THE PHYSIOLOGY AND PHARMACOLOGY OF LUNG EDEMA

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TABLE OF CONTENTS

I. INTRODUCTION

Pulmonary edema is a pathologic state in which there is abnormal extravascular water storage in the lung. It is important because it results in ventilatory and diffusion obstruction to respiration and can be either a direct or a contributory cause of death in numerous diseases. For two hundred years there has been an accelerating growth of literature on the subject, a fact that testifies to its unsolved state as well as to its importance. There have been numerous reviews of this accumulating literature and we do not propose to repeat an annotated bibliography of the subject at this time.[1]

Our present purpose is to present the subject in the context of a theoretical analysis of the physics and physical chemistry of edema production in the anatomic realities of the lung as an organ in a functioning body.

We do not propose, however, to oversimplify the problem for the sake of schematization and we therefore first present three tables of orientation data. Table I is a list by Cameron (35) of the main necropsy findings in one hundred cases of pulmonary edema in routine autopsies in a general hospital. Table II presents data from the same source on the frequency of lung edema as a necropsy finding in certain disease states. It will be apparent from Table I that clinical pulmonary edema occurs in numerous diseases; the clinical literature contains reports of the occurrence of lung edema in association with many diseases other

[1] This review will cite a minor fraction of the references in the literature bearing upon pulmonary edema which have been consulted by the authors. In most instances where several papers cover the same topic, only a few are referred to herein. The remainder of the references are available to those desiring a more complete bibliography, including full titles of the papers and arranged in subject categories, by requesting Document #4982 from the American Documentation Institute, Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. (Advance payment is required, $10 for photoprints or $3.50 for 35 mm microfilm. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.) The above-mentioned list is not claimed to be entirely complete in any part, and is especially incomplete in relation to edema produced by lung irritant gases, because no effort was made to search for special reports from military research laboratories.

TABLE I

*Main necropsy findings in 100 cases of pulmonary edema**

Pathology	No. of cases
Severe coronary disease	34
Congestive cardiac failure	32
Carcinoma of various sites, including lung	27
Wasting, moderate	25
Wasting, 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 hemorrhage	9
Cerebral tumor	7
Tuberculosis	6
Cirrhosis of liver	6
Fractured skull	3
Multiple fractures (excluding skull)	2

* Cameron, G. R. 1948 (35).

TABLE II

*Frequency of pulmonary edema in 500 necropsies of cardiovascular disease, cerebral injury, and multiple fractures**

Pathology	Total no. of cases	No. showing pulmonary edema
Hypertensive disease (excluding chronic nephritis)	94	81 (86%)
Chronic nephritis	50	37 (74%)
Complete coronary obstruction	66	45 (68%)
Cerebral hemorrhage	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%)

* Cameron, G. R. 1948 (35).

than those listed here. In this series, the largest number of cases occurred in coronary artery disease and congestive heart failure. As shown in Table II, 86% of patients dying of hypertensive disease showed lung edema as an autopsy finding. It is therefore not surprising that heart failure has been looked upon since before the time of Welch (297) as a major factor in the dynamics of this disease state. To the contrary, it is somewhat surprising that the views of Welch have been so vigorously attacked, as by Cameron (35) who wrote, "For many years we have come under the tyranny of the theory of the dissociation of output from the

right and left ventricles. . . . Despite criticism from time to time this theory has held the field for 70 years either in its original form or in a modified version." In justification of critics of Welch, it must be said at the outset, however, that in its literal form the Welch theory is inadequate. But recent work certainly tends to substantiate his major thesis which, although somewhat unfortunately stated, stressed the importance of elevated pulmonary venous pressure and pulmonary vascular bed congestion as the major factors in the ordinary forms of the disease.

Because of the central role that the Welch theory has played in thought about this problem, it seems appropriate to quote his own statement (298) elaborating upon his original paper (297), concerning the major mechanism in acute pulmonary edema, namely "A disproportion between the working power of the left ventricle and of the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart". He (298) went on to say in amplification of his views, "It is hardly necessary to state that such factors as changes in osmotic pressure, alterations in the capillary endothelium, interference with the absorption of lymph, which have become prominent in the later discussion of the cause of edema, may be utilized in the explanations of pulmonary edema, as of congestive edema elsewhere, but I find great difficulty in conceiving any of these factors alone to be the primary cause of acute general edema of the lungs". It will be noted that Welch did not hold that there would need to be prolonged imbalance of actual output of the left and right ventricles in order to produce the effect in question. His theory requires only that imbalance exist for such times and extents as to overfill the pulmonary vascular bed and maintain it in that state. Nor did Welch deny the role of other factors. The Welch view will undoubtedly stand as the most perspicacious insight into the mechanism of the commoner varieties of lung edema, even though it is certainly not a completely adequate explanation under all circumstances.

Lung edema in man is rarely more than a complication of other diseases, except in the case of poisoning by the lung irritant gases. Therefore, although it can be the immediate cause of death, one must ordinarily look to correction of the more fundamental defect for its effective treatment. It is for this reason that knowledge of the dynamics of its production is of practical importance. Both the direct and the remote causes of pulmonary edema must be known in order to prevent it or cause it to regress.

Theoretically it is possible to distinguish between intracellular, interstitial and alveolar types of lung edema, and there can be combinations (229). Actually, the practical situation of unique importance in lung edema is the filling of alveoli, alveolar ducts and the bronchial tree with fluid. Such fluid impedes or prevents aeration of alveoli and thus of the blood flowing through their capillaries. Interstitial edema is of importance functionally by virtue of the change in lung elasticity which it causes and because of changes in extravascular pressure influencing the lung vessels. The occurrence of interstitial edema may also be of importance to an understanding of the physiologic processes involved in edema production. Intracellular edema in the lung parenchyma has received little attention, appar-

ently because it would seem to be a very minor factor, if involved at all, in the genesis of alveolar edema.

II. DETECTION AND QUANTITATIVE STUDY OF PULMONARY EDEMA

The quantitation of the edema state is a difficult problem at any site. It is particularly so in the lung because the organ is relatively inaccessible in the intact animal and because standards of reference are difficult to establish. Nine methods are available for evaluation of the edema state. They are 1) ausculation of the chest, 2) observation and collection of frothy fluid in the larger airways during life, 3) X-ray density studies during life, 4) gross observation at autopsy, 5) microscopic observation of autopsy material, 6) measurements of lung weight to body or other organ weight ratios at autopsy, 7) chemical analysis of extravascular, extracellular fluid space in the lung at autopsy, 8) changes in electrical resistance of the lung parenchyma, 9) weight changes in the isolated perfused organ.

For quantitative studies the fourth and sixth methods have been more extensively used. Figure I, giving data from Courtice (60), shows the degree of correlation that can be obtained between the two. In studies on man during life, only

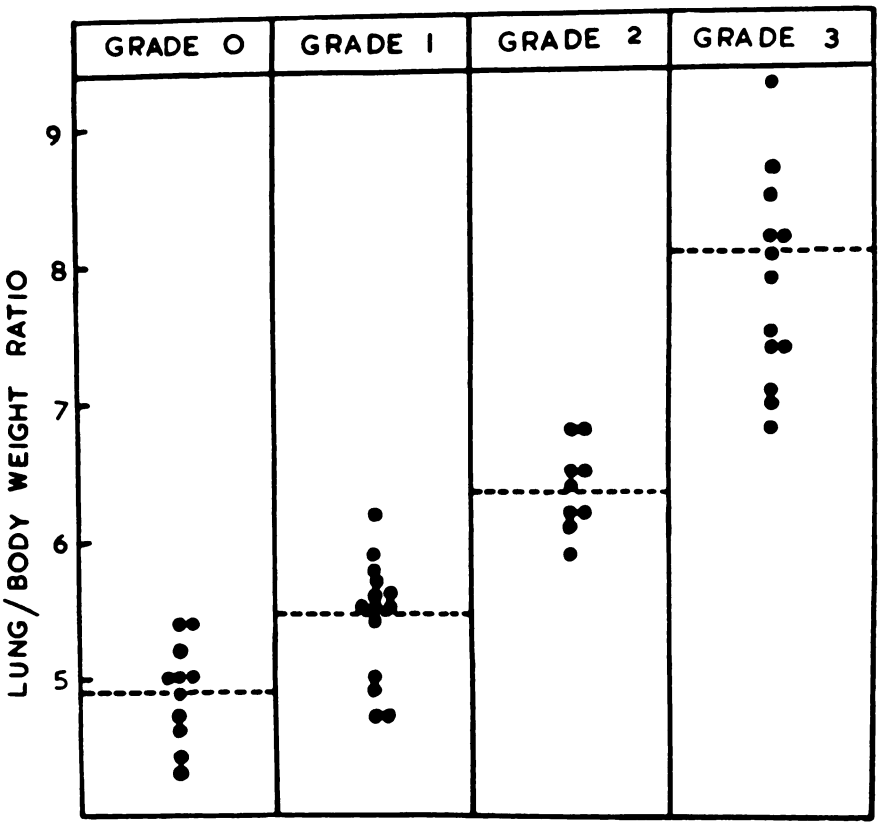

FIG. I. The relationship between the lung/body weight ratio and the estimated degree of pulmonary edema at post mortem in rabbits. From: Courtice, F. C., 1953 (60).

methods one, two and three are available. Unfortunately, the only potentially quantitative method, the third, is subject to great uncertainty. Westermarck (299) has pointed out that the particular lung shadows ordinarily interpreted as indications of lung edema are subject to decisive immediate alteration by procedures such as the Valsalva maneuver which change the blood volume in the pulmonary vascular bed. The central density ordinarily interpreted as evidence for lung edema is almost certainly, from Westermarck's work, to be ascribed to a large extent to distended blood vessels. Furthermore, in studies on the sheep and the goat in which massive lung edema occurs when such animals are maintained in the dorsal recumbent posture, we found that it was impossible to detect X-ray density changes in the dependent portions of the lungs at times when highly significant edema, as evidenced by gross observation and lung weight to body weight ratio, had occurred. X-ray evidence in this situation occurred only when the edema state approached lethal degrees.

Microscopic studies of fixed, sectioned and stained material have also proved disappointing in our hands in experimental lung edema. We have frequently sectioned lungs with acute massive edema and found that there was no stainable material in the alveoli. This result is not surprising, because it is known that in early acute lung edema of several types the edema fluid may be nearly protein-free, as was shown by Koenig (166, 167) and others. The only early evidence of such lung edema that is visible microscopically is interstitial wall thickening, because protein-free fluid in alveoli is undetectable in conventional histologic preparations.

Chemical analysis of lung tissue with a view to quantitation of edema is possible but tedious. Greenberg (112) developed a method of measuring interstitial edema by employing the chloride space. Hemingway (136) and Hemingway and Campbell (138) employed estimations of the several fractions of lung tissue protein to estimate the degree of excess of water in the lungs. This method is elegant but perhaps unwarrantedly difficult. Simple wet and dry weight determinations have been employed, but they suffer from uncertainties resulting from the unknown proportions of red cells to plasma in blood trapped in lung vessels or in hemorrhagic deposits. Electrical resistance measures were used successfully by Lambert and Gremels (178). Isolated perfused lung weight has been employed usefully by Born (26).

Except for special purposes, the authors have concluded that gross observations and lung weight to body or heart weight ratios provide the most reliable practical methods for quantitation of lung edema. If changes over time are important, the resistance and the lung weight methods are useful, provided that changes due to blood storage or release can be ruled out or measured.

Table III lists the various types of experimental lung edema arranged in broad categories according to the type of indirect cause, with references given to publications dealing with studies on each type. This list is presented partly to indicate the extremely wide variety of conditions and agents which are associated remotely or more directly with the induction of lung edema. It is apparent on inspection that common denominators are not obvious.

