LECTURES ON THE EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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I.—THE STANDARD OF HEALTH.

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.

GENTLEMEN,—The usual mode of investigating the action of a remedy is to give it to a patient during an illness and observe what changes occur in the symptoms after its administration. But it not unfrequently happens that medicines are given without any distinct change in the symptoms ensuing; and, even when one does take place, we very often cannot be sure that it is due to the medicine, and not to the course of the disease or some other modifying cause. For, if the remedy and the disease are both at work together, it is obviously impossible for us to decide what part of the result is due to the one and what part to the other, if we neither know what the course of the disease would have been had the medicine been given, nor what action the medicine would have had if the disease had not been present. Any attempt to investigate the action of a remedy by giving it under such circumstances is like that of a rifleman to learn shooting by practising only at dusk, when he cannot see the butt, much less the bull's eye. He might go on practising for ever in this way without making any improvement; for, when he missed, he would never know whether it was because he had not seen the mark properly or had not aimed steadily at it. If he wish to learn, he must practise by daylight, when he can clearly see the mark, and can thus be sure that every miss is due to unsteady aim. He will fire high or low, to one side or the other, as he finds necessary, and, by gradually correcting every error, his aim will at last be sure. Should he then be called on to stand sentry on some dark night, and shoot at some suspicious object without hitting it, he would know that his failure was due to his not having seen the object distinctly, and having consequently aimed in a wrong direction. And just as the rifleman, before he stands sentry in the dark, must learn to shoot by daylight, when he can note the effect of each alteration in the position of his rifle on the course of the bullet, so ought we to investigate the action of our remedies in circumstances and under conditions which we know and can vary at will, marking the effect of each variation upon their action till we thoroughly and exactly understand what it is, before we proceed to give them in disease, when not only the conditions under which they operate are at present in a great measure unknown, but the effects they produce cannot be definitely ascertained from insufficient knowledge of what the result would have been had they been withheld. Of late years, it is true, vigorous efforts have been made to determine what course diseases run when not interfered with by medicines; and, although it is often difficult to say what the sequence of symptoms will be in any particular case, depending as it does not only on the general course of the disease, but on individual peculiarities of the patient and on the varying circumstances in which he is placed, we may nevertheless ascertain with tolerable accuracy whether or not our treatment is beneficial in a general way, even when we cannot determine its effects in detail.

Very inexact and very unsatisfactory as such a knowledge of medicines as this necessarily is, it must for the present be our guide in practice in a large number of instances; and our treatment at present and for some time to come will be chiefly empirical, because our knowledge of pharmacology, and perhaps still more of pathology, is not yet sufficiently advanced. For there is hardly any disease in which we know the exact nature of the morbid changes which are occurring, or the precise organs or tissues which are their seats; and, with some exceptions, we are but very imperfectly acquainted with the structures on

which our remedies act, and the exact mode in which these are affected by them. Day by day, however, our ignorance is diminishing; and we may hope that ere long rational treatment will to a great extent supersede blind empiricism. It not unfrequently happens at present that we meet with a case which bears a very close resemblance to others which we have treated successfully, and which nevertheless obstinately resists the remedies which we had previously found serviceable. Our failure astonishes and vexes us; but we are ignorant of its cause, and we can only select some other drug by guess and try it: we cannot at once choose the one which will have the desired effect.

PATHOLOGY.—In order to choose a drug which will have the effect that we desire to obtain, we must know where the morbid changes are taking place, and what their nature is; and we must be sure that our medicine will act on the affected part, and in such a way as to counteract the disease. We must trace every symptom which we see, back to its unseen source; every flush on the cheek, every quickening of the pulse, back to the vaso-motor or cardiac nerves, which have allowed the capillaries to become dilated, and thus produced the redness, or have permitted the heart to beat more rapidly than its wont. We must then inquire what has produced this alteration in the nervous system, and so on, till at last we discover, if possible, the hidden cause of the mischief. We will then give that remedy which will act in the proper way on the part which we believe to be the seat of the morbid process; and, if the expected result does not ensue, we shall, at any rate, have discovered what the pathology of the disease is not; and, by trying a remedy which will act in a different way or on a different structure, we may find out what it really is.

When I speak of the pathology of a disease, I do not mean those obvious alterations in the structure of an organ which we meet with in *post mortem* examinations, but the so-called functional changes which precede and are the cause of both them and the symptoms. For example, the disorganisation of a man's liver by the presence of an abscess, or of his kidneys by fatty degeneration, is not the disease from which he suffered, any more than a field strewn with slain or crowded with heaps of wounded is a battle. The disease was the alteration in the nervous and vascular systems, and in the nutrition of tissues, which we call the inflammatory process, and which produced the abscess and degeneration, and the disturbance of the same systems to which these lesions in their turn give rise; just as an army may not only lose the battle for want of the assistance which its slain and wounded would have given, but its retreat may be embarrassed by their presence.

