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PULMONARY OEDEMA*

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Once again we have assembled to do honour to one of our great men, Sydney Ringer. With pride we recall Ringer's achievements as an original investigator whose discoveries brought fame to this Medical School and its parent, University College, his outstanding qualities as a physician, and his genial humanity. We like to think, with the ancient Greeks, that "a spirit of reverence pervades our public acts," and it is with humility I add my small contribution to the distinguished offerings which have preserved the memory of Sidney Ringer in his spiritual home.

I have chosen the topic of pulmonary oedema with some diffidence, though I believe it to be a subject which would have interested him; possibly he, too, would have found cause for dissatisfaction in the imperfection of our knowledge of an unusually elusive problem. I doubt whether any remarks of mine can do much to bring light into our darkness, but at least I can try to place before you some facts which I hope may arouse thought and lead to future action.

In defining my problem I can do no better than quote the words of the great Laennec (1834): "Oedema of the lungs is the infiltration of serum into the substance of this organ, in such degree as evidently to diminish its permeability to the air, in respiration." It comes on most commonly with other dropsical affections, in cachectic subjects, towards the fatal termination of long-continued fevers or organic affections, especially those of the heart. It often takes place only a few hours before death, though it may last several weeks or even months. The morbid appearances of the lungs excite curiosity through the loss of the slightly rose tint of the normal organs, the failure of the organs to collapse when the chest is opened, and the dense heavy tissues which retain the impression of the finger more tenaciously than the normal lungs. When cut into, an abundance of fluid, which is either colourless or very slightly tawny, transparent, and "just perceptibly spumous," flows from the severed surfaces. When of recent occurrence the fluid is very frothy and resembles white of egg dissolved in equal parts of water, adhering to the bottom of the vessel containing it when this is reversed. No change in the integrity of the alveolar structure of the lung is apparent. The symptoms are those of impeded respiration, with slight cough and more or less watery expectoration, and the master of the stethoscope recorded that respiratory sounds are much feebler than might be expected from the great dilatation of the thorax, and bubbly sounds can be heard on auscultation. A century of investigation has added little to Laennec's description, though, as I hope to show, some progress has been made in the elucidation of its aetiology.

Before confining myself to that section I should like to draw attention to two Tables prepared from a survey of our necropsy records. Table I is an analysis of 100 unselected cases of pulmonary oedema, and illustrates the diversity of pathological conditions which may terminate in lung oedema. It also shows that certain of these conditions appear much more often than others. In Table II

TABLE I.—*Main Necropsy Findings in 100 Cases of Pulmonary Oedema*

Pathology	No. of Cases
Severe coronary disease	34
Congestive cardiac failure	32
Carcinoma of various sites, including carcinoma of lung (15 cases)	27
Wasting, moderate	25
" severe	19
Bronchopneumonia	23
Hypertensive disease	18
Chronic bronchitis alone	14
Carcinoma of liver	11
Obstruction of pulmonary veins by carcinoma	11
Massive pulmonary embolism	10
Cerebral haemorrhage	9
Cerebral tumour	7
Tuberculosis	6
Cirrhosis of liver	6
Fractured skull	3
Multiple fractures (excluding skull)	2

TABLE II.—*Frequency of Pulmonary Oedema in 500 Necropsies of Cardiovascular Disease, Cerebral Injury, and Multiple Fractures*

Pathology	Total No. of Cases	No. Showing Pulmonary Oedema
Hypertensive disease (excluding chronic nephritis) ..	94	81 (86%)
Chronic nephritis	50	37 (74%)
Complete coronary obstruction	66	45 (68%)
Cerebral haemorrhage	66	44 (67%)
Mitral stenosis	84	55 (65%)
Fractured skull	38	24 (63%)
Multiple fractures (excluding skull)	28	17 (61%)
Pulmonary embolism	74	23 (31%)
Total	500	326 (65%)

I have gathered together a fairly large series of the special cases, and have recorded the frequency with which extensive oedema of the lungs was found at necropsy. I might say that only two pathologists were concerned in the examination and that microscopy confirmed the diagnosis in every instance. I think it will be agreed that cardiovascular disease, especially hypertensive forms, is a potent factor, but no less striking is the association between central nervous disturbance and oedema of the lungs. These conclusions are in agreement with recorded experience; they represent the starting-point of much experimental work, which is still yielding a bountiful harvest of ideas. To these observations of everyday practice must be added many from the more specialized fields of toxicology, industrial

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medicine, and even war. Lung oedema arising from the action of gases and drugs has proved a fruitful field of investigation because of the ease with which these agents lend themselves to controlled experimentation. It will be my aim to disentangle from this complex mass of facts some general principles which I trust will prove useful in planning future investigations into an unsolved puzzle.

Oedema Caused by Irritating Gases

My interest in lung oedema was first aroused in 1937, when a member of the department of chemical pathology in our medical school contracted jaundice for which no cause could be found. His physician, Dr. Max Rosenheim, discovered that there had been exposure to the gas ketene for some little time. A vague impression existed among chemists that ketene is dangerous, though no real reason for this view was known, and I had to admit that I could give no opinion. We discussed the problem with Professor C. R. Harington, who encouraged us to go ahead with an investigation of the properties of the gas. Working with mice, Cameron and Neuberger (1937) soon found ketene to rival phosgene in its action on the lungs: oedema of the air spaces developed with great rapidity, and the animals showed bizarre leaping and struggles in a veritable dance of death. We found no changes other than asphyxial in the tissues, and since the heart continued to beat for some time after death we decided that ketene caused respiratory failure through a direct action on the protoplasm of the lung capillaries whereby they became extremely permeable to the blood plasma, which gushed out into the vital air spaces, drowning the animal. Our results, modified slightly in assessment of activity, were subsequently confirmed by a group of workers led by Professor H. Emeleus at the Imperial College of Science.

