CLINICAL PROGRESS

Acute Pulmonary Edema
Pathology, Physiology and Clinical Management

By A. A. Luisada, M.D. and L. Cardi, M.D.

Acute pulmonary edema may be associated with the most varied clinical conditions including cardiovascular, renal, cerebral, and pulmonary diseases, trauma to the skull or chest, infections, and shock. Many drugs and physical means have been employed in the treatment of this syndrome. Two main clinical types of pulmonary edema may be differentiated because of the different effect of therapy in each of them. Antifoaming therapy, a purely symptomatic method of treatment, tends to break a vicious circle and may be lifesaving. It should be employed initially while the patient is being examined and drugs or other remedies are being selected for possible additional treatment.

No better definition of edema of the lungs can be given than that of Laennec (1834): “Edema of the lung is the infiltration of serum into the substance of this organ, in such degree as evidently to diminish its permeability to the air, in respiration.” While edema of the lungs is initially similar to edema of other organs, the structures surrounding the capillaries are so thin that an immediate outpouring of fluid into the alveolar cavities* occurs. In this respect, pulmonary “edema” is followed by pulmonary “exudation.”

The term “pulmonary edema” carries with it different associations to different specialists: to the pediatrician, acute glomerulonephritis or rheumatic carditis; to the surgeon, thoracic or abdominal intervention; to the neurologist, cerebrovascular accident or trauma to the skull; to the cardiologist, hypertension, coronary occlusion or mitral stenosis.

Etiology

Contrary to a widely accepted view, acute pulmonary edema can be encountered in a great variety of conditions, as shown by necropsy findings (table 1). The frequency of pulmonary edema in the various diseases is indicated in table 2. A more detailed study of the various conditions which may be associated with acute pulmonary edema is presented in table 3.

A large number of clinical cases succumb without pulmonary edema; this disorder, therefore, is not a “terminal” or “agonal” phenomenon to be considered as the necessary precursor of death.

A brief review of the most common causes of pulmonary edema in clinical cases follows.

(1) Pulmonary Edema and Arterial Hypertension. This type of pulmonary edema was in the past most common but is now seen less frequently, partly on account of more effective treatment of various clinical conditions, and partly because other types tend to predominate. Chronic nephritis with uremia is frequently accompanied by episodes of edema of the lungs. In certain cases, moderate nitrogen retention may be the only evidence of renal insufficiency and there may be little or no acidosis. All other forms of hypertension, including essential hypertension and that of coarctation of the aorta, may present pulmonary edema. Cases with malignant hypertension have these paroxysmal attacks more commonly than others.

(2) Pulmonary Edema and Coronary Heart Disease. The observation that severe coronary occlusion is frequently accompanied by pulmonary edema has led to the belief that minor coronary episodes may also contribute to these
attacks. However, no certain proof has been presented, and the mechanism of production of the edema might be somewhat different from that in hypertensive patients. Cardiogenic shock is more frequently associated with pulmonary edema than other types of shock. Protracted forms are common in coronary heart patients.

(3) Pulmonary Edema and Cerebral Diseases. The occurrence of pulmonary edema in cases of meningitis, encephalitis, or brain tumor is relatively common, in children as well as adults. Cerebrovascular attacks, including hemorrhage, embolism, or thrombosis, and subarachnoid hemorrhage, as well as trauma to the skull, are frequently followed by pulmonary edema. Undoubtedly, coronary lesions and pre-existing hypertension may be contributing factors in certain cases. However, in others, no evidence of such lesion or disorder can be demonstrated clinically following recovery, or at autopsy.

(4) Pulmonary Edema and Pulmonary Heart Disease. Contrary to current opinion, this association is far from rare. Pulmonary edema may follow pulmonary embolism. Occlusion of a stem of the pulmonary artery causes increased flow in the other, and this may favor high capillary pressure in one lung. Even occlusion of smaller branches may cause diffuse, bilateral edema, a fact which has led to numerous speculations. In chronic cor pulmonale with right ventricular hypertrophy and pulmonary hypertension, acute pulmonary edema may develop. This is particularly true in the forms causing no destruction of capillaries and no pulmonary ischemia.

It is likely that vascular obstruction or destruction of a number of vascular districts (fibrosis, emphysema) favors pulmonary edema of other areas and districts. It is known that one-half of the pulmonary vessels can carry the entire flow of the lesser circulation without any increase in pressure. However, this is obtained through distention of the normal vessels which, in itself, predisposes to edema. Whenever an increase of venous return takes place in such patients, the already distended (normal) vascular districts are taxed beyond physiologic limits and transudation is likely to occur. In addition, sudden pulmonary edema was observed in cases with deformity of the chest (pulmonary cardiac failure of Chapman, Dill and Graybiel). It is self-understood that, whenever other causes of pulmonary edema are present, this condition may develop in cases of chronic cor pulmonale like in others. This particularly applies to systemic hypertension and coronary heart disease. Anoxia would favor the edema; narrowing of arterioles would decrease its severity, at least in the involved districts.

(5) Pulmonary Edema in Trauma to the Chest. This syndrome, called by surgeons "traumatic wet lung," has been the object of considerable speculation and is of particular interest because of its spreading from the damaged to the intact areas of the lungs.

TABLE 1.—Main Necropsy Findings in 100 Unselected Cases of Pulmonary Edema (from Cameron)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe coronary disease</td>
<td>34</td>
</tr>
<tr>
<td>Congestive failure</td>
<td>32</td>
</tr>
<tr>
<td>Carcinoma of various organs (carcinoma of lungs = 15 cases; obstruction of pulmonic veins = 11 cases)</td>
<td>27</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>18</td>
</tr>
<tr>
<td>Massive pulmonary embolism</td>
<td>10</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>9</td>
</tr>
<tr>
<td>Cerebral tumor</td>
<td>7</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>6</td>
</tr>
<tr>
<td>Fractured skull</td>
<td>3</td>
</tr>
<tr>
<td>Multiple fractures (excluding skull)</td>
<td>2</td>
</tr>
</tbody>
</table>

TABLE 2.—Frequency of Pulmonary Edema in 500 Autopsies of Special Conditions (from Cameron)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Total No. of Cases</th>
<th>No. Showing Pulmonary Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive heart disease (excluding chronic nephritis)</td>
<td>94</td>
<td>81 (86%)</td>
</tr>
<tr>
<td>Chronic nephritis</td>
<td>50</td>
<td>37 (74%)</td>
</tr>
<tr>
<td>Coronary occlusion</td>
<td>66</td>
<td>45 (68%)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>66</td>
<td>44 (67%)</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>84</td>
<td>55 (65%)</td>
</tr>
<tr>
<td>Fractured skull</td>
<td>38</td>
<td>24 (63%)</td>
</tr>
<tr>
<td>Multiple fractures (excluding skull)</td>
<td>28</td>
<td>17 (61%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>74</td>
<td>23 (31%)</td>
</tr>
</tbody>
</table>
### Table 3.—Clinical Conditions Associated with Acute Pulmonary Edema

