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PULMONARY OEDEMA: PHYSIOLOGICAL CONSIDERATIONS *

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In this paper I propose to attempt to evaluate our knowledge of the mechanisms of acute pulmonary oedema in experimental animals, and to enquire how far it can be applied to our understanding of the phenomenon in man. Our knowledge of the mechanisms of lung oedema is extremely meagre; yet in some respects it may be integrated, with advantage to future investigations. The first issue which should be raised is the relation of pulmonary oedema in man to that produced experimentally. Is there any evidence that clinical pulmonary oedema, which is generally associated with diseases of the cardiovascular system and of the lungs themselves, is produced by similar processes to those which are caused by a variety of means in healthy and in most cases anaesthetized animals? In the former group there is a pathological background, in the latter there is a relatively normal physiological background. I raise this question because we should be extremely cautious in assuming that the chain of biological events which leads to the production of experimental pulmonary oedema is similar to that causing clinical lung oedema.

Let me now refer to specific mechanisms which have been regarded as causative factors.

"BACK-PRESSURE"

The first is that pulmonary oedema is due to left ventricular failure, giving rise to "back-pressure" effects on the pulmonary vascular bed and consequent capillary dilatation, and leading to an increased capillary permeability. This view was largely based on the experiments of Welch, who, in 1878, showed that ligature of the aorta or compression of the left ventricle in rabbits caused pulmonary oedema; it held sway for a considerable time. Unfortunately Welch did most of his experiments on rabbits, which are particularly prone to pulmonary oedema, and later observers working on other animal species were

* Read in opening a discussion at the January 1946 meeting of the Association for the Study of Diseases of the Chest.

unable to confirm that back-pressure effects always caused oedema (Teissier and Guinard, 1901 ; Montanari, 1911 ; Kotowschtschikow, 1913 ; Antoniazzi, 1930). It should be stressed that in practically all the experiments on entire animals in which back-pressure effects were produced, such as by ligature of the aorta, a complex series of reflexes resulted in which the lungs sometimes played a part. Thus, the type of experiment performed by Welch, even if pulmonary oedema was produced, gave us no clear-cut evidence that a left ventricular failure was the main causative factor. This theory received a further setback when it was found that experimental obstruction of the pulmonary veins did not always cause oedema. However careful one is in analysing these experiments, it is extremely difficult to come to any clear-cut conclusion. They seem to indicate that a high pulmonary venous pressure may, under certain conditions, be a predisposing factor in the production of experimental oedema of the lungs, but that it is not a decisive one. My own experience suggests that, if the lung capillaries are already more permeable than normal, then back-pressure effects favour the production of pulmonary oedema.

It was only natural that Welch's experiments directed attention towards the responsibility of cardiovascular disease in producing lung oedema. In this connexion Luisada (1940) assessed the clinical literature and mentioned that acute pulmonary oedema is associated with four main groups of cardiac lesions : aortic insufficiency, mitral regurgitation, diffuse sclerosis of the myocardium, and coronary thrombosis. Luisada states that these diseases comprise the greatest number of cases of acute pulmonary oedema observed clinically in adults ; and this fact constitutes the main clinical basis on which the left ventricular failure theory rests. But he also observes that the frequency of acute pulmonary oedema in the four groups of heart disease may very well be due merely to the frequency of these conditions. It is clear that the statisticians might be able to give valuable aid in the assessment of this problem.

Pulmonary oedema is a not uncommon terminal event in Starling's heart-lung preparation, and there is evidence that the abnormal nature of the perfusate, which in the majority of experiments has been defibrinated blood, is the main causative factor (Lambert and Gremels, 1926 ; Newton, 1932). When the heart is failing, " back-pressure " effects may become significant if the left heart is overloaded (Knowlton and Starling, 1912 ; Matsuoka, 1915 ; Barry, 1923), but it should be stressed that unless special precautions are taken it is not easy to assess left ventricular " back-pressure " effects in the heart-lung preparation (Anrep and Bulatao, 1925 ; Daly, 1926 ; Berry and Daly, 1931).

The position can be fairly summarized by saying that the left ventricular failure or " back-pressure " theory does not receive very strong support from the experimental physiologist, and that the clinical evidence requires further statistical examination before " back-pressure " can be considered as a major mechanism in the production of clinical lung oedema.