During the late war my experience of irritating gases was greatly extended at the Experimental Station, Porton, and I want to say something about one of these gases—phosgene. Much human experience accumulated in the 1914–18 war suggests that phosgene is a poison for the lung capillaries. All clinical features of the catastrophe which follows upon exposure can be explained by the simple hypothesis of fluid outpouring into the lungs and the consequent modification of the blood of the individual. Investigations in which I have been closely associated with F. C. Courtice, R. H. D. Short, and G. L. Foss have confirmed the old view. Just as with man, laboratory animals exposed to quite low concentrations of phosgene pass through a latent period in which little seems to be happening, although some species—e.g., the guinea-pig—present unmistakable features of bronchial spasm or obstruction, and others—e.g., dogs—may suffer for a time from slowing of the heart-beat. But sooner or later more serious respiratory symptoms set in and pulmonary oedema spreads over the lungs with increasing speed until the animal is engaged in a desperate battle for life. Whether or not death is to be the outcome depends to a large extent upon the severity of exposure to the gas.

An exact analysis of this type of pulmonary oedema is now possible because of the numerous studies carried out in this country and in the United States (Coman *et al.*, 1947). Everyone agrees that inhaled phosgene exerts its effects on the lung capillary membranes and in so doing is rapidly hydrolysed so that none of the gas reaches the general circulation to poison tissues elsewhere in the body. Attempts to demonstrate structural modification of affected capillaries have for the most part failed, largely owing to technical difficulties associated with the very thin lining cells of these vessels. However, Short (1942) with great skill succeeded in showing that the mitochondria of endothelium split up and disappear before the capillaries begin to leak. Since mitochondrial reactions are accepted as the most sensitive cell responses to injury I believe we must accept Short's demonstration as satisfactory.

The fluid which fills the air spaces contains a high percentage of plasma protein but for a long time is almost free from cells, hence it is a true transudate from the blood vessels. Large amounts of protein may be lost from the circulation in this way, and the depletion is reflected in a fall in the protein concentration of the blood. By the use of modern methods for the estimation of the plasma volume of animals we have shown

that an increasing oedema of the lungs is closely paralleled by a decrease in the circulating blood plasma (Cameron and Courtice, 1946). By weighing the lungs of dogs and goats killed at varying times after exposure to phosgene, and comparing the protein content of fluid gently expressed from such lungs with the amount of protein lost from the circulation, we could establish fairly satisfactorily a transfer of plasma from blood to lung spaces. As the result of this plasma loss the blood becomes very much more concentrated, for the blood-cell volume persists unchanged or is even somewhat augmented.

A strange anomaly was encountered when rabbits were used for similar experiments. No haemoconcentration developed despite massive losses of plasma into the lungs, so that it appears that the rabbit, in contrast to the dog and goat, must carry a readily available store of fluid from which it speedily replaces the lost plasma. When rabbits were kept on a drier diet than usual before exposure to phosgene pulmonary oedema was frequently accompanied by concentration of the blood, an observation which suggests that our explanation is correct.

Whilst the plasma is pouring into the air passages an interesting phenomenon is going on in the lymphatic circulation of the lungs. The researches of C. K. Drinker and his school have provided us with satisfactory methods for collecting lymph from the lungs of the dog, and we at Porton were fortunate enough to obtain instruction in canalization technique from Professor J. Yoffey, of Bristol, himself a distinguished worker in the field of lymphatic physiology. Dr. Courtice soon became a master of these difficult procedures and was able to follow the flow of lymph from the lungs of animals exposed to phosgene. He found that, as oedema develops, the lung lymph steadily increases and may reach a level many times the normal. Short and I had already been impressed by the extraordinary dilatation of the lymphatic plexuses closely associated with large pulmonary blood vessels and the bronchi, an observation which receives its explanation from Courtice's studies on lymph flow.

For a time, no doubt, this increased drainage compensates for plasma outflow from the injured lung capillaries and helps to keep the lungs dry, but sooner or later the rather sluggish mechanism breaks down at the bottle-neck where the copious intrapulmonary lymphatics converge to form a few main lymph channels, and oedema then progresses unchecked unless the capillaries regain their normal impermeability for proteins. The major risk is anoxia as fluid fills up the air spaces, and this is reflected in the dyspnoea which now sets in along with biochemical changes in the blood. Giving the animal unlimited amounts of oxygen brings no relief (Boche *et al.*, 1947). At this stage, too, extreme haemoconcentration may add its burden to the circulation, and a falling blood pressure gives warning of a labouring heart. Apparently little in the way of relief from the intolerable load of oedema fluid can be expected by way of direct absorption through the lung capillaries.

It has long been known that simple fluids such as physiological saline are removed with speed from the air spaces (Colin, 1873; Winternitz, 1920). Courtice and Phipps (1946), in confirming this observation in rabbits and dogs, have shown that most of the saline is absorbed direct into the blood capillaries; for in the dog, at least, there is only a small increase in lymph flow from such lungs. Serum, in contrast, is very slowly absorbed from the air passages, persisting in the lungs for about four days. The little that is removed seems to leave by way of the lymphatics. These important observations of Courtice and Phipps must be of great interest to pathologists, since they afford an explanation of the slow resolution of a pneumonic exudate. No doubt retained protein favours bacterial growth, and I am reminded of the emphasis placed upon pulmonary oedema as a precursory state to pneumonia by Robertson (1938).

Further evidence of the abnormal permeability of the lung capillaries after gassing with phosgene is seen in the striking experiments of Courtice and Foss (1946) on the effects of plasma replacement. Arguing that severe circulatory collapse in the late stages may be due partly to falling plasma volume, the outcome of lung oedema, they transfused gassed dogs and goats with large amounts of concentrated serum and normal plasma and serum, only to find that the transfusate left the circulation very rapidly and the general condition of the animals worsened.

Courtice and Foss concluded that transfusions are contra-indicated in the presence of gross pulmonary oedema—a statement which deserves careful consideration from clinicians. American investigations are in close agreement with the British studies.

