1975

Humoral factors in the pathogenesis of shock lung in dogs

Van Dang Chau
Yale University

HUMORAL FACTORS IN THE PATHOGENESIS OF SHOCK LUNG IN DOGS

CHAU VAN DANG

1975

YALE

MEDICAL LIBRARY

Permission for photocopying or microfilming of "Humoral Factors in the Pathogenesis of Shock Lung in Dogs"

(TITLE OF THESIS)

for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

HUZ DAVID VAN ZWAM

Signature of Author

March 31, 1975

Date

HUMORAL FACTORS IN THE PATHOGENESIS OF SHOCK LUNG IN DOGS.

presented by

CHAU VAN DANG

to the Faculty of the Yale University School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine.

January 1975.

ACKNOWLEDGEMENTS.

I would like to thank Dr. M.D. Kerstein, my thesis advisor, without whom this study could not have been done. His support, guidance and constructive criticisms are greatly appreciated.

I would like to thank Mr. Parker Bailey, Mr. Al Gauthier, Mrs. Joellyn Bradley, Mrs. Barbara Meek, Dr. Gueh-Djen E. Hsiung, Mrs. Roslyn Straus and the technicians in the Arterial Blood Gas Laboratory at the West Haven V.A. Hospital for their invaluable support and expert technical assistance.

DEDICATIONS.

This thesis is dedicated to my parents, Dr. and Mrs. Dang Van Chieu, and to my wife, MyDung, for their unfailing love and support.

CONTENTS:

The syndrome of respiratory insufficiency occurring a few days after apparent recovery from an acute insult to the human organism, be it non-thoracic trauma, hemorrhagic hypotension, septic shock, or other clinical insults, has received increasing interest in recent years, and has prompted many clinical and experimental studies. The results of those studies are often contradictory with one another and the definition of the syndrome itself often has not been agreed upon. Lewin (57) has extensively reviewed the litterature on the subject.

It is the purpose of this paper to briefly review the history of the syndrome in man, the various pulmonary findings in experimental models of hemorrhagic hypotension, and to present the data and the discussion of an attempt to demonstrate a possible humoral pathogenetic factor involved in the lung lesions found in dogs subjected to hypovolemic hypotension.

*****

HISTORICAL ASPECTS.

Although the syndrome has attracted wide interest only recently, it has been intermittently described since the time of Laennec's writings on massive pulmonary collapse (55). Moutier (73) in 1918

reported on pulmonary edema and alveolar hemorrhage found in soldiers who had suffered bullet wounds of the head. During the Second World War, pulmonary lesions associated with burns were described by Mallory (60). Burford in 1945 observed patients with pulmonary failure following chest trauma and coined the phrase "traumatic wet lung" to designate that entity (13). In 1946, Wilson referred to blast injuries as one of the situations where lung lesions were found (109), and the following year, Jenkins coined the term "congestive atelectasis" to describe a pulmonary lesion found following excessive intravenous infusion of fluids (49).

The war in Indochina in the 1960's brought the syndrome into sharper focus. With the availability of markedly improved evacuation and transport systems and of intensive resuscitative care, soldiers who were wounded and in shock could be managed over the acute hypotensive and traumatic period. After apparent recovery from the acute insult, however, a small number of the patients were found a few days later to develop progressive pulmonary insufficiency with bilateral, diffuse, and fluffy infiltrates appearing on their chest roentgenograms. More often than not, they did not survive that complication (39,66).

Mills estimated that the incidence of isolated pulmonary failure in Vietnam was approximately one per cent of the severely wounded (66).

Similar cases of pulmonary insufficiency have also been studied and reported in civilian practice, most of them having developed shock following operative or traumatic blood loss, or sepsis (4,43,58, 67).

Moore (67) has succintly described four phases comprising the pulmonary insufficiency syndrome which sometimes occurs following trauma.

Phase I is that which immediately follows the acute injury, be it hemorrhage, surgery, or sepsis. Shock occurs, and resuscitation usually involves multiple blood transfusions and intravenous administrati of crystalloid solutions and antibiotics, among other things. The patient often is found to have a mixed respiratory and metabolic alkalosis. This is due to spontaneous hyperventilation, metabolism of citrate found in infused blood or blood products, infusion of bicarbonate or lactate, and withdrawal of gastric juice.

Most patients recover completely following resuscitation and do not go into Phase II. However, in a few, cardiovascular instability persists,

necessitating continued blood and fluid infusion. These become increasingly refractory to therapy and the patient enters Phase II a short period thereafter, usually a few days after the acute insult.

Phase II is characterized by apparent stabilization of the circulatory system, but signs of beginning respiratory difficulty are present: continued hyperventilation and a falling arterial pO_2 which does not respond totally to inspiration of 100% oxygen. Clinically, the patient still appears to be fine.

Increased tidal volume with hypocarbia and hypoxemia ushers in Phase III. Respiratory assistance is necessary, but the hypoxemia becomes less and less responsive to increased concentrations of inspired oxygen. A bilateral infiltrate is often seen at this stage in the chest roentgenogram. There is increased tracheo-bronchial secretion, and pulmonary infection is a frequent complication.

The final phase begins with an ominously rising arterial pCO_2. There is increased dead space ventilation, decreased spontaneous respiratory drive with increasing hypoxemia. A mixed respiratory and metabolic acidosis is observed. Finally, bradycardia, then asystole, supervenes.

*****

It is obvious that a variety of different injuries can result in a clinical picture similar to that described by Moore (67). However, pure hemorrhagic shock in itself without significant concomitant trauma is yet to be reported to cause the syndrome. Usually, as pointed out by Blaisdell (9), hypovolemic shock plus another factor is commonly observed in clinical situations. That factor can be endotoxinemia, ischemic damage to a major muscle mass, exposure of blood to a foreign surface as seen in cardio-pulmonary bypass procedures, or transfusion reaction. In fact, Ratliff (78), during an eight months' experience in Vietnam, observed twenty patients who died of postoperative pulmonary insufficiency. Over half of the cases occurred more than a week after the injuries were sustained, and more than half died of rapidly progressing pneumonia and sepsis. The remainder succombed after aspiration, fat embolism, blast injury or massive crystalloid overload. He observed no cases of "shock lung" as such. Shires (84), studying forty-nine civilian patients who had post-traumatic pulmonary difficulties, concluded that "shock lung" correlated with sepsis rather than with shock itself.

It appears then that the term "shock lung" tends to be used rather loosely and mainly as a matter of convenience by physicians to indicate pulmonary insufficiency occurring after any type of disturbance

to the homeostasis of the human organism. It is well to remember that etiologies are numerous (84), as listed and discussed by Shires: among them are ischemic pulmonary injury, pulmonary infection, sepsis, aspiration fat embolism, microembolism associated with soft tissue trauma, multiple transfusions, or intravascular coagulation, fluid overload with crystalloid or colloid, perfusion with a heart-lung machine, oxygen toxicity, microatelectasis, direct pulmonary injury or massive cerebral injury. The pathogenetic mechanisms may not be identical in all cases.

The etiology of "shock lung" may be diverse, but the pathologic findings have been fairly constant and uniform.

Hardaway (43) described pulmonary congestion, hemorrhage, atelectasis, edema, and capillary thrombi in patients who developed respiratory insufficiency following severe shock. Nash (76) studied oxygen toxicity and observed hyaline membrane formation and alveolar cell hyperplasia in the lungs of patients who died following prolonged oxygen therapy and artificial ventilation. Martin (61) again described hemorrhage and congestion in lungs subsequent to shock or trauma. This was confirmed by Lewin (58),

and reviewed by Moore (67, p.112) : the principal feature of "shock lung" is interstitial edema; there also are fibroblastic proliferation, hyaline and fibrinous deposits on alveolar walls and in alveoli, focal alveolar and interstitial hemorrhage with hyperplasia and hypertrophy of alveolar lining cells. Baird (4) also described septal thickening as being the main characteristic feature.

Studying lung biopsies taken from patients, Blaisdell (7) reported on the sequence of the changes observed.

During the first eighteen hours following the clinical insult, there are a few scattered areas of congestion and atelectasis in the dependent portions of the middle and upper lobes. Pulmonary veins and capillaries are engorged, and there is beginning interstitial edema. From eighteen to seventy-two hours after the shock period, more severe hemorrhage is observed perivascularly and intra-alveolarly. After seventy-two hours, hyaline membrane formation and bronchopneumonia supervene.

It is evident that complete hemodynamic studies are difficult to perform during the early stages of shock in man, as patients are usually seen only after a certain unavoidable delay. This is particularly true for the hemodynamic changes

in the pulmonary circulation. However, as reviewed by Shires (84) and Shoemaker (85), it is well established that following hemorrhage, there is increased total peripheral resistance, acceleration of the heart rate, and venoconstriction with subsequent increased venous return. The obvious teleological purpose of those changes is to maintain blood pressure and vital perfusion of the heart and brain, this at the expense of such organs as skin, intestine and kidneys. As the deficit in intravascular volume increases, progressive hypotension will ensue, the compensatory mechanisms being overcome. Ratliff (78) did report that the pulmonary venous resistance was increased while the pulmonary arterial pressure was maintained during shock. Sykes (97), on the other hand, mentioned that in shock not due to cardiac failure (as in peripheral circulatory failure), the pulmonary arterial pressure, along with the pulmonary capillary, venous, and left atrial pressures, were decreased.

More studies are needed regarding the pulmonary hemodynamic changes occurring after various types of shock in man.

*****

While data are lacking in humans, they abound

for experimental animals.

For the purpose of this paper, the phrase "shock lung" will specifically designate the pathological pulmonary changes seen in the dog or other animals subjected to experimental hemorrhagic shock. It is obvious that the findings in experimental animals cannot all be applied to human cases without critical evaluation, but animal models do afford investigators liberty with manipulations and experimentations that could not be obtained in humans.

Investigators have studied pulmonary lesions in animals subjected to various procedures since the beginning of this century.

In 1924, Hanzlik (42) produced pulmonary lesions in guinea pigs subjected to anaphylactoid shock. He observed capillary congestion, infiltration with polymorphonuclear leukocytes, intra-alveolar hemorrhage and atelectasis. In 1934, Hurtado (48) described similar lung lesions produced by hypoxemia in guinea pigs. von Haam (103) in 1939 produced lung lesions with artificial fever. Two years later, Davis (27) reported similar lesions following dehydration shock. Fegler (31) in 1946 subjected rabbits to low barometric pressure and observed congestive atelectasis in their lungs. The same year, Cleghorn (18) traumatized muscle and produced

pulmonary lesions. The first report of lung lesions produced by blood loss in dogs was published the following year by Eaton (29). In 1949, Campbell (14) produced congestion and hemorrhage in the lungs of dogs subjected to increased intracranial pressure. Since that time numerous other investigators have attacked the problem of shock lung, each with a specific favorite hypothesis as to its pathogenetic mechanism in mind. It is useful to reiterate here that the pulmonary lesions are certainly not specific for any conditions, and that they most likely represent the limited ways in which the lung parenchyma reacts to any injury or to any disturbance of its integrity.

Among the various theories which attempt to explain the lung lesions, several have been pursued intensively.

Microembolism is considered by some to be of major importance. These microemboli could come from multiple transfusions of whole blood. Support for this theory came from studies of changes in screen filtration pressure by McNamara (64). Blaisdell (8) demonstrated that the venous return following declampin a cross-clamped aorta in dogs contained embolic material, and that platelet aggregates could be observed in pulmonary capillaries. The pulmonary

pathologic changes under those experimental conditions seemed to be favorably influenced by controlled ventilation and heparinization (90).

In the same context, diffuse intravascular coagulation is believed by others to be the underlying pathogenetic factor (Hardaway (43)).

Fat embolization certainly can play a significant role in certain situations where extensive soft tissue trauma and/or multiple long bone fractures occur. In human cases, it is obvious that aspiration (Hedden (46)), oxygen toxicity (Nash (76)), and superimposed pulmonary infection (Collings (20)) can complicate the clinical picture and add to the pulmonary insufficiency. For the most part, however, animal experimental models have been focused on either a neurogenic or a humoral pathogenesis of the shock lung syndrome.

In 1966, Sealy (83), using a modified Wiggers' shock model (107), showed that 15 out of 24 dogs subjected to shock had lung involvement. Various-sized areas of hemorrhage were seen macroscopically, and there were interstitial edema, perivascular cuffing by leukocytes, and hemorrhagic atelectasis on histological examination. The amazing feature was that these changes occurred acutely during a two-hour period of shock and were not accompanied by major

alterations of pulmonary function. This certainly was at variance with the clinical syndrome seen in patients where the pulmonary lesions developed only after a certain lag period and where changes in pulmonary function were prominent.

The findings in dogs were subsequently confirmed by Henry (47), Cook (21), Sugg (94), Bryant (10), and Barkett (5), although the percentage of shocked dogs developing lung lesions varied from 32% (104) to 90% (82).

Meyers (65), however, questioned the significance of those pulmonary lesions. He observed no changes in the lungs of 30 dogs subjected to hemorrhagic shock when he fixed the lungs in an expanded state using either intrabronchial or intra-arterial perfusion of the lungs with the fixing solution.

Pulmonary lesions consisting of interstitial thickening, interstitial or alveolar hemorrhage, atelectasis and congestion were also observed in cats subjected to hemorrhagic shock (Wilson (111)) and baboons in shock (Moss (68)). Here again, Buckberg (11) could not confirm the findings in shocked baboons and only observed occasional minimal segmental atelectasis, which he ascribed to incomplete

aeration of the lungs, and occasional subpleural hemorrhage over the upper lobes, possibly resulting from the thoracotomy and manipulation of the lungs.

The canine shock preparation continues to be popular among investigators, however.

Barkett (5) studied the role of surfactant in shock lung, and concluded that one would have to postulate a direct inhibitor of surfactant material if surfactant were to be significant in the pathogenesis of shock lung. The turnover rate of surfactant is from 18 to 24 hours, and there was no decrease of surfactant material within 24 hours of shock, while the lung lesions appeared during the two-hour shock period.

In 1967, Willwerth and Crawford (108) reported that the lung lesions in shocked dogs could be prevented by exclusion of the lung from the circulation during the period of shock. The excluded lung continued to be free of lesions following re-establishment of the circulation at the end of the shock period. The authors concluded that the lung lesions in the contra-lateral lung were caused by "functional demand" in the face of low blood flow. The possibility remained, however, that circulating factors were responsible for the lung lesions, and

that the excluded lung was not exposed to those circulating factors and was thus protected. For this to be valid, one would have to postulate that the circulating factors were inactivated very quickly or that they were produced locally in the lung during shock in order to explain the absence of lesions even following re-establishment of the circulation. Or else, continued exposure of the lung to those factors for an unknown minimal amount of time would have to be necessary to cause the pathology of shock lung.

Interest increased when in 1968 Sugg (92) reported that the lesions could be prevented by prior total denervation of the lung achieved by completely removing and re-implanting it in the dog. He concluded that neurally-mediated factors played an important role in causing shock lung. He expanded on the issue in 1969 (93).

