ADDRESS IN THERAPEUTICS,

BY

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ON THERAPEUTICS AS AN APPLIED SCIENCE.

MR. PRESIDENT AND GENTLEMEN,—In entering upon the task which the Council of the Association has imposed upon me, of delivering an address on therapeutics before this meeting, it is my duty to thank that body for the honour which their confidence that I am in any degree competent for the work confers upon me. One qualification, and one only, I may venture to acknowledge. This is an interest in therapeutics quite outside its practice as a profession—an interest in it as a branch of natural science, may I say?—at any rate, as a department of human knowledge and a subject of investigation by scientific methods. I may acknowledge also a confidence, which grows with my years, in the power we can exercise over the processes of disease, and an unwavering belief that therapeutics has laws which are discoverable; that these laws are correlated with the laws of chemistry and physics, and that, sooner or later, therapeutics will enter the circle of the sciences.

The belief to which I have just given expression will be the keynote of my discourse to-day; no mere exposition of a branch of the therapeutic art would satisfy you or me, or would be worthy of the occasion or of the opportunity. I shall do what in me lies to lay before you therapeutics from the point of view of science.

I need scarcely say that therapeutics must always belong to the order of applied sciences, and will bear much the same relation to physiology in an extended sense as engineering to mathematics. Just as engineering is applied mathematics, therapeutics will be applied physiology. As in engineering, there will always be room for the exercise of individual skill. The strength of materials is known equally to one engineer as to another, the mathematical principles on which this knowledge can be applied to the greatest advantage are common property; but one man builds a bridge which disappears under the first severe trial, while the work of another outlasts the centuries.

When we say that therapeutics will take rank among the sciences, we mean that therapeutic facts and phenomena will be referred to physical and chemical laws, or, in other words, will be capable of explanation on chemical and physical grounds. In vital phenomena, different as they are from the phenomena of non-living things, there is no suspension or reversal of physical and chemical laws, but only change of the conditions under which they operate; there is no modification of atomic or molecular affinities, but these affinities have a wider and more varied field of action.

Some sciences are predominantly deductive—that is, from general principles, called in mathematics axioms and postulates, an infinity of conclusions are reasoned out; others are essentially inductive—that is, individual facts and observations are collected and grouped until a generalisation is reached which applies to them all and to all like phenomena. In proportion as a science is perfected, deduction and induction meet; there is a perfect agreement between the conclusions of reason and the teachings of experience. The laws or general principles being true and the methods of reasoning from them accurate, the conclusions are in accord with the facts of observation; and, on the other hand, all observed facts fall into order under generalisations of ascending comprehensiveness until we reach first principles.

Now therapeutics must be essentially inductive, and must proceed by observation and experiment. But we are at once met by this difficulty—that there is no constancy in our results. In chemistry an experiment can be repeated over and over again with exactly the same results; and, by a chain of experiments, the relation of one atom or molecule to another, and to every other atom or molecule, can be definitely ascertained, and thus this magnificent science has been steadily built up. In therapeutics nothing of this sort is possible. A given drug will have apparently a quite

different effect on different men, and on the same man at different times. The very ground of induction seems to be cut from under our feet. It does not follow, however, that there is any real inconstancy in the action of the medicaments. The relation between the drug and the organism is always the same, but the conditions of the organism vary, and we have no command over the conditions, and no means of recognising variations which may have a determining influence on the action of the substance administered. Some variations we can understand, and we may thereby illustrate variations which are unknown to us. We can see at once, for example, that it must make a great difference to the action of a drug whether it is taken into a fasting or a full stomach. In the one case it is diluted by a relatively enormous amount of food in process of digestion, which competes with it for absorption, and may, indeed, alter it chemically; in the other it may at once enter the blood current, and reach the nerve centres or other organs in much larger proportions; or, independently of recent food, the vascular system may be in a state of repletion or depletion.

We can see, again, that the peptic chemistry of herbivorous animals, dealing mainly with starch mixed with a minute proportion of vegetable proteids, must be very different from the peptic chemistry of carnivora, whose food contains no starch or sugar, and consists exclusively of highly nitrogenous matters and fat. The hepatic chemistry, again, of these different classes of animals must be quite different. In herbivora the raw material on which the liver cells have to work, and from which they manufacture the constituents of blood, will be chiefly saccharine, in carnivora almost entirely albuminoid.

Cells which have such different work to perform must have correspondingly different chemical relations with organic matters, perhaps also with inorganic matters, since vegetable foods contain a larger proportion of salines, and especially of potash, than animal foods, and we should expect a different reaction to medicaments.

The results of experiments, therefore, made on rabbits do not necessarily apply to cats and dogs, or to human beings; and the different digestive capabilities and natural inclination for different kinds of food in different individuals is suggestive of peptic and hepatic chemistry in one approaching the herbivorous, in another the carnivorous type.

This line of reasoning might be pursued indefinitely. For example, the functional endowments of the highest nervous centres vary so greatly in different classes of animals, that the nerve-cells of these centres must have different degrees of stability and energy, must react with differing readiness and vigour to stimuli of various kinds.

Now such differences of "discharge," to use the term felicitously employed by Dr. Hughlings Jackson, argue differences of chemical composition and reaction, and would lead us to expect what we actually see, that substances which act on the highest nerve centres produce different effects in different animals, and it is interesting to note that no such difference is observed in poisons which act on the lowest centre, the spinal cord. Strychnine acts alike on all animals which have a spinal cord, from the frog up to man. When, however, we leave the vertebrate series even strychnine ceases to be deadly, and black beetles consume with impunity the poisons containing this substance laid for rats and mice. So, at least, I am informed by an eminent chemist, who tried by means of strychnine to exterminate the cockroaches which infested his kitchen.

It is obvious, then, that in therapeutics induction is surrounded with peculiar difficulties, and the building up, step by step, of general laws when the conditions are not under our command seems a hopeless task. We must look, therefore, for aid from the general laws of chemical and physical science, taking them as guides for investigation and in explaining processes and results. They are great lights let down into our darkness. This is exactly what has been done in all sciences. The circuit of the planets, even after the simplicity of the Copernican system had replaced the confusion which prevailed while the earth was regarded as the centre of the universe, remained a mystery until the principle of gravitation was discovered and applied to their movements, when not only was the harmony of the heavenly bodies made clear, but the existence of new planets was inferred and their place calculated out long before they were themselves discovered. A theory of the evolution of the universe has, indeed, grown out of it.