Early Circulatory Embarrassment

I must now discuss the possibility of early circulatory embarrassment in this type of pulmonary oedema, for it might be argued that much of the trouble results from increased filtration of fluid from capillaries in which the hydrostatic pressure has been raised well above the colloid osmotic pressure of the plasma. Let me first remind you of the main facts about pulmonary circulation. The lungs consist of a gigantic though extremely thin membrane across which diffusion of the gases of respiration takes place. In close contact is an immense capillary plexus 120 to 140 square metres in extent, in which the blood is separated from the air by an average distance of about 1.4μ (Roughton, 1945). Not all of these capillaries are open at any given moment when the individual is at rest or engaged in mild exercise (Cohnheim and Litten, 1875; Toyama, 1925; Wearn *et al.*, 1934), but when the emergency arises a greatly increased vascular bed becomes available as a blood depot.

In resting man only one-twentieth of the total lung surface suffices to maintain normal oxygenation of the blood, hence the margin of safety is great. With each contraction of the heart about 3.12 litres of blood per minute per square metre body surface is expelled (Cournand *et al.*, 1945) at the rather low head of pressure in the pulmonary artery of 18–30 mm. Hg (Bloomfield *et al.*, 1946). This amount of blood takes something like three seconds to traverse the lung circulatory bed, though there is some disagreement about the lung circulation time (Blumgart and Weiss, 1927; Weiss, 1942), of which 0.75 ± 0.25 second is spent in passing through the capillaries (Roughton, 1945). No doubt the velocity of flow varies in different parts of the lungs, being slower at the base than in the upper parts. Here, too, because of gravity the pressure within the vessels is somewhat higher. The capillary hydrostatic pressure is not known with any certainty, but it must be less than the normal diastolic pulmonary arterial pressure, which is about 11 mm. Hg, and greater than the pulmonary venous pressure, which is near to 7 mm. Hg (Bazett, 1941). Probably 9–10 mm. Hg is a fair estimate.

Obviously the effective peripheral resistance of the pulmonary system is low and normally plays a small part in controlling the circulation. Now, the colloid osmotic pressure for pulmonary blood is, so far as we know, that of the blood in general, which is variously stated as 18.3 to 25 mm. Hg (Verney, 1926; Landis, 1930; Muntwyler *et al.*, 1933; Kerkhof, 1937). This means that conditions favour retention of fluid within the pulmonary capillaries even when we take into consideration the sub-atmospheric ("negative") intrapleural pressure fluctuating about a mean of 5 cm. water (Prinzmetal and Kountz, 1935; Drinker, 1945), which favours outflow from the capillaries. Of course, some water does leave these vessels as vapour in the alveoli, but it is small in amount. In other words, circulatory arrangements within the normal lungs are such as to keep the air passages dry. Moreover, the generous safety margin at the disposal of the vascular bed allows for considerable enhancement of blood content without a serious strain being placed upon the vessel walls. And, finally, there are compensatory devices available in the form of reflexes (Bainbridge, 1915), by which a rising pressure within the pulmonary veins initiates acceleration of cardiac contraction, with more rapid removal of blood from the lungs.

The experimental study of phosgene oedema has given no evidence of interference with the pulmonary circulation, or of right heart embarrassment until the last stages are reached (Barcroft *et al.*, 1918; Patt *et al.*, 1946). Shaw Dunn (1919–20), working at Porton during the 1914–18 war, stressed the importance of intracapillary thrombosis, but Dr. Short and I convinced ourselves that such capillary findings are the result of stasis from concentration of the blood due to loss of oedema fluid. The American investigators working under the leadership of Professor R. W. Gerard, of Chicago (Patt *et al.*, 1946), found that dyes pass through the pulmonary vessels quite easily.

Their demonstration of a prolonged pulmonary circulation time with adequate oxygenation of the blood also shows that no extensive block can exist. It is only when oedema becomes pronounced that serious disturbance of the lung circulation sets in. Likewise, cardiac dilatation and venous engorgement are inconstant and usually of late occurrence, venous pressure rarely shows an appreciable increase (Eyster and Meek, 1926; Patt *et al.*, 1946), and no reason for accepting back-pressure effects in the lungs emerged from direct measurements of right ventricular and pulmonary artery pressure in gassed dogs and cats. I must emphasize that the American work was carefully controlled and involved all extremes of severity of gassing. The conclusion is inescapable that the compensatory mechanisms and vascular reserve of the lungs are so well developed as to be capable of dealing with all but the most violent disturbances of heart and circulation.

The lesson which emerges from these studies is that pulmonary oedema may result from injury of the lining cells of the lung capillaries alone, whereby the permeability for proteins is increased and escape of plasma into the air spaces follows, leading eventually to anoxia and death from respiratory failure in the most severe cases.

Although the functional investigation of the effects of a number of gases is not as complete as in the case of phosgene, there is little reason to doubt that similar mechanisms are concerned. Among such gases may be included mustard-gas vapour, lewisite vapour (Cameron, Courtice, and Short, 1947), chlorine, nitrous fumes, ammonia vapour (Miller and Matthews, 1909), acetic ether (Miller and Matthews), and many irritating smokes.

In conclusion, I wish to make it clear that the march of events in all these examples is a fairly slow one, extending over hours and sometimes days rather than minutes. Nevertheless, a paroxysmal course may be encountered when high concentrations are breathed or when, as human experience suggests, a severe demand is placed upon the circulatory system by violent exertion.

Pulmonary Oedema due to Absorption of Chemicals

It has been known for some time that a variety of drugs can produce pulmonary oedema after absorption into the blood stream. Among these are acetic and butyric ether, iodides, methyl salicylate, muscarine, eserine, and the newly introduced compound thiourea and its chemical relatives. No doubt many other examples could be added to this list. The ethers act with rapidity when injected intravenously into rabbits or dogs, and disturbances of circulatory function have been recorded. Thus a rapid increase in pressure within the left auricle and pulmonary artery, together with a fall in systemic arterial pressure, was noted by Löwit (1893) in some animals. Although not infrequently reverse effects were obtained by him, pulmonary oedema was equally severe in either case. Since these disturbances were only transitory, Löwit concluded that there could be no question of lung stasis as the initiating mechanism for the oedema, and he argued, with some astuteness, that the main factor must be alteration in the vessel walls with leakage of fluid, since oedema in other tissues often occurred in the presence of these agents.