In the meantime, Moss (69) showed that there was an increase in interstitial sodium ions as seen under the electron microscope in lungs of baboons subjected to hemorrhagic shock. He postulated that an increase in affinity of collagen for sodium might be the initiating factor for interstitial edema. If this were true in dogs also, the sodium uptake by interstitial collagen fibers might well prove to be a sensitive and early index of shock lung changes.

Lewin (57), using a slightly different canine shock model (the dogs were at 60 mmHg systolic blood pressure for 15 minutes, then at 40mmHg for 90 minutes, instead of the usual two hours of 40 mmHg systolic blood pressure) and a modification of Moss'method of fixing and staining lung tissue, suggested that there was no consistent increase in interstitial sodium in the lungs of shocked dogs as compared to normal controls.

With the above considerations in mind, a standard canine shock preparation was used in this series of experiments, and an attempt was made to determine whether:

- interstitial sodium was increased in shocked dogs, and whether

- plasma obtained from dogs in shock could cause the pathology of shock lung when infused into normal dogs.

MATERIALS AND METHODS.

Fifteen mongrel dogs were used.

The animals were fasted for approximately sixteen hours and were then anesthetized with intra-venous Sodium Pentobarbital (Nembutal), 25 mg/kg body weight, followed by supplementary Nembutal as needed. A cuffed endotracheal tube was inserted into the trachea, and the animals were allowed to breathe room air spontaneously.

Both femoral arteries and veins were exposed. A siliconized P-220 catheter was inserted into one femoral artery and advanced until the tip was positioned in the thoracic aorta. Another catheter was inserted into a femoral vein and advanced until the tip was in the intrathoracic portion of the inferior vena cava. The catheters were connected to a Sanborn apparatus for arterial blood pressure and central venous pressure monitoring. Arterial blood was withdrawn from the arterial catheter for determination of pH, pO_2, and pCO_2.

A large bore catheter was inserted into the other femoral artery and was used to rapidly bleed the animal when indicated. Another large bore catheter was inserted into the second femoral vein and was used to either collect blood at the end of the shock period, or to infuse plasma, as the experiments indicated.

At the end of each experiment, a rapid right

thoracotomy was performed, the broncho-vascular bundle to each lobe was cross-clamped, and the lobes were rapidly removed.

The middle lobe was intrabronchially and intra-arterially perfused with the perfusion solution described by Moss (69): a catheter was introduced into the middle lobe artery and was connected to a reservoir hanging 50 cm above the lung specimen. The perfusion solution was allowed to flow into the lung by gravity, with occasional slight flushing when the system was clogged. A Pasteur pipette was used to slowly instill the perfusion solution into the middle lobe bronchus. The specimen was so perfused for 30 minutes. Four small specimens were cut out from grossly normal areas of the dorsal aspect of the lobe. They were immersed in the same perfusion solution for another two hours at 4 degrees C. The specimens were then dehydrated in increasingly concentrated solutions of alcohol (50% alcohol for 5 minutes, 70% alcohol for 5 minutes, 80% alcohol for 5 minutes) and were kept in a 95% alcohol solution at 4 degrees C until they were embedded in Epon, thin-sectioned and stained with Uranyl acetate and Lead citrate for examination under the electron microscope.

Lung specimens were also obtained from the inferior area of the upper lobe and the superior segment of the lower lobe, fixed in 10% formalin

solution, sectioned and stained with hematoxylin and eosin for examination under the light microscope. These specimens were also taken from grossly normal areas.

Preparation of the Perfusion Solution:

For each dog, 200 ml of fresh solution were used.

3.2 grams of Potassium Pyroantimonate (Fisher Scientific Lab.) were dissolved in 120 ml of distilled water with the aid of heat. The solution was allowed to cool.

Two grams of Osmium Tetroxide (Fisher Scientific Lab.) were dissolved in 50 ml of distilled water and 4 ml of 0.1N HCl. This was added to the Potassium Pyroantimonate solution.

The pH was adjusted to a value of 7.6 with the addition of 0.01N Acetic Acid, and the volume was made up to 200 ml by addition of distilled water to make up a final solution of 1.6% Potassium Pyroantimonate and 1.0% Osmium Tetroxide.

Groups of Dogs:

The dogs were divided into four groups. See Table 1 on page 75 for a summary.

1. Group A: 2 dogs. Normal Controls.

The dogs were prepared as indicated above. Baseline data (blood pressure, central venous pressure, respiratory rate, arterial pH, pO_2 and pCO_2) were obtained. An hour later, a right thoracotomy was performed without any other procedures.

2. Group B: 2 dogs. Recipients of "Normal Plasma".

The dogs were prepared as above. Baseline data were obtained, then "normal plasma" obtained from non-shocked dogs was infused through the femoral vein. Ten minutes after completion of the infusion, data were again obtained. Fifty minutes later, a right thoracotomy was performed and the right lung taken out.

3. Group C: 6 dogs. Shocked Dogs.

The dogs were prepared as above, and baseline data were obtained. The dogs were then rapidly bled from the femoral artery to bring the arterial systolic pressure to 40 mmHg within 15 minutes. The blood collected at this time was used to obtain the "normal plasma" which was infused into Group B dogs. The Group C dogs were kept at 40 mmHg for two hours, then data were obtained. As much blood as possible was subsequently obtained from the femoral artery and the femoral vein, the plasma separated to constitute "arterial shock plasma" and "venous shock plasma",

respectively. These plasmas were infused into Group D dogs. After blood was obtained from the Group C dogs, a right thoracotomy was performed and the right lung taken out.

4. Group D: 5 dogs. Recipients of "Shock Plasma".

The dogs were prepared as above. and baseline data obtained. "Shock plasma" obtained from shocked dogs was infused through the femoral vein and data were again obtained ten minutes after completion of the infusion. Fifty minutes later, the dogs'lungs were removed as described above.

RESULTS.

The data of each experiment can be found in the Appendix, pp.60 to 74.

Light Microscopy Results.

These are summarized in Table 2 on page 76.

The changes in the lungs were graded from 1+ to 3+ according to both the severity of the pathologic findings themselves (i.e., capillary congestion, polymorphonuclear leukocyte infiltration, interstitial thickening, interstitial or intra-alveolar hemorrhage, and atelectasis) and the extent and diffuseness of the changes as determined by looking at six to nine lung sections for each dog:

1+ : slight changes. See Figure 1 on page 79.

2+ : moderate changes. See Figure 3 on page 80.

3+ : severe changes. See Figure 6 on page 81.

No fibrinous or hyaline deposits were observed intra-alveolarly in any dogs, and scattered intra-alveolar hemorrhage was seen only in the Group C shocked dogs.

Five of the six Group C shocked dogs showed extensive changes consistent with the reported pathological findings of shock lung, as did three of the five Group D dogs that had received shock plasma. However, one of the two Group B dogs infused with normal control plasma also demonstrated 3+

histological changes.

The two normal control dogs (Group A) did not show completely "normal" lungs either. Dog #S-13066 (Experiment #10) had patchy, mild capillary congestion, slight infiltration with polymorphonuclear leukocytes, and even a mild degree of atelectasis and interstitial thickening (1+ changes). The other dog (Experiment #15) had more extensive and severe involvement and was graded as having 2+ changes.

Electron Microscopy Results.

Two major criteria were used to determine the ultrastructural changes in the lungs.

The first was disruption of the interstitium, as evidenced by interstitial clear spaces, increased thickness of the interstitium, and disruption of the collagen fibers.

The other criterion examined was the distribution and extent of electron-dense deposits which were purported to represent sodium pyroantimonate complexes. Three kinds of electron-dense materials were observed. The first kind was small dots, distributed diffusely over the interstitium and the intracellular space of most lung sections, more so over the collagen fibers than elsewhere. They were most clearly seen at a magnification of 20,000-fold or more, and are illustrated by Figures 11 and 14 on pages 85 and 88.

The second type was larger aggregates of electron-dense material, found less often that the first kind but again present in comparable amount in all dogs. They tended to be mostly in the capillary and alveolar spaces, near the surface of cells. They are represented in Figures 9 and 14 on pages 83 and 88.

The third kind of deposit of note was elongated, less electron-dense material looking like crystals of some kind, which were found in some interstitial clear spaces of a few dogs belonging to all four groups. They can be seen in Figures 16 and 2 pages 90,98.The nature of these crystal-like deposits is unknown, but the first two kinds probably represented sodium.

Both the interstitial disruption and the extent of interstitial sodium deposition were graded from 1+ to 3+ as with the light microscopic changes. The results are summarized in Tables 3 and 4 on pages 77 and 78 , and examples of the electron-microscopic appearance of lungs can be seen in Figures 9 to 27 on pages 83 to 101.

There were only occasional platelets seen in the capillary spaces. The pinocytic vesicles of endothelial cells did not seem to be increased in the Group C shocked dogs, contrary to what was observed by Barkett (5). There was blunting of the type II pneumocyte epithelial microvilli in the Group C

shocked dogs, as can be seen in Figure 18 on page 92. Otherwise, there was no gross difference in type I or type II alveolar cells between normal or shocked dogs. The intracytoplasmic granules of type II pneumocytes were found to be empty in most dogs, normal as well as shocked.

DISCUSSION.

The question of neurogenic versus humoral pathogenetic mechanisms operative in shock lung has always fascinated investigators.

As early as in 1949, Campbell (14), working on pulmonary edema in dogs subjected to increased intracranial pressure, postulated that the increase in intracranial pressure caused a vagal discharge, thus accounting for the observed bradycardia and decreased cardiac output. Pulmonary venous pressure would subsequently rise and cause fluid to extravasate from the pulmonary circulation.

In 1956, Maire and Patton (59) produced pulmonary edema in rats by placing lesions in the animals'pre-optic nucleus. The pulmonary lesions were circumvented by adding lesions in the caudal part of the hypothalamus or by cervical cord transection. They hypothesized that the caudal part of the hypothalamus had an activity to cause pulmonary edema by way of the cervical cord, and that this was antagonized by the pre-optic nucleus. They did not measure pulmonary hemodynamic changes, however.

As mentioned above, Willwerth (108) in 1967 showed that total denervation of the lung prevented lesions from developing during shock in dogs. Barkett (6) could not reproduce this in 1971, but that group

simply stripped the pulmonary hilum instead of completely transecting and re-anastomosing the pulmonary vessels. A possibly incomplete denervation thus could not be excluded.

In 1970, Simeone (87) postulated that the central nervous system was the site of hypoxic metabolic derangement during shock. Disturbances in hypothalamic oxidative metabolism in particular would trigger pulmonary complications through an autonomically mediated increase in venular resistance and capillary hypertension in the lung.

In 1971, Moss (70), using carotid artery perfusion with mixed external jugular and superior vena cava blood, succeeded in producing isolated cerebral arterial hypoxemia in the dog. Hypocarbia secondary to hyperventilation was prevented by adding CO_2 to the inspired air. Eighteen out of eighteen dogs subjected to that type of cerebral hypoxia showed pulmonary lesions. None of the eight controls developed lesions. Moss (71) and his group further elaborated on the possible cerebral etiology of the shock lung syndrome in 1972. In 1973, Staunton (91) from the same laboratory reported similar lung lesions in calves, pigs, monkeys and rabbits subjected to isolated cerebral hypoxia. The lung lesions were

prevented by prior pulmonary denervation in all the above species.

Thus, there seems to be good evidence that neurogenic factors are at least necessary for the development of lung lesions during shock in the dog. These neural factors could account for the increased pulmonary vascular resistance observed (Cook (21)). Humoral factors, however, can also play a role in producing increased pulmonary vascular resistance.

The question now arises as to which of three alternatives actually causes the increase in pulmonary vascular resistance: arteriolar constriction, venoconstriction, or possibly a combination of the two.

Increased pulmonary vascular resistance has also been shown by Kho (51) and Desai (28) to occur in shocked dogs. Desai (28) demonstrated a slight fall in mean pulmonary arterial pressure during the shock period, but the pulmonary venous pressure was not measured. The increased pulmonary vascular resistance persisted during resuscitation with transfusion, and caused an increase in mean pulmonary arterial pressure during and after resuscitation. Subsequent work by other investigators provided evidence for both venoconstriction and arteriolar constriction in shocked dogs.

Sugg (92) found that the pressure in the small pulmonary veins of dogs fell less than the left atrial pressure during shock, and that the pulmonary arterial pressure was slightly more than the pulmonary venous pressure throughout the shock period. Complete denervation of the lung seemed to decrease the pressure in the ipsilateral small pulmonary vein during shock to a greater extent than that in the contralateral innervated lung. Sugg thus postulated that during shock, constriction of the post-capillary bed at the small pulmonary vein level, possibly caused by neurogenic factors, induced increased capillary hydrostatic pressure and extravasation of plasma and blood. Keller (50) similarly postulated pulmonary venous constriction to be the primary event leading to the pathological changes of shock lung. Support for this theory of venoconstriction came from direct in vivo observation of venoconstriction in the microcirculation of the lung during shock (Kusajima (54)).

Veith (101,102) and Wilson (110), on the other hand, believed that pulmonary arteriolar vasoconstriction was the primary event. Working with hemorrhagic shock, homologous blood transfusions and pump-oxygenator procedures, Veith (101) showed that all the above situations led to lung lesions typical of "shock lung" in dogs. He observed increased

pulmonary vascular resistance without capillary engorgement, and he noticed that the earliest lesion seen was peri-arterial hemorrhage. Direct *in vivo* observations yielded the exactly opposite results to those reported by Kusajima (54). There was arteriolar constriction and no venoconstriction. Veith thus postulated that a variety of conditions, possibly including humoral agents circulating in blood, could lead to active arteriolar constriction, thus causing peri-arterial hemorrhage. Secondary vasodilatation would occur, leading to capillary engorgement, diffuse pulmonary hemorrhage and edema. These changes were also observed by Veith in isolated perfused lungs, thus excluding total dependence on central neurogenic factors or cerebral hypoxia as a necessary factor in the pathogenesis of shock lung.

The question of venoconstriction *versus* arteriolar constriction thus is still unresolved, and the additional concept that humoral agents and not neurogenic factors are primarily responsible for the lung lesions provides ground for more controversy and discussion.

Relating to the blood vessel constriction, Gilbert (37), in 1958, working with isolated perfused dog lungs, showed that histamine usually increased venous resistance. Serotonin, on the other hand,

usually increased arterial resistance more than venous resistance. The pressure in small pulmonary veins consistently rose after administration of epinephrine and norepinephrine. In 1965, Sukhnandan (95) also showed that histamine, serotonin, epinephrine and endotoxin proved to be vasoconstrictor, both at the arteriolar and the small pulmonary venous level, in the isolated perfused dog lung. Bradykinin was not a vasoconstrictor. Daicoff (24) in 1968 injected serotonin intravenously into dogs and produced pulmonary arterial hypertension without significant changes in left atrial or pulmonary venous pressures measured just outside the pericardium. Aviado (2) reviewed the effects of various vasoactive agents on the pulmonary microcirculation. He commented that the agent or agents responsible for the pathogenesis of the pulmonary lesions would have to be able to increase pulmonary airway resistance, increase pulmonary vascular resistance and decrease pulmonary compliance. ATP is unlikely since it is rapidly hydrolyzed to ADP in the circulation. ADP does not constrict pulmonary blood vessels, although it does aggregate platelets and thus may cause obstruction to blood flow and release of serotonin from platelets. Serotonin and catecholamines both cause platelet

aggregation and constrict blood vessels. Histamine increases venous resistance more than arterial resistance, but has no effect on platelet aggregation.