Chemistry has borrowed from physical science the refined and far-reaching spectrum analysis and the mathematics of molecular

motion appears to throw light on the laws of chemical combination and constitution.

If therapeutics is to be in any true sense scientific all the great generalisations of chemical and physical science must apply to the action of remedies, all physiological processes and therapeutic action should be capable of explanation on chemical and physical grounds, and should be capable of expression in the terms of chemical and physical science.

We must have a definite idea in our minds of what we mean by science in therapeutics and a criterion by which to direct our endeavours to estimate our approximation to the scientific stage. Some even of those who think on the subject are disposed to look upon such effects as the action of quinine in ague, the effects of opium in relieving pain, the influence of mercury on syphilitic affections, the purgative action of jalap or elaterium, and the irritation of the skin produced by mustard or cantharides as ultimate facts which depend upon some relation between the substance and the organism as inscrutable as the affinity of hydrogen for oxygen, into which therefore it is useless to inquire.

In this case, when the farthest extent and utmost exactitude of knowledge was attained, therapeutics as a science would stand apart from other sciences and from science in general. It would, in effect, be no science.

By therapeutics we mean all those measures by which we combat and endeavour to subdue disease, and if we ask what would fulfil the conditions of therapeutics as a science, the answer would be a complete knowledge of the processes of disease on the one hand, and of the mode of action of remedies on the other.

We must have, then, some definite idea in our minds of what we mean by disease. Numerous and varied definitions have been given, but I shall not attempt to enumerate, still less to discuss, them. The idea which has guided me is one which I arrived at when I first began to lecture on medicine twenty years ago. It is an application of Herbert Spencer's definition of life. This great philosopher, after a long discussion, enunciates the following as conveying the broadest and most simple definition of life: "The adjustment of internal relations to external relations." Life is defined as a process, you will observe, not as an essence or as a force. Put briefly, life is the continuous adjustment of an organism to its surroundings. A living organism is subjected to influences which, were it not living, would tend to its disintegration, but by its reaction it turns to its own advantage these external forces, and employs them in building up its structures.

With this conception before our minds our definition of health and disease is clear. We have health when the adjustment is efficient and complete; disease when it falls short. Let me point out for a moment how this fits in with facts. In the first place, it recognises that health is not the same thing in different constitutions, at different ages, under different modes of life, and in different climates. Whether the individual is old or young, strong or weak, active or inert by nature, living a sedentary or open-air life, eating much or little, so long as the adjustment is complete and the organism is undergoing no deterioration of structure, and is discharging all its functions efficiently, we have health. When, on the other hand, either from the fault of the organism or from the stress of unfavourable influences, function is imperfect, or its exercise is attended with pain, or structural changes are taking place, there is disease.

Health, then, not being an identical state of things in different constitutions and under different conditions, still less has disease, called by the same name, necessarily the same significance.

This conception of disease, again, gives further extension to the fact, with which we are all familiar, that not every departure from normal action must be considered to be disease, and combated as such. When the organism has been subjected to some unusual external condition, it must react by some unusual process of adjustment, which, in a sense, is abnormal. The vomiting and purging by which indigestible food is got rid of will suggest itself to all of us as an illustration. Are we sure, let me ask, that pyrexia, which we combat so diligently, is not sometimes a part of the process of readjustment?

Again, looking upon life as a sort of conflict between the organism and the forces outside, we can see that the disturbing influence of incident causes of disease will vary with the vigour of the organism. A fragile constitution will maintain its integrity through a long life under favouring conditions, while it would succumb to the first blow of real hardship; and a strong constitution will, at one time, yield to influences which, at another, it

would successfully resist when the vital swing is vigorous, just as a top, when spinning rapidly, takes no notice of a push which, later, makes it swerve in circles, and finally totter and fall. The circles which our top describes in order to maintain its equilibrium represent those perturbations of a living organism through which it passes in righting itself after exposure to some morbid influence—its oscillations represent disease, and its fall death.

What has been said of the organism as a whole applies, *mutatis mutandis*, to the separate organs of the body and to the individual cells of each organ. There is a continuous adjustment of the cell or organ to its environment, which, when exactly performed, constitutes its health, and if imperfectly effected is disease; the environment of cell being, of course, the blood, or rather the exudate from the blood into the intertextural spaces.

With such a view of the organ and its environment before our minds, it becomes evident that disease may result either from the violence of the incident disturbance, or from faulty reaction on the part of the organism. Now this will correspond very closely, though by no means absolutely, with acute and chronic disease.

In acute disease, some exciting cause is usually traceable, or, if not known, is assumed; in chronic disease, without special disturbing influences, the reaction to normal average surroundings is imperfect or perverted.

In acute disease, therefore, a question will occur to our minds which will not arise when we are dealing with chronic affections. The attack we are watching—is it a process by which the organism is adjusting itself to the incidence of some extraordinary disturbing influence? or is it one which, having been thus initiated, has gone beyond the necessities of the occasion, or in which a flame, having been lighted for a given purpose, has spread and become destructive? Let me recur again to the simple illustration offered by vomiting and diarrhoea. Are they merely getting rid of offending material, or do they indicate a catarrh which has been set up by the irritation, and which persists when the original object has been accomplished? This sort of question might arise were the starting point not the ingestion of excessive or indigestible food, but derangement of the chemistry of the gastric follicles or liver cells by an emotion or a chill.

A question of another kind arises with regard to the specific fevers. How far does the definite series of changes which constitute the disease represent the successive phases of the life history of the microbe? or in what degree is the febrile disturbance reactive or defensive? Is there any shred of truth in the old notion that the end and object of the febrile process is to eliminate a poison which has gained access into the system? I cannot discuss these questions; to do this adequately would require all the time at my disposal, and more. I may just say in passing that the enormous increase of the specific poison during the disease, taken in connection with the fact that no such increased multiplication of specific micro-organisms takes place in the system in health is clear evidence of the causal relation between the active multiplication of microbes and the symptoms, probably through the medium of ptomaines, produced by the microbes. But what I wish to point out is this, that the object or aim of our treatment will be different according as we endeavour (1) to destroy the specific germs, or control and check their multiplication; or (2) to aid or regulate a defensive reaction or process of adjustment; or (3) to promote a process of elimination. Our power of intervening actively for the benefit of the patient would be greatest if we could destroy the microbes; but there is no evidence as yet that this can be accomplished.