Since lung edema is a remote consequence, one or more operative steps re-

TABLE III
*Indirect determinants of experimental pulmonary edema**

I. Primary hemodynamic alterations
  A. Heart and great vessels
    1. Ventricular obstruction: left (47, 52); right (47, 171)
    2. Coronary occlusion (21, 246, 252)
    3. Compression or occlusion of left ventricle (2, 99, 115, 116, 117, 297)
    4. Compression or occlusion of left atrium (117, 171, 251)
    5. Valvular defects: aortic insufficiency (224, 247); mitral insufficiency (247); mitral stenosis (122, 211)
    6. Occlusion of aorta and/or its branches (52, 143, 171, 222, 251, 297)
    7. Compression of pulmonary veins (161, 173, 192, 297)
  B. Hypervolemia (53, 61, 121, 134, 163, 291, 313)
  C. Arterial hypotension; shock, hemorrhage: (86, 212, 213, 214)
  D. Embolism (85, 96, 146, 240, 287, 292)
II. Alterations of the central nervous system
  Brain lesions: compression or stimulation (39, 42, 44, 63, 104, 152, 199, 200, 204, 255)
III. Alterations of the peripheral nervous system
  A. Vagotomy (2, 19, 93, 193, 239, 266, 275)
  B. Vagotomy with tracheotomy (94, 95, 106, 262, 312)
  C. Faradic stimulation of lung root (155)
IV. Alterations of the respiratory system
  A. Airway obstruction: inspiratory (121, 159, 239, 316); expiratory (121, 159, 315); inspiratory and expiratory (7, 13, 239)
  B. Hypoxia with heart overload or failure (61, 71, 137, 154)
  C. Respiratory burns and heat (9, 98, 206, 215)
  D. Drowning (10, 32, 157, 282)
  E. Intratracheal fluids (176, 184, 210)
  F. Chest wounds (71)
  G. Blast (46, 51, 172)
V. Pharmacological effects
  A. Vasoactive drugs: muscarine (114, 117, 211); acetylcholine (4, 82); neostigmine (4, 16); histamine (213, 238, 250); amyl nitrite (306); epinephrine (7, 15, 25, 87, 130, 156, 224, 228, 263); pentylenetetrazole (Cardiazol®, Metrazol®) and nikethamide (Coramine®) (123, 124, 153, 242, 243); picrotoxin (243); nicotine (89)
  B. Lung irritant gases (29, 36, 40, 55, 90, 100, 109, 164, 191, 211, 236, 237, 267, 279, 280, 304, 310); oxygen poisoning (11, 18, 22, 23, 27, 74, 139, 158, 217, 223, 268)
  C. Other agents: alloxan (8, 118, 231); ammonium ion (41, 149, 150, 166, 167, 201, 260); thiourea compounds (79, 84, 132, 144, 188, 203, 241, 303); methylene violet, methylene blue (174, 177); methylsalicylate (49, 171, 277, 278); acetic, sulfuric, and butyric ether (171, 195); acetic ether and iodide solution (211); amyl salicylic ether (48); iodine and sodium iodide solution (314); iodoacetamide (118); bile and bile salts (214); urethane (305); carbon monoxide (113); carbon dioxide (103, 311); barbiturates (16, 169, 214)
  D. Metabolic effects: alkalosis (168); hypoglycemia (202, 265)
VI. Miscellaneous
  Hyperthermia (120, 127); sensitivity phenomena (45, 80); mechanical irritation of the bronchus (155)

* Pulmonary edema has been induced by the methods indicated in each of the sub-heads.

moved from the initial experimental variable in all cases except lung irritant edema, it has seemed to us that we should deal with the facts in relation to the *direct* and to the *indirect* or *remote* determinants so as to bring more order into the treatment. We therefore propose to deal first with the basic mechanisms and then attempt to relate to these the remote or indirect factors.

III. SOME THEORETICAL CONSIDERATIONS

It may be well to state at the outset the basic premises accepted by the present authors as the grounds for their analysis of the problem. As noted above, pul-

monary edema is considered to be a state in which there is an excess storage of water (and solutes) in the lung parenchyma and/or alveoli. Since there is no present evidence that water movement across the pulmonary capillary walls occurs by any other mechanism than by normal osmotic or hydrostatic pressure gradients, we shall assume that water transport is determined solely by such forces acting across imperfect dialyzing membranes capable of acting as ultrafilters. Therefore we shall assume that lung edema production is a phenomenon capable of description in terms of the movements of water produced by abnormal hydrostatic pressure and concentration gradients across normally or abnormally permeable membranes. We propose especially to distinguish between the direct and the remote causes of lung edema. We shall point out that no single mechanism is responsible for all forms of lung edema, unless it be said simply that such edema is a result of an excess of the rate of water movement out of the blood vessels of the lung over the rate of return into the blood of the body. This statement, however, is simply a definition of the edema state.

Table IV lists the several immediate determinants involved in water storage in the lung. These factors are the immediate determinants of storage in the sense that an independent change in any one of them is capable of increasing or decreasing the storage rate. However, they are not independent of one another. Thus the pulmonary capillary pressure is itself ordinarily the major determinant for the filtration area, and the latter is very possibly a determinant of the membrane permeability, because with a tube of fixed wall volume, changes in its internal volume must determine the wall thickness, which in turn must influence, perhaps critically, the permeation characteristics of the membrane. Likewise, the membrane permeability is a determinant of the colloid content of the interstitial fluid. It is possible to consider separately each of the immediate determinants for storage and thus analyze more fruitfully the actual mechanisms responsible for lung edema. This will be done first for the capillary pressure.

1. Capillary pressure. By considering the pulmonary capillary pressure it is possible partly on theoretical and partly on observational grounds, to analyze the

TABLE IV

Immediate determinants in the genesis of pulmonary edema (water storage in the lung)

Factor	Condition promoting edema
1. Pulmonary capillary blood pressure	Elevation
2. Filtration area	Increase
3. Pulmonary capillary permeability to colloid	High permeability
4. Plasma colloid osmotic pressure	Depression
5. Lymphatic vessel pressure	Elevation by obstruction
6. Colloid content of alveolar or interstitial fluid	Elevation
7. Interstitial fluid pressure	Depression will promote filtration from the capillaries. Elevation will promote movement into alveolar spaces and/or into the blood and lymphatics

TABLE V

Direct determinants of pulmonary capillary pressure (Considering in each case a change in only one variable at a time)

Variable	Direction of change	Direct effect on pulmonary capillary pressure	Effect on pulmonary venous pressure
Pulmonary arteriolar bore	Constriction	Fall	Fall
	Dilatation	Rise	Rise
Pulmonary venule bore	Constriction	Rise	Fall
	Dilatation	Fall	Rise
Pulmonary artery pressure (without arteriolar bore change)	Rise	Rise	Rise
	Fall	Fall	Fall
Pulmonary venous or left atrial pressure	Rise	Rise	(pulmonary venous pressure is the determining variable)
	Fall	Fall	

factors which are directly responsible for its magnitude. Table V lists the four possible direct determinants of pulmonary capillary pressure maintained in an intact circulation. This list does not include changes in bore of the capillaries themselves, because to have any maintained effect on pressure such changes would need to be associated with changes in other variables in the list. For example, capillary dilatation would in an otherwise fixed system momentarily lower intracapillary pressure, but if the pulmonary artery pressure is kept constant and arteriolar and venule resistances are unchanged, the capillary pressure will return approximately to its original value. In this table are also indicated the predicted effects of directional changes in these determining variables upon capillary and pulmonary vein pressures. The multiplicity of primary factors which determine pulmonary capillary pressure is a major reason for the complexity of the analysis of the action of remote mechanisms in producing water storage in the lungs.

In order to focus attention upon the practical problem at hand, we list in Table VI several of the well-recognized experimental alterations capable of inducing lung edema, along with their effects upon the pulmonary capillary pressures, when known, and our suggestions as to the mediating mechanisms. Citations to the relevant literature will be found in Table III. The capillary pressure changes are largely inferred from measurements of pulmonary great vein pressures. It will be noted that in all cases the remote determinants are capabale of increasing pulmonary capillary pressures by the intervention of mediating mechanisms. There are other "indirect determinants" of pulmonary edema which operate to produce elevations in lung capillary pressure and volume by various mediating mechanisms, but the list given will suffice to illustrate the general types of mechanisms involved.

2. Filtration area. Although the filtration area is perhaps the second factor in importance in determining the rate of fluid movement in an ultrafilter system, there are no studies upon pulmonary edema in which it has been quantitated. The inference may properly be drawn from the *in vivo* microscopic studies of Hall

TABLE VI

The influence of some indirect determinants of lung edema upon pulmonary capillary pressure

Initiating factor	Mediating mechanisms	Ultimate effect on pulmonary capillary pressure
Aortic pressure elevation (obstructive)	1. Increased residual blood in left ventricle: Increased left atrial pressure	Elevation
	2. Pressoreceptors: Heart rate reduction. Increased atrial pressure	Elevation
Increased intracranial pressure	1. Vagal stimulation: Heart rate reduction. Increased atrial pressure	Elevation
	2. Sympathetic discharge: Elevation in systemic arterial pressure. Increased left ventricular end—systolic volume	Elevation
Increased blood volume	1. Increased right heart filling: Increased pulmonary artery pressure and blood flow. Increased pulmonary venous pressure	Elevation
Epinephrine	1. Systemic vasoconstriction	
	a. Left ventricular strain. Increased left atrial pressure	Elevation
	b. Decreased systemic vascular bed volume. Increased filling of right heart with elevation of pulmonary artery pressure	Elevation
	c. Improved work capacity of heart	Fall
	2. Reflex bradycardia: Increased atrial pressures	Elevation
Bilateral cervical vagotomy	1. Laryngeal obstruction: Lowered intrathoracic pressure. Increased right heart filling and increased pulmonary artery pressure	Elevation
	2. Asphyxia: Heart failure. Increased atrial pressures	Elevation
	3. Interruption of normal reflex paths.	
	a. Changes in blood distribution between greater and lesser circulation?	Unknown
	b. Vasomotor changes in lung?	Unknown
Respiratory obstruction		
A. Inspiratory resistance	1. Lowered intrathoracic pressure: Increased right heart filling and increased pulmonary arterial pressure	Elevation
	2. Asphyxia: Heart failure. Increased atrial pressures	Elevation
B. Expiratory resistance	1. Elevated intrathoracic pressure: Decreased right heart filling.	Fall (temporary)
	2. Decreased right heart filling and asphyxia: Progressive heart failure. Increased atrial pressures	Elevation (ultimate effect)
Mitral stenosis	Elevated left atrial volume and pressure	Elevation
Posture alterations. Example: Goat in the dorsal recumbent posture	Increase in hydrostatic pressure head on pulmonary veins in dependent portions of lung	Elevation (limited to levels lower than heart)

(126) that with the larger number of open alveolar capillaries at high pulmonary artery pressures, there will be proportionate increases in filtration area. Likewise with increased distending pressure due to pulmonary vein pressure elevation, or with venule constriction, there would be predicted an increase in capillary vol-

ume and area, at constant wall elasticity. And even without pressure change a decline in the coefficient of elasticity of the capillary walls would of necessity result in greater surface area. Thus any nervous, chemical or physical change which altered small blood vessel tone could affect the filtration area and thus the ultrafiltration rate. This fact is particularly pertinent because of the general association of pulmonic congestion with lung edema, even when pulmonary vein pressures are not elevated, as in phosgene poisoning as noted by Hebb and Nimmo-Smith (135).

3. Membrane permeability. Landis (182) has called attention to the difficulties of measurement of the permeation characteristics of capillary walls. The permeability of such a membrane as the lung capillary endothelium cannot be measured by observing the rate at which substances pass through it, unless the nature and the magnitude of the forces producing the movement are also known. The main permeability problem in edema formation is in connection with protein. The classical studies of Landis (179) leave little room for doubt that normal capillary membranes under low pressures are only slightly permeable to plasma proteins. The quantitatively low permeability, more fully studied by Pappenheimer and Soto-Rivera (227), is, however, responsible for the protein present in the tissue fluid and in the normal lymph.

The present reviewers do not interpret the results of Landis (179) as proof of an absence of relationship between capillary wall distention and permeability. The studies on which the latter conclusions were based utilized the rates of appearance of dyestuffs put into the blood in the extravascular spaces around capillaries, the pressures in which were measured by direct puncture and the sizes measured by optical micrometer. It was found, making single measurements on a large number of capillaries in frogs, that there was a strong negative correlation between the time of visible staining of tissue fluid and the ambient capillary pressure, but no correlation with capillary diameter. The conclusion drawn suffers, we believe, from at least one important defect. It depends upon the implicit assumption that, in a random population of capillaries from many animals, those of larger diameter would be under the greater stretch. Actually, the data show no tendency for a positive correlation between pressure and diameter, otherwise there would have been a negative correlation between size as well as between pressure and time for dye appearance. The absence of correlation between pressure and diameter therefore precludes the assumption that the larger capillaries are the more distended relative to some basal rate. The conclusion could as well be drawn that the larger bore vessels studied were, on the average, simply the larger vessels in terms of structural material.

