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The Arris and Gale Lectures

ON

SOME POINTS IN THE PATHOLOGY OF HEART DISEASE

Delivered at the Royal College of Surgeons of England on Feb. 22nd, 24th, and 26th, 1897

BY

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The Arris and Gale Lectures

ON

SOME POINTS IN THE PATHOLOGY OF HEART DISEASE.

LECTURE I.

Delivered on Feb. 22nd.

On the Compensatory Mechanisms of the Heart.

Mr. President and Gentlemen,—In these lectures I propose to deal with certain points in the physiology of the heart and circulation, which are of importance for the understanding of the conditions met with in heart disease. In almost all cases of heart disease we find at some period or other in the course of the disease a hypertrophy of the muscular walls of this organ; and here, as invariably where we meet with hypertrophy of the muscle, we ascribe the hypertrophy to an increased strain thrown on the muscle or to an increased amount of work done by the muscle. We have, therefore, in the first place, to discuss the various physiological mechanisms, in virtue of which the heart is able to re-act to an increased strain thrown upon it in the carrying out of its functions.

The energy of the ventricular contraction is expended in two ways: Firstly, in forcing a certain amount of blood into the already distended aorta, against the resistance presented by the arterial blood-pressure, which itself is directly conditioned by the resistance in arterioles and capillaries; and secondly, in imparting to the mass of blood so thrown out a certain velocity. Thus the energy of the muscular contraction is converted partly into potential energy in the form of increased distension of the arterial wall, and partly into the kinetic energy represented by the momentum of the moving column of blood. The work done at each beat may be calculated from the formula:— $W = w R + \frac{wv^2}{2g}$, where W stands for work, w for the weight of blood expelled at each contraction, R is the arterial resistance or pressure, and v is the velocity of the blood at the root of the aorta. In this equation w R is the work done in overcoming the resistance, and $\frac{wv^2}{2g}$ is the energy expended on imparting a certain velocity to the blood. It will be seen that the energy expended in the second manner is almost negligeable as compared with that spent on dis-

tending the arterial wall, and thus on keeping up the mean arterial blood pressure. Thus, if we take the ordinarily accepted figures of 50 grms. of blood for the output from the left ventricle at each contraction, and half a metre per second as the velocity of the blood in the aorta during systole, and 150 mm. Hg as the pressure in the aorta, w R = 102 gram. metres of work, and $\frac{wv^2}{2g}$ = 0·64 gram metres. Even if the velocity of the blood is quadrupled, as may occur after production of hydræmic plethora, this latter amount will only be increased sixteen times, and so will not nearly approach w R. We may, therefore, neglect the velocity factor in considering pathological changes in the work thrown upon the heart. Any important increase in the work done by the heart can only be conditioned by an increase in one or both of the other two factors—viz., w and R—the amount of blood to be expelled at each stroke, and the resistance offered by the pressure obtaining in the arteries, or caused by any morbid narrowing of any of the orifices of the heart.

In almost all cases of heart disease there is an increase in one or both of these factors. Thus in the case which can be most easily imitated experimentally—viz., stenosis of the aorta—R is largely increased. On the other hand, in pure aortic regurgitation, R may be normal or slightly diminished. During each diastole, however, the ventricle is receiving blood from both sides—viz., from the auricles as well as from the aorta. If compensation occurs, the heart expels almost all the excess of blood which it has received, so that there is a large increase in the factor w. If, as is so frequently the case, stenosis is associated with incompetent valves, both w and R are increased, with a corresponding rise in the work thrown on the ventricular muscle.

Now it is found that the healthy heart is endowed to a high extent with what is known as reserve power, and will respond to largely increased demands on it by the performance of more work, so that the nutrition of the peripheral parts of the body may not suffer. The power of adaptation possessed by the heart can be well shown by imitating experimentally certain well-known pathological conditions. Thus, since the maintenance of the normal arterial blood pressure is intimately dependant on the beat of the heart, any inadequacy in the heart-pump will be at once evidenced by a fall of arterial pressure and a rise of pressure in the large veins near the heart, so that the arterial pressure will serve to indicate whether or not the heart is pumping the normal amount of blood from the venous to the arterial side. Now it is found that we can increase the resistance to be overcome by the heart to three or four times the normal amount without altering in any way the quantity of blood expelled at each beat. Thus we may put a ligature round the pulmonary artery and gradually tighten it until the lumen of this vessel is reduced to a third of its normal extent, without causing any material change in the arterial blood pressure, although,

if we connect a manometer with the cavity of the right ventricle, we find that this side of the heart has to perform three or four times its ordinary proportion of work, in order to expel the proper quantity of blood into the pulmonary vessels and so into the left heart. This same power of adaptation is shown if the ligature is applied to the aorta instead of to the pulmonary artery. Instead of increasing the resistance to the outflow of blood from the ventricles, we may augment the work thrown on the ventricular walls by increa-ing the inflow of blood into them during diastole. This increased diastolic volume of the heart may be brought about either by pressure on the veins of the abdomen, so increasing the venous inflow into the heart, or by destroying the aortic valves and allowing regurgitation to take place from the aorta during diastole. In either case the work done by the ventricles is increased, causing a rise of mean arterial pressure in the first instance and preventing any fall of mean arterial pressure in the second instance. A large number of similar experiments may be devised, but they all teach the same lesson—viz., that within very wide limits the output of the heart is independent of the resistance to the output. Thus the heart possesses in a high degree the power of adaptation to changed conditions, which is the essential characteristic of living organisms; and we have now to see how far we can refer this power to the physiological mechanisms with which the heart is endowed.

Wherever in the higher animals one meets with marked powers of adaptation we are at once inclined to refer such powers to the regulative activity of the central nervous system. We know that the heart is intimately connected by afferent and efferent nerves with the central nervous system, and our first inquiry must be how far these connexions are responsible for the adaptive processes met with in this organ. The nerve-supply of the heart is derived from two sources: from the medulla by means of the vagus and from the spinal cord by the upper three or four dorsal nerves through the intermediation of the sympathetic system. In determining the action of these two sets of fibres on the work done by the heart we must measure their effect on w, the output, and on R, the arterial pressure. The measurement of arterial pressure can be easily carried out by connecting some large artery with a mercurial manometer and registering the excursions of the column of mercury. The measurement of output presents somewhat greater difficulties. Stolnikow and Pawlow practically cut out the systemic circulation altogether, and caused the blood from the left ventricle to traverse an instrument (current-measurer, Stromaiche) which rejected automatically the amount of blood that went through it. This method suffered from the defect that the arterial pressure is, in consequence of the absence of external resistance, extremely low, so that the heart is throughout under highly abnormal conditions. It enjoys, however, the corresponding advantage that R,

though low, is constant throughout the experiment, and the work done hy the heart is therefore directly proportionate to the output. Better methods are those hased upon the application of plethysmography to the heart *in situ*. We may either, as in Tigerstedt's method, employ the pericardium itself, filled with oil or air, as the plethysmograph, and register the changes in the volume of the heart by connecting the cavity of the pericardium with some form of piston recorder, or we may make use of Roy's cardiometer, a brass sphere which is applied round the heart and is filled with oil. In the latter case the changes in the volume of the heart are recorded hy connecting the cavity of the cardiometer with a modification of Roy's oncograph Useful data may also he ohtained by recording directly the extent of contraction of the auricular and ventricnlar muscle.

Experiments carried out hy these methods have led to the following conclusions: 1. On exciting the peripheral end of the vagus the heart is slowed, the diastole prolonged, and the amount of blood expelled at each systole increased. There is, however, a fall of mean arterial pressure, and the increased outpnt is not proportional to the diminished freqnency of the beat, so that the total output in any given time is less than that occurring hefore or after the stimulation. R and w being hoth diminished, the total work done hy the heart is lessened. 2. On excitation of the nerves which reach the heart through the sympathetic system the heart-beat is quickened and there is very often a rise of arterial blood pressure. In nearly all cases the output in a given time is raised above normal, so that the total work done hy the heart is increased. The effect of stimulation of these nerves on the output at each systole is variahle, and the result of stimulation seems to depend on the kind of nerve-fihre stimulated. Excitation of certain of the cardiac hranches of the sympathetic causes a constant increase in the strength of each ventricnlar heat, and therefore raises the output at each heat. This augmentation of the ventricular contraction may or may not he accompanied hy acceleration.

In the living animal the activity of these nerves can only be evoked reflexly or by conditions which affect the medullary centres directly. Of these reflexes the most important are prohahly those which originate in the heart itself and are carried to the central nervous system hy the sensory fibres of this organ. Thus, as Wooldridge showed, stimulation of the central ends of the nerve-fihres, which run to the ventricular walls, may act on the cardiac medullary centres and produce reflexly inhihition or acceleration of the heart's beat or on the vaso-motor centre and cause a rise or a fall of blood pressure. The afferent fihres of the heart, by whose intermediation the reflex fall of hlood pressnre is prodnced, in many animals take a separate course, as the well-known depressor nerve.

