

stand still for a moment and see the direction in which modern therapeutics is tending. Connected on the one hand with chemistry and physiology, and on the other with pathology and medicine, it is justifiable to expect that the recent advances in these departments of knowledge would have a stimulating effect on the progress of therapeutics.

Dr. Lauder Brunton, in his address (which we print in full) before the Section of Pharmacology, illustrated one aspect of this influence by discussing the connection between chemical constitution and physiological action. It will readily be seen from a study of his remarks how important an effect the line of research which he indicated will have on the progress of rational therapeutics, which is based on a knowledge of the physiological action of a drug. Dr. Brunton's address shows a hopeful sign of advance in the treatment of disease by scientific methods and not by mere empiricism.

One of the most important communications made to the Association, and deserving of mention here, was that by Prof. O. Liebreich, of Berlin, on lanolin as a therapeutic agent. This substance, which is a cholesterin-fat from sheep's wool, is much more rapidly absorbed by the skin than glycerol-fats or vaselin, this property being probably connected with the fact that in nature it is closely associated with, if not formed by, keratin-containing cells, such as those of the skin, hair, feathers, &c. Such a readily absorbable fat, which is unirritating, and will serve as a vehicle for medicaments, has long been a desideratum, and it is probable that lanolin will be a most important agent in the treatment of skin diseases and of local disorders beneath the skin, as in the joints.

Space does not admit of a discussion of the numerous other interesting subjects, chiefly technical, introduced at the meeting of the Association. The interesting questions brought forward by Dr. Taafé in his address on public medicine included the spread of scarlatina by means of milk, a subject the investigation of which has been undertaken by the Local Government Board, and will no doubt yield important results to preventive medicine.

### ON THE CONNECTION BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION<sup>1</sup>

THE meeting of the British Medical Association is not for mutual instruction only; it is also for recreation; and, probably, many members of this Association will utilise the opportunity which a meeting at the sea-side, like the present one at Brighton, affords them of indulging in that excellent occupation for an idle man—of watching the waves on the seashore and speculating how far each of them will come. If one have only half an hour to spare, it is difficult to say whether the tide is ebbing or flowing; it is only by watching for a longer time that one can be certain that the water is really moving in one direction or another. Probably a great part of the charm which this occupation possesses is due to the resemblance which one involuntarily traces between the ebb and flow of waters and that of human affairs—individual, national, or racial. The life of a single man is very short in comparison with the history of race; and it is often very difficult to say whether mankind is advancing or retrograding, unless we compare his condition at epochs widely removed from one another.

On doing this, we find a general consensus of opinion, to the effect that civilisation has steadily advanced; and this advancement is usually divided into four stages, characterised by the nature of the tools or weapons employed. In the first, or Palæolithic Age, man employed weapons or tools of flint roughly chipped into shape and unpolished. In the next, or Neolithic Age, the implements consisted of stone, but they were polished. The next age is characterised by the employment of bronze as a material, and the fourth and highest stage by the employment of iron. These stages are not all marked off from one another, for we find them together in the same country or in different countries. Thus, the age in which at present we live is recognised as the Iron Age, on account of the large employment of that metal; but we find that in various countries stone, more or less rudely fashioned, is still used in the manufacture of weapons or tools.

<sup>1</sup> An Address delivered at the opening of the Section of Pharmacology and Therapeutics, at the Annual Meeting of the British Medical Association held in Brighton, August 1886. By Thomas Lauder Brunton, M.D., F.R.S., Lecturer on Materia Medica and Therapeutics at St. Bartholomew's Hospital; President of the Section.

