LECTURES

ON THE

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

BY T. LAUDER BRUNTON, M.D., D.Sc.,

Joint Lecturer on Materia Medica, and Casualty Physician, at St. Bartholomew's Hospital; etc.

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 Vasomotor 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.

COMPARISON OF THE EFFECTS OF DRUGS.—Before proceeding to examine separately the different structures through which a drug may act on the blood-pressure, it is advisable to compare the effects which it produces on animals of different kinds, such as dogs and rabbits, as well as the action of larger and smaller doses on animals of the same kind. Continuing to take as an example the action of atropia, admirably investigated by Von Bezold, we find the following results.

With a small dose of atropia injected into the jugular vein towards the heart:

The blood-pressure rises in both rabbits and dogs:

The pulse becomes quick, rising in rabbits from 256 to 288; in dogs, from 80 to 240.

With a larger dose:

The blood-pressure, in both rabbits and dogs, falls at first and afterwards rises to the normal.

The pulse becomes quick in both.

With an additional dose:

The blood-pressure in rabbits falls very low as the poison reaches the heart; afterwards rises; and falls again below the normal.

The pulse becomes slower, and then quicker.

With a very large dose:

The blood-pressure sinks instantly in both rabbits and dogs.

The pulse in rabbits becomes slower and weaker, and then stops; in dogs, it becomes quick.

This comparison between the effects which atropia produces in different animals, and in large and small doses in the same animal, shows us that it sometimes raises and sometimes lowers the blood-pressure, but that it always quickens the pulse, except when a large quantity of the poison is introduced at once into the heart of the rabbit. On consulting the table already given (BRITISH MEDICAL JOURNAL, June 3rd, page 583), it will be seen that quickening of the heart may be due to stimulation of the sympathetic, either directly by the drug or indirectly by diminution of the blood-pressure; to stimulation of the cardiac ganglia; or to weakening or paralysis of the vagus. Any one of these conditions may cause quickened pulsation; and, in order to determine which of them really does it, we must test each one of them separately by farther experiment.

MODE OF DETERMINING THE EXACT CAUSE OF SYMPTOMS.—The plan which we follow is this: we suppose for the time being that the

cause which we are testing is the true one, and consider what effects it will produce under certain conditions. We then supply these conditions experimentally, and see whether or not the results we obtain correspond with those which we should find if our supposition were correct. So in the present instance we first ask, Is the quickening of the pulse due to indirect stimulation of the sympathetic roots by diminished blood-pressure or not? We suppose for the moment that it really is so, and we consider that if we raise the blood-pressure we shall remove the cause of quickening and bring the pulse down again to its normal rate. We then proceed to raise the pressure, and see whether or not the pulse is rendered slow, as we expect it to be. In the case of atropia, a special experiment is not necessary for this purpose, as we have seen that small doses do not lower but raise the blood-pressure, at the same time that they quicken the pulse; consequently the quickening cannot be due to indirect stimulation of the sympathetic. Other drugs, however, such as nitrite of amyl, even in small doses, lower the blood-pressure at the same time that they quicken the pulse; and in their case we must raise the blood-pressure artificially.

MODE OF RAISING BLOOD-PRESSURE.—This may be done either by injecting a sufficient quantity of the defibrinated blood of another animal of the same species, warmed to 98 deg. Fahr., into the carotid or crural artery towards the heart, or by compressing the aorta. The aorta may be either compressed by the thumb of the operator, or by a narrow pad of cork laid over it and pressed upon it by a tourniquet, of which the strap has been passed round the animal's body.