Now so far as our experiments go, they appear to indicate

that all these reflex mechanisms are directed not so much to the compensation of vascular disorders by increased efforts on the part of the heart as to the sparing of the heart by the production of some reflex effect which shall counteract the original deviation. Thus a sudden rise in arterial blood pressure as is produced by a general vascular constriction would in itself tend to increase the work of the ventricles. We find, however, that every such rise of arterial pressure or resistance is accompanied by a slowing of the heart's beat in consequence of stimulation of the vagus centre. This stimulation is partly a direct effect of the high pressure of the blood circulating in the brain and partly a reflex from the walls of the heart itself. Moreover, it seems probable that any increase of resistance to the emptying of the ventricles excites the terminations of the depressor nerve in the heart, so that impulses ascend to the vaso-motor centre which depress the activity of this centre and cause dilatation of the vessels in the abdomen and other parts of the body. On the other hand, a fall of blood pressure is followed by a quickening of the heart-beat, brought about partly by inhibition of the vagus centre and partly by a reflex stimulation of the accelerator fibres. None of these mechanisms, therefore, seem to be directed for the purpose of maintaining that cardiac adaptation which is the necessary condition of compensation in heart disease ; and this conclusion is confirmed by the fact that we may divide all the nerves, afferent or efferent, which supply the heart without diminishing to the slightest extent its power of compensation. After such a procedure we find, as before, that an increase of the resistance in the pulmonary artery to three or four times its normal amount does not alter the arterial pressure, the contractions of the right ventricle being augmented in force to the amount of increased resistance to be overcome. The power of adaptation or compensation must, therefore, be an endowment of the muscular tissue itself.

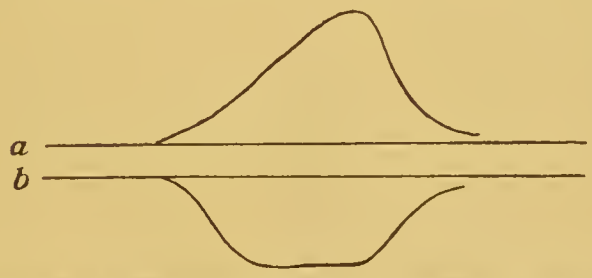
We have now to inquire what are the factors which condition this power of adaptation possessed by the cardiac muscle. Is it peculiar to the heart muscle or does it depend on properties common to all kinds of contractile tissue ?

In every case where, in consequence of morbid conditions, increased work is thrown on the heart muscle the contraction is preceded or accompanied by an increased tension of the muscle. In aortic stenosis the increased tension is thrown on the muscle during contraction, whereas in aortic or mitral regurgitation the increase of tension is present just before the contraction in consequence of the augmented diastolic filling of the heart. Now on examining other forms of contractile tissue we find that in all cases increased tension or increased resistance to shortening of the muscle acts as an excitant or additional stimulus, in that the contraction occurring in the presence of such conditions is more powerful and often more extensive than in the unloaded muscle. In recording the contractions of skeletal muscle

two methods are made use of, known as the isotonic and isometric methods respectively. In the first the muscle is loaded with a constant weight, which, in order to avoid deformation of the curve, is applied near the axis of the lever which records the muscle contraction. In the second the change of form of the muscle is hindered by making it contract against the resistance of a strong spring. The minimal movement of the spring is magnified to a large extent by a long, light lever, so that we get in this way the changes of tension in a muscle, contracting against a resistance which it cannot overcome. In the first method the tension of the muscle remains the same throughout the contraction; in the second the tension is continually changing, while the length remains practically constant. A comparison of the curves obtained from a muscle by the two methods brings out at once certain important facts. We find that in the isometric contraction the maximum tension of the muscle is attained much sooner than is the maximum shortening in the isotonic curve. Moreover, the isometric curve is flat-topped as compared with the isotonic, so that the effort of the muscle, so to speak, is more prolonged when it contracts against an insuperable resistance than when its contraction or shortening is unchecked. Now the isometric twitch is exactly comparable to the conditions which obtain in aortic stenosis. Under ordinary circumstances the ventricular muscle, after attaining a certain stage of contraction, overcomes the resistance offered by the aortic pressure, and can now shorten without any further check, as is shown by the fact that the systolic plateau of the intra-ventricular pressure curve is usually horizontal. In aortic stenosis, on the other hand, just as in the isometric contraction of the frog's gastrocnemius, the resistance to the shortening of the muscle fibres persists throughout the contraction, so that we have a quicker rise of intra-ventricular pressure to a height above normal and a persistence of this abnormally high pressure somewhat beyond the ordinary duration of a ventricular contraction. Even in the isotonic contractions of voluntary muscle an increase in the load to be lifted, within limits, augments the amount of work done during the contraction. This is estimated by multiplying the weight lifted into the height to which it is raised, and it is found that, although in most cases the height diminishes steadily as the weight is increased, its diminution is not at first proportional to this increase, so that up to a certain point the product of the two factors W and H increases with the increase in W. In a few cases it has been found that there may be even an increase in the height of the contraction with an increase in the weight to be raised.

The effect of tension in augmenting the energy of the muscular contraction is, however, much more strikingly shown if the increased tension be applied before the beginning of the contraction. Thus, if, when using the isometric method, the initial tension on the muscle is

raised from 0 to 25 grms., the height of the curve increases steadily with the augmentation in tension. Heidenhain showed that the same held good for isotonic contractions and that a muscle-twitch is always higher in a loaded than in an after-loaded muscle. Moreover, this increase in mechanical effect is accompanied by an augmentation of all the chemical processes which take place during contraction, as is evidenced by a considerable rise in heat-production found under these circumstances This excitatory effect of initial tension seems to be common to all forms of contractile tissue, and was, in fact, studied on heart muscle before it had been established for skeletal muscle. Thus it has long been known that the apex of the frog's ventricle will not contract under normal circumstances, but will do so if its cavity is distended with normal saline at a pressure of from 45 to 50 cm. water. In this case a small mechanical stimulus is usually required to bring about the first contraction, which is then followed by a whole series of spon-



Contraction of skeletal muscle in response to a momentary excitation.
a. Isotonic; *b*. Isometric.

taneous beats. If the lower third of the frog's ventricle be isolated physiologically in the living frog by crushing a ring of tissue between it and the upper part of the ventricle it will, under normal conditions, never beat again. It can, however, as Heidenhain showed, be made to beat rhythmically by clamping the aorta, so raising the pressure in its interior and thereby the tension on the muscle fibres in its walls. Similar observations have been made on the smooth muscle of the ureter as well as on the thin-walled tube which forms the snail's heart. In the latter case the spontaneous beats may often be entirely abolished if the tension within the heart be reduced by cutting it and allowing the contained blood to escape. The spontaneous rhythmic beats may be at once brought back by raising the pressure in the heart a few mm. water by allowing a little snail's blood to flow into it.

We must conclude, therefore, that this susceptibility to tension is a general property of all contractile tissues. In many respects the effect of tension resembles that of a constant electrical stimulus, so that it is said that tension

increases the excitability or is itself an excitant of contraction. The acceptance of this view, however, lands us in apparent conflict with certain other properties of the cardiac muscle. One of the chief distinctions between skeletal and cardiac muscle lies in the fact that whereas in the former the height of contraction is, within certain limits, proportional to the strength of stimulus, in cardiac muscle the contraction is always maximal and is the same whatever strength of stimulus be employed. How, then, can we compare the tension of the muscle to an electrical stimulus and speak of increased excitation by increased tension causing a greater contraction? The same difficulty, however, exists also in the case of voluntary muscle, since the beneficial effects of tension on the subsequent contraction is to be observed even when maximal stimuli are used throughout. The maximal contraction of a stretched muscle is greater than the maximal contraction of a muscle which is unextended before it begins to contract In the case of the heart all contractions are maximal—that is to say, are not altered by strength of stimulus used. They are, however, altered considerably by the tension on the ventricular walls before and during contraction. What the exact nature of this tension effect is it is difficult to say. That, however, it resembles an excitatory effect in causing increased tendency to katabolism of the muscular substance is shown by recent experiments in Heidenhain's laboratory. This observer found that mere extension of a muscle caused an increased formation of acid in the muscle, just as occurs during an actual contraction. Moreover, as Professor Horsley has recently pointed out to me, although a short loading of a muscle increases its effectiveness, prolonged loading causes fatigue. We must, therefore, at present be contented with regarding the improving action of tension on the contractibility of muscle as a general property of all contractile tissues, leaving an explanation of this action to further investigation.