For example, when I was in the Colonial Exhibition lately with Mr. Norman Lockyer, he pointed out a kind of threshing implement, such as is now used in Cyprus. It consists of a flat board, in the under side of which are embedded a number of stone celts exactly like those made by prehistoric man, and perhaps used by him for a similar purpose as well as for axes. In the same way that we recognise four stages in the development of the implements used by man in the arts or in warfare, we may, I think, recognise four stages in the development of the implements he has used in the treatment of disease. In the first stage crude drugs were employed, prepared in the roughest manner, such as powdered cinchona or metallic antimony. In the next stage these were converted into more active and more manageable forms, such as extracts or solutions, watery or alcoholic. In the third stage the pure active principles, separated from the crude drugs, were employed, e.g. morphine and quinine. In the fourth stage, instead of attempting to extract our medicines from the natural products in which they are contained, we seek to make for ourselves such substances as shall possess the particular action we desire. Now, just as we find stone and iron implements occasionally used together in the same country, so we find that drugs belonging to the different stages mentioned are used at the same time. For example, we may find crude powders, alcoholic extracts, and pure alkaloids all contained in the same pill. Nay more, we may sometimes give to the patient in addition to all these, a medicine made artificially. But, while this condition still exists, we notice that crude drugs are being less and less used, and their place is gradually being taken by pure active principles. We may say, then, that we are passing at present from the Stone Age into the Bronze Age of pharmacology; and may indeed be said to be just entering on the Iron Age. This age may be said to have begun about twenty years ago, when the researches which my predecessor in this office, Dr. Fraser, made with Prof. Crum Brown upon the connection between physiological action and chemical constitution, inaugurated a new era in pharmacology. They found that, by modifying the chemical constitution of strychnine, they could also alter its physiological action, and convert it from a poison which would tetanise the spinal cord into one which would paralyse the motor nerves.

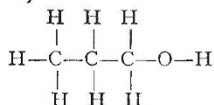
We might perhaps date the beginning of this age from Blake's attempts to show that a connection exists between the form in which various bodies crystallise, and the mode in which they act upon an animal body. Richardson, too, had observed that, amongst various compounds of carbon, certain differences existed in physiological action which might be supposed to correspond to differences in their chemical composition. And at the same time that Crum Brown and Fraser were making their experiments, Schroff in Vienna, and Jolyet and Cahours in France, had independently arrived at somewhat similar conclusions; nevertheless, I think we may fairly say that it was the experiments of Crum Brown and Fraser which fairly started pharmacology in the new direction in which it has since been steadily advancing. It would be impossible for me to enter at all fully into the recent development of this branch of research, but I think it may be both interesting and useful to try to give you a short and popular account of the chief points already made out; and, in doing so, I may perhaps be excused for using, almost to the extent of abusing, similes which are not precisely exact, but which may be useful in giving you a rough idea of a somewhat complicated subject.

We have all heard of the "flesh-pots of Egypt"; but I find that everybody is not acquainted with the "flesh-pots of Shiloh," though "good little Samuel" has probably been frequently held up before us as an example to be followed, and possibly the naughty sons of Eli as an example to be avoided. When these sons of Eli were priests in Shiloh, their custom was, when any man offered a sacrifice, to send their servants with a "flesh-hook" of three teeth, in his hand, which he struck into the pan, or kettle, or cauldron, or pot; and all that the flesh-hooks brought up the priest took for himself.

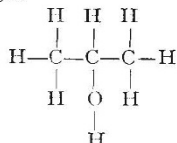
It is obvious that what the priest's man brought up would depend very greatly on two things, viz. the contents of the pot and the nature of the hook—whether it were large or small, sharp or pointed, single-pronged or many-pronged. It is obvious, too, that a very slight alteration of the points, by the judicious application of a file or whetstone, might considerably influence the savouriness of the priest's dinner. With the small pots that they were likely to have in Shiloh, it would not matter much what the nature of the handle was; but it would matter



is exactly what we find in the case of alcohol. For example, primary propyl alcohol,—

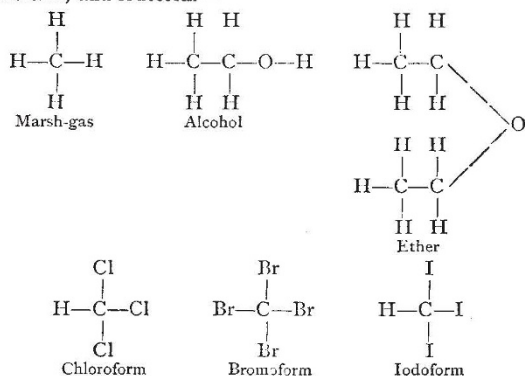


where the hydroxyl is attached to the terminal link, appears to produce steadily increasing paralysis of the nerve-centres; but secondary propyl alcohol, where the hydroxyl is attached to an intermediate link, thus—



scratches up or stimulates the nerve-centres before it paralyses them (Efron Pflüger's *Archiv*, Band xxxvi., 1467).

