The Arris and Gale lectures on the physiological factors involved in the causation of dropsy : delivered before the Royal College of Surgeons of England on February 17th, 19th, and 21st, 1896 / by Ernest H. Starling.

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ON THE

PHYSIOLOGICAL FACTORS INVOLVED IN THE CAUSATION OF DROPSY.

Delivered before the Royal College of Surgeons of England on February 17th, 19th, and 21st, 1896.

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PHYSIOLOGICAL FACTORS INVOLVED IN THE CAUSATION OF DROPSY.

LECTURE I.

The Production of Lymph.

Mr. President and Gentlemen,—The term dropsy is used to denote the condition in which there is an abnormal accumulation of lymph in the connective tissue spaces, including the serous cavities of the body. Under normal circumstances these spaces contain lymph, but the amount present never exceeds a certain limit. Under no physiological conditions can we speak of the spaces as distended with fluid. Now, the lymph in these spaces is derived from the blood plasma circulating in the capillaries. From these in all states of activity the lymph is transuded, but as fast as it tends to accumulate in the spaces it is removed by an absorbent apparatus represented chiefly by the lymphatics. As I shall show in my second lecture, the lymphatics are aided in this work of absorption, under probably certain defined conditions, by the blood capillaries themselves. In health, therefore, the two processes of lymph-production and absorption are exactly proportional. Dropsy depends on a loss of balance between these two processes—on an excess of lymph-production over lymph-absorption. A scientific investigation of the causation of dropsy will therefore involve, in the first place, an examination of the factors which determine the extent of these two processes and, so far as is possible, of the manner in which these processes are carried out. In the second place, we must inquire how it is that, under the clinical conditions in which we know dropsy to occur, there is an upset of the balance of these two processes in favour of lymph production. My first lecture, then, will deal with the first of the two processes—i.e., Lymph-Production.

In studying the factors which regulate the production of lymph we must have criteria by which we may judge of the amount of lymph produced. To this end several methods are open to us. The most simple method, and one which was the earliest to be used, is the production of œdema. As a rule, as I shall explain later, we may look upon the production of œdema as due to increased lymph-production. Far more delicate, however, than this method is the observation of the lymph-flow from a cannula placed in a lymphatic trunk, which drains the part under investigation. Most delicate of all, but subject, perhaps, to most fallacies, is the ingenious method devised by Roy and used by Lazarus-Barlow, in which the specific gravity of the tissues is determined. The second of these methods is

the one by which most work has been done and which I have used almost exclusively in my own investigations. It is evident that the only constant source of a lymph-flow must be the bloodvessels, and our first object must be to see how the amount and composition of the lymph formed in any given part may be changed by experimental alterations of the pressure and chemical composition of the blood flowing through the capillaries of that part as well as by changes in the walls of the capillaries themselves. In dealing with the functions of any part of the body we can often obtain hints as to the manner of its working from a study of its structure, and I would like, therefore, in the first place to draw your attention to some points in the structure of blood capillaries. These have long been known to consist of tubes whose walls are formed of a simple layer of flattened, nucleated endothelial cells, which are united together by a small amount of cement substance, as it is called, the lines of junction between the cells staining deeply with nitrate of silver. A Russian observer, Kolossow, has added somewhat to this simple account. According to this observer each endothelial cell consists of two parts, a hyaline "ground-plate," which immediately borders the lumen of the capillary, and outside this a protoplasmic granular part in which is embedded the nucleus. The ground-plates of the adjoining cells come in intimate contact with one another, but are in no way continuous, so that there is a linear cleft between the adjacent portions of every two cells. The protoplasmic portions of the cells, on the other hand, are continuous with one another by means of processes. If the capillary be stretched in any way the ground-plates, which are inelastic, are separated from one another, so that the clefts between them are increased in size. Hence we see in nitrate of silver specimens made under these conditions that the lines of reduced silver are much broader than in normal capillaries. Outside the capillary one finds in most instances an ill-developed adventitia which is continuous with the surrounding connective tissues. The picture thus afforded of a capillary must suggest at once that it will not be, so to speak, water-tight, but will permit of filtration between the cells, and if this were the case we would have to look upon the lymph, which is separating from the plasma circulating through the capillaries, as a filtrate. The fact that the lymph from most parts of the body contains less proteid than the blood plasma is no argument against this hypothesis. If we filter serum through porous filter paper the filtrate will have the same composition as the original serum. If, however, we take a more closely-meshed filter, such as a porous clay cell or an animal membrane, we shall find that the filtrate is considerably poorer in proteid than the original serum, the big proteid molecule being apparently unable to go through the smaller pores of such a filter. Now this hypothesis, that the lymph is to be looked upon as a filtrate under pressure from the plasma, has been the guiding idea in the most important works on lymph-forma-

tion which have appeared during this century. Though we find it more or less distinctly in the works of the older writers—Hales, Hewson, and others—it is to Ludwig and his pupils that we owe its most systematic examination. According to this hypothesis, the amount of lymph produced in any given part must be proportional to the difference between the pressure in the capillaries and the pressure in the extra-vascular spaces. In most of Ludwig's earlier experiments on the subject this condition was found to hold good. On leading defibrinated blood through a limb the lymph-production in the limb was found proportional to the pressure at which the blood was led through it. In the testis ligature of the pampiniform plexus was found to increase largely the lymph production in this organ. In the arm and in the leg extensive ligature of the veins led to an increased flow of lymph. In all these cases, therefore, an increased flow of lymph was obtained by increasing the capillary pressure of the part. Ludwig found it more difficult to prove any constant alteration of lymph production incident on vaso-motor changes, although Rogowicz, working later in Heidenhain's laboratory, found that vaso-dilatation did give a certain definite increase in lymph-production, and also showed clearly that the vaso dilatation of the tongue produced by excitation of the lingual nerve was followed by an increased lymph-production in the tongue, which might at times amount to an actual unilateral œdema of this organ.

In dealing with the laws affecting lymph-production one is hampered by the fact that in the limbs of an animal at rest there is under normal conditions no lymph flow at all, so that when we wish to study the effects of our various procedures on the lymph-production in the limb we have artificially to bring about a lymph-flow by kneading and massaging the limb. Now this fact introduces at once an arbitrary element into the experiment, and Heidenhain suggested, therefore, that the best place to investigate the truth of the filtration hypothesis would be on the lymph-flow from the thoracic duct. This writer, therefore, carried out a long series of researches on the various conditions in which the lymph-flow from the thoracic duct might be increased or diminished, and came to the conclusion that the results of his experiments were irreconcilable with the filtration doctrine, and that we must assume that the cells forming the walls of the capillaries take an active part in lymph-formation—i.e., that lymph must be looked upon as a secretion rather than as a transudation. A renewed examination of Heidenhain's experiments, combined, however, with a more thorough investigation of their conditions, has shown me that, so far from overthrowing the filtration hypothesis, they furnish the strongest arguments which have yet been adduced in its favour.

In dealing with the lymph-flow from the thoracic duct it is essential to know from what parts of the body this lymph is derived, especially since, as is well known, the lymphatics from all parts of the body, with the exception of the right

upper extremity and right side of the neck, converge to pour their contents into this duct. In placing a cannula in the duct in order to collect and measure the lymph the ducts from the left side of the neck and left upper extremity are ligatured. From the hind limbs we know that in an animal at rest on the table there is no lymph-flow at all. Hence the sources of the lymph are confined to the trunk. We can, moreover, exclude the thorax and its contents, since ligature of the thoracic duct just above the diaphragm absolutely stops the lymph flow. Therefore, when dealing with the lymph-flow from the thoracic duct we deal only with the lymph coming from the abdominal viscera. As I shall show presently, the abdominal viscera, so far as their lymph is concerned, may be divided into two groups: (1) the viscera drained by the portal vein, and (2) the liver.