There is yet a further result of morbid conditions in the heart which we have not yet considered, and that is the dilatation of the cardiac cavities so generally met with in heart disease. Now it must be remembered that dilatation occurs under purely physiological conditions. When we speak of the existence of dilatation we mean that the residual quantity of blood in any of the heart cavities at the end of systole is increased above normal. The experiments carried out by Roy and Tigerstedt by plethysmographic methods, as well as those by Hürthle on the duration of outflow during systole, have proved that under no circumstances are the ventricles completely emptied by their contraction, and the experiments by the two investigators first mentioned have shown that the residual quantity of blood is a varying factor depending, (1) on the resistance to be overcome in the arteries, and (2) on the diastolic filling of the ventricles The curves given by Roy and Adami indicate a constant increase in the systolic volume of the heart when-

ever there is a rise of arterial pressure or whenever, by pressure on the abdomen or injection of normal saline or defibrinated blood into the circulation, a rise of venous pressure is produced, with increased diastolic inflow into the ventricles.

It must not be thought, however, that this physiological dilatation is necessarily a beginning or sign of heart failure. I have already pointed out that although the work performed by a loaded skeletal muscle during its maximal contraction is greater than that performed by an unloaded muscle, yet the amount of contraction—i.e., the height to which a lever is raised—is less in the former than in the latter case. The same thing holds good for heart muscle. If, for instance, we assume, in order to simplify the problem, that the left ventricle is spherical it is evident, as Roy pointed out, that a certain amount of dilatation will increase the efficiency of the contractions of the muscle fibres. For, whereas the length of the muscle-cells will vary directly as the radius or circumference, the tension on them will vary as the square of the radius and the amount of blood contained in their cavity as the cube of the radius. Hence as the heart becomes more dilated, although the tension on the individual muscle-cells is greater, yet a very much smaller contraction or shortening of the muscle-cells suffices to drive out the normal amount of blood than is the case in the undilated condition. In fact, here, as in skeletal muscle, with increased load, we have stretching of the muscle fibres (dilatation), diminished shortening or height of contraction, and increased amount of work done. It is evident, too, that if the abnormal strain on the heart walls is permanent the length of the muscle cells will also become permanently altered, just as—to choose the reverse example—the skeletal muscles become permanently shorter in this relaxed condition when there is a lasting impediment to their extension. It is probable that this permanent change in length is conditioned by the connective tissue framework of the muscle, whether in the heart or limbs.

We are now in a position to examine in detail the sequence of events in the two examples of lesions of the cardiac orifices which we selected at the beginning of this lecture. Supposing, for instance, that aortic stenosis is suddenly produced, as may be done experimentally, the next following contraction of the ventricles is called upon to meet an increased strain. The greater tension thus thrown upon the fibres excites them to more powerful contraction; the augmentation in the contractile power is not, however, sufficient to make up for the increased extension of the muscle fibres, so that at the end of systole there is a certain amount of physiological dilatation, the residual blood is greater than before, and the output during the systole has therefore been below normal. This diminished output is not, however, a lasting effect, for during the next diastole the normal amount of blood flows into the ventricle, so that at

the beginning of the next systole the heart is overfull. This increased diastolic distension exercises a strong augmenting effect on the ventricular contraction, so that not only the power but also the extent of the contraction is increased above normal, and this increase might be sufficient to empty the ventricle to its usual degree even against the higher resistance offered by the stenosis. This would leave the heart in the same condition as it was after the application of the ligature round the aorta, so that we should have an alternation of weaker and stronger beats. As a matter of fact, on trying the experiment one finds that the increased contraction excited by the abnormal diastolic distension does not diminish the volume of the heart to its normal systolic amount, but is only sufficient to expel the ordinary quantity of blood into the aorta—i e., that quantity which it has received in the previous diastole. This, however, is sufficient to secure complete compensation of the lesion; the arterial pressure remains at its normal height through the performance of an increased amount of work by the ventricular muscle. It is evident that this increased work would speedily result in fatigue and failure of the heart muscle were it not for the physiological regulation, which ordains that increased work performed by a muscle is followed by hypertrophy of the muscle, provided that the increase is not too excessive in amouut. The exact cause of this hypertrophy has not yet been fully worked out. We know that greater activity of a muscle is followed by vascular dilatation and more plentiful blood-supply, so that there is a more abundant transudation of lymph and supply of proteid to the muscle cells. We have evidence that a hypertrophy of any part involving not only increased growth of any individual cells, but also a multiplication of cells, can be brought about by increasing the lymph-supply. Moreover, the katabolic changes which accompany activity of muscle cause a marked rise of osmotic pressure within the muscles, which therefore, swell up and become turgescent in consequence of imbibition of fluid (lymph) from the surrounding tissue-spaces. Activity, therefore, induces increased supply of nutritive material, especially proteid, to the constituent elements of the active cells, and thus a hypertrophy and multiplication of these cells.

As an example of another kind of lesion we may now take a case in which the mitral valves are incompetent. Here during the systole of the ventricle the blood escapes in both directions into the aorta and through the incompetent mitral orifice into the auricle. The auricle, therefore, during the succeeding diastole is abnormally distended, since the blood flowing into it from the veins is added to that which it has already received from the ventricle. The first strain, therefore, falls on the auricular wall, and here, as in the case of the ventricle. the increased diastolic tension causes more powerful contraction and a larger output of blood into the ventricle. This latter at the commencement of its next systole is therefore over-distended and contracts more

vigorously, having at the same time less resistance to overcome than under normal conditions. Again, there is a partial escape of the blood back into the auricle, and this process goes on until the amount of blood expelled from the ventricle at each stroke is sufficient to send the normal amount into the aorta, in addition to the amount which leaks back into the auricles. If the aortic pressure is maintained at its normal height it is evident that in mitral stenosis the work done by the left ventricle must be increased above its ordinary amount, since a certain fraction of the work is wasted in driving blood back into the auricles. Hence the result of mitral incompetence is, first, increased diastolic dilatation of the left auricle and left ventricle, which later becomes more or less permanent; and, secondly, hypertrophy of the muscular walls of both these cavities.

It seems probable that a mere perforation of the mitral or tricuspid valves in a heart otherwise normal gives rise to very little disturbance of the circulation or in the conditions in the heart itself. Owing to the arrangement of the muscular fibres of the heart there is a strong circular band of fibres round each of the auriculo-ventricular orifices. This ring contracts with the rest of the ventricular muscle, thus acting as a sphincter and practically closing these orifices. It is not until fatigue of the cardiac muscle sets in, or the orifices are held permanently open by development of hard connective tissue around them, that mitral or tricuspid regurgitation can occur to any considerable extent. Unfortunately there is a limit to the adaptive powers of the heart, as of all the other organs of the body. If the strain on the cardiac muscle becomes too great or too prolonged, or the reserve power of the muscle itself is diminished in consequence of malnutrition, we get failure of compensation and the appearance of all those symptoms characteristic of defective working of the heart pump. There is no doubt that cardiac muscle, just like skeletal muscle, is susceptible of fatigue, which, as in the latter, may be caused either by too great a strain on it during its contraction or by too great a stretching or distension between the contractions. If the limit of the reserve power of the heart be once overstepped every contraction of the heart is worse than its predecessor. A vicious circle is established, in which each contraction leaves a greater amount of blood in the heart than before, and the smaller amount flowing into the arteries affects the circulation injuriously, so that the supply of oxygen and fresh nourishment to the heart muscle is diminished. Without a speedy alteration of the circulatory conditions the heart fails within a few minutes, as is the case in asphyxia. As a rule, however, the primary change in the circulation causes reflexly inhibition of the vaso-motor centre and inhibition or functional paralysis of the skeletal muscles, so that a certain amount of relief is necessarily afforded to the over-distended ventricles. A constant recurrence of such condition of overstrain must lead

to a steady deterioration of the contractile powers of the heart and the production of the chronic results of the failure of compensation, some of which we shall study in the next two lectures.

LECTURE II.

Delivered on Feb. 24th.

The Effects of Heart Failure on the Circulation.

Mr. President and Gentlemen,—In my previous lecture I discussed the conditions which may lead to a failure of the compensatory mechanisms of the heart. In this lecture I propose to deal with the effects of such failure on the circulation generally, that is to say, on the blood, and the pressure and velocity of this fluid in the different parts of the circulatory system.

