LECTURES

ON THE

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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I.—THE STANDARD OF HEALTH.—*Concluded.*

Modes of Investigation.—Pathology.—Pharmacology.—Life.—Conditions of Health and Disease.—Effect of Drugs.—Direct and Indirect Action.—Local and Remote Action.—Dose.—Modification of Dose.—Cumulative Action.—Effect of Habit, Climate, Fasting.—Form of Administration.—Effect of Large and Small Doses.—Homœopathy.—Constitution and Idiosyncrasy.—Explanation of these from Experiments on Animals.—Connection of Chemical Constitution and Physiological Action.

DIRECT AND INDIRECT ACTION.—When any drug is taken up by a structure and acts upon it as curare on the ends of motor nerves, we term this its *direct* action. But, as all parts of the body are dependent on one another, some other structure may be affected, not by the action of the drug upon it, but by that which it has exerted on the first part. This is its *indirect* action. Thus, when curare has been given to an animal, it occasionally happens that the nerves going to the respiratory muscles become paralysed before those which go to the extremities. The muscles of respiration then cease to act, the blood is no longer arterialised, carbonic acid accumulates, and, by irritating the nerve-centres, produce convulsions, which cease when the action of the poison extends to other nerves. In this case neither the muscles, the blood, nor the nerve-centres, are acted on directly by the curare. The muscles will contract if stimulated, and, if the lungs be artificially supplied with air, the blood will be arterialised as usual, the convulsions will cease, and life may be preserved. The non-arterialisation of the blood, the occurrence of asphyxial convulsions, and death, are thus due to the *indirect* action of curare.

LOCAL AND REMOTE ACTION.—Before curare could reach the nerves on which it acted directly, it was necessary for it to enter the circulation, but it had no marked action on the spot whence it was absorbed. Other substances, however, produce an effect on the spot to which they are applied, and this may be independent of any effect which they produce after absorption. This is termed their *local* action. Thus strong sulphuric acid taken into the stomach combines with its tissues and forms a slough: this is its *local* action. But besides this, the irritation in the stomach produces through the nervous system a weakening effect on the heart, the circulation stops, and the person dies. It is not the sulphuric acid which has found its way into the circulation and acted on the heart, but the irritation in the stomach conveyed to it through its nerves. This is the *remote* effect of the acid.

DOSE.—The effect produced by any remedy depends on several conditions. The first of these is the *amount existing in the blood* at any given time, which we may call the *actual dose*, to distinguish it from the usual dose administered by the stomach or otherwise, a part of which may not be absorbed, but remain inert at the point of introduction. The action which a drug has on the body is not dependent on its absolute amount, but on the proportion it bears to the body on which it is to act, so that an amount which is a small dose for one person is a very large one for another. Thus if a grain of some active substance be injected at the same time into the veins of a full-grown man and into those of a boy of only half his weight, it will be distributed through twice as much blood in the man as in the boy, and each tissue will only receive half so much of it. The dose of a drug must therefore be regulated by the weight of the patient; and thus women, being lighter, require a smaller amount than men, and children less than adults. Though it would be more exact, it is not always convenient, to weigh patients; but in experiments on animals the weight of the animal should always be carefully ascertained, as well as the amount of the drug administered. If a substance be injected into the veins, the whole of it mixes with the blood and becomes active immediately, and the maximum effect is thus at once obtained, and will again diminish as the substance is excreted. But the case is different if it be injected subcutaneously, and still more if it be given by the stomach or any other mucous cavity; for as soon as some of it is absorbed excretion begins, and thus part of the drug is passing out of the blood while another part is being taken in. The amount in the blood is, then, *only the difference between that absorbed*