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Cardiovascular disease</td>
<td>1—Syphilitic heart disease (aortic insufficiency; aortitis; aortic aneurysm) 2—Rheumatic heart disease (acute rheumatic carditis; mitral insufficiency; mitral stenosis; aortic insufficiency; aortic stenosis) 3—Coronary heart disease (severe, acute coronary occlusion; minor occlusion plus extensive ischemia or fibrosis of the myocardium) 4—Hypertensive heart disease (pheochromocytoma, essential hypertension; acute glomerulonephritis; hypertensive nephropathies, especially if there is uremia; toxemia of pregnancy) 5—Congenital heart disease (coarctation of the aorta; atrial or ventricular septal defect, patent ductus; Eisenmenger complex; Lutembacher syndrome) 6—Acute or chronic pulmonary heart disease (pulmonary embolism; chronic cor pulmonale) 7—Shock (including that caused by exposure to x-ray radiation) 8—Congestive failure</td>
</tr>
<tr>
<td>(B) Diseases or lesions of the central nervous system</td>
<td>1—Trauma to the skull 2—Subarachnoid hemorrhage 3—Cerebrovascular attack (hemorrhage, thrombosis, embolism, abscess or tumor) 4—Encephalitis, meningitis, poliomyelitis, tetanus</td>
</tr>
<tr>
<td>(C) Diseases or lesions of the respiratory system</td>
<td>1—Pneumonia, bronchopneumonia (especially influenzal) 2—Drowning, strangulation, asphyxia, respiratory obstruction (edema of the glottis, bronchial asthma, foreign bodies) 3—Inhalation of irritant or toxic gases (including those used in warfare); respiratory burns 4—Following rapid thoracentesis 5—Following trauma to the chest 6—Following lobectomy</td>
</tr>
<tr>
<td>(D) Allergy</td>
<td>Angioneurotic edema; serum sickness; following injection of gold preparations; following inhalation of penicillin aerosol.</td>
</tr>
<tr>
<td>(E) Following stimulation of hollow viscera</td>
<td>1—Distention of esophagus, stomach, or gall bladder. 2—Following too rapid emptying of distended bladder or ascites.</td>
</tr>
<tr>
<td>(F) Surgical and obstetrical cases</td>
<td>1—During pregnancy or after labor (especially, but not only, in cases with rheumatic heart disease, eclampsia, or toxemia) 2—Following transfusions or infusions (especially, but not only, in cardiac or anemic patients) 3—Following surgical manipulation of stellate ganglia</td>
</tr>
<tr>
<td>(G) Toxic</td>
<td>Following use or overdose of thiourea derivatives, iodes, muscarine, eserine, prostigmine, opium, methyl salicylate, acetic and butyric ether, phenylcarbamide.</td>
</tr>
</tbody>
</table>

(6) **Pulmonary Edema in Mitral Stenosis.**  
The occurrence of pulmonary edema in cases with a persistent block proximal to the left ventricle contradicted the established theory which attributed these episodes to acute left ventricular failure. It is only in recent years that an adequate dynamic explanation has been found. Patients with mitral stenosis occasionally cough up large amounts of pure blood. This syndrome, called "pulmonary apoplexy," is closely related to pulmonary edema and has a similar, though not identical, mechanism.

(7) **Pulmonary Edema and Infections.** It has been clearly established that pulmonary edema and pneumonia may be closely interrelated. Pneumonia may predispose to pulmonary edema and vice versa; furthermore, they may simulate each other. Many other febrile diseases may be complicated by pulmonary edema, partly through inflammatory lesion of the heart, lungs, or brain, and partly through overload of the circulation caused by therapeutic intravenous infusions. Unexplained edema of the lungs may also develop during the chill phase of a febrile reaction.10

(8) **Pulmonary Edema and Shock.** Shock is frequently associated with pulmonary edema. It is not known whether shock itself causes pulmonary edema or whether both shock and pulmonary edema result from a common cause.
Since cardiogenic shock is frequently associated with pulmonary edema and the latter disappears when shock is alleviated, the vascular mechanism of shock is probably of fundamental importance.

The Clinical Episode

An attack of pulmonary edema may occur at any time of day or night. Precordial oppression or pain, restlessness, weakness, and dry, non-productive cough may precede the attack. If this occurs at night, a nightmare frequently precedes the paroxysm. Respiration becomes difficult and labored and is usually accelerated. The patient sits up in bed and may lean forward. Within a few minutes, gurgling sounds can be heard, and the patient repeatedly emits a white, yellowish or pink frothy sputum. This may vary from a few bubbles to enormous amounts (as much as 2000 to 3000 cc. of foam within one to two hours). Cold, clammy extremities, paroxysms of suffocation and vomiting may occur. The pulse and blood pressure differ in the two main types of attacks as follows:

1. In most cases connected with coronary occlusion, pulmonary embolism or allergic shock, the pulse is rapid and small (and may be irregular), and the blood pressure drops gradually, sometimes reaching shock level. Some cases of rheumatic mitral lesion also exhibit a drop in blood pressure.

2. Other cases, particularly those with hypertensive or syphilitic heart disease or those with a cardiovascular accident, present a full pulse and a blood pressure either equal to or higher than the previous level.

Physical examination reveals a high, tympanic percussion note over the lung fields and innumerable moist rales over the entire chest, which arise in the small bronchi, and gurgling sounds created by the foam in the trachea.

X-ray of the chest reveals extensive shadows in both lung fields (fig. 1).

The temperature is usually normal during the attack except with inflammatory edema, but may rise soon afterwards because of re-absorption of altered proteins from the lungs.

The sputum has a chemical composition similar to the fluid of angioneurotic edema or allergic coryza, and to the inflammatory effusions of large serosal cavities. This is true, not only of clinical episodes, but also of experimentally induced attacks.

Catheterization of the right heart has revealed that pulmonary arterial pressure is severely increased and that pulmonary “capillary” pressure rises to 32 to 54 mm. Hg during the attack.

Experimental Pulmonary Edema

Experimental pulmonary edema has been obtained by using a great variety of methods.

1. Acute left ventricular strain has been obtained by ligation of the aortic arch in the rabbit, but this procedure is far from being constantly successful, especially if the chest is open, and cannot be duplicated in the dog. Acute right ventricular strain has been provoked by inducing pulmonary embolism.

2. Acute ventricular damage was obtained by reducing the left ventricular chamber and by necrosis of either the left or the right ventricular walls.

3. Acute obstruction of the pulmonary veins was tried in animals, but was not particularly successful.

4. A complex mechanism involving the cardiovascular and nervous systems leads to pulmonary edema following the intravenous injection of epinephrine or l-norepinephrine. This procedure is consistently successful.
in the rabbit, guinea pig and rat, but not in the dog or cat. A similar mechanism seems to occur in hypoglycemia.3

(5) Trauma to the chest18 and limited pulmonary embolism72 are of particular interest because they cause bilateral pulmonary edema in the dog.

(6) Enormous doses of intravenous infusions19-22 or rapid intracarotid infusion of somewhat smaller doses of saline or plasma are successful in producing pulmonary edema in the rabbit,23 cat3 or dog.3, 22

(7) Direct irritation of the bronchial tree is obtained by inhalation of toxic gases,24-24 or intrabronchial injection of hypertonic solutions.3

(8) Toxic pulmonary edema follows the injection of methyl salicylate,47 muscarine28, 29 or alloxan,56 or the ingestion of thiourea derivatives30, 31 or ammonium chloride.32-34

(9) Cerebral damage or dysfunction has been obtained through occlusion of the carotid arteries in the rabbit,45, 46 trauma to the brain in the dog,27, 38, 39 destruction of the hypothalamus in the rat40, 41 or the intracisternal injection of veratrin42 or fibrinogen plus thrombin43, 44 in the rat, rabbit or dog.

(10) A combination of stress applied to the left ventricle (aortic insufficiency) plus intravenous epinephrine or central nervous system stimulation was successfully employed in the dog.45 A similar result was obtained by aortic insufficiency plus unilateral nephrectomy and contralateral narrowing of the renal artery.71

**Pathogenesis**

The mechanism of production of pulmonary edema has been explained in different ways. Most writers have attempted to evolve one theory which might apply to all causes of pulmonary edema. It is the feeling of the authors that this is not feasible and that different mechanisms should be advocated.

The oldest theory, advanced by Cohnheim19 and Welch7 in 1878, postulates acute left ventricular failure causing a rise of pulmonary venous pressure and then pulmonary edema (fig. 2A). This theory met with wide acceptance and is even now currently invoked. Several objections can be raised:

(1) Many clinical cases of pulmonary edema have a normal left ventricle and the initial sequence of events involves either the central nervous system or the lungs. Some cases have severe mitral stenosis or cor pulmonale and the right ventricle is the cardiac chamber under strain.

