LECTURES ON THE EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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IV.—DETERMINATION OF THE EXACT STRUCTURES THROUGH WHICH DRUGS AFFECT THE HEART AND VESSELS.

Comparison of the Effects of Drugs on different Animals in different Doses.—Mode of determining the Exact Cause of Symptoms.—Mode of raising Blood-pressure.—Modes of counting the Beats of the Heart.—Causes of Quickened Pulse.—Direct Stimulation of the Sympathetic.—Stimulation of Cardiac Ganglia.—Paralysis of the Vagus-roots and Fibres, and of its ends in the Heart.—Causes of Slow Pulse.—Irritation of Vagus-roots.—Mode of supplying the Head and Body with different kinds of Blood.—Indirect Irritation of Vagus-roots through the Blood-pressure: mode of lowering and raising it.—Reflex Irritation of Vagus-roots.—Indirect Irritation through the Respiration.—Irritation of Vagus-fibres.—Increased Conducting Power of Fibres.—Stimulation of Vagus-ends.—Paralysis of the Sympathetic.—Paralysis of the Cardiac Ganglia.—Part of the Ganglionic Apparatus Affected.—Nervous System in the Heart.—Motor Ganglia.—Stimulating Ganglia.—Inhibitory Ganglia.—Connecting Apparatus.—Action of Drugs on the Inhibitory Apparatus—Nicotia, Muscaria.—Antagonism of Atropia and Physostigma: bearing of this on Therapeutics.—Paralysis of Co-ordinating Apparatus.—Paralysis of the Muscular Fibres of the Heart.—Blood-pressure: mode of determining whether changes in it are due to alterations in the Heart or Vessels.—Elimination of the Action of the Heart: Division of its Nerves.—Irritation of Vagus.—Ligature of Aorta.—Artificial Circulation; in Mammals, in the Frog.—Observation of Vessels.—Action on Vaso-motor Centre; on Vascular Walls.—Influence of the Action of Parts surrounding the Vessels upon them.—Action of the Pulmonary Circulation on the Blood-pressure.—Use of the Sphygmograph.

ACCELERATING GANGLIA IN THE HEART.—We infer the presence of quickening ganglia in the heart, from the effects produced by irritating the vagus after its inhibitory power has been destroyed by the administration of nicotia or atropia. When irritation is then applied to the nerve, it no longer produces retardation, but, on the contrary, a decided acceleration of the cardiac pulsations. This shows that the vagus contains fibres which quicken the heart, and that these are unaffected by the drugs which have paralysed the others. The quickening, however, does not take place till some time after the application of the irritant; and, if it be applied only for a short time, no acceleration may take place till after its removal; but, after it does occur, it remains for a considerable time. If we irritate the heart directly, instead of irritating the nerve, its beats are quickened at once, and the acceleration does not last long after the irritation is discontinued. This shows that, when we stimulate the quickening nerves, we do not act directly on the motor ganglia *M* (Fig. 12), as we do when we irritate the heart itself, or as we should do if the quickening fibres ended directly in them; and we therefore infer the existence of the accelerating ganglia *Q* between the quickening nerves *S* and the motor ganglia *M*. The accelerating apparatus seems to be stimulated by veratria; for we find that the cardiac pulsations are increased by its administration to mammals in which the spinal cord, vagi, sympathetics, and depressors, have all been divided, or when it is applied to the excised heart of a frog.

IS QUICKENING OF THE EXCISED HEART DUE TO PARALYSIS OF INHIBITORY OR STIMULATION OF ACCELERATING GANGLIA?—It is possible that the quickening may be due to paralysis of the inhibitory ganglia in the heart, and not to stimulation of the quickening ganglia. This can be decided by paralysing the inhibitory ganglia by means of atropia, before administering veratria. If the latter poison exercise a stimulating action on the quickening ganglia, it will quicken the heart after atropia has been applied. If it simply paralyses the inhibitory ganglia, it will have no further effect after the power has been destroyed by atropia. In the diagram, I have figured intermediate structures *C* and *D* between the quickening nerves and ganglia, so as to correspond with those of the inhibitory apparatus; but whether they really exist or not, we cannot at present say.

IS THE CO-ORDINATING APPARATUS OF THE CARDIAC GANGLIA

PARALYSED?—Regarding this apparatus we know almost nothing. When the heart is dying, its rhythm is often disturbed, and two or three contractions of the auricles may occur for every contraction of the ventricle. When laudanum is poured into the heart, the rhythm is quite reversed; for after each pause the ventricle contracts first, and contraction of the auricle follows it. Digitalis and some other poisons cause peristaltic movements in the ventricle; and occasionally some spots in the ventricle continue to pulsate while the rest of it remains firmly contracted and motionless. These effects are probably due to disturbance of the apparatus which connects the different motor ganglia in the heart and causes them to work in unison.

ARE THE MUSCULAR FIBRES OF THE HEART PARALYSED?—We test this by applying an irritant to them directly, and seeing whether or not they contract. If the motor ganglia be uninjured, the application of an irritant generally produces a rhythmic contraction of the whole heart; but, if they be paralysed while the muscular fibre is healthy, the irritation only causes a local contraction of the part to which it is applied.