MODE OF COUNTING THE BEATS OF THE HEART.—Now, if we wish to determine the blood-pressure at the same time with the pulse-rate, we may count the latter from the oscillations which each beat of the heart produces in the tracing of the kymographion, or from the sphygmoscope attached to it; but this is not always necessary, and we may wish to ascertain the pulse-rate without going to the trouble of opening an artery and using a manometer. We may do this in three ways—1. By feeling the pulse in one of the large arteries, such as the crural, with the finger; 2. By listening to the beats of the heart with a stethoscope; 3. By the motion of a needle stuck into the ventricles. For this purpose a fine harelip-needle is inserted at the point where the apex beats, and is pushed upwards into the substance of the ventricle. At its upper end it may have either a knob, or a loop to which a thread can be attached, and a barb at the point will prevent it from changing its position in the heart when traction is made upon it. In rabbits, the point where the needle should be inserted is in about half an inch to the left of the sternum in the third intercostal space, and the length of the needle used should be about three inches. Various means have been proposed for counting the oscillations more readily than can be done by simply watching the movements of the needle itself. The knob of the needle may be allowed to strike against a wineglass, and the pulsations may thus be counted by the ear; or a needle without a knob may be used, and a rice-straw with a piece of bright-coloured paper attached to it may be slipped over it, so that its vibrations, amplified by the long straw, and made more visible by the bright-coloured paper, may be readily counted by the eye.

A convenient way of registering the oscillations on an upright cylinder is one devised by Professor Stricker. One of Marey's cardiographic levers is fixed on a rod close to the side of the animal and some distance above it, and a small piece of cork attached to the lever. One end of a fine thread is then fastened to the needle, and its other end pulled through a slit in the cork till it is sufficiently tight to make the lever vibrate with each movement of the needle; it is then fastened by twisting it round the lever, or by a little sealing-wax. If the lever be not raised several inches above the needle, it is pulled too much to a side and not sufficiently downwards to give a good tracing. The tracing may be taken either on plain paper with a glass-pen or camel's hair-brush attached to the lever by a piece of cork, or with a dry point on smoked paper. Instead of a vertical cylinder a horizontal one may be used, and is perhaps still better. In this case the lever should be nearly on a level with the needle, and not raised much above it.

IS THE QUICKENING OF THE PULSE DUE TO DIRECT STIMULATION OF THE SYMPATHETIC?—If so, the injection of the drug should cause an increase in the pulse-rate after the vagi have been divided as well as when they are intact. We, therefore, divide the vagi, inject the drug into the veins, and see whether or not the pulse-rate is increased. On doing this with atropia it is found that the pulse becomes slower rather than quicker, showing that the drug does not stimulate the quickening nerves of the heart. The increased rapidity of the pulse which it produces when the vagi are intact is, therefore, not due to this cause.

IS THE QUICKENING DUE TO STIMULATION OF THE CARDIAC GANGLIA?—The experiment just mentioned shows that it is not, for if it were, injection of atropia should cause quickening after division of the vagi. Supposing, however, that it had caused quickening, the question

whether the acceleration was due to the ganglia or the sympathetic would have to be decided by dividing all the nerves going to the heart with a platinum-wire heated by electricity, and then injecting the drug, or by applying it to the heart of the frog in a way which I shall afterwards describe. If it quickened the beats of a heart thus separated from all other nerves, it could only do so by acting on the cardiac ganglia themselves.

IS THE QUICKENING DUE TO PARALYSIS OF THE VAGI?—The exclusion of the other causes leads us to believe that it is due to this; but, in order to avoid the possibility of error, we must try to confirm our conclusion by other experiments; and, moreover, we have still to find out which part of the vagus is affected—its roots, its fibres, or its ends in the heart.