Increased Capillary Permeability

Agents increasing capillary permeability may be considered next. We know that the effect of drugs on the pulmonary capillaries of animals varies very considerably. For instance, although adrenaline produces pulmonary oedema in the rabbit (Cavina, 1911 ; Luisada, 1928), it rarely has this action in other animal species. It is uncertain whether this is the direct action of the alkaloid on the lung capillaries or the result of a reflex set up by the concomitant rise in blood pressure. Poison gases—and in particular phosgene, the effect of which upon the lungs is, curiously enough, relieved by vagotomy (Laqueur and Magnus, 1921)—have been studied extensively in connexion with lung oedema. The guinea-pig is especially prone to pulmonary oedema in anaphylactic shock and after histamine injections. These two findings bind together, for it has been shown that histamine is released as a result of the antigen-antibody reaction.

To the experimental physiologist these are well-known ways of producing pulmonary oedema, but our great problem is the sudden and unexpected appearance of pulmonary oedema which sometimes occurs in apparently normal lungs. For example, it has been found that in the lungs of the dog perfused with its own blood, good expansion and good blood-flow in the lungs may take place over a period of ten hours, but in about 10% of experiments carried out apparently under identical conditions some oedema—although not always acute—may appear within one and a half to two hours. This is our experience in over 500 experiments. It would be expected that blood taken from animals of the same species would be the best environment for the capillaries. Yet we have found when perfusing dogs with horse blood that the lungs of the animal keep in as good condition as when the dogs are perfused with mixed dog blood (Daly and Weatherall, 1945). With horse blood as a perfusate, the dogs have been kept alive with activity of the respiratory centre for eight hours. Again, the surest and most rapid method of producing pulmonary oedema in dog lungs is to perfuse them with surplus human blood, when blood-stained fluid pours out in large quantities from the trachea within fifteen to ninety minutes. In these experiments we may be dealing merely with different blood groups in the two species, but a study of the literature suggests it is unlikely that this is the whole story, especially as horse blood has an extremely complex agglutinogen-agglutinin structure. However that may be, it focuses attention on the capillary toxin factor and leads me to enquire how far the possibility of a toxic factor in the blood of patients suffering from cardiovascular disease has been considered. A number of physiologists hold the view that capillary toxins play the major part in producing experimental pulmonary oedema.

Nervous Mechanisms

The third causative factor to come under review relates to some type of nervous mechanism. On the experimental side we should start with the

condition known as vagal pneumonia produced by bilateral section of the cervical vagi which include the recurrent laryngeal nerve fibres. These experiments have a long history, for as long ago as 1812 Legallois observed that bilateral section of the vagi produced, among other pulmonary changes, red hepatization of the lungs. Since that time many well-known physiologists—to mention a few—Magendie (1817), Schiff (1850), Claude Bernard (1858), Traube (1878), Frey (1877), and Sharpey-Schafer (1920)—have examined this problem, and it is still exciting interest (Weiser, 1932; Farber, 1937; Lorber, 1939; Short, 1944). Briefly, the effects of bilateral vagal section in the neck are complex owing to the concomitant section of the nerve supply to the alimentary tract and laryngeal muscles. The lung effects which have been described are inflammation, congestion, emphysema, and, on occasions, oedema. Schiff regarded the pulmonary effects as due to paralysis of vasoconstrictor fibres to the pulmonary vascular bed—so-called neuroparalytic hyperaemia (Genzmer, 1874). Later workers have shown that, if steps are taken to prevent the effects of laryngeal obstruction and of inhalation of stomach contents by the insertion of a tracheotomy tube, gross changes in the lungs do not always appear; instead, only minor changes—for the most part pulmonary hyperaemia and excess of bronchial secretion—are seen, especially in the smaller and younger animals (Lorber, 1939). These may be partly due to the fact that the insertion of a tracheotomy tube in small animals causes some constriction of the airway, which leads to partial asphyxia and over-distension of the lungs, with resulting emphysema and capillary distension or even rupture, as suggested by Claude Bernard. It also appears that the insertion of a tracheotomy tube may so immobilize the larynx that mucous secretion is not removed in the normal manner. The bronchial tubes become gradually plugged with mucus and slow asphyxia ensues (Short, 1944). With the exception of Farber's (1937) experiments, close scrutiny of the results of these investigations does not encourage the belief that so-called vagal pneumonia is caused by the interruption of vagal pulmonary vasomotor fibres. This statement is made without prejudice to the view that pulmonary vasomotor fibres run in the vagal nerve trunks.

