Let it not be supposed that the improved teaching of pathology would add much to the labours of the already overburdened medical student, or that it would have the tendency to make him a pathologist rather than a practitioner of medicine, whose chief duties, after all, will be to heal the sick. It would merely systematise his studies; he would be better prepared for his clinical work, and it would be of the greatest advantage to him afterwards in the exercise of his practice; for, as one of my predecessors in this chair has rightly said, "Pathology is the basis of every rational system of therapeutics."

After these few somewhat disjointed remarks, which express not only my views, but also the views of many practitioners whom I constantly meet, and who appreciate fully the advantages of a systematic training in pathology, I will ask you to turn your attention to the work of this Section, which, both as regards the subjects for discussion and the papers to be read, promises good results. In selecting subjects for discussion, we cannot be said to be behind the age, for as nerves and micro-organisms occupy now-a-days so much of our attention, peripheral neuritis, one of the most recent chapters of nerve-pathology, and the etiology of pneumonia, a disease which by many is now held to be parasitic and infectious, may be considered very fashionable subjects. In the third subject for discussion, aneurysm, we see the close relation of pathology to practical medicine and surgery. These discussions, in which some of our best and ablest workers have promised to take part, will leave but little time for the reading of papers; but these, though small in number, yet cover a very large ground, and are sure to add largely to the useful work on which this Section is about to enter.

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.

ON THE CONNECTION BETWEEN CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION.

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 seaside, 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 Paleolithic 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. 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 imbedded 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 Professor 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 very greatly if the priests had to go fishing in the brazen sea of Solomon, for there, with a short handle, they might not be able to reach the tit-bits in the middle, and if the handle were too long, they

might go plunging their hooks about the opposite side of the vessel, with the same result as if their handle were too short. Now, in the drugs which we use in medicine, we may find a certain analogy with these flesh-hooks, some part of the drugs being comparable to the hooks, and others to the handle. Perhaps the analogy would be even more correct if we were to regard the hooks as having movable points, which could be taken off and replaced by others of a different form or sharpness. If we take alkaline salts as an example, we may regard the base as the handle, and the halogen as the hook; and by modifying either of these, we may alter the parts of the body affected and the manner in which they are affected. We might, indeed, compare chloride of sodium, in which we have the chlorine attached to sodium, with the low molecular weight of 23, to a hook with so short a shank that it did not reach the big joints lying in the middle of the cauldron; while potassium, with a molecular weight of 40, was just long enough to do this; and rubidium, with a molecular weight of 85, was so long as to go plunging about on the other side. In fact, we find that this is very nearly what occurs in the muscles of the animal body after the administration of the chlorides of sodium, potassium, or rubidium; for, while potassium chloride is a powerful muscular poison, the action of sodium and rubidium chlorides on the muscles is very slight.

We have seen what changes would follow alterations in the shank of our flesh-hook; now let us see the effect of altering the prongs. If we put on a small one like chlorine, it may go dragging about catching everything, but bringing out nothing; a bigger one, like bromine, may lay hold of a lung or a brain; and a bigger one still, like iodine, may lay hold of a big joint. Now, what we find in the body seems to be somewhat similar. The chlorides circulate in the blood without producing any marked alteration beyond that which is due to the substance with which the chlorine is combined. The bromides attack the brain and nerve-centres, and the iodides tend more especially to affect the muscles and the glands.

It is evident that another important factor besides the sharpness of the hooks is the number of prongs, and the three-pronged hook seems to be the generally effective one. Now, in pharmacology, there is one substance,—nitrogen,—which appears sometimes to have three, and sometimes five prongs, or affinities, as chemists term them, and it is a substance having a very general and powerful influence over the body. When combined with hydrogen in the form of ammonia or of ammoniacal salts, it affects nerve-centres, motor nerves, and muscles, tending first to stimulate and then to paralyse them. But as we would expect, the effect of the ammonia is modified by its combination with iodine, chlorine, and bromine; and we find that, while the ammonium-chloride generally attacks the spinal cord and causes irritation, ammonium-iodide paralyzes the motor nerves and muscles.

When nitrogen has oxygen combined with it in place of hydrogen, so as to form nitrous acid, its action is exerted more especially upon the blood and blood-vessels, so that it causes the blood to become chocolate-coloured, and the blood-vessels to dilate. This power of dilating the vessels is sometimes exceedingly useful in the treatment of disease; and we have been enabled to vary the action of our drugs so as to attain, to a great extent, the end we desire, by our knowledge that the action depends upon the nitrous acid, and not on the substance to which the acid may be attached; or, to return to our own comparison, the effect depends on the nature of the hook rather than on the kind of shank to which it is attached. Thus, where rapid dilation is desired, we use nitrite of amyl; but where a slower and more prolonged action is desirable, we employ nitrite of soda or nitroglycerine.