BLOOD-PRESSURE.—The blood-pressure depends on two things—1, the activity with which the heart pumps the blood into one end of the arterial system; 2, the rate at which it flows out at the other end into the veins. The rate is regulated by the small arteries and capillaries, which dilate and contract so as to quicken or slow it. The power of contraction is denied to the capillaries by many physiologists; but Stricker has, I think, conclusively shown that they do possess it.

The rapidity with which the blood flows through them does not depend entirely on the width of the capillaries, but also on the pressure on the arteries which is forcing the blood into them. The higher this is, the more rapidly does the blood flow; and in proportion as it diminishes, does the current become slower. From this circumstance we can judge of the force of the heart-beats from the form of the curve which we obtain with the sphygmoscope. When the heart contracts with great force, it drives the blood out of the ventricle into the arteries so quickly that there is no time for much to escape from the capillaries while the systole lasts; and so the tension rises high. This increased tension makes the blood run quickly out of the capillaries, and we have a fall of pressure, rapid at first, but gradually becoming slower as the tension diminishes. This is shown in Fig. 13. When the heart

Fig. 13.

contracts less forcibly, it sends in the blood more slowly, and there is time for a greater quantity to escape by the capillaries during the systole; and the tension does not rise so high. From the tension being lower, the outflow of blood is not so quick; and the pressure therefore sinks more gradually than in the former case. This is represented in Fig. 14. Both of these figures were obtained by connecting a sphyg-

Fig. 14.

moscope with a schema of the circulation such as I have already described, and compressing the India-rubber ball which represented the heart with greater or less force and suddenness; care being taken, however, to empty it completely each time, so that the amount of air sent out should always be alike.

As variations in the blood-pressure may be due to alterations in the activity of the heart or the size of the capillaries, or to both together, we cannot say when it is due to the one and when to the other, unless we can keep one of them constant while we allow the other to alter, or unless we examine them both separately.

ELIMINATION OF THE ACTION OF THE HEART.—We may keep the action of the heart tolerably constant, and thus ascertain with considerable exactitude the action of any drug on the exit-tubes—whether they be arterioles or capillaries matters not—by separating the heart from the nerve-centres, and then injecting the drug into the circulation.

DIVISION OF CARDIAC NERVES.—This separation can be effected to a considerable extent by dividing the sympathetics, vagi, and depressors in the neck; but it is done much more effectually by dividing

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the nerves near their entrance into the heart by a fine wire heated by means of a galvanic battery.

As poisons generally produce their most marked effects on the heart of mammals through the nervous centres whose connexion with the heart we have thus severed, alterations in the blood-pressure will be due to changes in the vessels, except in so far as the drug may have affected the cardiac muscle or ganglia. But, just as we obtained the most exact results when we examined the heart altogether apart from the blood-vessels, so we shall probably come to the most satisfactory conclusions regarding the vessels by observing them apart from the heart. You will remember that, during the diastole, the circulation is carried on entirely independently of the heart by the pressure of the blood in the arteries; and, if we can prolong the diastole sufficiently, we shall be able to tell whether the vessels are dilated or contracted by simply seeing whether the pressure sinks quickly or slowly.

If we prevent any blood from being pumped into the aorta by the heart, the arterial system will come to resemble a bottle with a hole in it, from which the fluid which it contains is running. The larger the hole, the more quickly will it run out and the bottle become empty, and *vice versa*; and, in the same way, the more dilated the capillaries are, the quicker will the blood run out of them into the vein, and the pressure sink in the arteries; the more contracted the capillaries are, the more slowly will the blood flow through them, and the more gradual will be the fall of pressure. In the case of many poisons, we may do this by irritating the vagi before poisoning, and seeing how quickly the pressure falls while the heart is standing still; and then repeating the experiment after injecting the poison. If the pressure fall more quickly in the second case, we know that the vessels have become dilated; and if more slowly, that they have contracted. Of course, only those parts of the tracings in which the pressure has been the same are to be compared with each other; but, if we stop the heart long enough, we can always get parts in both which are capable of comparison.

When the poison paralyses the vagus, as atropia does, this method fails; and then we must open the thorax, perform artificial respiration, and put a ligature round the aorta.

ARTIFICIAL CIRCULATION IN MAMMALS.—As an animal quickly dies when the aorta is ligatured, it is better to carry on artificial circulation by a syringe through a cannula inserted into the aorta, as Hering and Horvath have done in their researches on the connexion between arterial movement and respiration. This method I have already described. After the blood has circulated once, it may be defibrinated, shaken with air warmed to 40 deg. Cent., and reinjected. Instead of using a syringe, the cannula in the aorta may be connected with the nozzle M, Fig. 6, and the blood put in the flask 3. It can thus be kept at a constant temperature more

easily than when a syringe is employed. The pressure may be alternately increased and diminished so as to imitate the beats of the heart by raising and depressing the flask A. This may be done by passing a string over a pulley, and attaching one end to the flask and the other to a treadle worked by the foot. Warm blood has the disadvantage, that it undergoes change and becomes decomposed quickly; and cold blood may, therefore, be sometimes preferred. When cold blood is employed, only the flask which contains the blood is necessary; and it may be raised or lowered in the same way as the other.