The insufficiency of present modes of treatment, and the urgent necessity which exists for an accurate knowledge of pathology and pharmacology, are shown by the manner in which any new remedy is seized upon and applied in all sorts of cases, even in those where a knowledge of the morbid processes going on, and of the action of the remedy itself would at once have indicated that harm, and not benefit, must ensue from its application. It is unnecessary to discuss here the manner in which pathology must be studied in order that an accurate knowledge of it may be obtained: I may merely indicate as examples the works of Cohnheim, Brown-Séquard, Sanderson, Stockvis, Stricker, and many others.

PHARMACOLOGY.—In studying pharmacology, our first object is to find out on what structures a remedy acts. For this purpose, it is of no use to give it to a man either sick or well. We may do so in order to find out what general symptoms it produces; and from these symptoms we may guess at the structures affected; but, in order to convert our hypothesis into certainty, we must apply it to these structures or organs, and to them alone, and see whether the general result is the same; or we may prevent it from reaching them while it is applied to all other parts of the body, and observe whether the effect is absent. For this purpose, we cut off from one or other parts of the body the supply of blood which carries the drug along with it, or we may so injure the part that its function is abolished, and no action exerted upon it can produce any effect. But it is impossible to do this in man, and so we must have recourse to the lower animals, in which we can produce at will the conditions we desire. Although the administration of medicine to a patient is really an experiment, we vary the conditions in which it acts to so much greater extent in animals, that it is convenient to call the latter mode of investigation the *experimental method*, and the former that of *clinical observation*.

Now pathology and pharmacology may go on hand in hand both in teaching and study, but they must always be preceded by physiology; for, unless we know the processes which take place in the healthy organism, it is impossible to understand the changes they undergo in disease, or the effect of drugs upon them. I will, therefore, here say a few words regarding the processes in which life consists, before proceeding to speak of the mode in which they may be modified by the action of remedies.

LIFE.—We meet with life only in certain bodies composed of carbon combined in a very complicated manner with oxygen, hydrogen, and nitrogen; and it may, generally speaking, be said to be the power which these bodies possess of assimilating to themselves other substances, of decomposing them, and of evolving energy, which is shown in active motion, active growth, etc. Evolution of energy in this way is the distinguishing mark of life. When we look at a grain of wheat, an egg, or a dried wheel-animalcule, we are unable to say whether or not it is alive; it is only when it begins to evolve energy, either by moulding other substances into conformity with its own constitution in active growth, as in the seed or egg, or by active motion, as in the animalcule, that we are able to decide the question. We cannot say how these bodies originally came to possess their complicated constitution and wonderful powers; but the evolution of energy by which we recognise the continued presence of life seems to be more intimately associated with chemical affinity than with other forms of energy, such as light, heat, or electricity. All these forms of energy modify the processes which occur in living beings, both those which are chemical and those which we term vital, and apparently in much the same degree; but whether they modify the vital only through the chemical, we are at present unable to say. Instances may readily be found in which life continues active, although one or other of the forces mentioned is not supplied to the living body from without, and is only secondarily present as a result of chemical changes going on within. Thus a seed in the earth, a fungus in a cellar, or a proteus in its dark cave, live and thrive without a ray of light; and the whale and walrus in the Arctic seas are independent of any external heat, their temperature being only maintained by combustion taking place within their own bodies. But there seems to be no instance of vitality alone continuing active when a stop has been put to the occurrence of chemical changes. Sometimes both chemical and vital processes are suspended together for a time, as in a grain of wheat or a rotifer when it is kept dry, or in an egg when kept cool and coated with varnish to exclude air. So long as chemical activity remains dormant, no other form of energy can awake the latent vitality. Only when the conditions necessary for chemical transformation of the proper kind and amount are supplied, does it again become manifest. Thus light or heat may be applied in any amount or any proportion to an egg, a seed, or a dried rotifer, and still they will not grow or move if the air be withheld from the former or the moisture from the two latter, which is essential for the production of chemical changes within them.