ARE THE VAGUS-ROOTS PARALYSED BY THE DRUG?—We are enabled to answer this question by our knowledge of the fact, that poisons only act on the parts to which they are carried by the blood, and that when introduced into the circulation they do not reach every part of the body at once, but are carried on with the blood-stream first to one part and then to another, and will reach a part near the point where they were introduced before one which is farther off. Thus if we inject a drug into the carotid it will be carried direct to the head, and will act on the medulla oblongata and the roots of the vagus before it reaches the heart; but if we inject it into the jugular vein it will reach the heart and act on the vagus-ends in it before it reaches the roots in the medulla. If atropia paralyse the vagus-roots, then its injection into the carotid towards the head should be followed by rapidity of the pulse more quickly than its injection into the jugular; but if it act on the vagus-ends in the heart, the pulse should become rapid more quickly after injection into the jugular vein towards the heart than after injection into the carotid. On testing this experimentally, it is found that, when atropia is injected into the jugular vein towards the heart, the pulse at once becomes quick, even before the injection is finished; but, when it is injected into the carotid towards the head, the pulse is not quickened for a quarter of a minute or more, or, in other words, till the poison has had time to pass through the capillaries of the head and go through the veins to the heart. This, then, shows that it is the vagus-ends in the heart, and not the roots in the medulla, that are paralysed by it.

ARE THE VAGUS-FIBRES PARALYSED?—From the rapidity with which paralysis of the vagus occurs after atropia reaches its ends, we have already come to the conclusion that the ends are the part affected rather than the roots or fibres; but it is well to substantiate our conclusion by further experiment. We divide the vagus and galvanise its peripheral extremity. If we do this to a normal vagus, the heart will beat more slowly or stand still altogether; but if either the fibres or ends of the nerve have been paralysed, no change will be produced in the heart's rhythm by the application of galvanism to its trunk, and this we find to be the case after the administration of atropia. But this experiment does not enable us to decide which part of the nerve is paralysed—the fibres or the ends, for in either case the effect would be the same. We may do this, however, by observing the effect which irritation of the vagus-trunk produces on such of its fibres as do not go to the heart. If it were the fibres which were paralysed, we should expect that those which go to the heart would not be the only ones affected, but that those going to other parts would be paralysed likewise.

I have hitherto spoken of the vagus as if it were a simple nerve containing only inhibitory fibres for the heart, but it is really a most complicated bundle, containing centripetal fibres having probably no fewer than eleven different functions, and centrifugal ones having nine or ten; so it is little wonder that it has long been a puzzle to physiologists, and even yet its functions are not completely investigated. Among these fibres are some which produce contraction of the oesophagus and muscles of the larynx; and if we find that irritation of the vagus continues to produce contractions in these parts after it has ceased to render the heart's action slow, as is the case after injection of atropia, we conclude that the fibres are not paralysed. Dr. Rutherford has shown that the best mode of observing the effects of irritation of the vagus on the muscles of the larynx, is to open it in front and place the animal so that the light may be reflected from the inner surface of the arytenoid cartilage, as the slightest movements can then be readily detected. In this way it is found that atropia produces complete paralysis of the cardiac branches of the vagus, while the others are unaffected; and we are forced to conclude that it acts not on the fibres but on the ends of the heart. A more direct method is to apply the drug dissolved in an indifferent fluid, such as half per cent. solution of chloride of sodium, to the vagus itself, and then to irritate the nerve above this point, and see whether the irritation produces its usual effect. This may be done by dropping the solution on the nerve after placing a piece of gutta-percha tissue below it, so as to keep the fluid from reaching the tissue below and being absorbed.

HOW DOES A DRUG RENDER THE HEART'S ACTION SLOW?—We have now gone over the experiments which are necessary to determine what the structure is through which a drug quickens the heart's action, and we have now to consider those which we require when investigating the action of one which renders it slow. It may do so by irritating the vagus-roots, fibres, or ends; by increasing their excitability, so that they act more strongly when stimulated; or by paralysing the sympathetic, the cardiac ganglia, or the muscular substance of the heart itself.

