ON THE FACTORS CONCERNED IN THE PRODUCTION OF PULMONARY ŒDEMA.

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In most of the previous work on pulmonary œdema, stress has been laid on the part played by the mechanical factors involved in its production. In view of the ease with which the mechanical conditions of the circulation can be controlled in the heart-lung preparation, and the frequency with which at some time or other in the course of experiments employing this method œdema of the lungs supervenes, it seemed to us that a study of the factors influencing the onset of œdema in the heart-lung preparation might throw light on the general question of its causation. In this preparation it is easy to measure at any time the pressure in, and the flow through, any part of the circuit—whether in the heart cavities or the vessels—so that an analysis of the mechanical factors at work can be made at any given moment. Such control is impossible, as such measurements are impossible to procure, in the intact animal.

Methods. The heart-lung preparation was prepared in the usual manner as described by Führer and Starling(1). Dogs were used in the experiments, anæsthetised by intravenous chloralose (0·1 gm. per kilo) following ether-chloroform induction. The circulating fluid was defibrinated blood, a sufficient quantity being obtained by bleeding a second dog, and using the mixture. Systemic pressure was taken by a mercury manometer near the outflow from the heart, and pressures from a branch of the pulmonary artery to the upper lobe of the right lung, and from the right or left auricle were taken by water manometers. The coronary flow was measured by means of a Morawitz cannula introduced through the right auricle. The temperature was maintained at 36° C. The average weight of the dogs was 10 kilos.

The course of experimental pulmonary œdema is difficult to follow with any degree of accuracy. The indicators used have always been gross changes in the appearance of the lungs upon the collection of a sufficient amount of fluid, or the production of râles of various types. In order to

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obtain more exact knowledge as to the time of onset and progress of the œdema, we adopted a method suggested by Dr D. T. Harris, of determining the changes which occurred in the electrical conductivity of the lungs. As expected, this was found to increase up to a certain point, in proportion to the amount of œdema fluid which collected in the lungs. The late collection of fluid in the larger bronchi and trachea, however, did not appear to modify the conductivity to any appreciable extent.

The apparatus was the usual Wheatstone Bridge with an induction coil and telephone receiver, as used in determining the conductivity of electrolytes; current being supplied by two dry cells. (If it is so desired, audion valve amplification and a loud speaker can be added.)

The electrodes first used were two needles held fixed distances apart, penetrating the lungs to fixed depths. Upon increasing the distance between the needles, however, it was found that a proportionate decrease in conductivity did not occur (Fig. 1, *A*, *B*, *C*). In order to ascertain

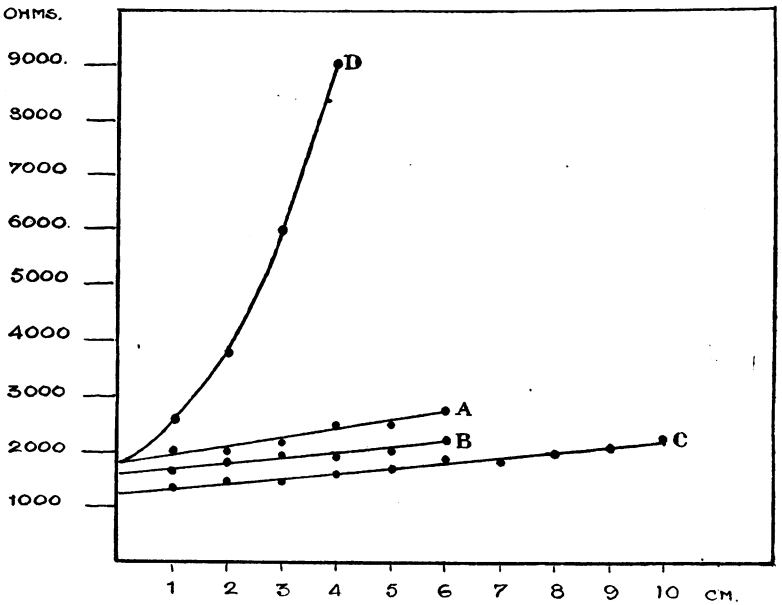

Fig. 1. Measurements of conductivity along dead lung tissue, with approximate curves. *A*, *B* and *C* represent measurements along intact lung; *D*, along a strip of excised tissue. All the curves exterpolate to a finite quantity of ohms.

