Therapy of Experimental Pulmonary Edema in the Dog
With Special Reference to Burns of the Respiratory Tract

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The results of analysis of edema fluid and excised lungs show that there is leakage of protein-rich fluid into the lung tissue and ultimately into the respiratory passages. This leakage cannot be explained by the reduction in oxygen uptake as observed in lung tissue slices. The ultimate cause of pulmonary edema is not known. The survival time of anesthetized dogs suffering from thermal edema can be prolonged by inhalation of oxygen and by administration of antihistaminic drugs and pulmonary vasodilators.

CHEMICAL COMPOSITION AND OXYGEN UPTAKE OF NORMAL AND EDEMATOUS LUNGS

The search for procedures that might prove useful in the therapy of pulmonary edema has been largely limited to survival studies in smaller laboratory animals such as mice, rats, guinea pigs and rabbits. The protection in such animals against an agent that provokes edema has been utilized as presumptive evidence for the usefulness of a particular procedure. The use of antifoaming agents and ganglion-blocking drugs in man is based on such evidence, but the application of many other agents has been slow, probably because of the remoteness of the experimentally-induced edema from the clinical forms and also because the exact mechanism of protection is not clear (see 1, 2 for reference).

Functional concepts of the pulmonary circulation have been derived from larger animals such as cats and dogs, but it is surprising to note that procedures for treating pulmonary edema are rarely tested on such animals. Survival studies are not feasible for economic reasons so that the success of therapy will have to depend on the continuous detection of the severity of edema in the living animal. The electrical and radioactive methods for detecting pulmonary edema in the dogs breathing spontaneously have been reported elsewhere. Three possibilities remain: analysis of edema fluid collected in the course of the development of pulmonary edema to determine if the concentration of plasma protein in it will serve as a guide for the severity; chemical analysis of portions of the lungs excised at various times, also to detect if severity of edema is related to the contents of hemoglobin, soluble protein and moisture; and measurement of oxygen uptake of lung slices to obtain a rough indication of any metabolic defect. It should be stated at the outset that these three types of studies have not revealed any useful lead for continuous assessment of pulmonary edema in the dog. However, the results of analysis of lungs and edema fluid are reported below because they serve to emphasize the problems and suggest some mechanisms relating to the leakage of plasma protein into the edema fluid during pulmonary edema following the inhalation of steam and the injection of alloxan.

METHODS

Dogs under morphine (2 mg./Kg.) and chloralose (70 mg./Kg.) anesthesia were used. Pulmonary edema was induced by one of the following methods: inhalation of steam under atmospheric pressure for 30 sec. in a manner previously reported (14 dogs); intravenous injection of freshly prepared solution of alloxan monohydrate 0.1 Gm./Kg. (8 dogs); and intravenous injection of...
saline 200 ml./Kg. for 15 min. while dogs were subjected to inhalation of 5 per cent oxygen and negative pressure breathing (5 dogs). Non-edematous lungs were obtained from 17 dogs that were killed by intravenous injection of pentobarbital sodium (120 mg./Kg.).

Edema fluid was collected from a tracheal cannula and blood samples were obtained from a catheter in the femoral artery. In some dogs, the chest was opened under artificial respiration to allow the excision of the peripheral segment of a lobe which was first clamped by 2 hemostats and ligated to prevent the leakage of blood and fluid. After death from edema, both lungs were ligated at the hilum and the entire lungs including the trapped fluid and blood were weighed and subsequently analyzed for: (1) wet weight of aliquot portion (about 5 Gm.) after the whole lung was minced in a Waring blender for 10 min.; (2) dry weight of the same aliquot portion after 24 hours in 150 C. oven; (3) hemoglobin content of another aliquot portion by a method described previously; (4) soluble and nonsoluble protein by method described by Hemingway; and (5) oxygen uptake of lung slices by the usual manometric technic of Warburg and with the details specified by Barron, Miller and Bartlett.