Recently, more attention has been paid to the metabolic function of the lungs, and this was succintly reviewed by Fishman and Pietra (33). Of particular relevance are the synthesis by the lungs of various vasoactive agents such as prostaglandins, the capability of the lungs to discharge similar substances (histamine, kallikreins,...) into the circulation, and certainly the normal role of the lungs in metabolizing and inactivating such humoral agents as serotonin, bradykinin, adenine nucleotides, norepinephrine and prostaglandins E and F.

It is tempting to speculate that during periods of shock or other acute insults to the lung, the endothelial cells may be so adversely affected as not to be able to metabolize either local or systemic hormones, allowing them to accumulate and affect the permeability and/or the integrity of the endothelial barrier. This would facilitate the passage of fluid and other substances into the interstitium. Obviously, more will have to be known before one can prove or disprove that concept.

Thus, humoral substances may well mediate the changes in the lungs seen in hemorrhagic shock,

either by producing vessel constriction, as shown above, or maybe by altering the integrity of the endothelium, or possibly by a combination of the two. Substances being released into the circulation during shock have attracted the attention of many investigators, and the possible role of these substances in maintaining or worsening the shock state has been looked into with increasing interest.

As early as in 1944, Westerfeld (106) noted that human urine kallikrein injected into dogs caused hypotension and death from respiratory failure. Edema of the lungs was observed in one dog. However, in 1959, Webster (105) failed to reproduce the results: infusion of either pancreatic or urinary kallikrein did not kill the dogs even when massive amounts of kallikrein were given. Measurements of kallidinogen content of plasma from dogs killed with either endotoxin or by irreversible shock indicated that small amounts of kallikrein might have been released, however. As noted by Westerfeld (106), kallikrein is readily inactivated in serum, so one would not expect the plasma used in the Group D dogs described in this paper to contain significant amount of kallikrein.

In the 1950's, Ravin (80) isolated a toxic factor from the plasma of dogs subjected to hemorrhagic

shock which could cause death when infused into reversibly shocked rabbits. That factor, however, had many of the characteristics of bacterial lipopolysaccharide. One must always be cautious in interpreting the results of experiments where endotoxin or sepsis may be involved. Septic shock is quite different from hemorrhagic shock, although there always remains the possibility that endotoxin can be absorbed through the damaged intestinal mucosa during hemorrhagic shock. Schweinburg (81), from the same laboratory, showed that 96% of shocked dogs reinfused with their own blood survived the experiment, whereas only 31% of shocked dogs reinfused with shock plasma survived and only 20% of shocked dogs reinfused with their own red cells and shock plasma survived. Again, the toxic factor was thought to be a bacterial toxin, since the blood and plasma used were sterile and pre-treatment of the shocked dogs from which shock plasma was obtained with non-absorbable antibiotics increased the survival rate of recipient dogs.

Swank (96), in 1964, using ^{14}C-labeled 5-Hydroxytryptamine, observed increases of up to 600% in the circulating radioactivity during hypotension. The radioactivity increased earlier and was greatest in the portal venous blood. There was concomitant

increased platelet adhesiveness as shown by glass wool filtration experiments.

In 1965, Fukuda (34) reported the isolation of an endogenous shock-inducing factor from the plasma of dogs in hemorrhagic shock. He believed the factor was different from endotoxin because it produced no leukopenia nor increased glucose tolerance.

Bradykinin was shown to be released in significant amounts during shock in humans (Attar (1)) and was believed to contribute to the hypotensive state through vasodilatation. Olcott (77), on the other hand, did not detect measurable elevation of plasma bradykinin in 5 patients with diffuse intravascular coagulation following major trauma who demonstrated microthrombi and changes indicative of increased capillary permeability in the lungs. He pointed out that the presence of bradykinin locally in the lungs could not be ruled out.

Of possible relevance was the characterization of a vascular permeability-enhancing factor isolated from human platelets by Nachman (75). This factor, besides increasing vascular permeability in rabbit skin, could also release histamine from mast cells. It is well known that mast cells are present in the lungs in appreciable quantity.

Chryssanthou (17) found a polypeptide in the lungs and various other organs of mouse, man, dog and other species that increased responsiveness of smooth muscle organs (including blood vessels) to vasoactive substances, and which also could increase vascular permeability. Rabbits subjected to hemorrhagic shock showed a four-fold increase in the plasma level of this polypeptide.

Substances released into the superior mesenteric vein following occlusion of the superior mesenteric artery caused congestion, edema and capillary changes in the lungs when they were infused into the pulmonary artery (Hashimoto (45)). The role of endotoxin in this setting may be significant.

Lefer (56) isolated a myocardial depressant factor (MDF) from the portal venous blood of cats subjected to shock. He believed this polypeptide to originate from the pancreas. Pre-treatment with Trasylol, a proteinase inhibitor, was found to decrease the level of MDF. Trasylol was also found to increase the survival rate of rats shocked by trauma, mice shocked by burns, and dogs subjected to anaphylactic shock (Back (3)). Glenn et al. (38) used Aprotinin, another proteinase inhibitor, and found that cats subjected to hemorrhagic shock and treated with this

agent did not exhibit a significant plasma accumulation of MDF. Thus, it is believed that kallikrein and other proteases from pancreatic secretions could be released in significant amount during shock and would break down circulating polypeptides into smaller peptides, some of which might possess biologic activity and influence other organs. In support of this theory, Spath (89) found that severe prolonged pancreatic hemoperfusion contributed significantly to lysosomal disruption, as evidenced by elevations of plasma cathepsin D activity and plasma beta-glucuronidase activity, and concomitant production of MDF. Normal perfusion of the pancreas while the remainder of the organism was in shock prevented approximately half of the increase in lysosomal enzymes and markedly reduced the level of plasma MDF. The role of MDF and similar polypeptides in the pathogenesis of shock lung is not known.

Other investigators, among whom Soma (88), thought that hemorrhagic enteritis secondary to shock in dogs might have a pathogenetic role in producing pulmonary lesions through the absorption or release of vasoactive substances from the gut. The gut would be damaged by pancreatic enzymes and vasoactive materials would form and enter the circulation following re-establishment of blood flow to the gut. However,

Henry (47) and McKay (63) found pulmonary lesions in many shocked dogs which did not have hemorrhagic enteritis. Hemorrhagic enteritis conceivably could contribute to the pulmonary pathology in some cases.

In summary, the prospect that vasoactive substances are involved in the pathogenesis of shock lung is very exciting, but it has never been unequivocally proved. Attempts at demonstrating those substances through cross-perfusion experiments by Green (40), using ischemic compression shock in dogs, and by Clermont (19), using hemorrhagic shock in dogs, have been unsuccessful.

In the infusion experiments described in this paper, plasma was used instead of whole blood (except in Experiment #4) to avoid the homologous blood syndrome described by Veith (101,102). The plasma was kept overnight at 4 degrees C before infusion into Group B and D dogs the following day, and it is likely that many substances were degraded or inactivated and other materials were liberated in the process. The plasmas were not assayed for the various vasoactive materials.

The amount of plasma to be infused into Group D dogs (recipients of shock plasma) was not much of a problem because relatively little blood could be obtained from the Group C shocked dogs, this in

spite of choosing bigger and heavier dogs to be the donors of plasma. From 4.4 ml/kg body weight to 9.75 ml/kg BW of shock venous plasma were infused into Group D dogs, while the control Group B dogs received from 6.55 ml/kg BW to 6.77 ml/kg BW of normal plasma.

Shock was induced in Group C dogs by acutely removing from 38 ml/kg BW to 71.5 ml/kg BW of arterial blood (the mean was 54.7 ml/kg BW and the average was 50.7 ml/kg BW). This was slightly more than the average amount reported by Wiggers (107), i.e., 40-45 ml/kg BW of whole blood, that had to be removed in order to bring the systolic arterial pressure down to 40 mmHg in dogs. Two of the dogs died before the end of the two-hour shock period, and complete data could be obtained in only three out of the six dogs. These three showed metabolic acidosis compatible with a severe degree of shock.

Discussion of Light Microscopy Results.

See Table 2 on page 76 for a summary of the results.

To avoid chronic lung changes which are apt to occur in the apices and the bases secondary to previous pneumonias, lung specimens used in these experiments were taken from the inferior aspect of the upper lobe and the superior aspect of the lower lobe.

Sugg reported that the light microscopic findings were not influenced by re-infusion or non-reinfusion of shed blood (92), by mechanical ventilation, heparinization or position of the animal during the shock period (94). The protocol employed here used no heparin and no mechanical ventilation. Shed blood was not re-infused and the dogs were either supine or lying on their left side during the experiments.

As Meyers (65) pointed out, the way the lung was fixed and manipulated might have a great and significant influence on the histological appearance. In this series of experiments, the lungs were not fixed in an inflated state, and this probably resulted in one of the two Group A normal control dogs having 2+ changes. However, this dog might not have been

entirely normal at the start of the experiment. Obviously, more normal control lungs need to be looked at.

Both of the Group B dogs (recipients of normal plasma) showed changes similar to those observed in Group C shocked dogs and Group D dogs (recipients of shock plasma).

The etiology of this appearance of apparently normal lungs is unknown. It could be related to the way the lungs were manipulated and fixed (65). Sugg (94) found similar changes in normal dogs, and the changes were not affected by treatment of the dogs with antibiotics. The lung tissue was sterile on culture. Thus, despite the presence of polymorphonuclear leukocytes, this most likely does not represent any acute bacterial infection.

The appearance of the lungs of the control Group A dogs made it difficult to evaluate the effect of infusion of plasma and of hemorrhagic shock, although the Group B,C and D dogs generally showed more severe changes than Group A dogs.

The findings in Group B dogs showed that infusion of normal plasma by itself was capable of affecting the histology of the lung. The number of experiments was too small to allow any statistical

analysis of the significance of the lung changes. Veith (100) did report that only perfusion with fresh, ACD blood at 25 degrees C of isolated, *in situ* lungs did not cause morphologic, functional and hemodynamic changes in the lung. Other circumstances of perfusion led to lung lesions, and the results with autologous and homologous blood were comparable. Although Veith used isolated lungs, it is possible that simple infusion of homologous plasma by itself into living dogs can cause pulmonary changes. More dogs, with careful controls, will have to be studied before this question can be definitively resolved.

In summary, the light microscopic findings are suggestive that infusion of plasma, whether it be normal or obtained after the shock period, can produce morphologic changes in lungs that are consistent with "shock lung". The rate and the amount of the infusion may be critical.

Discussion of the Electron Microscopic Results.

Interstitial Disruption:

The results are summarized in Table 3 on page 77.

Many investigators have looked at the lung in shock under the electron microscope. Teplitz (98), working with rats, described the alveolar walls in the lung as comprising essentially of two regions: a thin segment region and a thick segment region. The thin segment has a combined thickness of approximately 100 millimicra and is composed of alveolar cells and endothelial cells, with little interstitium and few organelles. The thick segment contains most of the pulmonary interstitium. In addition to pneumocytes and alveolar cells, it has collagen fibrils in abundance and scattered elastic fibers. It is of interest that Cottrell (22) in 1967 described that pulmonary edema produced by occluding the pulmonary venous outflow and rapid infusion of isotonic saline in dogs occurred first in the thick segments of the alveolo-capillary membrane. There were widened spaces and dispersion of collagen fibers. The endothelium, epithelium and their basement membranes appeared intact. This is essentially what was described as 3+ interstitial disruption in the lung sections examined in this series of experiments.

In 1969, Barkett (5) described the ultrastructure of canine shock lungs. There were blunting of epithelial microvilli, rarefaction and vacuolization of the cytoplasmic matrix, "smudging" of the lamellated inclusion bodies of type II cells, and general disruptio of the architecture. There was no significant change in the endothelium except for a minimal increase in the number of pinocytic vesicles.

In the Group C shocked dogs examined in these experiments, there was blunting of the type II epithelial microvilli, but this was also observed in a few lung sections obtained from Group A normal dogs. The number of endothelial vesicles was very difficult to evaluate, but it would seem that there was no significant obvious increase in pinocytic vesicles after shock or infusion of plasma. Most of the inclusion bodies of type II cells that were observed were almost empty, both in normal and in shocked dogs. It is possible that this represented an artifact of the fixation process, but it may be that the stress of the experimental procedures itself caused the discharge of the contents of the granules which are purported to be surfactant material.

Ratliff (79), in 1970, described the ultrastructural changes in the lungs of cats subjected to

hemorrhagic shock. The type I pneumocyte was swollen to a varying degree, and there also was blunting of type II cell microvilli. The significant difference was the finding of platelet aggregates in the capillary space, but the author did re-infuse shed blood to the cats following shock, and this might well have caused platelet microembolization to the lungs. Ratliff also observed extensive electron-lucent spaces in the interstitium, separating connective tissue elements. The latter finding is consistent with what was observed in the Group C shocked dogs and the Group D dogs that had received shock plasma (3+ interstitial disruption).

Moss (68) found similar changes in shocked baboons, and Lewin (57) confirmed that there was interstitial thickening and disruption in the lungs of shocked dogs.

The results of the experiments described in this paper are strongly suggestive of the presence of humoral substances in the plasma of shocked dogs which are capable of disrupting the pulmonary interstitium of recipient dogs. Four out of six shocked dogs had 3+ interstitial disruption, as did three of the five dogs infused with shock plasma. None of the four control dogs had severe disruption of the collagen

fibrils or extensive interstitial electron-lucent spaces.

There seems to be little correlation between the light microscopic findings and the electron-microscopic changes. It is obvious that only a small specimen of lung could be examined with electron microscopy, and this may not be representative of the changes in the whole lung. It appears, however, that the histological findings were not helpful in deciding whether a dog had pulmonary changes reflecting shock lung or not. As noted above, normal control dogs did not exhibit completely histologically normal lungs, and this prevented any meaningful comparison from being made. The appearance of the interstitium as seen under the electron microscope may reflect the changes of shock lung more reliably.

Discussion of the Electron Microscopic Results.

Interstitial Sodium:

See Table 4 on page 78 for a summary of the results.

The interstitial disarray commented on above is the end result of a process the mechanism of which is still obscure. Is the interstitial fluid accumulation the result of increased vascular permeability, decreased lymphatic drainage, increased affinity of the interstitium for fluid, or a combination of the above ?