whether this was the case because of extremely large contact resistances, determinations were made upon excised strips of lung tissue, with small relatively uniform cross-sections of about 1 sq. cm. On comparing the

curve thus obtained (Fig. 1, *D*) with the former, the cause of the phenomenon became evident. The lines of current are apparently distributed throughout the lungs as in an electrolytic cell, the position of the contacts being of relatively little importance. As all these curves should exterpolate back to zero, the finite electrical resistance which appears by this means was interpreted as occurring at the contacts. Accordingly, although the initial amount of electrical resistance depends partially upon the electrodes, the changes which occur during the course of œdema were relatively the same whether these contacts consisted of two needles penetrating the lung, two plates applied to opposite sides of the lung, a needle imbedded in the tracheal wall with another penetrating the lung, or a needle in the tracheal wall with a plate applied to a lung.

The needle electrode on the tracheal wall, with a plate on the lung was finally adopted, as this method has several advantages over the others. Firstly, when a needle penetrates the lung, there is an initial increase in conductivity, presumably due to effusion around the injury. Secondly, the plate and needle involve but one variable contact, the tracheal electrode being kept constant by covering its entrance with a small wet pad. The variation in the other contact only occurs to any marked extent as the surface of the lung becomes wetter during the course of the œdema. And finally, the application of a suitably curved electrode (Fig. 2) is exceedingly simple, the electrode being passed between

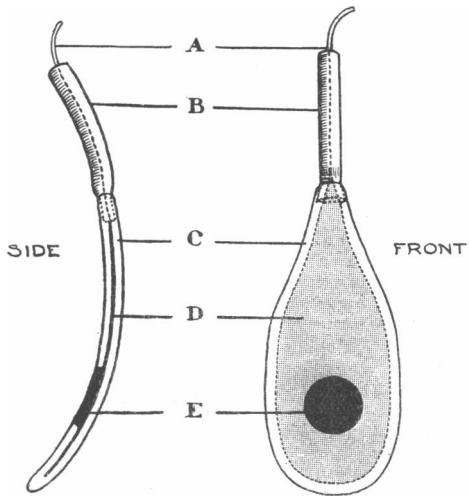

Fig. 2. Plate electrode used on lung. *A* = wire; *B* = rubber insulation; *C* = paraffin shell; *D* = metal plate soldered to wire; *E* = exposed metal contact soldered to plate.

the chest wall and the lung, and held *in situ* by the lung itself, which slips over it, but which does not alter the conductivity.

Care must be taken to prevent certain sources of error. The trachea must not be allowed to dry around the needle electrode, the plate electrode must always be completely covered by the lung, and the degree of inflation of the lungs must be kept constant by controlling the apparatus used for artificial respiration. There is even a variation of the null point from inspiration to expiration, so that readings should be taken either at one phase or the other. There is little error caused by current short-circuiting around the other tissues of the animal. Measurements kindly made during an experiment by Mr L. Bayliss showed that a current of ·5 micro-amperes passed along the chest wall parallel to one in the lungs of 30 micro-amperes. Furthermore, this fraction is a constant, and should not influence the œdema curve. On the other hand, there is considerable alteration in conductivity if a pool of blood be allowed to accumulate in the thoracic cavity, and this should be prevented by passing tube drains through the most dependent portions of the chest wall on either side.

The conductivity curve obtained during œdema was checked against the percentage weight of water gained by the lungs in the following manner. Pulmonary œdema was produced in a series of intact cats by intravenous infusion of normal saline solution. (It was not thought necessary to determine the effect of the added electrolyte to the blood, as precisely similar changes in conductivity were obtained when œdema was produced by several other less practical methods.) At intervals during the course of the infusion the conductivity was measured, and small portions of the lungs excised. These pieces were then dehydrated to constant weight in an oven at 110° C. It was found that a maximal gain in water of from 80 p.c. to 92 p.c. or 93 p.c. took place synchronously with the change in conductivity (Fig. 3). Variations in the blood content of the pieces of lung were apparently not sufficient to produce an error, as constant results were obtained, both for non-œdematous and fully œdematous specimens.

A further check was made to determine whether increased blood flow through the lungs would alter their conductivity. This was found not to be the case in the heart-lung preparation, where the amount of blood flowing through the lungs was varied by altering the inflow into the right heart.

