LECTURES

ON THE

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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III.—ARTIFICIAL CIRCULATION: INVESTIGATION OF BLOOD-PRESSURE.

Artificial Circulation of Blood.—Circulation of Warm and of Cold Blood.—Fever.—Mode of Conducting Artificial Circulation.—Application of this Method to Pharmacological Investigations.—Schema of the Circulation.—Circulation in the Living Body.—Importance of the Arterial Elasticity.—Arterial Tension or Blood-Pressure.—Oscillations in it produced by the Heart and Respiration.—Causes of Variation in the Blood-Pressure.—Influence of Nerves upon it.—Cardiac Ganglia.—Inhibitory Nerves of Heart.—Quickening Nerves of Heart.—Vaso-motor Nerves.—Vaso-inhibitory Nerves.—Action of Counter-irritants.—Tabular View of the Causes of altered Pulse-Rate and Blood-Pressure.—Application of this to Pathology.—Experimental Examination of Blood-Pressure.—Forms of Manometer.—Kymographion.—Mode of Using the Kymographion.—Reduction of the Kymographion Tracings.—Mode of Recording Experiments.—Graphic Method of Representing Experiments.

ARTIFICIAL CIRCULATION OF BLOOD.—A constant supply of arterial blood to all parts of the body is necessary to preserve their vitality; and if the supply to any part be cut off by stopping its circulation, that part will die. Thus, if the circulation be stopped in an arm or leg by tying its arteries, or through their becoming plugged by emboli, mortification, or death of the part, ensues; and if the heart cease to beat, and the circulation be thus stopped in all parts of the body, they all die. But, if we supply arterial blood artificially to any one part, we may keep it alive at least for a certain time after the rest of the animal is dead; and the muscles may be made to contract, the lungs to excrete carbonic acid, the lymphatics to pour forth lymph, and the excised liver to secrete bile, for hours after the rest of the animal has been consigned to the dust-bin.

CIRCULATION OF WARM AND COLD BLOOD.—For this purpose, blood may be used either at the temperature of the room or of the body; but these have not exactly the same effect, and experiments made with blood at one temperature must not be compared indiscriminately with those made with blood at another. Professor Ludwig, to whom we owe this method, has discovered by its means the curious fact that the muscles of a warm-blooded animal may be artificially endowed with the properties of those of a cold-blooded one. Those of a frog or other cold-blooded animal retain their irritability, and contract, when stimulated, for a long time after they have been removed from the body; while those of warm-blooded animals quickly lose theirs, and will no longer contract on the application of a stimulus, no matter how powerful it may be. But if the muscle of the warm-blooded animal be quickly cooled by passing a stream of cold blood through its vessels immediately after it has been excised from the body, and before it is stimulated, it will retain its irritability for a long time, and respond to stimuli applied again and again, like that of the cold-blooded frog.

FEVER.—In the same way, by supplying the heart of a mammal with cold blood, it may be made to resemble that of a frog or turtle; while, on the other hand, if the heart of a frog be supplied with warm blood, it will become like that of a mammal; and, if the temperature be still further raised, the quick and weak beats of fever are produced.

MODE OF CONDUCTING ARTIFICIAL CIRCULATION.—When we wish to pass blood, at the ordinary temperature of the room in which we are working, through any organ, we defibrinate the blood of the animal itself from which the organ has been obtained, or the blood of an animal of the same species; dilute it somewhat with salt solution of 1 per cent; and put it into a flask with two necks, one of which is near the bottom of the flask, as seen at A, Fig. 6. We then introduce a cannula into the principal artery of the organ, and ligature, if necessary, the smaller arteries and branches; fill it carefully with blood by means of a fine pipette, so that no air-bubble remains in it, and connect it with the lower neck of the flask. By then simply raising the flask, the blood flows out of it through the cannula into the vessels, and out again by the veins, from which it may be collected, shaken with air, and used over again. As the lips of the divided veins are sometimes apt to fall together and hinder the exit of blood, it is advisable to put a

cannula into them as well; and great care must be paid to the adjustment of these, in order that they may be fairly in a line with the lumen of the vein, and not form an angle with it, which would present an obstruction to the flow of blood from it.

For the purpose of passing a stream of blood at the temperature of the body, we use the same apparatus; but the flask containing blood (E, Fig. 6) is then placed in a water-bath, kept constantly heated to 98 deg. F. As this prevents us from conveniently raising the flask high enough to obtain the pressure required to carry on the circulation, we supply the want by compressing the air in the upper half of the flask, E, by means of two other bottles, A and C, containing mercury or water. On raising A, the fluid which it contains runs into C, and compresses the air in its upper half; and, as this communicates with E by an India-rubber tube, the pressure is freely transmitted to it, and exerted on the surface of the blood which it contains.

