm, angelica, etc., that of Benedictine.

Bread

The pleasant odour of new bread is due to the presence of furfuraldehyde. The aromatic principle in rye bread is a derivative of furfuraldehyde. Biacetyl, the odorous constituent of butter, is also present in bread in small quantities and may contribute to its flavour. White bread which has been deprived of its bran, middlings and germ by modern milling methods has very little taste. Wholemeal bread, on the other hand, has a pleasant nutty taste. The wheat germ, which is available under the name " Bemax," has the same nutty flavour, much more pronounced. Since the wheat germ contains the

valuable vitamin B, thiamine or aneurin, it is clear that it is more beneficial to eat the pleasantly flavoured wholemeal than the tasteless refined product. People who eat white bread ignore the promptings of the tongue. (*Food Manufacture*, **6**, 314, 1931.)

Fruits

The pleasant flavours of fruits are due to the esters and acids they contain. In addition, the attractive odour of the oils in the rind, especially of the citrus fruits, is outstanding.

Unripe fruits contain a good deal of starch, and as the fruit ripens this starch is gradually changed into sugar, so that in ripe fruit there is no starch but a lot of sugar. Hence the increase in the sweet taste as the fruit ripens. Most of the sugar is fructose or lævulose and the remainder usually either glucose or sucrose (cane-sugar). All fruits have a high water-content, usually about 80 per cent.

Apples, for instance, are 80 per cent. water, and when ripe contain about 14 per cent. sugars and about 0·7 per cent. malic acid, which gives the tart flavour. It may be noted that the peel is dietetically the most valuable part of the apple and contains most of the ascorbic acid present. Cider apples contain more tannin than others and have an astringency which detracts from their flavour for eating. On cutting and exposing to the air they rapidly turn brown. Apart from the sweetness due to the sugars and the tartness due to the malic acid, the flavour or aroma of apples depends on esters. It can be imitated by isoamyl isovalerate.

Apricots and tomatoes are useful sources of carotene. Most of the other fruits are poor in this substance. The flavour of apricots can be imitated by a mixture of isoamyl butyrate and isoamyl alcohol.

Ripe bananas are particularly rich in sugars.

The flesh of oranges consists of 84 per cent. water, 5 per cent. sugars and 1·4 per cent. citric acid as well as ascorbic acid. The flavour is due to these and to esters as well as to the essential oil which is chiefly concentrated in the rind. The bitter principle of the navel orange was identified by Higby (*Jour. Am. Chem. Soc.*, **60**, 3013-18, 1918) as isolimonin, a substance which had been earlier found in orange seeds. It occurs in the section-covering of the fruit as a non-bitter water-soluble substance, but when the tissues are ruptured it is converted by the juice to the intensely bitter form. Feist and Schulte (*Ber.*, **69B**, 1322-3, 1936) isolated from lemon-seeds an optically active " citrolimonin " which may be the same bitter constituent as is found in orange-pips. Lemons and grape-fruit (shaddock) are similar. The main constituents of their essential oils were considered in Chapter 13.

Grapes are 80 per cent. water and have a high sugar content, 17 per cent. Their acidity is due to tartaric acid and potassium hydrogen tartrate. Raisins are grapes which have been dried so that their water content is only about 20 per cent., consequently their sugar content is about 65 per cent.

The flavour of the pineapple is imitated with ethyl butyrate, the pear with propyl acetate and the Jargonelle pear with amyl acetate.

The ratio of sugar to acid in a fruit largely determines its flavour. The strawberry growing wild has a ratio of 2 sugar to 1 acid, the cultivated American strawberry a ratio of 4 : 1, and the English cultivated berry a ratio of 9 : 1. The reader will probably have noticed the tartness of the wild berry. In the cultivated raspberry, which is noticeably tarter than the cultivated strawberry, the ratio is about 3 : 1. Essential oils contribute to the flavour of both these fruits. The flavour of strawberries may be imitated by a mixture of 2 parts of ethyl acetate and 1 part of amyl acetate.

Vegetables

The flavours of vegetables are as a rule mild. Exceptions are the onion and leek which owe their pungency to allyl disulphide. Some of the root crops are sweet, e.g. the turnip has 7 per cent. sugar, and the sugar-beet averages 16 per cent., although the original vegetable from which it has been developed contained only 2 per cent. The locust bean-pod is one-third sugar, 23 per cent. sucrose and 11 per cent. glucose. Green vegetables like the cabbage have a useful ascorbic acid content, but this is reduced by long cooking and completely destroyed if soda is added, as it sometimes is to protect the colour during cooking.

The offensive odour of decayed or old greens is due to the presence of sulphur compounds. Soy is a piquant sauce made from the soya bean, and its flavouring constituents have been the subject of considerable research in Japan. Udo (*Jour. Agr. Chem. Soc. Japan*, **8**, 675-84, 1932, and *Chemical Abstracts*, **27**, 1059, 1933) considered that the taste of soy was due to mixtures of salts of glutamic and succinic acids and amines such as arginine, histidine, putrescine, cadaverine and choline. Akabori and Kaneko (*Jour. Chem. Soc. Japan*, **57**, 828-37, 1936, and *Chemical Abstracts*, **31**, 1355, 1937) showed that the characteristic flavour was due to the presence of (γ-methylmercapto) propyl alcohol, $CH_3S \cdot CH_2 \cdot CH_2 \cdot CH_2OH$. This substance itself had a disagreeable odour, but when added in small quantities (10 parts per million) to soy sauce it improved it and increased the characteristic odour. Later they showed that two other flavouring agents which contributed to the odour were (δ-methylmercapto) butanol and (γ-methylmercapto) propaldehyde.