A little later Van Zeissl (1895) reached a similar conclusion from his studies with iodides, wherein he demonstrated rising left auricular pressures but inconstant alterations in pulmonary arterial pressure. He, too, emphasized changes in the pulmonary capillaries and suggested that these might obstruct the blood flow from the lungs. Much the same uncertainties about circulatory behaviour were experienced by Grossman (1887, 1891) and Löwit with muscarine oedema, and by Teissier and Guinard (1901) with methyl salicylate oedema. The latter, working with curarized vagotomized dogs, sometimes obtained a rise in left auricular pressure, sometimes a fall. More recently Lathrop (1932) and Lindsey (1937) have emphasized toxic damage to small blood vessels in various parts of the body as the result of salicylate poisoning. A respiratory factor may also be concerned, for hyperpnoea and acidosis are not uncommon features due to medullary damage (Troll and Menten, 1945). Unfortunately, all such studies are far from complete, often open to serious criticism on technical grounds, and seldom well controlled.

Of great interest is the pulmonary oedema which develops a few hours after the administration by various routes of certain sulphur derivatives of urea. Richter and Clisby (1942) noted early pleural effusion accompanied by progressive exudation of fluid into the air spaces when rats were fed phenyl thiocarbamide, and recognized these effects as being due to a primary toxic action on the capillaries. No oedema appeared in tissues other than the lungs and pleurae. Since some of the compounds we were concerned with at Porton had affinities with thiourea, our colleague, Miss R. P. Jones, decided to investigate their properties, especially their action on the thyroid gland; for Astwood and his co-workers had already drawn attention to this aspect of certain members of the group. She found that four compounds— α - and β -naphthyl thiourea and $\alpha\alpha$ - and $\beta\beta$ -dinaphthyl thiourea—in toxic doses induced massive pleural effusions and pulmonary oedema which might lead to death in one to two days or resolution in about four days. No impairment of circulatory or nervous function was apparent in any of these animals until the last moments of life, and no pathological changes were discovered in the organs apart from the respiratory system and the thyroid gland (Jones, 1946). It seems likely that we are dealing with a specific action on the lung capillaries accompanying an even more specific influence on the cells of the thyroid gland. Drinker (1945) has reached a similar conclusion from investigations on dogs, and Dr. Courtice is in agreement, although his findings have been somewhat variable.

The interest of this group of agents is that they modify the permeability of the lung capillaries, apparently without affecting any other capillary conglomerates. This action is a steadily progressive one and is completely divorced from serious disturbance of the cardiovascular, renal, and nervous systems. Localized oedemas, however, are by no means confined to the lungs, as witness the oedema of the head and face induced in rabbits by the administration of paraphenylene diamine (Tainter and Hanzlik, 1924-5) and the oedema of the sexual skin of monkeys (Zuckerman and Fulton, 1934). The angio-neurotic oedemas of man and uraemic lung oedema may belong to the same category.

Pulmonary Oedema Associated with Nervous Disturbance

There is a widespread opinion among clinicians that acute pulmonary oedema not infrequently terminates the course of many disturbances of the central nervous system. The list of lesions is fairly long and includes cerebral haemorrhage, thrombosis, embolism, tumour, encephalitis, myelitis, meningitis, tabes dorsalis (Fourneau, 1897-8; Lian, 1931, Bezançon *et al.*, 1932; Gernez and Marchandise, 1933; Hess, 1934), epilepsy (Shanahan, 1908; Ohlmacher, 1910; Langeron, 1925), and head injuries with cerebral laceration and intracranial haemorrhage (Moutier, 1918; Laubry and Cottet, 1935; Benassi, 1937; Weisman, 1939). Our necropsy records at University College Hospital show a high incidence of severe lung oedema in patients dying from cerebral haemorrhage (not traumatic—67%) or fractured skull (63%).

The experimental elucidation of this serious complication has made little progress, though guesses have not been wanting about its mechanism. The chief obstacle is the lack of a reliable method of producing neurogenic oedema. Bilateral vagotomy is often quoted as satisfactory (Farber, 1937; Luisada, 1928), despite the demonstration by Frey (1877), Schafer (1918-20), and, more recently, Short (1944) that the lung lies open to the aspiration of food and oral secretions because of laryngeal paralysis. Short was impressed with the importance of slow asphyxia as a factor in causing pulmonary changes, among which was oedema, though this was by no means a constant development. I believe he has done good service in emphasizing this complication, for many of the methods employed in the demonstration of neurogenic oedema are such as to induce anoxia, and no conclusion can be drawn about nervous action on vascular permeability. This criticism may well apply to the experiments of Jores (1906), in which the insertion of foreign bodies within the smaller bronchi led to rapidly developing localized lung oedema. Faradic stimulation of lung also gave oedema, which Jores attributed to vasomotor disturbance, but unfortunately his experiments were imperfectly controlled and could not be confirmed by Kotowschtschikow

(1913). Other methods claimed as satisfactory for inducing neurogenic oedema include obstructing the blood supply to the brain (Mayer, 1878; Meurers, 1925), suboccipital injection of veratrine (Jarisch, Richter, and Thoma, 1939), and stimulation of the stellate ganglia (Brown-Séquard : quoted by Gernez and Marchandise, 1933), but information is usually incomplete and results appear to be uncertain.