(2) Many clinical cases with acute left ventricular failure die in shock (cardiogenic shock) without pulmonary edema. This is probably due to the fact that pulmonary capillary pressure rises only if there is good venous

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**Fig. 2.** Scheme of mechanism of pulmonary edema according to three theories. (A) Left ventricular failure (passive congestion). (B) Pulmonary vasodilatation (active congestion). (C) Peripheral constriction with pulmonary congestion. [Pr. = periphery.]
return to the right heart with a strongly active right ventricle.

A second theory was advocated by Teissier in 1900. Disregarding cardiac elements, he considered pulmonary edema as due to an active, sudden dilatation of the pulmonary vessels (fig. 2B). Even though this theory could not be accepted, the importance of reflex changes of the pulmonary vessels has been emphasized by one of the authors (A.A.L.) and his co-workers, as well as by Cameron and Kuo. The following experimental data seem to confirm the importance of these reflexes in the production of pulmonary edema, even though they may also be interpreted according to other theories.

(1) Bilateral stellectomy is effective in preventing pulmonary edema caused by intravenous epinephrine in the rabbit.

(2) Rapid infusions produce different results depending upon whether they are given intravenously or injected into the carotid arteries. Denervation of the carotid sinus area prevents this type of pulmonary edema.

(3) Anesthetics, sedatives and sympatholytic agents are more effective in preventing most types of pulmonary edema than vasodilators.

Another theory was advocated by Peserico in 1930 and revived by Sarnoff in 1952. This “neurohemodynamic pulmonary edema” emphasizes the massive displacement of blood from the greater to the lesser circulation caused by strong sympathetic stimulation (fig. 2C).

Three elements should be considered of importance in the production of pulmonary edema.

(1) High Pressure in the Pulmonary Capillaries. This is usually the result of forceful cardiac dynamics. A sudden displacement of blood from the greater to the lesser circulation may favor the edema, especially in the presence of decreased reserve of the left ventricle or mitral block. Severe peripheral vasoconstriction may be caused by epinephrine (anger, fright, exposure to cold), angiotonin (renal ischemia), or vasomotor stimulation (central lesions, reflex stimulation). This vasoconstriction causes increased arterial resistance resulting in left ventricular strain on the one hand, and increase of venous return to the right heart on the other. This tends, therefore, to produce a high pulmonary capillary pressure through a dual mechanism.

High pulmonary arterial pressures are usually found in experimental pulmonary edema and were also observed in clinical cases through catheterization. However, only a few such cases have been studied so far. Pulmonary edema, induced by inhalation of phosgene, fails to show pulmonary hypertension and seems to have a different mechanism. It is theoretically sound to assume that pulmonary capillary pressures above 25 mm. Hg would lead to a transudation of plasma. However, much higher capillary pressures are required for causing pulmonary edema in animals, whereas pressures of 30 to 40 mm. Hg are not unusual in mitral patients without evidence of edema. Mitral patients experience a rise of pulmonary “capillary” pressure from 25 to 30 mm. Hg to 32 to 54 mm. Hg during an attack of edema. It is interesting to note that similar pressure increases are observed in either mitral patients or hypertensive patients in failure, during exercise tests without the appearance of edema. Even though it is possible that minimal edema is quickly drained via the lymphatic vessels, it seems likely that other protective elements are also involved.

A close relationship exists between humoral and mechanical elements. This is well illustrated by the observation that histamine exerts a more powerful constrictive effect on the venules than on the arterioles of the lungs. Thus histamine, by causing a marked increase of pulmonary capillary pressure, may be one of the contributing elements of pulmonary edema.

(2) Increased Permeability of the Pulmonary Capillaries. This is favored by increased pulmonary flow (leading to dilatation of the capillaries), allergy, poisons, anoxia, dyspnea (suction effect), chronic heart failure, inhalation of toxic gases. Speculations on whether capillary permeability may be altered by nerve impulses without concomitant changes of capillary pressure have not, as yet, been supported by conclusive evidence. There are,
however, suggestive experiments, including the production of pulmonary edema without pulmonary hypertension through faradic stimulation of the stellate ganglion.44

The part played by specific substances in increasing permeability has been the object of several investigations. The histamine content of certain organs, especially of the lungs,58 is increased after an injection of epinephrine.58, 59 Large amounts of this substance are liberated during experimental pulmonary edema.58, 60 Corticotropin (ACTH) decreases the mortality of animals from experimental pulmonary edema,52, 60 and this has led to speculation that adrenal cortical hormones also play some role in the mechanism of the attack.52, 60 This effect of corticotropin explains why different “stress reactions” inhibit pulmonary edema in animals.52, 53, 60 The unexplained effect of splenic substances in favoring pulmonary edema of the rabbit69, 105-107 might be interpreted as being due to increased permeability of the pulmonary capillaries caused by substances which are either formed by or are stored in the spleen.

(3) Decreased Osmotic Pressure of the Blood. This occurs after prolonged saline infusions, in lipid nephrosis, starvation or liver diseases. The effect of this factor is widespread. Therefore, either pulmonary edema is part of a diffuse anasarca or is favored by other edematogenic factors.

A comprehensive work on pulmonary edema of 25 years ago3 divided the factors of pulmonary edema into mechanical, neurogenic, and humoral. It is now possible to modify this view by recognizing that most elements are interrelated: chemical and endocrine products may cause vasoconstriction and changes of permeability; blood pressure changes may cause reflex release of hormones or chemicals; and neurogenic elements may act either through the vasomotor system or through hormones. Moreover, the part played by the various factors is different according to the various causes and associated elements of pulmonary edema.

Among the conclusions reached by experimental workers, the following have a special importance:

Extreme stimulation of the brain or the carotid body leads to direct or reflex stimulation of the sympathetic system, followed by severe vasoconstriction. This leads to increased peripheral resistance with increased loading of the left ventricle; displacement of a large mass of blood from the arterioles, capillaries, and blood reservoirs towards the veins; increased venous return; and, finally, filling of the blood vessels of the lungs with a large quantity of blood. In other words, this stimulation causes an increased output of the right ventricle, and, at the same time, increased difficulty in the emptying of the left ventricle. This mechanism assumes great importance if there is left ventricular strain, and even more so if there is left ventricular failure. Whether or not it is sufficient to cause pulmonary edema with an intact heart is still open to question.

The possible role of vascular phenomena of the lesser circulation in favoring pulmonary edema is still speculative. It is known that arteriolar constriction in the lungs is present in many clinical conditions associated with high pulmonary arterial pressure and prevents an excessive increase in pulmonary capillary pressure. Any relaxation of these arteries would favor flooding of the capillary bed and edema. Some of the possible causes of loss of arteriolar tonus, such as reflex vasodilation, direct effect of hormones, and direct effect of anoxia, still require investigation.

Anoxia causes a direct dilatation of the pulmonary vessels and a reflex (carotid body) increase of cardiac output.56 The combination of these two elements strongly favors pulmonary edema.

The following considerations attempt to explain the various clinical forms of pulmonary edema.

(1) Pulmonary Edema Following Massive Myocardial Infarction. When the power of the left ventricle is suddenly decreased, there occurs a marked increase of left atrial and pulmonary capillary pressures. However, the latter persists only if adequate venous return is maintained. Therefore, a severe (but not too severe) lesion of the ventricle is the most effective. A peripheral mechanism initiated by cerebral ischemia, carotid-sinus hypotension or carotid-body
hypothesis, may contribute to the disturbance by causing peripheral vasoconstriction. The accumulation of blood in the lungs is, therefore, very probably due to both a cardiac and a vascular mechanism. The peripheral effects of serotonin, liberated in the area of infarct, are still speculative.