The distinctive flavours of vegetables such as the parsnip, celery, etc., are found in their essential oils which have already been discussed. An interesting flavour component is found in oil of cucumber viz. nonadienal, together with the corresponding alcohol. The aldehyde has a strong odour of fresh cucumbers (Janistyn, *Seifensieder Ztg.*, **67**, 16, 25-6, 1940).

Foods of Animal Origin

The pleasant flavour of butter is largely due to small quantities of diacetyl, a yellow oil with a pungent sweetish odour. Volatile acids, particularly butyric, also contribute to the flavour. Butter fats are mainly glycerides of oleic, palmitic, stearic and myristic acids and are practically odourless. Goat's butter contains also capric, caproic and caprylic acids.

Margarine is made from many unsaturated fats of both vegetable and animal origin. The unsaturated fats are liquid at ordinary temperatures and have strong odours. Chemical saturation is effected by catalytic hydrogenation, and the saturated fats are both odourless (or nearly so) and solid at normal temperatures.

The proteins are built up by plant life and occur in small quantities in all vegetable matter such as grass. Peas and beans have much larger protein contents. When animals feed on this vegetable matter the proteins are used in body building, but are not greatly changed. They consist of long amino-acid chains and usually have about 0·8 per cent. sulphur in them. When protein foods are fresh, e.g. meat, fish and eggs, they have relatively mild odours, but if kept until decomposition starts, then the large molecules break down into smaller residues of amino-acids, amines and acids which give a high flavour to the food, e.g. poultry or cheese. In fish amines predominate, in the egg the sulphur compounds formed give rise to objectionable odours. Much protein food is preferred in a partly decomposed state, as the flavour is then better developed and probably the products are easier to digest. Cheese is ripened and a bird is hung, but no unnecessary delay is countenanced in the case of an egg.

Sweets

Sweetening agents are nearly always odourless. Sucrose is far and away the most usual sweetener, followed by glucose and by the fructose we eat in fruits. Most of the sweets we eat are flavoured with odorous materials, and the combination of pleasant odour and sweet taste seems to give most satisfaction. Sugar is usually taken with tea, coffee and cocoa, each of which contributes its own aroma. Chocolate is usually flavoured with vanilla. Cakes and puddings incorporate fruits, spices and essences. From the standpoint of dietetics too much sugar is eaten, and from that of gastronomy the same is true, for the intensely sweet taste of sugar overwhelms the more subtle flavours of many foods. In war-time when sugar is scarce, saccharin is the usual substitute. Sufferers from diabetes also use saccharin.

Spices

Spices are productions of plants which are characterized by aromatic odours and pungent tastes. They are obtained from different parts of the plant, e.g. allspice from the berries of *Pimenta*

officinalis, cinnamon from the inner bark of *Cinnamomum zeylanicum*, cloves from the calyx and flower-buds of *Eugenia aromatica*, and ginger from the roots of *Zingiber officinale*.

Many spices, such as pepper and cinnamon, have been known from antiquity. In the year 408 part of the ransom of Rome demanded by Alaric was 3,000 lb. of pepper. In the Middle Ages spices were greatly esteemed, but comparatively expensive. They constituted one of the riches of the East, which induced the Portuguese to find the sea-route, round the Cape of Good Hope, in 1498. The Spice Islands, now known as the Moluccas, were a rich source, especially of cloves. The Dutch, in 1605, wrested the Spice Islands from the Portuguese, and attempted to confine the clove tree to the island Amboyna. They rigorously extirpated the plant from all other islands in their attempt to keep the monopoly, but without success. The development of this spice trade with the Moluccas, naturally brought to the West an abundant supply of spices at more reasonable prices. This movement has been assisted by the introduction of the spice-bearing plants to many other parts of the world.

More recently, the Italians, during their occupation of Abyssinia, were quick to investigate the potentialities of the native spices and the oils from them. The oil from the Abyssinian *Coriandrum sativum* was found, for example, to have a linaloöl content of 66 to 70 per cent.

It will be of interest to consider the outstanding characteristics of some of the common spices.

Cinnamon has a fragrant odour and a warm, sweetish taste and is employed in cookery and as a flavouring material—for chocolate and liqueurs. It is liable to be adulterated with the cheaper—but harsher—cassia. The best cinnamon comes from Ceylon and is light yellowish-brown in colour. Like other spices, it gives an oil when distilled in steam ; and the essential constituent of oil of cinnamon is cinnamic aldehyde. The oil is used in the preparation of dentifrices and Oriental perfumes.

Cloves have a distinctive and well-known odour, and a slightly acrid hot taste. The species of myrtle on which they grow is a beautiful evergreen plant, which attains a height of 40 feet ; and is cultivated not only in the Spice Islands but also in Zanzibar, Java and Sumatra. Cloves are used as a condiment in cooking and confectionery, e.g. to spice apple-tart and stewed pears, as well as in the preparation of liqueurs. Oil of cloves is mainly eugenol, and, in addition to its use for flavouring dentifrices and soaps, it is a valuable relief for toothache.

Allspice, or Jamaica pepper, the berries of the pimento, combines the flavours of cloves, cinnamon and nutmeg. It is used for gingerbread and pickles and is a usual constituent of curry powder. An infusion of allspice in brandy is used in making spiced wine. The essential constituents of its oil are eugenol and cineol.

Pepper is commonly available in several varieties. Black pepper consists of the dried unripe berries of *Piper nigrum*, a climbing shrub indigenous to Travancore and Malabar, but now also grown in Java, Sumatra, Penang, Malaya and the Philippines. Singapore was the great distributing centre for it. White pepper is obtained from the same fruits but in the ripe state. It has a finer flavour but is less pungent. Usually, white pepper has been bleached and has lost much of its flavour in the process. Paprika is a large-fruited variety of pepper, but not so hot or pungent. Long pepper is the fruit of *Piper longum*, and Ashanti pepper that of *Piper Clusii*. The essential constituent of pepper is piperine, and it will be remembered that the relation of "peppery" taste to chemical constitution was discussed in detail in Chapter 6.