Samples of femoral arterial blood were analyzed in duplicate for plasma protein, hemoglobin and moisture content. The 2 latter determinations were used to calculate the content of blood in the lungs, the details of which have been described previously. Kjeldahl determination of protein nitrogen was performed on edema fluid.

**RESULTS**

Most forms of experimental pulmonary edema are characterized by the presence of protein in the edema fluid except the edema following the injection of either ammonium salts or thiourea. None of these studies include dogs so that the initial problem was to ascertain the nature of edema fluid derived from such animals.

**Edema Fluid Following Steam Inhalation.** The inhalation of steam for half a minute was consistently followed by the appearance of edema fluid in the trachea within one half hour after inhalation. Death occurred within 1 hour after the injury. The edema fluid was collected in each of 5 dogs; the total volumes were 20, 80, 120, 150 and 180 ml., respectively. Five milliliter samples were collected every 10 min. until death and the results are summarized (fig. 1). Two dogs showed protein values averaging 5.1 and 4.8 Gm./100 ml.; the values for the individual samples of edema fluid obtained from each dog varied within 0.3 Gm. The 3 other dogs had similar average values of protein content but the value of the initial was lower than the terminal sample by 0.6, 0.6 and 1.4 Gm./100 ml.

The protein concentration of edema fluid was 85 per cent of the respective blood samples drawn at the time of fluid collection. In 2 dogs, the concentration in the terminal fluid sample even exceeded that in the plasma by as much as 0.5 Gm./100 ml. This may not necessarily mean that the fluid leaking from the alveolar wall contained higher protein than plasma, because the subsequent reabsorption of water as well as its evaporation up to the time of collection cannot be excluded.

**Edema Fluid Following Alloxan.** The edema fluid collected from 4 dogs developing pulmonary edema initiated by the intravenous injection of alloxan had similar concentration of protein to that collected from dogs suffering from thermal edema. The average values for protein content were 4.3, 4.6, 4.9 and 5.3 Gm./100 ml.; the individual samples from each dog varied by not more than 0.3 Gm. These values were from 75 to 95 per cent of the respective protein content of blood plasma and there was no instance in which the latter was exceeded by the content of edema fluid (fig. 1). There was no evidence suggesting that the progress of edema formation was accompanied by an increasing concentration of protein in the edema fluid.

**Edema Fluid Following Saline Infusion.** It was difficult to collect edema fluid from dogs subjected to saline infusion. In 3 dogs, edema fluid appeared terminally but it was possible to collect fluid for about one half hour prior to death in 2 other dogs. All the samples contained 0.7 to 1.8 Gm./100 ml. fluid, and that is 25 to 70 per cent of protein content in the blood plasma (fig. 1). The lower content of protein in edema fluid, both absolute and
relative to blood plasma, may possibly mean either no defect or a different type of defect in capillary permeability as compared to the other types of edema characterized by higher content of protein in the edema fluid. This was not explored further because of the difficulties in measuring capillary permeability. All of these results support the general conclusion that edema fluid contains protein but this observation cannot be used to judge the severity of edema.

**Chemical Analyses of Lung Tissue.** The lungs derived from 14 dogs dying of thermal edema and of 8 dogs dying of alloxan edema were analyzed and compared with lungs of 17 nonedematous lungs. (These dogs included those subjected to analysis of edema fluid.) The essential features of the edematous lungs are as follows:

Increased lung weight. Although all the nonedematous lungs weighed from 100 to 250 Gm., the edematous lungs ranged from 200 to 450 Gm. (fig. 2).

Increased total moisture content. The increase in total lung weight was accompanied by a significant increase in moisture content with the following average values: normal 77.1 per cent, thermal edema 85.2 per cent and alloxan edema 82.6 per cent (fig. 3).

The difference in moisture content expressed per 100 Gm. lung weight was small but statistically significant. If the increase in total lung weight was considered, the total amount of additional moisture in the edematous lungs was actually more than doubled that of the normal lungs. The additional moisture in the edematous lungs could be accounted for by the edema fluid, but an increase in amount of blood also contributed to the increase and was calculated by analysis of hemoglobin content.