Cottrell (22) proposed that the collagen fibers might act as sponges to take up any excess of fluid appearing in the interstitium prior to its transit to lymphatic vessels. Interstitial edema would indicate saturation of the collagen fibers. Teplitz (98) thinks that large amounts of albumin can traverse the endothelial layer during shock. Albumin is cleared more slowly than protein-free fluid, and thus can stay around in the interstitium and exert an osmotic force leading to transudation of fluid. Moss (69), on the other hand, thinks that there is increased affinity of collagen for sodium in shock, and he apparently demonstrated this in shocked baboons, using pyroantimonat to localize sodium.

The technique of using pyroantimonate to

localize sodium ions was first described by Komnick (53) in 1963. Pyroantimonate was found to have great affinity for sodium, and sodium pyroantimonate is an insoluble compound which is electron-dense. Bulger (12) in 1969 used pyroantimonate to localize sodium ions in rat kidney tissue. With in vitro experiments, he found that other cations, among which potassium, magnesium and calcium, also formed precipitates with pyroantimonate. However, pyroantimonat was ten times more sensitive for sodium as for the other cations. Thus, extra-cellular precipitates would mostly represent sodium since sodium is the major extra-cellular cation. Intra-cellular precipitates must be interpreted with caution. Torack (99) in 1970 also thinks that potassium pyroantimonate is a valuable and valid substance for localizing sodium extracellularl although a low pH and addition of osmium tetroxide as a fixative seem to favor the production of non-specific electron-dense deposits.

The use of the perfusion solution in these experiments, prepared as described by Moss (69), for the estimation of interstitial sodium thus seems to be justified.

Moyer (74) in 1965 mentioned that collagen developed a heightened affinity for sodium and water

following various kinds of stress. Gump (41) in 1971 showed that in patients with acute pulmonary failure after trauma or surgery, injection of radioactive ^{22}Sodium into a central vein yielded only an 85% recovery of radioactivity in a peripheral artery, as compared to 95% in normal controls. Simultaneous injection of tritiated water yielded complete recovery of the radioactivity in all cases.

Fulton (35) placed purified collagen sheets obtained from dog tendons and aponeuroses in the subcutaneous tissue of dogs which were subsequently subjected to hemorrhagic shock. He found that there was a significant increase in the sodium content of the collagen. As mentioned above, Moss (69) found a marked increase in interstitial sodium in shocked baboons, using *in situ* perfusion of the lung with a potassium pyroantimonate solution.

Lewin (57), using a slightly different canine shock model than that usually used (the dogs were maintained at 60 mmHg for 15 minutes, then at 40 mmHg for 90 minutes instead of 40 mmHg for two hours) and an *in vitro* method of perfusing the removed lung with potassium pyroantimonate, suggested that there was no obvious increase in interstitial sodium after shock, in spite of the finding of

interstitial disarray consistent with shock lung.

In this series of experiments, *in vitro* perfusion of the lung was used, and the dogs were maintained at 40 mmHg systolic pressure for two hours.

Of the three kinds of electron-dense deposits described under Results, the first two probably represented sodium as they resembled the deposits described by previous investigators (12, 53, 99). The crystal-like materials may be non-specific deposits. A control experiment wherein a perfusion solution not containing potassium pyroantimonate would have been used was not done.

These experiments tended to confirm the findings of Lewin (57): there was no consistent increase in interstitial sodium in shocked dogs, and there certainly was not any marked sodium "smudging" in the interstitium around collagen fibers as described by Moss (69). This means that either there was no observable increase in affinity of collagen for sodium in shocked dogs, or that the procedure used was not adequate for demonstrating interstitial sodium in dogs. Moss (69) used an *in situ* perfusion preparation with his baboons, and he clamped the aorta a short period after beginning the perfusion. It is possible that the brief pumping action of the

heart during the initial perfusion period and the increased resistance to outflow caused by cross-clamping of the aorta increased the pulmonary capillary pressure to such an extent that both plasma and perfusio solution were forced into the interstitium. This could account for the spectacular "smudging" seen in the interstitium. However, the normal control baboons did not exhibit this smudging and only showed discrete and small sodium deposits comparable to those observed in both Group A and Group C dogs in these experiments. It could still be postulated that the endothelial layer was in fact damaged in some way by shock, and that the leakage of fluid was significantly potentiated by the perfusion procedure. Naturally, species differences can also be invoked to explain the failure to find consistently increased interstitial sodium in shocked dogs.

Another point to be raised here is the osmolality of the perfusion solution, which was not measured. The possibly deleterious effect of perfusing the lung with a solution which may not be isosmotic has to be considered, even when control experiments are done.

Returning to the work done on baboons, it is of interest that Gilbert (36) showed that lactic acidosis by itself did not increase interstitial

sodium, although Moyer (74) cited low pH as one of the conditions leading to increased affinity of collagen for sodium. On the other hand, infusion of aldosterone (Gilbert (36)) into baboons did result in increased interstitial sodium. It is well established that aldosterone is increased in shock (Farrell (30)). McCaa (62) even showed that hemorrhage greatly enhanced aldosterone secretion in the decapitated and nephrectomized dog, if the serum potassium was allowed to rise following the hemorrhage.

Serum potassium and aldosterone were not measured in this series of experiments, nor was it done in the shocked baboons of Moss (69).

Analysis of Arterial Blood Gases.

See Table 1 on page 75 for a summary of the blood gases.

The thin segments of the alveolar-capillary membrane were preserved during shock. Thus, it is not surprising that the arterial pO_2 was well maintained during shock, and this is in accordance with the findings of Sealy (82) and Chien (15). In a few dogs, the pre-experiment gases showed a relatively low pO_2 and a relatively elevated pCO_2. This could either be due to previous pulmonary disease, which could not be detected with histological examination of only part of the lungs, or due to over-sedation with Nembutal. At no time, however, did the arterial pO_2 drop during shock. There was hyperventilation with a decreased arterial pCO_2.

With regard to pH, the Group C shocked dogs did develop metabolic acidosis and had interstitial disruption. The Group D dogs that had received shock plasma did not drop their pH, and yet developed interstitial edema. It thus seemed that acidosis was not a necessary condition for interstitial edema to occur.

Darby (26) showed that in shocked dogs, increases in blood epinephrine levels followed the

development of uncompensated acidosis. Correction of the acidosis with sodium bicarbonate reduced the blood epinephrine level by at least 50%. He hypothesized that the adrenal gland was stimulated by acidosis to secrete epinephrine. Norepinephrine levels were not determined, but this study may well have relevance to the shock lung syndrome, in which the catecholamines may be important pathogenetically. Kim (52), working with dogs, felt that acidosis itself led to prolonged increase in pulmonary vascular resistance, thus predisposing to or itself causing shock lung in the post-shock period. Correction of the acidosis with bicarbonate led to no lung pathology in eight shocked dogs, whereas four of the ten dogs which were in shock without infusion of bicarbonate developed lung lesions grossly. These results certainly are impressive and can be significant if gross and histological findings can be relied on. Shubrooks (86) observed similar correlation between acidosis and increased pulmonary vascular resistance in dogs. It is repeated here that lactic acidosis failed to cause increase in interstitial sodium in baboons (36).

The results of the experiments reported in this paper suggested that acidosis was not necessary for the production of lung lesions in dogs.

Comment on Hematocrit.

The hematocrits were not determined in this series of experiments, so a meaningful evaluation of the role of anemia as a predisposing factor in shock lung is impossible. Moss (72) and Daniels (25) from the same laboratory reported that all six dogs with hematocrits of 31 ± 5% that were bled developed lung lesions, whereas all six dogs with hematocrits of 42 ± 5% that were similarly bled had no lesions.

In these experiments, the Group C dogs that were bled seemed to have a very high hematocrit toward the end of the two-hour shock period. Only approximately 15-20% of plasma could be separated from the blood collected. This obviously was not a good measure of the hematocrit, but the amount of plasma extracted was still unexpectedly small. The arterial blood collected at the beginning of the shock period yielded only about 23% of plasma. It can only be speculated at this point that the dogs used in these experiments might have been dehydrated , since they were completely fasted for the previous sixteen hours. This question can only be resolved by further experiments that would include accurate measurement of hematocrits.

Kho (51) described a drop in hematocrit from 34% to 29% in dogs subjected to graded hemorrhage,

a procedure which might have allowed time for the dogs to compensate for hypovolemia by internal fluid shifts.

Hematocrits obviously do not necessarily reflect the degree of shock. As pointed out by Harkins (44), the hematocrit value depends on the type of fluid lost (whether it be whole blood, plasma, or a mixed type) and the compensatory adjustments of different fluid compartments in the body. The situation in the dog is further complicated by the presence of a large and contractile spleen which can release cell-rich blood following hemorrhage (Chien and Gregersen (16), p.23). This would tend to increase the hematocrit and the blood viscosity in response to hemorrhage. Indeed, Chien (15) found that in dogs with intact spleens subjected to hemorrhage, the minimum hematocrit following re-transfusion was 40% with an average of 47%, which presumably was higher than the pre-hemorrhage level. The lower values reported by Kho (51) could reflect adjustments of body fluids following the slower and graded hemorrhage that he used. Chien (15) also commented that high blood viscosity tended to increase the mortality of shocked dogs. In fact, Crowell (23) observed that the optimum hematocrit for surviving shock in dogs

varied from 30 to 35 per cent, the corresponding optimal viscosity permitting an easier delivery of oxygen to the tissues.

SUMMARY.

This study tried to demonstrate the presence of circulating factors in the plasma of shocked dogs which would be capable of causing lung lesions when infused into normotensive dogs.

It was found that light microscopy was of limited value in demonstrating shock lung under the circumstances of these experiments. Fixing the lung in an inflated state may be more helpful.

There was no consistent and striking increase in interstitial sodium in the shocked dogs that could be demonstrated with this method of perfusing the lung with a potassium pyroantimonate solution. Only two supposedly normal control dogs were examined, and this may not be adequate for a conclusion to be reached with regard to the amount of interstitial sodium expected in normal lungs.

Interstitial edema and disruption of the collagen bundles were consistently found in shocked dogs and in dogs that had received shock plasma when the lung tissue was examined under the electron microscope. The normal controls and dogs infused with normal plasma showed only minimal changes under the EM.

Thus, there seems to be circulating factors

during hemorrhagic shock which may be important in the pathogenesis of shock lung in dogs. A neural influence was not ruled out by these experiments, and further study will have to be done on denervated lungs using the same approach of infusing shock plasma as was used here in order to evaluate the role of neurogenic factors in the pathogenesis of shock lung.

The relevance of the results obtained in dogs to the clinical picture of shock lung as seen in humans is open to question. Certainly, the syndromes in humans and in animals are quite dissimilar in two important aspects. First, shock lung usually develops in humans only after a certain lag period of a few days following the acute injury, whereas the lung lesions can be demonstrated in dogs early in the shock period. Secondly, the syndrome is characterized by profound disturbances in pulmonary function in man. A host of factors are at play in the patient which may contribute to the pulmonary insufficiency. among which loom infection, aspiration, fluid overload and complications of oxygen therapy. Attention to the latter may help to decrease the incidence of so-called shock lung.

*****

APPENDIX.

1. Data of individual experiments.
2. Tables summarizing results.
3. Selected photomicrographs.
4. Selected electron micrographs.

Experiment #1. Group C.

Dog #71. Sex: Female. Weight: 17 kg.

Position during experiment: Supine.

Total Nembutal used: 25 mg/kg BW

Pre-Shock Data:

BP: 180/150 pH: not measured

CVP: 2 mmHg pO_2: not measured

RR: not recorded pCO_2: not measured

Shock:

Volume of blood withdrawn to induce shock: 700 ml over 15 minutes (41 ml/kg BW).

Shock period: 3 hours.

Post-Shock Data:

BP: 55/35 pH: not measured

CVP: -1 mmHg pO_2: not measured

RR: not recorded pCO_2: not measured

Volume of venous blood withdrawn after shock period: 400 ml. Venous shock plasma obtained: 80 ml, to be infused into Dog #79 (Exp. #2) the following day

Perfusion of Middle Lobe: good, but delayed for 5 min.

Results:

Light microscopy: 3+

Electron microscopy:

Interstitial sodium: 2+

Interstitial disruption: 3+.

Experiment #2. Group D.

Dog #79. Sex: Male. Weight: 18.2 kg.

Position during experiment: Supine.

Total Nembutal used: 24.7 mg/kg.

Pre-Infusion Data:

BP: 150/125 pH: not measured

CVP: 8 mm Hg pO_2: not measured

RR: not recorded pCO_2: not measured

Infusion:

80 ml (4.4 ml/kg body weight) of venous shock plasma over 15 minutes (@ 320 ml/ hour).

Post-Infusion:

The blood pressure dropped slightly to 140/120 for about 5 minutes, and the respiration was ataxic, with an increased rate. The CVP was maintained.

Arterial pH, pO_2, pCO_2 were not obtained.

At 1 hour: BP: 130/120

CVP: 8 mmHg

RR: not recorded.

Perfusion of Middle Lobe: good.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 1+

Interstitial disruption: 2+.

Experiment #3. Group C.

Dog #S-13061 Sex:Male. Weight:29.1 kg.

Position during experiment: on left side.

Total Nembutal used: 26.2 mg/kg.

Pre-Shock Data:

BP: 145/100	pH: 7.36
CVP: 6mm Hg	pO_2: 96 mm Hg
RR: not recorded	pCO_2: 29 mm Hg

Shock:

Volume of blood withdrawn to induce shock: 1100 ml over 15 minutes (38 ml/kg body weight).

Shock period: 2 hours 50 minutes.

Post-Shock Data:

Total volume in: 200 ml Normal Saline.

Total volume out: 1700 ml blood.

BP: 45/25	pH: 7.10
CVP: 6 mm Hg	pO_2: 100 mm Hg
RR: 32/min	pCO_2: 28 mmHg

Volume of blood withdrawn and used for infusion into Dog #S-13069 (Exp. #4) the following day: 100 ml.

Perfusion of Middle Lobe: good.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 3+.

Experiment #4. Group D. This dog received whole venous "shock" blood instead of plasma.

Dog# S-13069. Sex: Female. Weight: 13.6 kg.

Position during experiment: on left side.

Total Nembutal used: 42.2 mg/kg.

Pre-Infusion Data:

BP: 145/110	pH: 7.35
CVP: 3 mmHg	pO_2: 122 mmHg
RR: 32/min	pCO_2: 24 mmHg.

Infusion:

100 ml of whole venous "shock" blood (7.35 ml/kg) plus 150 ml ACD over 45 minutes. (@330 ml/hour).

This blood was collected into two ACD-containing bags and was not separated into plasma before infusion because the plasma thus obtained was too little in quantity. The dog showed fasciculation of the tongue and the limb muscles and might have had hypocalcemia secondary to citrate infusion.

Post-Infusion:

There was immediate marked hyperventilation.

At 15 minutes:	BP: 135/105	pH: 7.24
	CVP: 2 mmHg	pO_2: 118 mmHg
	RR: 30/min	pCO_2: 31 mmHg

At 1 hour : BP and CVP unchanged.