and that excreted in a given time, and absorption may be so slow or excretion so quick that there is never a sufficient amount of the substance in the blood to produce any effect. Thus Bernard found that a dose of curare which would certainly paralyse an animal when injected into the veins or even subcutaneously, would have no effect when introduced into the stomach; and Hermann showed that this was due to the kidneys excreting the poison as fast as it was absorbed from the stomach, by tying the ureters, when the animal became paralysed as surely as if the poison had been introduced at once into the veins, though not so quickly. The more rapid the absorption, or the slower the excretion, of any drug, the greater will be its effect. Thus the effect produced by the same dose of a medicine will be in proportion to the rapidity of its absorption from the different parts to which it has been applied, unless the differences be so slight or the excretion so slow that there has not been sufficient time for the removal of any considerable quantity from the blood. On this account we must diminish the dose of a medicine in order to obtain the same effect, according to the rapidity of absorption from the place to which we apply it. Absorption is quickest from a serous membrane, then from intercellular tissue, and lastly from mucous membrane. The vascularity and rate of absorption from intercellular tissue is greater on the temples, breast, and inner side of the arms and legs, than their outer surfaces or back. It should not be forgotten that any drug introduced into the stomach but not absorbed into the blood is as much outside the body as if it were in the hand, for any effect it will have on the system, provided always it have no local effect on the gastric walls. By the differences between absorption and excretion under different circumstances or in different individuals, the cumulative action of drugs, the effect of idiosyncrasy, habit, climate, condition of body, as fasting, etc., disease, and form of administration, can to a great extent, though not entirely, be explained; but experiments on some of these points are deficient, and the explanations now given are to some extent theoretical.

CUMULATIVE ACTION.—If a substance be naturally so slowly excreted from the body that the whole of the dose in ordinary use is not excreted before another is given, the amount present in the body will gradually increase, just like the curare in Hermann's experiment, and will produce an increasing or cumulative effect. Examples of this are to be found in metallic preparations, such as those of mercury or lead, which are excreted very slowly, or in some of the organic alkaloids, such as digitaline, if given in sufficiently large and frequent doses. The size of the dose and the frequency with which it must be repeated in order to produce a cumulative effect will differ according to the rapidity with which the drug is excreted; for, if excretion be rapid, a larger dose, or more frequent repetition, will be required. The long time which elapses before a dose of opium takes effect on some individuals is probably due to its being very slowly absorbed; and the power of one man to take, without apparent effect, an amount of alcohol or opium which would intoxicate another, to its either being more slowly absorbed from the stomach or intestine, or more quickly excreted by the lungs, skin, or kidneys, so that the amount present in the blood at any one time is never sufficient to produce toxic effects. If excretion from the skin and lungs be stopped, as by going from a warm room into the cold air outside, while alcohol is still being absorbed from the stomach, the amount of it in the blood is increased just as with curare, and intoxication ensues.

EFFECT OF HABIT, CLIMATE, FASTING, AND FORM OF ADMINISTRATION.—The effect of habit in lessening the action of drugs may be due to increased power of excretion or diminished absorption; and that of a warm climate in increasing the action of narcotics, such as hyoscyamus, to their excretion being hindered by the diminution in the amount of urine consequent on the increased cutaneous transpiration. A medicine taken by a fasting person is generally more rapidly absorbed and has a greater effect than if the stomach be full, as is well known in the case of alcohol. The form of administration has also an effect on the rapidity of absorption. When a drug is given in a soluble form in small bulk it is more quickly absorbed, and will have greater effect than when given in an insoluble form or much diluted. So a glass of brandy will have a greater and more rapid effect if taken raw than if diluted with a large amount of water; for if three times its bulk of water have been added to it, the stomach must absorb four times as much fluid before the same amount of alcohol could enter the blood-circulation: at the same time the greater amount of water in the blood increases excretion by the kidneys, and thus we have the actual dose of alcohol diminished both by slower absorption and by quickened excretion. It must not, however, be forgotten that the action of alcohol in the blood is complicated by its local effect on the stomach, and this is greater when it is given undiluted.