In the present communication only those experiments will be considered in which pulmonary œdema developed spontaneously in the

absence of other complicating features, or in which it was artificially produced. In most instances the œdema came on slowly, but in others, generally as the result of some special procedure or accident, the onset was rapid. For the sake of convenience we have dealt with these two types of experiment separately, although probably no hard and fast line can be drawn between them.

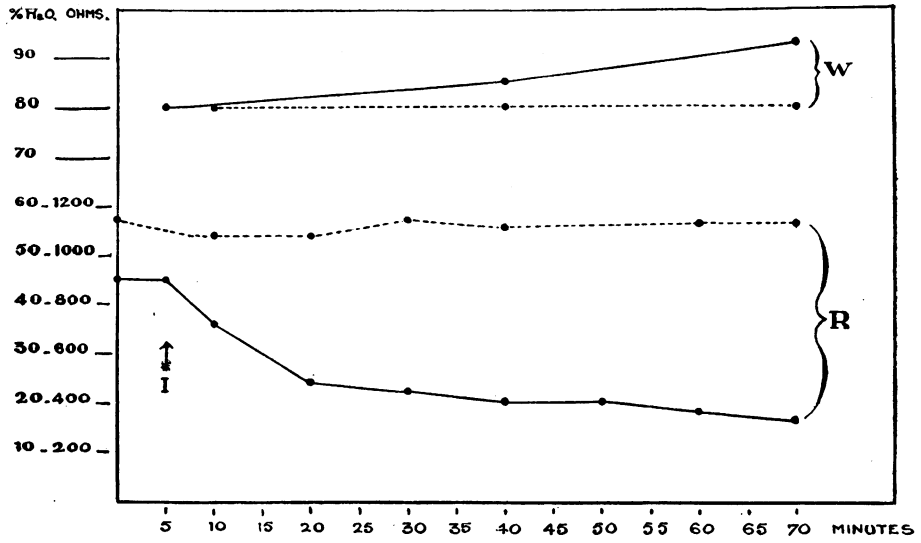

Fig. 3. Measurements made on lungs of intact cats during pulmonary œdema caused by infusing normal saline. W = percentage of water by weight; R = resistance. Dotted lines signify controls.

Slow œdema.

The heart-lung was prepared as rapidly as possible, the apparatus arranged for the observations, and then none but absolutely necessary manipulations performed until end-stage œdema was present. In eight experiments œdema appeared at any time from 1 to 4 hours after the completion of the preparation, the usual time being 3 hours.

In each of the experiments, the electrical resistance of the lungs dropped slowly, until when it had about halved its original amount (measured in ohms) the evidence of gross œdema was apparent. At this point the lungs were wet and moist râles were heard, but we shall refer to the stage as "early" œdema, for as yet no collection of fluid could be made out in the trachea. From this point on, very little change in conductivity took place, but within another ½ to 1 hour, the larger bronchi

and trachea were filled with fluid, which stage we have called "late" œdema.

From the beginning of the experiment to early œdema the coronary output gradually increased, the rise as a rule being absolutely synchronous with the change in conductivity, so that at the early œdema point the output per minute was usually about double its original figure. From early to late œdema, however, while the conductivity showed practically no alteration, there was a very striking increase in coronary flow so that some final readings were as high as five times the original figure.

Either the inflow to the heart or the output was kept constant during each experiment, usually the former. With a constant inflow, the output of the heart as measured in the usual manner diminished as more blood flowed through the coronaries. The total output (systemic plus coronary), however, kept fairly constant, in accordance with the recent work of Anrep and Bulatao(2); slight variations occurring probably due to unavoidable changes of the inflow during measurement, etc.

Up to the time of early œdema there was uniformly a slight total rise in pulmonary arterial pressure of from 2–5 cm. water, occasionally preceded by an original drop of from 2–3 cm. from the first reading (Fig. 4). As removing the coronary cannula at early œdema gave a further rise up to 7 cm., proportionate with the amount of rise when the cannula was *in situ*, most of the rise in the pulmonary arterial pressure of early œdema was probably due to the added inflow from the coronaries; the initial rise when the cannula was *in situ* being from the venæ Thebesii and the posterior cardiac veins.