In testing the filtration hypothesis on the lymph-flow we have to investigate whether the flow is always proportional to the difference between the intra- and extra-capillary pressures. We may regard the extra-capillary pressure as not varying to any large extent, so that we have to see what effect is produced on the lymph by variations in the intra-capillary pressure in the intestines and the liver. The simplest experiments on the subject are those in which some large vessel is obstructed. Speaking generally, we may say that obstruction of a large vein raises the pressure in the capillaries immediately behind it, whereas obstruction of an artery will diminish the pressure immediately in front of it. If, for instance, we ligature the portal vein the arterial pressure is very little affected, while the pressure in the vein behind the ligature rises enormously. In consequence of this there is a large rise of pressure in the capillaries of the intestines and spleen, so that the spleen swells and the intestines become black from venous congestion and hæmorrhages are produced into their mucous membrane. The effect of this ligature on the lymph-flow from the thoracic duct is to increase it four or five times. The lymph also becomes bloody and its total solids are diminished. The diminution in solids is due solely to a diminution in proteids, the salts remaining the same as before, so that we have here an increased capillary pressure, causing an increased transudation of lymph containing a diminished percentage of proteid—a result which is also obtained when proteids are filtered with pressure through dead animal membranes. The presence of red blood corpuscles in the lymph is not a necessary consequence of a rise of pressure in the portal vein. If a less excessive rise of pressure be produced by ligaturing the vein, not at its entry into the liver, but just below the pancreatic duodenal vein, thus leaving a circuitous route for the blood to the liver through the anastomoses of this branch, an increased flow of lymph is produced, containing less proteids than normal lymph, but which may be quite free from blood corpuscles.

A still more striking effect is produced by obstructing the vena cava just above the diaphragm. The lymph is increased

from ten to twenty-fold, and it is found that the lymph obtained after the obstruction is free from red blood corpuscles and is more concentrated than normal lymph. What is the cause of this increased lymph-flow and why is it more concentrated? To answer these questions we must find out, firstly, the source of the lymph, and, secondly, the condition of the capillary pressure in the organ or organs from which the lymph is derived. We can determine the source of the lymph by a process of exclusion. Ligation of the kidney vessels and lymphatics has no effect on the usual consequences of obstructing the inferior vena cava. On the other hand, if we ligature the lymphatics in the portal fissure which carry off the liver lymph we find that a subsequent obstruction has no effect on the lymph-flow, or, indeed, may slightly diminish it. We must conclude then that the increased flow of lymph is more concentrated than intestinal lymph. In order to answer the second question as to this increased production of lymph in the liver we must investigate the changes in the circulation produced by the obstruction. On obstructing the inferior vena cava and recording the blood pressure in the chief vessels of the abdomen we notice that the pressure in the aorta drops almost at once to a third of its previous height, whereas there is a very considerable rise of pressure both in the portal vein and inferior cava. It is probable that the effect of the rise of portal pressure on the intestinal capillaries is more than counterbalanced by the severe fall in arterial pressure, so that there is a fall of pressure in the intestinal capillaries. This conclusion is borne out by the fact that if the abdomen be open the obstruction of the inferior vena cava is seen to be at once followed by a blanching of the intestines ; on the other hand, the effect of the simultaneous rise of pressures in the portal vein and vena cava must be to raise the pressure in the capillaries of the liver to three or four times the normal amount. We have, then, as the results of this experiment, no rise of pressure in the portal area and no increase of lymph-flow from the portal area, a large rise of pressure in the hepatic capillaries, and a very large increase of lymph-flow from the liver.

The only other experiment of this nature which I need describe is one in which the thoracic aorta is obstructed. The results of this obstruction on the lymph-flow are somewhat variable. In most cases the lymph is diminished to one-half or one-third its previous amount ; in a few cases the lymph is unaltered in quantity or even slightly increased. In all experiments the amount of proteids in the lymph is increased. Now if we investigate the state of the circulation under these conditions we find that obstruction of the thoracic aorta causes an enormous fall of pressure in the aorta below the obstruction and a corresponding fall in the portal vein, whereas the pressure in the inferior vena cava is unaltered or in some cases even slightly increased. We must conclude, therefore, that in the intestinal capillaries the pressure has fallen considerably below its normal limits,

while in the hepatic capillaries the pressure is very little altered or may even be somewhat increased. Hence the only region of the body below the point of obstruction where the capillary pressure is not much diminished is the liver. Now we find that the liver is also the sole source of the lymph obtained under these circumstances. If the hepatic lymphatics be ligatured and the thoracic aorta be then obstructed, the flow of lymph from the thoracic duct is absolutely stopped. In these three cases, therefore, the lymph production in the organs of the abdomen is found to be absolutely proportional to the changes of the capillary pressures in these organs. In another set of experiments we find that a marked increase in the lymph-flow is produced by a general rise of capillary pressure in all the organs of the abdomen. Such a general rise of capillary pressure may be produced by the injection of large quantities of normal saline fluid into the circulation, giving rise to a condition of hydræmic plethora. Under such circumstances the lymph may be increased from 50 to 100 times in amount, and may in some cases run from the cannula in the duct in a steady stream. Now, in hydræmic plethora there are two changes in the circulation which might possibly be responsible for the increased production of lymph: firstly, the change in the composition of the blood, and, secondly, the increased pressure in the capillaries of the abdominal viscera. We can decide which of these two factors is responsible for the increased lymph-flow by a very simple experiment. Previously to injecting 300 c.c. of normal saline we bleed the dog to 300 c.c., so that after the injection the total amount of circulating fluid is the same as at the beginning of the experiment. In this way we entirely avoid any rise of capillary pressure, while we have diluted the blood to an even greater extent than in the experiments in which hydræmic plethora was produced. The effect of such a simple hydræmia is to increase the lymph-flow from 3 c.c. in 10 minutes to 4 or 6 c.c. in 10 minutes, whereas if hydræmic plethora were produced the lymph would be increased from 3 c.c. to 30, 50, or 100 c.c. in 10 minutes. It is evident, therefore, that in the production of this increased lymph-flow the all important factor is the rise of capillary pressure.

Exactly the same interpretation holds good for the action of a certain class of bodies which were grouped together by Heidenhain in the second class of lymphagogues. These include bodies such as salt, sugar, potassium, iodide, &c. The injection of a strong solution of dextrose (30 grms. in 30 c.c. water) into the veins of an animal causes a considerable increase in the lymph-flow from the thoracic duct. The lymph at the same time becomes more watery than at the commencement of the experiment. Heidenhain ascribes this effect to a specific excitation of the secretory activities of the endothelial cells. The effect, however, can be explained in a much more simple fashion. All these solutions have an osmotic pressure which is considerably higher than that of normal blood plasma. A solution of dextrose that should be

isotonic with the blood plasma would contain from 5 to 6 per cent. of this body. When we inject a solution containing from 50 to 75 per cent. of dextrose it will attract fluid from the tissues until its percentage is reduced to 5 or 6 per cent., that is to say, 45 c.c. of fluid containing 30 grms. of dextrose will attract water from the tissues until its total volume is increased to 500 c.c. Of course, this estimate is merely a rough approximation at the truth, since before the sugar has had time to attract all this fluid a considerable amount of it will already have left the vessels by diffusion. As a matter of fact, however, we find that injection of a strong solution of dextrose is followed in a few minutes by a considerable dilution of the blood, caused by an increase in its volume. In some experiments of von Brasol the volume of the circulating blood was thus increased to twice or three times its previous amount; and these observations have been fully confirmed in a series of careful experiments made by J. B. Leathes. As we should expect, this increase in the volume of the circulating blood is attended by a large rise of capillary pressures in the abdominal viscera, and we have here again to decide whether it is this rise of capillary pressure or the change in the chemical composition of the blood that determines the increased lymph-flow. This question can be solved by using the same method that we adopted when dealing with the production of the increased lymph-flow in hydræmic plethora. We can entirely obviate the rise of capillary pressure if we bleed first to 300 c.c. and then inject a concentrated solution containing 18 grms. of dextrose. In this case the fluid that is dragged by the sugar from the tissues into the blood-vessels only just suffices to make up for the previous loss of blood. No hydræmic plethora is produced; there is no rise of capillary pressure, and there is no increase in lymph-flow, although an abnormally large amount of dextrose is present in the circulation. We must conclude, therefore, that the increased flow of lymph caused by injection of the second class of lymphagogues is entirely due to the rise of capillary pressure thereby induced, and is in no wise conditioned by a stimulation of the secretory activities of the endothelial cells.

There is one point in the effects of the injection of these bodies which has been looked upon as a strong argument for the secretory hypothesis, and which I must therefore mention shortly here. If we analyse the lymph and the blood at different periods after the injection we find that the amount of sugar in the blood steadily diminishes, while the sugar in the lymph first rises to a maximum and then diminishes parallel with that in the blood plasma At a given period after the injection it is found that the lymph contains more sugar than does the blood plasma, and this fact was held to point to an undoubted secretory activity of the endothelial cells in the production of lymph. This conclusion, however, is by no means justified. The lymph flowing at any given moment from the thoracic duct does not represent the tran-

sudation from the blood at that moment, but is derived from the lymph that has been formed some time previously. If we had a solution of sugar in gradually diminishing strength flowing into a lymphatic trunk of the leg it is evident that this fluid would mix with the lymph in the other lymphatics, through which it flowed on its way to the thoracic duct. Later, the solution of sugar would have displaced practically all the lymph from these channels and would flow through the thoracic duct almost undiluted. It would take, however, some considerable time to flow from the leg to the thoracic duct, so that the outflow from the duct would represent not the fluid which was being injected into the leg at that moment, but the stronger solution which had been flowing in some time previously. If one compared, therefore, the percentage of sugar in the fluid flowing from the duct and in the fluid flowing into the leg lymphatic at different times after the beginning of the injection we should obtain a curve exactly similar to those obtained by Heidenhain after the injection of sugar into the circulation, and looked upon by him as undeniable evidence of secretory activity.