Decreased lung hemoglobin. The hemoglobin content of the edematous lungs was decreased as compared to the normal lungs. This could not be attributed to hemodilution because blood hemoglobin concentration was higher in the dogs with edematous lungs (fig. 4). The hemoglobin values allowed the calculation of the amount of blood in the
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lungs based on the assumption that the concentration of hemoglobin in peripheral blood was the same as that of blood in the excised lungs. The average values as represented in figures 3 were as follows: normal lungs, 22.2 ml.; thermal edema, 17.5 ml.; alloxan edema, 17.2 ml. blood/100 Gm. lung weight. This reduction in per cent content of blood is relative since the increase in total lung weight would still mean an increase in total amount of blood remaining in the edematous lungs.

Increased lung soluble protein. Some of the excised lungs were analyzed for soluble proteins. The 3 normal lungs contained 3 to 4 Gm. protein/100 Gm. lung weight, whereas the 7 edematous lungs contained 4.5 to 9.5 Gm. (fig. 5). This increase was in line with the above observation that edema fluid contained protein. The content of insoluble protein in the lungs varied in the normal as much as in the edematous lungs so that this could not be utilized as an expression of extent of edema. The content of soluble protein was also unrelated to the lung hemoglobin content. This suggested that both measurements were not affected to the same extent by the development of edema.

Repeated lung samples. All dogs described in the preceding paragraph had 3 lung samples removed during a period of 1 hour prior to the removal of the terminal sample. The contents of soluble protein, insoluble protein and lung hemoglobin of the earlier samples did not significantly vary from the terminal sample. The moisture content increased by as much as 5 per cent in 3 out of 7 dogs, but there was an equivalent decrease in the remaining dogs. The progress of edema could not be detected by per cent moisture of an excised sample because this could be upset by an increase in weight of the remaining lung tissue.

Oxygen Uptake of Lung Tissue. The average oxygen uptake of slices of nonedematous lungs (17 dogs) was as follows: 0.64 ml. ± 0.06 oxygen/100 Gm. wet weight/min.; slices derived from thermal edematous lungs averaged 0.67 ± 0.11; the difference was not statistically significant. The average oxygen uptake of alloxan edematous lungs was lower than of nonedematous lungs, 0.51 ml. ± 0.9. When all these values were expressed in terms of dry weight, the oxygen uptake value for alloxan edematous lungs remained lower than that of normal lungs (fig. 6).

Three dogs subjected to steam inhalation and 3 others subjected to alloxan were studied by the additional removal of 3 samples of lung tissues 1 hour prior to death from edema. The oxygen uptake value of the earlier samples did not vary significantly from that of the terminal sample.

DISCUSSION

The studies of oxygen uptake in vitro of normal lung tissue reported above agree on the whole with those reported in the literature. The value of 0.64 ml. oxygen/100 Gm. wet weight of tissue slice per minute falls within the range of values (0.2 to 0.8 ml.) reported for dog's lungs perfused via the bronchial artery. The value of 0.04 ml.
The oxygen uptake of lung slices is summarized in Figure 6, and it is equal to that reported by Stadie, Riggs, and Haugaard, using tissue slices and is about half as much as that reported by Bostroem and Lochner using the dog's lungs perfused via the pulmonary artery. The oxygen uptake of lungs of rats, mice, and guinea pigs average 0.13 ml., about 3 times larger than that of canine lungs. The explanation and significance of this difference are still unknown.

The observation that the oxygen uptake of thermal edematous lungs is about equal to that of normal lungs means that thermal injury and the development of edema does not interfere with the oxygen uptake measured in vitro. The reduction in oxygen uptake of alloxan edematous lungs is not related to the formation of edema, but appears to be a primary action of alloxan. These results do not lend themselves to the measurement of severity of edema but serve to emphasize that thermal edema is not a hopelessly irreversible situation, at least from the standpoint of tissue oxygen consumption.