CONDITIONS OF HEALTH AND DISEASE.—These changes of which I have been speaking consist in the assimilation of certain substances, their decomposition within the organism, and the rejection of waste products. A due proportion between these constitutes health. Just as a fire can only be kept bright by raking out the ashes and supplying fresh fuel as that in the grate burns away, so an organism can only be kept healthy by removing the products of waste and supplying fresh nutriment as its tissues get decomposed during action. The conditions necessary for this purpose are secured in the simplest forms of life, such as the amoeba, by the little mass of protoplasm moving about in a fluid which can supply the oxygen to keep up combustion and evolve energy, and the nourishment necessary to replace the material thus used up, and can at the same time remove the products of waste. In higher organisms, the little masses of living material of which they are composed, and which are for the most part fixed, are nourished by a fluid in which they are bathed, fresh portions of it being supplied by its constantly flowing over them, instead of their moving like the amoeba through it.

It will simplify our conception of this subject if we fix in our mind's eye one little mass of protoplasm or cell, and consider what changes will be produced in it by different conditions. Any alteration in the amount of the nutrient fluid, or in its composition, will necessarily produce a change in the nutrition of the living matter to which it is supplied. If nutriment be withdrawn, the cell will begin to burn away. If oxygen be withheld, or the products of waste be not removed, combustion will cease, and the cell will die. If nutriment or oxygen be supplied in insufficient quantity, or the products of waste only partially removed, the cell may adapt itself to the altered circumstances, and its nutritive and functional processes go on in the same way, but to a less extent than before; or they may become deranged—that is to say, the cell becomes diseased. The limits within which the cell can adapt itself to changes in nutrition are the limits of its health. The higher animals, however, are no mere aggregation of cells, each nourishing itself independently of the others; for each cell has its own peculiar function, each its special kind and amount of nourishment; and none must do either too much or too little work, none must have too much or too little nourishment, or the nutrition and functional activity of the body as a whole cannot be properly main-

tained. This delicate adjustment of the several parts to one another is secured by means of the nervous system, which regulates at once the activity of any organ, the quantity of nutritive fluid supplied to it, and the amount of material it shall take up. The means by which it acts are, its direct influence on the nutrition of cells themselves, as is seen in the salivary glands; or its indirect action through the circulation in slowing or quickening the heart, which propels the blood, in contracting or dilating the vessels which convey it to any part, or the capillaries which allow the actual nutritive fluid or lymph to filter out and bathe the tissues. Besides thus regulating the supply, it also regulates the composition of the nutritive fluid by maintaining a due relation between the activity of the body, the supply of new material by digestion, and the separation of effete products by the excreting glands. On account of this mutual dependence of all the parts of the body on one another, if one gets wrong, it puts the others out of order. Thus a sudden chill may act on the vaso-motor nerves, and cause contraction of the vessels of the skin; and the blood they contain is thus thrown back on the internal vessels, and congestion and inflammation of the kidneys ensue. In consequence of this, they no longer excrete as they ought the effete products, which then accumulate in the blood, react on the nervous system, and this again on the muscles; and so the circle goes on. In the case supposed, the renal arteries have not had power to contract sufficiently to resist the increased pressure and prevent congestion; while in another they might have done so, only allowing so much blood to pass as to increase secretion, and, by thus lessening the fluid in the blood-vessels, to counteract the effect of vascular contraction in the skin, restore the normal pressure, and preserve health. When all the organs are able to accommodate their nutrition and function to great alterations, we say the health is strong; but when they can only do so to slight ones, we say the health is weak; and when this is the case with one organ alone, we say that it specially is weak.

EFFECT OF DRUGS.—The nutrition of a cell may not only be altered by changes in its supplies of nutriment and oxygen; but it may be modified or destroyed by the addition of certain substances to the nutrient fluid. Thus a weak solution of alkali may increase or diminish the rapidity of the changes which it undergoes, by hastening the removal of waste products if they be acid, or retarding it if they be alkaline; while a weak acid will have an opposite effect. Certain metallic salts may stop them altogether by forming a firm compound with the substance of the cell, while other bodies may enter into combination with it for a time (possibly replacing some ordinary ingredient of its nutriment), again passing out and leaving it in its primitive condition, but altering during their stay its physical characters and functional properties. Such seems to be the case with curare, which, when injected into the blood, paralyses the peripheral ends of motor nerves; but, if life be preserved by artificial respiration, the poison is excreted, and its effect passes off. No change can be noticed in the nerve-fibres, either by the naked eye or microscopically, during the paralysis; and this was supposed to show that great functional alterations may occur without any structural change. But this is not the case; for Kühne (Stricker's *Histology*, Power's translation, vol. i, p. 221) has ascertained that, when the ends of motor nerves in muscles are examined microscopically, their outline is found to be more distinct during the action of the poison. It is possible that the change in physical properties shown by this distinctness of outline may be only the indication of some more important alteration in their chemical composition; but, whether it be more chemical or physical, a change at any rate takes place; and to this, I believe, we must attribute the alteration in function.