The dependence of lymph-formation on capillary pressure is not, however, the only important relationship brought to light by these experiments. The amount and composition of the transudation through a membrane depend not only on the pressure at which the transudation is effected but also on the nature of the membrane. According to the permeability of the membrane, so the amount and composition in proteids of the transuding fluid will vary. You will doubtless already have noticed that after obstruction of the inferior vena cava the pressure in the intestinal capillaries, although it probably sinks below its normal height, is yet as high as that in the hepatic capillaries. Nevertheless, we get a very small amount of transudation through the intestinal capillaries and a very large amount through the hepatic capillaries. It is evident, then, that the permeability of the liver capillaries must be very much more marked than that of the intestinal capillaries. In the same way we may compare the permeability of the intestinal capillaries with those of the limb capillaries. Normally from the limb there is no flow of lymph at all, whereas a probably equal pressure in the intestinal capillaries suffices to give rise to a steady flow of lymph. If we ligature all the veins of the leg a lymph-flow may be set up, but such a flow is incomparably smaller than that produced on ligature of the portal vein. We can, therefore, arrange the capillaries of the body in a descending order of permeability, the liver capillaries being the most permeable and the limb capillaries the least permeable. I have already mentioned how, on filtering solutions of proteids through various membranes, the percentage of proteids in the filtrate increases with the permeability of the membrane. As we have seen, exactly the same thing holds good for the capillaries in the body. The lymph in the limbs, the filtrate

through the impermeable limb capillaries contains only from 2 to 3 per cent. proteids. That from the intestines contains from 4 to 6 per cent. proteids, while that from the permeable capillaries of the liver contains from 6 to 8 per cent. proteids—in fact, almost as much as the blood-plasma itself. It is conceivable that we might alter the amount of lymph produced in any organ by changing, not the intracapillary pressure, but the filtering membrane—i.e., the endothelial wall of the capillaries. Such a change can be brought about in the body by various means. A whole group of bodies has been described by Heidenhain as his first class of lymphagogues. These substances, which are mostly of the nature of albumoses, can be extracted from various of the lower animals and include leech extract, mussel extract, crayfish extract, and commercial peptone. On injecting a small amount of any of these extracts into the bloodvessels of an animal the lymph from the thoracic duct is much increased in quantity and becomes more concentrated. Now all these bodies are poisons; they alter the blood, diminishing its coagulability, and when given in sufficiently large doses cause a great fall of blood pressure in consequence of paralysis of the heart and vessels. I have shown that the changes in the circulation produced by these bodies are insufficient to account for the increased lymph-flow, but that the increased flow is due to an alteration of the capillary walls in the abdominal organs, especially in the liver. The hepatic capillaries become even more permeable than before, so that a pressure within them which is little above normal is sufficient to cause a great increase of transudation through them.

Another substance which seems to act directly on the capillary wall is curare. This body, however, differs from the class of lymphagogues just mentioned in the fact that its chief action is on the vessels of the limbs. The effect of curare in increasing the lymph-production in the limbs was noticed long ago by Paschutin working in Ludwig's laboratory. Its direct action on the endothelial wall of the capillaries can be easily demonstrated in the living frog's web. It may be seen that after the injection of curare the capillary walls become apparently more sticky, so that the capillaries become filled with a number of leucocytes adhering to their walls. A still more potent method of altering the permeability of the limb capillaries is to plunge the limb into water at 56° C. for some minutes. If a cannula has been previously placed in one of the main lymphatics of the leg it will be noticed that, in a very short time after this scalding, lymph begins to drop spontaneously from the cannula. The lymph which is thus produced is much richer in proteids than is lymph from a normal leg. The amount of lymph flowing from the leg can now be varied within wide limits by altering the pressure in the capillaries either by ligature of the vein or artery, injection of salt solution, or production of vaso-motor paralysis. By this scalding, in fact, we may reduce the limb capillaries to the condition of liver capillaries.

In conclusion, from this study of the conditions of lymph-production in the various parts of the body we must conclude that the endothelial cells of the vessels take no active part in the production, their vital activities being confined to the maintenance of their integrity as a filtering membrane with properties differing according to the part of the body in which they happen to be situated. The amount and composition of the lymph transuded in any part are determined solely by two factors: (1) the permeability of the vessel wall and (2) the intracapillary blood pressure. The more permeable the capillary the greater is the amount of lymph transuded under any given pressure, the greater is its concentration in proteids, and the more easily is the amount of lymph altered by slight changes of pressure.

LECTURE II.

The Absorption of Fluids from the Connective Tissue Spaces.

Mr. President and Gentlemen,—We have now to consider the second physiological factor which is involved in the production of dropsy. Two ways of absorption have been generally described—viz., absorption by the lymphatics and absorption by the bloodvessels; and we find that at different periods in the history of the subject each of these has in turn been looked upon as the most important, or even exclusive, channel. There can be no doubt that absorption may take place by both these ways Since the mechanism of absorption by the lymphatics is the more evident and familiar we may consider this way first.

All parts and organs of the body possess a well-developed system of lymphatics. These channels are in direct communication with the tissue-spaces and can be easily injected from these spaces. They are lined by a layer of endothelial cells, which are continuous except at the very point of junction of the lymphatics with the tissue-spaces. The larger trunks possess also an outer wall of connective tissue in which in some situations we find unstriated muscular fibres. All the lymphatic trunks, with the exception of those draining the upper extremity and right side of the head and neck with the adjacent parts of the thorax, converge to join the thoracic duct, which pours its contents into the blood in the angle between the left jugular and subclavian veins. All the larger lymphatics possess numerous valves so arranged that the lymph can only flow in them towards the thoracic duct. It is evident from these anatomical arrangements that any excess of fluid in the connective tissue spaces will make its way into the lymphatics and so finally attain the blood by way of the thoracic duct. There is one point,

however, which I think is not sufficiently appreciated, and that is the importance of muscular movements both for emptying the spaces into the lymphatics and for propelling the lymph onwards through the lymphatics. If we have a manometer in the peripheral end of one of the lymphatics of the leg and inject fluid under pressure into the connective tissue spaces of the foot we find that the manometer in the lymphatic rises extremely slowly, so that the pressure in the spaces may be many times the pressure that obtains in the lymphatic. We have now only to flex the foot on the leg once or twice to immediately send up the pressure in the lymphatic to a height equal to or above that in the connective tissue spaces. Our knowledge of the importance of muscular movement for the normal lymph-flow we owe to the labours of Ludwig and his pupils. In all tendons and aponeuroses we find a double system of lymphatics—a deep system, consisting of vessels running parallel to the tendon-bundles and communicating by cross branches, and a superficial network with polygonal meshes in the peritendinous connective tissue. Both networks are in direct communication and neither of them possess any valves. The superficial network drains into larger lymphatic trunks provided with valves. Each time that the underlying muscle contracts the deeper system is pressed upon and its contents emptied into the superficial system and so into the valved lymphatic trunks. When the muscle relaxes the fluid cannot get back past these valves, so that the two systems of lymphatics are emptied and ready to receive more fluid from the connective tissue spaces. A similar double system was described long ago by Ludwig and Schweigger-Seidel in the central tendon of the diaphragm, and these writers showed how beautiful injections might be made from the peritoneal cavity by injecting Berlin blue into this cavity and then carrying out artificial respiratory movements. As I have mentioned in my last lecture, it is impossible without such aid as muscular movements or passive flexion and extension of the limb to get any lymph-flow at all from a cannula placed in the lymphatics of the leg or arm. It will be evident to you therefore what an imperfect conception of the normal lymph-flow we obtain from a study of the flow in an animal anæsthetised and secured on its back on the operating table, when during normal existence every breath we draw and every movement or twitch of the muscles helps to pump lymph from the extremities into the thoracic duct and so into the blood.