Although the oxygen uptake of the thermal edematous lungs is different from that of the alloxan edematous lungs, the chemical analysis of both types of edematous lungs is alike in many respects. The edematous lungs are characterized by increases in total weight and in total and per cent moisture contents, but reductions in per cent lung hemoglobin and in per cent blood content. The increase in moisture content is accompanied by an increase in soluble protein and this in turn is related to the appearance of protein in the edema fluid collected from the trachea. These observations did not prove helpful in testing the severity of the edema, but they serve to emphasize the fact that pulmonary edema is marked by leakage of fluid that is rich in plasma protein. The ultimate elucidation of this transudation will depend on additional studies directed at measurements of capillary blood pressure prior to burning; abscissa, response; two marks connected by a dotted line, improvement in blood pressure after intravenous injection of either diphenhydramine or tripeleinni.
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Lary permeability. Since alloxan and thermal edema is preceded by capillary distention and congestion, it is not certain if the leakage is either a secondary accompaniment of distention, or the outcome of some independent action by heat or alloxan on the capillary wall. If leakage is a secondary accompaniment of congestion, therapy directed at the primary cause of the congestion is indicated, i.e., release of pulmonary venular constriction.

THERAPY OF BURNS OF THE RESPIRATORY TRACT

The final outcome of burns of the respiratory tract has been documented by several reports of civilian and military casualties. A detailed investigation of such burns induced in anesthetized dogs has identified the following functional changes: hyperthermia, blood hemolysis, obstruction of respiratory passage by laryngospasm and bronchospasm, disturbances in the reflex regulation of respiration, cardiovascular collapse, and pulmonary hypertension, congestion and edema. This report consists of a further analysis of systemic and pulmonary circulation following such burns in anesthetized dogs. All the details of the cardiovascular changes are not yet known, but sufficient information is available to warrant the trial of therapeutic procedures if human cases are encountered: antihistaminic drugs for the peripheral circulatory collapse, oxygen inhalation for the relief of anoxemia, and pulmonary hypotensive drugs to relieve pulmonary hypertension and edema. The experimental basis for the suggested clinical use of these procedures will be discussed.

METHODS

Dogs anesthetized with morphine (2 mg./Kg.) and chloralose (70 mg./Kg.) were used. The trachea was cannulated to allow the inhalation of steam for 30 sec. from a manifold described previously. Systemic blood pressure was measured by a mercury manometer or a Statham transducer from 1 femoral artery, and pulmonary arterial pressure by a Statham transducer from a catheter inserted under fluoroscopic guidance. Electrocardiograms were obtained by the standard limb leads recording on a Viso-Carliette.

The 62 dogs were divided into smaller groups:

6 dogs in which blood plasma potassium concentration was measured; 7 dogs in which blood histamine level was measured by the method of Code consisting of extraction of histamine and assay for contraction of the isolated gut of the rabbit (the lungs of 5 of these dogs were assayed for histamine content using the method described by Daly, Peat and Schild); 5 dogs in which femoral arterial blood was collected and analyzed for oxygen and carbon dioxide content, hemoglobin content and per cent saturation; 4 dogs in which local action of a drug was tested by perfusion of the left lower lobe, as depicted in figure 7; 5 dogs in which capillary blood volume in the lung was measured by injection of 10 ml. of blood tagged with phosphorus and continuous monitoring by means of an end-window Geiger counter tube inserted between 2 ribs; and 5 dogs in which plasma protein, tagged with I131, was measured.

RESULTS

Nature of Circulatory Collapse. All 62 dogs inhaling steam for 30 sec. developed a fall in aortic blood pressure. Eleven dogs developed a precipitous fall in blood pressure and died within 10 min. after injury. The remaining 51 showed a fall in pressure within 15 min. which ranged from 10 to 90 mm. Hg (fig. 8). Subsequently, the hypotension became progressively more severe. Most of them were subjected to various studies, some of which altered the intensity of shock and length of survival. In the absence of therapy, hypotension ultimately led to death within 1 hour after injury.