With questions such as these just indicated in our minds, we do not blindly interfere with everything which we recognise as wrong. We bear in mind the fact that acute disease has a limited duration, and that if the structural injury of important organs can be prevented, and tendencies to death can be counteracted, there will be a return to health. Our success in this endeavour will, of course, be measured by our knowledge of the particular disease, and our judgment in applying it. We try to estimate the significance of each departure from the normal operations of the system, and we aid or counteract it according as it makes for recovery or tends to death.

In febrile affections to lower the temperature is not necessarily to relieve the disease. When protracted high temperature becomes in itself a danger as in typhoid fever, it is well to deal with it as such, and the treatment of this disease by cold bathing has saved many lives; but if the disease is of short duration, with a natural termination by crisis, such as pneumonia, I see no object

in trying to bring down the temperature, which, according to my observation and judgment, is not the peril to be eluded.

When, again, the nervous system loses control over the temperature and hyperpyrexia sets in, if we mean to save the patient we must recall the organism to its senses by the cold bath; and here it is not merely abstraction of heat, but a powerful impression on the nervous system which is required, and a violet drenching with ice-cold water and an ice-cold enema will be effectual when a graduated bath will be utterly useless. I need hardly remind my hearers that antipyretic drugs are of no avail in such an emergency, and in typhoid fever I have seen nothing but harm from their continuous employment. These wonderful antipyretics, which are ultimately destined to render great service, not merely in the treatment of disease, but—when we know their exact mode of action—by throwing light on the heat-forming and heat-regulating processes in the body, are in the meantime doing harm as well as good. They afford an easy triumph to the medical man, and he may persuade himself as well as the sufferer and his friends that the diminished febrile heat is a step towards recovery, when the remedy may not only lower the temperature but depress the patient.

While, however, I deprecate the indiscriminate employment of antipyrin and its congeners, I must not omit to mention that at the outset of pneumonia, given early and in repeated doses, it sometimes appears to cut short the attack. The opportunity is soon after the rigors and long before the development of physical signs. I have seen this in old people in whom an attack of pneumonia must have been fatal.

But we may consider the vital processes, the perversion of which constitutes disease, from another point of view. In relation to the principle of the conservation of energy, the normal operations taking place in the organism fall into two great classes—the integration of structure and the evolution of force; these are at the same time essentially antagonistic and mutually independent. In the integration of structure or nutrition we have the building up of complex molecules, which is attended with the fixation or absorption of energy: the evolution of energy, on the other hand, of whatever kind—heat, motion, electricity, nerve energy—takes place at the expense of molecular disintegration; but evolution of energy is dependent upon and is conditioned by antecedent tissue formation and nutrition, and at the same time the nutritional processes are only carried on by the aid of the evolved force.

In warm-blooded animals the maintenance of the temperature of the body constitutes the great demand for blood and tissue oxidation. A given temperature is a necessary condition for the due performance of all their nervous functions, and in all classes of animals heat exercises great influence on the organic processes.

Heat is the great intermediary through which the molecular motion, which we call chemical action, becomes appreciable to our senses and available for our use. It is the mode of motion through which the force stored up in fuel is transmuted into mechanical energy by our steam engines and into electrical energy by the dynamo, and thus back into that mightiest of all forms of energy—light, the creative power which, through the vegetable organism, shakes loose the atoms of CO_2 , water and ammonia, and builds them up into organic compounds.

Heat is the least specialised of all forms of energy, and is a sort of pool from which they may be obtained and into which they tend to return. Whether in the animal organism heat plays an intermediary part in the evolution of motor force by the muscles, and of nervous force by the nerve centres, as is suggested by the constant temperature required by the nervous system, and by the simultaneous liberation of heat in all muscular action, we do not definitely know; there is more probably a direct transformation of chemical energy into these forces. Whether, again, heat is actually, as well as potentially, absorbed in the building up of structures we do not know, but from the fact that almost all forms of disease are attended with elevation of temperature, it seems clear that when the nutritive operations are disturbed, the energy which should have been fixed in building up structure is liberated in the form of heat, as was pointed out by Dr. Ord in his presidential address to the Medical Society of London.

Were there time, it might be shown that diseases also may be ranged under two heads—those characterised mainly by abnormal evolution of energy, and those characterised primarily by perverted nutritional activity. It may be pointed out again, in passing, that our organic remedies influence, for the most part, the

evolution of energy, and our inorganic remedies the nutritional processes.

I have, perhaps, detained you too long in the regions of pure speculation, but that the application of logical methods and the pursuit of philosophical speculation may be turned to profitable account has been shown by Dr. Harry Campbell in his remarkable work on the *Etiology of Disease*.

Recurring now to the idea of disease as a rupture of the normal relations between the organism and its environment, the aim of therapeutics is to restore these relations. We cannot immediately and directly modify the reaction of the organism. We cannot, for example, make old and worn out tissues respond as if they were young and fresh, or prevent the gouty constitution from pursuing the perverted metabolism which produces uric acid. We can only act through and upon the environment. But this leaves enormous powers in our hands. A single dose of a powerful medicament may modify the environment of every cell in the body. It is mostly by conditions included under this term that disease is initiated, and by reversal of conditions which have affected the organism unfavourably we aid its return to a normal mode of action. What we have to do, then, is to make some change in the influences which tend to harm. In patients admitted to hospital such a change of great importance is effected by the simple fact of his removal from unwholesome surroundings, and by the cleanliness, care, and feeding; and this is a powerful element of successful treatment in hospital. An equally important change in an opposite direction is made when an overfed and pampered patient is sent to bed and fed on simple diet.