The pulmonary arterial pressure, in the interval between the onset of œdema and its later stages, rose continuously and rapidly, and the final readings were usually at least triple those taken at the beginning of the experiment. As has been previously stated, the coronary output also increased markedly. At the end point it was not possible to obtain a further proportionate rise in pulmonary pressure by withdrawing the coronary cannula, and it is likely that other factors besides the increased inflow into the right heart contribute toward the causation of this extreme elevation of pressure. It seems likely to us that, in view of the obvious microscopic damage to the blood vessels, described later, changes in the lumina from desquamated and swollen intimal cells would be sufficient to cause a certain amount of damming back of the blood stream. At the same time, the accumulation of fluid in the alveolar spaces may also exert sufficient pressure on the blood vessels to alter the resistance to passage of blood through them. Such suppositions of course cannot be

proved, but the facts are, that in this type of experiment the œdema and the increased coronary flow occur before the rise of pulmonary

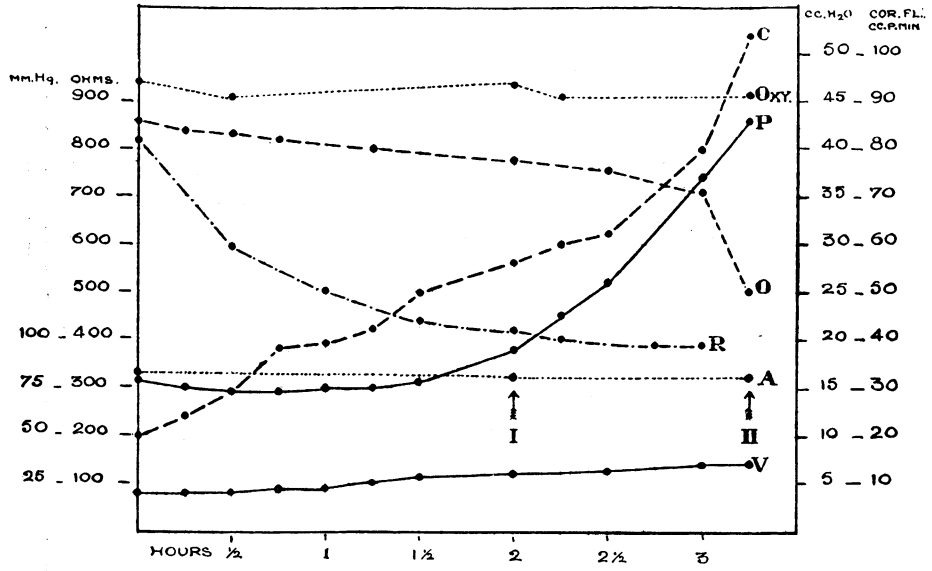

Fig. 4. Spontaneous slow œdema. Oxygen given throughout. Inflow kept constant, and total output (systemic plus coronary) between 536 and 504 c.c. blood per minute. Early œdema present at *I*, and late œdema at *II*. *C* = coronary output in c.c. blood per minute; *Oxy* = percentage oxygen saturation of the blood; *P* = pulmonary arterial pressure in cm. water; *O* = systemic output in c.c. blood per 10 seconds; *R* = electrical resistance of the lungs in ohms; *A* = systemic arterial pressure in mm. mercury; *V* = inferior vena cava pressure in cm. water.

arterial pressure, and that in the early œdema the rise in coronary flow accounts for any rise in pulmonary arterial pressure which occurs.

In no case was there more than a very slight increase in either auricular pressure up to the time of late œdema. In one experiment a sufficient degree of heart failure was present to produce a rise of right auricular pressure of 5 cm. water. This was reduced to 3 cm. by removing the pericardium (Starling(3)). At the same time, however, there was an increase in pulmonary arterial pressure of 23 cm. water.

Desaturation of the blood was always present to a certain extent after the first hour or so of an experiment if no oxygen was given, and as œdema progressed it became very marked. Early œdema gave an average saturation of 74 p.c., while in late œdema readings of anywhere from 50 p.c. to 60 p.c. were obtained. In order to determine whether the increased coronary flow was a result of this condition of the blood

(Hilton and Eichholtz(4)), oxygen was given throughout two experiments. Even during the most marked œdema, sufficient oxygen passed into the remaining aerated alveoli to keep the saturation well up (Fig. 4), and precisely the same changes in the coronary output, as well as in the other particulars of the experiment, took place.