Much more difficulty exists with regard to the absorption of fluid from the connective tissue spaces by the blood-vessels, and this question has been the subject of many investigations. Many years ago Majendie devised a number of ingenious experiments in order to show that poisons introduced into the serous cavities and connective tissue spaces of the limbs were absorbed not by the lymphatics but by the bloodvessels. These researches have been continued and extended of late years by Ascher in the case of the

connective tissues of the lower limbs, by Tubby and myself in the case of the pleural and peritoneal cavities. We found, for example, that after injecting methylene blue or indigo carmine into the pleura the dye-stuff appeared in the urine within five minutes, whereas the lymph presented no trace of blue for another twenty minutes or even two hours. It is evident then that in this case the dye must have been taken up by the bloodvessels and not by the lymphatics, and that this vascular absorption takes place with extreme rapidity. In a later series of experiments Leathes has shown that after introduction of various salt solutions into the serous cavities an interchange of constituents takes place directly between the blood and the injected fluid, so that the latter in a very short time becomes isotonic with the blood plasma. Now in this mode of absorption by the bloodvessels the so-called absorption really consists in an interchange between blood and extra-vascular fluids—an interchange apparently dependent entirely upon processes of diffusion between these two fluids. So long as any difference in composition exists between intra- and extra-vascular fluids so long will diffusion-currents be set up tending to equalise this difference. This power of interchange between blood and tissue juices is probably of great importance in the normal metabolism of the tissues. Supposing for example, that a tissue cell is storing up in itself a large amount of calcium or secreting it away from the tissue fluids into the lumen of a gland duct, it is evident that the percentage amount or partial tension of the calcium salts in the fluid surrounding the cell will be diminished. Diffusion currents will therefore be set up, and there will be a flow of calcium from the blood to the lymph until the normal calcium tension is restored. We must conclude, therefore, that for the ordinary metabolic activities of the tissues no lymph-flow at all is necessary, the cell being able to obtain all its diffusible food stuffs from the blood by means of diffusion even through a stationary layer of lymph.

These experiments, however, have no direct bearing upon the absorption of dropsical fluids by the bloodvessels. In the case of dropsical fluids the exudation resembles in all points blood plasma, the only difference between the two consisting in the fact that the dropsical fluid is rather poorer in proteids than the plasma. Here, as we have fluids almost identical on each side of the endothelial wall of the vessels, no conditions are present which would favour the setting up of diffusion currents. As a matter of fact, we may say that diffusion currents bring about an interchange of constituents between the two fluids, but can under no circumstances effect a total absorption of fluid. We have therefore to inquire whether, under any circumstances, an absorption of dropsical fluids or of isotonic salt solutions can be carried out by the bloodvessels. We may arrange the experiments upon this point under three headings.

1. In the first set observations were made on the absorp-

tion of isotonic salt solutions and blood serum from the pleural and peritoneal cavities. Orlow, working under Heidenhain's direction, found that such fluids were absorbed rapidly from the peritoneal cavities of living animals, while the lymph-flow from a cannula placed in the thoracic duct showed no (or only slight) increase in no way comparable to the amount of fluid absorbed. He concluded, therefore, that the absorption was affected by the bloodvessels, and was dependent on the vital activity of the cells lining the serous cavities or of the endothelial cells of the capillaries. Leathes and Hamburger confirmed these results, but showed that they could not depend on any vital activity of the endothelial cells, since absorption took place with equal rapidity even when poisonous solutions of sodium fluoride were made use of. The great objection to these experiments is that they do not prove conclusively absorption by the bloodvessels. It is still possible that the fluids had been taken up by the sub-serous lymphatic network and had not reached the thoracic duct during the experiment. This is an objection raised by Cohnstein, who concludes from very similar experiments that these fluids are carried away solely by the lymphatics. It might be thought that this question could be easily decided by observing whether fluids were still taken up from the serous cavities after ligature of both thoracic ducts. I have made a number of experiments of this description, but have failed to get decisive results. It is true that after ligature of both thoracic ducts as well as of the right innominate vein isotonic salt solutions were taken up fairly quickly from the serous cavities. In none of these cases, however, could I be certain that the lymph was absolutely shut off from the blood. As a rule I injected on three succeeding days several hundred c.c. salt solution into the peritoneal cavity, the last injection containing carmine granules in suspension. On killing the dog two days after the last injection the peritoneal cavity was generally found to be empty, and carmine granules could be traced along the glands of the anterior mediastinum, showing that, in spite of the ligature of both thoracic ducts, there had been a passage of lymph upwards and through the chest. We must, therefore, look to other methods to decide this question.

2. There are a whole series of experiments made by other observers which to my mind prove conclusively the power of the bloodvessels to take up fluid from the tissue spaces. If an animal be bled several times it will be found that the blood obtained in the later bleedings is more watery than that obtained at the beginning of the experiment. Now this diminution of total solids in the blood seems to be due chiefly to a dilution of the serum ; the serum contains less solids than before and is increased in volume relatively to the blood corpuscles. I may here quote some observations which show this point.

Dog, 11·4 kilos. Solids of serum = 7·72 per cent. Dog then bled to 220 c.cm. Thirty minutes later solids of serum = 7·14 per cent.

In another experiment the solids of the serum were at first 6·98 per cent.; after bleeding to 200 c.cm. = 6·57 per cent.; after further bleeding to 100 c.cm. = 6·37 per cent.

In a smaller dog (6·5 kilos.) withdrawal of 150 c.cm. blood reduced the solids of the serum from 7·77 per cent. to 6·47 per cent.

It must be noticed that this attempt to regulate the amount of the circulating blood by bringing it up to its normal volume is carried out with great rapidity, so that even while we are bleeding an animal we find that the later portions of blood are more dilute than the earlier portions. That the fluid which is added to the blood in these cases is derived from the tissue spaces is shown by Barlow's experiments. Now this dilution of the blood takes place even when the thoracic duct is tied or when the lymph is conducted away by placing a cannula in the duct, so that it cannot be due, as was formerly thought, to an increased lymph-flow into the blood.

3. In order to be absolutely certain of the power of the bloodvessels to take up isotonic solutions and dropsical fluids from the tissue spaces I have carried out a series of experiments in which I led defibriated blood through the bloodvessels of amputated limbs. In each case I had a double set of transfusion apparatus and sent one-half of the blood many times through a limb which had been rendered dropsical by the injection of isotonic salt solution, while at the same time fluid was flowing at the same pressure through the other limb, which was not dropsical, and thus served as a control. In each case the blood was analysed and its hæmoglobin estimated before the experiment and from both limbs after the experiment. It was invariably found that, whereas the blood which had passed from twelve to twenty-five times through the sound limb had become rather more concentrated, the blood which had passed through the œdematous limb had taken up fluid from this limb. I may here quote one of these experiments as an example :—

—	Total solids.	Percentage of HbO_2
1. Blood before experiment	21·2%	100
2. After twenty passages through normal leg ...	21·4%	103
3. After twenty passages through œdematous leg	20·5%	95·5

We must conclude, then, that isotonic salt solutions and dropsical fluids may be taken up by the blood circulating through the capillaries and that this process may occur fairly rapidly. In the last lecture we saw how any excess of intracapillary pressure, such as accompanies plethora, causes an increased transudation from the capillaries, so that the

volume of circulating fluid is diminished. Now we see that, on any diminution of capillary pressure taking place, as after bleeding, the fluid in the tissue spaces goes back into the vessels to make up for the volume of circulating fluid lost. This wonderful balance between capillary pressure and lymph production or absorption is I think, well illustrated by Lazarus Barlow's observations. While not agreeing with my views on lymph-production, this observer has shown that the slight plethora produced by wrapping up the limb in Esmarch's bandage causes an appreciable increase in the transudation in other parts of the body, so that the specific gravity of the tissues of the upper limb, for instance, falls, while the specific gravity of the blood rises. The reverse is the case when circulation is restored to a limb which has been kept anæmic for an hour or two. Here there is considerable hyperæmia of the affected limb produced, and corresponding anæmia of other parts of the body. We find then that absorption as well as transudation through the capillary wall is determined by the intra-capillary pressure. When the pressure rises transudation is increased, when the pressure falls absorption is increased. We have seen that the dependence of transudation on capillary pressure is susceptible of a fairly simple mechanical explanation (filtration hypothesis). We have now to discuss the mechanism of the absorption process.