Cayenne pepper is prepared from the dried fruit of *Capsicum annuum*, a native of South America, but also cultivated in the East Indies. The dried fruits of the capsicum are narrow, bright red pods, known as chillies, and Cayenne pepper may be made by drying and grinding these fruits. Alternatively, the dried fruits may be mixed with flour and made into a cake, baked, ground and sifted. The chillies are also used, especially in tropical countries, for flavouring food. Chillie paste rubbed on the skin produces redness and a warm glow, a modality of the common chemical sense.

Nutmeg is the kernel of the fruit of *Myristica fragrans*. The outer covering of the nutmeg is a fibrous network which is removed and is known as mace. Both nutmeg and mace are largely used for flavouring milk puddings and custards. They have undesirable effects in excess.

Ginger is the year-old rootstock of *Zingiber officinale*, a native of the East Indies. Its use in gingerbread, ginger-ale, ginger-beer and ginger-wine, has made its sweet pungent flavour familiar to everyone. Its oil is used medicinally as a carminative.

All spices gradually lose their pungent and aromatic characteristics if left exposed, this being due to loss of their volatile oils. Consequently they are usually bought in small quantities and are best kept in a spice-box.

An investigation of the loss of volatile oil on storing spices was carried out by Griebel and Hess (*Z. Untersuch Lebensm.*, **79,** 184-91, 1940, and *Chemical Abstracts*, **34,** 4828, 1940). They found that, after 10 months, cinnamon had lost 25 to 30 per cent. of its oil and pepper about 20 per cent. The type of package used did not make a very great difference, e.g. bags made from cellulose film were nearly as good as bottles.

When used for flavouring food a mixture of spices is usually taken. A highly spiced hot cross bun may contain ginger, coriander, caraway, cloves, allspice, cassia and nutmeg.

A great variety of spices may be used in curry powder. The essential constituents are coriander and turmeric, a variety of ginger,

but others that may be found are capsicum, cumin, fenugreek, pepper, mace and cloves. Other examples of the use of spices in foods are

Ginger and cinnamon in gingerbread.
Cloves and cinnamon in apple tart and spiced plums.
Pepper, allspice, cloves and mace in spiced salmon.
Pepper, ginger, cloves, nutmeg and mace in spiced beef, the spices being sprinkled over and rubbed into the meat before cooking.

The use of spices in moderation enhances the appeal of foods, but owing to their potent physiological action, which is a manifestation of the common chemical sense, their too frequent use is to be avoided. Persons with certain types of weakness have to eliminate them completely from their diet. Other reflections of this physiological action are to be seen in the use of tinctures and oils from spices in medicine, and in the feeding of spice to fowls to stimulate egg-production.

In accordance with the modern tendency to refine foods, it is becoming increasingly common to use the oil from a spice, instead of the whole spice. It is claimed that the food-products are brighter in appearance and more uniformly flavoured when the oils are used, and that the cost may be lower (Fairbrother, *Food Manufacture*, **6**, 74/5, 1931). If the quantity of oil to be added is very small compared with the bulk of the foodstuff, it may first be made into a solution or an emulsion to facilitate mixing. Refining of foods in other directions has brought disastrous results. Whether harm will result from the use of oils, instead of the whole spices, may be doubted, in view of the small quantities concerned, but it is by no means out of the question that valuable food accessories may be lost in this way. The quantities of oil used are, of course, much less than the spice which would be necessary. Thus :

1	lb.	of allspice	is replaced by	0·03	lb. oil.
1	,,	caraway seed	,,	0·05	,,
1	,,	celery seed	,,	0·03	,,
1	,,	cinnamon	,,	0·01	,,
1	,,	cloves	,,	0·17	,,
1	,,	coriander seed	,,	0·005	,,
1	,,	nutmeg	,,	0·125	,,

Another development, in a similar connection, is revealed in U.S. Patent 2,284,822 (Heller), which describes how comminuted pepper or ginger is used to absorb essential oils, the product being a seasoning suitable for sausages and other meats.

One object of the use of spices is to improve the keeping quality of the foodstuff. If, however, the imported spices are contaminated with moulds and bacteria this advantage will be lost. Yesair and Williams (*Food Research*, **7**, 118-26, 1942) showed that, in the case of pepper, the moulds and bacteria could be destroyed by treatment with steam at 15 lb. pressure for 15 minutes, although the pepper

lost 10 per cent. of its strength in the treatment. H. W. Smith (*Food Industries*, **12**, No. 11, 50-1, 1940) showed that sausages made with pasteurised spices kept 33 per cent. longer than when spices were used without pasteurisation. It is maintained that the use of aseptic spices in perishable foods will improve their keeping quality. In this respect, the use of oils instead of whole spice is probably advantageous.

Spices are usually ground before use, and as in other dust-producing industries, the danger of explosion in spice-grinding plants has to be guarded against.

Adulteration of spices with starch is best detected by microscopical examination.

Since the value of a spice depends on its oil-content, the estimation of this is important. A method has been described by Sabetay (*Ann. chim. anal. chim. appl.*, **22**, 217-18, 1940). It consists of distilling the spice with ethylene glycol *in vacuo* until the distillate no longer makes water turbid, of diluting the distillate with brine, and extracting the oil from it with pentane. The pentane is evaporated under reduced pressure and the residual oil weighed. Typical results were : cloves gave 17·6 per cent. oil, white pepper 1·45 per cent. and caraway 2·2 per cent.