Electrocardiographic Changes and Potassium Liberation. Peaking of the T-wave immediately followed steam inhalation. This
Fig. 9. Electrocardiographic effects of steam inhalation. Note peaking of T-wave on the third row, taken 1 min. after injury. This disappeared immediately after injection of calcium gluconate (fourth row).

was a consistent finding in all dogs and suggested the causative role of liberation of potassium ion. Support for this explanation was derived from 2 additional observations: The peaking of the T-waves was immediately reversed by the intravenous injection of calcium gluconate solution (0.5 Gm. total) (fig. 9). This response exemplified the well-known potassium-calcium antagonism, but this was true only for the electrocardiographic pattern since the blood pressure continued to remain low. Furthermore, measurement of plasma potassium concentration in 6 dogs showed a mean preburn level of 4.2 mEq./L. plasma and a mean 5 min. postburn sample of 6.1 mEq. The highest rise encountered was to a level of 8.6 and this dog died 8 min. after injury. The 5 other dogs survived from 15 to 60 min., during which time the potassium level gradually approached the control level, but rose for the second time just before death (fig. 10).

The most likely sources of potassium ion were the erythrocytes that had been hemolyzed by heat during their passage in the lungs. The increase in potassium level accounts for the electrocardiographic changes, but the corresponding alteration in myocardial function has not been investigated. The hyperpotassemia is not the sole cause of systemic hypotension because the peak blood levels do not coincide with the progressive fall in blood pressure. Another substance that may be liberated during lung injury was considered next.

Increased Blood Histamine Content. It is
natural to investigate the role of histamine in causing shock of lung burns because the lungs have long been known to be a potential reservoir. The blood of 7 dogs was analyzed for histamine with variable results. Two dogs showed no detectable amounts of histamine in the blood, the remaining 5 showed levels of 2, 4, 5, 12 and 20 μg./10 ml. blood 10 min. after steam inhalation. The blood level remained high until death. The severity of hypotension among these dogs did not correlate with the level of blood histamine. The latter is probably related to the metabolic fate of liberated histamine as well as to the total amount released from the lungs.

That the lungs were the source of the blood histamine was suggested by analysis of the lungs (excised after death) of 5 of the dogs described in the preceding paragraph. The histamine contents of each of these lung samples were as follows: 1, 7, 11, 17 and 32 μg./Gm. tissue. All of these values were low compared to the 30 to 60 μg./Gm. of normal lung tissue. The depletion of histamine content in the lungs following thermal injury may account for the high histamine level in the blood, but more direct evidence is still lacking.

In 2 dogs, an intravenous injection of 0.5 mg./Kg. of compound 48-80, known to liberate histamine, caused a 30 per cent fall in aortic blood pressure. Subsequent inhalation of steam caused a further fall. On the other hand, in 2 other dogs, the shock following an initial steam inhalation was not further exaggerated by a subsequent injection of compound 48-80. If the shock in both instances is due to a common release of histamine, it appears that this mechanism is exhausted by steam inhalation, but not completely by the use of a chemical agent.

Efficacy of Antihistaminic Agents. From the therapeutic standpoint, the most important group of experiments concern the effects of either diphenhydramine or tripelennamine injected after the hypotension had appeared. The improvement in blood pressure is summarized in figure 8. It can be noted that the improvement seen in 9 dogs lasted for only 30 to 60 min. and all dogs subsequently died in a state of shock, this time complicated by pulmonary edema.

These observations suggest the practical use of antihistaminic drugs in the therapy of hypotension following burns of the respiratory tract. The bases for this are as follows: Injury to the lungs causes the liberation of histamine from lung tissue and the high level of histamine in the blood may contribute to the shock. The antihistaminic drugs can in turn block the vascular effects of liberated...
histamine. A review of the literature on burns reveals that no other type of burns is known to initiate a series of events similar to that outlined for lung burns. Skin burns cause a rise in histamine level in blood and skin, but the local effects on the skin cannot be counteracted by antihistaminics. The histamine liberated in skin burns exerts its major action locally, but the histamine liberated during lung burns is circulated to the general circulation and contributes to the hypotension. The antagonism of the hypotension by antihistaminic agents is analogous to antagonism against the vascular effects of injected histamine.

