LECTURES

ON THE

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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II.—ACTION OF DRUGS ON PROTOPLASM: GENERAL DIRECTIONS FOR EXPERIMENTAL INVESTIGATION.

Modes of Experimenting.—*Caution.*—*Action of Drugs on Protoplasm.*—*Action on Vibrios and Bacteria.*—*Contagium Vivum.*—*Action on Fungi;* on Fermentation; on Putrefaction; on Oxidation; on White Blood Corpuscles; on Inflammation.—*Action of Gases.*—*Steps of an Investigation.*—*Administration of Drugs.*—*Observation of Effects.*—*Interpretation of Results.*—*Minimum Fatal Dose.*—*Various Channels of Administration.*—*Excretion.*—*Mode of securing Animals.*—*Instruments required.*—*Mode of making Cannulae, T-tubes, and Pens.*—*Narcotising Animals.*—*Action of Narcotics.*—*Introduction of Cannulae into Vessels.*—*Injection of Fluids.*—*Division and Irritation of Nerves.*—*Artificial Respiration;* in Mammals; in Frogs.—*Administration of Gases or Vapours.*

GENTLEMEN,—In experimenting on the effect of drugs, our great object must be to localise their action—to be able to say with certainty, This is the organ on which this medicine acts, and such and such is the action which it exerts upon it. There are two ways in which this might be done.

1. We might give the medicine to animals of all kinds, from those consisting of one simple cell upwards to the highest forms of life, and mark how its action became modified as we advanced farther and farther from the simple mass of sarcode, and organ after organ became differentiated and developed. Unfortunately, however, the knowledge of comparative anatomy and physiology which is required to interpret the effects that we might thus obtain is so great, and possessed by so few, that this method is at present of little use.

2. We might take a highly organised animal, not very unlike man in its general structure, and, by operative procedures, allow the medicine to act now on one and now on another part of the body, but never on all at once, till we find out those parts for which it has a particular affinity.

This second method is the one which we chiefly employ, but sometimes we may very conveniently use them both, as in the case of protoplasm, the physical basis of life.

CAUTION.—As I intend not only to describe the ways in which experiments on the action of medicines are to be performed, but also to give examples of the conclusions drawn by various observers from the experiments which they have made and of the way in which these conclusions have been applied, I take this opportunity of strongly warning you, once for all, that you must distinguish very carefully between the observations actually made by any one and the conclusions which he draws from them. Observations on the effect of a drug may be correct, and yet the theory of its mode of action be erroneous; and both of these may be right, and still the proposed application of it to a disease may be valueless from ignorance of its real pathology. All observations, too, are not to be taken as facts: they must be confirmed by frequent repetition either by the first observer himself or by others before they can lay claim to this title. Their value depends to a great extent on the observer, and is in proportion to his power of seeing correctly what is before him, and the exactness of his description of what he has seen. Perhaps erroneous statements are due in great measure to the results of experiments not being noted at the time when they were done, but written down from memory some time afterwards. When this is the case, they lose in a great measure their claim to the name of observations, and they become merely thoughts or ideas of the observer. *All experiments should be noted down at the time when they are performed;* and if they are not, the time which elapsed before they were written should be stated, that future workers may know what value to attach to the observation, and not be put to the unnecessary trouble of disproving it if it be erroneous. Before beginning an investigation, it is convenient to write out the questions which we propose to ourselves, and to note down what experiments will be necessary to answer them. We are thus less likely to make experiments at random, and to waste time without coming to any certain conclusion.