It should also be noted that some evidence in favor of a positive correlation between filtration pressure and capillary permeability to protein has been provided by Landis *et al.* (183), employing another method of study. These authors utilized the "reduced arm volume" technique in conjunction with chemical studies of arteriovenous differences in plasma protein concentration to measure the protein concentration in the tissue fluids formed under elevated venous pressures. Their calculations indicate that the fluid filtered into the arm tissues when the venous

flow was obstructed at 80 mm Hg pressure had 1.5% protein, whereas at 40 mm Hg the protein in the ultrafiltrate appeared to be close to zero. Thus, over the lower ranges of pressure the human capillary appears to have a constant low permeability to protein. Only at excessive pressures may the normal capillary become protein-permeable.

The studies of Pappenheimer and Soto-Rivera (227) have a bearing on the problem of the effect of capillary distention upon the permeability of their walls to protein. These workers found a linear relation between the mean hydrostatic pressure in the capillaries and the osmotic pressure of the plasma protein at which net filtration or absorption was zero, in the case of the perfused hindlimbs of cats and dogs. Their studies covered mainly pressures between 12 and 22 mm Hg, only two observations being reported at values above 22 mm Hg, and none in the range above 30 mm Hg. This type of study deserves repetition at higher pressures. It can be accepted as fairly well established that the hindleg capillaries did not show protein permeability changes with hydrostatic pressure alterations within the range of 12 to 22 mm Hg, but it would not be proper to extrapolate from this range to higher pressures.

Unfortunately, no measurements of the blood in the vasculature of the limbs were made in these studies. In view of known facts about the elastic characteristics (the existence of hysteresis and stress relaxation) of blood vessels, this may be a serious defect. Furthermore, the validity of the calculations given by Pappenheimer and Soto-Rivera depends upon the assumption of an array of symmetrical capillaries, all behaving alike, to the extent that arithmetic means of their various parameters and functions may be employed. What is known from microscopic study of capillaries suggests that this assumption is questionable. For example, it may be questioned whether extrapolation to zero flow may properly be used to find the "isogravimetric capillary pressure", when the number of open capillaries almost certainly varies with the pressure conditions that are altered to reduce the flow. It is possible to conceive of a system in which the "isogravimetric" state is reached with relatively high pressures in some fully open capillaries and with much lower pressures in some collateral less fully open vessels, into which the fluid filtered from the first group is being continuously reabsorbed. The "mean effective capillary pressure" becomes, then, a multiple-factor quantity because qualitatively different factors such as diffusion rates and distances, and flow rates, are incorporated into its quantitation. It is, in other words, not a simple measure of effective colloid osmotic pressure of plasma but is rather a composite quantity of several dimensions, including the colloid osmotic pressure.

Mayerson (208) and Wassermann *et al.* (293) have made important observations bearing on this question. Employing dextrans of known particle size, they showed that with normal blood volumes only the smaller particles escaped rapidly from the blood stream, whereas when the circulating blood volume was increased the larger particles were lost from the blood and appeared in the lymph. These findings can be interpreted most readily on the assumption that the permeability of the capillary wall is directly influenced by the degree of distention of the blood vessel.

A further point in connection with capillary distention and permeability should be noted. If "stretching" is a major factor in the permeability of an ultrafilter, it should be recognized that factors other than mechanical ones can bring this about. The extension of a sheet depends as much upon its elastic properties as upon the stress exerted upon it to produce extension. The elastic properties of living membranes are not fixed but depend upon their chemical state and environment. It will be a major problem for future investigation to ascertain precisely what factors influence capillary membrane elasticity and the relation between extension and porosity. There is convincing evidence that under certain circumstances pulmonary edema occurs without an elevation in capillary pressure above the colloid osmotic pressure. Hebb and Nimmo-Smith (135) point out that pulmonary edema can be produced in phosgene-poisoned isolated lungs with perfusion pressures of 6 to 12 cm of water. Moreover, Daly *et al.* (68) found that the pulmonary capillary blood volume is increased in gassed lungs, indicating a change in capillary wall elasticity.

Information concerning permeability can, under some circumstances, be derived from the composition of fluids passing through membranes. Tissue fluid and lymph arise from such passage and have been studied extensively in several situations. Lung lymph has been analyzed as to its albumin and globulin content by various workers, including Cameron *et al.* (38). The lung lymph ordinarily contains less of both varieties of protein than the plasma, the difference being greater in the globulin fraction, as might be expected, because the protein has been derived from plasma through a membrane which is permeable in only a small part of its area to molecules of protein dimensions, and in any sieve system with pores of a range of sizes more of the area will be available for passage of small than of large particles.

The high levels of albumin in the lung lymph, that is, two-thirds or more of the plasma level, are sometimes, mistakenly we believe, taken to be a proof of high capillary permeability to protein. That the lymph protein level is not identical with tissue fluid protein levels, has been discussed by Wiggers (301), among others. Lymph from a part may have a protein concentration several times that in tissue fluid. The differences seem to be due to reabsorption of water from the contents of small lymphatic channels. In this connection the work of Lee (189, see also 288) on intestinal lymph is of interest. He found that when D_2O-enriched fluids were placed in loops of intestine from which the lymph and venous blood were collected directly in the mesentery of the particular loop, the lymph had a D_2O concentration very close to the arterial blood levels and far below the venous blood concentration. He found the lymph flow to be increased when hypotonic solutions were being absorbed, so he concluded that the increase must have occurred in large part in the mucosa. The only interpretation open to him was that water exchanges freely across lymph vessel walls in contact with or in proximity to capillaries supplied with arterial blood, after the lymph has left the mucosal layer. Thus it appears that the concentration of materials to which the lymph vessel wall is relatively impermeable might be changed in one direction or another during passage. An increase in concentration of lymph protein could occur if the

TABLE VII

*Protein content of lung edema fluid**

Method of edema production	Animal	Protein content total g%	Reference
Methyl salicylate, intravenous	Rabbit	7.62	172a
Adrenalin, intravenous	Rat	5.20	172a
Oxygen poisoning, 5 days	Guinea-pig	4.25	172a
Cisternal fibrin injection	Rabbit	5.50	172a
Cisternal fibrin injection	Rat	4.68	172a
Saline infusion into carotid	Rabbit	1.25	172a
Sodium carbonate, intravenous	Cat	1.1	168
Sodium carbonate, intravenous plus Dibenamine	Cat	4.8	168
Ammonium chloride, gavage and intraperitoneal	Cat and guinea-pig	0.2	167

* Kwok-Kew Cheng, in Cameron, G.R., 1948 (172a); Koenig *et al.*, 1952 (168); Koenig, H., and Koenig, R., 1949b (167).

lymph vessels passed through tissues where capillary blood pressure was low and the net flux of water was into the capillary. A decrease in concentration of protein could occur if lymph vessel passage were through regions where capillary pressure was higher than in the site of original formation of the lymph. The fact that lymph ordinarily has higher protein levels than does tissue fluid speaks for the probability of the first-named situation.

In the case of the lung, the edema fluid in the airways has been analyzed, though tissue fluid proper has not. Values ranging from zero to levels considerably above the simultaneous concentrations in the plasma have been reported, as indicated in Table VII. The fact that alveolar edema can occur with very low protein content proves that excessive permeability to protein is not a requisite for lung edema production. And the fact that large quantities of protein are sometimes lost through the alveolar capillaries also shows that those capillaries can become abnormally permeable to colloid. But the more interesting question in the context of the present discussion is whether the protein levels in the lung edema fluid are reliable measures of the degree of permeability of the capillary walls to protein. We believe the answer is in the negative. We know of no mechanism by which concentrations of protein in the edema phase could be higher than in the plasma phase, except one which abstracted water or its vapor from the edema phase after removal from the site of formation. We have found no reports of measurements of protein in edema fluid collected from alveoli. All collections have been from large airways and water absorption from the edema fluid during its passage from alveoli has not been studied. Thus one must conclude that at the present time there is unfortunately no reliable information concerning the degree of increase of permeability of the lung capillaries to protein in various types of pulmonary edema, although the fact that there is an increase, especially with the chemical poisons, cannot well be doubted.

The role of low oxygen tension in altering capillary permeability to the filtration of water, presumably by increasing its leakiness to protein, is one which has received a great deal of attention. Landis (180) showed that at oxygen tensions approaching zero, capillaries in the frog mesentery become more leaky. Hendley and Schiller (140) studying rat hind limbs perfused with nitrogen-washed Ringer's fluid also found greater leakage of macromolecules and water than when the perfusion fluid was oxygenated. They also showed (140a), however, that an adrenergic blocking agent, Dibenzyline® (N-benzyl-N-(α-methyl-β-phenoxyethyl)-2-aminoethyl chloride), and an antihistaminic agent, Neoantergan® (Pyrilamine Maleate U.S.P., Mepyramine Maleate B.P., 2-[(2-Dimethylaminoethyl)-(*p*-methoxybenzyl)amino]pyridine), afforded complete or partial protection against such leakage. It is altogether possible, although the authors discount the likelihood, that alterations in pressures within the small vessels accounted for these findings.

Most careful studies on the possible effects of moderate, physiologically probable, degrees of hypoxia on net water movement between capillaries and tissues have been performed by Nairn (216), who in numerous experiments perfused hind limbs of dogs with blood from the veins of another limb of the same animal. He found no evidence whatever that edema occurred more rapidly or was more massive when the limb was perfused with blood at 50 % oxygen saturation than at full saturation, and concluded that within physiological limits hypoxia was not a factor in the genesis of edema. McMichael and Morris (209) found no increase in rate of swelling of the human arm exposed to increased venous pressures upon administration of 9.5 % oxygen in the inspired air. However, Henry *et al.* (142) calculated the percentage of protein in ultrafiltered fluid in normal human subjects exposed to varying degrees of hypoxia and their results would indicate an increase in protein permeability of capillaries when the venous oxygen saturation is below 25 %. The reliability of the method of calculation is thrown into question, however, by the frequency with which they calculated negative protein loss with venous occlusion cuffs at 60 and 80 mm Hg. Since there is no reasonable mechanism by which protein could enter the capillaries under such circumstances, it must be concluded that there are defects either in the methods of measurement or the calculation, especially since the results do not agree with the direct observations on protein content of edema fluid as cited below.

Stead and Warren (273) found the protein content of edema fluid in two patients with arterial oxygen saturations of 50 % and 60 % to be 0.2 and 0.1 g % respectively. They state "the marked anoxemia had not increased the permeability of the capillaries of the lower extremities". Maurer (205) studied the effects of carbon monoxide on lymph production and composition. He found an increase in lymph flow with a decrease in protein content along with complex changes in hemodynamics in dogs which he interpreted to indicate increased capillary permeability. However, other alternative explanations are equally possible and, indeed, more likely in view of the fact that the protein content of the lymph was not increased as would have been expected if there were increased permeability to macromolecules.

The much-quoted conclusion of Drinker (83), that hypoxia promotes a develop-

ment of pulmonary edema through an increase in the permeability of the lung capillaries to water, was apparently based upon one experiment on a dog subjected to inspiratory resistance plus hypoxia. In this animal, which was compared with another subjected to the same inspiratory resistance, breathing oxygen, there happened to be at autopsy slightly more lung edema than in the dog given oxygen. Two serious defects mar the conclusions of Drinker. First, he has ignored the well-established effects of hypoxia in promoting heart failure (see 61), and second, he has ignored the great variability in the reaction of individual animals to such stresses as resistance breathing. In 16 anesthetized normal dogs Zinberg *et al.* (316) found variations from 5 to 72 hours in the survival time on a standard inspiratory resistance of 20 cm H_2O. They also found comparable variability in the extensiveness of lung pathology, ranging from absence of recognizable lung edema to massive involvement of all lobes of the lung. The extensiveness of the pathology was completely unrelated to the time of survival. The studies of Haddy *et al.* (121) clarified the situation by showing that the occurrence and the extensiveness of the pulmonary edema was positively correlated with the pulmonary venous pressure during the last quarter hour of life, which could be used as an index of left heart failure.