Tobacco

The bodies which impart the aroma to tobacco do not seem to have been identified. An ethereal oil and certain resins have been extracted but these determine only partially the aroma.

Great care is exercised in the growing and drying and fermentation to secure a mellow flavour. The plants which grow 7 to 8 feet high are protected from sun and rain by screens of cloth supported on poles. The tobacco must be kept free from contamination by other odours which it readily picks up. The character and aroma is largely determined by blending. The nicotine content is usually between 1 and 3 per cent. and in a good cigarette tobacco will be about 1·2 to 1·5 per cent. A high content of protein or organic acid lowers the quality. The smoke of the best tobaccos is nearly neutral. It stimulates not only the olfactory nerves but also the common chemical sense.

In the case of snuff various essential oils or ground orris-root or Tonquin beans may be added to flavour the tobacco.

It will be remembered that the benzoxazoles possess a tobacco odour, and that the isoamyl ether of β-hydroxypropionaldehyde diethyl acetal has an odour of burnt tobacco.

Removal of Undesirable Flavours

Many foods, wines and tobacco which have agreeable flavours will readily acquire disagreeable flavours if stored close to other odorous substances. Great care is therefore exercised to store such materials suitably.

Other materials, particularly water, acquire undesirable flavours through causes beyond our control. Then adsorption is frequently

resorted to. The purification of water is carried out with charcoal or chalk which adsorbs the offensive material, or the latter may be oxidized with chlorine or ozone and the odour thus removed.

An instance of odour being removed from wheat which had been partly damaged by fire and had a burnt odour was described by Marchadier and Goujon (*Ann. fals.*, **7**, 259-60, 1914). By repeated shaking with bran the wheat was deodorized. It was separated from the bran by sieving.

U.S. Patent 2,146,958 (1939) describes how foods such as flour are mixed with about 0·01 per cent. of finely divided active carbon to remove tastes.

Sometimes a bitter principle may be distilled out of a substance with steam, e.g. the bitter taste and burnt smell from malt extracts and worts.

Chemical action may also be used, e.g. U.S. Patent 1,813,642 (1931) describes the removal of taste and odour from petrolatum stock material, which is used medicinally. The method adopted was to warm with fresh aluminium chloride and remove the sludge, subsequently washing and drying.

In the case of a natural product which has an objectionable odour, the latter may be masked by other strong odorants. Thus Australian Patent 20,127 (1929) describes the masking of castor oil with saccharin, vanillin and oils of lemon and peppermint. Similarly, U.S. Patent 2,058,162 (1936) suggests the use of oils of celery and sage to improve the taste of castor or cod-liver oils. The nauseous taste of some cod-liver oils is due to the oil remaining in contact with the decomposing organic matter before extraction, and nowadays it is expressed as soon as possible to avoid this.

Metal articles such as cutlery often acquire a taint. Silver exposed to various sulphur compounds such as onions, leeks and mustard acquires a " silver odour." Raub and Nann (*Mitt. Forschungsinst. Probieramts. Edelmetall*, **7**,, 51-64, 1933, and *Chemical Abstracts*, **29**, 3957, 1935) investigated this and found that with different metals the odour varied in character and intensity. Gold and platinum were slightly tainted. Nickel-and-chromium plated brass remained odourless. Alloys of silver with tellurium and selenium also remained odourless. The odour could be removed from any of the metals by treatment with dilute hydrochloric acid or nascent hydrogen or by heating. German Patent 614,352 (1935), by Raub, describes a method of treating the articles with oxidizing agents that do not attack the metals, such as hydrogen peroxide, or neutral aqueous solutions of perborates.

We conclude with a practical note from Mrs. Beeton's " Household Management." To remove the smell of paint from a newly-painted room, stand in it a bucket of water, in which a handful of hay or a few sliced onions are immersed and the odour will disappear overnight.

Absolute. Alcoholic extract of a flower, etc., freed from wax and from which the alcohol has been removed, leaving the "absolute" odorous principle.

Absorption bands. Dark lines in the spectrum of light caused by the neutralization of vibrations of certain frequencies.

Acidogen. Sour-producing group, e.g. —COOH or $—SO_3H$.

Actinomyces. Tiny ray-fungus.

Adamsite. A war gas. A heterocyclic arsine.

Adaptation. Change in state of receptors on continued stimulation, causing fatigue.

Adenoids. Hypertrophied tissue at the back of the nose.

Adrenalectomized. Having had the adrenals removed.

Affective reaction. A mental process.

Afferent nerve fibre. One which transmits messages from the peripheral receptors to the central nervous system.

Agraphia. Inability through disease to write well-understood words.

Albinism. Lack of pigment in the skin, hair, etc.

Alliaceous. Like garlic.

Amarogen. Bitter-producing groups, e.g. —SH.

Ambergris. Odorous product of the sperm whale. Used as a perfume fixative.

Ambrosial. Fragrant, delicious, fit for the gods.

Amiurus. Catfish.

Amœba. Microscopical protozoa, inhabiting ponds.

Amphioxus. Lancet-fish. Intermediate between invertebrates and vertebrates.

Amphirhine. Having paired nostrils.

Anærobic. Without oxygen.

Ångström unit. A tenth-metre, i.e. 10^{-10} metres.

Annelids. Round worms.

Anosmic. Without the ability to detect smell.

Anterior nares. The nostrils.

Anthophilous. Flower-loving.

Aphasia. Inability to read and speak well-understood words. A disease.

Aphrodisiac. That which excites sexual feelings.

Arachnids. Class of arthropods; spiders, scorpions, etc.

Aroma. Sweet smell.

Arsenical smokes. War gases, e.g. Adamsite.

Arthropods. Phylum of jointed-leg animals. Comprises crustaceans, arachnids and insects.