LARGE AND SMALL DOSES.—The effect produced by a small dose of a drug is sometimes exactly the opposite of that produced by a large

one. We cannot say exactly why it is so; but we very generally find that any substance or any condition, whether it be acid or alkali, heat or electricity, of which a moderate amount increases the activity of cells, destroys it when excessive.

HOMŒOPATHY.—This opposite action of large and small doses seems to be the basis of truth on which the doctrine of homœopathy has been founded. The irrational practice of giving infinitesimal doses has of course nothing to do with the principle of homœopathy—*similia similibus curantur*: the only requisite is that mentioned by Hippocrates, when he recommended mandrake in mania; viz., that the dose be smaller than would be sufficient to produce in a healthy man symptoms similar to those of the disease. Now in the case of some drugs this may be exactly equivalent to giving a drug which produces symptoms opposite to those of the disease; and then we can readily see the possibility of the morbid changes being counteracted by the action of the drug and benefit resulting from the treatment. For example, large doses of digitalis render the pulse extremely rapid, but moderate ones slow it. In this instance its moderate administration when there is a rapid pulse is homœopathic treatment, and this has sometimes been beneficial. But it is not proved that all drugs have an opposite action in large or small doses, and homœopathy, therefore, cannot be accepted as an universal rule of practice.

CONSTITUTION AND IDIOSYNCRASY.—Variations in the action of a drug cannot be entirely explained, however, by the varying amount in which it may be actually present in the circulation and acting on the body. Another modifying element of great power is *constitution*. In animals generally, we have certain arrangements for producing motion, others for the regulation of these, and others, again, for supplying them with the material necessary for the performance of their functions. But the parts which enter into each of these are not equally developed in all animals; in some one part preponderates; in others, another. Even in animals of different species, and in individuals of the same species where the relative size of organs seems the same, differences nevertheless exist; and the presence of a few cells more or less in a ganglion, and a few fibres more or less in a nerve, may alter to a very great extent the action of any substance on the organism. When a medicine given to one person produces an effect slightly differing from that which it generally causes, the difference is said to be due to *constitution*; when its difference is great, it is said to be due to *idiosyncrasy*. Now, these effects may be merely due to differences in absorption and excretion, as has been already explained, or to the different *relative development* of other parts, especially parts of the nervous system. It is easy to understand the altered effect which may be thus produced, and to perceive the ambiguity of such terms as “nervous stimulant”, when we recollect that different parts of the nervous system act exactly in the opposite way to others; and if anything should act on both of these, it will produce an opposite effect according as one or other part is more developed and more powerful. Thus the vagus nerve has the power of rendering the heart's action slow, and the sympathetic of quickening it; and any drug which irritates them both, will make the heart's action slow if the vagus be more developed, or quicken it if the sympathetic be stronger. Thus two horses of unequal strength, pulling in opposite directions, may counterbalance each other; but if both be struck with a whip at the same moment, the power of the stronger becomes evident, and he pulls the weaker after him.

A good example of this action is given by muscarin, an alkaloid obtained from a poisonous mushroom, *Agaricus muscarius*. Professor Schmiedeberg, of Dorpat, has shown that this alkaloid produces great irritation of the vagus nerve, so that in frogs the heart will stand still for hours together. When given to dogs, it sometimes makes the pulse slow, but sometimes it quickens it; and one might therefore be inclined to say that when it produces quickening it cannot be acting on the vagus. But the explanation of this phenomenon is, that muscarin does not act on the vagus alone, but has also an effect on the vaso-motor nerves, producing dilatation of the vessels and diminution of the blood-pressure in them. Now, lessened pressure acts as a stimulant to the sympathetic, and quickens the heart. In this way, muscarin stimulates both vagus and sympathetic, and the pulse is rendered quick or slow according as the power of the one or other is greater in the particular dog to which it is given. In frogs, the blood-pressure has no great action on the heart, and in them the effect of the vagus is not interfered with.