Perfusion of Middle Lobe: fair, slightly delayed.

Results: Light microscopy: 2+

Electron microscopy: Na^+: 2+ Interstitial disruption : 3

Experiment #5. Group B.

Dog #S-13070. Sex: Female. Weight: 12.2 kg.

Position during experiment: on left side.

Total Nembutal used: 53 mg/kg.

Pre-Infusion Data:

BP: 135/105 pH: 7.35

CVP: 1-2 mmHg pO_2: 71 mmHg

RR: 20/min pCO_2: 39 mmHg

Infusion:

80 ml of "normal plasma" (6.55 ml/kg) over 9 minutes (@ 530 ml/hour).

Post-Infusion:

At 0 min: no change in BP or CVP, or RR.

At 6 min: pH: 7.37

pO_2: 80 mmHg

pCO_2: 33 mmHg

At 1 hour 11 min: BP: 135/100

CVP: 1 mmHg.

Perfusion of Middle Lobe: good.

Results:

Light microscopy: 2+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 1+

Experiment #6. Group C.

Dog #S-13065. Sex: Female. Weight: 17.7 kg.

Position during experiment: on left side.

Total Nembutal used: 34 mg/kg.

Pre-Shock Data:

BP: 130/105 pH: 7.35

CVP: 1-2 mmHg pO_2: 86 mmHg

RR: 16/min pCO_2: 37 mmHg

Shock:

Volume of blood withdrawn to induce shock: 850 ml over 5 minutes (48ml/kg body weight).

Shock period: 1 hour 30 minutes.

The dog died before "shock blood" could be obtained.

Post-Shock Data:

BP: 42/35 mmHg pH, pO_2, and pCO_2 could not be obtained.

CVP: -3 to -2 mmHg

RR: 32/min

Perfusion of Middle Lobe: good, but delayed.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 2+.

Experiment #7. Group B.

Dog #S-13082. Sex: Female. Weight: 17.7 kg.

Position during experiment: on left side.

Total Nembutal used: 36.7 mg/kg.

Pre-Infusion:

BP: 110/85 pH: 7.28

CVP: 8 mmHg pO_2: 85 mmHg

RR: 28/min pCO_2: 32 mmHg

Infusion:

120 ml of "normal plasma" (6.7 ml/kg BW) over 9 minutes (@ 800 ml/hour).

Post-Infusion:

At 0 min : BP: 100/80

At 10 min : BP: 100/80 pH: 7.30

CVP: 8 mmHg pO_2: 84 mmHg

RR: 28/min pCO_2: 32 mmHg

At 1 hour: BP: 110/85

CVP: 8 mmHg

RR: 16/min

Perfusion of Middle Lobe: good, without any delay.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 1+

Interstitial disruption: 1+.

Experiment #8. Group C.

Dog #S-13064. Sex: Male. Weight: 30.5 kg.

Position during experiment: on left side.

Total Nembutal used: 32.7 mg/kg.

Pre-Shock Data:

BP: 110/90 mmHg	pH: 7.32
CVP: 2 mmHg	pO_2: 75 mmHg
RR: 20/min	pCO_2: 43 mmHg

Shock:

Volume of blood withdrawn to induce shock: 1900 ml over 15 minutes (62 ml/kg BW).

Shock period: 2 hours.

Post-Shock Data:

BP: 40/30	pH: 7.25
CVP: 0 mmHg	pO_2: 79 mmHg
RR: 32/min	pCO_2: 21 mmHg

Total volume in: 100 ml Normal Saline.

Total volume out: 2400 ml of blood.

450 ml of arterial "shock blood" and 250 ml of venous "shock blood" were obtained for use in Exp.#9.

Perfusion of Middle Lobe: delayed, done through pulmonary vein because of technical difficulty. Samples for electron microscopy were obtained from visibly fixed areas of the lobe.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 3+.

Experiment #9. Group D.

Dog #S-13031. Sex: Male. Weight: 18.2 kg.

Position during experiment: on left side.

Total Nembutal used: 46.5 mg/kg.

Pre-Infusion Data:

BP: 135/110 pH: 7.29

CVP: 0 mmHg pO_2: 57 mmHg

RR: 8/min pCO_2: 55 mmHg

The dog thus was in respiratory acidosis. This probably was due to an overdose of Nembutal.

Infusion:

70 ml of "arterial shock plasma" (3.85 ml/kg) were infused over 7 min (@ 600 ml/hour), then 30 ml of "venous shock plasma" were infused over 4 minutes (@ 450 ml/hour). There was no change in vital signs after the infusion of "arterial shock plasma", but there was a slight increase in the respiratory rate after the infusion of "venous shock plasma".

Post-Infusion Data:

At 5 min : BP: 130/105 pH: 7.33

CVP: -1 mmHg pO_2: 75 mmHg

RR: 16/min pCO_2: 47 mmHg

This probably reflected the lessening of anesthes

Perfusion of the Middle Lobe: very good.

Results:

Light microscopy: 2+

Electron microscopy: Na$^+$ 2+ Interstitial disruption : 3+.

Experiment #10. Group A.

Dog #S-13066. Sex: Male. Weight: 19.1 kg.

Position during experiment: on left side.

Total Nembutal used: 39.3 mg/kg.

Baseline Data:

BP: 140/110	pH: 7.25
CVP: 2 mmHg	pO_2: 64 mmHg
RR: 8/min	pCO_2: 53 mmHg

The dog was in respiratory acidosis caused by an overdose of Nembutal. After one hour, the right lung was taken out.

Perfusion of Middle Lobe: very good, a bit delayed.

Results:

Light microscopy: 1+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 1+.

Experiment #11. Group C.

Dog #s-13060. Sex: Male. Weight: 30 kg.

Position during experiment: supine.

Total Nembutal used: 28.2 mg/kg.

Pre-Shock Data:

BP: 185/140 pH: 7.36

CVP: 5 mmHg pO_2: 82 mmHg

RR: 20/min pCO_2: 40 mmHg

Shock:

Volume of blood withdrawn to induce shock: 1320 ml over 26 minutes (44ml/kg body weight).

Shock period: 2 hours 20 minutes.

Post-Shock Data:

BP: 50/40 pH: 7.27

CVP: 0-1 mmHg pO_2: 92 mmHg

RR: 32/min pCO_2: 23 mmHg

Total volume in: 400 ml Normal Saline.

Total volume out: 1900 ml of blood.

300 ml of arterial shock blood and 200 ml of venous shock blood were obtained for use in Experiment #12.

Perfusion of Middle Lobe: very good.

Results:

Light microscopy: 3+

Electron microscopy: Na^+: 2+

Interstitial disruption: 3+.

Experiment #12. Group D.

Dog #s-13054. Sex: Female. Weight: 10 kg.

Position during experiment: supine.

Total Nembutal used: 35 mg/kg.

Pre-Infusion Data:

BP: 165/140	pH: 7.31
CVP: 4-5 mmHg	pO_2: 79 mmHg
RR: 20/min	pCO_2: 50 mmHg

Infusion:

75 ml of "arterial shock plasma" were infused over 6 minutes (@750 ml/hr). There were no changes in BP or CVP, but the respiratory rate increased to 28 per minute. Then 75 ml of "venous shock plasma" were infused over 6 minutes (@750 ml/hour). A total of 15 ml/ kg BW was thus infused.

Post-Infusion Data:

At 15 min :	BP: 170/135	pH: 7.30
	CVP: 2 mmHg	pO_2: 97 mmHg
	RR: 28/min	pCO_2: 41 mmHg

At 1 hour: BP: 160/130. No change in CVP or RR.

Perfusion of Middle Lobe: good, but delayed for 10 min.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 2+

Interstitial disruption: 3+.

Experiment #13. Group C.

Dog #s-13083. Sex: Male. Weight: 19.5 kg.

Position during experiment: supine.

Total Nembutal used: 33.2 mg/kg.

Pre-Shock Data:

BP: 185/150	pH: 7.36
CVP: 4 mmHg	pO_2: 83 mmHg
RR: 20/min	pCO_2: 37 mmHg

Shock:

Volume of blood withdrawn to induce shock: 1400 ml over 10 minutes (71.5 ml/kg body weight).

Shock period: 1 hour 15 min.

The dog sustained cardio-respiratory arrest at 1 hour 15 min. He was then put on a respirator and an open cardiac massage was performed for about 10 minutes, during which time 200 ml of normal saline were infused and 250 ml of "venous shock blood" were collected for use in Experiment #14. The vital signs at 1 hour were: BP: 45/30

CVP: 0-1 mmHg

RR: 32/min

Perfusion of Middle Lobe: good, with a 15 minutes' delay.

Results:

Light microscopy: 2+

Electron microscopy: Na^+: 1+

Interstitial disruption: 2+.

Experiment #14. Group D.

Dog #S-13085. Sex: Male. Weight: 12.3 kg.

Position during experiment: supine

Total Nembutal used: 34.5 mg/kg.

Pre-Infusion Data:

BP: 150/135 pH: 7.34

CVP: 4-5 mmHg pO_2: 72 mmHg

RR: 32/min pCO_2: 37 mmHg

Infusion:

120 ml of "venous shock plasma" were infused over 18 minutes (9.75 ml/kg @ 400 ml/hour).

Post-Infusion Data:

At 0 min : BP: 155/125, CVP: 4 mmHg, RR: 32/min

At 5 min : BP: 140/110, CVP: 2 mmHg, RR: 48/min.

pH: 7.34 pO_2: 79 mmHg pCO_2: 32mmH

Thus, there were a decrease in blood pressure and an increase in respiratory rate following infusio

At 1 hour: BP: 140/110. CVP: 5 mmHg. RR: 40/min.

Perfusion of Middle Lobe: very good.

Results:

Light microscopy: 3+

Electron microscopy:

Na^+: 1+

Interstitial disruption: 2+.

Experiment #15. Group A.

Dog #S-13103. Sex: Female. Weight: 16.8 kg.

Position during experiment: supine.

Total Nembutal used: 38.5 mg/kg.

Baseline Data:

BP: 145/105	pH: 7.30
CVP: 2-3 mmHg	pO_2: 86 mmHg
RR: 24/min	pCO_2: 37 mmHg

The dog was at baseline for an hour, then the right lung was taken out.

Perfusion of Middle Lobe: very good, although some pressure had to be applied to the intra-arterial perfusion because it was repeatedly clogged.

Results:

Light microscopy: 2+

Electron microscopy:

Na^+: 1+

Interstitial disruption: 1+.

Table 1: Description of Groups of Dogs and Summary of Arterial Blood Gases Determinations

GROUP A	GROUP B	GROUP C	GROUP D
Normal Control	Recipients of Fresh Plasma*	Shocked Dogs	Recipients of Shock Plasma**
$pH/pO_2/pCO_2$	$pH/pO_2/pCO_2$	$pH/pO_2/pCO_2$	$pH/pO_2/pCO_2$
#10: 7.25/64/53		#1: pre-shock not measured post-shock not measured	#2: pre-infusion not measured post-infusion not measured
#15: 7.30/86/37	#5: pre-infusion 7.35/71/39 post-infusion 7.37/80/33	#3: pre-shock 7.36/96/29 post-shock 7.10/100/28	#4'': pre-infusion 7.35/122/24 post-infusion 7.24/118/31
	#7: pre-infusion 7.28/85/32 post-infusion 7.30/84/32	#6'*: pre-shock 7.35/86/37 post-shock ---	
		#8: pre-shock 7.32/75/43 post-shock 7.25/79/21	#9: pre-infusion 7.29/57/55 post-infusion 7.33/75/47
		#11: pre-shock 7.36/82/40 post-shock 7.27/92/23	#12: pre-infusion 7.31/79/50 post-infusion 7.30/87/41
		#13*: pre-shock 7.36/83/37 post-shock ---	#14: pre-infusion 7.34/72/37 post-infusion 7.34/79/32

*: Fresh plasma was obtained from arterial blood bled from Group C dogs to induce shock in the latter.

**: Shock plasma was obtained from blood bled from Group C dogs after the shock period.

'': Dog #4 received whole shock blood and not plasma.

'*: Dog #6 was in shock for only 1 1/2 hour and died before blood could be obtained.

*: Dog #13 died after 1 1/4 hour of shock and shock blood was obtained while open cardiac massage was performed.

Table 2: Summary of Light Microscopy Results.

GROUP A	GROUP B	GROUP C	GROUP D
Normal control	Recipient of normal plasma	Shocked dogs	Recipient of shock plasma
#10: 1+		#1: 3+	#2: 3+
#15: 2+	#5: 2+	#3: 3+	#4*: 2+
	#7: 3+	#6**: 3+	
		#8: 3+	#9: 2+
		#11: 3+	#12: 3+
		#13≚: 2+	#14: 3+

*: Dog #4 received whole shock blood instead of shock plasma.

**: Dog #6 was maintained at 40 mmHg systolic pressure for only 1 1/2 hour and died before shock blood could be obtained.

≚: Dog #13 died after 1 1/4 hour of shock and had to undergo open cardiac massage and receive controlled ventilation while shock blood was obtained for use in Experiment #14.

Table 3: Summary of Electron Microscopy Results.
Interstitial Disruption.

GROUP A	GROUP B	GROUP C	GROUP D
Normal control	Recipient of normal plasma	Shocked dogs	Recipient of shock plasma
#10: 1+		#1: 3+	#2: 3+
#15: 1+	#5: 1+	#3: 3+	#4*: 2+
	#7: 1+	#6**: 2+	
		#8: 3+	#9: 2+
		#11: 3+	#12: 3+
		#13≠: 2+	#14: 2+

For the explanations of *, **, ≠, see the footnotes on page 76.

Table 4: Summary of Electron Microscopy Results.
Interstitial Sodium.

GROUP A	GROUP B	GROUP C	GROUP D
Normal control	Recipient of normal plasma	Shocked dogs	Recipient of shock plasma
#10: 2+		#1: 2+	#2: 1+
#15: 1+	#5: 2+	#3: 2+	#4*: 2+
	#7: 1+	#6**: 2+	
		#8: 2+	#9: 2+
		#11: 2+	#12: 2+
		#13*: 1+	#14: 1+

For the explanations of *, ** and *, see the footnotes on page 76.

None of the lungs was graded as having 3+ sodium deposition in the interstitium.

LIGHT PHOTOMICROGRAPHS.