Asafœtida (devil's dung). Gum-resin with objectionable odour.

Asclepiad.	A genus of plants including vanilla tree.
Asphyxiant.	Suffocant. A class of war gases.
A Stoff.	War gas. Chloracetone.
Astringency.	A contracting or drying taste, e.g. that of borax.
Attar of roses.	Also otto of roses. Essential oil of roses.
Aubepine.	Anisaldehyde.
Autotox.	Group which if present in a substance with a toxophore group confers toxicity (analogous with auxochrome).
Auxogluc.	Group which if present with a glucophore group confers sweetness.
Avogadro's number.	Number of molecules in a gram molecule of a substance. About 6×10^{23}.
Axis cylinder.	The nerve fibre. The term does not include the medulla or sheath.
Axone.	The nerve fibre. The term does not include the medulla or sheath.
Balsam.	A resin, e.g. balsam of Peru, balsam of Tolu.
Barbel.	Beard-like appendage of certain fresh-water fish or the fish itself.
Bibi.	A war gas. Dibromomethyl ether.
Bittersweet.	Woody nightshade. The root tastes first bitter then sweet.
Bivalves.	A class of molluscs, e.g. oysters.
Blast injection test.	A method of measuring the minimum identifiable odour.
Bouquet.	Odour exhaled by a wine or perfume.
Bowman's glands.	In animals these secrete a pigmented fluid in the nasal cavities.
Brightness of smell.	Concept of quality of smell similar to evanescence or volatility. Opposite to "dull." Also applied to taste.
Buccal.	Concerned with the cheek.
Buffer solution.	Solution, e.g. of an acid to which a salt is added to depress the ionization of the acid. The salt acts as a buffer between the solvent and the acid.
Cachalot.	Sperm whale.
Cacodyl.	$As_2(CH_3)_4$.
Caffeine.	The alkaloid of tea and coffee. Trimethylxanthine.
Camera inodorata.	Large box, normally quite free from odour, in which odours are measured (cf. camera obscura).
Caprilic.	Empyreumatic. Also goat-like.
Carminative.	Medicine to relieve bowel trouble, e.g. ginger, peppermint.
Castor.	Animal perfume from the beaver. Used as a fixative.
Cell.	The "brick" of animal architecture.

Central nervous system.	Brain and spinal cord.
Cephalopods.	Class of molluscs, e.g. squids, octupuses.
Cetacea.	Whales, porpoises, etc.
Cerebellum.	Hind-brain controlling muscular activity.
Cerebrum.	Forebrain controlling association, reflection, etc.
Chemoreceptor.	Receptors activated by sapid, odorous, or chemically irritant substances.
Chemotropism.	Habit of moving to or away from chemical irritant.
Choana.	The passage joining the back of the nose to the throat.
Chorda tympani.	Part of the 7th cranial (facial) nerve concerned with taste.
Cilia.	Hairs carried by cells.
Circumvallate.	Large papillæ towards the back of the tongue. Contain many taste-buds.
Cis and trans.	Terms used to distinguish certain stereo-isomers.
Citral.	Aromatic aldehyde. Open-chain terpene.
Civet.	Glandular secretation of the civet cat (Abyssinia) used as a fixative.
Civetone.	Odorous principle of civet, Δ^9 cycloheptadecen-1-one.
Clark I.	War gas, diphenylchlorarsine.
Clark II.	War gas, diphenylcyanoarsine.
Cleft.	See "olfactory cleft."
Cœlenterates.	A phylum of invertebrates. Includes corals, jelly-fishes, sea anemones. Tissue stage.
Common chemical sense.	Sensibility to chemical irritants.
Conchæ.	The turbinates.
Concrete.	The alcoholic extract from the enfleurage wax, after the alcohol has been evaporated. Contains wax as well as the odorous principles.
Conditioned reflex	An unnatural reflex, induced by habit.
Coniine.	The hemlock alkaloid.
Contracted reaction.	A brain process, e.g. on smelling pine oil to be reminded of turpentine.
Corps épuisés.	Enfleurage wax after removal of the bulk odorous principles by extraction. Suitable for pomades.
Corpus callosum.	White matter of brain. Chiefly medullated fibres.
Cortex.	Layer of grey matter on outside of brain. Receiving station of brain.
Cranial.	To do with the skull.
Critical frequency of gustation.	Frequency of the nerve impulses on tasting.

Critical flicker frequency. That at which a flickering light appears to fuse into a continuous light.

Crustaceans. Class of arthropods. Lobsters, etc.

Crystallose. Sodium salt of saccharin.

Cyclostomes. Class intermediate between invertebrates and fishes, e.g. the monorhine *Petromyzon*.

Dendrites. Branching processes of a nerve.

Dextrose. Glucose.

Differentiation. A change whereby organs become specialized.

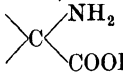
Diphasic electric current. Continuously alternating current.

Dipole. In substances containing reactive groups these groups may arrange themselves like the two poles of a magnet. Such substances are dipolar.

Dipole moment. The magnetic moment exerted by a dipole.

Diuretics. Medicines causing urination.

Dorsal. Belonging to the back (of the tongue, the upper surface).

Dulcigen. The group  Gives a sweet taste.

Dulcin. Synthetic sweetener. *p*-ethoxyphenyl urea.

Dytiscus. Water-beetles.

Efferent nerve fibre. Fibre which conveys messages from the brain to the muscles.

Effluvia. Disagreeable vapours.

Egocentric reaction. A mental process, focussed on self, e.g. on smelling a rose to think of " soothing."

Electrochemical series. Table in which the elements are arranged in order, from the electropositive, e.g. potassium, at the top to the electronegative, e.g. halogens, at the bottom.

Emergence. Appearance of a new feature.