(2) Pulmonary Edema of Patients with Hypertension, Aortic Insufficiency or Aortic Stenosis; of Cases with Minor Coronary Attacks; and Following Transfusion in Surgical, Obstetrical, Anemic or Cardiac Cases. Left ventricular strain is followed by increase of left atrial and pulmonary venous pressures. Excitement, exposure to cold, fear of death or exertion, cause sympathetic stimulation and redistribution of the blood with its accumulation in the lungs, favoring thereby acute pulmonary edema. The increased peripheral resistance may transform ventricular strain into ventricular failure. Or else, transfusions or infusions, by directly increasing the volume of blood in the lungs and lowering osmotic pressure, further favor the edema.

(3) Pulmonary Edema of Nephritic Patients, Especially if Uremic. A mechanism similar to that of (2) can be postulated. Retention of metabolites increasing capillary permeability (nephritis) or decreased osmotic pressure of the blood (nephrosis) may be among the favoring causes.

(4) Pulmonary Edema Following Trauma to the Skull or Lesion of the Central Nervous System. In this type, there is severe central sympathetic stimulation. This causes vasoconstriction and increased resistance placing a severe load on the left ventricle; it also leads to redistribution of the blood and its accumulation in the lungs. While these elements favor pulmonary edema, other factors should also be taken into consideration such as dilatation of pulmonary vessels and liberation of substances increasing capillary permeability (histamine, hyaluronidase, etc.).

(5) Mitral Stenosis. The outflow of blood from the lungs is impeded by the mitral block, even during rest. Sympathetic stimulation caused by excitement, exertion, exposure to cold, anger or fright leads to: (a) tachycardia, with shorter diastole and impaired emptying of the left atrium; and (b) vasoconstriction, with redistribution of the blood and its accumulation in the lungs. The effect of the mitral block is proportionally increased by greater venous return to the heart.

(6) Exposure to Toxic Gases. Here the most important effect seems to be damage to the capillary endothelium followed by liberation of substances increasing capillary permeability. The role of reflexes arising in the mucosa of the respiratory passages is still to be evaluated. These reflexes and the effect of anoxia have special importance in cases of strangulation, asphyxia or drowning.

Clinical Types of Pulmonary Edema

While different signs have led to the recognition of various clinical pictures of pulmonary edema, duration of the episode allows division as follows: (1) fulminating (5 to 10 minutes); (2) acute (10 to 60 minutes) and (3) protracted (1 to 36 hours).

However, the attention of one of the writers was called several years ago to the fact that two groups deserve separation because of the different effect that treatment exerts on the clinical picture and on the final course.

Patients of the first group, which seems to be the most numerous, present evidence of increased blood pressure, rapid circulation, increased cardiac output, and extreme rise in pulmonary arterial pressure. This group includes cases with hypertensive heart disease; syphilitic or rheumatic heart disease with isolated aortic insufficiency; some of the cases with cerebrovascular accidents, mitral insufficiency or minor coronary episodes; and patients treated with too abundant venous infusions or transfusions. It is apparent that any method which succeeds in decreasing venous return to the right heart will be most effective in this type of edema.

Patients of the second group, less numerous but tending to increase, present either no change or a drop of blood pressure, decreased cardiac output and a more moderate rise in pulmonary arterial pressure (some cases may even have a normal pulmonary arterial pressure). This group includes cases with massive myocardial infarct, some of the cases with
severe mitral or aortic block, some cases following inhalation of toxic gases, some cases of cerebrovascular accidents and some cases with toxic, rheumatic or bacterial myocarditis. While a reduction in venous return may be useful in these cases, it also carries with it the danger of precipitating shock.

**Therapy**

The multiple etiologies and the various mechanisms, which may be involved in pulmonary edema, have led to the employment of a multiplicity of drugs and physical measures. Unfortunately, tradition on the one hand and erroneous concepts on the other have prevented, so far, a rational approach. Although little agreement exists between different groups of physicians, each group treats all cases of pulmonary edema in a similar manner. Table 4 summarizes the various drugs; table 5, the physical or physicochemical methods of treatment.

**Drug Therapy**

*Morphine.* The empirical use of opiates is old. The value of morphine was demonstrated in various types of experimental pulmonary edema.\(^8\), \(^16\), \(^32\), \(^63\) Morphine terminates most of the mild and some of the severe clinical attacks. However, the best results are obtained in

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**Table 4.** Pharmacologic Treatment of Pulmonary Edema

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Contraindication</th>
<th>Mechanism of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atropine</strong></td>
<td>Coronary occlusion, CVA attacks</td>
<td>Other cases</td>
<td>Blocks vagus (increased heart rate helps if there is severe bradycardia)</td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>Hypertension, coronary occlusion, mitral stenosis</td>
<td>Shock, allergy, toxic gases, pregnancy, drowning, CVA attacks</td>
<td>Slower respiration, decreased metabolism, decreased reflexes, decreased venous return (probable), decreased peripheral resistance</td>
</tr>
<tr>
<td>Barbiturates, chloral</td>
<td>See above</td>
<td>See above</td>
<td>Increased dynamics of both ventricles (mostly the right if the left is damaged or there is mitral obstruction)</td>
</tr>
<tr>
<td>Mercurial diuretics</td>
<td>See above</td>
<td>See above</td>
<td>Peripheral vasodilatation with shift of blood from lungs toward periphery</td>
</tr>
<tr>
<td>Sympatholytics, spinal anesthesia</td>
<td>See above</td>
<td>Shock, toxic gases, drowning</td>
<td></td>
</tr>
<tr>
<td>Aminophyllin</td>
<td>All cases</td>
<td>See above</td>
<td>Prevention of histaminic effect on capillary wall, possible central sedation</td>
</tr>
<tr>
<td>Antihistaminics</td>
<td>All cases</td>
<td>—</td>
<td>Decreased permeability of capillary wall</td>
</tr>
<tr>
<td><strong>Heparin(^*)</strong></td>
<td>All cases</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^*\) So far, only experimental pulmonary edema.
cases with hypertension, uremia or mitral stenosis. The untoward effect of morphine in cerebral accidents or lesions and in chronic cor pulmonale, may contraindicate or limit its use in such cases. The deleterious effect of morphine on the fetus may indicate the need for a cautious use of this drug in attacks occurring during pregnancy. Even in cases of coronary occlusion, large doses of morphine may favor the onset of shock.

The mechanism of action of morphine is not completely known. This drug depresses the respiratory center and decreases the suction effect of dyspnea (which in turn may decrease the edema). In pharmacologic doses, morphine causes no apparent changes of cardiovascular dynamics, and the pulmonary vessels are affected only by extremely large doses. Pulmonary arterial pressures of cardiac patients, studied by catheterization, decreased in 26 out of 34 cases, but increased in the other eight. It is, therefore, difficult to foresee whether the effect of morphine will be beneficial. Alleviation of anxiety and interruption of harmful reflexes may be a useful action of morphine, especially in coronary patients. Vomiting may be deleterious and even dangerous. Morphine decreases the basal metabolic rate; this should decrease the work of the heart and lower the venous pressure. However, it may take some time for this effect to become apparent.

Morphine is usually administered subcutaneously, in doses of 10 to 15 mg. It may be given intravenously, as shown by one of the authors (A.A.L.) in 1928. Intravenous administration is followed by more rapid effects, but causes nausea more frequently.

Atropine. Atropine was used empirically in England for a long time before any publication described its beneficial effect in pulmonary edema. It is likely that the well-known "drying" effect of atropine on secretions and the results obtained in bronchial asthma (which originally was not clearly separated from other syndromes) were responsible for its being prescribed in pulmonary edema.

Atropine was found either mildly beneficial or harmful in intact animals and only slightly beneficial in tracheotomized animals, when pulmonary edema was induced by means of epinephrine or rapid intracarotid infusion. Atropine does not improve pulmonary edema caused by ingestion of ammonium chloride while it is beneficial in pulmonary edema caused by the central nervous system lesions. The latter effect seems due to prevention of extreme bradycardia, one of the possible factors of pulmonary congestion. The clinical use of atropine should be limited to neurologic conditions with bradycardia and to some cases of coronary occlusion, also presenting bradycardia. In the other cases, tachycardia, caused by atropine, and vagal inhibition in general may be detrimental. Bronchodilation caused by atropine has been considered either harmful or useful according to different theories. For the above reasons, Demerol, a drug with both an atropine-like and a morphine-like action, should not be preferred to morphine, except in cases with a definite indication for the use of atropine.