Whatever be the composition of protoplasm, the substances which are associated with it in the composition of different cells are at any rate different; and, although the same nutritive fluid is supplied to them, they do not all take out from it, or give out to it the same substances in the same proportions, but some take up more of one thing, and some more of another. And they do just the same with drugs added to the nutritive fluid. Thus lime-salts naturally exist in the blood, and are carried by it to every part of the body; but, while the bone-cells take them up in large amount, nerve-cells assimilate an almost infinitesimal quantity. And if we feed an animal on madder, which has an affinity for lime-salts, the bones become deeply stained, while the nerves and fat retain their normal colour. It is possible, too, though experiments on this point are wanting, that a substance added to the nutritive fluid may be taken up by two structures, but may have a very different effect on the one from what it has on the other; just as a grain of sand, which would have no effect on the machinery of a locomotive, may totally stop the movements of a watch. We do not know whether sulphocyanide of potassium and curare are taken up equally by nerves and muscles or not; but the former salt will paralyse the muscles without affecting the nerves, while curare will paralyse the nerves, but leaves the muscles intact.

The cells composing one structure, then, take up and are acted on by some drugs, and not at all by others; while other structures are much affected by the very substances which had so little action on the first.

[To be continued.]

CLINICAL LECTURE

ON

THE USE OF THE LARYNGOSCOPE.

Delivered at the Manchester Royal Infirmary.

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GENTLEMEN,—Many of you have witnessed the use of the laryngoscope in my out-patients' room, and in the wards of this hospital. But as its use requires a certain amount of skill in manipulation, not all at once acquired, I think it is desirable to give you some general directions, which may clear up a few difficulties, and shorten the period required to render you its masters. It is scarcely necessary to say anything in the way of apology for so doing. The aid given by the laryngoscope in the diagnosis and treatment of disease is now acknowledged by all who know anything of the matter. No doubt there are practitioners still living who decry its merits, just as all means of physical diagnosis have in their turn been decried. Auscultation and percussion have almost, but even now not quite, emerged from this condition. The thermometer is not so generally used as it will be; and I have heard of an ophthalmic surgeon still living, who "does not believe in the ophthalmoscope." But if you meet with a case of hoarseness with partial loss of voice, as I have done, which has been treated for nineteen years in London and the provinces with internal medicines and external blisters, etc., and find, on looking into the larynx, that the supposed chronic laryngitis is due to a tumour attached to one of the vocal cords, you will learn to appreciate the value of the laryngoscope. Although its employment is at first a little difficult, and although some never acquire the dexterity of others, there is no reason whatever why it should remain in the hands of the few, or why it should not become the familiar companion of the many. And though there are valuable monographs and papers in our own language, such as Czermak's, translated for the New Sydenham Society, Dr. Morell Mackenzie's, Sir Duncan Gibb's, etc., besides numerous others in French and German, I am induced to give you, as students, some familiar and practical remarks on the mode and manner of its successful employment. And this for two reasons; one is that, while students, you will perhaps scarcely find time for the study of monographs on what some of you may consider a by-subject; and the other, that they are rather intended for the practitioner than for the student.

The history of the laryngoscope need not detain us. Like most other discoveries, it has had foreshadowings, some more distinct than others; but the claim of Dr. Babington, as being the first who used a laryngeal mirror at all resembling those now employed, is very strong. This was in 1829. Dr. Czermak, of Pesth, however, has done more than any one else to bring the instrument into general use. Without dwelling further on its history, which you will find in the monographs referred to, I will proceed to the more practical question as to the best mode of using the laryngoscope.

First of all, you require a lamp, for ordinary daylight is not sufficiently intense, sunlight is too rarely available, and moonlight—which Sir Duncan Gibb states that he has experimentally ascertained to be more suitable than daylight—is still less to be commanded. In towns and, indeed, in most villages, you have gas, which is the most convenient light you can obtain. An Argand burner is the best for our purpose. In the out-patients' room, we use an arrangement devised by Dr. Morell Mackenzie, consisting of a double arm, carrying an Argand burner, which can be raised and lowered by means of a rack, and also moved horizontally. The burner is provided with a metal chimney, which shuts in the light on all sides but one, where a plano-convex lens is placed to act as a concentrator of the light. In the wards, we use a German reading lamp with an Argand burner and Tobold's condenser. In my consulting room, I am in the habit of using a similar lamp with Dr. Mackenzie's portable light-concentrator, which you see here. There are various other concentrators in use, but you will find Mackenzie's or Tobold's sufficient for all your requirements. Mackenzie's