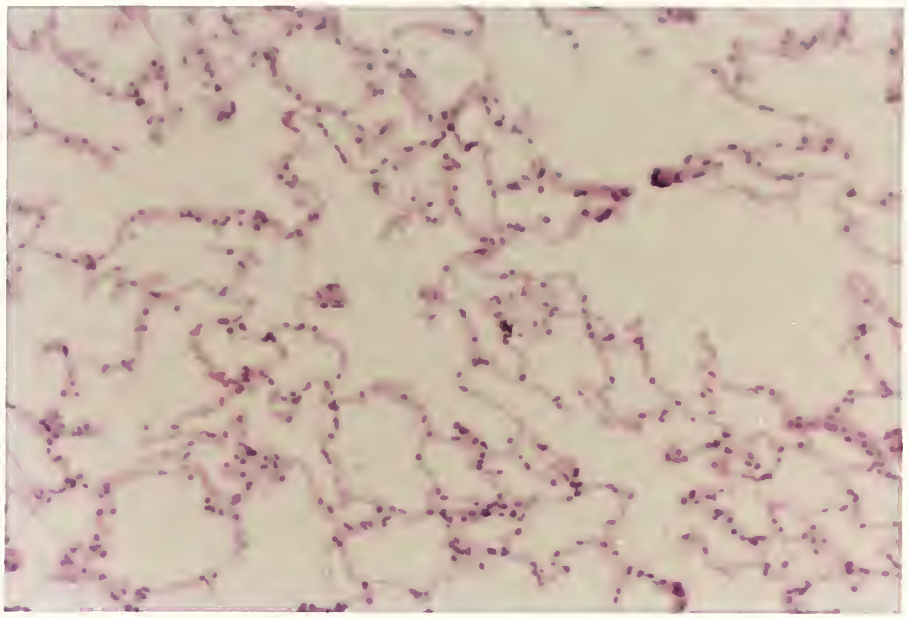

Figure 1: Lung section from a normal dog (Experiment #10) demonstrating thin and normal alveolar septae (1+ changes). There is slight alveolar collapse due to the fixing procedure.

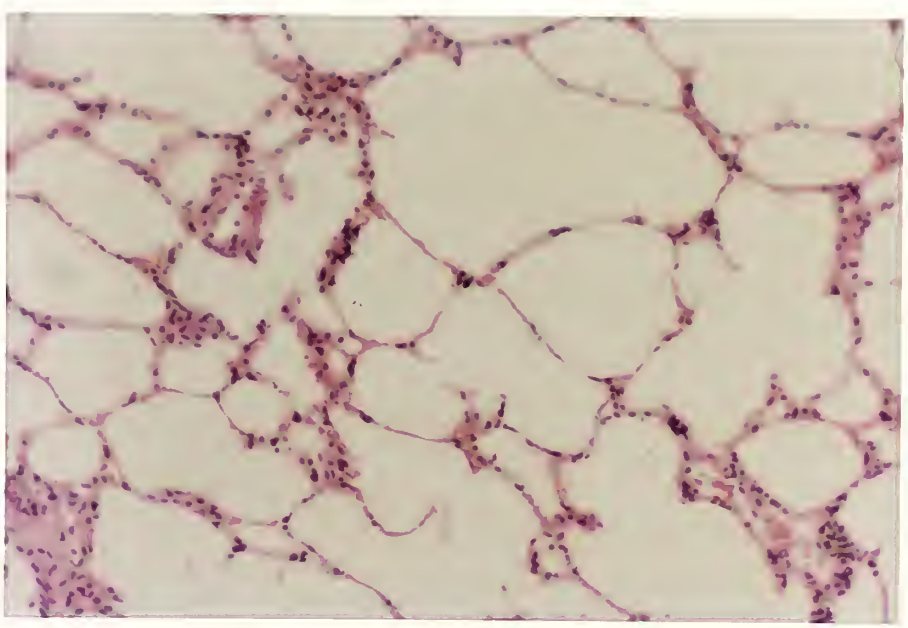

Figure 2: Lung section from the same dog (Experiment #10) showing patchy alveolar septal thickening and polymorphonuclear cell infiltration (1+ to 2+ changes). The alveoli are well distended in this field.

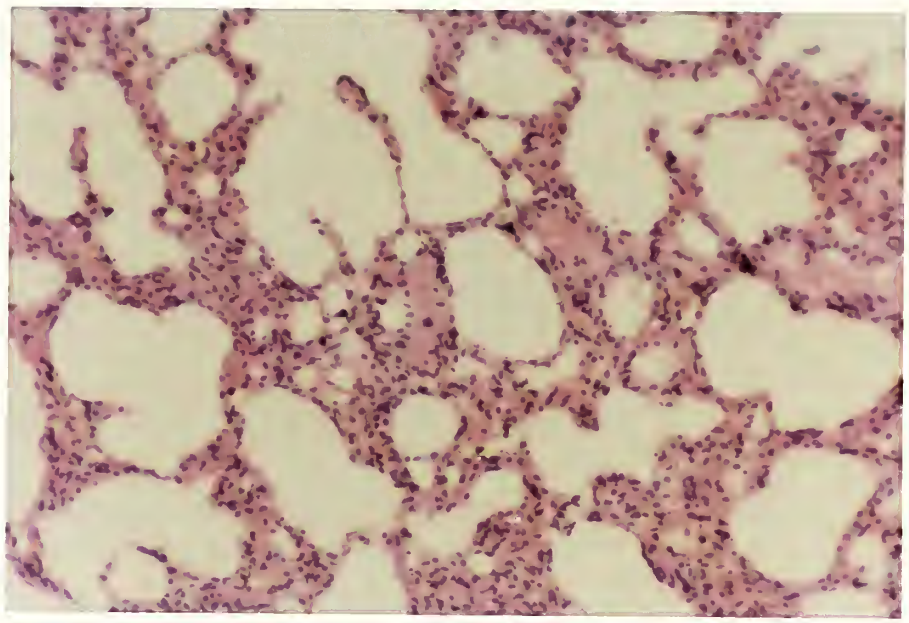

Figure 3: Moderate (2+) changes in the lung of a "normal" dog (Experiment #15), showing septal thickening, inflammatory cell infiltration, without hemorrhage or exudate.

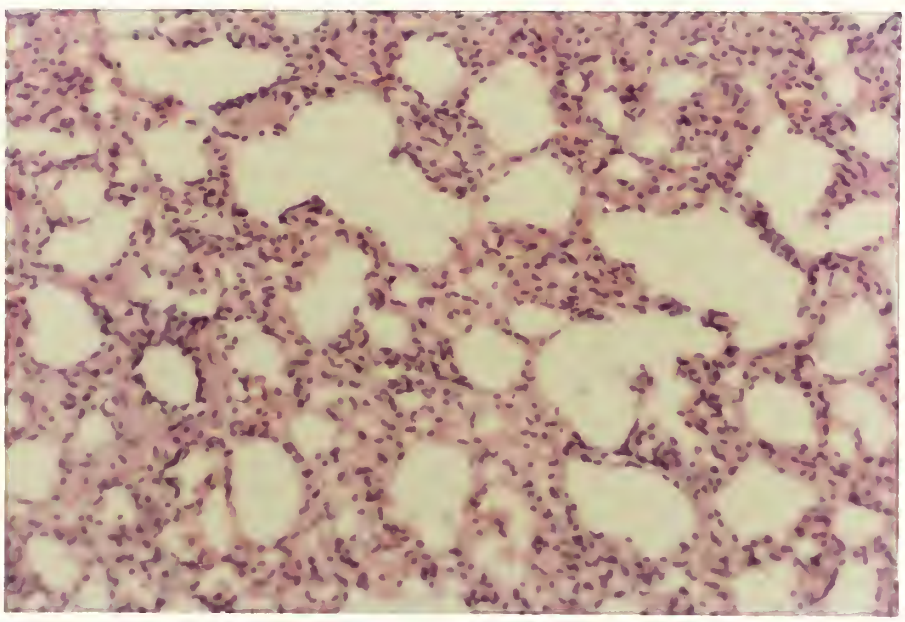

Figure 4: Similar 2+ changes are found in this lung section from a dog that had received normal plasma (Experiment #5).

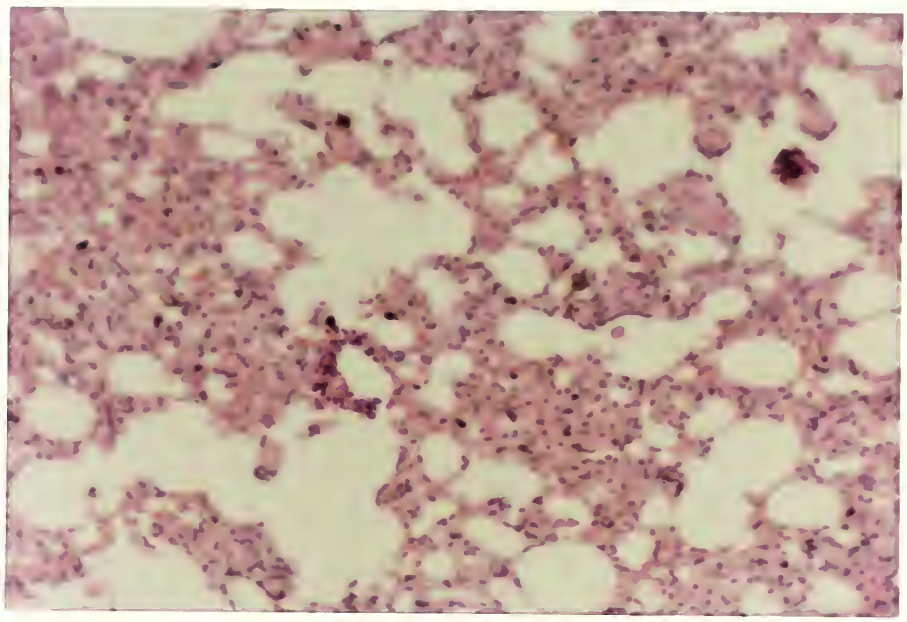

Figure 5: Lung section from a dog infused with shock plasma, again demonstrating 2+ changes. There is minor hemorrhage, but the findings are essentially identical to those in Figures 3 and 4. (Experiment #4).

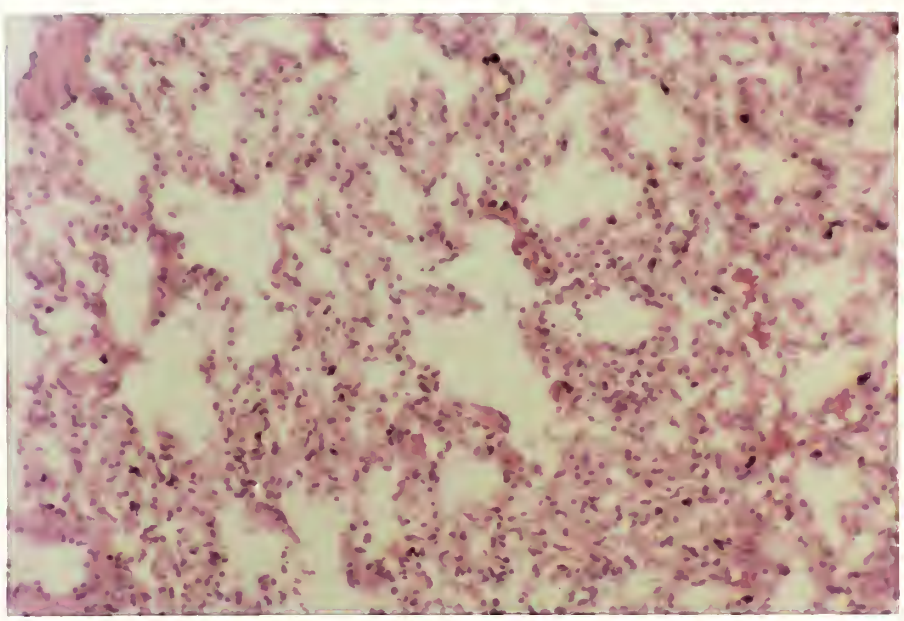

Figure 6: Severe disruption (3+ changes) of the lung in a shocked dog (Experiment #3). Interstitial thickening is less obvious here, but there is extensive congestion, hemorrhage and patchy atelectasis.

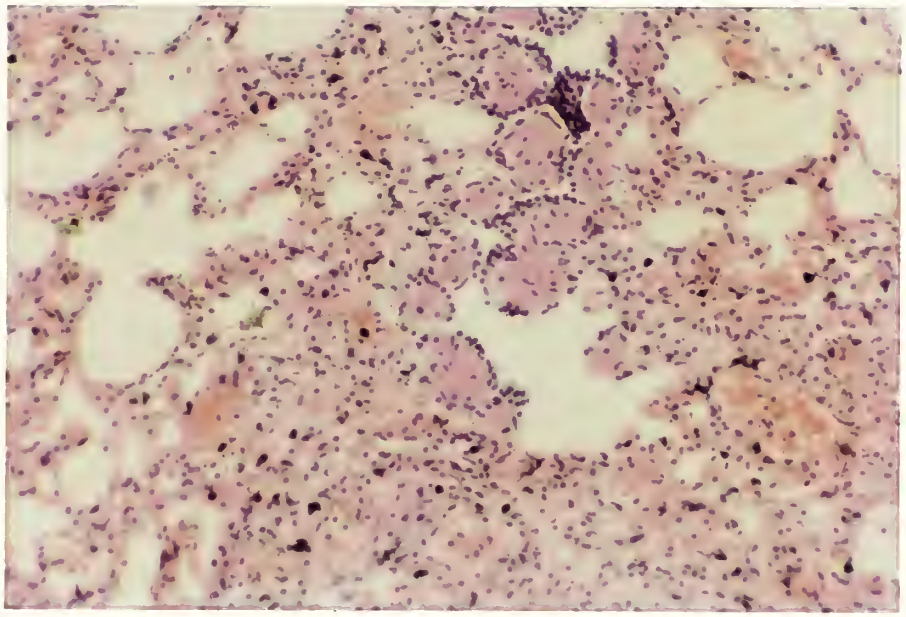

Figure 7: Lung section from another shocked dog showing intra-alveolar hemorrhage and congestion, in addition to atelectasis, septal thickening and inflammatory cell infiltration. (Experiment #1, 3+ changes).

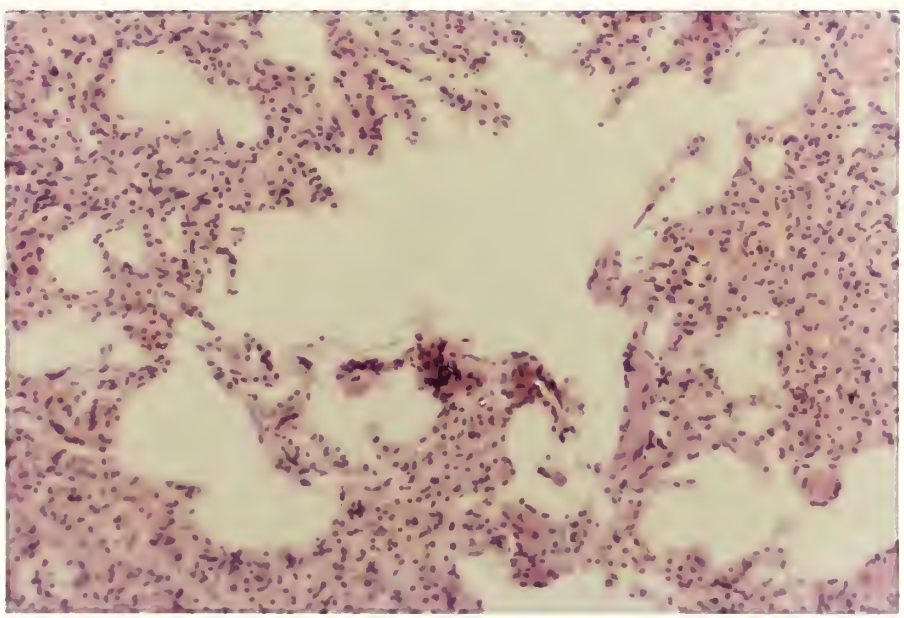

Figure 8: Another view of the lung of the same shocked dog, demonstrating atelectasis, septal thickening and extensive polymorphonuclear leukocyte infiltration. No intra-alveolar hemorrhage is seen. (Experiment #1).