Barbiturates-Chlortal. Barbiturates and chloral hydrate have been shown to be of value in experimental pulmonary edema. Their intravenous administration in man was attempted long ago and their value in several cases of pulmonary edema has been shown since 1930. However, these drugs may be ineffective and, in certain cases, one cannot escape the impression that the deep sedation produced by them hastens the patient's demise. Venous return is decreased by chloral and barbiturates, and it is only logical to avoid use of these drugs in patients of the second group, those in danger of shock.

Aminophyllin. This drug is a mild vaso-dilator, a bronchodilator, and a stimulant of the respiratory center. The first action is useful though inadequate, the second is of doubtful utility (see atropine) and the third is definitely detrimental. For these reasons, aminophyllin should not be used in the emergency treatment of the attack. The routine use of aminophyllin, practiced in certain hospitals, cannot be recommended.

Papaverine. Intravenous injection of papaverine in association with other drugs has been advocated by one of the authors (A.A.L.) since 1930. Papaverine is a smooth muscle
relaxant and a vasodilator. Its usual dose is 10 mg. intravenously. Possible objections to its use are: (1) if the patient belongs to group 1 (high output), papaverine is too mild a vasodilator to be effective; (2) if the patient belongs to group 2 (low output), even a moderate decrease of venous return can be dangerous.

Amyl Nitrile. This drug is used empirically by inhalation in some hospitals. It is very probable that its powerful vasodilator effect may be useful in certain hypertensive patients, in spite of its extremely short duration of action. However, since this drug may dilate the pulmonary vessels, the authors do not recommend it, even in cases of group 1. As far as patients of group 2 are concerned, the use of amyl nitrite presents the same dangers as that of other vasodilators.

Mercurial Diuretics. Mercurial diuretics are injected intravenously in pulmonary edema in many hospitals. Empirical use of these agents undoubtedly rested on the hope of rapid dehydration of the patient obtained through promotion of diuresis. This action, however, would hardly be adequate and timely for improving the circulation during the attack. Another property of the mercurials was subsequently described, when cardiac catheterization revealed that Novurat causes an important drop of pressure in the right atrium and ventricle within 20 to 30 minutes. This drop in pressure is still unexplained and may be due to venous constriction decreasing venous return. This effect should be considered useful in patients of group 1 (high output) but unwanted and possibly dangerous in patients of group 2 (low output).

Sympathomlytics. Drugs inhibiting or preventing stimulation of the sympathetic system have been considered helpful following demonstration that bilateral stellactomy was useful in preventing pulmonary edema in man as well as in experimental animals, and also that spinal anesthesia produced similar beneficial effects in man. In animals, sympatholytic drugs have been shown to favorably affect the course of the edema caused by intravenous epinephrine, rapid intracarotid infusion of saline, ingestion of ammonium chloride, or intracisternal injection of fibrin. Scanty clinical reports seem to indicate beneficial effect in man. Like all hypotensive drugs, sympatholytics (Dibenamine, Hydergine) and ganglionic blocking agents (Arfonad, tetraethylammonium chloride) may induce shock in patients of group 2. Disadvantages of these drugs are their lasting action and the difficulty of counteracting their effect, whenever this proves to be harmful.

Digitalis Glycosides-Ouabain. According to the theory of left ventricular failure, attacks of pulmonary edema are caused by an acute weakening of the left ventricle. Therefore, intravenous administration of drugs stimulating the myocardium, like strophanthine (or ouabain), was advocated since the early twenties in the emergency treatment of these attacks. More recently, intravenous Digitoxin or lanatoside C were substituted for strophanthine and in many hospitals intravenous Digitoxin has become part of the routine therapy. A recent study advocates small doses of ouabain (0.05 to 0.2 mg.) in the treatment of cardiogenic shock with pulmonary edema.

This therapeutic concept presupposes: (1) that the left ventricle can still be stimulated although this may not be possible when the ventricular wall is damaged by recent coronary occlusion or prolonged and severe coronary insufficiency and (2), that the right ventricle is not unduly stimulated by the drug, so that no further rise of pulmonary arterial pressure will take place. It is interesting to note that, according to many authors, digitalis glycosides have their greatest effect whenever the myocardium is functionally under stress while not structurally damaged. This seems to apply more to the right than to the left ventricle during an attack of pulmonary edema because the right ventricle is under stress on account of acute pulmonary hypertension and is seldom damaged to the extent of the left.

Digitalis glycosides rapidly lower venous pressure; however, this effect is mainly due to improved function of the myocardium. Therefore, and purely on theoretic grounds, digitalis and ouabain should be useful after the attack in hypertensive patients even though
these drugs might be detrimental during the attack in cases of myocardial infarction.*

A special case should be made for patients with mitral stenosis. In these patients, the high pressure of the pulmonary capillaries is caused by high right ventricular output in the presence of mitral obstruction.† Rapid digitalization can increase the severity of the edema, if performed during an attack, and may even precipitate pulmonary edema by increasing right ventricular output while the outflow from the lungs is impeded by the mitral block.111 A striking demonstration is given (fig. 3). Injection of 1.2 mg. of Digitoxin in a patient with mitral stenosis during catheterization was rapidly followed by pulmonary hypertension and pulmonary edema. Morphine and venesection lowered pulmonary pressure and this was followed by cessation of foaming.

Antihistaminics. The concept that liberation of histamine was the final event preceding edema of the lung has been advanced by one of the authors (A.A.L.) and co-workers since 1930. This concept seemed to be corroborated by subsequent studies60 but is still far from being conclusively demonstrated.

Antihistaminics (Phenergan) seemed to give good results in experimental81, 82 and clinical83 pulmonary edema. However, the former effect has not been confirmed.84 Depression of the central nervous system caused by these synthetic drugs may contribute to the results obtained.

If the main action of the antihistaminics is at the site of liberation of histamin, it is likely to be exerted within the walls of the pulmonary capillaries (fig. 4).

Heparin. Heparin was found beneficial in experimental pulmonary edema80, 80 Clinical reports are still unavailable. As this drug is known to decrease capillary permeability and the other anticoagulants do not share its beneficial action in pulmonary edema,60 the effect of heparin is probably due to local action on the capillary wall.

Corticotropin (ACTH). Corticotropin has been found beneficial in acute pulmonary edema of rabbits.53, 80 Considering that its effect was obtained after four days of treatment, this drug might be considered in the

* Experiments testing intravenous digitalis in pulmonary edema are being done in this laboratory.
† In certain cases, vasoconstriction of the pulmonary arterioles prevents an excessive rise of pressure in the capillaries of the lungs.

FIG. 3. Pressure of the pulmonary artery and right atrium during cardiac catheterization in a patient with mitral stenosis. Injection of 1.2 mg. of Digitoxin via the catheter was followed by pulmonary edema. Morphine and venesection terminated the attack (from Lenègre and Scébat80).

FIG. 4. Site of action of the most used drugs
ACUTE PULMONARY EDEMA

prevention of the clinical attacks, but not in
their therapy.

Physical, Physicochemical and Surgical Treatment of Pulmonary Edema

Several physical or physicochemical procedures have been used. Some are effective
and should be considered in certain cases.

A hot bath (Sitzbath) has been used empirically and may be of help by causing peripheral vasodilatation. It is particularly indicated in patients with hypertension or aortic insufficiency.