A distinction should be made between increased permeability to protein and extravasation of whole blood. Lung edema is frequently complicated by microscopic or gross hemorrhage into the alveoli and bronchial tree. By definition the two processes are quite different, and we do not propose to deal with the factors that promote pulmonary petechial hemorrhage, except to say that α-naphthylthiourea and the lung irritant gases have this property to a marked degree, and to point out that agents which increase pulmonary vascular (presumably capillary) fragility can obviously cause lung pathology which may be confused with true lung edema. It may also be pertinent to note that if the state of the intercellular cement substance controls both the protein permeability of a membrane sheet and its fragility, the two phenomena could be related, a change in protein permeability being a result of a smaller change in the structure than might be necessary for the occurrence of actual rupture.

4. Plasma and interstitial fluid colloid osmotic pressures. In processes involving ultrafiltration and diffusion of water, the difference in colloid osmotic pressure across the membrane will necessarily be a determinant of first importance. If, as they appear to be, capillary walls are diffusion and ultrafiltration barriers, the colloid osmotic pressure should be, among other factors, determining as to net flux rates for water. Water flux across any such barrier with both concentration and hydrostatic pressure differences across it will be a composite of several components. Diffusion occurs in both directions at rates dependent upon activity values. Filtration is a unidirectional process at any particular site. Therefore the net flux rate at any small segment

$$R_{net} = R_{do} - R_{di} + R_u \tag{1}$$

where R_{do} is the diffusion rate out of the segment of capillary, R_{di} the diffusion rate into the segment, and R_u the rate of ultrafiltration, considered positive when occurring outward and negative when inward.

Since pressure and concentration gradients need not be, and apparently are not, identical at all points along the length of a capillary, the sum of the fluxes along the extent of the capillary must be taken in order to obtain the value for the net flux over a whole capillary or in a capillary bed in a volume of tissue.

Therefore

$$\sum R_{net} = \sum R_{do} - \sum R_{di} + \sum R_{u} \quad (2)$$

Under steady state conditions

$$\sum R_{net} = 0, \text{ and } \sum R_{u} = \sum R_{di} - \sum R_{do} \quad (3)$$

But when

$$\sum R_{u} = \sum R_{di} - \sum R_{do} \quad (4)$$

storage must occur or removal must be accomplished by some other means, such as lymph drainage. We call attention to the fact that when the hydrostatic pressure head in the capillary tissue space system exceeds the colloid osmotic pressure gradient $\sum R_u$ will be positive, and it will be negative when the reverse is true.

It is important to note that osmotic diffusion of water and ultrafiltration are quantitatively related processes of quite different magnitude. Colloid osmotic pressure is measured in terms of pressure head for ultrafiltration necessary to equate precisely net diffusion flux with ultrafiltration flux. Exchange diffusion of water in a system with membranes like a mammalian capillary and its surrounding fluid is approximately twenty-five thousand times as rapid as the net diffusion flux due to osmotic pressure differences. The above number is calculated from the differences in mol fraction of water in two solutions differing by 0.002 M protein, which is approximately the concentration in plasma. It is obvious that total water turnover between blood and tissues can have an entirely different order of magnitude from the net flux due to ultrafiltration during steady state conditions.

In spite of the known significance of colloid osmotic pressure to generalized edema formation (261), relatively little attention has been paid to this factor in lung edema. With the plasmapheresis method of lowering plasma colloid osmotic pressure, Darrow *et al.* (73) induced generalized anasarca but did not report lung edema. However, Paine *et al.* (221) found with the isolated heart-lung preparation that when hypoproteinemia was induced lung edema occurred, without change in heart function. Cleland (50) reported that in some instances lung edema regressed after the administration of concentrated plasma protein solutions.

Zinberg (315) perfused the lungs of rats with various solutions and found that with 3% gelatin in Ringer's fluid the water content of the lung did not change appreciably in 60 minutes of perfusion at 9 cm H_2O. In the absence of the colloid there was a 57% increase in water content in 45 minutes. He found further that if the 45 minutes perfusion without colloid was followed by a period of an hour of perfusion at the same pressure with 4.5% gelatin added to the Ringer's fluid there was a statistically significant decline in water content averaging one-third of the increase induced by the period of low-protein fluid perfusion.

A most interesting observation of Pappenheimer *et al.* (226) is that when a change in protein concentration is made there is a long delay (one hour) in the establishment of a new equilibrium in "isogravimetric" pressure. No evident reason for this deviation from physico-chemical predictions, which would require very rapid assumption of new steady state values, is available. This peculiar phenomenon would appear to warrant further study in relation to the problem of membrane permeability to protein.

The role of particulate matter in determining the permeability of capillaries to macromolecules and therefore determining the effective colloidal osmotic pressure, has received attention. Danielli (72) showed that the addition of platelets to fluids perfusing the frog hind limbs decreased capillary permeability to various macromolecules including serum albumin, hemoglobin, ovalbumin and gum acacia. He concludes (75), "The average diameter of the protein-permeable pores in the perfused frog is about 6 mμ or less in the absence of platelets, and in their presence a few pores of this diameter persist."

In some unpublished experiments Zinberg and Visscher (317) noted that the addition of small amounts of India ink to the fluid perfusing isolated rat lungs decreased the rate of accumulation of water in those lungs. They did not establish the mechanism of the effect, but considered it likely that the considerations applied by Danielli could account for the phenomenon. Further work on the role of microscopic particulate matter in determining the frequency of pores of large size in capillaries is indicated.

It may be suggested that changes in colloid osmotic pressure are less critical causative factors in lung edema than in body edema, because in the lung capillaries the hydrostatic pressure is normally below the colloid osmotic pressure along the entire length of the vessel, while in capillaries in the remainder of the body higher pressures prevail, so that smaller changes in colloid content may be effective in changing the direction of net water movement. This fact is of importance to the normal "dryness" of the lung. Water introduced intratracheally is absorbed into the blood rapidly (54); plasma protein solutions so administered are very slowly absorbed (62).

5. Lymphatic vessel and interstitial fluid pressures. We have found no measurements of tissue fluid pressure in the edematous lung and only one study of lymphatic vessel pressure, by Paine *et al.* (222). The latter observers found that in the open-chest dog the pressure in the right thoracic duct, which drains largely from the lungs, varied between 1.5 and 34 cm H_2O. Furthermore, there was some correlation with the concurrent jugular venous pressure. They found that complete blockage of the large terminal lymph vessel did not cause lung edema. The possibility of alternate channels for lymph flow was not explored, but could obviously vitiate any simple conclusion drawn from such an observation.

The majority of the studies on lung lymphatics concern the rate of lymph production at zero outflow pressure. Warren and Drinker (290), Courtice (59) and others have found that lung lymph flow frequently increases when pulmonary edema occurs. Therefore complete obstruction to lymph drainage is not necessary for lung edema to occur, because lymph flow continues at an accelerated rate.

The question may properly be raised, however, whether the innate low capacity of the lymphatics to drain off superfluous tissue fluid may not sometimes be the limiting factor in determining edema production. According to Warren *et al.* (290) and Cameron and Courtice (37), the rate of lung lymph flow in the normal dog (with lung weights between 200 and 300 g) is from 1 to 5 ml per hour. A 10% increase in lung weight is the least that can be called a beginning lung edema. Using the larger figures for calculation, it can be seen that complete obstruction of lymphatics would produce such barely detectable edema in 6 hours. Since massive lung edema can occur in as many minutes, one cannot suppose that simple lymphatic obstruction is the usual prime factor in the causation of acute edema. The lung lymph flow in edema reaches 1 ml per minute, but even so does not approach the rates of edema fluid accumulation in the lung, which may be 15 ml/min in dogs. Our interpretation is that the lymphatics are not capable of serving beyond a rather narrow range in protection of the lung against flooding its tissues by excessive ultrafiltration. Still, it is altogether possible that chronic excessive ultrafiltration might result in increasing the run-off capacity of the lymphatics and account for the long-time survival of patients with mitral valve disease in some of whom relatively high pulmonary venous, and therefore capillary, pressures exist without evidence of lung edema. The possibility of adaptive changes in lymph channel capacity in the lung has not been studied. It should be noted at this point that it has not been established that pulmonary capillary mean pressures above the colloid osmotic pressure actually occur for extended periods without lung edema. There are reports to this effect by Allison and Linden (3) and others, but the high left atrial pressure values obtained were either under anesthesia with an open chest or for very short periods by bronchoscopic puncture. In neither case is there assurance that the values obtained reflected the state under more usual circumstances. To the contrary, Haddy *et al.* (122) found in dogs with surgically produced mitral stenosis, that elevations of pulmonary vein pressures to 20 mm Hg or above were associated with early death and pulmonary edema. Thus, although one must still entertain the possibility that lung lymphatic adaptation occurs in disease, this has not been demonstrated.

A major theme in some clinical writing on treatment of lung edema in the last decade has dealt with positive pressure breathing. This problem is introduced at the present juncture because it has been suggested that pressure breathing in essence raises alveolar and tissue pressures in the lung and thus promotes reabsorption of alveolar and interstitial fluid. If ambient atmospheric pressure is taken as the point of reference, it is obviously true that the above-mentioned pressures are raised. But if the virtual intrapleural pressure is considered, as it should be, as the point of reference, the fallacy of the reasoning becomes apparent, because the intrapleural pressure rises with the intrapulmonic. Since the heart is exposed to intrapleural pressure, it works from the latter as its zero and therefore any changes in pulmonary vascular pressure referable to the intrapleural as zero, must depend upon cardiac work output (right ventricular) and not on the raising or lowering of the general pressure levels in the thorax. In reality, the first effect of raised intrathoracic pressure due to pressure breathing is a decline in venous

return to the right heart. The heart puts out less blood because of lesser filling (97), and pulmonary vascular changes are thus secondary.

Brecher and Mixter (31) have measured the inflow into the heart in relation to the intrathoracic versus atmospheric pressure difference. They found a doubling of inflow in going from a 2 to a 4 mm Hg pressure difference, and a plateau beyond 8 mm Hg, indicating an inadequate upstream pressure head in the extrathoracic large veins to sustain flows at maximal values for the size of the vessel when the pressure gradient increased beyond the last mentioned value. Obviously, however, the cardiac filling is a function of intrathoracic pressure at physiological values, and the effect of positive pressure breathing on cardiac output is readily accounted for.

Concerning the possible occurrence of changes in interstitial lung tissue pressure with reference to intrathoracic pressure as the zero, it was noted at the outset in this section that there are apparently no observations on the question. Theoretical considerations would lead to the prediction that the situation in the lung would differ from that in tissues elsewhere, because the alveoli provide a drainage channel at approximately atmospheric pressure which allows ready escape of fluid in great quantity. This is in contrast to the condition in an extremity, where the skin can act as a somewhat rigid bag, allowing a build-up of pressure which would eventually allow a balance of the forces between filtration and absorption.

IV. SOME PERTINENT ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

1. On the existence of valves in pulmonary veins. In an extensive review on valves in all types of veins, Franklin (101) cites an extremely scanty literature on pulmonary veins. Hildebrandt, in 1830–32, (145) cites studies on amphibians and some mammals, indicating that membranous protrusions resembling rudimentary valves may exist at sites where branches enter trunks at acute angles. Fully developed semilunar valves were reported in sheep by Hales in 1744 (125) but are apparently never found in man, according to Boyden (28). This subject is mentioned because, if valves were present in pulmonary veins, it could not properly be assumed that pulmonary capillary mean pressure must always be greater than pulmonary venous pressures when flow is occurring.