As the rise in pulmonary pressure in these experiments was so evidently secondary, and as during the entire course of the œdema the coronary flow steadily increased, the initial changes were in all probability vascular. These changes were outwardly manifested by increased permeability and consequent œdema in the vessels of the lungs, and by dilatation in the vessels of the heart. The factors in the blood, or otherwise, upon which the vascular changes in this type of experiment depend, have not been determined, but will be discussed later.

Rapid œdema.

In 4 experiments rapid pulmonary œdema was produced within ½ to 1 hour, after the heart-lung had been prepared. As the cause of the

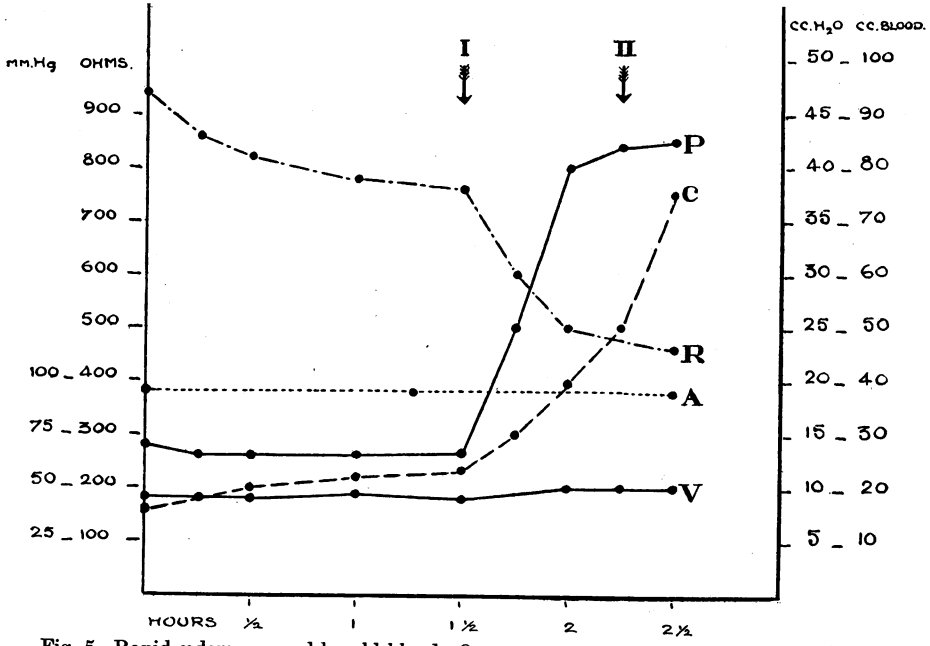

Fig. 5. Rapid œdema caused by old blood. Oxygen not given. Inflow kept constant. No œdema present at *I*; 100 c.c. old blood added and 100 c.c. good blood withdrawn. Late œdema present at *II*. *P* = pulmonary arterial pressure in cm. water; *C* = coronary output in c.c. blood per minute; *R* = electrical resistance of the lungs in ohms; *A* = systemic arterial pressure in mm. mercury; *V* = inferior vena cava pressure in cm. water.

œdema was of the same general nature in two experiments, and probably as well in the third, and as all the observations were uniform, one typical experiment is shown in Fig. 5.

In the first experiment 100 c.c. of dog's blood, drawn the previous day and kept on ice, were added to the inflow reservoir and the same amount of good blood withdrawn. In the second, 5 c.c. of 1 p.c. silver nitrate solution was added to the reservoir. The third experiment was originally intended to demonstrate the usual form of slow œdema, but rapid œdema took place instead. The only reason that could be found was that ordinary ink had been used to colour the manometer solutions and that a certain amount had inadvertently made its way into the blood stream.

In these three experiments the early stages of œdema, so well marked in those previously described, were obliterated by the rapidity of progression from the onset to the final stage. In the first two experiments, the instillation of a toxic agent caused an immediate drop in the electrical resistance of the lung, and a rise of pulmonary arterial pressure to the level of late œdema. In the third experiment the pressure was high from the beginning and gradually rose to the end figure within a short time, somewhat confirming our belief as to the cause. The coronary flow, and all the other features of the experiments rapidly became identical with those in the late stage of slow œdema.