There are two other experimental conditions which are alleged to produce pulmonary oedema, namely the suboccipital injection of veratrine (Jarisch, Richter, and Thoma, 1939), and injuries to the base of the brain (Brown-Séquard, 1871). These are examples of oedema caused by central nervous system stimulation. Another procedure which produces pulmonary capillary dilatation and occasionally pulmonary oedema has been investigated recently in my own laboratory, namely, decompression of animals to pressures equivalent to altitudes of 35,000 to 45,000 ft. In the rabbit and guinea-pig it has been found by Dr. Catherine Hebb and Professor Fegler that such decompression causes congestive atelectasis, and it is interesting to note that, post mortem, the lungs when blown up become quite pale, indicating the presence of capillary congestion as distinct

from intrapulmonary haemorrhage. We have not examined the mechanism in detail. There is, therefore, suggestive but hardly conclusive evidence that a nervous factor is operative in producing pulmonary oedema in experimental animals.

On the clinical side acute pulmonary oedema has been associated with emotional disturbances (Merklen, 1908) and with injury or disease of the central nervous system (Moutier, 1918 ; Cornil, Hamant and Mosinger, 1930 ; Weisman, 1939). Thus trauma to the skull, cerebral haemorrhage, encephalitis, polioencephalitis, meningitis, brain tumour, and abscess have all been held responsible. Again, spinal injuries involving the spinal cord in any position from the midcervical to lower lumbar region are regarded, at any rate by some French authorities, as being a potent factor in producing such lung changes. Pulmonary oedema is alleged to follow distension of the abdominal organs, particularly the stomach (Hochrein, 1938). It seems to me extremely unlikely that such a distension reflex by itself could produce pulmonary oedema in healthy adults, for, as far as can be ascertained, the marked distension of hollow viscera which is not an infrequent accompaniment of flights at high altitudes has never given rise to pulmonary oedema.

The body of evidence, both clinical and experimental, points to some influence of the central nervous system on lung capillary permeability, but underlines the absence of evidence of direct connexions between the central nervous system and the capillaries ; the matter is still *sub judice*. Interest may be revived in the problem, since we now have what appears to be unequivocal evidence that some part of the pulmonary vascular bed is supplied with functionally active vasomotor fibres. I do not wish to enter into the difficulties of obtaining such proof, except to mention that, in demonstrating functionally active pulmonary vasomotor fibres in response to electrical stimulation, it is necessary to eliminate concomitant changes in cardiac output and in bronchial calibre which might produce passive effects on the pulmonary vascular bed. Recently we have achieved this by perfusion of the whole animal, each ventricle of the heart being replaced by a constant-output blood pump. The animals are fully atropinized to prevent bronchomotor changes. In such perfused whole-animal preparations, and in isolated perfused lungs, it has been shown that stimulation of the stellate ganglia or the sympathetic chain between the third and fourth thoracic ganglia may cause pulmonary vasoconstriction or dilatation (Daly and Weatherall, 1945 ; Daly, 1936). Pulmonary vasoconstrictor fibres in the cervical vagosympathetic nerves have also been demonstrated (Daly, Elsden, Hebb, Ludány, and Petrovskaia, 1942). If perchance some of these fibres constrict the pulmonary veins rather than the pulmonary arterioles, then capillary distension and increased permeability might ensue, but so far this specific activity of nerve fibres to the pulmonary vascular bed has not been demonstrated. It is true, however, that motor nerve endings have been described in the pulmonary veins and arterioles, and, indeed, in the

capillaries (Ponzio, 1906 ; Jones, 1926 ; Larsell and Dow, 1933 ; Takino, 1933). Physiological investigations of this kind are still in their infancy, and it may be that in the course of time an answer to these problems will be forthcoming.

Taking the evidence as a whole, the position may be summarized by the statement that capillary toxins are potent in the production of pulmonary oedema. They should, perhaps, receive more attention in the investigations of clinical pulmonary oedema. Any mechanical change in the circulation promoting an increased lung capillary pressure appears to contribute to oedema, and gross disturbances in the central nervous system also lead to oedema by processes which at the moment are obscure. Further than this we cannot go.

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