Venesection or application of tourniquets is an old procedure. It is extremely effective in patients with arterial hypertension or aortic insufficiency and in certain cases of mitral stenosis with high venous pressure. As the main result is decreased venous return, venesection is contraindicated in patients of group 2 because it may induce shock. The general procedure is withdrawal of 500 to 600 cc. of blood from an antecubital vein by means of a 15 gage needle or after cutting the vein with a scalpel. If the tourniquet procedure is used, these bindings are applied to the four limbs with a moderate pressure; each is released and reapplied every 20 to 30 minutes in order to avoid venous thrombosis.

Oxygen was used at first only in cases with pronounced cyanosis. As anoxia may occur in pulmonary edema either as a primary or as a secondary factor, the use of oxygen is rational. Moreover, clinical improvement follows its use in certain cases. It is unfortunate that foam in the bronchioles prevents oxygen from reaching many of the alveoli. Oxygen is usually administered in the form of 100 per cent oxygen with a humidifier in order to prevent drying of the mucous. As oxygen in high concentrations is irritant, its administration should be interrupted by periods of normal air breathing.

Pressure respiration has been advocated in the treatment of pulmonary edema. The theoretic basis of this method is that the increased pressure in the broncho-alveolar system counteracts the high pulmonary capillary pressure and decreases transudation. Following animal experimentation, Barach and associates43 suggested breathing against a positive pressure of 3 to 6 cm. water. This procedure produced useful results in several clinical cases and seemed particularly indicated in pulmonary edema due to gas poisoning.46

It has been shown that positive pressure respiration, by increasing intrapleural pressure, decreases venous return.104 This procedure, which may be useful in patients of group 1, presents some danger in patients of group 2, where impending shock might be precipitated.*

Spinal anesthesia was tried by Sarnoff and Farr76 with encouraging results in clinical cases of protracted pulmonary edema which were refractory to other therapy. The intensive vasodilatation which follows spinal anesthesia decreases venous return to the right heart and lowers pulmonary arterial pressure. It is likely that the mechanism of action and the contraindications of this technic are similar to those of sympatholytic drugs (page 123).

Stellate block has proved useful in experimental pulmonary edema, when tried by a co-worker of the author.48 Clinical use of this method was made in 1952 by Pierach and Stotz.103 They blocked the right stellate ganglion with procaine in eight clinical cases of pulmonary edema with hypertensive, coronary or rheumatic heart disease. Excellent results were reported. The authors state that only the right ganglion should be blocked while block of the left would increase pulmonary congestion. Explanation of the mechanism of action is only tentative.

Antifoaming Therapy

Pulmonary edema, whatever the initial cause, starts a vicious circle of events which tends to prolong the attack. This cycle is based

* While positive pressure obtained by an expiration valve definitely decreases venous return, positive pressure respiration with modern apparatus seems to increase intra-alveolar pressure only for an extremely brief time. If this is confirmed, the latter method might be applied to any case of pulmonary edema without danger.
on high pulmonary capillary pressure, transudation and accumulation of fluid in the alveoli, foaming and local anoxia, which in turn leads to more transudation, more foaming and more anoxia. While any procedure tending to lower pulmonary capillary pressure is undoubtedly the most effective in patients of group 1, these procedures are either poorly effective or actually dangerous in patients of group 2.

Since 1950 we have tried a new approach, that of attempting to break the cycle by acting on the foaming process itself. It was shown long ago that large amounts of fluid may be present in the air passages with little danger to life; as soon as the surface tension of the fluid reaches a critical point, foaming starts. This leads to extremely severe effects, partly through the enormous increase in volume (foam) and partly through modification of the normal alveolar function which is based upon surface tension effects between humid alveolar surface and air.

Since impairment of the normal gas exchanges of the lungs is followed by anoxia which in turn causes increased permeability of the capillaries, the foaming process in itself may be responsible for the continuation of the attack and may be a cause of death. If a modification of the surface tension of the foam is brought about, the bubbles burst and the fluid composing the thin separating layers then occupies a much smaller volume.

Antifoaming or defoaming agents (ether, octyl alcohol, capryl alcohol and ethyl alcohol) were tested by one of us in the form of vapors or aerosols in four different types of experimental pulmonary edema. While the use of long chain alcohols did not seem to improve the outcome, ether had a mildly beneficial action and ethyl alcohol (ethanol) produced excellent results. The inhalation of oxygen with a high concentration of ethyl alcohol vapor was followed by a decreased mortality, a lower lung-body index and the easy expectoration of fluid. The systemic effect of alcohol was slight, both on account of its being only a mild sedative and vasodilator, and because of poor absorption. This was shown by the observation that beneficial effects of alcohol by other routes were obtained only when administered in doses which induced deep anesthesia.

Experimental studies have also been made by others with silicone in ether or in water, both were found beneficial. We have recently compared several antifoaming agents including silicone mixtures. Three agents were definitely beneficial: 10 per cent silicone in water, freon and ethyl alcohol. Since freon may present some dangers if administered for long periods, only alcohol and silicone were considered for clinical use. While alcohol yields superior results in experimental pulmonary edema induced by adrenalin, it has a moderately irritant effect on the bronchial mucosa. This should favor the use of aerosol solutions of silicone in forms of pulmonary edema caused by lung irritants (chlorine, etc.). Experiments in this direction seem to confirm this viewpoint.

The effectiveness of silicone aerosol tends to support the opinion that the utility of alcohol vapor is not due to systemic effect, but rather to its effect on surface tension of the foam.

Several studies with antifoaming agents in clinical cases of pulmonary edema have been reported. At first, the tolerance for alcohol and the best method of administration were studied in normal volunteers as well as in cardiac patients without pulmonary edema. Two methods which gave excellent results are: (1) Use of a face mask and a 20 to 30 per cent alcohol solution. This technic is especially suited for comatose patients. (2) Use of a nasal catheter and a 95 per cent alcohol solution. This method is to be preferred in conscious patients.

In both methods, the alcohol is placed in the usual humidifier bottle, connected to an oxygen tank. The oxygen flow is kept at 2 to 3 liters per minute for the first few minutes. Then, when the patient's mucosa become adapted to the irritant gas (local anesthesia?), the flow rate is gradually stepped up until, after 10 to 12 minutes, it reaches 9 or 10 liters per minute, and is maintained at such level.*

* It should be emphasized that prolonged alcohol vapor treatment should be done only by alternating periods of inhalation (30 to 40 minutes) and periods of rest (10 to 15 minutes) during which the patient is
By means of this technic, alcohol vapor was administered to 14 patients during 17 severe or extremely severe attacks of pulmonary edema. In 14 of the attacks, previous conventional therapy had failed; in the other three, alcohol was the only therapy used. When oxygen-alcohol vapor was administered, the results were dramatically favorable in 10 of the attacks and definitely helpful in the other 4.

It was noted that patients with severe attacks responded most dramatically and that those with attacks of shorter duration had a more rapid recovery following alcohol vapor inhalation. Usually, subjective relief preceded objective improvement, so that the patient felt completely recovered even though some chest rales were still audible.

The beneficial effects of alcohol vapor were also noted by Goldmann and Primiano in one obstetrical case,97 by Gootnick and co-workers98 in two cases (one of them in shock) and by Weyl in seven surgical cases.102 A further report summarized the results of alcohol therapy in 50 attacks99 (table 6).

Another method was tried by Sadove100 12 per cent alcohol aerosol by face mask. His results were equally good.

The following abridged case reports illustrate the efficacy of this method of treatment.

Case 1. A 50 year old white female with hypertensive cardiovascular disease was semicomatose and unimproved one hour and a half following the onset of acute pulmonary edema of 4 plus severity. Oxygen bubbling through 85 per cent alcohol was administered via nasal catheter and dramatic improvement ensued. Forty-five minutes after therapy was begun, improvement was 4 plus subjectively and objectively. Therapy was discontinued after two hours and 15 minutes. No other treatment for acute pulmonary edema was given before or after the inhalation. The patient was later discharged to the Cardiac Clinic.