Recently Dr. S. N. De and I, while working on the production of hydrocephalus, hit upon a method of producing pulmonary oedema which offers great possibilities. We set out to glue the meninges of rats together by injecting intracisternally a solution of fibrinogen followed immediately afterwards by thrombin, the idea being that a fibrin film would be formed within the cisternae which would interfere with the circulation of the cerebrospinal fluid (Fig. 1). To our surprise most of

FIG. 1.—Diagram showing site of intracisternal injection of fibrin; the manoeuvre leads to pulmonary oedema in rats and rabbits.

the animals died of acute pulmonary oedema within a few minutes. The experiment has been repeated many times now, both in rats and in rabbits, and always with the same result. The lungs of such animals are remarkably similar to those gassed with phosgene. Since the fibrinogen was obtained from human sources it was essential that its "foreignness" be controlled, and De showed that intracisternal injection of human plasma in comparable or greater amounts gave no oedema. Varying the pressure of introduced fluids apparently plays no part. Preliminary studies suggest that dividing both vagi reduces or even prevents the occurrence of lung oedema. The investigation is being pursued vigorously at the moment and it would not be wise to draw many conclusions until the work is complete, but it is our impression that we are dealing with a cerebral type of pulmonary oedema, possibly the result of disturbance of intracranial pressure. That pressure upsets can lead to lung oedema seems apparent from experiments performed on dogs and rabbits by Benassi (1937), in which pressure was raised by intracranial injections of fluid after trephining. I believe that we have in the fibrin method a valuable tool for the study of many problems associated with neurogenic oedema.

Luisada and Sarnoff's Method

Another experimental method which deserves consideration has recently been described by Luisada and Sarnoff (1946). If massive quantities of saline or blood are rapidly injected under high pressure into the common carotid arteries of dogs in the cranial direction of the vessel, acute pulmonary oedema develops within a few minutes (Fig. 2). Similar amounts of fluid introduced into the femoral arteries or veins give oedema with much less frequency. The systemic and venous pressures rise for a short time, but are not maintained, and there is only slight cardiac disturbance. Oedema is more severe when viscous fluids are used than with saline, probably because of slower excretion. Denervation of the carotid sinus reduces the extent of the oedema, but vagotomy has no influence. Drugs such as phenobarbitone and morphine inhibit the oedema. Luisada and Sarnoff suggest that reflexes arising in the carotid sinus or from the cardiovascular system elsewhere as the result of a sudden increase in blood volume or pressure bring about

changes in the pulmonary vessels with altered permeability and leakage of fluid.

Dr. K. K. Cheng has lately shown that the same procedure works with rabbits. He has estimated the protein content of the oedema fluid and finds this to be about 1%, which suggests that much of the fluid may be the saline which was injected or, alternatively, that permeability of lung capillaries is not greatly increased. Whatever the explanation of the oedema may be, it seems to me that experiments of this kind are worth while as a starting-point for the further study of the vexed question of nervous influence on capillary permeability.

There is little doubt that the lungs are richly supplied with nerve fibres (Larsell and Dow, 1933) emanating from the vagus and sympathetic systems. Some of these are closely connected with the blood vessels and may be concerned in the control of the blood-storing capacity of the organ, though uncertainty still handicaps our theories (Wiggers, 1921; Daly, 1933). Others terminate around the bronchioles and alveolar ducts, where they pick up the stimuli which initiate and control respiration. A series of reflexes adjust the pressure and blood-flow relationships between the lungs on the one hand and the cardiovascular system on the other. Sensitive receptors are present in the pulmonary artery (Daly and Verney, 1927; Brunelli, 1933; Schwiegl, 1935; Heymans, 1938), pulmonary veins (Brunelli, 1933; McDowall, 1935; Nonidez, 1937), right auricle (McDowall, 1934, 1935), and the ventricles (Daly and Verney, 1927; McDowall, 1934; Rubino, 1937), as well as the venae cavae (Bainbridge, 1915; Sassa and Miyazaki, 1920; Nonidez, 1937), from

FIG. 2.—Diagram showing anatomical details of Luisada and Sarnoff's and of Cheng's method of producing pulmonary oedema by intracarotid infusions.

which nerve impulses stream to the carotid sinus, peripheral vessels, and brain (Heymans *et al.*, 1933; Hochrein and Keller, 1934; Jarisch *et al.*, 1939; Jarisch, 1940) as well as from one vascular component to the other. How important these are in the fully compensated organism remains to be determined. A close relationship surely exists between the systemic and pulmonary circulation, but how much of this is nervous is still undecided. For some time the impression has been growing that some such nervous mechanism may influence the permeability of the lung capillaries, and disturbance of this at various functional levels may be responsible for neurogenic oedema (Teissier, 1900; Wassermann, 1933; Luisada and Sarnoff, 1946). Convincing evidence scarcely exists, and I would put forward a plea for a re-examination of the problem.

Pulmonary Oedema resulting from Circulatory Failure

Without doubt pulmonary oedema is met with most often in association with some degree of circulatory failure, and standing high in the list of pathological favourites are hypertensive disease, with or without chronic nephritis, advanced mitral stenosis, and obstruction of the coronary vessels (see reviews by Hess, 1932; Frugoni, 1930; Parker and Weiss, 1936; Harrison *et al.*, 1934; Weiss, 1942). Our necropsy records disclosed severe lung oedema in 86% of 94 hypertensive cases, in 68% of 66 cases of complete coronary obstruction, and in 65% of 84 cases of mitral stenosis, an experience which is in agreement with the general run of necropsy findings. In most instances the oedema involves both lungs, and the lower and middle lobes are the sites of election, though we have encountered it in the upper lobes alone or in the "butterfly" or "fan-shaped" perihilar arrangement which is said to be common in uraemic cases (Doniach, 1947).

Like other observers, I have been impressed with the frequent history of dyspnoea, in all these cases, often very severe or paroxysmal immediately before the oedema reached its clinical crisis, and I incline to the view that such respiratory embarrassment plays an important part in the cause of the oedema. But I have been unable to convince myself of a simple mechanical explanation of the circulatory disturbance in the lungs, although I accept the emphasis placed upon failure of the left ventricle. Nevertheless, I have seen an instance of lung oedema where right heart failure seemed to be more important than left. I must confess, however, that I experience great difficulty in sorting out the state of the two ventricles, and am compelled to refer the decision to the clinician and the experimentalist.