I would, in the first place, remind you of some of the elementary facts in the physiology of the circulation. It must be remembered that the vascular system forms a closed circuit of elastic tubes. In one part of this circuit is included a pump—the heart, the contractions of which will, in consequence of the presence of valves, propel the contained fluid in one direction only. In this system there is a resistance to the flow of blood in consequence of the friction between the blood and the vessel wall in the small arteries and to a lesser extent in the capillaries. There is also a difference in the structure of the walls of the tube on the arterial and venous sides, so that a small rise of pressure in the veins will cause a considerable dilatation and increase in capacity of these vessels, whereas on the arterial side the injection of a small quantity of fluid will bring about a large rise of pressure. If the blood is at rest in the system, and assuming that all parts of the system lie in one plane, it is evident that the pressure in all parts of the system must be the same. This pressure was termed by Weber the mean systemic pressure (not to be confused with mean arterial pressure), and amounts in a large dog to about 10 mm. Hg. If the heart now commences to beat, fluid is pumped from the venous side into the arterial side, where it accumulates to a certain extent in consequence of the resistance in the smaller arteries and capillaries, so raising the pressure on the arterial side and lowering the pressure on the venous side. The fall, however, on the venous side is not directly proportional to the rise on the arterial side, since, as I have pointed out above, a large change in the capacity of the veins is only attended by a small variation of the pressure within them, whereas the blood removed from the veins cannot be pumped into the much less distensible arteries without causing in them a

considerable rise of pressnre. Somewhere in the circulation there must be a point where the pressure is neither raised nor lowered and where, therefore, the pressnre is independent of the cardiac activity. At first sight it might be thought that this neutral point must lie in the situation of the peripheral resistance—viz., between the arterioles and capillaries. It must be remembered, however, that even when the blood is circulating there is not necessarily. although there may happen to be generally, a fall of pressure all the way round the system. What does fall from the heart through the arteries, capillaries, and veins back to the heart is the energy in the fluid at any given point. The total energy of a mass of blood at any point in the system is represented, not only by the hydrostatic pressure at that point, but also by the kinetic energy of the moving mass of fluid ($= \frac{1}{2} mv^2$). In the capillaries, in consequence of the great area of the bed. the velocity is very small and rapidly increases in the veins. Hence the proportion of the total energy represented by $\frac{1}{2} mv^2$ is relatively small in the capillaries and relatively large in the veins. The other factor—the pressure—must be therefore relatively large in the capillaries and small in the veins. It thus follows that the neutral point in the vascular system, where the mean systemic pressure is neither raised nor lowered by the inauguration of the circulation, lies considerably on the venous side of the capillaries—at any rate, in most parts of the body.

Now in such a system it is evident that a failure of the heart pump however induced. whether by vagus-inhibition, by damaged valves, aortic stenosis, or cardiac fatigue, can only cause a return of the pressures in the various parts of the system to one level—the mean systemic pressure We shall, therefore, have a rise of pressure on the venous side of the neutral point and a fall of pressure on the arterial side. By actual experiment we may ascertain the extent and direction of the change of pressure in the various parts of the circulation. To this end we may register the pressure in the arterial system, in the vena cava, and in the portal vein. We may deal in the first place with the case in which the vessels are removed from the interference of the vasomotor centre by section of the cord or splanchnic nerves, so that we may study the pure effects of cessation of the circulation. In snch an experiment the pressures before cardiac inhibition were : Femoral artery, 58 mm. Hg ; portal vein, 73 mm H_2O ; and femoral vein, 62 mm. H_2O. On exciting the peripheral end of the right vagus the heart stopped, and ten seconds later the pressures were : Femoral artery, 20 mm. Hg ; portal vein, 72 mm. H_2O ; and femoral vein, 68 mm. H_2O. After three minutes the pressures were : Femoral artery, 6½ mm. Hg = 84 mm. H_2O ; portal vein, 83 mm. H_2O ; and femoral vein, 82 mm. H_2O ; so that complete equilibrium was established between the pressures at all parts of the system. Here the total failure of the heart pump caused a considerable fall in arterial pressure, a con-

siderable rise in the vena cava pressure, and practically no alteration in the portal vein. The last represents, therefore, a neutral point of the system; in all parts distal to the portal vein there must have been a fall of pressure. The only part of the body, therefore, where heart failure can by itself cause a rise of pressure is in the large veins of the trunk and possibly in the capillaries of the liver.

In the living body, however, we never get a reproduction of so uncomplicated conditions. In a closed circuit of tubes, as described by Weber, the mean systemic pressure can only be increased by injecting a further amount of fluid into the system or by diminishing the capacity of the system. In the body neither the amount of circulating fluid nor the calibre and capacity of the vessels forming the system are constant quantities, and it is possible that changes in the heart leading to its failure may have as an immediate consequence an alteration either of the capacity of the system or of the amount of circulating fluid. We might therefore have, as the remote effect of heart-failure, an increase in the pressures, not only near the heart, but also in the peripheral capillaries. Thus, if we repeat the experiment of vagus inhibition just described, but carry it out on a normal animal, we find that at first the results of stoppage of the heart are exactly similar to those already described. After the inhibition has lasted from twenty to forty seconds the anæmia of the brain causes a strong excitation of the vaso-motor centre. We therefore get extreme vascular constriction, with diminution in the capacity of the system, as is evidenced by a considerable rise in portal, vena cava, and arterial pressures. We may, in fact, in consequence of this constriction, obtain a doubling of the mean systemic pressure. Another point which we must bear in mind is that the quantity of circulating fluid is intimately dependent on the pressures at various parts of the vascular system. Almost every fall of arterial pressure gives rise to a diminished concentration of the blood due to the taking up of fluid by the blood-vessels from the tissues, whereas a rise of blood pressure augments the concentration by causing increased transudation. With these varying factors to take into account it is impossible to predict in our study chairs what will be the effect of failure of the heart pump on the pressure and distribution of the blood throughout the different parts of the body, but we must in each case have recourse to experiment.

In attempting to deal with this subject experimentally one is met at the outset by the difficulty of reproducing clinical phenomena in the laboratory. We have to choose a method of interfering with the action of the heart-pump which resembles in some degree the chronic processes of nature; artificial stenosis or valvular lesions are useless for this purpose, owing to the wonderful powers of compensation possessed by the normal heart, so that the margin between complete compensation and absolute failure becomes too

narrow for experiment. The best method is perhaps that adopted by Cohnheim—viz., the interference with the action of the heart by the injection of oil into the pericardium. By this means we may effect an impairment of the heart's action of considerable duration without running the risk of stopping its action altogether. In the experiments of this nature carried out by Cohnheim, this observer measured the pressures in the carotid artery and in the jugular vein, and noticed that as the diastolic expansion of the ventricle began to be affected by the injection of oil into the pericardium there was a fall of arterial, accompanied by a rise of venous, pressure. The jugular vein is, however, so near the heart and so influenced by the diastolic suction of this organ that one cannot deduce a general rise of venous pressures from the occurrence of a rise in this vessel. I have, therefore, repeated Cohnheim's experiment with two modifications. In the first case I have measured simultaneously the pressures in the inferior vena cava, in the portal vein, and arterial system, while at the same time oil was being injected into the pericardium. In the second series of experiments I have observed the influence of the pericardial injection on the circulation in the limbs, using as my guide the volume of the limbs.

We will consider, in the first place, the effects of injecting oil into the pericardium on the pressures in the portal vein, vena cava, and in the arterial system. In these experiments the animal having been anæsthetised with a large dose of morphia and A.C.E. mixture, cannulæ were placed in the central end of the splenic vein, all other vessels of the spleen having been ligatured, in the central end of the iliac vein, and in the central end of the carotid or femoral artery. The venous cannulæ were connected with manometers filled with coloured $MgSO_4$ solution, so that the height of the fluid could be easily read off on the graduated scales behind the tubes. The arterial cannula was connected with an ordinary mercurial manometer, the excursions of the meniscus being registered on the blackened surface of a kymograph. At the end of the experiment, the abscissæ having been taken, the readings were plotted out as curves. After the attachment of the manometers the chest was opened in the middle line and a cannula tied into an opening in the pericardium for the injection of oil, which was allowed to run in from a graduated burette. In one experiment of this sort the pressures at the beginning of the experiment were: arterial, 90 mm. Hg; portal vein, 128 mm. $MgSO_4$; and vena cava, 36 mm. $MgSO_4$. 20 c c. of oil were then allowed to flow into the pericardium. This had no influence on the pressures in any of the vessels. Injection of another 20 c.c. then caused a slight rise in the vena cava to 40 mm. $MgSO_4$, but no distinct change in the other vessels. Injection of another 20 c.c. caused a rise—the vena cava to 58 mm. $MgSO_4$. a slight but temporary fall in the arteries, and no change in the portal vein. Another 10 c.c.

injected gave a large rise to 76 mm. in the vena cava, a slight rise to 134 in the portal vein, and practically no effect on the arterial pressure. I had now arrived, after the injection of 70 c.c. of oil, at the limits of compensation possessed by the heart and vascular system for the hindered diastolic expansion. Injection of another 20 c c of oil now caused a very marked change in all the pressures. The arterial pressure sank to 56 mm Hg, while the portal pressure rose to 160 mm., $MgSO_4$, and the vena cava pressure to 124 mm. $MgSO_4$. The injection of a further 10 c.c. put a stop to the circulation altogether. The arterial pressure sank to 26 mm., and then as the heart stopped to 18 mm., while the portal vein and vena cava rose first to 180 and 170 mm., and then with the stoppage of the heart, to 215 mm., the pressures in both vessels being practically the same. The oil was now suddenly let out of the pericardium, and the heart, after a short pause, re-commenced beating. The first effects of the re-establishment of the circulation were striking. With the very first heart-beat the pressure in the vena cava sank with extreme rapidity to its normal pressure of 36 mm., and then rose slightly to about 40 mm. $MgSO_4$ The arterial pressure rose with equal rapidity to a point far above its previous height—viz., 146 mm. Hg., to fall rapidly to 84 and then rise gradually towards the end of the experiment. The pressure in the portal vein, instead of falling, like that in the vena cava, continued to rise rapidly on the re-commencement of the heart-beats until it attained the enormous height of 322 mm. $MgSO_4$ whence it fell in the course of the next six minutes to 148 mm. $MgSO_4$—i.e., somewhat above its height at the beginning of the experiment.