But it is not my intention to occupy your time by remarks on the therapeutical value of rest and food. Therapeutics, as a branch of natural science, is concerned with the action of drugs, and, while not denying the importance of the advice we are able to give our patients on climate, food, and drink, clothing, mode of life, we must admit that the characteristic mark of the physician is the employment of drugs for the cure of disease, and it seems to me foolish to minimise the value of remedial agents of this class. We have no doubt whatever as to the lethal power of the poisons. There is no question as to the purgative action of certain substances, and if we cannot turn such properties to profitable account it can only be from want of skill. To deprecate the use of drugs simply because our knowledge of their action is vague and imperfect, and because, therefore, we are liable to make mistakes, is to shirk our duty. What we ought to do is to render our knowledge definite. No work is more valuable than experimental investigation of the action of drugs. To mention only one illustration, with how much greater confidence do we employ digitalis and remedies of this class since such investigation has taught us that they are not cardiac sedatives, but that by their action on the cardio-vascular muscular fibres they increase at the same time the vigour of the cardiac systole and the tone of the arteriole walls.

Many of the finest intellects of our time are engaged in the resolution of the physiological problems which bear directly or indirectly on the action of drugs, for therapeutics, as I have said, is applied physiology. Prodigious labour is being expended in the elucidation of normal and morbid processes in all parts of the civilised world, and it is delightful to see the enthusiasm with which research is being prosecuted in our own great schools, especially may I say at Cambridge and Edinburgh. The enlightened policy of this Association in encouraging research by grants of money is bearing rich fruit. From all sides there is a convergence of light and of effort upon experimental medicine.

But even experimental medicine does not fully meet the difficulty. It is true that the knowledge obtained is more definite, there is a more complete command over the conditions under which a given substance exerts its action on the organism. The method of difference can be applied, and, besides the power of securing approximately the same conditions in successive experiments and of varying the conditions in different directions, there is the power of making definite changes in the substances administered and observing the differences in the effects. What can be more important, for example, or more definite than the knowledge that some substances, such as curare, muscarin, and belladonna, produce their characteristic effects by action on the nerve endings; while morphine acts on the cerebral cortex and strychnine on the motor cells of the anterior cornua of the cord? Or what more clear and interesting than the modification of the action of the alcohol series by the changes in the radical molecule? But with regard to the action of curare, belladonna, m x-

phine, strychnine, and digitalis, while our knowledge is in many respects definite it is still only mediate. We may know precisely the part of the nervous system on which they act and their effects, but we do not know how the effects are produced. It is to this we must ultimately get down, and it is this which will be found to be a fact of chemistry.

The explanation then will come through deductions from the great general principles of chemical and physical science taken as guides for investigation.

Let us follow for a moment one or two of such deductions. We have accepted as a starting point the postulate that all physiological action and all therapeutical action comes under chemical laws. This being so—

1. The physiological and therapeutical effects of drugs must be identical in their nature, and any apparent differences must be due to changes of conditions existing in disease. The effects of small and large doses of the same medicament, again, often apparently diverse or even opposite, must be alike capable of explanation by the chemical relation between the substance and the organism. This last conclusion will present no difficulty when we reflect upon the illustrations of the varying results of the reaction between two substances according to concentration and other conditions which are presented by the simplest chemical experiment. Strong sulphuric acid, for example, will char and destroy starch, while, diluted, it changes it into glucose.

2. Substances having similar chemical constitution must have similar physiological and therapeutical action, or, if not, the diversity must be capable of explanation on chemical grounds.

3. There must be a quantitative relation between the drug and its effects and a dynamic explanation of such effects.

Nothing more need be said with regard to the first of these deductions. Of the truth of the second, "that substances having similar chemical constitution must have similar physiological and therapeutical action," every chemical series is an illustration. Just as the ethers and alcohols are gaseous, liquid, or solid, according to the size of the radical molecule, there are corresponding differences in their physiological effects. Their action is speedy and fugitive or slow and durable according as they enter the blood readily and escape quickly, or are slowly absorbed and gradually excreted. Their influence is obviously related to the oxygen-carrying function of the hæmoglobin, with which they interfere in varying degree according as they are, from their physical and chemical properties, capable of replacing oxygen in the corpuscles. When they cease to be volatile they are inert.

Another interesting illustration of the definite modification of physiological action by change of a given kind in the molecule of the substance administered has recently been brought to my notice by Dr. W. Hunter, who has himself already made his mark in medical science. There are three substances, xanthin, theobromine, and caffeine, which differ from each other in the substitution of methyl (CH_3) for hydrogen in the xanthin molecule; in theobromine two atoms of hydrogen have been replaced by methyl; in caffeine three; one is dimethyl xanthin, the other trimethyl xanthin. Professor Wilhelm Fiehn, of Erlangen, recognising in this series an opportunity for testing the relation between chemical constitution and physiological action, obtained the following results:

In frogs xanthin has two distinct effects: it renders the muscles rigid by direct action on their substance, and it exerts a paralyzing influence on the spinal cord. Dimethyl xanthin (theobromine) and trimethyl xanthin (caffeine) have exactly similar effects, but in a minor degree, and caffeine is less powerful than theobromine. A larger dose of theobromine than of xanthin is required to produce the same effects on the cord, and a still larger dose of caffeine. The rigidity, again, is less marked and the heart muscle is not affected by the two others as it is by xanthin. No doubt, if a mono-methyl xanthin exists, its effects will be intermediate between those of xanthin and theobromine. The addition of methyl groups (CH_3) to the nitrogen atoms of the xanthin molecule has the effect of diminishing both the tetanising action on the muscles and the paralyzing action on the cord.

Results of this kind are important for more than one reason. By proving the truth of the corollary they increase our confidence in the postulate, and they also throw light on the processes which are concerned in the evolution of muscular and nervous energy. The tetanising effect of the xanthin is not simply a coagulation of the muscle protoplasm; it is an imitation of the chemical change attending muscular contraction, and it would seem that

the xanthin molecule, rendered heavier and less mobile by the substitution of CH_3 for hydrogen, is less apt for this. Another noteworthy point in the results of this investigation is that the same agent which tetanises muscle paralyzes the cord; this is suggestive of a similarity in the chemical changes which attend the evolution of motor and nervous energy, and all the more when the introduction of successive methyl groups into the xanthin molecule diminishes, *pari passu*, the effects both on the muscles and on the cord.