For many years we have come under the tyranny of the theory of dissociation of output from the right and left ventricles. This view derived from the demonstration by Friedländer (1873) that compression or ligation of the rabbit's ascending aorta between the heart and the innominate trunk gives sudden massive oedema of the lungs associated with severe stasis. Welch (1878), working in Cohnheim's laboratory, obtained similar results with dogs and rabbits, the latter species being especially inclined towards oedema after compression of the aorta. Under such circumstances the carotid arterial pressure increased but the pulmonary arterial pressure showed little change. Welch showed that nearly all the venous outflow from both lungs must be obstructed before oedema develops and that a large part of the left ventricle and auricle can be shut off by clamping without oedema appearing (Fig. 3). On the other hand, when the wall of the left ventricle of a rabbit is crushed without affecting the right ventricle, pulmonary oedema sets in rapidly, but paralysis of the right ventricle does not produce oedema provided the left ventricle carries on its function normally. From these experiments Welch concluded that disproportion between the mechanical efficiency of the left and right ventricles, provided resistance within the pulmonary vascular bed remains unaltered, leads to oedema, for the left heart is unable to expel in a unit of time the same quantity of blood as the right heart. Despite criticism from time to time, this theory has held the field for seventy years, either in its original form or in a modified version.

Scrutiny of Welch's paper shows that he used very few animals, his results were very variable, he gave little information about the extent of the oedema, and he employed artificial respiration with the thorax wide open. Extraordinary degrees of interference with cardiac output were necessary to induce oedema, the most serious grades of which were seen when the animal became unconscious from cerebral ischaemia. Quite recently Dr. Cheng has repeated some of Welch's experiments for me with rabbits, and has experienced much difficulty in obtaining even mild lung oedema by ligating the aorta near the heart. I shall return to Cheng's results a little later. Much of the criticism of Welch's theory has come from investigators who have failed to confirm his results or who could not establish a correlation between pulmonary haemodynamics and the degree of cardiovascular impairment. Part of the trouble originates, I believe, from the grossly abnormal nature of the experiments. It is certainly difficult to justify the conclusions reached by many workers on the evidence they offer (Sahli, 1885; Löwit, 1893; Teissier and Guinard, 1901; Kotowschtschikow, 1913; Coelho and Rocheta, 1933). Some record increased pressure within the left auricle and pulmonary artery after severe aortic obstruction or cardiac compression;

FIG. 3.—Diagram of heart and aorta showing sites of obstruction in Welch's experiments.

others record little increase or even a fall in pressure. Löwit (1893), for instance, states that prolonged artificial respiration alone can lead to pulmonary oedema in rabbits, yet the pressure in the pulmonary artery, left auricle, and carotid falls, and he concludes that pulmonary stasis is not the cause of ventilation oedema. Löwit suggests that the main factor is increased capillary permeability associated with excessive stretching of the lung capillaries.

Production of acute cardiac failure by injection of necrosing chemicals—e.g., silver nitrate—into the heart muscle of either ventricle (Coelho and Rocheta, 1933; Cataldi, 1937) or by blocking the left coronary artery (Samuelson, 1881; Bettelheim, 1892; Löwit, 1893; Coelho and Rocheta, 1933) has likewise given irregular results. Thus Bettelheim obtained a rise of left auricular pressure, slowing of the heart, and shallow respiration, but no change in pulmonary artery pressure and no pulmonary oedema, when he ligated the left coronary artery of dogs; but success was claimed by other workers. How far such positive results may be applied to the intact animal is uncertain. I cannot help thinking that much of the obscurity comes from technical imperfections: careful experiments such as those of Johnson *et al.* (1937) show that marked sudden changes in systemic blood pressure have but little immediate effect on pulmonary arterial pressure, partly because of the capacity of the pulmonary vessels to increase their blood content very considerably with but little change in pressure, and partly because of compensatory mechanisms which readjust the balance between the lesser and greater circulations. Hence no more than a transitory dissociation of output from the ventricles is conceivable, for just as soon as the pulmonary vessels become engorged automatic regulation of cardiac function occurs with compensation of back pressure. Experiments on obstruction of pulmonary blood flow certainly lead to the conclusion that oedema of the lungs can be produced in this way, but only when a tremendous handicap is placed upon the circulation which brings the organism very near to death. I am forced to the opinion that some other factor may be necessary in addition to a higher head of filtration pressure within the capillaries in order to precipitate an attack of pulmonary oedema. What this is I cannot say, but I feel sure it may act through modifying the permeability of the vessels. Perhaps a moderate degree of anoxia, which alone will not give oedema, may suffice to tip the balance (Warren and Drinker, 1942): a dyspnoeic seizure with a further increase in pulmonary congestion (Fraser *et al.*, 1928; Harrison *et al.*, 1934) and a lowering of subatmospheric intrapleural pressure (Prinzmetal and Kountz, 1935), an attack of bronchitis, or a moderate depletion of the plasma protein leading to diminution of colloidal osmotic pressure of the plasma might well qualify for this category of contributory factors.

Studies on the mechanism of pulmonary oedema using the Starling heart-lung preparation, though of limited application to the problem, afford some support for the views I have put forward. This method has the great advantage of allowing accurate records being made of the blood-flow through the lungs. There is agreement among physiologists who have carried out such experiments that the pulmonary arterial and venous pressures have to be raised very considerably before oedema of the lungs sets in (Modrakowski, 1914), and, conversely, oedema may develop before any rise in pulmonary arterial pressure can be detected (Lambert and Gremels, 1926). Changes in the perfused blood, as when it is stale or after addition of metallic poisons or with dilution of the blood colloids, further the development of oedema, no doubt because of injury to the capillary endothelium (Modrakowski, 1914; Barry, 1923; Lambert and Gremels, 1926). Professor C. Lovatt Evans informs me that contamination of the perfusate with a streptococcus is a potent factor in initiating the lung oedema. A pathological lung becomes oedematous with some ease when perfusing pressure is only slightly raised or venous outflow is impeded. All such observations have their value in the analysis of the problem, but they must not be pushed too far.