Empyreumatic. Burnt.

Encephalon. The brain.

Enfleurage. Method of extracting the odorous principle from flowers in a mixture of fats.

Epidermis. Cuticle. External covering for the true skin.

Epiglottis. Cartilage at root of tongue which partly closes the larynx.

Epithelium. Skin or mucous membrane.

Erectile tissue. Tissue that may be swollen, e.g. that surrounding the air-passages in the nose.

Erythema. Skin disease or inflammation.

Essential oil. Oil containing the odorous and sapid principle, e.g. of a spice or a flower.

Ethereal. Spirit-like. Volatile. Similar to ether.

Ethmoid. One of the cranial bones which extends to the bridge of the nose.

Exaltone. Synthetic musk-like substance, cyclopentadecanone.

Exaltolide. Synthetic musk-civet-like substance, pentadecanolactone.

Expanded reaction. A mental process moving from the particular to the general, e.g. on smelling pine oil to think of Norway.

Expression. Method of separating the essential oil from fruit rinds.

Exteroceptors. Distance receptors, e.g. of the nose and ear.

Fatigue. Unresponsive state of receptors on continued stimulation, due to adaptation.

Fauces. Upper part of throat between root of tongue and gullet.

Filiform. Kind of papillæ covering the dorsum of the tongue. Not connected with gustation.

Fixative. Relatively non-volatile substance, e.g. musk or ambergris, which, added to a perfume, fixes or renders more permanent the odour of the volatile constituents.

Flagella. Olfactory hairs.

Flagellates. Very low form of life from which both plants and animals have evolved.

Flavour. Combined sensation of odour and taste.

Fœtid. Having a strong offensive odour.

Fœtor. A stink.

Foliate. Kind of papillæ consisting of vertical ridges on edge of back of tongue. Connected with gustation.

Formicary. An ant-hill.

Frankincense. A resin.

Fungiform. Kind of mushroom-like papillæ on the tongue. Concerned with gustation.

Fusel oil. Objectionable impurities in alcohol, chiefly amyl alcohols.

Ganglia. Swellings on nerves just before they enter the central nervous system.

Gastrocnemius muscle. The muscle that bulges the calf of the leg.

Gastropods. Class of molluscs. Snails, slugs, etc.

Genital. Relating to reproduction.

Glossopharyngeal. The 9th cranial nerve, dealing with a part of gustation.

Glucophore. Main sweet-producing group. Operative only if accompanied by an auxogluc.

Glucoside. A compound with glucose, e.g. dulcamarin.

Goblet cells. Cells which discharge mucus.

Great peacock. A moth.

Gullet. Passage from the mouth to the stomach.

Gustation. The sense of taste or act of tasting.

Gustatory hair. Protoplasmic hair carried by a taste-cell. Analogous to olfactory hair.

Gymnemic acid. An acid which abolishes the sense of sweetness and restricts that of bitterness, but leaves the tastes salty and sour more or less unchanged.

Hag. Hagfish.

Hard palate. Front part of the roof of the mouth.

Heliotropin. Piperonal.

Huiles antiques. Perfumes with an olive-oil base.

Hydra. A fresh-water cœlenterate.

Hydrotropism. Habit of turning to (or away from if a negative tropism) water.

Hyoid. A bone at the base of the tongue.

Hyperosmia. Unusually keen olfaction.

Hypertrophied. Over-developed.

Hypoglossal. The 12th cranial nerve. The motor nerve of the tongue.

Indirect reaction. Multi-stage mental process, e.g. on smelling vanillin to think of Tennyson via Lotus Eaters.

Induction. Enhanced sensitivity of a receptor is caused by induction from an adjacent fatigued receptor.

Infra-red. Light waves of lower frequency than the visible spectrum.

Innervation. The supply or service of nerve-endings on any part of the body.

Insalivation. Process of mixing food with saliva.

Insipidity. Tastelessness.

Integration. Fusing to a composite whole of impulses from different receptors.

Intermolecular. Between molecules.

Interoceptor. Receptors requiring contact of the stimulating substance, e.g. those of taste and touch.

Intramolecular. Within the molecule.

Invertase. Enzyme which causes the hydrolysis of sucrose.

Invertebrates. Animals without backbones.

Ionone. A synthetic with a strong odour of violets.

Irone. The active principle of violets.

Isohydric. Having equal hydrogen-ion concentrations.

Isolate. A pure chemical isolated from natural products, e.g. citral from lemon-grass.

Isotonic salt solution. Equal concentration of salts to that in the blood.

Jacobson's organ. The vomero-nasal organ.

Labyrinth. Part of the internal ear which is the site of equilibrium apparatus.

Lachrymatory. A tear-producing compound such as many war gases.

Lævulose. Fructose.

Lateral-line organs. Sense organs of fishes not shared by man. Probably " touch at a distance."

Lecithin. Phosphorus-containing protein, occurring in the brain.

Lemon-grass. Fragrant perennial grass, yielding citral.

Lepidoptera. Butterflies, moths, etc.

Lesions. Injuries.

Lewisite. A vesicant war gas. Chlorovinyl dichloroarsine.

Light-spots. Primitive light-sensitive organs. The forerunner of eyes.

Limbic. Area of the brain concerned with taste and smell.

Lipoids. Fatty substances.

Macrocyclic. Group of compounds with a large ring in the molecule.

Macrosmatic. Possessed of exceptionally keen scent, e.g. dogs, foxes.

Marsupials. Animals carrying young in a pouch.

Masking. Term used when two odours neutralize each other.

Mawkish. Loathsome, maggoty.

Meatus. Canals, e.g. passageways, through which air travels between the turbinates.

Mechano-receptor. Receptors actuated by pressure differences, e.g. those of touch and hearing.