Is absorption effected by the active intervention of the endothelial cells or are there physical factors at work which will serve to explain it? An explanation of absorption which will strike anyone who investigates this problem is the possibility that absorption may take place in the same manner as lymph production—i.e., by a process analogous to filtration. From the work of Ludwig and Noll we know that the pressure in the lymphatics is extremely low; but the experiments I mentioned earlier in this lecture show that there may be a considerable pressure in the tissue-spaces without communicating itself to the fluid-filling lymphatics. Landerer, who has written a whole book on the subject of tissue tension, places the pressure in these spaces at a high level, from one half to three-quarters of the capillary pressure. It is evident that if this were the case and the capillary pressure suddenly sank 50 per cent. the pressure in the extravascular spaces would be higher than that in the capillaries and a backward filtration of lymph might occur. A series of mechanical experiments by Klemensiewicz would seem at first sight, however, to show that such a backward filtration is impossible. Klemensiewicz points out that if fluid be passing at a given pressure through a permeable tube contained within a rigid tube transudation will occur until the pressure of the transuded fluid is equal to that of the fluid flowing through. At a certain point in the experiment the pressure of the transuded fluid will exceed the pressure at the outflow end of the tube. The tube will collapse and the flow through it be stopped. He imagines that the same sequence of events occurs in the living body in

the presence of a considerable transudation. Arteries, capillaries, and veins are bathed in the transuded fluid. The fluid transuded from the capillaries will, if a free outflow for it be absent, after a time attain a pressure near that ruling in the capillaries and higher than that of the venous pressure. The veins will therefore collapse, venous obstruction will be produced, and the capillary pressure and transudation will be higher than ever, so that we have a vicious circle of events tending continually to increase the œdema of that part. Now, Klemensiewicz's objections are true only under one condition—i.e., that the venous tubes should run freely through the lymphatic spaces of the tissues. If, however, we consider a system in which the inner tube is connected at various points in its circumference to the outer tube by strands of inextensible fibres, it is apparent that a rise of pressure in the space surrounding the inner tube will only serve to extend this tube still further. No collapse will take place, but a back filtration will be possible. Now, if we cut sections of injected connective tissues we find that the capillaries are bound to surrounding parts by radiating fibres which might possibly prevent their collapse under high extravascular pressure. In the larger veins, on the other hand, the arrangement of the fibres of the adventitia is circular and not radial, so that a high extra-vascular pressure would apparently cause collapse of the veins. From these anatomical facts one would conclude that a backward filtration is possible provided that the extravascular pressure be raised only in the region of the capillaries. If, however, the pressure be freely propagated through the tissues so as to affect the larger veins draining them we shall have collapse of the veins and increased œdema. Here, as in so many other cases, we cannot get a decisive answer to our physiological questions by purely anatomical investigation, but must have recourse to physiological experiment.

The question that we have immediately to decide is whether an increased tissue tension augments or leaves unaltered the flow of blood through the tissues or whether it causes venous collapse and so diminishes the flow. In the former case a back filtration would be possible and in the latter case impossible. I have investigated this point in various regions of the body, the connective tissues of the leg, the tongue as a type of muscular tissue, and the submaxillary gland as a type of glandular tissue. In all these cases I have found that a rise of tissue tension above the pressure in the veins causes collapse of these veins, a rise of capillary pressure, and a diminished flow of blood through the part. In these regions of the body, therefore, absorption of lymph by a backward filtration is impossible.

Hamburger, finding that serum and isotonic fluids are absorbed from the peritoneal cavities that had been dead some hours, concludes that the life of the endothelial cells can have nothing to do with the process and ascribes the absorption to processes of capillary and molecular imbibition,

so that the absorption of fluids would be analogous to the taking up of fluids and gases by animal charcoal. Though these factors probably coöperate to a certain extent in the distribution of the fluid through the tissues surrounding the serous cavities, it is evident that they would be much more pronounced in dying and disintegrating tissues, and could with difficulty explain the taking up of fluids by the bloodvessels. They would certainly not explain the wonderful balance which exists between the intracapillary pressure and the amount of fluid transuded from or absorbed by the bloodvessels. What, then, is the explanation of this absorption? The explanation is, I believe, to be found in a property on which much stress was laid by the older physiologists and which they termed the high endosmotic equivalent of albumin. It must be remembered that the older physiologists used animal membranes in their experiments on osmotic interchanges. These membranes permit the passage of water and salts but hinder the passage of coagulable proteid. The application of semipermeable membranes to the measurement of osmotic pressures showed that the osmotic pressures of salts and other crystalloids are enormously higher than those of colloids such as albumin, and it has therefore been supposed that the osmotic pressure of the proteids in the serum being so insignificant must be of no account in physiological processes. The reverse is, however, the case. Whereas the enormous pressures of the salts and crystalloids in the various fluids of the body are of very little importance for most physiological functions, the comparatively insignificant osmotic pressure of the albumins is of great importance and for this reason. It has been shown that bodies in solution behave in most respects like gases. Now there can be no difference in pressure between two gases in a vessel which have no partition between them or only divided by a screen freely permeable to both gases. In the same way if we have two solutions of crystallised substances separated by a membrane which offers free passage to the water and the salts on either side there can be no enduring difference of the osmotic pressure on the two sides, especially if a free agitation of the fluids on both sides is kept up. The pressures on the two sides will be speedily equalised, and then any flow of fluid from one side to the other will cease. Now the capillaries in the living body represent such a membrane. Leathes has shown that within 5 minutes after the injection of sugar or salt into the bloodvessels the osmotic pressures of the blood and lymph have become equal. Supposing, however, that we have on one side of this membrane a substance to which the membrane is impermeable, this substance will exert an osmotic pressure and will attract water from the other side of the membrane with a force proportional to its osmotic pressure. This attraction of fluid must go on until all the fluid has passed through the membrane to the side where the indiffusible substance is.

Now the capillaries of the body are almost impermeable to proteids. In consequence of this impermeability the fluid which is transuded from the capillaries under pressure contains very little proteid. From what I have just said it follows that the proteid left in solution within the capillaries must exert a certain osmotic attraction on the salt solution outside the capillaries. It is easy to measure the value of this attractive force. If we place blood-serum in a small thistle funnel over the open end of which is stretched a layer of peritoneal membrane soaked in gelatin, and immerse the inverted funnel into salt solution which is isotonic or even hypertonic as compared with the serum, within the next two days fluid will pass into the funnel and will rise in its stem to a considerable height. I have found that the osmotic pressure of the non-diffusible portions of blood-serum measured in this way amounts to 40 mm. Hg. Now you will see at once the importance of this fact. Although the osmotic pressure of albumin is so insignificant, it possesses an order of magnitude comparable to that of the capillary pressures, and whereas capillary pressure determines transudation the osmotic pressure of the proteids of the serum determines absorption. Moreover, the osmotic attraction of the serum for the extravascular fluid will be proportional to the force expended in the production of this extravascular fluid, so that at any given time there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids. With increased capillary pressure we shall have increased transudation until we get equilibrium established at a somewhat higher point, when there is a more dilute fluid in the tissue spaces and therefore a higher absorbing force to balance the increased capillary pressure. With diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid until this becomes richer in proteids, and the difference between its osmotic pressure and that of the intravascular plasma is equal to the diminished capillary pressure.

Here, then, we have the balance of forces necessary to explain the accurate regulation of the quantity of circulating blood, according to the conditions under which the animal may be placed, and it seems unnecessary to invoke the aid of vital activity to explain the process. Certain corollaries of this mode of explanation agree well with observed facts of experiment. Thus, the more impermeable the capillary the smaller will be the amount of proteid exuded with the lymph. A higher capillary pressure will therefore be needed in its production and there will be an equally high force tending to its reabsorption. A rise of capillary pressure will only increase the amount of lymph in the extravascular spaces to a certain extent, but will at the same time cause this lymph to be more dilute, so that there will be a corresponding rise in the force tending towards absorption. In consequence of this sequence of events considerable alterations of capillary pressure may be produced in impermeable

capillaries, such as those in the limbs, without causing any appreciable increase in the lymph-overflow from the limbs. On the other hand, where the capillaries are very permeable very little pressure will be required to cause a transudation, since no work is done in the concentration of a proteid solution, and we find, as a matter of fact, that capillaries where the pressure is lowest—i.e., in the liver—are also those which are the most permeable. Here, moreover, the absorbing force will be insignificant, since there is very little difference in the percentage of albumin between liver blood and liver lymph.