Another instance may be given where an apparent difference in the effect of a drug on two animals may be removed by reducing their organs to the same condition. In most animals, the slowing action of the vagus on the heart is constantly exerted during health; and when it is cut the heart beats much faster. But in the rabbit, its power is comparatively small, and the increased rapidity of the pulse after its division is but slight. In most dogs, on the contrary, its power

is great, and, if it be cut, the heart beats very much quicker, and sends more blood into the arteries, so as to raise the pressure in them. If we measure the pressure of the blood in the arteries of a rabbit and of a dog, and then cause them to inhale nitrite of amyl, we find that the small vessels have become widened and allow the blood to pass easily out of the arterial system into the veins, so that the pressure sinks considerably in the rabbit, but it sinks only slightly in the dog. The effect seems at first sight different; but when we examine it more closely, we find that the heart of the dog is no longer beating slowly, but very quickly, so as to keep up the pressure, notwithstanding the rapid flow of blood through the widened vessels, while the heart of the rabbit was going so fast before that it could not go much more quickly. If we cut the vagi in the dog, so that the heart goes as quickly as in the rabbit before it begins to inhale, the blood-pressure sinks during the inhalation, just as it does in the rabbit.

I have given these examples at length, because of their important bearing on the question how far conclusions as to the action of medicines on man may be drawn from those which they exert on the lower animals. Now, the action of curare in paralysing the ends of motor nerves is one of the simplest and least complicated examples that we can take, as the very nature of its action prevents disturbances in other systems from showing themselves; and we find that it is exactly the same in the Indian who accidentally wounds himself with his poisoned arrow, in the game which he shoots, or in the frog on which we experiment.

Motor nerves, the structure on which curare acts, are alike present in all, and in all are its results the same.

And as we have seen that, in the lower animals, differences in the action of drugs are produced by differences in the structure of the animal, and that the former disappear when the latter are removed, we are, I think, justified in concluding that, when the organs or structures on which a drug acts are similar in man and the lower animals, the action will be alike, and that variations will be observed just in proportion to the difference between his structure and theirs. But as it may be difficult or impossible to detect these differences except from their effects, we ought to test our conclusions as to the action of remedies by giving them to a healthy man, and observing whether their effects are such as we have been led, from our experiments on animals, to expect.

DISEASE.—The different effects of a medicine in disease from those produced by it in health may be partly due to differences in the dose actually present in the blood from altered absorption and excretion, and partly to the alterations produced by disease in other organs, which may interfere with their direct, and probably to a much greater extent with their indirect, action. But what the alterations in each disease, and the ways in which they will modify either the direct or indirect action of remedies, really are, can only be determined by an increased knowledge of pathology and by actual clinical observation.

CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION.—I have spoken thus far only of the changes in the body and the various effects which they produce; but I must not leave this subject without mentioning the wide field of research which has been opened up by the remarkable discovery made by Drs. Crum Brown and Fraser, of the relation which exists between chemical constitution and physiological action. It was known before that one drug would act only on one part of the body, another on another part; but they have shown that changes in the chemical composition of a drug may not only alter its action, but transfer it to a different structure: so the addition of sulphate of methyl to strychnia, brucia, or thebaia, causes them to act on the terminal branches of motor nerves instead of on the spinal cord, while a similar addition to other alkaloids removes some of their actions but leaves others unchanged. Further researches of this kind may enable us to determine what parts will be acted on by a drug after a definite change has been effected in its chemical constitution; and the progress of physiological chemistry in ascertaining the composition and properties of the tissues renders it not impossible that such knowledge may yet be acquired as that spoken of by Locke in the following words. “Did we know the (mechanical) affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file, which by rubbing on them will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep.” And even though our knowledge should never reach this extent, the rapid advances which it has made of late years, the power of altering the chemical composition of the organic alkaloids, and along with it their physiological action, which we now possess, and the fact that one of them (conia) has already been made synthetically, incline us to believe that we may by and bye make substances which will produce the physiological effects which we desire, and that a future lies before therapeutics of which at present we can hardly dream.