DOES IT ACT BY IRRITATING THE VAGUS-ROOTS?—In order to answer this question, we divide both vagi and then inject the drug. We thus separate the heart from the vagus-roots and deprive them of any influence over it, so that, if they have been the cause of slowness of the pulse in previous experiments, it will not occur in this; but if the slowness have been due to other causes it will, with one or perhaps two exceptions, be noticed in this experiment just as it would had the vagi been intact. These exceptions, which we will consider afterwards, are increased excitability of the vagus-fibres and ends. The vagus-roots can only act on the heart through the medium of the fibres and ends; if the drug itself should affect these structures, its action on the heart may be much altered or even destroyed. If the vagus-ends be paralysed, the roots can exert no more action on the heart than they can after we have cut through the trunks; and if the excitability of the ends be increased, the power of the roots over the heart will be greatly augmented, so that the heart's action may be made slow without there being any actual irritation either of the roots or ends. In order, then, to find out what effect the drug has on the vagus-roots themselves, we must inject it into the carotid, so that it may reach them before it reaches the fibres or ends; and note what change occurs in the heart-beats immediately after injection. This is the effect of the drug on the roots themselves; and, by comparing it with the pulse-rate a quarter of a minute or so afterwards, when the drug has reached the vagus-ends, we may discover whether their excitability has been increased or diminished. Thus, in the experiment already mentioned for ascertaining whether or not the vagus-roots are paralysed by atropia, we find that, when we inject it into the carotid, we get immediate slowness of the pulse, showing that the vagus-roots are irritated by the drug; but whenever it gets round to the heart it paralyses the vagus-ends, and the slowness at once disappears. If we were to keep the head alive by supplying it with an artificial stream of blood containing atropia, and prevent any of the poisoned blood from reaching the heart, the slowness might be continued indefinitely.

MODE OF SUPPLYING THE HEAD AND BODY WITH DIFFERENT KINDS OF BLOOD.—In his researches on respiration, Hering employed a method of this sort, at one time supplying the brain with blood loaded with carbonic acid while the blood of the body was richly arterialed, and at another sending arterial blood to the brain while respiration was stopped and the blood circulating in the body was intensely venous. For this purpose he opened the thorax and tied the left carotid and innominate close to the aorta, and the vena cava superior close to the heart in a cat; he then introduced one cannula into the innominate artery, and another into the vena cava, and injected dog's blood, defibrinated and warmed, into the innominate artery, while he allowed it to flow out by the vein.

In atropia, we have an example of a drug which acts on more than one part at once, and whose action on one part completely neutralises the effect which its action on the other would produce. In the case of others, however, we have the action on the different parts strengthening each other, as in veratria, which, like atropia, stimulates the vagus-roots, but, instead of paralysing the ends, increases their sensibility, and thus greatly augments the effect which the excited roots would have exercised over the heart, even had the ends remained unaltered.

ARE THE VAGUS-ROOTS IRRITATED DIRECTLY BY THE DRUG OR INDIRECTLY THROUGH INCREASED BLOOD-PRESSURE?—Along with the slow pulse, produced by the injection of atropia into the carotid, a rise occurs in the blood-pressure; and how are we to determine whether the irritation of the vagus-roots is due to this increase, or to the direct action of the drug itself? This is a question very difficult to solve in the case of atropia, on account of the rapidity with which the vagus-ends are paralysed and all influence of the root over the heart destroyed. In the case of other drugs, however, where time is allowed, the question might be settled by diminishing the blood-pressure and seeing whether or not the slow pulse returned to its normal rate, and then raising it again and observing whether the pulse again became slow.

MODE OF LOWERING AND RAISING THE BLOOD-PRESSURE.—The blood-pressure may be lowered by opening a large artery, such as the carotid or crural, and allowing the blood to flow out into a vessel warmed to 98 deg. Fahrenheit, and again raised by injecting the warm blood back into the artery. Or we may adopt Ludwig and Asp's plan, of inserting into the central end of the carotid a straight tube with a

stopcock in its middle, and the moist bladder of a small animal, well emptied of air, tied to its free end. When the stopcock is opened, the blood rushes from the carotid into the bladder, and the tension in the arteries is diminished; but, when we press the blood out of the bladder back into the arteries, the tension on them is again increased.