Median septum. The middle division in the nose, between the two nostrils.

Medulla oblongata. Top of the spinal cord.

Medullated. Sheathed.

Mephitic. Foul, poisonous.

Microsmatic. Not possessed of exceptionally keen scent, e.g. man.

M.I.O. Minimal identifiable odour.

Minimum stimulus. The smallest stimulus that just evokes sensation, e.g. the lowest concentration of a gas detectable by odour.

Modality. Differentiation of a sense, partly or fully emerged.

Mollusca. Phylum of invertebrates, including cephalopods, gastropods and bivalves.

Monophasic current. Rectified electrical current.

Monorhine. Having only one nasal orifice, e.g. *petromyzon.*

Mosaic eye. Multiple eye commonly possessed by insects.

Motor axone. Efferent nerve fibre.

Mucus. The slimy fluid secreted by the mucous membrane. The discharge of the goblet cells.

Muguet. Lily-of-the-valley.

Musc ambrette. A fine artificial musk.

Musc Baur. Artificial (toluene or xylene) musk.

Muscone The odorous principle of musk, 3 methyl-cyclopentadecan-1-one.

Musk. Glandular secretion of the musk-deer. Used as a fixative.

Mustard gas. Vesicant war gas. Dichloro diethyl sulphide.

Mustelus. Dogfish.

Nares. Openings to the nose (nostrils and choana).

Nasal cavities. The internal parts of the nose.

Nasal septum. The median septum.

Nasolacrymal duct. The canal which carries tears from the eye to the nose.

Nasopharynx. The lining of the back of the nose.

Nerve fibre. The link between the peripheral receptors and the central nervous system.

Nerve ladder. Two strand-like concentrations of nerve cells with cross connections. Typical of some invertebrates.

Nerve net. Concentration of nerve cells in the form of a ring or net.

Neuron. Nerve fibre and receptor cells.

Niobe oil. Methyl benzoate.

Notochord. A spinal rod, the precursor of the spinal cord, in such animals as *amphioxus*.

Nubile. Ready to mate.

Oak eggar or banded monk. A moth.

Oak moss resin. A lichen growing on trees. Used as a fixative.

Odorant. An odorous substance.

Odoriphore. Odour-producing group.

Odorivector. An odorous substance.

Oesophagus. The gullet, joining the pharynx to the stomach.

Oil of neroli. Essential oil of orange-flowers.

Oil of wintergreen. Methyl salicylate.

Olfactie. Unit of odour stimulus (Zwaardemaker).

Olfaction. Perception of odour.

Olfactometer. An instrument for measuring odour intensity.

Olfactory apparatus. The olfactory cells, hairs and nerves.

Olfactory bulb. Part of the brain into which the olfactory nerve leads.

Olfactory cells. Long narrow cells furnished with hairs which are smell-receptors.

Olfactory cleft. Part of the nasal cavities, high up and to the back, in which the olfactory cells are situated.

Olfactory coefficient. The smallest volume of vapour of a substance necessary for the identification of its odour.

Olfactory hairs. Fragile protoplasmic filaments on the olfactory cells.

Olfactory-negative. That which reduces odour, e.g. the influence of an electropositive element in a compound.

Olfactory pit. Elementary olfactory organ found in invertebrates and lower vertebrates.

Olfactory prism. A method, devised by Henning, of representing six fundamental odours as the corners of a prism.

Olfactory region. Seat of the smell receptors.

Opoponax. A resin.

Orris-root. Rhizomes of a variety of iris. Used in violet perfume.

Orticant. Irritating to the skin.

Osmic frequency. The Raman shift, described by Dyson as characteristic of any specific odour.

Osmics. The science of smell.

Osmoceptor. Smell receptor.

Osmophore. A smell-inducing chemical group.

Osmoscope. Instrument for measuring odour intensity.

Osmyl. An odorous substance.

Palate. The roof of the mouth. Also taste sensibility.

Palpi. Sensitive organs near the mouth of insects.

Papillæ. Little projections on the tongue, which give roughness to the surface.

Paramecium. A protozoan animal.

Parietal. The area of the brain concerned with skin sensation.

Parotid secretion. Part of the salivary flow.

Patchouli. Essential oil of *Pogostemon patchouli*.

Pedipalps. Leg-like chemically sensitive appendages.

Pentalarm. A warning odorant, chiefly amyl mercaptans.

Perceptions brutes. Vague, diffuse, poorly-defined sensation.

Perceptual pattern. Integrated result of present sensation and past experience.

Persistence. Duration of sensation.

Perstoff. A war gas. Diphosgene.

Petitgrain. Essential oil from the leaves and twigs of the orange tree.

Petromyzon. A cyclostome.

***p*H.** A measure of the hydrogen-ion concentration : $p\mathrm{H}=7$ is neutral, $p\mathrm{H}<7$ is acid, $p\mathrm{H}>7$ is alkaline.

Pharynx. The upper part of the gullet behind the nose and mouth.

Phototropism. Habit of moving to or away from light.

Phrenic nerve. That which brings about the rhythmic contraction of the diaphragm.

Phylogenetically. How a characteristic has changed through evolution.

Phylum. A great class into several of which all animals are arranged, e.g. protozoa.

Piperine. The alkaloid of pepper.

Planaria. Turbellarian worms.

Plasma. The living matter of a cell. The liquid part of blood.

Platyhelminthes. Flatworms.

pO. An evaluation of the odour intensity, e.g. of water (Fair and Wells). Low pO indicates little odour.

Pons varolii. Part of the brain, below the cerebellum.

Porifera. Sponges.

Posterior nares. The passages joining the back of the nose with the throat. Same as "choana."

Proprioceptors. Receptors which send information to the central nervous system regarding the movements and posture of the body.