2. Vascular innervation. In connection with the control of the various parts of the pulmonary vascular bed and lung edema, the innervation of the lung vessels is of potential importance. The blood vessels in the lungs are supplied with both parasympathetic and sympathetic nerve fibers. Ponzio (235), Larsell (185, 186), Takino (276), Larsell and Dow (187) and Gaylor (105) have described the innervation of the lung in some detail. The lung nerves enter the hilum from the vagus and sympathetic trunks and become arranged into a periarterial and peribronchial plexus. The periarterial plexus is made up of bundles of unmyelinated fibers which form a network of longitudinal mesh about the pulmonary artery and its branches. Few myelinated cells are found with these bundles. Endings were found by Larsell and Dow and by Gaylor in the adventitia of the pulmonary artery and its branches and also around the capillaries in alveolar

walls, which latter had been described by Ponzio. Larsell and Dow comment on the fact that nerve twigs "end in relation to the capillary walls, but whether on endothelial cells or on some other type of cell in the capillary wall could not be ascertained. . . ." These authors do not describe such endings in the walls of veins. No functional significance has as yet been established for nerves with endings in the alveolar or capillary walls in the lung. It would seem that a further analysis of possible functions would be warranted, because on teleologic grounds it would seem unlikely that such regularly distributed nerves would have no function.

Takino (276) made a comparative study of the distribution of nerves to the pulmonary arteries and veins, the bronchial arteries and veins and the subcutaneous arteries and veins in the same animal in several species. In the case of the rat, he found a rich distribution of nerve fibers in the neighborhood of arterioles arising from both bronchial and subcutaneous arteries, whereas he found such nerve endings in the arterioles only rarely in the pulmonary system. With respect to the innervation of venules, he described sparse but significant innervation in both the subcutaneous and bronchial systems, but made the positive assertion that nerve fibers are not demonstrable in the pulmonary venule system. In the case of the somewhat larger vessels he found a more abundant distribution of nerves to the smaller pulmonary veins than to bronchial or subcutaneous veins of the same size. In comparing the distribution of nerves to the pulmonary veins in various species of animals, Takino found that the bat, mouse, rat, bovine species and pigeon showed a distribution of nerves that extended much farther toward the venules than was the case in either the rabbit, the dog or the cat. (The human species was not included in his study.) The form and position of the nerve endings in the media, according to Takino, particularly their relationship to the smooth muscle, shows that the pulmonary veins are more richly innervated by vasomotor than by sensory nerves, whereas the opposite is true for the pulmonary artery. It might be predicted from these observations that there could be considerable species variation in the precise response of animals to nerve stimulation with respect to pulmonary hemodynamics.

3. The musculature of the vascular walls in the lung. Takino (276) has published the most comprehensive study of the general anatomy of the pulmonary blood vessels. He points out that there is a wide range of differences in the thickness of the walls of pulmonary arteries and veins in various species of mammal. Relative to the diameter of the vessel, the medial layer of the pulmonary artery and its branches is greater in the guinea-pig, rabbit and calf than it is in man, which again is thicker than in the cat or the rat. The pulmonary vein also has the thickest media in the guinea-pig, the human and rabbit having the thinnest. He finds in the calf and hog that circular muscle around the vein is most prominent in vessels of 20 to 40 μ diameter. The existence of muscle in this situation is important to the consideration of mechanisms by which pressure within the capillaries could be controlled by regulation of small vein bore. Attention is called to these observations because there has been almost complete neglect, except by Aviado *et al.* (8), of the role that such venomotion might play in the genesis of pulmonary edema.

Sarnoff and Berglund (259) studied the pressure volume characteristics in the pulmonary vascular bed of the dog, and noted one point of interest in connection with the pulmonary edema problem, namely, that there is an important stress relaxation in these structures. The result of this characteristic is that the pressure necessary to maintain a given volume is less than that necessary to produce it. They found this characteristic to obtain in the case of the isolated left auricle and the pulmonary veins and also in the case of the entire pulmonary vascular bed. This property has significance in connection with the deleterious effects of temporary high pressures on the venous side of the pulmonary bed. It may account partially for the difficult and slow reversibility of lung edema, especially if extension of the capillary surface is itself a determinant of permeability to protein.

4. Regulation of the blood flow through the lungs in relation to edema. Despite intensive study by many methods, the problem of the regulatory mechanisms for the pulmonary vascular bed is still unsettled. Daly (66) summarized the evidence available at that time concerning the role of vasomotor nerves in controlling the resistance to blood flow through the lung. Daly *et al.* (67) showed that in the perfused dog preparation in which the pulmonary vascular bed is fed at constant inflow pressure, a stimulation of the upper thoracic sympathetics may reduce the lung blood flow by as much as 30%. Daly *et al.* (70), using the innervated perfused lung preparation, demonstrated that stimulation of the upper thoracic sympathetic chains and the cervical vagal sympathetic trunk was invariably associated with pulmonary vasoconstriction, as judged by a rise in pulmonary arterial pressure and a decrease in outflow through the pulmonary veins. It is of some interest to note that they found the base line of pulmonary blood flow in intervals between stimulations to be lower the higher the pH of the blood. In fact, the changes due to alterations in pH were very much greater than those induced by sympathetic nerve stimulation, leading one to suggest that chemical factors may exceed in importance the nervous ones in the control of the pulmonary vascular bed. Daly and Hebb (69), employing dogs which had been subjected to unilateral pneumonectomy, found that the lung blood vessels appear to be innervated, in part at least, by nerve fibers derived from the contralateral cervical and thoracic sympathetic nerves.

The arterioles in isolated perfused lungs may respond by constriction to epinephrine and to histamine (26, 65). But such drug administration and nerve stimulation in animals with functionally intact nervous and chemical regulatory mechanisms have yielded most unsatisfying irregularities of response, which lead one to suspect that some important underlying principles are still undiscovered or are being ignored.

Elevations in pulmonary artery pressure by arteriolar constriction could not theoretically, as noted above, and have not been observed, to cause pulmonary edema. Born (26) has recently studied edema production in perfused lungs and reports that although adrenaline and histamine increase the perfusion pressure necessary to drive fluid through the bed, they do not induce lung edema. In human disease pulmonary arterial hypertension is not a recognizable cause of lung edema. Even in mitral valve disease pulmonary arterial hypertension oc-

curs without lung edema. Pulmonary arteriolar constriction and mechanisms for its control may in fact be of prime importance in preventing lung edema. Although this discussion has centered on the factors involved in producing edema, equally important questions arise in connection with the reasons for failure of lung edema to occur in certain situations, as in pulmonary hypertension. We suggest that processes regulating resistance to flow (pressure drop) through lung arterioles may be of the highest importance here. Consideration should be given not only to the muscular contraction mechanisms under nervous or humoral control, but also the structural alterations affecting geometry and elasticity. The former could be of crucial importance in short-term periodic adjustments and the latter in chronic adjustments. We call attention to the fact that a five-fold or greater increase in cardiac output and pulmonary blood flow occurs in exercise, and is accomplished in normal individuals, with rare exceptions, without acute pulmonary edema. Pulmonary artery pressure in diastole decreases in exercise (245) in spite of the increase in pulmonary blood flow.

Several microscopic studies have been made of capillary blood flow in the lungs. Wearn *et al.* (295) studied the circulation in the cat lung by microscopic observation in the closed chest with a pleural "window" employing direct illumination through the diaphragm. They found considerable intermittency of blood flow in the microscopic vessels under normal circumstances. Administration of pituitrin was generally followed by arteriolar constriction and disappearance of capillaries occurred occasionally. Epinephrine given intravenously had extremely variable effects, probably related to the effects on cardiac output, prior state of tone of the vessels, etc. Administration of histamine was followed most commonly by arteriolar constriction, but again results were not uniform.

V. A TENTATIVE ANALYSIS OF THE MECHANISMS OF PULMONARY EDEMA CLASSIFIED WITH REGARD TO SOME INDIRECT DETERMINANTS

An attempt to trace fully the intricacies and complexities of the connections between cause and effect in the scores of indirect mechanisms by which lung edema occurs naturally in disease or has been produced experimentally, would be impossible, because in almost all instances some of the important factors have not been studied, and would be a fruitless task both for writers and readers alike. We do propose, however, to analyze and correlate facts in connection with the more fully studied types of lung edema.

1. Lung edema following the administration of some chemical agents. a. Adrenaline. Employing rabbits given adrenaline intravenously (approximately 0.3 mg/kg body weight), Luisada (197) found a 40% mortality rate, with lung edema as a major pathologic change. He found that chloral hydrate (0.5 g/kg) and papaverine (40 μg/kg) afforded complete protection. Morphine (10–20 μg/kg) gave protection in two-thirds of the cases, as did paraldehyde, chlorobutanol (chlorbutol, Chloretone®) and sodium phenobarbital (Luminal®). Intravenously-administered hypertonic solutions of glucose or calcium chloride also exerted some protective action against adrenaline-induced lung edema.

The administration of large doses of adrenaline to the intact unanesthetized

animal may, under suitable circumstances, be followed by lung edema in all species of mammal that have been studied (references in Table III). However, this agent did not produce edema in the isolated perfused lung in the hands of Born (26). Furthermore, in the intact animal edema of the lung fails to occur after adrenaline when extensive sympathectomy has been previously carried out. Boggian (25) reported that simple stellate ganglionectomy prevented adrenaline lung edema under his experimental conditions. Bariety and Kohler (15) showed that sympatholytic agents had protective action.

In a carefully controlled study, Korner (170) investigated the production of pulmonary edema in rabbits by the simultaneous infusion of noradrenaline and Ringer-Locke solution. In this situation noradrenaline at the rate of 0.3 μg/kg min considerably increased the susceptibility to pulmonary edema. The increased susceptibility was not abolished by atropine or by reducing the total blood volume by bleeding. This investigator employed an ingenious method for estimating pulmonary vascular bed capacity, namely by determining the lung to body weight ratio with and without noradrenaline before and after administration of excess fluid. He found a significant shift in blood volume from the systemic to the pulmonary circuit upon administration of noradrenaline. The rise in the lung to body weight ratio, indicating lung edema, occurred with a very much smaller excess fluid load with noradrenaline than in the control animals. Korner is inclined to attribute the increased blood volume in the lungs to a vasomotor redistribution of blood rather than to left ventricular failure. This conclusion may be considered in the light of the observation of Opdyke *et al.* (219), who showed that upon increase of the blood volume by rapid infusions of blood or saline, the left atrial pressure always increased more than did the right. They found likewise that central vagus stimulation, bringing about systemic hypertension, resulted in a much greater increase in left than right atrial pressures. They inferred that the left atrial-venous system has a higher volume elasticity coefficient than does the right under the conditions of their experiments. The studies of Korner are particularly important in shedding some light on the mechanism by which pulmonary edema may be produced by hypertensive agents without primary heart failure. It will be obvious that redistribution of the blood in the body so as to increase the fraction in the pulmonary bed will, in the absence of any change in volume elasticity, increase pulmonary capillary pressure. In this connection the study of the effects of vasoactive agents upon the elastic characteristics of the several parts of the pulmonary vascular bed would be of the highest importance, particularly in analyzing in more detail the mechanism by which the large variety of drugs and other chemical agents influence the edema state.

Luisada (196) has provided convincing proof that adrenaline in large intravenous doses (0.1 mg in a cat of 2.85 kg) causes a sustained large rise in left atrial pressure. He also showed that such doses bring about a sustained rise in lung vascular volume, using an oncometer method.

Paine *et al.* (224) found that when dogs to which adrenaline had been administered developed pulmonary edema, the left atrial pressure rose to values as high

as 90 cm of water. They noted that pulmonary edema was produced more regularly in dogs which had previously been subjected to aortic valvulotomy, in which case left atrial pressure elevations of large magnitude regularly occurred. It may be noted that the left atrial pressure was not greatly elevated by making the valvular lesion alone. The experiments of Paine *et al.* were conducted with the chest of the dog open and the heart available for inspection. Although these authors made no quantitative measurements, they state that "conspicuous dilatation of the heart was noted in all instances" after the administration of adrenaline. They made the same observations when pulmonary edema occurred following cerebral embolization. These authors concluded from their experiments "that although stress against the damaged myocardium may be of neurogenic character, the generation of pulmonary edema is due to a cardiogenic mechanism." Thus it may be seen that the controversy concerning whether pulmonary venous hypertension is due to redistribution of the blood between the systemic and pulmonic beds, or to failure of the left ventricle to deliver enough blood per contraction so that the pulmonary venous pressure can be kept at normal limits, is partly and perhaps entirely a semantic one. If by definition the ability of the left ventricle to receive blood from the left atrium in diastole and to eject it in systole at such a rate as to prevent pulmonary venous pressure rise is a criterion of left heart competence, then by definition there would be a relative functional incompetence whenever the pulmonary venous pressure rose.