To Drs. Crum Brown and Fraser belongs, so far as I know, the honour of leading the way in researches of this kind, and their investigations on the effects of substitutive changes in the morphine molecule were of extreme importance and interest. I see with pleasure that they have been resumed and extended by Dr. Ralph Stockman and Mr. Dott, who have made known their results in a valuable report to the Scientific Grants Committee of the Association quite recently published. The chemical constitution of morphine, they state, is not exactly known; but it is known that two of the oxygen atoms are present in hydroxyl (HO) groups, while a third probably acts as a connecting link between two carbon atoms. Now, the hydrogen of these hydroxyl groups is more easily replaced by radicals than the other hydrogen atoms of morphine, and one more easily than the other, and, while the change in the morphine molecule is limited to substitution of methyl, ethyl, or amyl radicals, or even radicals of another class, acetyl or benzoyl, for this particular hydrogen atom the change in the action on the nerve centres is one of degree only, not of kind. The same centres are affected, and in the same way, but in different degrees. A more decided modification of the action is produced by adding on chloride of methyl and other groups to the morphine molecule, but still it is one of degree rather than of kind. When, however, the body of the morphine molecule is attacked, as in metho-codeine or apomorphine, the physiological action is radically changed.

The most remarkable inorganic chemical group, considered with reference to the physiological relations of its members, is the phosphorus, arsenic, antimony, and bismuth series. Therapeutically and physiologically there is a striking similarity in their action which becomes rapidly less powerful as we ascend the scale of atomic weight, due allowance being made for a possible multiplication of the effects of arsenic, as pointed out by Dr. Odling. In the forms of anæmia, neurasthenia, and neuralgia in which arsenic is useful phosphorus is also beneficial, as may be antimony in a less degree. In some cases of neuralgia, especially spinal and enteralgic, phosphorus is of the greatest service. In the treatment of skin disease of the dry and scaly character, again, phosphorus may replace arsenic; antimony is apparently more useful in eczema. The general similarity in the action of antimony is obscured by its emetic property, which is probably a collateral action. This is a mere speculation of mine, but I am interested to see that Dr. Stockman and Mr. Dott have come to a similar conclusion with regard to apomorphine. Bismuth is inert in consequence of the insolubility of its compounds and the feebleness of its affinities. A striking point is the minuteness of the fatal dose, which is comparable to that of the powerful alkalis, especially taken in connection with the fact that the effects are not produced by action on a nerve centre, but by the general irritation of the gastro-intestinal mucous membrane which is set up, and, what is still more remarkable, by rapidly inducing a granular degeneration of the liver cells and of other structures. A preposterous and almost childish prejudice against phosphorus has been entertained on the ground of this degeneration produced by poisonous doses. A poisonous dose of the mineral acids produces the same effects, but we are not therefore afraid of employing them as tonics.

The powerful action of phosphorus and arsenic is still more interesting from the fact that it illustrates the dynamic action of drugs. The effect of phosphorus is clearly produced in the course of its passage from the uncombined state to the state of complete oxidation; it is not simply the presence of phosphorus which causes the disintegration of the cell protoplasm, but the commotion attending its oxidation. In the allotropic form, in which its affinity for oxygen is strangely suspended, it is inert. The phosphates have nothing whatever of the characteristic action of phosphorus, and an ounce of phosphate of soda may be taken without any effect on the liver cells. The hypophosphites, on the other hand, in which the oxidation of the phosphorus is incomplete, appear to retain some of its action, but I should have no doubt that if the hypophosphite is sufficiently stable in the pre-

sence of the hydrochloric acid in the stomach to resist decomposition, so that the hypophosphorous acid is never set free, that body will be inert.

The arseniates might be expected to be inert on similar grounds, but arsenic has almost as much affinity for hydrogen as for oxygen, and as Professor Odling pointed out, the arseniate may be reduced in one part of the system to be oxidised again in another. When arsenic is imprisoned in a perfectly stable molecule, as in the kakodyle compounds, it is harmless (unless it is responsible for the foul odour), and can be taken in large amount.

Mercury, again, is a remarkable metal, physiologically and therapeutically considered, both on account of the smallness of the poisonous dose of its soluble salts, and on account of the value and variety and constancy of its effects employed as a therapeutic agent. It is not easy to trace a dynamic explanation of these effects; they are no doubt intimately related with its powerful antiseptic action. In all its forms it is a deadly foe to minute organisms of every kind, vegetable as well as animal, contrasting in this respect with arsenic and antimony. Everyone who has dispensed medicines is familiar with the fungus which grows in a solution of tartar emetic—that is, if tartar emetic has not been banished from the *materia medica*—and arsenic does not prevent decomposition in vegetable infusions as mercury does. The antiseptic and therapeutic and poisonous actions of mercury are no doubt alike due to some relation of this metal with albuminoid substances.

But important as positive illustrations of the deduction that chemical groups ought to form therapeutical groups may be, it is not unlikely that explanation on chemical principles of apparent exceptions to the law may throw greater light on the mode of action of remedies.

When speculation as to the mode of action of remedies and poisons began to exercise my mind, this deduction, which is logically inevitable if the laws of chemistry and physics apply to the animal organism, was a great stumbling block in my path. No set of bodies can be more clearly related chemically than the chlorine, bromine, and iodine group, and yet there is nothing in the action of the chlorides and bromides comparable to the action of iodide of potassium on gummata and other tertiary syphilitic lesions. The explanation of this diversity by Professor Odling in his *Gulstonian Lectures* was like the lifting of a cloud from before my mental vision. It is no doubt familiar to all my hearers. The iodine acts like chlorine in bleaching; by its affinity for hydrogen it liberates oxygen, which in the nascent state oxidises the organic matter, and the reason why iodide of potassium is available as a vehicle for iodine is that the hold of iodine on potassium is so slight that the combination is easily broken in the presence of living protoplasm, and the iodine is set free to do its oxidising work. Chlorides and bromides are too stable to allow of this decomposition. An explanation of the special action of bromides in preventing epileptic attacks is greatly to be desired. I do not believe that it resides in any specific property of bromine, and I should not be surprised to learn that chloride of potassium had some analogous effect, unless, indeed, it is the displacement of chlorides of sodium and potassium by heavier bromides in the nerve elements which hampers their action and dulls their sensibility.