In some useful tools we have the two ends serving different purposes: one end for example being a hammer and the other end a claw for extracting nails; and we can easily imagine a flesh-hook constructed on the same principle, one end, let us say, having the prongs widely apart, and the other the prongs close together. With such a hook, it is evident that the viands which were fished up would be different according as one or other end was put into the pot, for the close prongs would bring up delicate little pieces which would simply slip through the wide ones. If we carry our illustration a step further, and suppose this hook to consist of two parts attached to one another by certain prongs while others were left free, we can see that, if only one prong were left free in each part, but these prongs were of different shapes, the pieces obtained by the man using it would be of a different kind, according as the prong belonged to one end or the other. Now we seem to find something of this sort in the union of nitrogen with carbon. Carbon is a substance with four affinities, while nitrogen appears sometimes to have three and sometimes to have five. When the nitrogen and the carbon are united in such a way that four affinities and each are connected together, leaving one free affinity or prong belonging to pentad nitrogen, thus,— $\text{N}\equiv\text{C}$, the compound

is exceedingly poisonous; whereas, when the free affinity or prong belongs to the carbon and the other three affinities are joined to triad nitrogen, thus,— $\text{C}\equiv\text{N}$, the compound is comparatively innocuous.

This fact shows us how very important the nature of the free affinity in the compound is in regard to physiological action.

We have just pictured to ourselves an instrument of two parts, joined together by small hooks, and consisting, in fact, of two links. In this instrument the links differ a good deal from each other; but one link—namely, carbon—has a great power of uniting with itself, so as to form long chains, straight or branching. It also forms what we may possibly regard as close chains, thus—

so stiff as to act the part of a shank, to which single hooks or long open chains may be attached. We may represent it graphically thus—

Now, if any of Eli's successors wanted to fish in Solomon's brazen sea with hooks attached to a flexible chain instead of to a stiff shank, the results of his fishing would not only depend on the hooks he used, but on the length of the chain, on the kind of chain, single or branching, and on the position of the links to which the hooks were attached.

Now, in the series of chemical substances to which alcohol belongs, we have an illustration of the modifications in physiological action which are produced by the length of the chain, the kind of chain, and the position of the hooks. The links, in the case of alcohol, consist of carbon atoms attached to each other by one affinity, so that each terminal atom, or link, has three affinities, or prongs, and the intermediate links have two each unattached, thus:

We may regard one prong of one terminal link as furnished with a sharp point, to which we give the name of hydroxyl, while all the others are furnished with blunt hydrogen points, thus:

All the alcohols attack the nerve-centres, and paralyse the brain, the spinal cord, and the centres of organic life in the medulla oblongata. In large doses they all produce death, and the longer the chain, the more deadly do they become, until the chain is so heavy that it can hardly be used at all, or, in other words, till the alcohol becomes so solid that it will not readily enter the body and produce its toxic action.

If we fix the sharp hydroxyl on one of the intermediate links, instead of the end one, we would naturally expect that it might simply scratch the pieces of meat instead of pulling them out, as it might do if it were attached to the terminal link; and this 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 paraldehyd 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 paralyzing 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 carbolic 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 ensure 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 carbolic 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 carbolic 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 of pyrocatechin, and only one-fourth 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 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 ensure 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.

AN ADDRESS

DELIVERED AT THE OPENING OF

THE SECTION OF OPHTHALMOLOGY,

At the Annual Meeting of the British Medical Association, held in Brighton, August, 1886.

By CHARLES OLDHAM, F.R.C.S.,

Senior Surgeon to the Sussex and Brighton Infirmary for Diseases of the Eye
President of the Section.

RECENT PROGRESS IN OPHTHALMOLOGY.

GENTLEMEN,—There are two primary duties incumbent on the members of this Association on whom you have conferred the great and responsible honour of presiding at your deliberations.

The first of these is to bid you all, in the name of your fellow-associates of this town, a most hearty welcome to the meeting which was yesterday inaugurated at the Dome. We sincerely trust that this meeting may be productive of the best results in every way; from a scientific point of view, that the papers read in this Section, and the discussions that will thereupon ensue, may materially tend to the advancement of the art and science of ophthalmology and also—for we do not forget the words of one of the most charming of poets—

"Neque semper arcum tendit
Apollo"—

that you may enjoy such social pleasures as we have done our best to provide for your entertainment, as fully as we, your hosts, could desire; and that after the meeting you may return home no whit the worse for the treatment you have received at the hands of "Dr. Brighton."

The second duty I have to perform is to crave your kindly and generous indulgence for the many shortcomings which I fear must inevitably occur in my conduct of your affairs. I can assure you that I bring a desire as earnest for your service, as I feel my capacity to be slender in respect of the position in which you have done me the honour to place me.

The last time the Association met in Brighton was in the year 1851. There was then no Ophthalmic Section. Nearly thirty years were to elapse before the Association, which at that date numbered only about 1,700 or 1,800 members in all, could boast of a body of its associates who devoted their time and abilities to the sole study and practice of the surgery of the eye. But that year was destined to be a memorable one in ophthalmic annals; for it was in 1851 that the great Helmholtz brought out the instrument of which it may be said (and it is an excellent illustration of Schopenhauer's just remark that all great thinkings are apparently obvious in proportion to their greatness) that its principle was apparently so obvious that we marvel that it had never been thought of before. I need not point out to you the entire change that has been wrought in our art by this discovery. It will suffice to say that diseases which, before its advent,