How are we to explain these results? It is evident that we have here at least two factors at work—viz, first, the gradual impairment and ultimate failure of the heart pump; and, secondly, a diminution of the capacity of the vascular system and consequent rise of the mean systemic pressure, brought about by the activity of the vaso motor centre. We have already seen that the effect of a pure stoppage of the heart is to cause a rise of pressure in the vena cava and a fall in the arteries, while the pressure in the portal vein, which represents the neutral point of the system, remains practically unchanged. In this case, however, the vena cava pressure not only rises to the height of the normal portal pressure, but attains nearly double this amount, this rise being accompanied by a parallel rise in the portal vein and a large fall in the arteries. Now we know that any anæmia of the vaso-motor centre, however caused, excites its activity, and therefore active constriction of the vessels all over the body, but especially in the splanchnic area. As soon, therefore, as the hindrance to the diastolic expansion becomes sufficient to diminish the normal outflow of blood from the heart in a given time there is a fall of arterial pressure, and the vaso-motor centre is excited and endeavours to restore the arterial pressure to its normal height by an active constriction of all the arteries. That at the moment in

the experiment when the heart stops the bloodvessels are constricted is shown by the enormous rise in pressure which occurs directly the heart re-commences to beat. The heart, which is richly supplied with blood from the distended venæ cavæ, propels this into the arteries, fills them up, and then has to overcome the resistance of the constricted arterioles, so that the pressure rises high above its normal amount, to sink again as this raised pressure furnishes a sufficient supply of blood to the vaso-motor centres of the brain, which, it seems, from the work of Bayliss and Hill and other observers, do not participate in any general vascular contraction. The rise of pressure in the portal vein is analogous to that which occurs in the arteries, and is due to the constriction of the branches of the portal vein in the liver, so that the trunk of this vessel is supplied with blood more rapidly than can be passed through the liver into the vena cava. This experiment brings out two facts which are of importance for our knowledge of the conditions in heart disease. In the first place, any heart failure will tend to be accompanied by active vascular constriction and a rise of mean systemic pressure, so that the pressure at the neutral point of the system, as well as on the venous side of this point, must be raised considerably above normal. In all cases, therefore, of heart failure there will be a large rise of pressure in the capillaries of the liver. In the second place, the existence of this vascular constriction shows that the heart, although inadequate to perform its functions, cannot relieve itself by calling on the depressor mechanisms when by so doing it would diminish below what is necessary the blood-supply to the vaso-motor centre.

We have now the important question to decide as to how far back this rise of venous pressure goes Is the diminution in the capacity of the vascular system consequent on the vaso-constriction ever so great as to raise the pressure in the small veins and capillaries in the peripheral parts of the body such as the limbs? To determine this question one must carry out an experiment similar to the above, but at the same time enclose one limb in a plethysmograph and record changes in its volume by means of a Marey's tambour or a piston-recorder connected with the plethysmograph. If an experiment be arranged in this way and oil injected into the pericardium, it is found that, while the arterial pressure remains constant, practically no change occurs in the volume of the limb, although there may be a rise of pressure both in the portal vein and vena cava. As soon, however, as the compensatory mechanisms become inadequate and the arterial pressure begins to sink, the volume of the limb also diminishes. Thus the volume of the limb, and presumably therefore the pressure in its smaller vessels, including its capillaries and veins, is directly proportional to the arterial pressure, and is not altered by considerable changes in the venous pressures consequent on heart failure. We may conclude, therefore,

that, even with coincident vascular constriction, the effect of heart failure must be a fall and not a rise of blood pressure in the capillaries and smaller veins of the limbs. Since this conclusion is opposed to the ordinarily accepted view, which we owe largely to Cohnheim, that failure of compensation in heart disease leads to a general rise of venous and capillary pressures in all parts of the body, we must inquire whether there may not be other factors at work by which a rise of pressure might be produced. Especially we can elevate the mean systemic pressure, not only by vascular constriction, but also by increasing the amount of fluid contained in the system—i.e., by causing a plethora. Are there any conditions in heart failure which might lead to a plethora sufficient to raise the venous and capillary pressures in the limbs in the absence of any arterial rise?

I pointed out last year that a slight degree of plethora must be the invariable consequence of any heart failure, since a fall of capillary pressure increased the fluid taken up from the tissues and diminished the transudation into the tissues. We therefore get a fall of specific gravity of the blood whenever the arterial pressure is lowered by heart failure or by bleeding. It will be noticed, however, that such an increased absorption of fluid from the tissues must come to an end as soon as the cause of the absorption is removed—i.e., as soon as the capillary pressure is restored to its normal amount, so that a plethora brought about in this way could never be made responsible for a rise of capillary pressure in the limbs. Of course, even when the pressure in the limb capillaries has attained its ordinary amount there is one factor left tending to produce a hydræmia or hydræmic plethora — viz., the diminished urinary flow in consequence of lowered arterial pressure,— and last year I thought that possibly this factor would be sufficient to cause a condition of hydræmic plethora in heart disease and raised capillary pressure in the limbs. Whether this is or is not the case can only be decided by direct clinical observation. If a condition of hydræmic plethora be present in uncompensated heart lesions we should expect to find—(1) a diminution in specific gravity of the whole blood; and (2) a diminution in the amount of hæmoglobin and number of corpuscles present in the blood.

With regard to the first point, it has been shown fairly conclusively by Lloyd-Jones that in failure of compensation there is a marked diminution in the specific gravity of the whole blood. Now this diminution might be due to a hyperplasmia of the blood, possibly brought about by a condition of plethora or to a decrease in the solids of the plasma or corpuscles or of both—i.e., either to hydræmic plethora or to hydræmia. In order to decide which of these two conditions is responsible for the lowered specific gravity we must have recourse to the determination of the hæmoglobin and corpuscles in the blood of such persons. On referring

to the various researches on the subject we find a considerable discrepancy. According to the majority of writers, the relative number of corpuscles in the blood of patients suffering from heart disease is increased, whereas according to others, such as Stintzing and Gumprecht, the exact opposite is the case. In face of this discrepancy Dr. Fawcett has undertaken a series of observations on the amount of hæmoglobin and the number of corpuscles in the blood of patients suffering from heart disease, whether accompanied or not by signs of so-called "backward pressure." Although these researches are not completed, he has kindly allowed me to quote some of his results in this lecture.

The first case investigated seemed at first to favour the hypothesis of the existence of hydræmic plethora.

CASE 1. *Mitral disease.*—This patient, aged thirty-three years, was admitted to hospital on Oct. 30th, 1896, with œdema and ascites of a month's duration. On Nov. 3rd the hæmoglobin amounted to 48 per cent.; on Nov. 14th it was 50 per cent.; on Nov. 24th, 54 per cent.; on Nov. 30th, 65 per cent.; and on Jan. 10th, 1897, 85 per cent. Here there was a marked increase in the percentage amount of hæmoglobin during the patient's stay in the hospital. It must be remarked, however, that the œdema and ascites had disappeared entirely by Nov. 11th, when the hæmoglobin was only 50 per cent., and that the condition of the blood only commenced to improve markedly with the administration of iron, which began on Dec. 7th. In all the other cases investigated the amount of hæmoglobin, even when marked ascites was present, was either above normal or very little below.

CASE 2. *Mitral stenosis and regurgitation, with tricuspid regurgitation.*—This was a patient aged twenty-eight years. On Nov. 11th the hæmoglobin amounted to 100 per cent. and there were œdema of the legs and ascites. On Dec. 12th the hæmoglobin was 97 per cent., and the ascites and œdema had disappeared.