This osmotic difference between blood plasma and tissue fluid will not serve to explain the absorption of proteids by the bloodvessels and would certainly not explain the absorption of serum from the serous cavities. It is difficult, however, if not impossible, to prove that serum or proteid is absorbed by the bloodvessels. In some of my transfusion experiments I have rendered a limb œdematous by means of serum, and in these cases have obtained no evidence at all of absorption by the bloodvessels. There is no doubt that serum may be absorbed from the pleural and peritoneal cavities, but the absorption of these fluids is very much slower than the absorption of salt solutions, and is in fact so slow that the whole of it can in most cases be effected by the lymphatic channels. A slow absorption of serum from tissue spaces by means of the bloodvessels is also physically possible. As the cells of the tissues feed on the proteids of the fluid the serum will tend to become weaker and weaker, so that the watery and saline constituents corresponding to the proteid used up can then be absorbed by the bloodvessels in the way I have indicated.

The physical process which I have described above as causing the absorption of lymph by the bloodvessels must be in action at all times in the body and must, therefore, be a predominant factor in the process of absorption. I have not been able to absolutely exclude the absorption of proteids by the bloodvessels, but, in the absence of direct experimental evidence that such an absorption does occur, the physical factors I have described in this lecture suffice to explain the phenomena of absorption observed both under normal and under pathological conditions.

LECTURE III.

The Causation of Dropsy.

Mr. President and Gentlemen,—Having in the two preceding lectures given a sketch of the working in the normal animal of the processes of lymph-production and lymph-absorption, I wish now to point out briefly the deviations in these processes which are found in the various pathological conditions associated with dropsy and which are responsible for the production of the dropsy. For the better understanding of this question I have drawn up a table of the various changes in the normal conditions of the body which will bring about, or help to bring about, an abnormal distension of the connective tissue spaces with lymph. In this table the changes which are the most important for the production of dropsy are italicised.

Factors Involved in the Causation of Dropsy.

I.—Factors causing increased transudation :—

A. *Increased intra-capillary pressure :—*

a. *Venous obstruction.*
b. Vasodilatation.
c. Plethora.

B. *Increased permeability of vessel wall :—*

a. *Local injury* by mechanical irritants.
,, ,, ,, thermal ,,
,, ,, ,, chemical ,,
b. *Malnutrition.*
c. *General injury by circulating poisons* (*?*).

C. Watery condition of blood (hydræmia).

II.—Factors causing *diminished absorption :—*

A. By lymphatics :—

a. Paralysis of limbs.
b. Obstruction of lymphatic trunks.

B. By veins :—

a. Venous obstruction.
b. Watery condition of blood.
c. Concentrated transudations.

It is important to remember that probably under no circumstances can dropsy be ascribed to an abnormal change in one of these processes. This, however, can also be said of any other diseased condition of the body. We know that the organism responds to a destruction of a

considerable part of the excretory apparatus of the kidney by sending up the general blood-pressure, and so driving an increased amount of blood through the still healthy glomeruli. We cannot thus say that two-thirds of the kidneys are practically inactive under normal conditions because excision of two-thirds causes no change in the general condition of the animal or any appreciable heaping up of urea in the blood. In the same way we find that the organism has various powers of accommodating itself to changed conditions in its lymphatic apparatus, so that it is in most situations difficult to upset the normal balance—i e., cause dropsy—by altering only one of these factors, unless the alteration be of a very extreme degree. In nearly all cases we shall find that the dropsy is due to the simultaneous alteration of two or more of these factors. In the following lecture I shall try to show, so far as our imperfect experimental knowledge allows, which of these factors are affected in the chief forms of dropsy known clinically, and also to show how the normal balance between production and absorption has been in each case upset.

The form of dropsy which is simplest in its pathology is that which is due to venous obstruction. Clinically one meets with dropsy of one extremity due to obstruction of the veins draining that part, either in consequence of pressure by growths or of thrombosis occurring in the vein itself. It would be natural to ascribe this dropsy to the increased lymph-production consequent on the raised intra-capillary pressure behind the obstruction. On investigating the subject experimentally, however, one finds that the causation is not quite so simple. Here, as in nearly all other cases, more than one factor is at work. It is a well-known fact that although obstruction of the femoral vein by a thrombus will give rise to pronounced œdema of the leg, yet ligature of the femoral vein in a healthy man may have no ill-effects whatever. On investigating the subject experimentally we find that ligature of the femoral vein, or even of the lower end of the inferior vena cava, in dogs produces no œdema of the legs. We can, however, produce an œdema if we raise the intra-capillary pressure still higher than in these experiments. Paschutin showed that ligature of all the venous trunks of the dog's leg caused œdema of the foot and ankle. Ranvier has shown that if, after ligature of the inferior vena cava, the sciatic nerve be divided on one side so as to produce dilatation of arterioles on that side, the limb in which the nerve has been divided will become œdematous. Cohnheim has shown that œdema may be brought about by injecting the veins of the leg with plaster-of-Paris. We see, then, that we can produce œdema in a limb provided we raise the intra-capillary pressure to a sufficiently high point. If only one or two veins be obstructed the outflow by the collateral circulation is sufficient in a healthy animal to ward off any œdema. If the lymph be collected by placing a cannula in one of the lymphatics of the leg it will be observed that

after these severe obstructions it becomes red from the presence of red blood-corpuscles. In my first lecture I mentioned that the presence of a quantity of red blood-corpuscles in the lymph showed that the rise of intra-capillary blood-pressure was, so to speak, hyperphysiological, and that one could obtain a very definite increase in the lymph-flow without the appearance of any red blood-corpuscles by raising the intra-capillary blood-pressure to a somewhat less degree. Why, then, do we not obtain œdema of the dog's leg by a simple ligature of the vena cava or femoral vein? In man we know that obstruction of either of these two vessels frequently brings about œdema of the lower extremities and that the œdema fluid present in the interstices of the tissues is colourless and free from red blood-corpuscles—i.e., corresponds to the lymph of moderate venous obstruction. The apparent discrepancy which is found here between clinical observations and the results of experiment depends on the fact which I have emphasised at the beginning of this lecture—viz., that it is impossible to upset the physiological balance, which prevents the occurrence of dropsy, by a moderate disturbance of either of the factors, lymph-production or lymph-absorption. Such an enormous rise of capillary pressure as is produced by filling all the veins of the leg with plaster-of-Paris probably rarely or never occurs under clinical conditions. The occurrence of dropsy in man in consequence of venous obstruction is nearly always due to the simultaneous working of two or more factors. We have therefore to decide, in the first place, why in a healthy animal with a moderate venous obstruction no œdema is produced; and, secondly, what are the subsidiary factors which in man combine with the venous obstruction to bring about an œdema.

In considering the first point, it is essential to remember that in the case of œdema of the limbs we are dealing with the most impermeable capillaries in the body, so that under normal conditions a considerable capillary pressure is required to separate the lymph from the blood, and the lymph so separated has lost the greater part of its proteid. I have already shown how, in consequence of this difference of composition between plasma and lymph, there is an accurate balance between the force tending to produce exudation—i.e, the capillary pressure, and the force tending to produce absorption—i.e., the difference of osmotic pressures between blood plasma and lymph. Now if in a normal animal a vein be obstructed the first effect is a rise of capillary pressure and increased exudation. Since, however, in the affected capillaries and veins the onward flow of blood is checked, the increased exudation must be at the expense of an increased concentration of the blood plasma. This increase in concentration must cause an increase in the difference between the osmotic pressures of plasma and lymph and the absorbing force—i.e., the osmotic pressure of the plasma—will rise until it is equal to the driving-out force—i.e., the capillary pressure. In a normal dog with normal

vessels the processes tending to cause œdema will be pulled up almost as soon as they have started, and no œdema will result from moderate venous congestion. It is easy now to see how we might cause œdema by venous congestion. In the normal animal the factor which restrains the appearance of œdema is the impermeability of the vessel wall, since it is this impermeability which maintains the difference in osmotic pressure between blood and lymph. If, therefore, we can increase the permeability in any way the balance of processes will be lost, exudation will predominate over absorption, and œdema will result. In my first lecture I mentioned to you several methods by which the permeability of the capillaries might be increased, with increased lymph-formation as the result. A much more trifling change in the vessel-wall than is produced by the agents mentioned in that lecture will suffice to cause marked effects on lymph-production where the intra-capillary pressure is considerably raised by venous congestion. Now it must be remembered that the capillary wall is alive and is composed of cells which have a metabolism of their own, and which, like all other cells of the body, are dependent for their proper nutrition on a free supply of oxygen and nutrient material and a free exit for their waste products. Their only function, so far as we know, is the maintenance of their integrity as a membrane with certain properties differing according to the region of the body in which they happen to be situated. If they are injured in any way the resistance of the membrane is diminished and its permeability is increased. Such an injury will follow if they be deprived for some time of fresh supply of nutrient material and oxygen. Cohnheim showed that after long-continued anæmia of the rabbit's ear the vessels became so permeable that the restoration of the normal circulation was followed by pronounced œdema of all the tissues. If the anæmia be of shorter duration no œdema is caused by restoration of the normal circulation, but can be called forth at once by ligaturing the principal vein draining the part. Now a long-continued venous obstruction must affect the vessel-walls in the same way as anæmia, since here also the cells will be starved or asphyxiated. Hence it is that in the chronic conditions which give rise to venous obstruction in man we have the production of œdema. Moreover, in the cases in man in which we obtain dropsy as the result of venous obstruction there are generally other conditions present which tend to damage the vessel-wall and so increase its permeability. Thus the mere occurrence of thrombosis points to a probable diminution of nutrition of the vascular endothelium, and occurs most frequently in patients suffering from anæmia or allied changes in the blood. The occurrence of malignant growths in the neighbourhood of a vein is, moreover, usually associated with a condition of cachexia, and therefore with an impoverished blood-supply to the endothelium. Now we have experimental evidence that the circulation of watery blood through the vessels, if continued for some length of time, alters the vessel-wall to