ELECTRON MICROGRAPHS.

Figures 9-12: Group A dogs (normal control)
Figures 13-15: Group B dogs (recipient of normal plasma)
Figures 16-21: Group C dogs (shocked dogs)
Figures 22-27: Group D dogs (recipient of shock plasma).

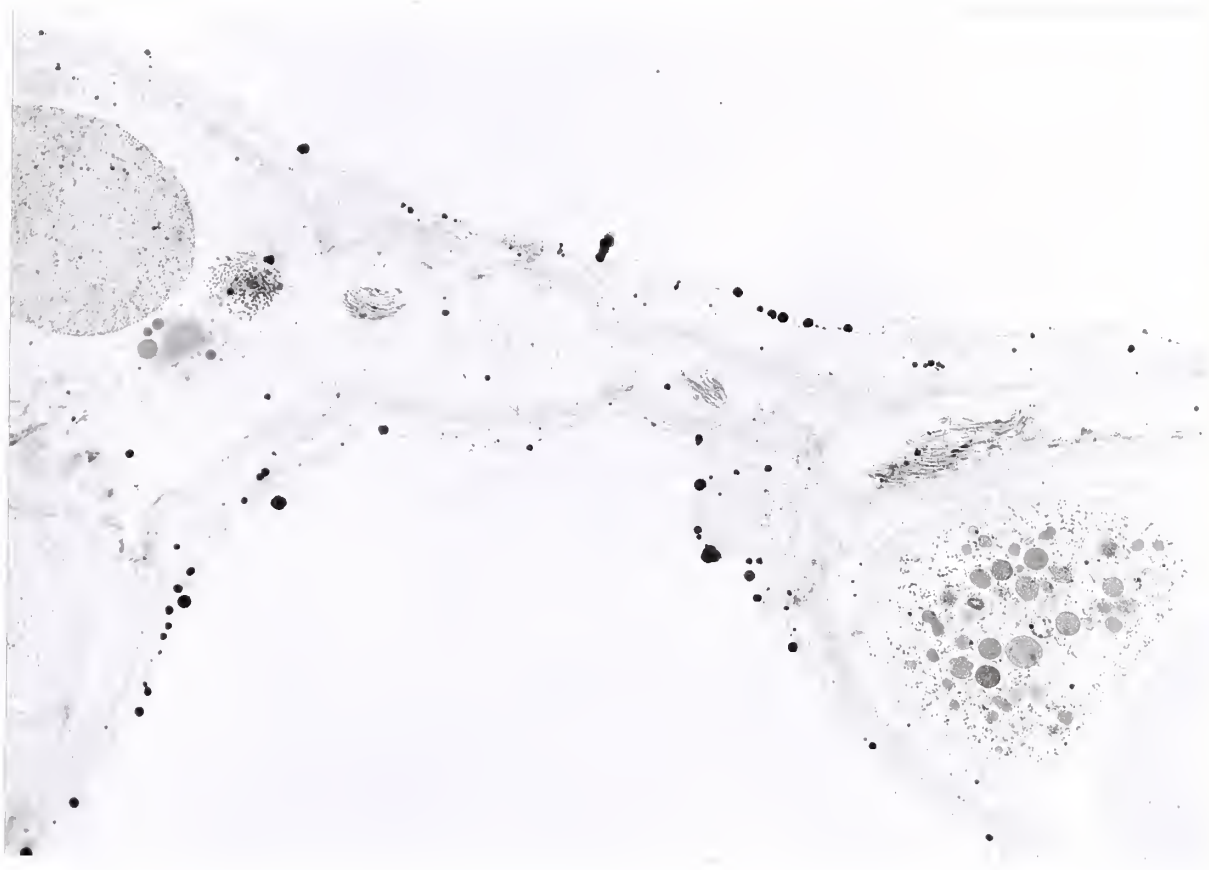

Figure 9: An example of 1+ interstitial disruption. This is a low-magnification view of the thick segment of a normal dog's alveolo-capillary membrane. There is no disruption of the interstitium and no clear spaces are seen. A capillary space can be seen to the right, with part of an erythrocyte and granules-containing cytoplasm representing either a platelet or a leukocyte. Pinocytic vesicles are present in the endothelial cell cytoplasm. Some large, round electron-dense deposits probably representing sodium pyroantimonate complexes can be seen in the alveolar spaces near the epithelium. (Experiment #10. Magnification: X10,800.)

Figure 10:A low-magnification view of a section where interstitium is more abundant in a normal dog. The collagen bundles are well seen, parallel and not disrupted. No extensive clear spaces can be observed in the interstitium(1+ interstitial disruption). Small electron-dense deposits are scattered over the lung tissue, more so over the collagen bundles. They probably represent sodium. See Figure 11 for a higher magnification of the area (1+ to 2+ interstitial sodium).

A type II pneumocyte with intracytoplasmic granules and prominent microvilli is seen in the upper right corner.(Experiment #15. Magnification: X7,020.)

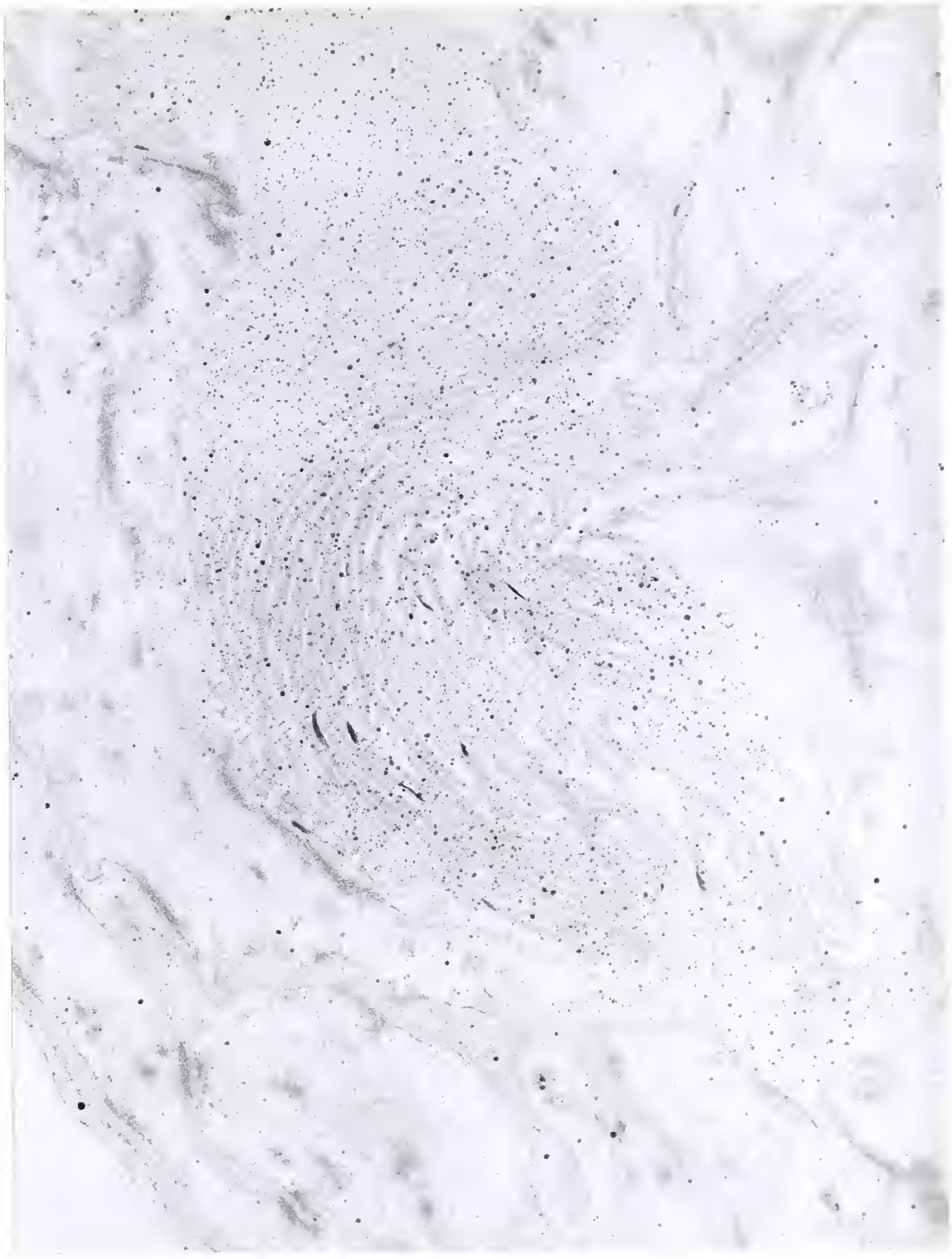

Figure 11: A high magnification view of regularly arranged collagen bundles in the interstitium of a normal dog. Small electron-dense materials probably representing sodium can clearly be seen lying over the collagen fibers. (1+ to 2+ interstitial sodium) (Experiment #15. Magnification: X24,000).

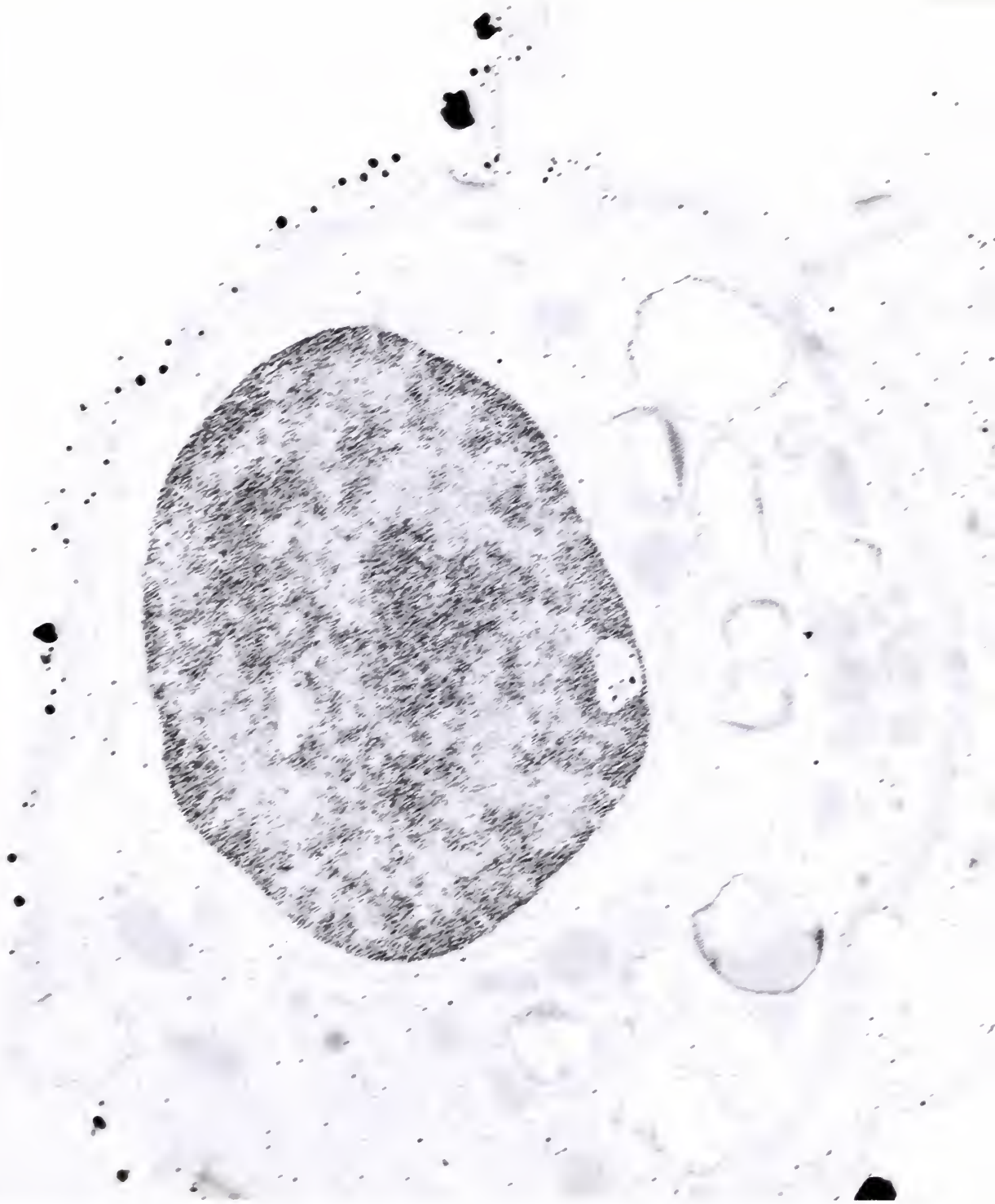

Figure 12: A type II pneumocyte of a normal dog. The granules, most of which are empty, as well as the epithelial microvilli and the intra-alveolar large deposits of sodium pyroantimonate, are seen to best advantage. (Experiment #15. Magnification: X19,680).