The effective use of antihistaminic agents against hypotension of lung burns is limited by the inability of these drugs to relieve other accompanying functional anomalies. The increase in plasma level of potassium, probably initiated by hemolysis, will continue to exert a deleterious effect. Pulmonary edema is not relieved by antihistaminic drugs, partly because the liberated histamine does not participate in the pathogenesis of edema, and mostly because the initiating cause for edema is direct thermal injury of the pulmonary capillaries and veins.

Correction of Anoxemia. Anoxemia was a consistent finding in all dogs. This appeared in varying severity before, as well as after the appearance of froth in the respiratory passages. In 3 dogs, the separate and combined outcome of inhalation of ethyl alcohol vapor, 100 per cent oxygen and positive pressure breathing were compared (table 1). Prior to the appearance of froth, only oxygen inhalation significantly improved the
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TABLE 1.—Per Cent Oxygen Saturation of Arterial Blood in Three Dogs Following Steam Inhalation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>Ethyl alcohol</th>
<th>Positive pressure breathing</th>
<th>100% oxygen</th>
<th>All 3 procedures</th>
<th>Back to normal respiration</th>
</tr>
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<tr>
<td>A</td>
<td>90</td>
<td>85</td>
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Before appearance of froth

After appearance of froth

Oxygen saturation of arterial blood. During the peak of edema, the inhalation of ethyl alcohol caused a partial relief of anoxemia, and a similar extent of relief could be derived from positive pressure breathing. The inhalation of 100 per cent oxygen brought about complete relief, and this occurred with or without the supplementary use of the other 2 procedures.

Relief of Pulmonary Hypertension. The ability of the following drugs to reduce pulmonary arterial pressure predominantly by vasodilatation has been described in earlier publications: aminophylline, ethoxy derivative of methoxamine (compound 45-50), tolazoline, and hexamethonium. Each of these drugs was administered in 2 or more repeated injections to 16 dogs following steam inhalation with the following results: The pulmonary arterial pressure which was initially high as a result of thermal injury (30 to 45 mm. Hg) abruptly fell in 3 of 5 dogs receiving tolazoline and in 4 of 5 dogs receiving aminophylline. The most consistent difference is that the 3 drugs caused a further fall of the systemic blood pressure, but the ethoxy derivative of methoxamine caused a rise (fig. 11). This last drug became ineffective in sustaining systemic blood pressure after repeated administration.

The most probable explanation for the fall in pulmonary arterial pressure following the injection of any of the 4 drugs is local pulmonary vasodilatation. This explanation is based on perfusion experiments of edematous lungs in a manner depicted in figure 7. Four dogs suffering from thermal edema were subjected to perfusion of the left lower lobe (fig. 12). Compound 45-50 caused a local vasodilatation to the same extent as an equal dose of aminophylline. On reaching the systemic circulation, aminophylline produced a fall in the aortic blood pressure but 45-50 had no such effect. The ability of edematous lungs to respond to pulmonary vasodilators also extends to include response to vasoconstrictors such as levarterenol and serotonin (fig. 12, A, C).

Failure to Reduce Congestion and Edema. In the absence of therapy, the effects of steam inhalation are an immediate increase in number of erythrocytes (tagged with P" \[\text{P}^{32}\] ) in the lung capillaries and a subsequent gradual accumulation of plasma protein (tagged with I" \[\text{I}^{131}\] ) in the lung tissue. The injections of pulmonary hypertensive drugs were initiated between the onset of capillary congestion and the onset of edema (shown by a rise in content of plasma protein in the lung tissue) in 5 dogs with the following results: There was no significant reduction in capillary congestion and the accumulation of protein proceeded in a manner similar to that seen in untreated dogs. The maximal rise in iodinated protein amounted to 16, 22, 27, 33 and 35 per cent for each of the 5 dogs, but the peak was reached at a later period than in the untreated dogs. The significance of this delayed rise is still uncertain and might mean that the process of edema formation...
actually had been delayed by the desirable pulmonary hypotensive action of the drugs. So far the radioactive methods have been used only as a qualitative indication of progress of edema, improvements in the method making it possible to assess the quantitative significance of the accumulation is desirable. Regardless of the final interpretation, the most significant observation was a prolongation of survival time.