Overloading the circulation with massive infusions of fluid or blood is not without risk of pulmonary oedema. Large amounts of physiological saline may be injected intravenously into animals with impunity if the organs of excretion are functioning normally and there is no impairment of the pulmonary

circulation and nervous system (Cohnheim and Lichtheim, 1877; Löwit, 1893; Kraus, 1913; Brunn, 1934; Warthen, 1935; Farber, 1940; Gibbon and Gibbon, 1942; Gibbon *et al.*, 1942-3; Luisada and Sarnoff, 1946). After sudden reduction of lung tissue by lobectomy, caution should be exercised in the use of transfusions, and human casualties under these circumstances have been recorded (Gibbon *et al.*, 1942-3). The pulmonary arterial pressure is said to be increased, but the systemic arterial and venous pressures remain unchanged. Further investigation is required before a satisfactory explanation of the oedema can be given.

Miscellaneous Varieties of Pulmonary Oedema

There remain for discussion some examples of pulmonary oedema which are difficult to fit into any classification at the moment because of incomplete knowledge of their nature or the suspicion that several factors are involved in their causation.

Continuous exposure of animals to high concentrations of oxygen leads to pulmonary oedema and pleural effusions (Karsner, 1916; Boycott and Oakley, 1932, 1933). Respiratory symptoms predominate at pressures of 0.8 to 2 atmospheres; nervous symptoms like those of strychnine poisoning appear at levels above these (Behnke, 1942; Stadie *et al.*, 1944). Anoxic features set in as the oedema progresses (Binger *et al.*, 1927), but oedema may be present without clinical signs (Paine *et al.*, 1942). The cause of the oedema is not known, though prolonged constriction of pulmonary vessels may play a part (Retzlaff, 1913; Tannenberg, 1942). Vagal bradycardia is often a feature of oxygen-poisoning—apparently a central nervous effect, for high oxygen concentrations give constriction of the vessels of the brain (Tinell, 1927; Wolff and Lennox, 1930; Cusick *et al.*, 1940). I cannot help wondering whether the oedema is neurogenic in origin, although there is no direct evidence for this view.

Rapid paracentesis is occasionally followed by acute oedema of the lungs, and may be due to blood pouring into the compressed lung, the vessels of which have become more permeable as the result of ischaemia which accompanies pulmonary collapse (Scriba, 1885; Kovacs, 1891; Ortner, 1899). Patchy oedema may accompany pulmonary embolism and is sometimes extensive (Friedländer, 1873; Shaw Dunn, 1919-20). Shaw Dunn showed that dyspnoea is an early feature of severe lung embolism. It is prevented by dividing the vagi, is independent of any alteration in the CO₂ or oxygen content of arterial and venous blood, and is not accompanied by any permanent diminution in the amount of blood which passes through the lungs in unit time. Hence he emphasized the importance of nervous factors in the production of the dyspnoea and the oedema. Another factor may be cardiac, for massive pulmonary embolism in dogs is accompanied by electrocardiographic findings which suggest interference with coronary flow (de Takats *et al.*, 1939), and there is some reason for accepting a close nervous relationship between the pulmonary and coronary circulations (Kauffmann, 1933; Scherf and Schönbrenner, 1937; de Takats and Jesser, 1940; Jarisch, 1940).

The nature of the pulmonary oedema which develops in rabbits when adrenaline is administered in large doses by the intravenous, subcutaneous, or intratracheal routes still remains obscure (Meltzer, 1904; Josué and Bloch, 1908; Auer and Gates, 1917; Luisada, 1928; Boggian, 1929).

1. Adrenaline increases peripheral resistance, which leads to a rise in systemic pressure, a partial failure of the left heart, and irregularity in cardiac action. A rise of pulmonary pressure has been claimed (Schafer and Lim, 1919) and refuted (Johnson *et al.*, 1937); but no great load is placed upon the right heart, because of the capacity of the pulmonary bed to increase its blood content (cf. Hamilton, 1932; Hochrein and Matthes, 1932, 1933).

2. A direct action of adrenaline on the pulmonary vessels, generally resulting in vasoconstriction but sometimes in vasodilatation, has been demonstrated in the perfused lungs of dogs (Cloetta and Anderes, 1914; Cloetta and Stäubli, 1919; Berry and Daly, 1931; Gaddum and Holtz, 1933; Daly *et al.*, 1940). Pulmonary arterial pressure increases and venous outflow may be augmented. How far these results are applicable to the intact animal is not known.

3. Adrenaline oedema is slight when the animal is kept alive by means of artificial respiration with the chest open and the vagi are divided (Auer and Gates, 1917; Wichels and Lauber, 1932). It

can be prevented by morphine and drugs, such as chloral hydrate, which act on the higher centres of the brain (Luisada, 1928), by injuring the mid-brain (Glass, 1928), and by division of the cervical spine (Luisada, 1928), though not by puncture of the cerebrum or thalamus or removal of the cerebrum. Respiratory stimulants favour the development of oedema (Luisada, 1928). These observations suggest that both cardiovascular and nervous factors are concerned in the oedema mechanism; but the problem needs reinvestigation with modern appliances. An adrenal factor has been claimed for the pulmonary oedema recorded from time to time with suprarenal tumours of the chromaffin type (Kolisko, 1913; Labbé *et al.*, 1922; Biebl and Wichels, 1925; Paul, 1931) and even with the oedema of cerebral trauma, but no convincing evidence in support of such suggestions is forthcoming.