Among inorganic substances, the different classes—alkalies, alkaline earths, earths proper—the iron group and so on have each certain physiological and therapeutical actions in common, but, as I have pointed out more than once before, there is, underlying the conspicuous similarity, say between the different members of the alkaline class, a profound diversity, as is shown by the fact that soda salts are found in the serum, potash salts in the corpuscles, and that potash in all combinations is a muscle poison arresting the heart's action when injected into the veins even in small quantity, while soda has no such action; that is, the relation of these two bases with the organic constituents of the body is quite different. I have long held the opinion that in addition to the horizontal classification of metallic substances, there will be found a vertical arrangement, a member of each class corresponding with a particular member of the several classes above it from the alkalies through the earths and baser metals, up to the noble metals. I should conjecture, for example, that lead at one end may correspond with sodium at the other, and gold (or perhaps mercury) with potassium. Such speculations as these, however, are premature, and at present perhaps unprofitable; but the projection of the scientific imagination into the unknown is a

legitimate preliminary to investigation. Facts may cluster round an idea, and crystallise into a general law.

The third of the deductions made is that there must be quantitative relation between the substance administered and the effects observed and a dynamic explanation of such effects.

The establishment of any quantitative relation between a substance introduced into the human system and the observed effects, seems to be a hopeless task, in view of the minuteness of the dose of the powerful poisons, and yet it must be done if therapeutics, or even physiology, is to be correlated with physical and chemical science. When we reflect that a single grain of anhydrous hydrocyanic acid, or of aconitine or strychnine, will destroy life; and try to calculate the proportion of the deadly agent present in the blood as it arrives at the nervous centre upon which it works destruction, the disproportion between cause and effect is bewildering to the imagination, even if we adopt the supposition of accumulation of the poison in a given part of the nervous system. One is tempted to think that the mode in which they act may best be illustrated by such a case as the presence of grease on the rails in front of a locomotive, when the engine, were the steam turned on, would for want of hold tear itself to pieces, or by grit among the wheels of a piece of machinery, which will bring it to a standstill. Here are effects altogether disproportionate to the cause, and to which the doctrine of the correlation of forces does not at first sight seem to apply. In a sense the illustration is just. CO, for example, combining with the hæmoglobin of the corpuscles and preventing the interchange of oxygen and CO₂, may not inaptly be compared to grit in the wheels, and the suspension of function of a part of the nervous system which is essential to life, or the allowing of a vital centre to expend its energy and run down, may perhaps present some sort of parallel to the damage of a valve in a steam engine, or the self-destruction of a locomotive when the wheels do not bite. Or there might be a liberation of stored-up energies, as the touching of a button launches a vessel, or the pulling of a trigger determines the explosion of gunpowder.

But these illustrations cannot be accepted as indicating an explanation of the apparently disproportionate effects of poisonous doses of the alkaloids. The consistency and constancy of the effects of smaller doses, and even more, the modification of these effects, already dwelt upon by changes in the chemical molecule, points to some definite relation between the drug and the special chemical processes concerned in the evolution of nervous energy in the particular centre upon which it acts.

Let us think for a moment what this implies. A grain or two, say, of anhydrous prussic acid is swallowed; a fraction of it is absorbed; the blood by which it is carried receives a first dilution by admixture with the general portal stream from the viscera; again, in the right side of the heart it is lost in the floods of blood arriving by the two *venæ cavæ*. The proportion of hydrocyanic acid in the blood carried to the brain must thus be incalculably minute, but it is sufficient to suspend the action of the respiratory centres, and thus to destroy life within a few minutes, with the accompaniment of frightful convulsions. Or we might take as an instance a fraction of a grain of aconitine injected hypodermically, which will more slowly, but almost more surely, prove fatal by paralysing the heart. Now we cannot admit that these effects are due to the mere contact of the poison with the nerve centres; this would be an absolute negation of the doctrine of the correlation of forces. There must be some dynamic action on the part of the drug—some evolution of energy which interferes with the evolution of nervous energy, or antagonises it; that is, there must be chemical change and dislocation of the constituent parts of the molecule, and this chemical change must be equivalent in amount, and probably opposite in character, to the chemical change which evolves nerve energy. This, if true, is a far-reaching conclusion. It shows that the quantivalence of nerve force is exceedingly small, and, again, that there is some definite relation between the chemical constitution of the poisonous alkaloids and that of the substances contained in the nerve cells, by change in which nerve force is liberated.

There are many other considerations which go to show that nerve force is characterised by intensity rather than quantity, and that its electrical analogue is frictional rather than galvanic, so that I have been led to the conclusion that the nervous impulse which determines muscular contraction is not the transmission of energy but the disturbances of equilibrium.

The sudden evolution of nerve force shows it to be of the nature of an explosion, and this implies chemical tension in the molecule

which yields it. The atoms, were they free to follow their affinities, would arrange themselves differently, just as in nitroglycerine the carbon and hydrogen are held apart from the oxygen by nitrogen and rush together with explosive violence when concussion shakes loose the unstable NO compounds. The absolute necessity of duly oxygenated blood for the functional activity of nerve centres shows that oxygen from outside the unstable nervous molecule takes part directly and immediately in the decomposition and recombination which liberates nerve force. The active nerve poisons should hypothetically, also, be so constituted as to be in a state of chemical tension, and, as far as my knowledge, now very imperfect, extends, they are all of the nitrite type of molecule, which is an extreme departure from the ammonium type in which the affinities of nitrogen and hydrogen are balanced. Successive atoms of hydrogen are abstracted till in amides we have NH_2 instead of NH_4 and in imides NH , and in nitrites N only. This leaves unsatisfied affinity and unbalanced forces which imply chemical tension. The analogy or the contrast of the chemical constitution of the molecule from which nerve force is evolved, and of the molecule of the poison by which nerve force is antagonised, ought to be full of instruction.

It has always seemed to me, if a dynamic explanation of the action of poisons is possible—and such an explanation is a scientific necessity—it should be yielded by prussic acid. Its composition and its constitution are simple. Dynamic change can only have one result—the separation of its atoms, and one tendency—deoxidation, in consequence of the seizure of oxygen by the carbon and hydrogen. The hypothesis which commends itself to my mind, and which I have many times propounded, is that in the presence of the affinities which evolve nerve force the dislocating influence of nitrogen comes into play; the molecule explodes, and its carbon and hydrogen seize upon the oxygen which is necessary to nerve action, and a vital nerve centre is thrown out of gear long enough to destroy life.