Case 2. A 65 year old, white female with acute pulmonary edema of 3 plus severity and of three hours duration was admitted to the hospital for treatment. Oxygen by mask for 30 minutes failed to induce improvement and no other treatment had been given. Thirty minutes after the inhalation of oxygen-alcohol vapor via nasal catheter was started, breathing air or oxygen. This prevents excessive absorption of alcohol which might lead to unwanted systemic effects.

<table>
<thead>
<tr>
<th>Mode of Therapy</th>
<th>Attacks Treated</th>
<th>Degree of Severity</th>
<th>Degree of Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-oxygen vapor only</td>
<td>3</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.O.V. given after failure of other procedures</td>
<td>11</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible contribu-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tory action of other procedures</td>
<td>3</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Total 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All methods</td>
<td>17</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total 40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* From Goldmann and Luisada99
Severity of attacks graded as follows: ++++ very severe, +++ severe, ++ moderate.
Improvement graded as follows: ++++ complete or almost complete, +++ good, ++ fair.

improvement was marked subjectively and objectively. Toleraton of the vapor was good. After 45 minutes, treatment was discontinued. A diagnosis of hypertensive cardiovascular disease, class III, with left ventricular hypertrophy, was established. After convalescence, the patient was discharged to the Cardiac Clinic.

Case 3. A 65 year old white female with coronary heart disease and calcific aortic stenosis suffered from a posterior myocardial infarction and developed shock and acute pulmonary edema of 4 plus severity. Morphine sulfate 15 mg., atropine sulfate 1.2 mg. and Desoxygin 10 mg., were administered intravenously. Notwithstanding these measures, her blood pressure dropped to 70/60 mm. Hg. Ninety minutes later, the patient was considered to be agonal and oxygen-alcohol vapor was administered by mask. Toleraton was good. Improvement was gradual and progressive, being 4 plus subjectively and objectively at the end of six and one half hours. After eight and one half hours, alcohol therapy was discontinued. The patient was discharged four weeks later.

Case 4.102 A 61 year old patient was suffering from pyloric obstruction and was scheduled for
**Table 7.**—Treatment of Pulmonary Edema following Failure to Respond to Antifoaming Therapy

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Arterial Pressure</th>
<th>Venous Pressure</th>
<th>Consciousness</th>
<th>Pulse</th>
<th>Drug</th>
<th>Physical or Surgical Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Cases with myocardial infarct</td>
<td>Above 100 (above 120 in hypertensive cases)</td>
<td>Normal or slightly elevated</td>
<td>Normal</td>
<td>Rapid and regular</td>
<td>Morphine 15 mg., mercurydrin 1 cc. i.v.</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Above 100 (above 120 in hypertensive cases)</td>
<td>Normal or elevated</td>
<td>Normal</td>
<td>Slow and regular</td>
<td>Morphine 15 mg., atropine 0.5 mg., mercurydrin 1 cc. i.v.</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Below 100 (100–120 in hypertensive patients)</td>
<td>Severely elevated</td>
<td>Lost</td>
<td>Rapid, slow, or irregular</td>
<td>Morphine 10 mg or Demerol 50 mg.</td>
<td>If i.v. fluids are necessary, use extreme caution (slow rate, moderate amount). If norepinephrine is given, use moderate doses. Pressure respiration. Venesection. No i.v. fluid. Spinal anesthesia. Procaine block of right stellate ganglion.</td>
</tr>
<tr>
<td>(2) Cases with cardiovascular accidents</td>
<td>High</td>
<td>Normal</td>
<td>Lost</td>
<td>Slow</td>
<td>Atropine 0.5 mg. (chloral 1 Gm.), mercurydrin 2 cc. i.v.</td>
<td>—</td>
</tr>
<tr>
<td>(3) Rheumatic heart disease (mitral stenosis or complex valvular lesions; possible carditis)</td>
<td>Low Above 100</td>
<td>High</td>
<td>Lost</td>
<td>Rapid</td>
<td>Morphine 15 mg., mercurydrin 1 cc. i.v.</td>
<td>Pressure respiration. Venesection</td>
</tr>
<tr>
<td></td>
<td>Below 100</td>
<td>Slightly elevated</td>
<td>Normal</td>
<td>Rapid and irregular</td>
<td>Morphine 10 mg, mercurydrin 2 cc. i.v.</td>
<td>Pressure respiration</td>
</tr>
<tr>
<td>(4) Hypertensive heart disease or syphilitic heart disease with aortic insufficiency</td>
<td>Above 200</td>
<td>Normal or slightly elevated</td>
<td>Present</td>
<td>Rapid</td>
<td>Morphine 15 mg., mercurydrin 2 cc. i.v. (chloral 1 Gm.?)</td>
<td>Pressure respiration. Venesection</td>
</tr>
<tr>
<td></td>
<td>Below 200</td>
<td>High</td>
<td>Present</td>
<td>Rapid</td>
<td>Morphine 10 mg.</td>
<td>Pressure respiration. Spinal anesthesia. Procaine block of right stellate ganglion</td>
</tr>
<tr>
<td>(5) Inhalation of toxic gases or bronchial obstruction</td>
<td>Above 100</td>
<td>High</td>
<td>Present</td>
<td>Rapid</td>
<td>Morphine 5 mg. or Demerol 25 mg.</td>
<td>Pressure respiration</td>
</tr>
</tbody>
</table>
gastric resection. Past history revealed exertional dyspnea and bilateral intermittent claudication after walking two blocks. An electrocardiogram showed low voltage and diphasic T in aVL. Induction of anesthesia and intubation were uneventful. Balanced anesthesia with circle absorption technique was used and respiration was assisted. Pulse and blood pressure were satisfactory (blood pressure, 140/80; pulse, 100) and color was good. One pint of blood was given in one and one-half hours. After the peritoneum was closed, only 50 per cent nitrous oxide oxygen was administered. At the end of the three-hour operation, cyanosis was noted. The pulse was 140; blood pressure 100/60. Sudden appearance of foam from the mouth then occurred and gurgling and bubbling sounds were heard. Immediate inhalation of oxygen-alcohol vapor was instituted by mask and, within 20 minutes, the pulmonary edema had subsided, the chest sounded clear, the color was pink, and the patient seemed improved. An electrocardiogram showed changes in aV1, T, and V6 through V1. Subsequent tracings showed definite evidence of an acute anterior wall infarct. The patient made an uneventful recovery and left the hospital six weeks later in good condition.

Case 5. A 43 year old Negro woman was admitted to the hospital because of hypertension complicating pregnancy. Hypertension had been noted during two earlier pregnancies; however, no interim examinations had been performed. Physical examination revealed an obese woman with blood pressure of 230/140, pulse 84, temperature 98.6 F., and respiration 20. The size of the uterus was consistent with a nine month gestation.

While lying supine following the examination, the patient became severely dyspneic and cyanotic, and developed acute pulmonary edema of the greatest severity, with continuous emission of copious amounts of pink, frothy fluid from the nose and mouth. The patient's head was elevated and positive pressure oxygen by mask was instituted. Successively, morphine sulfate 30 mg., aminophyllin 0.5 Gm., atropine sulfate 0.5 mg., sodium amytal 0.5 Gm. and Digalen (1 cat unit) were administered intravenously within 15 minutes from the onset of the attack. Forty minutes after these measures were completed, the patient was dubious and frothy sputum was still being emitted in copious quantities from the mouth.

Administration of alcohol vapor was then started via face mask. It was necessary to remove the mask frequently to permit removal of collected foam. Improvement was prompt, dramatic and progressive. Within 15 minutes, the foam became more liquid in character and expectoration was more effective. At the end of 30 minutes, the patient was able to sit up and speak clearly, although with some effort. Bubbling sounds and crepitant pul-

monary rales on auscultation were now markedly reduced. At this point, alcohol vapor was given and treatment was discontinued. Approximately seven hours later, the patient spontaneously delivered a female infant who required tracheal catheterization and oxygen.