Proteins. Complex organic substances, apparently synthesized naturally from amino-acids and characterized by peptide linkages —CO . NH—.

Protoplasm. The protein of which living matter is composed. Constitution not yet determined.

Protozoa. Animals consisting of only one cell, e.g. *amœba*.

Pseudopods. "False-feet." Temporary bulges in protozoa used to make progress and to engulf food.

Radioreceptors. Receptors activated by radiant energy, such as light and heat, e.g. those in the eye and the skin.

Raies ultimes. Very strong lines in absorption spectra.

Raman effect. Change of frequency of light on being scattered by a substance.

Raman shift. A measure of the change of wave-length due to the Raman effect.

Reaction time. The time that elapses between the application of a stimulus and the muscular response to it.

Receptor. The mechanism which is first stimulated, e.g. the olfactory hair or cell, or the gustatory hair or taste-bud.

Reflex action. Involuntary action, e.g. blinking, contraction of the pupil, sneezing, etc.

Reflex arc. The system of receptor, afferent fibre, central connection, efferent fibre and muscle.

Refractory period. The duration of time in which a neuron is in a refractory state.

Refractory state. The state of the neuron immediately following an impulse, during which it is unable to send another impulse.

Resinodor. The residue left after evaporating the alcohol from an alcoholic extract of a resin.

Rhinoscope. Instrument for examining the nose.

Ringer's solution. Aqueous solution of potassium, sodium, calcium and magnesium chlorides, the cations being present in approximately the same concentration as in the blood of an animal. Used as a medium in which tissue slices are suspended to observe their metabolism

apart from the body. The concentration varies according to the animal, e.g. frog's Ringer is different from mammalian Ringer.

Saccharin. A synthetic sweetener. *o*-benzoic sulphimide.

Sapid. Having taste.

Sapophores. Sweet-producing groups.

Sarcophagic. Flesh-devouring.

Schneiderian membrane. The mucous membrane lining the interior surfaces of the nose.

Sensation. Change in consciousness, resulting from despatch of impulses to the brain from the receptors.

Sensory mechanism. The receptors, nerve fibres and central connections.

Sesquiterpenes. Hydrocarbons of formula $C_{15}H_{24}$ and their derivatives.

Silvian fissure. A furrow on the surface of the brain.

Sinus. A cavity in a bone.

Soft palate. The hind roof of the mouth.

Soya bean. Bean rich in protein, from which soy sauce is made.

Specific smell strength. The reciprocal of the number of grams of a substance per litre that can just be smelled.

Specific tenacity of odour. The number of hours $\times$ 100 during which 1 gram of 1 per cent. solution of a substance in absolute alcohol retains its odour under defined conditions.

Sphenoidal. At the base of the skull.

Spikenard. An aromatic oil from an Indian plant.

Spray electricity. Electric charge formed by extruding, through a fine nozzle, various solutions, including those of odorants.

Stercoral. Excrement-devouring.

Sternutatory. Substance which causes sneezing.

Stimulus. That which excites the receptors, e.g. an odorous substance or a sapid solution or an electric current.

Storax. A resin.

Suffocant. Lung irritant, e.g. chlorine.

Supreme conchæ. Turbinates higher than the usual three.

Sustentacular cells. The main epithelial or supporting cells between which receptor-cells are sandwiched.

Synæsthetic reaction. A mental process. An apparently unconnected sensation, e.g. gustatory or auditory, on smelling something.

Synapse. Junction of nerve fibres.

Tannin. An astringent material present in many natural products, e.g. tea and coffee.

Taste blindness. A deficiency in taste perception.

Taste-buds. The end organs of the taste-nerves.

Temperature-tactile. Primitive sensibility before differentiation into temperature sensibility and touch.

Tenth-metre. 10^{-10} metre. An Ångström unit.

Tentorium. A membrane over the cerebellum.

Terpenes. Hydrocarbons of formula $C_{10}H_{16}$, and their derivatives.

Theobromine. The alkaloid of cocoa, dimethyl xanthine.

Threshold concentration. The minimum concentration which will arouse sensation.

Tincture. An extract, usually alcoholic, e.g. of a resin.

Tissue. The substance of which organs are constituted.

Tissue stage. The stage of development in invertebrates reached by the cœlenterates, as a result of possessing two kinds of cells.

Tonite. War gas. Chloracetone.

Toxophore. A group which in the presence of another group, an autotox, gives toxicity to a substance.

Trèfle. Clover. A trefoil.

Trigeminal. The 5th cranial nerve, largely responsible for common chemical sensation.

Tropism. Habit of going to or away from a stimulus, e.g. chemotropism, hydrotropism.

Turbinates or turbinated bodies. Cartilaginous bodies of scroll-like formation in the nose.

Ultra-violet. Light of shorter wave-length than visible light.

Unsaturation. Having free valencies, double or treble linkages.

Vagus. 10th cranial nerve, partly concerned with taste.

Vestibule. The inside of the nostrils.

Vetivert. Oil distilled from the odorous roots of khas-khas grass. Used as a fixative.

Visceral. Abdominal.

Vitamin A. Hydrolysis product of carotene.

Vitamin B or B_1. Aneurin or thiamine.

Vitamin B_2 Lactoflavine.

Vitamin C. Ascorbic acid.

Vitamin D. Calciferol.

Vomer. Bone which forms the lower rear part of the median septum in the nose.

Vomero-nasal organ. Olfactory (?) receptors present in many animals. Degenerated in man. They connect by a pore to the nasal cavity.

Wort. Unfermented beer.

Ylang-ylang. "Flower of flowers." Oil from *Cananga odorata*.

μ 10^{-6} metres=10,000 tenth-metres. Sodium light=0·59μ.

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And last, but not least, the invaluable

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