CASE 3. *Mitral stenosis (ulcerative endocarditis).*—This was a patient aged forty-one years. On Nov. 11th the hæmoglobin was 105 per cent., and there was much œdema. On Nov. 24th the hæmoglobin had risen to 110 per cent.; there was still much œdema, and the patient died on Nov. 27th.

CASE 4. *Bronchitis with heart failure.*—This was a patient aged twenty-three years. On Nov. 18th the hæmoglobin amounted to 97 per cent., and there were œdema and ascites. On Dec. 7th the hæmoglobin was 90 per cent., and the patient was in the same condition and died on Dec. 8th.

In nearly all cases it was found that the number of corpuscles was increased to a greater extent than the hæmoglobin, so that the corpuscles themselves contained less hæmoglobin than normal.

It will be seen that these results lend no support to the view that failure of compensation is attended by a condition of plethora. They tend rather to show that the amount of blood in the circulation is subnormal, unless we adopt the unlikely supposition that the defective aeration of the blood in this disease acts like mountain air, in stimulating the production of red corpuscles and hæmoglobin. We must, therefore, conclude that there is no condition of the plethora, hydræmic or otherwise, in heart disease, and that the lowering of the specific gravity of the whole blood is due to a diminution of solids of the plasma, and possibly also of the corpuscles—i e., there is hydræmia, but no plethora. Since the volume of the fluid contained within the vascular system is not increased, the only factor which can contribute to the raising of the mean systemic pressure, and a consequent production of a rise of pressure in the peripheral veins and capillaries by failure of the heart-pump, is the active vascular constriction caused by the anæmia of the vaso-motor centre We have already studied the limits of a rise of systemic pressure so produced, and have seen that it is inadequate to bring about a rise of capillary pressure in the limbs when the heart fails. We must, therefore, conclude that the ordinarily accepted notion is erroneous which assumes that the pressure in the capillaries and veins all over the body in uncompensated heart disease is raised. The pressure must in these situations follow the arterial pressure, and thus be lowered. The only parts of the body where there can be a rise of pressure in heart disease are the capillaries of the liver (whence the well-known "nutmeg" liver of this disorder) the great veins near the heart, and possibly in the system of capillaries which surround the tubules of the kidney. In the limbs, and probably in the abdominal viscera other than those just mentioned, the capillary pressure will be lower than in the normal individual.

For many years, and, indeed, since the time of Richard Lower, we have been wont to pride ourselves on our exact understanding of the factors responsible for the production of anasarca and ascites in heart disease, and have confidently ascribed the increased serous exudation to the rise of pressure in the capillaries due to the transmitted backward pressure from the incompetent heart, and the dropsy of heart disease is generally regarded as affording striking support to Ludwig's filtration hypothesis of lymph formation. The whole argument is, however, based on the false assumption that there is a rise of pressure in the smaller veins and capillaries in heart disease; whereas, as I have just shown, the reverse is the case. We must, therefore, seek for some other explanation of the dropsy in this disease.

LECTURE III.

On the Causation of Dropsy in Heart Disease.

Mr. President and Gentlemen,—The main object of the experiments on the circulation which I described in the last lecture was to determine so far as possible the factors which are responsible for the production of the anasarca and serous effusions met with in heart disease In dealing with this question it must be remembered that dropsy consists in the accumulation of lymph or the fluid which has transuded from the bloodvessels in the connective tissue spaces, and depends therefore on a disturbance of the balance which normally exists between the production and absorption of lymph in the affected parts. Since the questions to be considered and their experimental investigation differ according as we are considering the production of anasarca or of serous effusions, I shall treat of the causation of dropsy in these two situations under separate headings, although I hope to show that the factors involved in each case are essentially identical. We may deal first with the question of the production of œdema in the connective tissues in the limbs. In my previous lectures on the principles of lymph production I dealt chiefly with the lymph flow from the abdominal organs, since the existence of a continuous flow from the abdominal viscera in the animal at rest makes this region the most adapted for experimental investigation. As a result of my experiments I came to the conclusion that lymph formation must be looked upon as the product of two factors—viz., the pressure of the blood in the capillaries and the permeability of the capillary wall. The process, therefore, is analogous to filtration—increase of the filtration pressure or diminution of the resistance of the filtering membrane increasing the amount of filtrate—i.e., lymph. When we attempt to test the truth of these principles on the lymph production in the limbs, we are met at once by the difficulty that if one places a cannula in one of the large lymphatics in the limb of an animal at rest one obtains no lymph flow at all. In order to obtain any lymph in this manner it is necessary to knead or massage the limb or to carry out passive movements. We must not, however, conclude from the absence of a lymph flow through the lymphatics that there is no lymph produced in the resting limb since it is quite possible that lymph or fluid may have transuded from one portion of the capillaries and been absorbed by another portion. We have, in fact, in order to explain the absence of lymph flow from the resting limb, to consider not only the mechanism of the lymph production, but also the absorption of the transuded fluid. In this case

we can evidently leave the absorption by way of the lymphatics out of the question, since it is the flow, or rather the absence of flow, along these vessels that we are considering. It seems, indeed, probable that the lymphatic drainage system of the connective tissues carries on its functions only during activity of the limb or its component parts. All the experiments which have been made on the flow of lymph from the limb lymphatics bring out strongly the fact that extensive alterations in the filtration pressure—i.e., the pressure in the blood-capillaries—cause only slight changes in the lymph flow, in no way comparable to the effect which would be produced by similar changes in the vessels of the abdominal viscera. We must conclude, therefore, that, compared with the latter, the limb capillaries are extremely impermeable—i.e., present a great resistance to filtration. Now, as I have shown, the permeability of a capillary wall, as of an organic filter, may affect not only the quantity of fluid transuding from the plasma under a given pressure, but also the composition of this fluid. Thus if we filter serum through filter paper the filtrate has exactly the same composition as the original fluid. If we use a Chamberland filter we find that the filtrate contains less proteid than the original fluid, and the proteid which passes through becomes less and less as the filtration is continued and the pores become more and more stopped by the retained proteid. By soaking the porous cell in a solution of gelatin so as to fill all its interstices with this substance we may, as Martin has shown, make this impermeability to proteids absolute, without in any way affecting the passage of water and salts through the filter. Hence we may use this method to obtain the crystalloids and water of the serum or blood absolutely free from the proteids and other colloid constituents of these fluids. We should therefore expect to find that the capillaries of the limbs, which present so great a resistance to filtration, would at the same time keep back the larger part of the proteids, so that the transuded fluid would be extremely poor in these substances. Now, on analysing the few drops of lymph which can be squeezed from a cannula placed in a lymphatic of the limb, we find that the difference between the composition of this lymph and that obtained from the permeable capillaries of the liver is by no means so great as we should expect from the relative effects of changes of intra-capillary pressure on the amounts of transudation in these two situations. Whereas the lymph derived from the liver contains from 6 to 8 per cent. of proteids (almost as much as the blood-plasma itself), that from a lymphatic of the limbs contains 2, 3, or 4 per cent. We have no right, however, to assume that the lymph as obtained from a cannula in a limb lymphatic represents in composition the lymph or interstitial fluid which is transuded from the capillaries. Indeed, it may be shown that the fluid flowing from the cannula must be considerably more concentrated than the original transudation. In order to understand this point we must consider carefully the con-

ditions under which transudation and absorption are going on at all times in the connective tissues of the limb.

We have already seen that, given a certain degree of impermeability, the filtrate through a membrane contains less proteids than the original fluid. Now we know in the case of dissolved salts that the separation of water from the solution, leading to the concentration of such a solution, involves the expenditure of a considerable amount of energy. This concentration can be effected by evaporating the solution, in which case the necessary energy is supplied in the form of heat; but we may effect this concentration in a different way. A porous cell is permeable to water and dissolved salts; if, however, an amorphous precipitate of copper ferro-cyanide be deposited in the meshes or pores of such a filter it will then be found that the cell wall is no longer permeable to dissolved salts A cell wall thus impregnated with copper ferro-cyanide is generally spoken of as a semi-permeable membrane. If such a cell be filled with a solution of salt or other crystalloid, and be then sealed and immersed in distilled water, it will be found that, although no salt can diffuse out of the cell, water diffuses into the cell until the pressure inside has attained a considerable magnitude. In the few cases in which it has been possible to measure the pressure thus produced it has been found that this "osmotic pressure" is approximately equal to that which the dissolved molecules would exert if they were present in the cell in the form of gas If now the pressure inside the cell be raised artificially above the osmotic pressure of the dissolved substance, pure water will pass out of the cell, and the solution inside will become more concentrated, until its osmotic pressure is equal to the hydrostatic pressure in the cell. The question now arises whether similar reasoning may not hold good in the case of the separation of colloids—such as proteids—from their solutions. Since the osmotic pressure of a substance is equal to that pressure which it would possess were it in the form of a gas, it is evident that in a solution of given strength the osmotic pressure must be smaller the greater the molecular weight of the substance—i.e., the smaller the number of molecules present. Although our knowledge of the nature and properties of colloids is still very imperfect, it seems practically certain that all of them possess enormous molecules, if not in point of size, at any rate in point of molecular weight. That their size is probably also large seems to be indicated by the difficulty with which these colloids pass through fairly coarse pores, such as those of a Chamberland filter. We should, therefore, expect that the proteids of the plasma and serum, if colloids can be regarded as at all analogous to crystalloids in their solution, would possess a certain osmotic pressure, small, no doubt, in comparison with the huge osmotic pressures of fairly dilute salt solutions, but still large enough to be considered in relation to the forces acting in the body. In attempting to determine directly the osmotic pressures of salt solutions, the