Fig. 6.

A and C. Bottles containing mercury or water. B. Wooden blocks, by which A may be raised to the required height. If water be used, it is easier to suspend it from a pulley in the ceiling, so as to get sufficient pressure. D is a manometer, to estimate the pressure in C and E. E is a bottle containing blood. F is a small stand to raise the bottle E from the bottom of G, as it is otherwise apt to become too warm, and the bottom of the bottle cracks, or the blood is decomposed. G. A tin water-bath. At one side of it, is a trough with hollow sides, into which the warm water freely passes, and in which the organ to be experimented on may be laid. H is an iron stand supporting G. I is a Mitscherlich's burner. K is a thermomometer, by which the temperature of the water-bath is examined. L. Bunsen's gas regulator, as modified by Geissler. This apparatus consists of a wide glass tube W, divided into two parts by a septum, from the middle of which a tube runs down nearly to the end of W. The upper part is filled with mercury, which, of course, runs down the inner tube, and fills the bottom of W, compressing the air in it. A perforated cork Z is then put into the upper part of W, and the tube V pushed through the hole in its centre. Inside V, and shorter than it, is a second tube X, and the two are sealed to one another at their upper ends. The tube V is then connected to a gas pipe, and X to Mitscherlich's burner, by India-rubber tubing. So long as V is not pushed so deeply into W that the point of X dips into the mercury, the gas enters through V, passes down between V and X, comes up again through X, and goes to the burner. The apparatus is now set by dipping it into the water-bath, and heating the water to 98 deg., or any other temperature desired, and then pushing V down till the point of X is just covered by the mercury. The passage of gas through it is at once stopped, and the flame would go out, were it not that a very small hole in the side of X admits just enough gas to keep it alive. As the flame gets low, the temperature of the water-bath above it diminishes: the air and mercury in W contract and leave the end of X open, so that the gas again passes freely to the burner, and the flame becomes larger. The water-bath now regains its former temperature, the air and mercury expand, the end of X is again closed, and again the flame becomes small. By this apparatus, a water-bath may be kept for a very long time without varying more than half a degree.

APPLICATION OF THIS METHOD TO PHARMACOLOGICAL INVESTIGATIONS.—Besides its use in the experiments of Ludwig and his pupils on the secretion of bile and the formation of lymph, this method has been used by Cyon to show that urea is formed in the liver; but, so far as I know, no experiments on the action of medicines have yet been made by its means. It may seem, then, a strange thing that I should mention, in a course of experimental pharmacology, a mode of research which as yet has only been tried in physiology; but the good service it has already done the physiologist, and the splendid promise it gives to us, are, I think, a sufficient excuse. For we can thus take two similar organs, or two parts of the same organ, and supply them with the same blood, at the same temperature and the same pressure—in short, we may put them under exactly the same external conditions; but to the blood supplying the one we may add any drug whose action on the organ we wish to test. We can analyse the blood flowing into, and that flowing from, the substance of the organs before and after the experiment, the lymph produced, or the secretion poured forth; and by comparing the results when the drug was added with those obtained when it was withheld, we may, I think, gain such a knowledge of its action as could be got in no other way.

SCHEMA OF THE CIRCULATION.—In the living body, a constant stream of blood is kept up in the vessels, in exactly the same way that

a constant current of air is produced in Richardson's spray-apparatus. By removing the glass or metal tube from one of these, and attaching a nozzle with a small stopcock to the India-rubber tube in its stead, we obtain a very good schema of the circulation; and, by imitating on it the changes which occur in the heart and vessels, we may form a much clearer idea of them than we could otherwise do. The India-rubber ball will represent the heart; the elastic bag, surrounded by netting, will represent the elastic aorta and larger arteries; and the stopcock, which regulates the size of the aperture through which the air escapes, will represent the small arteries and capillaries, whose contraction or dilatation regulates the flow of blood from the arteries into the veins. If we turn the stopcock so as to present some resistance to the escape of air, and then compress the India-rubber ball, very little air will issue from the stopcock even while we are squeezing the ball; the greater part of it goes to distend the bag; and, when we cease to compress the ball, no air at all comes out from the stopcock. At the next squeeze, the bag becomes a little more distended; and a little air issues from the stopcock, not only while we are compressing the ball, but even when we relax our grasp. At each squeeze of the ball, the elastic bag becomes tighter, till it is so tense, and contracts so strongly on the air inside, that it can press all the extra amount of air forced into it when the ball was compressed, out through the stopcock, during the time when the ball is relaxed. When this is the case, every time we squeeze the ball we see the bag become a little fuller, and air issue more quickly from the nozzle. At each relaxation, while the ball is refilling, the bag gets a little slacker, and the air passes out of the nozzle a little more slowly, but never stops entirely. During the time the ball is filling, the valves between it and the bag and nozzle are closed, and cut it off from any connexion with them. All this time, then, the stream of air from the nozzle must be entirely independent of the ball; it is produced by the contraction of the elastic bag, and by it alone. The bag may be stretched, and the tension of its walls increased in consequence, in two ways: first, by working the ball more quickly; second, by lessening the opening of the nozzle, and thus hindering the passage of air through it. One trial will, I think, be enough to show you how much easier it is to alter the pressure by changing the size of the nozzle than by any alteration in the working of the ball, and thus convince you that alterations in blood-pressure probably depend much more on alterations in the lumen of the small arteries than on changes in the action of the heart.