A Unifying Principle

It must be apparent from these remarks that many gaps still exist in our knowledge of pulmonary oedema. In certain cases we are much better informed about the mechanisms concerned than in others. This is especially so with the oedema resulting from irritant gases and chemicals, in which there is no reason to suspect primary disturbance of the circulation in the lungs, the outpouring of fluid being referable to leakiness of the capillaries and failure of the lymphatics to remove the exuded plasma. With neurogenic and circulatory oedema we appear to be faced by more subtle conditions, and we are still unable to analyse these with precision. I believe it is possible to simplify the problem by paying some attention to the composition of the oedema fluid, and for that reason I asked Dr. Cheng to repeat a number of the recorded experiments with the object of estimating the protein content of the lung exudate. With care, this fluid can be obtained from the bronchi by aspiration in a state similar to that in which it exists within the air spaces.

Cheng's results are summarized in Table III. They show that the most divergent modes of production give a fluid with a high protein concentration. Not infrequently this

TABLE III.—Protein Content of Oedema Fluid from Lungs
(K. K. Cheng)

Method of Producing Lung Oedema	Animal	Protein Content of Oedema Fluid (G. %)		
		Total	Albumin	Globulin
I. Methyl salicylate intravenously	Rabbit	7.62	3.40	4.22
II. Adrenaline intravenously	Rat	5.20	3.0	2.20
III. Oxygen-poisoning for 5 days	Guinea-pig	4.25	2.75	1.50
IV. Injection of fibrin into cisternae	Rabbit	5.50	4.0	1.50
—neurogenic				
V. Infusion of saline into carotids	Rat	4.68	2.40	2.28
VI. Ligation of aorta proximal to left subclavian artery with ligation of both carotids	Rabbit	1.25	0.93	0.32
	"	5.30		

approaches the protein level of plasma. Even in the experiments where large quantities of normal saline were suddenly introduced into the arteries the protein concentration exceeded 1%, and it seems quite likely some of the injected saline was responsible for the lower level. Clearly we are concerned with a disturbance of capillary permeability in all such diverse instances of pulmonary oedema. Here is a unifying principle for future investigation. It must be our task to decide whether permeability of endothelium is controlled by nervous influences, as would seem to be the case in the experiments on neurogenic oedema; how far permeability can be modified by alteration of blood flow through the capillaries; and, above all, the mode of action of environmental variations, especially gaseous exchange. These problems are not peculiar to the lungs; they are restatements of the fundamental questions which puzzle us in fluid exchange throughout the organism. Armed with this simple conclusion from our discussion, we must return to the wards and the laboratories for further action.

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A NEW CONCEPTION OF ANGINA PECTORIS

BY

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Before considering angina pectoris it is necessary to recall certain physiological facts about the course of the vasodilator and protopathic pain fibres. The vasodilator fibres, to both the somatic and the visceral organs do not run in the parasympathetic system, nor do they relay in the various sympathetic ganglia in the body. Apart from a few fibres in the parasympathetic system the only known vasodilator fibres are those of unmyelinated type running in the posterior and trigeminal nerve roots and having their cell bodies in the corresponding ganglia. Thus stimulation of the peripheral ends of the posterior nerve roots produces vasodilatation in the corresponding dermatome and also in the deep tissues and viscera, and herpes zoster in the skin. Moreover, providing the sino-aortic nerves are intact, the raising of the blood pressure in the carotid artery or aorta in a sympathectomized animal still produces a normal reflex vasodilatation in other parts of the body (Bayliss, 1901, 1902). Lewis (1927) further showed that if the posterior roots are cut distal to their ganglia and their peripheral ends allowed to degenerate, the arterial "flare" of the "triple response" in the skin fails to occur after the application of noxious stimuli. This reactive hyperaemia occurs in all tissues when injured or stimulated (Love's reflex).

The whole of the sympathetic system may be removed and yet reflex vasodilatation will still occur in response to a stimulus to a tissue. A stimulus or injury to any tissue, including anoxia, must therefore result in a reflex activity in the unmyelinated posterior root vasodilator nerve fibres. These are, of course, the same fibres which conduct protopathic pain impulses, and are cholinergic in type. Such pain fibres supply the visceral and somatic blood vessels and run in the posterior nerve roots (Moore and Singleton, 1933). They are evidently the vasodilator fibres of these vessels. It has now been shown that an excessive arterial vasodilatation results in the experience of protopathic pain. This is seen, for example, during a migrainous attack and in cases of erythromelalgia. In the former, hanging the head down, which normally causes arterial vasodilatation, will also greatly exaggerate the pain. In the latter condition the affected limb exhibits arterial vasodilatation and is painful. Dependence of the limb increases both the vasodilatation and the pain, while elevation has the opposite effect. Thus the passage of excessive numbers of impulses in vasodilator fibres results in painful experiences.

Very many theories regarding the cause of anginal pain have been put forward. Allbutt (1915) championed the tam-bour theory, which supposed the pain to be due to bulging of the suprasigmoid portion of the mediastinum. This theory has been discarded, and it is now fashionable to ascribe all anginal pain to ischaemia of the cardiac muscle, due either to coronary arterial disease, anoxia, or anaemia, or to a low pulse pressure and so diminished flow in the coronary vessels. Anoxia is thought to cause the accumulation of metabolites, such as the P factor of Lewis (1931), which stimulate the nerve endings lying on the coronary vessels. Yet in some cases there is no evidence of coronary disease, anoxia, anaemia, or low pulse pressure, and it is then usual to invoke the hypothetical phenomenon of spasm in the coronary vessels to account for the anoxia thought to produce pain. There are many reasons to doubt that ischaemia or anoxia is always the cause of angina from cardiovascular disease. For example, severe coronary

Air transport and packing in dry ice were recently used for the first time to convey dried cultures of *Staph. pyogenes* in glass ampoules and bacteriophage in fluid from the Central Public Health Laboratories in London to Sydney, Australia, whence they were delivered to Miss Nancy Atkinson, bacteriologist at the Institute of Medical and Veterinary Science, Adelaide. B.O.A.C. staff renewed the ice at Lydda, Calcutta, Singapore, and Sydney. The journey took about four days.