In one experiment, œdema was rapidly produced in an entirely different manner. A certain amount of torsion of the lobes of the right side was present at the beginning of the experiment, which caused a slight obstruction to the venous outflow of the lungs, while at the same time not impeding the arterial inflow. The pulmonary arterial pressure rose gradually to 52 cm. water during the course of half an hour, and a well marked late stage œdema developed throughout the lungs. The auricular pressures remained low, and what is of extreme interest, the coronary flow only rose to 30 c.c. blood per minute, whereas in the other experiments it had often reached 90 to 100 c.c. at the end stages.

In the first three of these experiments the increased permeability of the lung vessels, and the dilatation of the cardiac vessels can be said to be due to a known toxic agent in the blood stream. The fourth experiment, in which œdema was produced by an entirely different mechanism, shows a relative absence of increased coronary outflow.

Histological changes in lungs and heart.

In order to correlate, as far as possible, the data given above with the actual condition of the vessels, sections of the lungs and heart were prepared at various stages of œdema. The tissues were fixed in Zenker's solution, prepared in the usual manner, and stained either with hæmatoxylin-eosin, or hæmatoxylin-Bassini. Three sections are described:

1. *Lung of moderately advanced œdema.* All the cells in the walls of arteries, arterioles and veins show swelling, while the nuclei of the intimal cells are occasionally poorly stained and broken. In some portions of the section there is even absence of the intimal cell nuclei. The capillaries are dilated and filled with erythrocytes, and their endothelial cells show similar nuclear changes. There is some swelling of the epithelial cells of the bronchial mucous membrane and occasional desquamation. There are collections of desquamated bronchial and alveolar cells in the lumina of the bronchi. The nuclei of the alveolar epithelial cells are generally normal in aspect, but the alveolar spaces are also filled with desquamated cells and amorphous masses, which probably consist of coagulated proteins.

2. *Lung of severe œdema.* The intima of the arteries, arterioles and veins in this section, shows marked alterations in the appearance of the cell nuclei. These are frequently absent, and the remainder poorly stained and vacuolated. There is an escape of erythrocytes through the walls of the arterioles. The capillaries are dilated, partially filled, and their cells show similar nuclear changes. The bronchi and their branches, as well as the alveoli, show similar changes as in the previous section, to a more marked degree. The bronchial epithelial cells occasionally show vacuolisation as well as swelling.

3. *Heart of severe œdema.* The intimal cells of the larger coronary branches have, as a rule, poorly stained nuclei, and there are aggregations of erythrocytes surrounding these vessels. The larger veins have the same appearance, but even to a more marked degree. The capillaries show exactly the same changes as in section 2. The heart muscle cells show some fragmentation, and in certain places are rolled up or wavy, but on the whole they appear normal, with well-stained nuclei. Collections of erythrocytes are seen interspersed among the muscle cells.

More sections are not described as they all show essentially the same changes, the variations being of degree only. There is some difference in appearance at the various portions of each section, the above description representing the average picture. The principal pathological process seems to be one involving the intimal layers of the small vessels and the capillaries of the heart and lungs. There are also, however, degenerative changes of other structures to a lesser extent, evident from the appearance of alveolar and bronchial epithelium and the heart muscle.

In these sections we do not observe one of the changes commonly seen in human pulmonary œdema, namely the filling of alveolar spaces with coagulated œdema proteins. This is probably due to the fact that the pieces of lung were excised and fixed immediately upon the inception of the various stages of œdema. At this time fluid can easily flow out and be expressed by the contraction of the tissue, while con-

siderable dehydration can take place during the preparation of the section.

Possibly the most important question to be considered is what part of the apparent damage to the vessels is caused by some direct toxic action of unknown nature, and what part is caused by imbibition and passage of fluid through the cells during the course of the œdema. The only direct evidence we have to throw light on this point is that marked œdema caused by saline infusions shows but little vascular change when compared to the other varieties. In some respects, however, they are not quite comparable. But the simultaneous alterations in the microscopic picture of the heart is suggestive of the fact that the vessel changes are primary and not secondary to the œdema. We must reiterate, that despite the changes in the appearance of the heart muscle, no gross heart failure was present at any time.

Discussion.