ARE THE VAGUS-ROOTS IRRITATED REFLEXLY FROM SOME OTHER PART OF THE NERVOUS SYSTEM?—There are two ways of deciding this: the first is to inject the poison in such a manner that it shall reach the vagus-roots before it reaches the other nervous structures through which we suspect it to act reflexly; the second is to remove these nervous structures themselves, or to destroy their function by means of some other poison. Thus, if we think that atropia, when injected into the carotid, acts on the medulla through the cerebrum, we may either remove the latter, or abolish its function by opium or chloral. The application of irritating vapours, such as ammonia or tobacco-smoke, to the nasal mucous membrane of a rabbit, produces still-stand of the heart. We ascertain that this is due to irritation of the vagus by cutting it and finding that the vapour then has no effect; and we next decide that the irritation is conducted to the nervous centres through the trigeminus and not through the olfactory nerve, by observing that section of the former likewise prevents the action of the vapour on the heart, while section of the latter does not affect it.

ARE THE VAGUS-ROOTS IRRITATED INDIRECTLY BY THE DRUG IMPAIRING RESPIRATION, AND THUS ALLOWING CARBONIC ACID TO ACCUMULATE IN THE BLOOD?—In the experiment just mentioned, we have ascertained that the vagus is irritated, and that irritation is conducted to the nerve-centres through the trigeminus, but we do not know that the irritation is directly reflected from the trigeminus to the vagus. It might be due to irritation of the vagus-roots by carbonic acid, which has accumulated in the blood from impeded respiration; for the irritating vapour applied to its nose causes the rabbit to close its nostrils and stop breathing for a while if the trigeminus be intact, but when it is cut no irritating impression can be conveyed to the brain, and so no closure of the nostrils takes place, either voluntarily or reflexly. The rabbit, therefore, continues to breathe freely; no carbonic acid accumulates in the blood, and no irritation of the vagus occurs. Other drugs, such as strychnia and curare, etc., impede respiration—not by causing closure of the nostrils and consequent obstruction to the passage of air to the lungs, but by acting on the muscles and nerves and diminishing the respiratory movements. Strychnia does this by producing tetanic contraction of the respiratory muscles, curare by paralyzing them, and chloral by diminishing the excitability of the respiratory nervous centre. In all such cases, in order to ascertain that indirect irritation of the vagus from impeded respiration is not the cause of the slowing of the pulse, we insert a cannula into the trachea and begin artificial respiration; we then note the rate of the pulse and blow the irritating vapour into the nostrils, or inject the drug into the veins, and see whether or not the pulse is rendered slow, taking care to keep up artificial respiration all the time. If the drug cause convulsive movements which interfere with the proper performance of artificial respiration, curare should be given so as to prevent their occurrence, and the experiment should be again repeated.

ARE THE VAGUS-FIBRES IRRITATED?—To ascertain this we apply the drug dissolved in an indifferent fluid, such as a solution of half per cent. of chloride of sodium, or serum, to the nerve, and notice whether any change occur in the heart-beats. Care must be taken that the solution of the drug be not applied in too concentrated a solution, as it might then have an irritant action, which it could not have if it reached the part through the circulation, and false conclusions might thus be arrived at.

IS THEIR CONDUCTING POWER INCREASED, SO THAT THE ROOTS CAN ACT THROUGH THEM ON THE HEART MORE READILY AND POWERFULLY?—If their conducting power be increased, other stimuli as well as those from the roots will act more powerfully on the heart. We therefore divide the vagi and irritate the peripheral end of one or both by means of one of Du Bois Reymond's induction-coils, and note at what distance from the primary coil the secondary one must stand in order to produce stoppage or slowness of the heart; we then apply the drug to the nerve below it and again irritate. If the excitability of the nerve be increased, stoppage or slowness should be produced when the distance between the primary and secondary coils is greater—that is, when the current is weaker than before. It is generally assumed that the fibres are not likely to be affected, and these experiments are rarely performed.