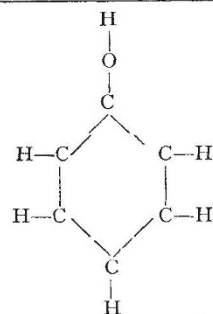
The whole of the carbon compounds, formed on the principle of an open chain, appear to have an action more or less like that of alcohol, though these are modified by the nature of the substances which "tip," as it were, the free affinities of the carbon links. Thus, marsh-gas, alcohol, ether, chloroform, bromoform, and iodoform—



all tend to paralyse nerve-centres, and to exert an anæsthetic action; but the chloral in the chloroform tends to make the substance paralyse the heart more quickly than marsh-gas, alcohol, or ether, which contain hydrogen alone, or hydrogen and oxygen; and in iodoform the effect of the carbon is to a great extent swamped by the iodine.

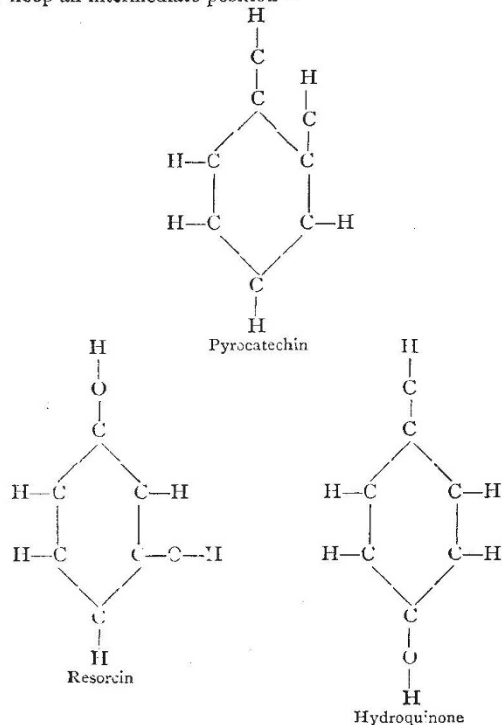
It is to Liebreich's recognition of the fact that similar carbon compounds possess a similar anæsthetic action that we owe the discovery of chloral. The knowledge of the depressing action on the heart of chlorine in such compounds led Schmiedeberg and Cervello to search for a hypnotic substance which should not contain chlorine, with the result that paraldehyde has been added to our therapeutic *armamentarium*; and the stimulant action of ammonia led Schmiedeberg to introduce a new hypnotic, urethane, which, like chloral, will produce sleep, but, instead of weakening, will stimulate the heart, and is thus admissible in cases where chloral might be dangerous.

Let us now turn to the other class of carbon compounds in which the atoms are arranged so as to form a close chain, or, as we may call it, a stiff nucleus or shank, to which either single hooks or open chains may be attached. This group of carbon compounds is termed the aromatic series. The substances belonging to it differ from those of the open chain or fatty groups, inasmuch as they tend to stimulate the nerve-centres, and produce convulsions or spasms before paralysing them. But the most marked property which they possess appears to be their power of reducing temperature, and of destroying low forms of life, so that they act both as antipyretics and as antiseptics. We have seen that in the open chains of the fatty series of carbon compounds, the increased number of links appears to increase the activity of the compound, and a condition which is similar, in some respects at least, is to be found in the aromatic series. For example, in phenol or carboic acid, as it is usually termed, we have one hydroxyl terminal, just as in ordinary alcohol; the other carbon affinities being saturated with hydrogen—



When these hydrogen atoms are replaced by methyl, the antiseptic power of the phenol is increased, and the increase appears to be in proportion to the number of methyl groups which are introduced into the compound. Turning again to our old illustration of the flesh-hooks, we might compare the benzene nucleus to the shank with six points, each of which might be armed either with a sharp hydroxyl hook, or with a blunt hydrogen one, or with a carbon chain. The more the blunt hydrogen hooks were replaced by chains, the more thoroughly would they sweep the pot; and, in fact, we may say that the more chains there are instead of hydrogen, the more thorough is the antiseptic action of the compound.