This is a thrice told-tale, and I crave your indulgence in once more repeating it. May I also trespass on your patience in again alluding to the fact which presented itself when I was experimenting with this substance, namely, that prussic acid is not a poison to frogs in the same way that it is to warm-blooded animals? When I dropped dilute hydrocyanic acid upon a frog's back, except that it seemed to sting him he took no notice of it unless he were put under a glass shade, when he would gradually become narcotised, but would recover in the open air. When I injected it under his skin he hopped about as if nothing had happened, until again I placed him in a confined atmosphere when both he and his companions were gradually narcotised, showing that he was impregnated with the poison.

My interpretation of this immunity is that the languid affinities concerned in the evolution of nerve force in batrachians fail to bring about the explosion of the hydrogenic molecule.

It is unnecessary to trace once more in detail the steps of our progress in regard to knowledge of morbid processes from the time when disease was looked upon simply as an assemblage of symptoms. First came macroscopic morbid anatomy, which reacted discouragingly on therapeutics. What could any treatment do in the case of lungs excavated by phthisis, or kidneys shrunk to a fourth of their volume, or a brain ploughed up by hæmorrhage? Scarcely less discouraging was microscopic morbid anatomy revealing damage to structure which was unsuspected on naked-eye examination, and cell changes underlying and leading up to tissue changes became the object of study.

It was inevitable that a sceptical attitude of mind should be generated by contemplation of the results of disease. But on the tracks of this registration of results came investigation of processes normal and morbid, experiment coming to the aid of observation, and, as processes were understood and their initiation traced, it became evident that they could be controlled.

To say nothing of inflammation, which in my student days was considered to be simply an affair of blood vessels, and of which the characteristic mark is now believed to be outwandering of leucocytes, while its initiation is coming into view as a dynamic influence. The crowning result, so far, of this persevering inquiry into processes is the discovery of the part which our enemies the microbes play in the production of disease. The influence of some organisms had been inferred in the specific fevers which, with other febrile affections, had been called zymotic, from the analogy of yeast, but Lister's demonstration of the disastrous effects of specific germs on open wounds was a revelation which revolu-

tionised surgical treatment of wounds and rendered possible operations till then undreamt of, and not only has the identification of one pathogenic micro-organism after another placed the zymotic origin of a certain class of diseases on a sure basis, but the study of the conditions governing their multiplication, and of the circumstances favouring or retarding their conquest of the human organism, has placed knowledge in our hands which is of enormous importance in the prevention of these diseases, and has in some, as for example malignant pustule, shown us how they may be treated successfully in an early stage. Already also this knowledge is giving greater precision to our treatment of fevers, and may ultimately enable us to deal with them more effectually.

Koch's discovery of the tubercle bacillus, again, besides extending our ideas as to the range of action of microbes, has brought order into our conceptions of the phthisical process.

But there are facts which are out of reach of explanation by structural lesions and cell changes, and, just as physiological chemistry is necessary in order that the functions of organs may be understood, so pathological chemistry is necessary in order that we may follow the effects of morbid processes.

Diabetes, Bright's disease, and gout, are very old illustrations of the importance of pathological chemistry, but an altogether new field is opening out in the study of the ptomaines and albumoses which appear to be intermediary agents in the injurious effects of bacteria.

The sugar and albumen and uric acid found in the urine, the significant modifications of the urinary colouring matters, are registers of results. In the identification of ptomaines and toxic albumoses we are penetrating into the region of processes.

One word in conclusion on the subject of therapeutic purpose (a phrase borrowed from Sir Andrew Clark)—the guiding idea which is present to our minds in every case we are called upon to treat.

It is of the utmost importance that this should be clear and well-defined and not a mere hazy conjecture or routine rule of thumb, and that it should be based upon positive and if possible personal knowledge and not upon the last *on dit* published in the journals. Therapeutic purpose no doubt is most safe when it is the outcome of registered and ordered experience, but it is most far-reaching when at the same time it rests ultimately on profound physiological knowledge. New and extraordinary morbid phenomena are then most likely to be understood and seen in their true relations, and in emergencies we can aim truly and strike hard because we see clearly.

Our therapeutic purpose, again, should be far-reaching and should have reference not only to the immediate effect but to the future of the patient.

It is one of the characteristics of the charlatan that his great aim is to produce some conspicuous effect regardless of after-consequences, and when these are disastrous he reckons confidently on the ignorance and credulity of the public, and finds it easy to persuade his victims that the very results of his mischievous activity have come about in spite of treatment which ought to have prevented them. How often, on the other hand, do we find a man who treats symptoms only involved in difficulties, the accumulated results of his own work? There is no class of remedies to which these remarks do not apply—purgatives, stimulants, sedatives, narcotics, even tonics.

Our therapeutic purpose, again, ought to have reference to the morbid process which constitutes the disease and not merely to one or more of its effects or conspicuous manifestations. When we find the urine habitually turbid from the deposits of lithates it is not sufficient to clear it by alkalies. The deposit may be due to nothing more than faulty diet or to imperfect digestion, or it may indicate a slackening circulation from heart failure, or the effects on metabolism of organic disease of some important organ. It is very short-sighted treatment of epilepsy, again, merely to give bromides for the repression of the attacks. When the fits are frequent it is a great gain—moral, however, very often, rather than physical—to prevent them, and now and then cases are actually cured, a habit of the nervous system being broken as sometimes a habit of sleeplessness is broken by a few doses of a narcotic. But when the intervals are long the drug given as a remedy has time to work more mischief than the convulsions ever would produce, and the sufferers are brought to a deplorable condition of bodily and mental weakness.

It requires courage and confidence on the part both of physician and patient to forego the immediate advantages which palliatives of various kinds offer, and it is not necessary to forego this altogether if it is borne in mind that they are palliative only and that

a cure must be sought by other means requiring careful and persevering research into the cause of the disease. It is the abuse not the use of such means against which I protest.

While insisting upon the necessity of going behind symptoms, we must admit that not infrequently these must constitute our chief guide. I remember to this day the impression made upon my mind by a paper published many years since on "Functional Medicine," by our President, Dr. Wade.

One more protest I must raise; it is against the rage for new drugs which seems to have taken possession of the profession. This is absolutely fatal to accuracy of observation and precision in treatment. When the action of a remedy has been worked out by such a man as Professor Fraser, we welcome it at once, as was the case with *strophanthus*, and the entire medical world owes him a debt of gratitude; but when the drugs are recommended simply by an advertising chemist, it is humiliating to see their statements command general acceptance. *Podophyllin* is said to act on the liver, and so is *calomel*, but can anyone who has given a moment's serious thought to the subject, or who has observed closely the effects of his treatment, suppose that a dose of *podophyllin* is the equivalent of a dose of *calomel*? I often wonder what we should have said if, having *podophyllin* and *iridin* and *cascara*, we had discovered *rhubarb* and *aloes* and *senna*.