ARTIFICIAL CIRCULATION IN FROGS.—Artificial circulation may be kept up in frogs by simply inserting a cannula into the aorta, and allowing blood to flow into it from a raised reservoir, as done by Rollett. By using two, as in the experiments on the frog's heart, normal blood may be allowed first to circulate through the vessels; and, the web being put under the microscope, their diameter may be measured; and then poisoned blood may be allowed to flow through them, and any change in their diameter noticed.

OBSERVATION OF VESSELS.—The parts best adapted for observing

changes in the size of vessels in mammals are the ear in rabbits and the mesentery. When the mesentery is chosen for observation, the abdominal parietes should be divided; but the peritoneum should not be opened, as changes in the diameter of the mesenteric vessels may be observed through it, and they are thus protected from the disturbing element which the irritation produced by the access of air to them would introduce into the experiment. The vessels in the rabbit's ear are readily measured by a micrometer used with one of Brücke's magnifiers, which is simply a telescope with an extremely short focus. The ear should be held up so as to allow the light to shine directly through it, and the magnifier placed horizontally.

The area of the capillaries may be lessened, and the flow of blood through them retarded in two ways; 1, by contraction of their walls; 2, by pressure exerted on them from without. They may be made to contract by irritation, 1, of the vaso-motor centres, 2, of the vaso-motor nerves, or, 3, of their muscular walls; and pressure may be exerted from without by the motions of muscles or of organs composed of involuntary muscular fibre such as the intestines. The movements of respiration also, as already mentioned, exercise an important influence on the pressure.

ELIMINATION OF RESPIRATION AND MUSCULAR MOVEMENT.—The influence both of respiration and of muscular movement may be eliminated by giving the animal curare, and keeping up artificial respiration, before beginning to experiment with the drug whose action we wish to examine.

ELIMINATION OF VASO-MOTOR CENTRE.—For the purpose of ascertaining whether the drug has acted on the vascular walls or on the vaso-motor centre, we divide the vaso-motor nerves going to a part before injecting it, and see whether it acts as it would have done had they been undivided. Thus, when we are observing the rabbit's ear, we divide the sympathetic in the neck; and, when looking at the mesentery, we cut the splanchnics before the injection, and see whether the vessels contract or dilate as we have previously seen them do under influence of the poison in animals in whom the nerves were intact.

For the purpose of ascertaining whether the drug acts on all the vessels in the body in the same way that it does on those of the ear or mesentery, we first cut the vagi, sympathetics, and depressors; and then divide the spinal cord between the occiput and atlas, or atlas and axis, so as to sever the connexion between the vaso-motor centre and vessels, and begin artificial respiration. We next note the blood-pressure, inject the poison, and see what alterations it produces. Experiments may also be made by irritating the vagus or ligaturing the aorta.

ACTION OF SURROUNDING PARTS.—It sometimes happens, as in the case of physostigma, that the drug produces no contraction in the vessels of the ear or mesentery when their nerves are cut—a fact which shows that it acts on them through the vaso-motor nerves, and not directly on their walls; and nevertheless, when injected into a vein after the cord has been cut, it may cause the blood-pressure to rise very considerably. At first sight, this would seem to indicate that the drug acted on the walls of some vessels in the body, if not on those of the ear or mesentery, directly, and not through their vaso-motor nerves. On examination, however, it is found that the obstruction to the flow of blood through the capillaries does not depend on their contraction, but on the occlusion of a large number of them in the intestine by spasmodic contraction of the intestinal walls in which they are imbedded.

INFLUENCE OF THE PULMONARY CAPILLARIES.—It has lately been pointed out by Holmes that when a drug such as ergot, which acts on the walls of the vessels and causes them to contract, is injected into the jugular vein, it has to pass through the pulmonary capillaries before it reaches the systemic ones; and, by contracting them, it will lessen the amount of blood sent into the aorta from the left ventricle, and will at first produce a fall in the arterial pressure, succeeded by a great rise when time has elapsed for the drug to reach the systemic capillaries and cause them likewise to contract.

USE OF THE SPHYGMOGRAPH.—For a description of the sphygmograph and the mode of applying it, we must refer to the special works on that subject, such as those of Marey and Sanderson. The indications which it gives are the following. 1. The greater or less pressure which is requisite to compress an artery and stop its pulsations enables us to estimate approximately the amount of pressure within it. The amount of pressure and the rapidity of the pulse help us to form conclusions regarding the motor and inhibitory apparatus of the heart, in the same way as in the experiments already mentioned, though, of course, to a much more limited extent and with much less certainty. 3. The form of the curve, like those in Figs. 13 and 14, shows, in the same way as those of the sphygmoscope, Figs. 13 and 14, the rapidity with which the pressure falls during the diastole; and from this curve and the amount of blood-pressure we can judge of the size of the capillaries.