In the case of antiseptics, all that we want is to insure a thorough destruction of the microbes, which give rise to putrefaction or disease; but when we come to deal with antipyretics we have a more complicated problem before us, for we wish to reduce the temperature in man or the higher animals, while at the same time we have to avoid producing any marked action on the nervous system in the way either of spasms or paralysis, and also to avoid depressing the circulation and causing collapse. Now several bodies nearly allied to carboic acid, and differing from it only in the fact that the benzene nucleus in them has two hydroxyl groups attached to it instead of one, as in carboic acid, have a strong antiseptic power. These bodies are hydroquinone, resorcin, and pyrocatechin; they all have an antiseptic action, but the strength of their action is very different, resorcin having only one-third of the strength, and pyrocatechin only one-fourth of that of hydroquinone. This difference in strength shows us here, also, how important the position of the hydroxyl groups is; because, in pyrocatechin they are close together, in hydroquinone they are as far apart as they can be, and in resorcin they keep an intermediate position—



But these bodies, perhaps from their simple structure, appear to be adapted to attack all parts of the animal organisation, and they are apt to affect the nervous system and circulation. In order to avoid these disadvantages, various attempts have been made to obtain bodies of a similar but more complicated structure, which should have a more specialised action, and would lower the temperature while leaving the nervous system and circulation unaffected. These attempts have been more or less successful, and we owe to them the introduction of three new remedies—kairin, thallin, and antipyrin. The former two, after a brief period of trial, have been found more or less unsatisfactory; but the latter is perhaps, upon the whole, the best antipyretic that we possess, reducing the temperature and, at the same time, having few disadvantages. Salicylate of soda is nearly allied in chemical constitution to resorcin, and as a general antipyretic it is almost equal to antipyrin, and superior to it in cases of rheumatic fever. It is possible that we may still obtain antipyretics more powerful than any we yet possess, and specially adapted to the febrile conditions arising from different causes, for these antipyretics do not appear to be equally successful in different kinds of fever. Antipyrin is best in hectic fever, and salicylate of soda in rheumatic fever, but an antipyretic which will be thoroughly satisfactory in typhoid fever is still a desideratum.

I have said that antipyrin is generally free from any disagreeable action; but this is not always so, for it sometimes may produce collapse. This shows us that in the action of all our drugs we have two factors to consider, namely, the drug itself and the body into which we introduce it. We have just been considering the alterations in physiological action which may be produced by changes in the chemical constitution of our drugs; but there is another factor which is perhaps more difficult to investigate, and still more important in the treatment of disease, namely, the condition of our patients. The failure of our drugs to produce the effects we desire is one of the most trying occurrences in medical practice. Thus, in fever, we sometimes find that drugs will not reduce the pulse as they do in non-febrile conditions, and digitalis in pneumonia sometimes appears to have lost its sedative action on the heart altogether. Some years ago I thought that possibly this might be due to the high temperature producing paralysis of the nervous apparatus which restrains the heart, and supposed that the peripheral ends of the vagus in the heart might be paralysed. I then made some experiments, which showed that I was wrong in this supposition. Several years afterwards my friend Dr. Cash and I made some further experiments, which showed that the failure of digitalis to slow the heart in febrile conditions is really due to paralysis of the regulating nerves of the heart; but the part of them which is paralysed by the heat is their roots in the medulla, and not their endings in the heart.

In other experiments which we made together we found that the muscle of a frog poisoned by barium could be restored to its normal condition by a high temperature, and also by the application of potash salts. It occurred to us that, if we could saturate the body of an animal with potassium, we should be able to render it proof against the poisonous action of barium. On trying this, we succeeded in rendering animals so far resistant to the action of the poison that they were alive and well after animals of similar size, but unprotected, had succumbed to the action of the same dose of poison, although we did not succeed in ultimately saving the animals.

But Dr. Cash has pursued this line of investigation far beyond the limits of our mutual research, and he has obtained results which seem to me to be amongst the most extraordinary and the most promising in pharmacology. Knowing, as he did, that corrosive sublimate was an exceedingly powerful disinfectant, it occurred to him that it might be more harmful to disease-germs than to the bodies of higher animals, and that he might be able, by the introduction of the poison into the body of an animal, to render it insusceptible to zymotic diseases. A similar idea had occurred to Koch, who injected corrosive sublimate into animals after previously inoculating them with anthrax; but his experiments failed, while Cash has proved successful by introducing the corrosive sublimate before inoculating with anthrax, and thus giving the drug the start of the disease. These experiments acquire an additional interest from the fact that M. Pasteur, although uncertain regarding the exact mode in which his process of inoculation for hydrophobia has brought about such satisfactory results, is disposed to think that the agent which prevents the disease is a chemical substance, and not a microbe.