very size of the results is the cause of great difficulty in their accurate measurement, the vessels leaking or bursting before the final pressure has been reached. Moreover, it seems to be very difficult to prepare a reliable semi-permeable cell by Pfeffer's method. In the case of the colloids of serum these difficulties do not arise. We have only to soak any disc of parchment, peritoneal membrane, or even fine wire gauze in gelatin to obtain a membrane perfectly impermeable to colloids, and the pressures we have to deal with are so small that a very little support of the membrane suffices to prevent leakage. If, for instance, we take a thistle funnel, over the open end of which such a membrane is stretched, fill its bulb with serum, and immerse it mouth downwards in salt solution (isotonic or even hypertonic as compared with the serum), we find that fluid (water and salt) passes into the serum and causes a considerable elevation of fluid in the stem of the funnel, which may amount to a height corresponding to a pressure of from 30 to 40 mm. Hg. Since this result is invariably obtained and the height of the pressure is proportional to the amount of proteids contained in the serum, we must look upon from 30 to 40 mm. Hg. as representing the osmotic pressure of the proteids of the serum. If at the beginning of the experiment the stem be also filled with serum to a height of, say, a metre, the fluid rapidly sinks in the stem, owing to the filtration of water and salt through the gelatin membrane, until the height is equal to 30 or 40 mm Hg. So that to concentrate a proteid solution by filtration one must employ a pressure which is greater than the osmotic pressure of the proteid in solution; and in this concentration, since the osmotic pressure of the fluid increases, its potential energy, as measured by it power of attracting water and raising it to a height, is increased. We must therefore conclude that whenever a proteid solution is filtered through a membrane more or less impermeable to proteids, with the production of a more watery filtrate, a certain amount of energy is used up in the process, the hydrostatic pressure used for the filtration being converted into an increased osmotic pressure of the concentrated fluid. In such a case the fluid within the cell or vessel will attract the more watery fluid outside with a force represented by the difference in the osmotic pressure of the two fluids, whereas the force causing filtration or transudation is only represented by the amount by which the hydrostatic pressure inside the vessel exceeds this difference in the osmotic pressure.

We may now apply these principles to the conditions as they exist in the living body. As the blood passes from the arterioles through the capillaries into the veins it gets from a region of high into a region of low pressure. We may therefore, in order to dissociate more easily the processes occurring in the tissues, divide the capillaries into two parts—the arterial and the venous capillaries. In the arterial capillaries the blood plasma is at a pressure which exceeds the osmotic pressure of the plasma proteids. From

these capillaries, therefore, a transudation of a watery fluid takes place much poorer in proteids than the plasma. The transudation thus produced reaches and bathes the outside of the venous capillaries. In these vessels, however, the pressure of the blood has fallen to a point below that corresponding to the osmotic pressure of the plasma proteids. Here, therefore, the force tending to the absorption of the water and salts—viz , the osmotic pressure of the plasma—is greater than the force causing transudation—viz., the hydrostatic pressure of the blood in the vessels. Now this absorption will affect only water and salts, since we know of no mechanism by means of which the proteid lying outside the vessel wall could be absorbed. We have therefore a continual exudation of a fluid very poor in proteid from the arterial capillaries and a continual taking up of the water and salts of this fluid by the venous capillaries. It is evident that the resultant of these two processes, the fluid which remains in the tissue spaces and is squeezed along the lymphatics with every movement of the limb or pressure on the spaces, must contain a considerably higher percentage of proteids than was contained in the fluid as it originally left the bloodvessels. Hence the difference between the proteid percentage of liver lymph and limb lymph is by no means so great as would correspond to the difference in the permeability of the vessels in these two situations. When the fact of the absorption of fluid by the bloodvessels was once definitely established it seemed difficult to account for the presence or use of the lymphatics. Why should a complete and special system of absorbents be developed in all parts of the body if the whole office of absorption might be and was normally carried out by the bloodvessels? If we assume, as many authorities do, that the vascular wall has the power of actively taking up proteids and fluids from the surrounding tissue spaces no work is left for the absorbents. There appear to be no grounds for such an assumption, and I have sought in vain for any evidence for the absorption of proteids by the bloodvessels. Any proteid which leaves these vessels with the transuded lymph is lost for the time to the vascular system. If it is not used up by the tissue elements it must be collected by the lymphatics and restored to the vascular system by way of the thoracic or right lymphatic duct. It is on account of this inability of the bloodvessels to absorb effusions which contain more than a certain percentage of proteids that it is so often necessary to remove such effusions by surgical means. In such cases there is no lack of bloodvessels in close connexion with the fluid to be absorbed. It is, however, the blocking of the surrounding tissue spaces and obliteration of the lymphatic channels which determines the failure of absorption. It might be thought that this impermeability of the limb capillaries would be of disadvantage to the organism, since it limits the supply of proteids to the tissues of the limb. So far as we know, however, the proteid metabolism of these tissues forms but a very small fraction of the total metabolism of the

body. Increased functional activity of the muscles, for instance, causes hardly any increase in the excretion of urea, while a marked increase is observed in the excretion of CO_2—that is to say, the muscle derives its food-supply chiefly from the diffusible constituents (e.g., dextrose) of the blood. On the other hand, it would be extremely disadvantageous if the limb capillaries at all approached the liver capillaries, or even those of the intestines, in permeability. The smallest change in position, in consequence of the effects of gravity, would alter the pressure in the capillaries and cause large changes in the amount of lymph poured out, so that the legs would have to be provided with a series of lymph hearts to pump up the lymph which was turned out in the upright position. We have an opportunity of observing the effects of such changes in the hydrostatic pressure of the blood in cases where the permeability of the capillaries has been altered in consequence of inflammatory conditions In such cases the beneficial effects of raising the limb in relieving tension—i.e., the distension of the tissue spaces by lymph—are well known.

We may now proceed to utilise the knowledge we have gained of the factors regulating the formation and composition of lymph in the limbs under normal conditions for the purpose of explaining the œdema of heart disease. As I have already mentioned, it has been customary to classify the œdema of heart disease with that due to venous obstruction, such as occurs when the large veins are pressed upon by growths or obstructed by thrombi. The production of œdema in consequence of venous obstruction was shown to be possible by the experiments of Paschutin and Emminghaus, and still more strikingly by Ranvier's experiment. The latter observer showed that if the inferior vena cava were ligatured and the sciatic nerve on one side cut, the leg on the same side became œdematous in consequence of the increased transudation induced by the high pressure in the capillaries. Many authors have observed the production of œdema as the result of an elastic ligature round the upper part of a limb In all these cases, however, the rise of pressure in the capillaries necessary to produce œdema is very considerable; and Cohnheim himself, in discussing the point, concludes that the œdema is not sufficiently explained by the increased venous pressure in heart disease. In my last lecture I showed that the immediate as well as the remote effect of heart failure, however caused, was to bring about a diminution rather than an increase of capillary pressure, and we know that such a diminution of pressure in the capillaries causes increased absorption from the connective tissue spaces, and therefore a less amount of fluid in these spaces. An experiment of Cohnheim gives some clue to the explanation of the difficulty. It is well known that ligature of one femoral vein in the dog is not followed by any œdema. Cohnheim found, however, that if a dog be bled every few days for a week or two before the operation, so as to render his blood hydræmic, ligature of

one femoral vein gives rise to œdema of the leg, extending all round the neighbourhood of the wound. If the hydræmia be brought about just before the ligature, by bleeding the dog and injecting a corresponding amount of saline fluid, no œdema results. Cohnheim concludes, therefore, that long continued hydræmia alters and injures the vessel wall, so making it more permeable, so that a rise of capillary pressure, which would be without effect in a normal animal, is now able to considerably increase the lymph transudation and cause distension of the tissue spaces. We have seen that, although there is no plethora, there is hydræmia in heart disease. Moreover, the nutrition of the vessel wall is injuriously affected by the failure of the circulation and consequent absence of a proper renewal of oxygen and nutrient material to the capillary wall. These factors coöperate in increasing the permeability of the wall to such an extent that a very slight increase in the intra-capillary pressure, such as may be brought about by a dependent position of any part, is sufficient to cause increased transudation and consequent œdema. In heart disease the capillary pressure is not higher, but rather lower, than in a normal animal. The dropsy is entirely conditioned by the state of the capillary wall.