such an extent that a moderate venous obstruction will produce œdema. I have already mentioned that ligature of the femoral vein in a healthy dog causes no œdema. Cohnheim has shown that if the dog be first rendered hydræmic by bleeding repeatedly at intervals of a few days ligature of the femoral vein will then be followed by œdema. It must be remembered that in this case we have still a third factor which helps in the production of œdema. There is no doubt that a more watery plasma will filter more easily through the vessel-wall, and the diminution of proteids in the plasma must be accompanied by a diminution of the osmotic pressure in the plasma, which is active in absorption. To sum up, we may say that œdema can never be brought about in the limbs by a moderate rise of venous pressure, provided that the capillaries retain their normal impermeability. Œdema will occur as soon as the permeability of the vessels is increased. The injury leading to this increase in permeability may be brought about in any of the following ways: (1) long-continued venous congestion (asphyxia of cells); (2) an excessive rise of intra-capillary pressure breaking down the normal resistance of the cells; and (3) mal-nutrition due to an impoverished state of the blood.

There is one method of producing œdema experimentally about which I must say a few words. Wooldridge showed that if a femoral vein in the dog be ligatured and a solution of tissue fibrinogen then injected, a considerable dropsy of the leg was produced, provided the dog survived the experiment. He ascribed this effect to the production of a disturbed relationship between the blood and the vascular wall. Now it is important to remember that the presence of fibrinogen in the blood has very little importance for the production of lymph. If we "kill" the blood by defibrinating it several times and reinjecting it, the lymph-flow from the thoracic duct remains unaltered. In this experiment of Wooldridge we have a concurrence of several factors. The most important of these is the occurrence of thrombosis in the veins of the leg, and this thrombosis is due, as Wright showed, to the fact that venous obstruction causes a heaping up of CO_2 in the blood, and therefore an increased susceptibility to the effects of tissue-fibrinogen. In repeating this experiment I have always found that the veins in the œdematous parts of the leg were thrombosed, and I am, therefore, inclined to look upon this experiment as very nearly analogous to Cohnheim's plaster-of-Paris experiment. We probably at the same time have an increased permeability of the vessels due to the poison injected, but that this direct action of the poison on the filtering membrane is of subsidiary importance is shown by the fact that if we inject the tissue-fibrinogen into a dog whose blood is defibrinated, so obviating the intravascular clotting, we escape at the same time the production of any œdema.

Much more frequent than the œdema due to local venous obstruction is the œdema which occurs as a consequence of uncompensated or imperfectly compensated heart disease. In

this class of cases we have much more complicated conditions than in the class I have just discussed The œdema of heart disease is generally looked upon as obviously due to a rise in venous pressure and consequent venous obstruction. Taking the existence of a high venous pressure in such cases as a fact, we have to inquire into the causes for this rise of pressure and whether this rise of pressure will extend to the capillaries. To investigate the causation of the dropsy in heart disease, therefore, we must first take into account the alterations in the circulation as well as the alterations in the absorption and production of lymph. The vascular system in an animal can be looked upon as a closed system of tubes having a definite capacity. If the circulation were brought to a standstill the pressures at all parts of the system would become the same. This pressure is called the mean systemic pressure, and in a dog is equal to about 10 mm. Hg. Now in such a system it is evident that the height of this mean pressure depends solely on the relation between the amount of contained fluid and the capacity of the system. If circulation be established by means of the heart's beat, the relation between the capacity and the volume of blood remaining unchanged, no alteration can occur in the mean pressure. All we have is an alteration in the distribution of the pressure. Behind the heart—that is to say, on its venous side—the pressure will sink below the mean systemic pressure ; on the arterial side the pressure will be raised above the mean pressure. If after the establishment of the circulation the action of the heart pump be interfered with, as by damage to the valves, or be checked altogether, the pressures on each side will tend to return to the zero of the system—i e., the mean systemic pressure. There will therefore be a fall of arterial pressure and a rise of venous pressure to this point. It becomes important, therefore, to know at what point in the system the pressure, while the circulation is going on, is equal to the mean systemic pressure. We find by experiment that this turning point of the circulation, so to speak, is situated in the region of the hepatic capillaries, in the abdomen, and about the level of Poupart's ligament in the femoral vein. Failure of the heart pump would therefore cause a rise of pressure in the vena cava and in the large veins of the neck, but a fall of pressure in the portal vein, in the peripheral veins of the legs, as well as in the arteries. It would seem, therefore, that failure of the heart's action, to whatever cause it may be due, can only bring about a fall of pressure in the capillaries of the intestines and peripheral parts of the body. How is it, then, that in morbus cordis we obtain such distinct signs of raised venous pressure in the peripheral parts of the body? The clue to this difficulty is, I believe, to be found in the fact that all cases of uncompensated cardiac lesions are associated with hydræmic plethora This association has been shown actually to exist by the observations of Stintzing and Gumprecht. I wish, however, to show you how such a condition of hydræmic plethora must be

an inevitable physiological consequence of the failure of the heart pump. We have just seen that heart failure causes a fall of pressure on both sides of the intestinal capillaries and limb capillaries, so that the first effect on these capillaries must be a fall of pressure. This fall of pressure, like that consequent on artificial anæmia, will disturb the relationship between the blood and the lymph; there will be an absorption of lymph from the tissue spaces, the blood will be increased in volume, and there will be, therefore, a certain rise of the mean systemic pressure and a shifting of the neutral point towards the periphery. The first effect of heart disease on the limbs will thus be to make them less full of lymph than they normally are, and a new condition of equilibrium will be established between the capillary pressure and the lymph absorption. This sucking of fluid from the tissues will affect also the alimentary canal. The extreme thirst—i.e., the increased absorption of fluid from the alimentary canal—which follows loss of blood is a familiar phenomenon Now this increased absorption of fluid from the alimentary canal will tend to continue until the pressure in the capillaries of the mucous membrane is restored to its normal height. We have, therefore, as the effect of heart failure an initial absorption of fluid from the connective tissues of the limbs and a continued absorption of fluid from the alimentary canal. At the same time, in consequence of the low arterial pressure, the loss of fluid to the body by way of the kidneys is diminished. The result of these last two factors is to cause a continual increase in the amount of circulating fluid—an increase which must theoretically go on until the capillary pressures in the intestines and kidneys are restored to their normal heights. The ultimate result of heart failure is a condition of hydræmic plethora and, therefore, a raising of the mean systemic pressure above its normal height. With the ever-growing balance in favour of absorption of fluid into the bloodvessels the rise of venous pressure extends further and further towards the periphery until the rise affects also the capillary pressure, and in all dependent parts of the body exudation predominates over absorption. The effect of this continued absorption is that the over-full veins present more and more blood to the heart—the heart which was unable to send onwards into the arteries even its normal quantity. It is evident that here we have a vicious circle of events tending to the death of the animal. If, however, the animal be freed from the normal struggle for existence the heart may be able to empty itself and so gradually undergo hypertrophy, and the cardiac disease may be compensated.

It is probable that in the production of the œdema of heart disease we have a concurrence of the same subsidiary factors as were mentioned when dealing with the subject of venous obstruction. In consequence of the failing circulation there is a stagnation of blood in the vessels, and the oxygenation and nutrition of the capillary walls cannot be normally carried out, so that their permeability is increased.