Most experimental work on pulmonary œdema has been by way of a search for a single etiological factor, to be applied under all circumstances. There are, however, a number of known factors, and presumably as many more unknown, which always participate. Their relative importance probably varies from case to case. We will deal here, in the light of our experiments, with the different factors to which the preponderant part in the production of lung œdema has been ascribed by various writers on the subject.

Increased pressure in the pulmonary blood vessels. When the heart and lungs are normal, the chief cause for the elevation of pulmonary arterial pressure is an increased venous inflow to the heart. As was shown by Patterson, Piper and Starling(5) in the heart-lung preparation, the circulation rate under these circumstances is increased to a marked degree through cardiac adaptation, without any other signal disturbance, and without altering the pulse rate. Moreover, in normal animals, the added compensatory mechanism of an increased pulse rate takes part. In the absence of cardiac failure, with the circulation intact, there is no reason to believe that by this means a sufficiently great filtration pressure is produced in the pulmonary vessels to cause transudation. Of course, such a rise of pulmonary pressure as is incidental to the generally increased circulation rate may accelerate the production of œdema in the presence of any other factors.

As was described by Führer and Starling(1), increasing the peripheral resistance will also increase the pulmonary pressure. The work

of Anrep and Bulatao(2) proves that this is not the result of "back-pressure," but of the increased total output of the heart due to added coronary flow. Accordingly there is no more reason to believe that this means alone could produce œdema, than directly altering the inflow.

In the case of true "back-pressure" œdema, the left ventricle is not able to express its contents completely, and the diastolic pressure is accordingly raised by the residual blood within it. At the same time dilatation takes place. Owing to the ensuing inability of each of the chambers of the heart to fully express its contents, as well as to possible valvular incompetence, the increased pressure is then transmitted to the lungs and right heart in turn. The simple fact is often overlooked that beyond a certain point this process is part and parcel of cardiac failure, and the extremely high pressures to which the lung vessels may thus be subjected by a failing heart may be sufficient to produce transudation. Matsuoka(6) says "in the production of obstructive œdema the output of the heart may be diminished to a minimum, and the pressures in the pulmonary artery, the inferior vena cava, and the right auricle may be increased to a maximum, all quite independently of the height of the arterial pressure and the amount of venous inflow." This description is used to illustrate œdema brought about through increased systemic resistance, but merely indicates heart failure taking place because of an impossible burden. True "back-pressure" œdema may also occur when there is an obstruction in the pulmonary veins. This is experimentally possible, but most infrequent as a natural patho-physiological process save where there is embolism or a left auricular thrombus (Wiggers(7)).

Another hypothetical mechanism of œdema, originally put forth by Welch in 1878, is a *dissociation of the outputs of the ventricles*. It is true that he produced pulmonary œdema in this manner by injuring the left ventricles of rabbits, but that such a condition can occur spontaneously has never been well established. Temporary differences in output take place upon alteration of the venous inflow directly, or through the medium of the peripheral resistance. But immediately upon the engorgement of the lung vessels, automatic regulation of the ventricles takes place, so that the condition becomes that which we have described before. Definite failure of the left ventricle is hardly conceivable, save for very short periods of time, without a concomitant failure on the right. Increased left intraventricular diastolic pressure is immediately transmitted to the right side, causing equal dilatation and failure; while any disturbance in coronary circulation instantly affects the nutrition of the musculature of the right heart. As any dissociation of output can only

occur as an extremely transitory phenomenon, we do not believe that *per se* it can play any important part in the causation of pulmonary œdema.

In our experiments it has become evident to us what heights the pulmonary pressure may reach, in the absence of cardiac failure, secondary to œdema of the lungs. When this condition obtains, however, heart failure is imminent, in which circumstances a vicious circle would be established. Here lies the value of decreasing the venous inflow to the heart, *i.e.* clinically by venesection, and preventing such a condition from occurring, by lowering the already high pulmonary pressure.

Changes in the blood. Changes in the blood may produce œdema, as can readily be demonstrated; in fact Barry(8) believes the heart-lung œdema to be caused mainly by dilution of the blood colloids. Saline infusions probably act in this manner, it being difficult to believe that small amounts of normal saline added to the blood should act other than by facilitating simple filtration. Such substances which when added to the blood, or produced therein, will deleteriously affect the blood vessels, are discussed below.