The above-cited observations on the pulmonary venous pressure rise and the capillary congestive effect of adrenaline in doses adequate to produce lung edema seem to provide adequate grounds for the conclusion that hydrostatic forces can account adequately for this form of pulmonary edema.

b. Histamine. It is of interest to note that the production of pulmonary edema by administration of histamine to experimental animals has proven to be very difficult. Moon and Morgan (213) reported its production after nine days of administration of 7.5 to 15.0 mg/kg body weight twice daily to dogs by subcutaneous injection. They reported without giving details that 0.5 mg/kg twice a day for an unspecified number of days resulted in pulmonary edema in guinea-pigs. Employing the rabbit, Bariety and Kohler (16) reported that the concomitant administration of histamine in doses of 0.2 to 0.5 mg/kg body weight, along with 0.05 mg/kg of adrenaline hydrochloride, induced pulmonary edema, while animals treated with the same dose of adrenaline alone were not so affected. Moreover, histamine alone was not followed by pulmonary edema in the doses employed. Halpern *et al.* (131), on the other hand, reported that the prior injection of 0.25 mg/kg of histamine is capable of protecting rabbits against the acute pulmonary edema of adrenaline. It seems unlikely that the lung edema reported after long-term injections of massive doses of histamine is due to direct actions on the pulmonary vascular bed, because Coelho and Rocheta (52) were unable to induce lung edema by direct injection into the pulmonary artery of 75 μg of histamine per kg body weight in dogs. Born (26) was unable to produce lung edema by addition of histamine to the perfusion fluid of isolated rabbit lungs. It seems more likely that when lung edema follows chronic histamine poisoning, the effect is mediated by more remote mechanisms, perhaps heart failure.

Jaques (150) found that young rats, which are resistant to ammonium chloride lung edema, have very much lower histamine levels in lung tissue than do older animals which develop lung edema more readily. In the older animals the lung loses histamine when edema develops. He found much less age dependence for skin histamine levels in rats and is inclined to ascribe significance to the lung levels in relation to the pathogenesis of pulmonary edema. The same author (149) found a doubling of the histamine content of the blood of rats made edematous with ammonium chloride. Three possibilities should therefore be given equal consideration: that general body effects are to be expected, that the histamine may act locally, or that the histamine release is without major effect in the production of lung edema. Any of the three is possible and the information which exists today is inadequate to allow a choice among the alternatives, although the facts cited in the following paragraphs are pertinent.

Jarisch *et al.* (151) reported that blood histamine levels were reduced in rabbits in which lung edema was induced by suboccipital injection of veratrine. MacKay *et al.* (201) and Winter (307) were unable to protect guinea-pigs or rats against ammonium chloride lung edema by the antihistaminic drug Phenergan® (Promethazine Hydrochloride B. P., 10-(2-dimethylaminoisopropyl)-phenothiazine). Stone and Loew (274) experienced similar failure of this agent to protect against adrenaline-induced pulmonary edema.

Inchley (148) devised numerous ingenious experiments to test the action of histamine on arteries and veins, particularly in the visceral bed. He found that the vasodilating effect described by Dale and Richards (64) of histamine on blood vessels perfused with Ringer solution containing 1:1000000 adrenaline (w/v) depended upon the dose of histamine and upon the perfusion pressure. He concluded that "histamine shock is best explained by venous constriction". By direct puncture measurement, Landis (181) found that intracutaneous histamine raised skin capillary blood pressure consistently and to a large extent. Such an effect could not occur, on hydrodynamic grounds, with capillary dilatation as the only process acting. It could occur as a result of venule constriction or arteriolar dilatation.

c. *Alloxan.* It was reported by Peralta (231) that alloxan in doses of 150 mg/kg body weight in the cat induced pulmonary edema. The mechanism of this phenomenon has been investigated by Aviado *et al.* (8) in intact anesthetized dogs and in the perfused isolated lung. They found the initial effect of alloxan to be a constriction of pulmonary arterioles as indicated by pulmonary artery hypertension in the absence of an increase in lung blood volume as measured by the content of P^{32}-tagged erythrocytes, recording the radioactivity from the surface of the lung by means of a beta counter inside an airtight channel that allowed closure of the chest. After a latent period of about a half an hour, they noted an increase in lung blood volume and the development of pulmonary edema. Left auricular pressure was measured and found not to increase significantly during the peak of the alloxan effect. The results in question could be interpreted from a hemodynamic viewpoint as being due to a pulmonary arteriolar constriction, which is followed by either an active or passive dilatation of the capillaries. A passive dilatation brought about by venule or small vein con-

striction is a possible interpretation, although a decrease in capillary wall elasticity could produce the same result. Gruhzit *et al.* (118) studied the effect of sulfhydryl donors on the actions of alloxan and ANTU. Their results were for the most part inconclusive because the agents employed, such as cysteine and BAL, themselves produced pulmonary arterial pressure rises in the heart-lung preparation, indicating pulmonary vasoconstriction. They were therefore unable to test critically their hypothesis that the lung edema produced by alloxan and ANTU was due to capillary damage by cell injury from the sulfhydryl acceptors.

d. Thioureas. Drinker (83) noted that α-naphthylthiourea (ANTU) induced lung edema in the dog. Latta (188) found that a massive pleural effusion was an associated phenomenon. Richter (241) found that 1 to 50 mg/kg body weight induced lung edema in the rat; the edema occurred a half hour or more after administration. The alveolar-arterial oxygen gradient is increased after ANTU poisoning in dogs, according to Williams (303). Drinker and Hardenbergh (84) found in the dog that lung lymph flow rises in ANTU poisoning. In the isolated perfused dog lung Brackney and Schafer (30) have found that ANTU induces edema while the pulmonary veins are at zero outflow pressure and the arterial perfusion pressure is below the colloid osmotic pressure of the blood. The permeability of the pulmonary capillaries to protein is without doubt increased following ANTU, but whether the increased leakiness is due to a decrease in capillary wall elasticity and consequent stretching, or to some more specific alteration in membrane character, cannot be decided on the basis of existing knowledge.

e. Ammonium salts. Koenig and Koenig (165, 166) reported the occurrence of acute pulmonary edema after the intraperitoneal administration of relatively large quantities of ammonium salts in guinea-pigs. They extended their studies to the rat, cat and rabbit and found that in the latter two poisoning with ammonium salts caused death from other causes before pulmonary edema occurred. The same authors (167) reported that the edema fluid from the lungs in two cats and one guinea-pig were free from measurable serum protein, while a third cat showed 0.7%. They therefore conclude that early in the lung edema process due to ammonium salts there was no great increase, if any, in alveolar capillary permeability. An important observation which they made in connection with the study, was that administration of the sympatholytic drug Dibenamine® (N-(2-chloroethyl)dibenzylamine) prevented the lung edema in most animals consequent to ammonium salt administration. They noted considerable arterial hypertension in almost all animals presenting lung edema. MacKay *et al.* (201) found that a large variety of adrenergic blocking agents completely prevented ammonium edema. It may be noted that these agents did not prevent death of the guinea-pigs employed, indicating that pulmonary edema is not the only possible direct cause of death from ammonium intoxication. Winter (307) and MacKay *et al.* (201) found that the antihistaminic, Phenergan, was without effect in protecting rats or guinea-pigs against pulmonary edema due to ammonium chloride. The greatest clarification of the mechanism of ammonium salt lung edema was reported by Sarnoff and Kaufman (260). They showed

that very large changes in left atrial pressure are produced in the cat by ammonium chloride administered intraperitoneally and suggested that "left ventricular failure plays a role in the development of ammonium pulmonary edema in the cat".

The studies of Koenig and Koenig (167) indicate that ammonium salt intoxication lung edema still occurs when cerebral decortication has been done but not after mesencephalic decerebration. The significance of the latter observation is clouded by the fact that surgical decerebration of this type is an extremely traumatic procedure and it is questionable whether normal neurovascular responses could be expected after it.

It seems unnecessary to look further for additional direct determinants of lung edema in this case. The currently unsolved problems in connection with ammonium salt intoxication have to do with the mechanism by which hypertension, pulmonary congestion and left heart failure are produced. Jaques (149) has begun such studies by analyzing the histamine content of the lung tissues, using a bio-assay method. He finds, relating the histamine to body weight rather than lung weight because the latter may be made up so largely of edema fluid, that the lung tissues contain only a third to a fourth as much histamine per unit body weight after treatment with ammonium chloride by intraperitoneal injection as in the normal; however, he did not find the released histamine in the edema fluid in appreciable amounts but observed a sizeable increase in the circulating whole blood.

f. Lung irritant gases. The mechanism of action of the lung irritants is of importance to this review because of the light which the studies of these toxic agents may shed on the basic problems of the pathogenesis of lung edema. The literature of the subject will, however, be quoted only to the extent necessary to point out the salient features, because a thorough digest of the numerous publications would require hundreds of pages. The important questions that concern us are: 1) where do the lung irritants act, and 2) how do they act to produce edema?

Winternitz (309) studied the microscopically evident changes in the lung of the dog after phosgene poisoning. In the later stages of such poisoning with lethal doses there is massive pulmonary edema with hemorrhage in the alveoli and desquamation throughout much of the bronchial system. However, early in the process the evidence of cellular damage does not extend into the alveoli. His description of the situation seems worthy of direct quotation. He states (p. 45), "As early as 2 hours after exposure there is histological evidence of necrosis of the epithelium of the finer bronchi . . . the nuclei are either pyknotic or completely disintegrated. . . . Conclusive evidence on the question of the difference in the degree of injury suffered by the proximal and distal portions of the respiratory tract in phosgene gassing, has been adduced by the use of vital stains. It will be recalled that vital stains, when administered in sufficient quantity, stain the cytoplasmic granules of certain types of cells. The nucleus of the living cell is, however, never stained; whereas that of a dead cell is deeply colored. The reaction to the vital stain thus constitutes a test of cell death. . . . The

bronchial epithelium shows staining of its nuclei and protoplasm in places, and as the final bronchioles are approached, the coloration becomes more marked and the change more uniform. . . . The staining seems more marked where there is distortion of the bronchiole, either contraction or dilatation. The entire bronchiolar wall is involved, but the stain does not spread to neighboring alveolar walls, and the flat alveolar epithelium is unaffected."

Thus one is entitled to doubt that lethal cytotoxic quantities of the gas reach the alveoli. This is not surprising, because phosgene reacts readily with water on the surface mucosa of the bronchial tree and, considering the small bore of the terminal bronchioles, the probability that a toxic concentration of molecules would remain in the gas reaching alveoli is small. The great damage to cells lining the terminal bronchioles would give grounds for believing that the reactions to injury at that site are probably crucial to the end results.

The hemodynamics in pulmonary irritant poisoning have been studied by Patt *et al.* (230). They reported a consistent decline in right ventricular pressure associated with a rise in pulmonary circulation time, but without evidence of right ventricular failure of large degree as indicated by changes in systemic venous pressure. They did not report cardiac output measurements. Gibbon *et al.* (108) reported on measurements of left atrial pressure in cats with marsupialized heart preparations. They found that after exposure to potentially lethal doses of phosgene, the left atrial pressure tended to fall and later to return toward pregassing levels. They concluded that their "data excluded abnormal hemodynamics as a cause of the increased permeability of pulmonary capillaries in phosgene poisoning. Therefore, despite our inability to find histologic evidence of endothelial damage, we must postulate that such damage is present". It may be pointed out, however, that Gibbon *et al.* (108) did not make measurements of pulmonary venule resistance or pulmonary capillary pressure or volume. Without such measurements their conclusions are not established.