ACTION ON PROTOPLASM.—We may study the action of drugs on

protoplasm either in unicellular organisms like the Infusoria, in cilia, in white blood-corpuscles, or in those minute bodies—bacteria and vibrios—to which attention has of late been so much directed, and which, despite their minuteness, possess so much importance from their power of producing fermentation and decomposition in dead organic matter, and not improbably of causing disease in living beings. For the purpose of studying it in Infusoria, we prepare an infusion of hay some days before we wish to experiment, and a solution in water of the drug which we wish to investigate. We then heat a piece of glass tubing in the middle, draw it out and cut it across, so as to obtain two little pipettes, which will deliver drops of nearly equal size. From one of these we let fall a drop of infusion of hay on a glass slide, and examine it under a low power of the microscope without a covering glass. We then let fall a drop of the solution of our drug upon it, mix the two drops well with a glass rod, and again examine them microscopically to see whether or not the infusorial animalcules are still moving. If they be moving, and continue to do so for some time, we prepare a stronger solution of the drug; but if they have completely stopped when we looked, we make a weaker one, and again mix a drop with one of hay-infusion, repeating the experiment till we have got a solution of such a strength that a slight movement of the animalcules can be observed just after mixing the drops, but ceases almost immediately, and cannot be brought back by adding water. We can then compare the action of different drugs by observing of what strength the solution of each must be, in order to produce precisely this effect.

Professor Binz of Bonn has found in this way that certain substances, such as common salt, chlorate, chloride and bromide of potassium, alum, etc., appear to stop the movements of infusoria by altering the amount of water which they contain, as strong solutions cause them to shrivel at first, and then to swell up and become motionless. Weaker ones make them swell likewise; but their effect at first is different, as they do not shrivel up the animals, but, on the contrary, render their movements more lively.

Other substances kill them in a way which we do not understand, stopping the movements at once without producing any apparent change in the animal's body to account for it. The most active of these substances are chlorine, bromine, corrosive sublimate, iodine, permanganate of potash, and creasote. After these comes quinine, less powerful than they, but far more so than other organic alkaloids. Even strychnia, so fatal to higher animals, has barely one-fourth the power over these lower organisms which is possessed by quinine, a substance which is dangerous to mammals only in such large doses that we are accustomed to look upon it as a remedy, but hardly at all as a poison.

ACTION ON VIBRIOS AND BACTERIA.—If a piece of boiled meat or white of egg be allowed to lie in water for a few days, or a little of Pasteur's solution be exposed in a glass, the fluid becomes milky, and vibrios and bacteria are formed in large numbers. Pasteur's solution is made by dissolving ten grammes of sugar, five decigrammes of tartrate of ammonia, and one decigramme of yeast-ash, in one hundred cubic centimetres of water; or a little white of egg may be added to the hay-infusion, when the infusoria soon disappear, and it remains full of bacteria and vibrios. A drop may now be taken, diluted with another drop of water, and the action of drugs on vibrios examined in the same way as on infusoria.

In this way it is found that the same substances which kill infusoria also prove destructive to vibrios and bacteria: and if they kill these organisms when outside the animal body, they should do likewise when they are inside, and thus cure diseases which may be caused by their presence. Now, bacteria have been said to be the cause of malignant pustule, and they are at all events frequently present in large numbers in the blood of animals affected by it, and their destruction can hardly fail to be advantageous. We are, therefore, not at all surprised to learn that Bouley and the French Commission found (*Compt. Rend.* lxxviii, 82) that, while all animals which they inoculated with this disease died when left to themselves, four recovered out of five to which they had given carbolic acid, and that other cases treated in the same way by others gave a like favourable result. The striking correspondence between the effect actually produced on the disease and that which we would expect from its action on bacteria, which we suppose to be the cause of it, seems also to be an evidence of the truth of the hypothesis that bacteria are the cause of the disease, and that carbolic acid cures it by killing them. Before we accept this as a fact, however, we should test it by adding to one portion of the blood of a diseased animal, carbolic acid in the same proportion as it was likely to be present in the blood of the one cured, and comparing it with another portion to which none had been added, and see whether the amount was sufficient to have any action on the bacteria. If it were not sufficient, we should have to look for some other action of the acid to explain its effect.

As cases of malignant pustule or other diseases in which bacteria and vibriones are found in the blood happily do not present themselves every day, Binz produced fever in dogs artificially by injecting infusion of hay or putrid animal matter into their veins, and then tested the action of quinine by injecting it either at the same time or shortly afterwards. The quinine diminished the effect of the infusion, but not to the extent which he expected; and this he thinks due to the infusion not containing vibriones alone, but gases and other products of decomposition, whose action would not be affected by quinine. Whether this be so or not, must be decided by further experiments. He believes also that hay-fever is due to vibriones; and he cured Helmholtz, who had suffered from it for several years, by injecting a solution of quinine into his nostrils.