Changes in the blood vessels. It must be remembered that in the heart-lung preparation, at the present time, it is necessary to use defibrinated blood as the circulating medium. Such blood has undergone profound changes in the process of defibrination, which, without interfering with its functions as a carrier of oxygen and carbon dioxide, as well as of soluble food and waste products, have given rise to the production of undefined substances which may have a toxic effect on the blood vessels and tissues. The strong vasotonic action of such blood is well known, and Eichholtz and Verney(9) have shown that this action makes it impossible to maintain circulation through an excised kidney by means of a mechanical pump. The circulation in a heart-lung kidney preparation is possible only because the lungs and possibly the heart exert some kind of detoxicating influence on the blood, removing its constricting effect on the renal vessels. A few minutes standing in glass leads to the fresh formation of the toxins, so that after 24 hours, kept defibrinated blood becomes extremely toxic for the heart-lung preparation.

But the absorption of these toxins in the heart-lung preparation is not without deleterious effects. Microscopic examination shows gradually increasing defects in the intima of the blood vessels and in the capillary endothelium. Any such change is known to increase the permeability of the capillaries—and we are therefore justified in regarding these capillary changes as the prime factor in the causation of the pulmonary

œdema. Any mechanical factors are only secondary in importance. If, however, the toxic action of the blood is excessive, as is the case when 24 hours old defibrinated blood is used, or when salts of the heavy metals are added, a marked change is produced at once in the capillary endothelium, giving rise to increased resistance and stasis in the capillaries and a marked rise of pulmonary arterial pressure. But this rise of pressure is secondary to the endothelial change, which is responsible for the increased exudation and œdema, and cannot itself be regarded as the cause of the œdema.

The great rise of pulmonary arterial pressure which comes on at the end of an experiment, when massive œdema of the lungs has already developed, is probably due to the changes in the vessel walls and the pressure exerted by the fluid filling the intercapillary spaces.

We should be inclined to ascribe a similar pathogenesis to many cases of acute pulmonary œdema in man, and to regard a toxic influence on the capillary walls as primarily responsible for the increased exudation. In these cases the extreme secondary rise in pulmonary pressure is probably also present. Furthermore, as not all clinical cardiac failure is accompanied by pulmonary œdema, the question arises as to whether in cardiac œdema some direct action of the blood on the capillaries does not take place either through anoxæmia or the formation of toxic substances.

Conclusions.

1. A method is described for following the course of pulmonary œdema.

2. In the heart-lung preparation, lung œdema supervenes at varying periods after the beginning of the experiment. In most cases the onset is gradual and a number of hours elapse before the œdema becomes so marked as to put an end to the experiment. Occasionally the œdema is much more rapid in onset, and it is always produced within a very short time if defibrinated blood which has stood for 24 hours, or metallic poisons are added to the circulating fluid.

3. In both cases, namely slow and rapid œdema, degenerative changes are found in the intimal cells of the blood vessels and in the capillary endothelium of the lungs and heart.

4. The principal cause of the œdema is the injury to the capillary endothelium, and the greater permeability thereby produced.

5. There is a gradual steady increase in the flow through the coronary vessels in the course of the experiment—which may amount to five times the original rate. Since changes in the intima of the cardiac vessels are

observed similar to those described in the lungs, we regard this increase as the response of the coronary vessels to the toxic effect exerted by the defibrinated blood.

6. The œdema, in its initial stages, is unattended by any changes in the resistance to the flow of blood through the lungs, as judged by the pulmonary arterial pressure. The small rise of pulmonary pressure observed is due entirely to the greater flow through the coronary vessels.

7. In the late stages of both slow and rapid œdema, there is a secondary marked rise in pulmonary arterial pressure. This is probably due to the mechanical influence of the œdema fluid on the pulmonary blood vessels, and to changes in the blood vessel walls themselves.

8. We suggest that in certain cases of pulmonary œdema, as observed clinically, similar effects may take place through toxic action of the blood on the pulmonary vessels. This factor may enter into the causation of cardiac œdema.

This work was conducted in the laboratory of Prof. E. H. Starling, and we are greatly indebted to him for his continued guidance and help. We also wish to express our thanks to Prof. A. V. Hill and Dr Anrep for many valuable suggestions.

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