We have here, moreover, a factor which was not present in simple venous obstruction—viz., an obstruction to the outflow by the lymphatics in consequence of the raised venous pressure at the opening of the thoracic duct. We see, then, that the production of dropsy in heart disease is by no means so simple as it at first appears, but that it is due to a complicated series of interacting mechanisms, all of which tend to the death of the organism. We may sum up the sequence of events which ensue on failure of compensation as follows:—
Stage 1.—Heart-pump failure; fall of arterial pressure; rise of pressure in the venous trunks near the heart; fall of capillary pressures in the peripheral parts of the body, in the kidneys, and in the intestine; and absorption of fluid by bloodvessels from intestines and peripheral tissues.
Stage 2.—Continued absorption from the alimentary canal with diminished excretion from the kidneys, and production of hydræmic plethora with rise of mean systemic pressure.
This leads to Stage 3—rise of capillary pressure in all dependent parts of the body, capillaries injured by malnutrition, and excessive transudation, leading to dropsy.
Stage 4.—The continued hydræmic plethora leads to ever-increasing over-filling of the heart cavities and to ultimate failure of the already incompetent heart.

I have already described to you Wooldridge's experiment on the production of œdema by the injection of tissue fibrinogen. This observer ascribed the dropsy of heart disease chiefly to an auto-intoxication of the organism by the fibrinogens contained in its lymph. Now it is apparent that the enormous rise of pressure in the liver in heart disease, which is instanced by the swelling and pulsation of this organ, must give rise to a greatly increased flow of lymph from the thoracic duct into the blood, so that we have the conditions present which are necessary for this auto-intoxication to take place. It is possible that there may be a certain amount of poisoning of the organism effected in this way, but in the light of my experiments, which I described to you recently, I do not think that this auto-intoxication can be looked upon as at any rate the chief factor in the production of the dropsy. I believe that careful experimental investigation will show that the production of the dropsy can be perfectly explained by an upset of the balance between the physical conditions which normally control filtration from, and absorption by, the bloodvessels in different regions of the body.

In these two classes of dropsy the primary factor is an alteration in the mechanical conditions of the circulation, bringing about a rise of capillary pressure and increased exudation in the part affected. In the next class with which we have to deal the primary change affects, not the intra-capillary pressure, but the vessel-wall. A change of the filtering membrane is thus produced, so that it becomes more permeable and allows, under normal capillary pressures, an excessive exudation, and the exudation is richer in proteids than is the normal lymph of the region in question. Since an alteration of the

vessel-wall is one of the main features of inflammation Cohnheim has classed all œdemas in which the primary affection is that of the vessel-wall as inflammatory œdemas. In my first lecture I pointed out various means by which the permeability of the capillary wall might be increased, and showed how, under these circumstances, the limb capillaries might be reduced to the condition of liver capillaries. Here, as in all other cases in which œdema occurs, we have more than one factor at work. The capillary pressure of the part remaining at its normal height, the increased permeability allows of a largely increased exudation—there is increased lymph-production. The lymph, however, contains more proteids than normal, so that the difference of osmotic pressure between it and the circulating plasma is diminished, thereby causing a diminution of the absorbing force In all cases of inflammatory œdema these two factors are at work concurrently—increased production and diminished absorption. This alteration of the vessel-wall may be brought about in two ways: either by the application of injurious agents to the vessels of any given part or by the introduction of poisonous substances into the blood-stream. Thus a local alteration of the vessel-wall may be caused by application of mechanical violence, crushing the tissues. It is possible that in this case we have at work, not only the direct result of the injury on the vessel-wall, but also a secondary injury of the capillaries in consequence of the development of poisonous products of disintegration in the bruised tissues surrounding the capillaries—e.g., tissue fibrinogens. We can produce the same change by exposing the tissues for a few minutes to a temperature of over 50° C. or by depriving them for some time of the normal blood-flow. All the local œdemas produced by inoculation of chemical or microbic poisons at the point of inoculation are of this nature. The swelling produced by the sting of a bee or by the inoculation of anthrax is due to the deleterious effects of the poison injected on the capillary walls at the point of inoculation. Metchnikoff has shown that the emigration of white blood-corpuscles occurring in inflammation is to be looked upon as a physiological reaction of the organism directed to its preservation, and it seems probable that the salutary import of this process may also hold good for the local œdema. As the result of the injury of the capillary walls a more concentrated lymph is poured out—i.e., a lymph containing more proteids to serve for the nutrition of the cells of the part. Whether or not this is the case, the presence of this concentrated lymph must be of great use to the organism in the regeneration of tissue which follows on inflammation.

We know less clinically of the cases in which the injury to the vessel-wall is brought about by a poison circulating in the blood. I have already described to you the class of animal poisons which were grouped together by Heidenhain as his first class of lymphagogues. I showed in my first lecture that the chief action of these bodies was on the

capillaries of the liver. Their action, however, is not absolutely confined to this organ. I have experimental evidence that there is a certain degree of increased permeability of the intestinal capillaries after the injection of these bodies—an increased permeability which is brought into evidence only after raising to a certain extent the pressure in these capillaries. These bodies, however, can also affect the capillaries of the skin. In a number of the experiments in which these bodies have been injected we may observe a rapid development of an urticarial eruption on the skin, and you are all familiar with the fact that the ingestion of the animals from which these bodies are derived (mussels, crayfish, lobster) is often followed in man by an eruption of urticaria, which may or may not be accompanied by other symptoms of poisoning. The sudden onset of urticaria and similar eruptions in man, combined with the fact that their distribution may correspond with that of a certain nerve, has given rise to the supposition that these œdemas may be nervous in origin; that, in fact, we have an increased production of lymph under the direct influence of the nervous system.

If lymph were to be looked upon as a secretion we should expect from analogy with other secretions to find it subject to the central nervous system, and at the time when I was fully imbued with the new faith, the secretory hypothesis, I made diligent search for direct evidence of the influence of the nervous system on lymph-formation. The results of my experiments were, however, opposed to such a hypothesis. In every case where nerve section or excitation gave rise to increased lymph-production in any part, I found that the increase was due primarily to a rise of capillary pressure in the part and was, therefore, only a secondary effect of the interference with the nerve. The best-marked case of so-called nervous œdema is the unilateral œdema of the tongue, which may be produced by stimulating one lingual nerve. Now the stimulation of the lingual nerve causes extreme vaso-dilatation of the vessels of the tongue, and the increased lymph-production in the tongue is evidently the direct result of this vaso-dilatation and consequently increased capillary pressure. Here, as in all other cases where one wishes to produce œdema, one must not rely simply upon one factor. In the majority of cases the œdema produced by stimulating the lingual nerve—i.e., by a simple rise of capillary pressure—is but slightly marked. One can, however, produce a very fine œdema of the tongue if one aids the filtration process and diminishes the forces tending to absorption by the injection of a large amount of normal saline solution into the circulation. I believe that all cases of so-called nervous œdema can be explained by the circulation of some lymphagogue substance in the blood combined with local vaso-dilatation, which may often be hysterical or central in origin.

One of the most important forms of dropsy—i.e., that which accompanies renal disease—was placed by Cohnheim

in the category of inflammatory dropsies, and this seems a necessary conclusion in view of the fact that we are unable to trace any adequate mechanical cause, such as raised capillary pressure, for the increased transudation. We know very little more about this form of dropsy than was known in Cohnheim's time. The discovery of lymphagogues naturally suggests that the change in the vascular endothelium in Bright's disease, which leads to its increased permeability, may be due to the circulation in the blood of some poisonous substance belonging to this group of bodies. This possibility is favoured by the results of one experiment in which I injected blood serum from a uræmic patient into a dog and obtained marked quickening of the lymph-flow from the thoracic duct. The conditions in Bright's disease are, however, much too complicated for us to come to any conclusions without carrying out a long series of experiments on the subject.

This cursory examination of the alterations of physiological conditions present in the various forms of dropsy brings to light one important fact—a fact on which much stress has already been laid by Cohnheim. In all cases the primary cause of œdema is an increased transudation. The normal mechanism of absorption may for some time hold this process in check, but in all cases where the increased exudation endures any length of time subsidiary events cause a breakdown of the absorbing mechanism and the occurrence of œdema. On the other hand we know of very few cases in which œdema can be ascribed primarily to a diminished absorption. Obstruction of the lymphatics can rarely occur, owing to the multitudinous anastomoses of these canals; when a complete obstruction does occur the result seems to be rather a general hypertrophy of the connective tissues (as in elephantiasis) than a true œdema. In all cases, however, where we find dropsy we may say that in addition to the primary increased exudation there is also a derangement of some part of the absorbing mechanism.