In adopting this view as to the exclusive responsibility of the change in the capillary wall for the œdema of heart disease we are confronted by an apparent difficulty. We are accustomed to regard increased permeability as connoting not only an increase in the amount of fluid transuded, but also in the concentration of the fluid. Now if we analyse the fluid of œdema in heart disease we find that it contains only from 0·3 to 0·5 per cent. of proteids—i.e., considerably less than that found in the lymph from the limbs of normal animals. How, then, can we speak of the permeability of the vessel wall being increased under these conditions? I think the answer lies in the fact that increased concentration is not the necessary sequence of increased permeability. Thus, to return to the example of various filters, a porous cell saturated with gelatin presents a much greater resistance to filtration than does a film of peritoneal membrane which has been soaked in the same substance. Yet in each case the composition of the filtrate is the same, no proteids having come through. On the other hand, we may increase the permeability of the gelatinised Chamberland filter by boiling it and dissolving out all the gelatin. After this, not only is the amount of the filtrate under a given pressure increased, but the filtrate is qualitatively different in that it now contains proteid. It is quite possible that the changes wrought on the capillary wall by the mingled effects of hydræmia and stagnation of the blood have the same result as the thinning of the colloid filtering membrane—i.e., merely a quickening of filtration. On the other hand, the changes met with in inflammation are much severer and have for an effect the utter alteration of the quality of the membrane.

It being allowed, then, that the qualitative permeability

may be normal while the quantitative permeability is increased, it is easy to account for the small amount of proteid present in the œdema fluid. For then not only is the original blood plasma poorer in proteid than it is normally, but the chief factor tending to increase the concentration—i.e., the absorption by the bloodvessels—is practically abolished. For the effect of the slow blood current is to equalise the pressures in veins and arteries, so that if the hydrostatic pressure in the arteries is sufficient to cause abnormal transudation an almost equal amount of fluid will be poured out by the veins. Absorption by the bloodvessels can now only occur when the capillary pressure in a part is considerably reduced by raising it above the level of the heart. It seems probable that the obstruction to the flow of lymph from the thoracic duct into the blood, as well as the distension of the duct from the largely increased lymph flow from the liver, may contribute to the production of œdema in the rest of the body. This factor must, however, be only a subordinate one, and is far transcended in importance by the increased transudation from the vessels which occurs in this disease.

The production of effusions into the serous cavities.—The arrangement of the vascular supply is so different in the case of the pleural and peritoneal cavities that it is desirable to consider the causation of effusion into these two cavities separately, and we will deal first with the question of pleuritic effusion. On this point a number of experiments were made by Leathes and myself, and we found that the conditions governing increased effusion into these cavities are very similar to those we have just studied in the limbs. Thus in the latter we saw that so long as the vessels are normal it is impossible by any moderate increase in the capillary pressure to produce any marked œdema or effusion. On the other hand, it is easy to produce effusion by alterations in the vessel wall, and when such alterations have been effected every rise of pressure is followed by a considerable increase in transudation. In our experiments on the pleura we attempted, first, to produce effusion by increasing the capillary pressure in the part. Since the blood from the pleural parietes has several different channels of exit, the only method one can use to bring about a rise of capillary pressure is the injection of large quantities of normal saline solution into the circulation. We tried at the same time to intensify the rise by obstructing the vena azygos at its opening into the superior vena cava, and also ligatured both thoracic ducts. Although in these experiments an enormous degree of œdema was found in the retro-peritoneal tissue and in the posterior mediastinum the pleural cavities themselves contained only 2 or 3 c.c. of fluid. On the other hand, the injection of small amounts of jequirity into the pleural cavity produced a typical pleuritis, with destruction of the endothelium, and fibrinous and serous exudations. In

such cases the injection of large quantities of normal saline into the circulation caused a large and rapid transudation of fluid through the injured capillaries into the pleural cavities, and the death of the animal within two or three hours from asphyxia. A simple destruction of the pleural endothelium, as by scalding or the injection of sodium fluoride into the pleural cavities, had no effect in producing effusion. We therefore concluded that for the production of effusion it was necessary that the tissues, and especially the blood-vessels in the peripleural connective tissue, should be affected. Any fluid which is poured out in the tissues lying under the pleural endothelium, whether in the chest wall or in the mediastinal tissues, rapidly finds its way into the pleural cavities, so that it is possible to kill an animal by asphyxia by allowing fluid to run into the carotid sheath, which is continuous with the connective tissue spaces of the posterior mediastinum. In such cases at the death of the animal both pleural cavities are found full of fluid, although the endothelium separating the mediastinum from the pleural cavity is still intact, and presents no apparent openings for the passage of the fluid.

The hydrothorax, therefore, of heart disease must, like the œdema of the limbs, depend in the first place on an alteration and increased permeability of the vessel wall occasioned by the stagnation and poor quality of the blood. Since, moreover, we have seen that obstruction of the thoracic duct causes distension of the mediastinal tissues, and that fluid can pass easily from these tissues into the pleural cavities, it seems probable that the obstruction to the flow of lymph into the blood through the duct, which is present in uncompensated heart disease, must materially contribute to the hydrothorax Whether an increased transudation in the lungs may also aid in the production of the effusion we have no experimental evidence to show.

In the peritoneal cavity there are two distinct systems of capillaries, either of which might be responsible for the production of ascites. On the one hand, we have the capillaries of the spleen and alimentary canal, which form the radicles of the portal vein; on the other, the liver capillaries which drain into the hepatic vein. We have already seen that these capillaries differ markedly both in their permeability and in the effect on the pressure in them of various changes in the circulation. Heart failure, for instance, such as is brought about by injection of oil into the pericardium causes a marked rise of pressure in the hepatic capillaries, but a fall of pressure in the intestinal capillaries. With regard to the ascites determined by changes in the portal system of capillaries, it would seem that the result of increased flow of lymph in this capillary region depends on the condition of the peritoneal endothelium. Thus ligature of the portal vein causes a very large increase of the lymph flow from the thoracic duct, but only a slight exudation of fluid into the peritoneal cavity; if, on the other hand, we increase the permeability of these

capillaries by plunging several coils of intestine into hot water, or even into distilled water, at the temperature of the body, we find that, although the lymph flow from the thoracic duct is hardly changed, there is a considerable exudation into the peritoneal cavity. In the latter case the transudation from the intestinal capillaries, instead of being confined beneath the endothelium and compelled to traverse the lymphatics towards the cisterna and thoracic duct, can escape easily through the damaged endothelium and adopts this path of least resistance. In heart disease, however, the most important source of the ascitic fluid is probably the liver. Even in the normal animal a slight exaggeration of the conditions present in heart disease will induce an ascites, which seems to be derived from the liver capillaries. Thus in one experiment I ligatured the thoracic duct and obstructed the inferior vena cava above the liver in order to raise the capillary pressures in this organ. A condition of hydræmic plethora was then produced by the injection of 1500 c c. of normal saline solution. Two hours later the animal was killed and the abdomen found to contain 100 c.c. of fluid. In another experiment the lymphatics of the liver were ligatured as they pass out of the portal fissure, and hydræmic plethora produced as before. In this case 230 c.c of fluid were found in the peritoneum

Since we know that the capillary pressure in the liver is largely increased in heart disease—and these experiments show that even in the normal animal an increased transudation in the liver combined with obstruction to the lymph flow causes ascites—we are warranted in concluding that the chief, if not the only, source of the ascitic fluid in this disease is the capillaries of the liver. This conclusion is confirmed to some extent by Hallihurton's analyses of the ascitic fluid in different disorders. He found that in heart disease the concentration in proteids of this fluid was greater than when the ascites was due to portal obstruction or cirrhosis of the liver. We know now that a similar difference in concentration obtains between liver lymph and lymph from other parts of the body, and it is on this account that the effusion in heart disease is more concentrated than that found in other disorders. From these experiments one would expect that ascites should be one of the most constant and earliest symptoms of heart disease. I do not know how far clinical observations would bear out this conclusion.

In these lectures I have endeavoured to give a connected account of the factors which lead to the production of dropsy in consequence of the failure of the heart-pump. The views which I have put forward must, however, be regarded only as the most probable in the light of our present physiological and pathological knowledge, and it is quite possible that we may have to modify them to some extent on further investigation of the subject.

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