Phosgene poisoning, according to Cameron and Courtice (37), is associated with a significant increase in lung lymph flow and, according to Underhill (283) and others, with a high degree of hemoconcentration. The lung lymph volume during the period of induction of pulmonary edema in dogs by phosgene is a relatively small fraction, about 15%, of the volume of the edema fluid produced as measured by differences in the lung to heart weight ratios, in gassed as compared with normal dogs. With the occurrence of pulmonary edema, Cameron and Courtice found that the lymph protein level fell. They present the data from eight experiments in which lymph protein level declined from their normal of 4.0% to 3.3% after gassing, while the edema fluid collected from the same animals showed protein concentrations averaging 5.4%. This value was considerably higher than the protein concentration at death in the same animals which averaged 4.1%.

It is obviously impossible for filtration through a leaky membrane to be the only process concerned in producing a fluid with higher protein concentration than that in the original fluid which was the source of the filtrate. The fact that edema fluid protein levels may be higher than plasma protein levels re-

quires the occurrence of some additional process, possible mechanisms for which have been discussed earlier.

There is general agreement that in lung irritant edema there is pulmonary vascular congestion. In the absence of pulmonary artery or left atrial pressure rise, capillary congestion could, it seems, be brought about only by one or both of two mechanisms, namely a pulmonary venule constriction or a decline in the elasticity of the capillary wall. There are at present, so far as we have been able to find, no data to indicate which process occurs.

The final point in question is whether there is a specific change in capillary permeability, or whether the congestive distention itself accounts for the protein leakage that occurs. As noted elsewhere herein, there is no necessity to postulate the specific effect of a toxic agent on permeability.

2. Hypo- and hypervolemia. Moon and Morgan (214) described experiments in which shock induced by burns, intraperitoneal implantation of muscle pulp, intestinal obstruction and bile salt administration by vein result terminally in pulmonary edema. They also report numerous instances of pulmonary edema associated with traumatic shock in man. In this connection the studies of Eaton (86) are of interest. He found that there was a marked increase in pulmonary lymph flow after an acute hemorrhage associated with a temporary rise in the hematocrit. He found these changes to be associated with a decrease in cardiac output, and falls in systemic arterial, venous and pulmonary artery pressures. He interpreted the terminal pulmonary edema which he saw as being due to changes in capillary permeability, but since he made no measurements of pulmonary venous pressure or of pulmonary capillary blood content during life, it is impossible to evaluate his interpretation directly. The early effect of acute hemorrhage is a fall in left atrial pressure (Opdyke *et al.*, 219; Haddy, 120). But Page (220) reported late rises in central venous pressure in shock, indicating terminal heart failure. In our experience (unpublished experiments) hemorrhage in the barbitalized dog is not a reliable method of producing pulmonary edema.

Numerous investigators have found that rapid intravenous injection of fluids can induce pulmonary edema. Altschule and Gilligan (6) observed an increase in pulmonary blood volume after infusions. Opdyke *et al.* (219) found that the left atrial pressure was elevated more than the right by infusions of blood or saline. Doyle *et al.* (81) showed that the pulmonary artery wedge pressure increased with intravenous saline infusions in man. Haddy *et al.* (121) found the pulmonary venous pressure to be elevated after large saline infusions which resulted in lung edema. Gibbon and Gibbon (107) demonstrated that the amount of plasma infusion necessary to induce pulmonary edema in the dog was less after removing parts of the lungs, indicating that the extent of the lung bed is a critical factor in determining the pulmonary vascular pressure rise in hypervolemia. Courtice and Korner (61) showed that hypoxia is a determining factor in the production of pulmonary edema by hypervolemia. In rabbits breathing 11% O_2, which by itself has no edemagenic effect, the amount of infusion of Ringer-Locke solution necessary to produce pulmonary edema was reduced to

half that required when room air was respired. They suggested that the hypoxia caused a reduction of cardiac output with a compensatory systemic vasoconstriction, which operated to shift a larger fraction of the blood volume into the pulmonary vascular bed, thus raising the pressures within it. Korner (170) found that simultaneous administration of amounts of noradrenaline which were themselves not edemagenic, also decreased the dose level of infusions necessary to cause pulmonary edema. The noradrenaline caused a shift of blood volume toward the pulmonary vascular bed. Since there is no evidence of primary heart failure in this situation, there is justification for ascribing the pathology to pulmonary congestion, but it must be pointed out that the congestion occurs because the left ventricle does not pump forward sufficient blood per beat to keep the left atrial pressure down to normal levels. In a sense, therefore, the heart has failed to meet the increased work load imposed upon it. Daniel and Cate (71) demonstrated no appreciable effect of removal of the stellate, second, third and fourth thoracic sympathetic ganglia and associated chain either on one or both sides, on the development of pulmonary edema induced by massive infusions of isotonic saline in the dog, indicating that pulmonary and cardiac sympathetic innervation are not crucial to the end result.

3. Intracranial pressure and brain lesions. Much of the interest in an experimental analysis of the mechanism of action of nervous factors in the production of lung edema, arises from the fact that the latter condition has been reported to occur in such a large variety of disorders involving the nervous system. For example, Weisman (296) reported that in two-thirds of 686 cases of intracranial hemorrhage, edema and congestion of the lungs was an important autopsy finding. Other neural disease states reported to be frequently or occasionally associated with pulmonary edema are brain tumor, head trauma, vertebral injuries, insulin hypoglycemic coma, cerebral embolism and thrombosis, encephalitis, vagus nerve disease, polyneuritis, tabes dorsalis, effects of lumbar punctures or of cervical sympathectomy, epileptic seizure, emotional disorders and hysteria. The large variety of the above-mentioned conditions speaks immediately for the intervention of mediating mechanisms, rather than direct effects of any of the particular disturbances in the induction of pulmonary edema. It seems most unlikely that such heterogeneous factors could each be acting in any direct way. Thus it becomes important to determine what intermediate factors are set in motion and ultimately affect the immediate determinants of "neurogenic" lung edema (141). Paine *et al.* (225) found upon study of autopsy material that, in more than three-fourths of the patients with neural disease exhibiting pulmonary edema at necropsy, there was concomitant evidence of heart disease and/or hypertension. They point out that a previously damaged or overloaded heart is more susceptible to the development of frank failure with small increments in loading, and interpret their data as supporting evidence for an essentially cardiac origin of clinical "neurogenic" lung edema.

Sarnoff and several collaborators (253–256, 258) have begun a systematic study of the "neurohemodynamics" of pulmonary edema in which they are measuring the pulmonary venous pressure in situations where so-called neuro-

genic factors are involved in the production of pulmonary edema. Similar studies had been conducted by Campbell *et al.* (42) who found that increased pulmonary venous pressure occurred in barbitalized dogs subjected to increased cerebrospinal fluid pressures. This effect of cerebrospinal fluid pressure elevation was associated with a bradycardia which was capable of prevention by atropine. The latter drug also protected against lung edema in this situation. Campbell and Visscher (44) found that bilateral cervical vagotomy protected guinea-pigs against the pulmonary edema otherwise induced by increased intracranial pressure. Bradycardia from vagal stimulation in the barbitalized dog is associated with an elevation of pulmonary venous pressure, according to Campbell *et al.* (43).

Sarnoff (253) has shown that the intracisternal injection of thrombin and fibrinogen which induces pulmonary edema is associated with an elevation of both pulmonary and systemic arterial and venous pressures in the dog. The elevations reported for the pulmonary vein or left atrium are as high as 60 mm Hg. Bilateral cervical vagotomy did not protect against the elevation of pulmonary venous pressure in this situation. However, extensive elimination of sympathetic innervation, either by surgery or by chemical means, had a profound effect in relieving the elevated pulmonary venous pressure. According to Sarnoff, "The use of the term neurogenic pulmonary edema has . . . ceased to be a useful means of explicit communication." He makes the suggestion that it be discarded in favor of the more meaningful term "neurohemodynamic pulmonary edema", which he defines as "a state wherein an increase in the rate of transfer of fluid from pulmonary capillary to the extravascular space of the lung is brought about by an increase in pulmonary capillary pressure, which in turn is brought about either directly or indirectly by nerve impulses". In the case of the intracisternal injection of fibrin, he suggests that the shift of blood from periphery to lung need not be due entirely to left ventricular failure, but may be dependent also "in part upon the fact that a vascular bed of high constrictor potential (systemic) can shift blood into an area of low constrictor potential (pulmonary) and thereby elevate the pressure in the latter". The importance of this changed emphasis in thought concerning the role of the nervous system in the genesis of pulmonary edema is that it allows relation of the phenomenon to measurable quantities and definable mechanisms. It is obviously essential that this be done in all situations where nervous factors play a part in producing the shift of water.

4. Vagotomy. The history of experimentation into pulmonary edema induced by vagotomy extends back many years. Vieussens, in 1716, (285) is credited with first noting the lung changes after vagotomy. Valsalva, in 1740, (284) noted hemorrhage as a concomitant process with edema. Haller, in 1757, (128) ascribed the lung lesions to aspiration of food and chyme. Legallois, in 1812, (190) was apparently the first to suggest laryngeal denervation as a causative factor in the lung edema following bilateral cervical vagotomy. Traube (cited by Frey in 1877 (102)) showed that tracheotomy protected rabbits against cervical vagotomy lung edema, but that esophageal ligation did likewise, and

that intratracheal instillation of esophageal secretions resulted in pulmonic edema. Thus he concluded that vocal cord paralysis with inspiratory leakage was the mechanism of the lung lesion. Schiff, in 1894, (262) introduced the suggestion that pulmonary vasomotor paralysis was the cause of the lung lesions because he found them to occur, in contradiction of Traube, even after esophageal ligation, and after tracheotomy. Claude Bernard, in 1858, (19) also interested himself in this problem and ascribed the lesions to altered respiratory dynamics. Thus nearly a century ago the outlines of the controversies over neurogenic and hemodynamic mechanisms were already drawn.

In 1937 Farber (93, 94) renewed interest in this problem with a series of papers reporting observations which he interpreted as favoring the conclusion that parasympathetic (vagal) denervation of pulmonary capillaries resulted in an increase in their permeability. His experimental methods have been critically analyzed by various students of the problem.

Among the more careful studies on the respiratory obstruction factor were those of Lorber (193, 194), who showed that in the rabbit and the guinea-pig unilateral cervical and contralateral intrathoracic vagotomy (the latter sparing the recurrent laryngeal branch) permitted indefinite survival, unless significant airway obstruction still occurred due to the unilateral laryngeal paralysis. He also found that with meticulous attention to removal of mucus secretions from the tracheobronchial tree after bilateral cervical vagotomy and tracheotomy, outspoken lung edema did not occur. However, after bilateral section of the recurrent laryngeal nerves alone, frank pulmonary edema did not occur. Therefore, factors other than simple laryngeal obstruction are involved in vagotomy lung edema. These factors may be 1) the altered pattern of breathing due to interference with the afferent arms of the Hering-Breuer reflex, or 2) changes in the control of the heart due to its parasympathetic denervation. The slowing and increase in amplitude of breathing are probably most important because, superimposed upon laryngeal obstruction, they would affect intrathoracic pressures and the venous return to the heart.

Reichsman (239) measured the duration of the inspiratory and expiratory phases before and after vagotomy in rats and found that, whereas normally a single inspiration lasted 0.2 sec, this value doubled after bilateral vagotomy. Since the expiration period did not change appreciably, it is obvious that the fraction of the total time of lowered intrathoracic pressure will be elevated by vagotomy, thus in itself inducing hemodynamic changes.

Some special points in connection with the consequences of vagotomy may be of importance. Farber (95) studied the changes in the blood volume following cervical vagotomy in rabbits. He noted decreases in the order of magnitude of 20% in total blood volume, with extremely variable changes in hematocrit. These changes indicate general shifts in body water from the vascular bed to the tissues. The magnitude of the change precludes the possibility that storage in the lung was the only pathologic process occurring. He also noted that during rapid intravenous infusion of salt solution in rabbits, the respiration increased in animals with intact vagus nerves, but not in those after vagotomy.

At the present time it is apparent that the major factor in vagotomy lung edema is airway obstruction, leading to consequences which can be in large part reproduced by artificially creating inspiratory airway resistance (see later section). Other effects of vagotomy on hemodynamics may play subsidiary roles.

5. Left ventricular failure. The data in Tables I and II have indicated the frequency with which pulmonary edema in man is associated with obvious left ventricular overload or failure. Numerous studies, some of which are referred to in Table III, approached the problem experimentally and the results may be summarized as indicating that whenever left ventricular failure occurs in a circulatory system in which left atrial and pulmonary vein pressures rise with such failure, pulmonary edema is promoted.