is portable, and by means of the side clips can be adapted to any lamp with a chimney of ordinary size, or even to a candlestick. It gives moreover a good light. Tobold's gives a somewhat whiter light, but is more bulky, and not so easily adapted to any but the reading lamp with upright stem. It could not be used, for example, with a moderator lamp, which answers extremely well for the laryngoscope, and to which Mackenzie's is perfectly suited. One great advantage of the reading-lamp is, that the upright stem allows of the light being raised and lowered. It is, moreover, always ready for its ordinary purpose when not required for special use. I saw a case in consultation the other day, where the gentleman in attendance on the patient brought a Bockett's lamp for the microscope, which answered sufficiently well for the laryngoscope.

You need, moreover, a reflector and a set of laryngeal mirrors, with one or two for examining the posterior nares. The reflector is a slightly concave circular mirror, about three inches and a half in diameter, sometimes perforated near the centre with an oval opening about half an inch long in the horizontal direction, and a quarter of an inch wide, and sometimes without perforation. This difference depends on whether you wear the mirror on the forehead or in front of the eye. If worn on the forehead, of course no aperture is required. There are various modes of fixing it, as by the forehead-band, the mouth-piece which Czermak at first used, and the strong spectacle-frame of Semeleder, which Dr. Morell Mackenzie and others use. Of these, the last is in my opinion the best. It is easier with this to fix the reflector quickly in the proper position, than with the forehead-band. The latter is elastic and very comfortable in use, but this elasticity itself renders the adjustment of the mirror a little troublesome. You place it as you think correctly, with a good light thrown in the right direction, but find that, on removing the hand, the mirror starts aside and requires a further adjustment.

Many skilled laryngoscopists, as Dr. G. Johnson, use the reflector on the forehead; but there are disadvantages in this position which do not obtain when it is worn in front of the eye. A very palpable one is that both eyes are exposed to the full glare of the concentrated light from the lamp. This is disagreeable and almost painful, and interferes much with our comfort in examining the larynx. To avoid this, some wear a shade, but this tends to complicate a simple matter, and make it look formidable, or at any rate fussy. There is, moreover, a theoretical objection to the position on the forehead, from the eye not being in the axis of the rays reflected into the throat. Without laying too much stress on this, I have myself a strong preference for the other position as a matter of comfort and convenience. Here, moreover, the line of vision and the rays from the reflector coincide. But a great practical advantage is, that both eyes are shaded from the glare of the lamp. If it be placed to the left of the patient, and the reflector before the observer's right eye, this is protected in consequence of the angle at which the rays from the lamp fall, and the reflector will be found, also, an efficient shade for the left eye likewise. The French are much in the habit of using direct illumination of the throat, and so of doing away with the reflector. But this apparent simplicity is really complex and troublesome. The lamp, provided with a lens, and having the side next the observer shaded, is placed on a small table between the observer and the patient. A good light is thrown into the throat, but the position of the physician is somewhat cramped by having an arm on each side of the lamp, and his face very near it. It is possible, indeed, to see the larynx with direct light not sufficiently powerful to be used with a reflector, but generally speaking the latter is preferable.

There is one mode of using it which has greater illuminating power than any other, and is admirably adapted for demonstrating the larynx. I refer to the oxy-hydrogen light, the use of which, by the courtesy of Dr. Mackenzie, I have had opportunities of seeing at the Hospital for Diseases of the Throat. As this, however, is only suited for special institutions, and not for private practice, we may pass on.

Assuming that you use the reflector, place the patient in a chair in front of you. The lamp must be on a table on one side. I prefer it on the left and near the patient's elbow, and I place the reflector in front of the right eye. The flame should be about the level of your eye, and the patient's head at the same height as your own. Now direct him to open his mouth, and so arrange the reflector as to throw a broad disk of light on the back of the fauces. You may find in your early trials that this brilliant light is a sort of will-o'-the-wisp, or *ignis fatuus*, and most apt to elude you when it seems securely fixed. The control of the light, indeed, is one of the most difficult of the preliminary acquirements necessary. A little practice, however, will enable you so to accommodate yourself to the slight movements of the patient, that you will soon be able to keep the light exactly where you wish. Now ask the patient to put out the tongue freely, but not uncomfortably, keeping the mouth well open. Then with the left hand,