**Prolonged Survival.** The comparative survival of the various groups of dogs is summarized in figure 13. Antihistaminic drugs did not significantly prolong survival. Improvement in oxygen uptake by positive pressure breathing combined with inhalation of alcohol vapor and oxygen prolonged survival to 2 hours. A similar prolongation resulted from repeated injections of compound 45-50. A final group of 5 dogs in which all procedures were utilized prolonged survival to 8 hours, but all of them still died of pulmonary edema and shock. Therapy simply postponed death rather than completely reversed the pathologic processes causing systemic hypotension and pulmonary edema.

**DISCUSSION**

The therapy of thermal edema has been approached in the same manner as any other form of pulmonary edema. Inhalation of oxygen and alcohol vapor and positive pressure breathing, as expected from reports by others (see references cited in recent review28), have proved useful in improving oxygen uptake by the edematous lungs. The results offer support for the use of pulmonary vasodilators in acute pulmonary edema. Compound 45-50 has some striking special features. This drug causes a complete reversal of the systemic shock and the pulmonary hypertension following lung burns. The pulmonary hypotensive action of this drug has been confirmed in the experiments, but the mechanism of pulmonary hypotension has been recently challenged by Gunning and Barer28 who believe that the reduction in pulmonary blood flow is the exclusive cause because they failed to observe a consistent vasodilator response in the perfused lungs. Our experiments reconfirmed the ability of this compound to dilate the perfused blood vessels of even the edematous lungs. In the intact animal, the fall in pulmonary arterial pressure is due to both a reduction in flow and to vasodilatation.29 Measurements of pulmonary vascular resistance in such dogs show an increase, but this does not necessarily mean that no active dilatation has occurred, as implied by others.28 A reduction in pulmonary blood flow is known to cause a passive increase in vascular resistance so that the observed increase by the drug is a combination of this passive increase minus an active decrease by the drug. The situation is different in the thermal edematous lungs because the constricted state of the lung vessels allows a more powerful active reduction in resistance.

The procedures reported for treating burns of the respiratory tract have succeeded in prolonging the period of survival. Although these studies were based on anesthetized dogs, trial in humans is indicated for 2 reasons. It is possible that injury in man may not be as severe as that induced in dogs by inhalation of steam for 30 sec. The unavoidable use of anesthesia in dogs may actually interfere with the normal processes of recovery from lung injury so that therapy might be more successful in the absence of general anesthesia. Confirmation in human patients would serve to establish the use of antihistaminic
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and pulmonary vasodilator drugs in burns of the respiratory tract.

SUMMARY

The development in anesthetized dogs of pulmonary edema initiated by either steam inhalation or intravenous injection of alloxan is characterized by the appearance of protein in the edema fluid, increase in amount of soluble protein in the lungs, increase in per cent and total moisture content of the lungs, and increase in total content of blood with a relative reduction in per cent hemoglobin. The oxygen uptake of slices of thermal edematous lungs does not differ from values of nonedematous lungs, but the oxygen uptake of alloxan edematous lungs is lower. None of these measurements can be used to judge the severity of pulmonary edema in the living animal.

The survival of anesthetized dogs subjected to steam inhalation can be prolonged from less than one hour, if untreated, to up to 8 hours by intravenous injections of diphenhydramine or tripelennamine, presumably by blocking the systemic hypotensive action of histamine liberated from the lungs; inhalation of 100 per cent oxygen combined with ethyl alcohol vapor and positive pressure breathing; and intravenous injection of compound 45-50 which reverses the systemic shock and reduces the pulmonary hypertension. The reduction in pulmonary arterial pressure is predominantly the outcome of dilatation of the vessels of the edematous lungs.

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