But our schema, as it at present exists, is not a perfect representation of the heart and vessels; for it draws its air from an inexhaustible reservoir, the atmosphere, and is not obliged each time to use that amount alone which it had previously driven through the nozzle; while the heart can only use the blood which has been forced by it through the capillaries and returned to it by the veins. In order to make our schema complete, we must connect its two ends by tying them into a bladder or large thin caoutchouc bag (such as is used, after inflation, as a toy for children), so that the air shall pass into it from the nozzle and be sucked out of it by the elastic ball. This will represent the veins. If we then repeat the experiment just described, we shall find that, when we begin to work the ball and stretch the elastic bag representing the arteries, the bladder, representing the veins, becomes empty and collapsed; and just in proportion as we fill the bag do we empty the bladder. If we now stop, the air will gradually escape from the bag to the bladder, till both are equally filled as they were at first.

CIRCULATION IN THE LIVING BODY.—The phenomena of the circulation in the heart and vessels are very much the same as in the spray-producer. When the heart stands still (as when the vagus is strongly galvanised), the blood flows from the arteries into the veins till they are nearly full and the pressure inside both is about the same. If the heart now begin to beat, it forces blood into the elastic aorta and arteries at each systole, and distends them, just like the elastic bag of the spray-producer; while at the same time it takes blood from the veins, and they become empty in proportion as the arteries become full. At every diastole, the elasticity of the distended aorta causes it to contract on the blood it contains, and keeps it flowing on through the capillaries till another systole occurs. During the diastole, the heart is completely shut off from the aorta by the sigmoid valves (just as the ball of the schema was shut off from the elastic bag), and the blood is kept flowing during this time by the elastic contraction of the aorta and large arteries. In general, the diastole is longer than the systole; so that for the greater part the circulation is carried on by the elasticity of the arteries, and not directly by the heart. The arteries become distended by the heart, just as the elastic bag was by the ball, and press more and more on the blood in them (so that it would spout higher and higher, if one of them were cut), till they are able during the diastole to press the same amount of blood through the capillaries into the veins as had been pumped into them during the systole. The

more these are stretched, the greater is the pressure they exert on the blood they contain; and the amount of this is termed the *arterial tension* or *blood-pressure*. These two terms mean the same thing, and we use one or other just as the fancy strikes us. At each systole, the fresh supply of blood pumped in by the heart stretches them more; that is, the arterial tension rises. During each diastole, the blood escapes into the wide and dilatable veins, and the arteries become relaxed; that is, the arterial tension falls.

Besides the oscillations which take place in the blood-pressure at each beat of the heart, a rise and fall in the form of a long wave occurs at each respiration. The wave begins to rise just after inspiration has begun, reaches its maximum just after the beginning of expiration, and then begins to fall again till a new wave succeeds it. The heart-beats are generally quicker during inspiration, and slower during expiration.

The blood-pressure thus oscillates up and down at each heart-beat and rises and falls with each respiration, and the average between the highest and lowest points is called the mean arterial tension or mean blood-pressure.

CAUSES OF VARIATION IN THE BLOOD-PRESSURE.—The pressure of blood in the arteries depends on two circumstances: first, the amount of blood pumped into them in a given time; and second, on the amount that flows out of them into the veins in the same time. If more be pumped in, or if less flow out, it will rise; if less be pumped in, or if more flow out, it will fall. It may, therefore, be raised—1. By the heart beating more quickly; 2. By a larger amount of blood being sent into the aorta at each beat; 3. By contraction of the small vessels. It may be lowered—1. By the heart beating more slowly; 2. By the heart sending out less blood at each beat; 3. By dilatation of the small vessels, allowing the blood to flow more quickly into the veins; 4. By contraction of the pulmonary vessels, or obstruction to the passage of blood through them.