In experimental animals and in man, mitral stenosis is associated with chronic elevation in pulmonary venous pressures and provides a crucial test of the capacity of the capillaries and lymphatic system to adapt to a changed pressure situation.

Haddy *et al.* (122) found in dogs with induced mitral stenosis that if the integrated mean pulmonary vein pressure was below 15 mm Hg, the lung to heart weight ratio at autopsy was normal (1.3), whereas in seventeen animals with pulmonary vein pressures above 15 mm Hg, the lung-heart ratio was 2.4, a highly significant difference indicating large water storage in the lung. Although they occasionally found animals with induced mitral stenosis which showed pulmonary vein pressures above 25 mm Hg, rarely did such an animal survive more than a few days.

Faquet *et al.* (91, 92) entered the left atrium in patients by needle puncture through a bronchoscope and measured pressures. Their reports indicate pressures as high as 40 mm Hg maximum pressure in mitral disease without pulmonary edema. However, they did not provide data for calculation of the time-integrated mean pressures, which would be the significant values, nor is there evidence that such pressures existed for more than a few minutes.

Connolly *et al.* (56) measured pulmonary artery wedge pressures in patients with open chests at surgery, and found some instances in mitral valve disease of pressures above 30 mm Hg both in the wedge and the left atrium. They did not indicate the presence or absence of lung edema.

In connection with other studies of pulmonary artery wedge pressures, Dexter *et al.* (78) stated, "It is our belief that the absence of gross pulmonary edema in these patients with 'capillary' pressures well in excess of 25 mm Hg at rest cannot easily be explained by an increase in tissue pressure in the lung but by the hypothesis that part of the observed elevation of 'capillary' pressure was transient and incidental to the stress of the catheterization procedure".

Gorlin *et al.* (111) found that all mitral stenosis patients with pulmonary artery wedge pressures above 35 mm Hg at rest exhibited frank pulmonary edema and that no patient "ever developed pulmonary edema in this laboratory without a marked elevation of pulmonary 'capillary' pressure at the time".

Coronary artery occlusion has been studied experimentally in relation to lung edema. The studies of Roos and Smith (246), employing the injection of starch

suspension to induce partial coronary artery occlusion, have shown that pulmonary edema is produced quite regularly if sufficient amounts of the occluding material are introduced gradually. They describe significant elevations in right atrial pressure while the systemic arterial pressure is maintained at normal or hypertensive levels, but no measurements were made of left atrial or pulmonary vein pressure. If it is assumed that the starch embolism affected right and left ventricles symmetrically, one might predict that measurements would show an elevation in pulmonary venous pressure.

Smith and Jensen (269), using the heart-lung preparation in which failure had been induced by administration of chloral hydrate, found that after treatment by theophylline aminoisobutanol associated with the fall in left atrial pressure from 11.0 to 6.6 cm of water and a decrease in ventricular dilatation, there was a "rapid clearing of pulmonary edema". They also reported that the same drug increased the blood flow through the pulmonary bed under a constant head of pressure. There was no change in coronary flow in the case of the representative experiment which they describe. They maintain that the improved myocardial function produced by theophylline aminoisobutanol is due to its action on the heart muscle. The increase in pulmonary blood flow under constant perfusion pressure, however, indicates, perhaps, that effects upon the pulmonary blood vessels may be of importance. The fact that xanthines dilate small veins has been reported by Sollman and Pilcher (270) and Bock (24).

Paine *et al.* (221) performed experiments on six heart-lung preparations in which they studied the effect of increasing the aortic pressure from 100 to 180 mm Hg by increasing the outflow resistance. In two experiments they produced left ventricular dilatation by sharp elevations of venous inflow. In both types of situation pulmonary venous pressure rose and lung congestion occurred with crepitant râles noted by direct auscultation. The fluid volume in the venous reservoir diminished rapidly and right thoracic duct lymph flow increased "beginning three to twelve minutes after the onset of congestion". Paine *et al.* (222) studied the effect of restriction of left ventricular output in heart-lung preparations in the dog upon the development of lung edema and the flow of lung lymph. They noted that lung lymph flow was regularly increased when the heart-lung preparation had been completed, as compared with the flow in the same lung after all preliminary steps prior to the isolation of the heart and lungs and the establishment of the external circulation had been made. They ascribed this increase to elevations in left atrial pressure due to the small arterial cannula used in the brachiocephalic artery. They noted that in the open-chest preparation in the otherwise intact dog, lymph pressure in the right thoracic duct varied from 1.5 to 34 cm of water, and found that the value of this pressure was correlated to some extent at least with the observed jugular venous pressure: the higher the values found for the latter the higher the lymph vessel pressure. They call attention to the fact that elevations in systemic venous pressure can therefore be of some significance in determining the rate of outflow of lung lymph. However, they were unable to induce pulmonary edema by blocking the lymph flow through the large terminal lymph vessel.

6. Bradycardia. It has already been noted that in several instances, as with increased intracranial pressure, a causative relation appears to exist between lowering of the heart rate and pulmonary edema. It is of some interest that extreme bradycardia without other obvious disturbances can be followed by lung edema. Starzl and Gaertner (272) showed that in dogs with surgically-induced heart block, without apparent damage to the ventricular musculature, there was in most instances severe pulmonary edema. Delius (77) reported that pulmonary edema occurred in man during sudden episodes of heart block. Jores (155) reported the occurrence of lung edema following stimulation of the peripheral end of the cut vagus nerve in the dog. Cooke (57) reported an instance of fatal acute pulmonary edema in man following the administration of 1 mg eserine. Adelson and Brunn (1) reported two cases of pulmonary edema following prostigmine therapy in patients with multiple sclerosis. Driessens and Clay (82) induced pulmonary edema in guinea-pigs with intravenous injections of acetylcholine, and Altschul and Laskin (4) reported frequent occurrence of similar findings with either acetylcholine or neostigmine. However, Bariety and Kohler (16) reported that very large doses of eserine (0.2 mg/kg) protected rabbits against the acute pulmonary edema ordinarily induced by 0.2 mg/kg of adrenaline hydrochloride. Such doses of eserine produce a wide variety of direct and indirect effects. They also reported that smaller doses of eserine (0.05 mg/kg) exerted an aggravating effect which is the expected result of bradycardia. Miller and Matthews (211) found that atropine exerted protection against the pulmonary edema produced in the dog by administration of muscarine. The various agents mentioned above influence parameters in addition to the heart rate, such as the bore of the bronchial tree, which could in turn influence the development of lung edema. But it is, we believe, important to recognize the general association of extreme bradycardia with pulmonary edema.

7. Resistance breathing. Interest in the mechanisms of the pulmonary edema after vagotomy and in such diseases as bulbar poliomyelitis in which there is airway obstruction, has stimulated study of the effects of inspiratory and expiratory airway resistance. Reichsman (239) showed that inspiratory airway resistance in dogs and rats was followed by massive pulmonary edema. Zinberg *et al.* (316) confirmed this observation in dogs and found further that expiratory resistance over long periods of time had the same end result on the lungs. Haddy *et al.* (121) clarified the mechanism considerably by utilizing the flexible catheterization technique for measuring pulmonary vein and artery pressures in the dog with a closed chest, submitted to inspiratory or expiratory resistances to breathing. They found that inspiratory airway resistance (breathing against 15–20 cm H_2O) in pentobarbital anesthetized dogs did not result in significant lung edema if the pulmonary venous pressure (integrated mean against intrathoracic as zero) did not rise above 13 mm Hg. The average maximum pulmonary venous pressure for the group failing to show lung edema was 6.5 mm Hg. On the other hand, in the cases in which massive lung edema occurred there was no instance of a pulmonary vein pressure less than 15.5 mm Hg and the average was above 20 mm Hg. There was a trend toward higher systemic

arterial pressures in the animals developing lung edema than in those not doing so. The same authors estimated cardiac output by the oxygen direct Fick method and found that terminally the values were generally low. They interpreted the elevated pulmonary venous pressures with low output to be evidences of progressing left ventricular failure. With expiratory airway resistance these authors found a comparable correlation between pulmonary venous pressure level and the occurrence of severe lung edema.

VI. MECHANISMS OF THERAPY OF PULMONARY EDEMA

The treatment of pulmonary edema is directed at two objectives: first, the amelioration of the alveolar ventilation defect; and second, the correction of the water storage defect. The defect in alveolar ventilation is diminished by 1) administration of oxygen at higher than atmospheric partial pressure (34); or by the use of helium-oxygen mixtures (12, 13) which decreases the energy cost of ventilation; 2) use of surface tension lowering (anti-foam) agents to remove blockage to airflow by bubbles in the airways (110, 198); 3) therapeutic posture, head down prone position to facilitate drainage (286) as a temporary expedient; and 4) tracheotomy and/or bronchial suction to remove mucous secretions and frothy fluids which are impediments to ventilation (76, 294).

The basic defect in water storage in the lung can only be corrected by removing its cause. In the presence of left ventricular failure two lines of approach to therapy are available. They are 1) to decrease the work load on the left ventricle, or 2) to increase the work output of the heart. The work load can be lowered either by decreasing the cardiac filling (and thus the output of blood) or by diminishing the resistance to ejection (lowering the arterial blood pressure by vasodilation). The work output can be increased either by increasing the efficiency or by increasing energy output at constant efficiency.

The classical treatment by venesection operates through lowering cardiac filling. Furthermore, numerous modern variants act through the same mechanism. Positive pressure breathing, as noted above, lowers cardiac filling. Venous occlusion cuffs on the extremities (133) do the same. Sympatholytic agents (300) decrease left ventricular work by lowering peripheral resistance. Spinal anesthesia (259) decreases both cardiac output and peripheral resistance. Diuretic agents have been employed as auxilliaries in the treatment of lung edema. They may act by decreasing the circulating blood volume.

The various cardiac glycosides are frequently employed successfully in lung edema associated with heart failure (5), and act by improving the efficiency of heart muscle (232). When bradycardia of vagal origin is associated with lung edema, as with increased intracranial pressure, atropine is a useful protective agent (42).

The mechanism of action of the most generally used agents, that is morphine and other opium alkaloids, is still obscure. Luisada (196) showed that large doses (14 mg/kg body weight) produced a marked fall in left atrial pressure in the cat under ether anesthesia. No studies have been found in which dosages closer to therapeutic levels have been employed. Further work on the morphine

effect in lung edema is obviously needed. It is possible that the effect in man is mediated by the lessening of apprehension, the depression of respiration and the lowering of cardiac work resulting.

Any agents which operate to improve the work capacity of the heart will be useful in lung edema due to left ventricular overloading. It is likely, but not proven, that the xanthines act in part by this mechanism and only in part by their diuretic action. Starr *et al.* (271), Howarth *et al.* (147) and Escher *et al.* (88) report increased cardiac outputs in man after xanthine medication.

In pulmonary edema due to toxic agents, where specific changes appear to occur in the lung capillaries, a great variety of therapeutic and preventive agents have been studied. Rothlin (248) reported successful treatment of mild phosgene poisoning by parenteral calcium salt administration and protection by ergot alkaloids and pitressin. Trethewie (280) reported on the treatment of phosgene poisoning with thymoxyethyldiethylamine. Halpern and Cruchaud (129) found another antihistaminic, N-dimethylamino-2-propyl-1-thiodephomylamine, to protect against chloropicrin. It is altogether possible that antihistaminics may act, not only upon the pulmonary vasculature, but also by preventing the damage to the heart which histamine causes (249).

VII. CONCLUDING REMARKS

We conclude this review with some references to the nature of the unsolved problems rather than with a conventional summary of data, since the entire paper is a summary. We believe that most of the superficial confusion which has existed concerning the pathogenesis of lung edema has arisen from a failure to distinguish between direct and indirect causes of the phenomenon, and the failure to recognize explicitly that water movement is a physico-chemical process which must be accounted for in precise physico-chemical terms if it is to be accounted for at all. It is, of course, easy to make such generalizations as these. It is much harder to measure permeability, or pulmonary capillary pressure, or to trace the nervous paths of circulatory reflexes. Nevertheless, these are the problems which await more adequate solution.

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