When we look back for twenty years and see how far pharmacology has advanced since Crum Brown and Fraser's experiments directed it into a new path, we may hope that twenty years more may not only have greatly added to our stock of new remedies, but will have enabled us so to ascertain the condition of our patients that, either by the proper modification of a single remedy, by the proper admixture of remedies, or by proper changes in the food or surroundings of each patient, we may insure the action we desire, and we shall not have to feel, as we painfully do at the present, that our patients often die for lack of knowledge, not on our part, but on that of our art.

Nothing is more painful to a medical man than having to answer in the negative the agonised appeal, "Oh, doctor, can you do nothing?" of those who see passing away friends who are dearer to them than their own life. It is because we medical men know the value of human life and the extent of human suffering; because we are called upon to prolong the lives of those whom not only their friends but their country and the world at large can ill spare; because we must, if possible, relieve pain sometimes amounting to extreme torture in the sufferers themselves, and felt hardly less keenly by their friends, that we consider it is not only permissible, but is our imperative duty to gain the knowledge we require to attain our object, even though we sacrifice the lives of animals, and inflict upon them some pain—never wantonly, never carelessly, and almost always slight in comparison with what we often see our patients feel. Moreover, the lower animals suffer from disease as well as men, and we may hope that the advance of pharmacology will give us the means of relieving pain and prolonging life in them as well as in man.

#### SCIENTIFIC SERIALS

*Journal de Physique*, June.—P. Garbe, experimental researches on radiation. Examination of the formulæ proposed by Dulong and Petit, by E. Becquerel, by Violle, and by Stefan. The author holds Stefan's law to be true for absolutely black bodies only. The verifications have been made by spectrophotometric measures of glow-lamps fed from accumulators.—G. Wyrouboff, the structure of crystalline bodies endowed with rotatory power. This is a remarkable paper, traversing several conclusions hitherto believed to be proven. The author states that the alleged necessary and constant relation between rotatory power and the existence of facets indicating non-superposable hemihedry is untrue, for of eighteen such substances known, only four have been proved to have such facets, while the nitrates of lead and of baryta which are cubic with facets of this kind have no rotatory power. The author now propounds the view, which he supports by the discovery of striated structures upon the facets in question and by various strong arguments, that the real physical cause of this rotatory power is that such crystals consist of superposed laminae crossing at different angles, and possessing biaxial refraction. In fact, he holds that these substances are only pseudo-symmetrical, and that the built-up mica plates of Reusch which show rotatory power are actual types of the phenomenon in general. He particularly refers to the optical behaviour of amethyst, and further declares that he has succeeded in proving that the true crystalline form of sulphate of quinine is clinorhombic. He regards as absolutely illusory, in the vast majority of cases, the so-called measurement of the angle of rotation by these substances.—L. Laurent, practical methods for the execution of objectives intended for instruments of precision. This paper describes means for testing during process of manufacture the curvatures, &c., of lenses intended for spectroscopes, goniometers, and such instruments.—Th. and A. Duboscq, saccharimeter for white light. This saccharimeter has a Senarmont polariscope placed between the polariser and analyser. The Senarmont polariscope consists of four wedges of quartz disposed so as to show two fringes with black central band, which in the dark field are situated exactly in line with one another. On introducing any substance that rotates the plane of polarisation, the fringes move right and left. A quartz compensator is added.—J. Voisenat, influence of nature and form of conductors upon the self-induction of an electric current. A summary of the recent papers of Hughes and H. F. Weber.—K. Ångström, on the diffusion of radiant heat from plane surfaces.—Ch. Soret, researches on the refraction and the dispersion of the crystallised alums.—E. Wartmann, the compensated rheolyser. This instrument consists of a circular modification of Wheatstone's bridge with mercurial conductors.—R. Pictet,