ACTION ON FUNGI.—When spores of the ordinary penicillium or mould-fungus are thrown into Pasteur's fluid or syrup, they grow and develop new spores. Two portions must be taken, and the drug to be tested added to one and none to the other, and the amount of it necessary to prevent the formation of spores must be noted. If carbolic acid, corrosive sublimate, or very strong solutions of quinine, be added to them, their growth is prevented.

ACTION ON FERMENTATION.—As butyric fermentation depends on the presence of vibriones and alcoholic on the yeast-fungus, we should expect that substances which kill these would prevent fermentation. To test this, two glass-tubes or flasks are filled with a mixture of milk-water, grape-sugar, and chalk (from which carbonic acid will be set free by the lactic acid formed), or with a solution of grape-sugar or yeast. To one of them a certain amount of the substance to be tested is added, and both are then inverted over mercury and kept in a warm place for several days. The amount of gas developed is then measured; and, if the addition of the substance have hindered the production of gas, we know that it has hindered fermentation in the same proportion. It has thus been found that quinine, amounting to $\frac{1}{180}$ th part of the mixture, completely stopped the development of vibriones or the production of gas; and other substances have a similar effect.

As many cases of indigestion, acidity, flatulence, vomiting, and summer diarrhoea, more especially in children fed by hand, are most probably due to the fermentation of starchy and saccharine food caused by vibriones, Binz thinks that creasote, quinine, etc., are serviceable in their treatment by stopping this. As it is the local action that is wanted, the longer the medicine remains in the intestine before being absorbed, so much the better will its effect be; and thus the greater benefit derived from bark than quinine in some such cases might be explained.

ACTION ON PUTREFACTION.—The antiputrescent action of drugs is tested by putting a square of boiled white of egg into each of two vessels containing water and setting them in the sun. To the liquid in one vessel the drug is added, and the rapidity with which the edges of the square of white of egg on it become decomposed and soft is noted and compared with that in the other vessel. Instead of white of egg, a piece of meat or bread may be used. The relative power of different drugs in stopping putrefaction does not always correspond to the ideas which we would be inclined to form; for who would think that quinine would be more powerful than such antiseptics as creasote, chloride of lime, or arsenic? and yet such is said to be the case. So powerful is quinine, that a piece of meat placed in a solution of $\frac{1}{4}$ per cent. of the sulphate, with a little dilute acid, remained in summer without decomposition till the fluid was dried up.

ACTION ON OXIDATION.—If fresh leaves of lettuce or dandelion are triturated with five or ten times their weight of water, with free access of air, the fluid filtered, and fresh guaiac tincture added to it, a blue colour is produced, showing that ozone is present in it. To test the action of a drug on the formation of ozone, two portions of the filtered fluid are put in test-glasses, and the drug added to one. Both are allowed to stand for one or two hours, with occasional shaking, fresh guaiac tincture is dropped cautiously into both, and by the greater or less depth of blue produced in each fluid we judge of the amount of ozone present in each. In this way it is found that quinine diminishes or stops the formation of ozone in these fluids, and at the same time the little protoplasma-granules with which they abound are rendered motionless and altered in appearance. There seems to be some connection between these protoplasma-granules and the formation of ozone, as the stoppage of the one runs parallel with the alteration in the other.

Quinine seems to have the power of diminishing oxidation within the body as well as out of it, since when injected into the blood it lessens the excretion of urea and diminishes the temperature both in health and disease during life, and hinders its rise after death; and this action is apparently not due to nervous centres regulating temperature, or to changes in the circulation allowing quicker cooling by the skin.