The influence on the pressure exerted by the amount of blood sent out by the heart at each beat, and by the number of beats, to a certain extent, though by no means completely, counteract each other; for, when the heart is going quickly, it has not time to fill completely, and so sends out little blood at each beat; but, when going slowly, it becomes quite full during each diastole, and sends out a larger quantity of blood at each contraction.

It must be remembered that we measure the blood-pressure in the systemic arteries; and, before the blood can get into them from the veins, it must come through the pulmonary vessels. Any contraction of the lumen of these vessels, by lessening the entrance of blood into the systemic arteries, will cause the pressure in them to fall.

INFLUENCE OF NERVES ON BLOOD-PRESSURE.—Both the quickness of the heart's beat and the contraction of the arteries are regulated by the nervous system; and it is generally by acting on different parts of it that drugs alter the blood-pressure, though they may also do so by acting on the muscular walls of the heart and arteries themselves. The parts of the nervous system chiefly concerned in regulating the circulation are:

1. The *cardiac ganglia* which lie in the walls of the heart, and are, in all probability, the cause of its rhythmical action.

2. *Inhibitory nerves*, which render the heart's action slow, and, if irritated very strongly, may stop its beating altogether, and produce still-stand in *diastole*. The inhibitory fibres have their origin or roots in the medulla, and proceed in the vagi to the heart. In man and in dogs, they are normally in constant action; and, after they are cut or paralysed, the heart beats in the dog three or four times as quickly, and in man twice as quickly, as before. In rabbits and cats, they act less, and their division only makes the heart go one-half or one-fourth faster. A drug may irritate them, and render the heart's action slow—

1. By acting *directly* on (a) their roots in the medulla, (b) their fibres, (c) their ends in the heart;

2. Indirectly, through its action on other parts, producing (a) increased blood-pressure, or (b) accumulation of carbonic acid in the blood, both of which act as irritants to the vagus-roots;

3. Reflexly, through irritation of sensory nerves, irritation of the intestines, of the sympathetic nerve, of the depressor, or of the vagus of the other side. Reflex irritation is only likely to be caused by drugs having a powerful local action.

Drugs may also paralyse the inhibitory fibres, and thus quicken the heart.

III. *Quickening Nerves*. These belong to the sympathetic system. They have their origin in the brain or medulla, pass down through the cervical part of the spinal cord to the last cervical and first dorsal ganglion (which are often united), and thence through the third branch of the ganglion to the heart. Quickening fibres are said by some to run also in the cervical part of the sympathetic cord. Unlike the vagus, the quickening nerves are not normally in constant action. They may be irritated—

1. By the direct action of drugs upon them.

2. Indirectly by the drugs producing a diminished blood-pressure, which acts as a stimulus to them.

IV. *Vaso-motor Nerves*, which cause the smaller arteries, and probably also the capillaries, to contract. These belong to the sympathetic system; and the most important of them are the splanchnics, which produce contraction of the intestinal vessels. As these vessels can, under certain circumstances, hold all the blood in the body, the influence of the splanchnics over the blood-pressure is very great; and division of these can lower it, or stimulation of them increase it very much. The centre of the whole vaso-motor system, however, seems to be in the medulla oblongata; and it is generally in constant action, keeping up a certain amount of contraction or tone in these vessels. Its activity may be increased, and the vessels made to contract—

1. By direct irritation of the centre.

2. By reflex irritation through (a) the cervical sympathetic, (b) the vagus, when the brain is intact, and the animal not narcotised, (c) sensory nerves. When the medulla is separated from the rest of the body by dividing the spinal cord at the atlas, it can, of course, no longer exert any influence over the vessels; and they consequently become dilated throughout the whole body, and the blood-pressure sinks very low. If the lower end of the divided cord be then irritated, the vaso-motor nerves which pass through it from the medulla to the body are stimulated, and the blood-pressure rises.

V. *Vaso-inhibitory nerves*. Irritation of these nerves is conducted to the vaso-motor centres, and acts on them in such a way as to cause a reflex dilatation of the small vessels, either (1) throughout the whole body, or (2) in one particular part of it.