Protracted pulmonary edema often starts suddenly but has a protracted course and is less likely to be a crucial issue for the prognosis. Ten such cases, all of them in poor or terminal state, were submitted to alcohol vapor therapy, in spite of the fact that none was considered likely to survive. Seven cases improved but the improvement was slower and less marked than in the acute attacks. It was good in three, moderate in two and minimal in two. The following case is an example.

Case 6. A 65 year old white male with coronary heart disease and congestive failure gradually and progressively developed pulmonary edema of 3 plus severity (over a period of 15 hours). Oxygen via nasal tube, morphine sulfate 15 mg. hypodermically, aminophyllin 0.25 Gm. and 3 units of Digalen intravenously, were given without noticeable improvement. Oxygen-alcohol vapor was started via nasal catheter and improvement was 3 plus objectively 20 minutes later. After 40 minutes of alcohol vapor treatment, improvement was so well established that this therapy was discontinued. The patient died suddenly on the following morning. Autopsy revealed a recent anteroseptal infarction, marked left ventricular hypertrophy and absence of froth in the tracheo-bronchial tree.

Following these reports, alcohol vapor treatment of pulmonary edema was instituted in various hospitals. It is unfortunate that, although the results are usually described as good, no other accurate clinical reports have been published.

The good results of another antifoaming agent, 2-ethyl-hexanol, was stressed by Reich and associates, following its use in 14 unselected cases. One-half of the patients showed a good response. Other antifoaming agents are being tested by various investigators including Sadove.

Management

Treatment of the Attack

At present, the directions for management of the attack are still tentative (table 7).
Further studies on the mechanism of action of the various drugs and physical procedures used in the different clinical types of pulmonary edema are necessary.

Antifoaming therapy is compatible with any other drug or physical treatment. Therefore, it is the viewpoint of the authors that all cases of pulmonary edema should be immediately treated with an antifoaming agent. In cases of pulmonary edema due to inhalation of toxic gases, silicone aerosol may prove to be the agent of choice. While the patient is undergoing inhalation treatment, a thorough examination of the causes leading to the attack should be made and their effects on the patient noted (pulse, blood pressure, electrocardiogram). After this routine examination, which may take from 20 to 30 minutes, and if the attack has not subsided, other procedures should be instituted.

Cases of pulmonary edema, associated with hypertension or aortic insufficiency, stenosis or coarctation, should receive 15 mg. of morphine and may also receive an intravenous injection of a mercurial diuretic. Sympatholytic drugs may be given but other hypotensive agents (such as nitroglycerine, papaverine), having a shorter action, may be preferred.

Cases with myocardial infarct and blood pressure above 100 or above 120, if there was hypertension prior to the attack, should also receive 15 mg. of morphine; 0.5 mg. of atropine may be administered if there is marked bradycardia. Mercurial diuretics may be given, but in small dose (1 cc. intravenously). If the blood pressure drops below 100 mm. Hg, the dose of morphine should be not more than 10 mg., and no mercurial may be given. The same rationale applies to cases of rheumatic heart disease and mitral stenosis.

Patients with cerebrovascular accidents should not receive morphine. They may be given atropine, mercurials and, possibly, chloral hydrate by rectum or intravenously.

Morphine should be given only in small doses (5 mg.) to patients who have inhaled toxic gases.

Spinal anesthesia or right stellate block should be used only in cases of cerebrovascular accidents or hypertensive heart disease with protracted edema, which is refractory to treatment, and then only if blood pressure is high.

Venesection occasionally may be a life-saving procedure. It should be employed only in cases of hypertension, cerebrovascular accidents, mitral stenosis or aortic insufficiency having high venous pressure or visible venous engorgement. Its use in other cases is more questionable, even in the presence of venous engorgement. As an example, in patients with myocardial infarct and systemic venous congestion, venesection may precipitate shock.

Pressure respiration has, in general, a favorable effect in pulmonary edema. However, patients with cerebrovascular accidents and depression of the respiratory center may respond poorly to this treatment.

Prophylaxis

It should be kept in mind that transfusions of blood and infusions of plasma or saline strongly favor pulmonary edema. Failure to consider this fact is responsible for many episodes of edema in medical and surgical wards. Moderation and wisdom in the administration of intravenous fluids may prevent many attacks, not only in cases with coronary or rheumatic heart diseases or anemia, but also in patients whose myocardium is less efficient because of anesthesia, surgical intervention or infection.

Prevention of pulmonary edema in hypertensive patients can be obtained in two ways: (1) by decreasing the load placed upon the left ventricle (salt poor diet, hypotensive drugs, sympathectomy, sedation); or (2), by stimulating the myocardium (digitalis glycosides). Both methods are extensively used. This may account for the impression that occurrence of pulmonary edema in these patients is less frequent than formerly.

Prevention of pulmonary edema in patients with coronary or cerebrovascular diseases is more difficult: prevention of the arteriosclerotic process would be the answer. Central sedation, especially at night, may prolong the life of these patients.

Prevention of pulmonary edema in rheumatic heart disease is based on avoidance of excessive physical work, on salt restriction,
use of diuretics and digitalization. Mitral valvotomy is effective in preventing attacks of pulmonary edema of patients with mitral block. In acute rheumatic fever, adrenocortical extracts are the best treatment, whenever the myocardium is severely damaged. The same treatment may be lifesaving in rheumatic heart disease with silent rheumatic carditis.

Most of the other forms of pulmonary edema are caused by unpredictable and often unavoidable events. The incidence of pulmonary edema in these cases will be reduced following improvement of working conditions (decreased exposure to toxic material), improvement of medical technics (slow removal of serosal fluids, moderation in the administration of intravenous fluids, rational anesthesia) and improved therapy of infections, including those involving the heart or the nervous system.

SUMMARY

Acute edema of the lungs is the infiltration of serum into the interstitial pulmonary tissue, followed by exudation into the alveolar cavities, frothing and expectoration of foam.

Acute pulmonary edema is encountered in a great variety of conditions including cardiovascular, renal, cerebral and pulmonary diseases, trauma to the skull or the chest, infections and shock.

Pulmonary edema may be fulminating, acute or protracted. Two clinical types can be recognized, that associated with a full pulse, a high blood pressure and a high output (group 1), and that associated with severe blood pressure drop, low output and tendency toward shock (group 2).

Experimental pulmonary edema can be produced by a great variety of methods. These range from damage to the heart or brain to ventricular strain; from trauma to the skull or chest to pulmonary embolization; from overload of the circulation to inhalation of toxic gases or administration of poisons.

The mechanism of production of pulmonary edema is still somewhat obscure. Three main factors seem of paramount importance: high pressure in the pulmonary capillaries, increased permeability of these capillaries, and decreased osmotic pressure of the blood. While strong sympathetic stimulation is one of the most common factors leading to displacement of a large mass of blood from the periphery to the lungs, the roles played by vascular phenomena in the lungs, secretion of endocrine glands and locally elaborated humoral agents are still under discussion.

Special aspects of the treatment of pulmonary edema in mitral stenosis, in massive myocardial infarct and in exposure to toxic gases are discussed.

Therapy of pulmonary edema is based on the use of drugs and physicochemical means. Among the most successful drugs are morphine, mercurial diuretics and sympatholytics, while oxygen therapy, pressure respiration and venesection may also be useful. Most of the above drugs and physical procedures tend to decrease venous return and cardiac output; therefore, while helpful in patients of group 1, they may induce shock in patients of group 2.

Digitalization during the attack is considered of questionable value, particularly in cases of myocardial infarct, mitral stenosis or exposure to toxic gases. It may be useful in the prevention of the attacks.

Antifoaming therapy is a purely symptomatic treatment which tends to break a self-perpetuating cycle by modifying the surface tension of the froth, thus reducing its volume. This procedure has been shown to be of definite value and should be used routinely as the first remedy, even preliminary to a brief study of the case. Drug therapy and other physical measures should be employed later, after an evaluation of the clinical picture, and, especially, if antifoaming therapy fails to terminate the attack.

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