ACTION ON WHITE BLOOD-CORPUSCLES.—To examine this, we take a drop of blood from the finger, put it on the under surface of a thin glass, and lay it over the opening in Stricker's warm stage (Stricker's

Histology; New Sydenham Society's Translation, p. 13), and examine it with a high power of the microscope, such as Ross's $\frac{1}{2}$ or Hartnack's No. 10, at a temperature of 98° F. After satisfying ourselves that the white corpuscles are in active motion, we take a solution of the drug in fresh serum, or in half per cent. solution of common salt; mix a drop of it with the blood and examine again. Or we may use Max Schultze's warm stage, which consists of a flat piece of brass covering the stage of the microscope, and having a long arm projecting at each side and a thermometer in front. When a lamp is placed under one or both arms, they conduct the heat to the middle part on which the object lies, and thus warm it to any desired temperature. The drop of blood must be placed on a piece of glass three and a half inches long and two and a half broad, which is then laid on the warm stage. The drop is next covered by a thin glass, and over all is put the lower part of a lamp-cylinder, through whose upper end the tube of the microscope slides, and round whose interior is put a piece of moist blotting-paper to prevent evaporation from the blood. The drug is applied as with Stricker's stage. Solutions of corrosive sublimate and veratrin, even in very minute quantity, stop the movements of the white blood-corpuscles, but neither is so active as quinine. Strychnia is rather less powerful than any of these, and many other alkaloids much less so.

ACTION ON INFLAMMATION.—During inflammation, the white blood-corpuscles are very active, and crawl through the walls of the capillaries in much greater numbers than usual. It is, therefore, interesting to inquire what will be the effect on this of any drug that stops their motions. For this purpose we curarise a frog and lay it on a large plate of cork with a hole at one side, and another piece of cork half an inch high at the other. We fix the body of the frog to the raised piece, open its abdomen with a pair of scissors, draw out the intestines, and fasten the mesentery with very fine pins over the hole. In an hour and a half or two hours afterwards, white corpuscles come rapidly out of the vessels and wander over the field. We may then inject our drug into the circulation or apply it locally to the mesentery.

Binz states that, when he injected quinine into the circulation, the number of corpuscles in the vessels became diminished, and they ceased to wander out, while those already out continued to wander further, so that, instead of being evenly distributed over the field, they left a clear space round the outside of the vessel, in which few were to be seen. If, on the other hand, it be applied locally, the corpuscles which are already out stop moving, while those in the vessel continue to migrate, and thus, instead of a clear space, a dense accumulation of corpuscles forms round the vessel. In order to produce this effect, $\frac{1}{250000}$ to $\frac{1}{200000}$ th of the animal's weight of quinine is necessary; and, if it were given to a man weighing 150 lbs., in order to stop the exit of corpuscles from the vessels in such a disease as peritonitis, three or four drachms of the medicine would require to be given within a short time. Binz's observations as to the effect of quinine on the white corpuscles have been confirmed by Martin, but have been denied by Schwalbe, so that farther investigations on this point are very desirable.

ACTION OF GASES.—This is examined by putting the cells to be examined on Stricker's warm stage, and bringing the gas into contact with them in the manner described by him (Stricker's *Histology*, Sydenham Society's edition, p. 8).

STEPS OF AN INVESTIGATION.—The animals which we chiefly use in experiments are frogs, rabbits, guinea-pigs, and dogs. In investigating the action of a drug, we examine—

1. What the symptoms are which a large dose produces.
2. Taking the most prominent symptom, we inquire (a) On what organ does the production of this symptom depend? (b.) How has it been affected by the drug? (c.) Has this affection been primary or secondary?
3. We examine other organs which we think may have been also affected.

ADMINISTRATION OF DRUGS.—To examine the general effect of a drug, we weigh the animal and then give it a large dose in our first experiment, in order to get exaggerated symptoms. It may be given by the mouth or by subcutaneous injection. In frogs, the substance may be injected either under the skin of the back or into the abdominal cavity. In rabbits, etc., it is most conveniently injected under the skin of the flank. In guinea-pigs, the abdominal parietes are very thin; and, if we wish to compare experiments with different doses, care must be taken not to push the point of the syringe into the abdominal cavity, as the absorption will be then more rapid, and the same dose produce a greater effect. If we wish to give the medicine by the mouth, we either put it well back on the root of the tongue and then hold the animal's jaws together till we think it has swallowed it, or we put a perforated cork between its teeth, push an elastic catheter through the hole in the cork down the œsophagus into the stomach, and inject the drug in solution through the catheter. Orfila used to introduce the drug into an opening in the œsophagus, which he then ligatured to prevent vomiting;

but since subcutaneous injection was introduced this method is rarely employed.