ARE THE VAGUS-ENDS EXCITED?—We may test this in the same way as the action on the roots, by injecting the drug at one time into the jugular and at another into the carotid. If it increase the excitability of the ends without affecting the roots, we should find it produce, when injected into the jugular vein, immediate slowness of the pulse,

which would not be increased in a quarter of a minute afterwards, when the drug had reached the roots. When injected into the carotid, no slowness should occur till sufficient time had elapsed for it to pass round to the heart. If it increase the excitability of both roots and ends, immediate slowness should occur, whether it be injected into the jugular or carotid, and this should become more marked after fifteen or twenty seconds. If, like physostigma, it increase not only the excitability of the vagus-ends, but that of the quickening centre in the head, injection into the jugular should be followed by immediate slowness, which would become less marked when the drug reached the head, and injection into the carotid by an immediate quickening, which would become less or give place to slowness when the drug reached the heart.

At first sight one might think that, after time had been allowed for the drug to pass round the circulation and be applied both to the vagus-roots and ends, its action on the heart would be the same whether it had been originally injected into the jugular or into the carotid; but this is not the case, for that organ towards which the drug was injected gets a larger dose, and its action is more strongly excited than that of the other. Thus when physostigma is injected into the carotid, the quickening centres are stimulated and the pulse-rate rises; and, although the pulse falls somewhat after the vagus-ends have also been acted on, it nevertheless continues above the normal, the stimulation of the vagus-ends not being able to counteract the still more excited quickening centres. When it is injected into the jugular, the vagus-ends get the largest dose; and, although the pulse, which is at first made very slow, may afterwards, become quicker, it does not reach the normal, the quickening centres being unable to counteract the more strongly excited vagus. If the vagus be cut, however, the pulse becomes quicker than it would have done had no physostigma been given; or, if the vagi be first cut and the drug injected, the pulse is quickened at once. One might think that, since the drug acts on the vagus-ends, its action should remain after the nerves themselves have been divided; but since it is by increasing the excitability of the ends that it acts, if we separate these ends from the roots, and thus remove their normal stimulus, their increased excitability can have but little effect. In order to measure the amount of increase, we divide the vagi and irritate them by an induction-coil, noting the strength of current required to produce still-stand or slowness of the heart before and after injection of the drug into the veins.

[To be continued.]

RUPTURE OF AORTA WITHIN THE PERICARDIUM.*

AT a recent *post mortem* examination, I obtained the morbid specimen now exhibited; and, as it appears to me of sufficient pathological interest to warrant my bringing it under your observation, I must beg your indulgence for a few moments while I narrate its history. It is a well defined instance of rupture of the aorta within the pericardium. It was procured from the body of a blacksmith, aged 34, who for the last twelve months had been constantly under my notice while at work in his forge, and who, during the whole of that time, was distinguished for energy and skill in his business. About fifteen months before his death, he consulted Dr. Kersey for palpitation and dyspepsia, and was also seen by me; but in spite of frequent and careful auscultation, no morbid cardiac sounds could ever be detected, and a little palliative treatment speedily put him to rights. Since then, if questioned about his health, he always affirmed that he was quite well, except on one occasion a few weeks since, when he complained to me of indigestion, but would not take anything for it.

On the evening of his decease, he worked hard at finishing a job up to seven o'clock, and was in his usual good spirits. He then made a hearty supper, and retired to rest. In less than half an hour, he suddenly exclaimed that he felt choking, and immediately expired. Being soon on the spot, I was able to gather these particulars with precision. A necropsy was made twelve hours subsequently. The body was that of a well nourished man, of medium height, and muscular development. All the thoracic and abdominal contents appeared normal, with the exception of the pericardium, which was much distended, and contained more than two pints of blood separated into liquor sanguinis and crassamentum, the latter very firm and unbroken. The source of this hæmorrhage was a small rent of the ascending portion of the aortic circle on the left side, not larger than a crow-quill. No distinct aneurismal pouch could be found; the rupture, therefore, appears to have been due to the giving way of a small atheromatous spot in the artery.

BENJAMIN BROWNING, Littlebourne.