1. The chief nerve which causes dilatation throughout the whole body is one which runs from the heart to the medulla, and is called, from its power of diminishing blood-pressure, the depressor nerve. Its fibres seem to be included in the vagus in the dog; but in the rabbit it generally runs separate from the heart to the level of the thyroid cartilage; here it divides into two so-called roots, one root going to the superior laryngeal, and the other to the vagus nerve. These are generally called roots, though, as the nerve conveys impressions from the heart to the brain, they are, physiologically, really branches. There seem to be also depressor fibres in the vagus itself; but this nerve contains fibres of many kinds, and, among others, some which cause contraction of the vessels and rise of blood-pressure—hence called pressor-fibres. The former seem to act on the vaso-motor system through the

medulla itself, while the latter affect it through a centre in the brain, so that, when the brain is perfect, irritation of the central end of the vagus causes increased contraction of the vessels and raised blood-pressure; but, when the brain is removed or its functions abolished by opium, it causes dilatation of vessels and diminished pressure.

2. When a sensory nerve is irritated, the action of the vaso-motor centre is suspended in the part supplied by the nerve, and in those which immediately adjoin it, so that their vessels become dilated, while at the same time contraction of the vessels in other parts of the body is produced. The blood-pressure is thus increased generally, and produces in the locally dilated vessels a very rapid stream of blood. This fact was first discovered, and its importance in therapeutics indicated, by Ludwig and Lövén.

ACTION OF COUNTERIRRITANTS.—The application of an irritant, whether mechanical, chemical, or thermal, injures the tissues of the part to which it is applied; and what better means of removing the injury and restoring health could be imagined than a copious supply of blood, and the removal of every hindrance to its free flow which contraction of the vessels might present?

● Experiments are still wanting to decide how far the vascular dilatation will extend in the neighbourhood of the irritated part when more or less powerful irritants are applied, or which the vessels are (if any) which especially contract, when certain others dilate; so that at present, when we apply a mustard plaster to the chest to relieve bronchitis, we are unable to say with certainty whether the relief is due to a more full flow of blood through the vessels of the bronchi, or to contraction of their lumen diminishing congestion, or (though this is unlikely) to some unknown action independent of the vessels altogether. The experiments of Sinitzin, however (detailed by a recent writer in the BRITISH MEDICAL JOURNAL, 1871, p. 535), which show that ulcers of the cornea, eyelids, and lips, occurring after division of the fifth nerve, rapidly heal when dilatation of the vessels of these parts is produced by extirpation of the superior cervical ganglion, render it in the highest degree probable that it is to the increased flow of blood that healing is due. As a general rule, too, the vascular dilatation seems to extend more widely the stronger the irritant applied; and we may thus see how a strong irritant, or one applied over a large extent of surface, may prove beneficial in a deep-seated inflammation when a weak one or one applied to a small surface has no effect.

For convenience of reference, I have put together the causes of alteration in the blood-pressure in the following table.

Causes of Alterations in Blood-pressure and Pulse-rate.

Blood-pressure may be diminished.	By slow action of the heart.	Irritation of vagus-roots. Irritation of vagus-fibres? Irritation of vagus-ends in the heart. Paralysis of sympathetic ends in the heart? Weakness of the heart.	{ Directly, by the action of the drug on them. Indirectly, by increased blood-pressure. Reflexly, by irritation of some other nerve.
	By smallness in the amount of blood sent into the heart at each systole.	Weakness of the heart. Contraction of the pulmonary vessels. Great dilatation of the venous system.	{ Paralysis of the cardiac ganglia. Paralysis of the cardiac muscular fibres.
By dilatation of the small arteries.	Paralysis of the vaso-motor centre. Paralysis of the arterial walls. Paralysis of vagus-roots. Paralysis of vagus-fibres. Paralysis of vagus-ends in heart.	{ Direct, by the action of the drug. Reflex, through the depressor. Reflex, through the vagus, when the brain is removed or the animal poisoned by opium. In operations by division of cord or of splanchnics.	
Blood-pressure may be increased.	By quick action of heart.	Stimulation of sympathetic roots. Stimulation of sympathetic fibres? Stimulation of sympathetic ends in heart? Stimulation of the cardiac ganglia.	{ Directly. Indirectly, by lowered blood-pressure.
	By larger amount of blood at each beat.		{ Directly. [of body. Indirectly, by causing increased temperature
By contraction of small arteries.	Irritation of vaso-motor centre. Direct irritation of vascular walls.	{ Direct. Reflex, through the cervical sympathetic. Reflex, through the vagus, when the brain is present and the animal is not narcotised. Reflex, through sensory nerves.	
		{ In operations by irritation of the peripheral ends of the divided spinal cord or splanchnics.	

[To be concluded.]