OBSERVATION OF EFFECTS.—After the drug has been administered, we allow the animal to move freely about, but prevent frogs from escaping by covering them with a large bell-jar. We then see whether the animal is restless or disinclined to move; whether its movements are perfectly performed or unsteady; whether or not its legs seem weak and paralysed, or convulsive movements or involuntary twitchings be present; whether its heart-beats or pulse, and respirations, are quick or slow, strong or weak; whether there is vomiting or purging diuresis; salivation; or dryness of the mouth; flow of tears, or dry conjunctiva; and whether the pupil be contracted or dilated. If the animal seem asleep, we pinch it to ascertain if reflex action continue after voluntary motion is gone; and if respiration cease, we ascertain if the heart still continue to beat. As soon as possible after death, we open the animal and see if the heart still be beating. If it have stopped, we note whether its cavities are full or empty, its walls flaccid or firm, and try whether it will still contract or not on pinching or scratching it, or on irritating it by an electric current. We observe whether the veins are turgid or empty, the lungs pale or congested, the stomach and intestines quiet or in active peristaltic movement, the spleen large or contracted, the bladder full or empty; and the urine may be tested for sugar.

INTERPRETATION OF RESULTS.—If we find in the course of these experiments that voluntary motion is increased or lessened, we may naturally conclude that the activity of the cerebrum is increased or diminished, unless the increase of motion should depend on pain, or its diminution on impairment of the motor apparatus. Unsteady movements, paralysis or convulsions, impaired reflex action on pinching, or stoppage of respiration before the heart, point to the spinal cord, to the nerves, or to the muscles; while quick or slow, strong or weak pulse, or stoppage of the heart before the respiration, point to the vaso-motor system or cardiac nerves; increased or diminished secretion, to secreting nerves; and full or empty bladder, and diminished or increased peristalsis, to the motor nerves of the bladder or intestine. We then try the effect of a small dose, and note in what respects it differs from that of a large one. We thus ascertain in a general way what the organ is, which is chiefly acted on by any drug, and afterwards proceed to investigate the nature of the action by a farther series of experiments.

MINIMUM FATAL DOSE.—If the drug be poisonous, we then try to ascertain the minimum fatal dose. For this purpose we weigh an animal and inject into it a dose which we think will not prove fatal, wait a short while, and then inject more till death is produced. We then reckon how much of the drug has been injected for every pound weight of the animal. We take another animal, and inject into it *at once* a quantity which will be somewhat smaller for its body-weight than that given to the first. The reason why a somewhat smaller quantity should be taken is, that some time was allowed in the former experiment for the excretion of part of the poison between each dose. If this amount prove fatal, we must give a still smaller quantity to another animal; but, if not, we must give more till we find the smallest quantity which will kill.

VARIOUS CHANNELS OF ADMINISTRATION.—The next point to be determined is, whether the effects are the same when given by the mouth or rectum, or other mucous surfaces, as by subcutaneous injection. If we should find, as Bernard did with curare, that a substance which is active when injected subcutaneously or into a vein, has no effect when introduced into the mouth, rectum, eye, or bladder, we must determine whether this is due to want of absorption or to decomposition of the drug by the secretions with which it becomes mixed. This is done by mixing it with these secretions, such as urine or gastric juice, allowing it to stand some time at the temperature of the body, and then injecting the mixture subcutaneously, and observing whether the usual effect is produced or not; or by ligaturing the ureters to prevent excretion.

EXCRETION.—Lastly, we examine in what manner it is excreted from the body. As most solids are excreted by the kidney, we generally restrict this process to evaporating the urine, or testing it either chemically or by injecting some of the extract into another animal.