Am I not right in my conjecture that they are most ready to fly to new medicaments who have least knowledge how to use the old and tried ones? May I take the dangerous liberty of indicating the points of my diagnosis of a weak medical man? They are, indiscriminate administration of stimulants in fever, a ready resort to narcotics and sedatives, treatment directed to symptoms only, and a fondness for new drugs with high-sounding names.

I have come down from the heights of scientific speculation to the most prosaic of practical observations. Nothing more remains but that I should renew my thanks to the Council, who have furnished me with this opportunity of giving imperfect expression to ideas which have wandered vaguely about my brain for many years, and thank you for the patience with which you have listened to me.

AN ADDRESS

DELIVERED AT THE OPENING OF

THE SECTION OF PATHOLOGY.

At the Annual Meeting of the British Medical Association, held in Birmingham, July, 1890.

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THE PATHOLOGY OF GASTRIC DYSPEPSIA.

INTRODUCTORY.

INSTEAD of delivering to you an address on one of the many abstract themes relating to the science of medicine, it has seemed to me that I might enlist your sympathies more heartily if I took as my text some disease whose pathology is of present interest, and which has a direct bearing upon every-day practice. Such a subject is "gastric dyspepsia." For while, even recently, there was not perhaps any disease of whose pathology we knew less, much valuable information has of late years been gained, both of what occurs in healthy gastric digestion and of what takes place when its even course is interrupted.

In choosing gastric dyspepsia as the topic of my address, however, I have been actuated not so much by the hope of contributing anything very original as by the desire to present to you a brief synopsis of some of the main facts which have lately come to our knowledge.

The aberrations in the "concoction" or digestion of the food introduced into the stomach being manifold, the name "dyspepsia" has no meaning in the sense of indicating one particular disease. The only significance we can attach to it is that of a not too strictly defined term indicative of something having gone wrong in the reduction of the food to a state fit to be assimilated. There exists, moreover, such intimate sympathy between the different organs concerned in digestion that it is often difficult to say which

is the primary offender; and, once the natural order of events has been disturbed in a particular organ, in how far this tends to modify and interfere with the functions of others.

The impression is, however, I think almost general, that in a large proportion of dyspepsias the first disruption in the natural chain of events takes place in the stomach, and it is to the pathology of these cases and more especially to the form known as "acid dyspepsia," that I would now briefly claim your attention.

Absence of Anatomical Lesion.—There is one fact which appears to be clearly enough made out, namely, that in a large proportion of cases of acid dyspepsia there is no evident anatomical lesion of the organ to which the malcoction of the food can be referred. By the time the stomach of man can be examined after death, unfortunately the alterations caused by the action of its own secretion are so great as in most cases to preclude its minute examination. The superficial part of the mucosa (twenty-four hours after death) has always become more or less dissolved, or otherwise so altered as to render it doubtful whether an abnormality is the result of disease or merely of *post-mortem* causes.

My own experience leads me to place little reliance on the morbid histology of the human mucosa, where, for instance, the condition of the epithelium and glands is a matter of question. It is most difficult to get hold even of an unaltered healthy human stomach. Thinness of the walls is often enough a feature of the stomach in chronic dyspepsias, more especially where the organ is dilated, and Fenwick¹ states that the glands are atrophied in such cases. Sachs² has attempted to show that in chronic feverish states of the body the principal and marginal cells shrink or take on a hydropic swelling. Were the conditions such as to permit of a reliable examination being made no doubt minute alterations would be found, at least in instances of chronic dyspepsia, but in the majority of cases, all matters considered, we are bound to conclude that gastric dyspepsia in the first instance is a purely functional derangement. Of course these remarks refer to instances of the disease not due to the action of acute irritants such as alcohol taken in excess or where the individual is suffering from acute catarrh. I speak at present of the habitually dyspeptic.

Acidity in Dyspepsia.—By the term "acid dyspepsia" I understand a condition in which the individual experiences, some time after the ingestion of food, a feeling of burning pain in the epigastrium; suffers from eructations which impart to the mouth the feeling of acidity; in which digestion of the meal is delayed; and in which the feeling of burning pain is relieved—it may be only temporarily—by the administration of sodic bicarbonate or other such salt with eructation of liberated carbonic acid.

Not only is there a feeling of acidity, but recent researches show, in spite of what has been asserted to the contrary, that an increased quantity of acid is present; and, moreover, that the particular acid to be found in the stomach at a given period after the taking of a meal is often the wrong acid. It is these contingencies which confer the peculiar acid features upon the affection. For our present purpose it is therefore necessary to be conversant with what acids ought to be in the stomach under a given regimen at particular periods, and to know in what quantity they should be found. Let us endeavour to settle these points.

Acids of Natural Digestion.—It is universally admitted that hydrochloric is the acid which confers acidity on the gastric juice. Hirsch³ found the quantity of hydrochloric acid in human gastric juice to be at least 2.5 per mille—a pretty reliable result, seeing that the estimation was made by the approved method of Cahn and v. Mering. After a rich mixed meal, however, the quantity of this acid found in the stomach contents may become greater than it is in the gastric juice itself (3.57 per mille), and new acids make their appearance. The quantity of hydrochloric acid seems to vary with the nature of the diet and the period of digestion at which the observation is made. In the course of natural digestion, however, a large quantity of lactic acid is also forthcoming, and under pathological conditions butyric and other acids may develop, or the acidity may in part be occasioned by acid phosphates.

Under Cahn's direction, Rothschild⁴ has made a number of observations relative to the amount of acidity in the different stages of digestion of meat. The subjects of these observations were himself and a healthy patient. After the administration of

¹ *Atrophy of the Stomach*, 1880, p. 457.

² *Arch. f. exp. Path. u. Pharmacol.* xxiv, 1888, p. 109.

³ *Beiträge zur Bestimmung d. Acidität d. Magensaftes*, Würzburg, 1887.

⁴ *Virchow and Hirsch's Jahresb.*, 1886, i, p. 146.