[To be continued.]

DR. H. O. STEPHENS, having resigned as Resident Medical Superintendent of the Bristol Lunatic Asylum, Stapleton, has obtained from the Town Council of Bristol a retiring allowance of £250 per annum upon the recommendation of the Committee of Visitors and the Commissioners in Lunacy, the latter of whom spoke in high terms of Dr. Stephens's "devotion to his duties and the success which had attended his efforts."

CLINICAL LECTURE

ON A

CASE OF STRUMOUS OPHTHALMIA, AND ON ONE OF SCIATICA.

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GENTLEMEN,—The two cases which I bring before you to-day may seem sufficiently diverse; yet I think, on a little consideration, you will see that the differences are superficial; and that, beneath an external dissimilarity, there exist some very real resemblances. The chief reason, however, why I have put them together, is to afford me the opportunity of saying a few words as to the management of tedious and difficult neuroses.

CASE I.—E. W., aged 10, admitted June 19th, 1869, was transferred to my care July 5th, 1869. She stated that she had suffered with her eyes since she was twelve months old. They had been cured two or three times, and had again become diseased. She was in St. George's Hospital for seven months in the summer of 1868, and, when discharged, she could see pretty well. This improvement continued four months, and then her eyes passed into their present state. She said that a cataract was removed from each eye while in St. George's. She had previously been in Moorfields Hospital. She suffered from toothache at times, but had no other special ailment. There were two or three markedly decayed teeth, but she ate her food fairly well. Her photophobia was extreme. When I first saw her, she sat before me with both eyes bandaged up thickly, and also her hands over her eyes. She affirmed that she saw light when her hands were removed. The first few days after she came in, she used to lie with her head buried in the bedclothes; she did not do this now. She was, of course, in a darkened ward. She never opened her eyes day or night. She did not sleep soundly at night, but often woke up. Much lacrymation occurred. When questioned, she said distinctly that it was the light that hurt her eyes; she was more comfortable in the dark. The urine was pale, feebly acid, not albuminous; pulse 123, weak.

September 10th. She was put under the influence of chloroform, but it was with difficulty that anaesthesia was produced. The lids, on being everted, were found non-granular; their lining membrane very red. An opacity was found on the left cornea; none on the right.—Nov. 5th. By this date she had left off her shade, and walked about all day without it. There was much contraction of the corrugator supercilii muscles, much frowning and lacrymation; the latter occurred especially when she was questioned by myself or clerk, but not when the ward-sister spoke to her. She also sneezed a great deal. By December 4th, she had improved much in general condition, had got fat and strong, and went then to a convalescent home at Hanwell. From this she returned in a month greatly improved. She looked up steadily, and faced the light quite well. There was nothing apparently amiss, except some tinea tarsi of the right side. She remained now as an out-patient till March 19th, when her eyes were becoming irritable again, as she was ill fed and cared for. There were moderate opacities on both corneae; nevertheless, she could make out a pattern of leaves and sprigs etched on glass. Since then I have not seen her.

The amount of improvement obtained in this case was very great, but it came very slowly, especially at first, and was interrupted by frequent relapses. Again and again one felt inclined to give up the treatment in despair. But the result proved that, with fair play, a cure was perfectly feasible, and that perseverance in the use of appropriate means was all that was requisite. I should weary you if I enumerated all the remedies that were employed; I need only say that they were nutritious food and the ordinary stimulants and tonics, frequently varied, and aided to some extent by local applications. Of the latter, I think free douching with cold water had the best effect. Instillation of strong solution of sulphate of atropia did good for a few days only; nor did aconite lotion or chloroform-vapour avail perceptibly. Some temporary benefit was obtained by the extraction of some decayed teeth, but it was of short duration. A fair trial was given to bromide of potassium when the disorder was at its worst, but it had no good effect; neither had small doses of potassio-tartrate of antimony, which are much praised by Dr. Mackenzie. When convalescence was fairly commenced, much good was done by change to a purer air; and I doubt not that this would have been of great benefit at an earlier period. The nutritious diet was of course a necessity; but I by no