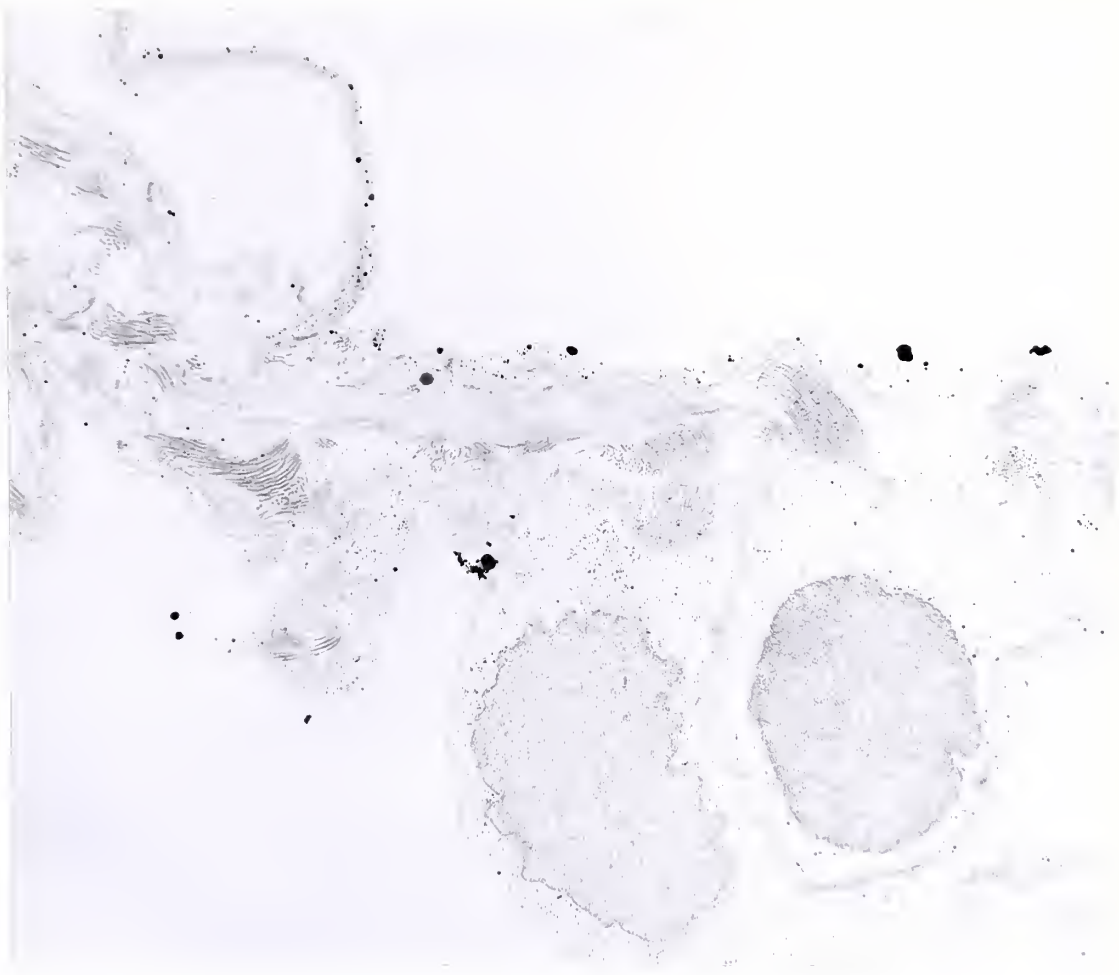

Figure 13: A low-magnification view of a thick segment of the alveolo-capillary membrane in a Group B dog (recipient of normal plasma). There is minimal disruption of the interstitium (1+ changes), and the interstitial sodium is not noticeably increased (1+ interstitial sodium). Both large deposits (in the alveolar spaces) and smaller sodium pyroantimonate complexes (in the interstitium mainly) can be seen. A type I pneumocyte adjacent to an endothelial cell lies in the lower right corner.
(Experiment #7. Magnification: X7,920).

Figure 14: A higher magnification of Figure 13, showing large and small electron-dense sodium pyroantimonate deposits more clearly. The collagen bundles are parallel and close to one another.

Endothelial vesicles can be seen in the upper left corner.
(Experiment #7. Magnification: X19,680).

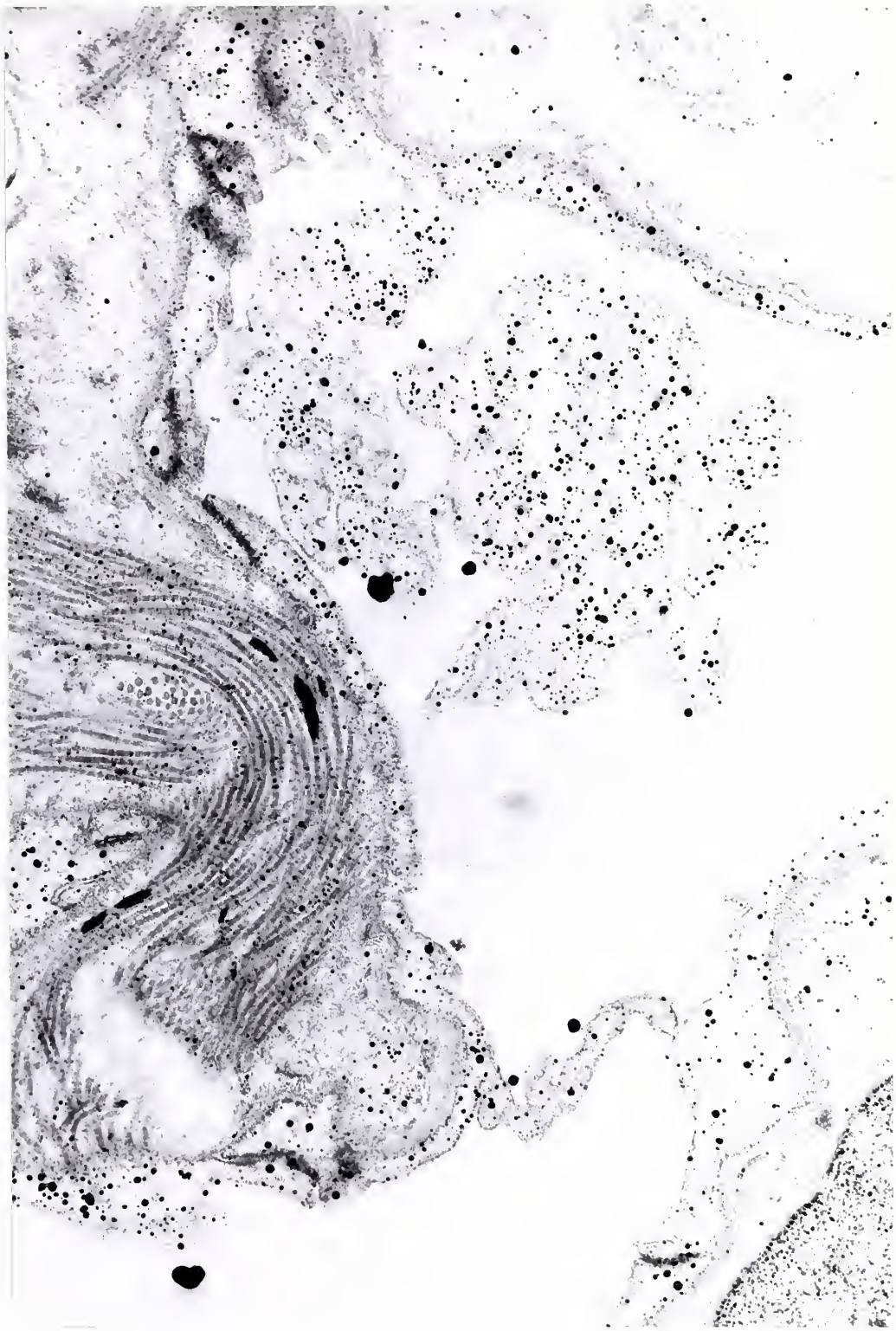

Figure 15: A high-magnification view of the regularly arranged collagen fibers and minimal interstitial sodium deposition in a Group B dog. There are some debris in the alveolar space. The intracytoplasmic electron-dense granules probably do not represent sodium and are not significant. (Experiment #7. Magnification: X24,000).

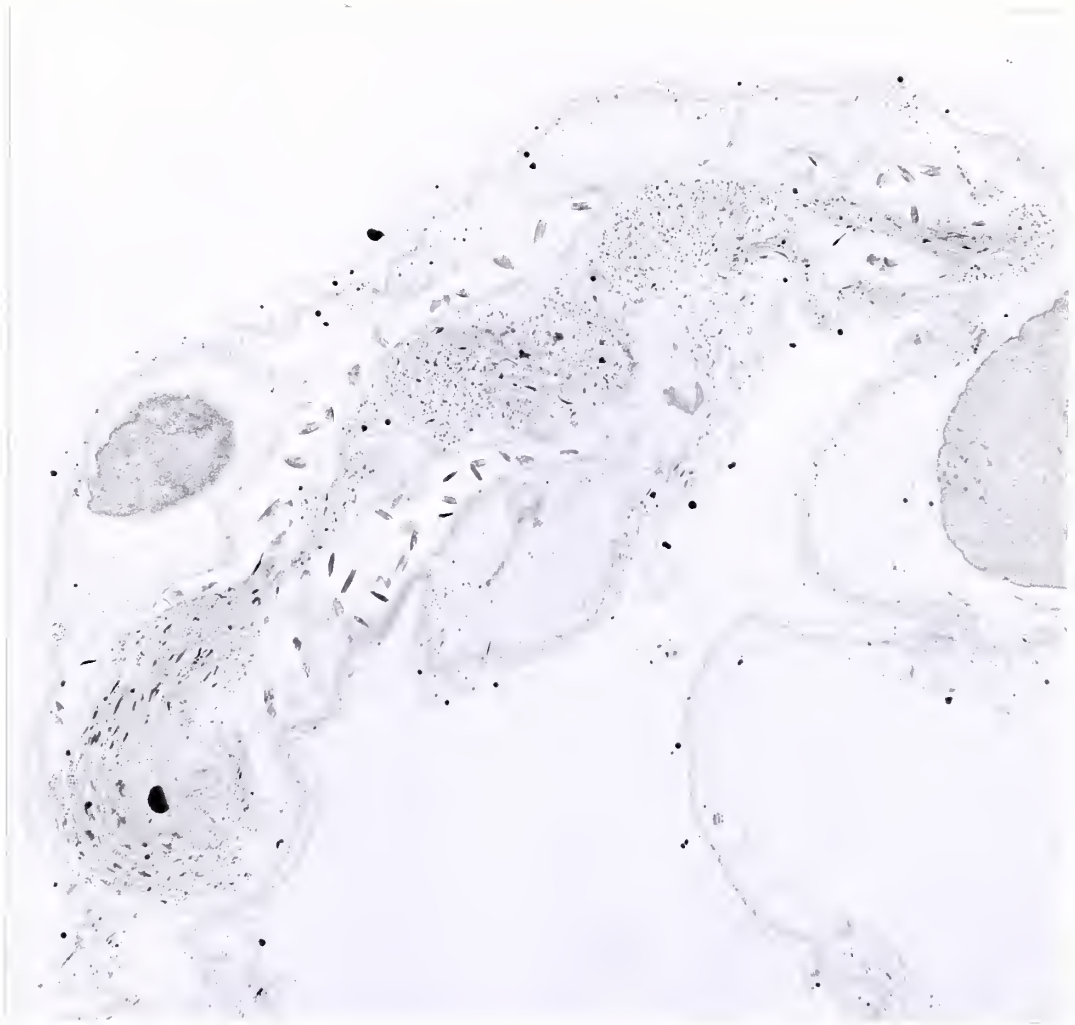

Figure 16: A low magnification view of a thick segment of the alveolo-capillary membrane in a Group C shocked dog, demonstrating 3+ interstitial disruption and 2+ sodium deposition. Thickening of the membrane with interstitial clear spaces is seen.

Crystal-like materials of undetermined nature are found in the clear spaces. Small sodium pyroantimonate deposits are observed mostly over the collagen bundles
(Experiment #6. Magnification: X7,920).

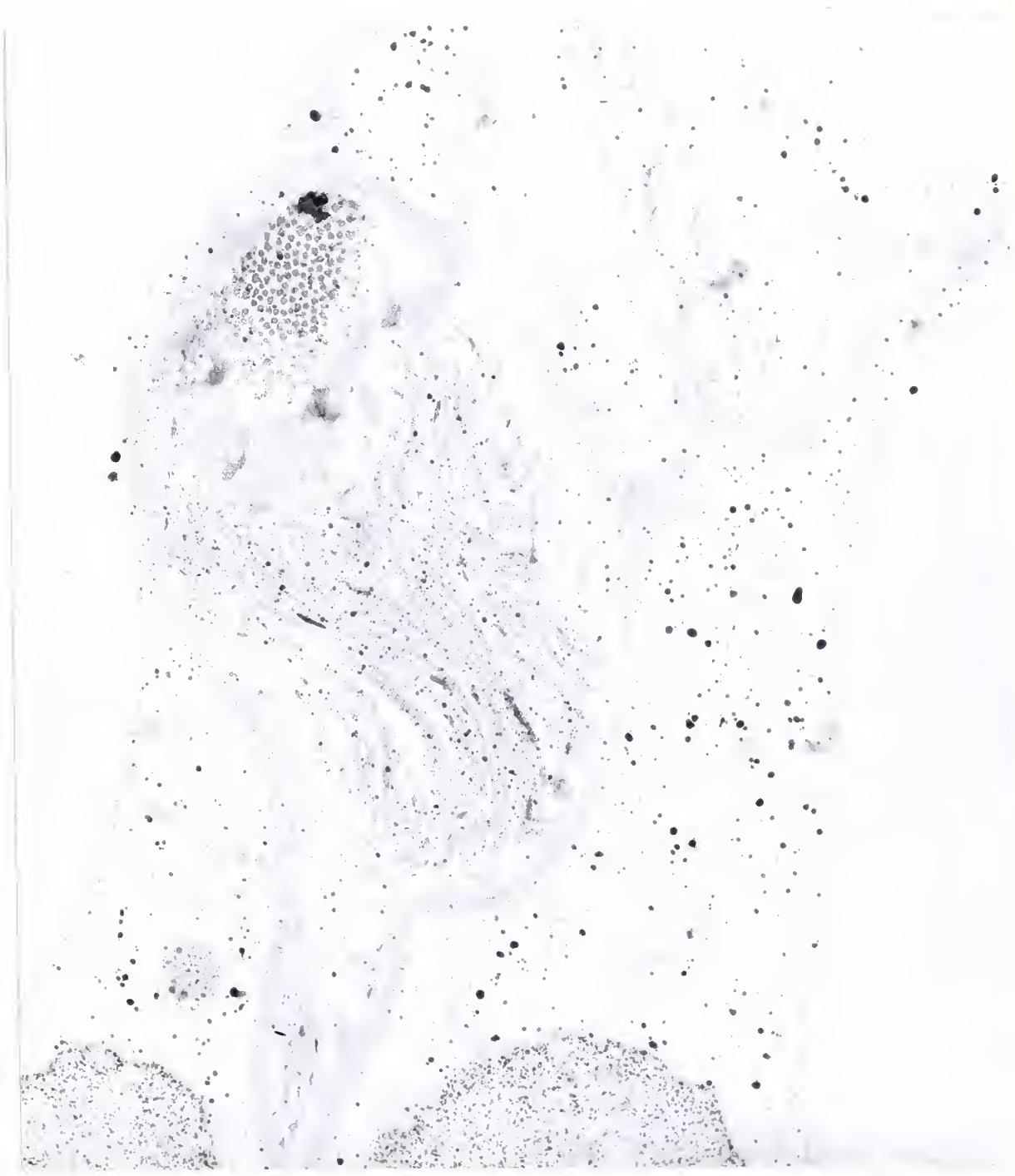

Figure 17: A high magnification view of the interstitium of a Group C shocked dog, showing disruption of the collagen fibers and surrounding clear spaces containing edema fluid (3+ interstitial disruption). Sodium deposits are sparse in the interstitium (1+). (Experiment #11. Magnification: X24,000).

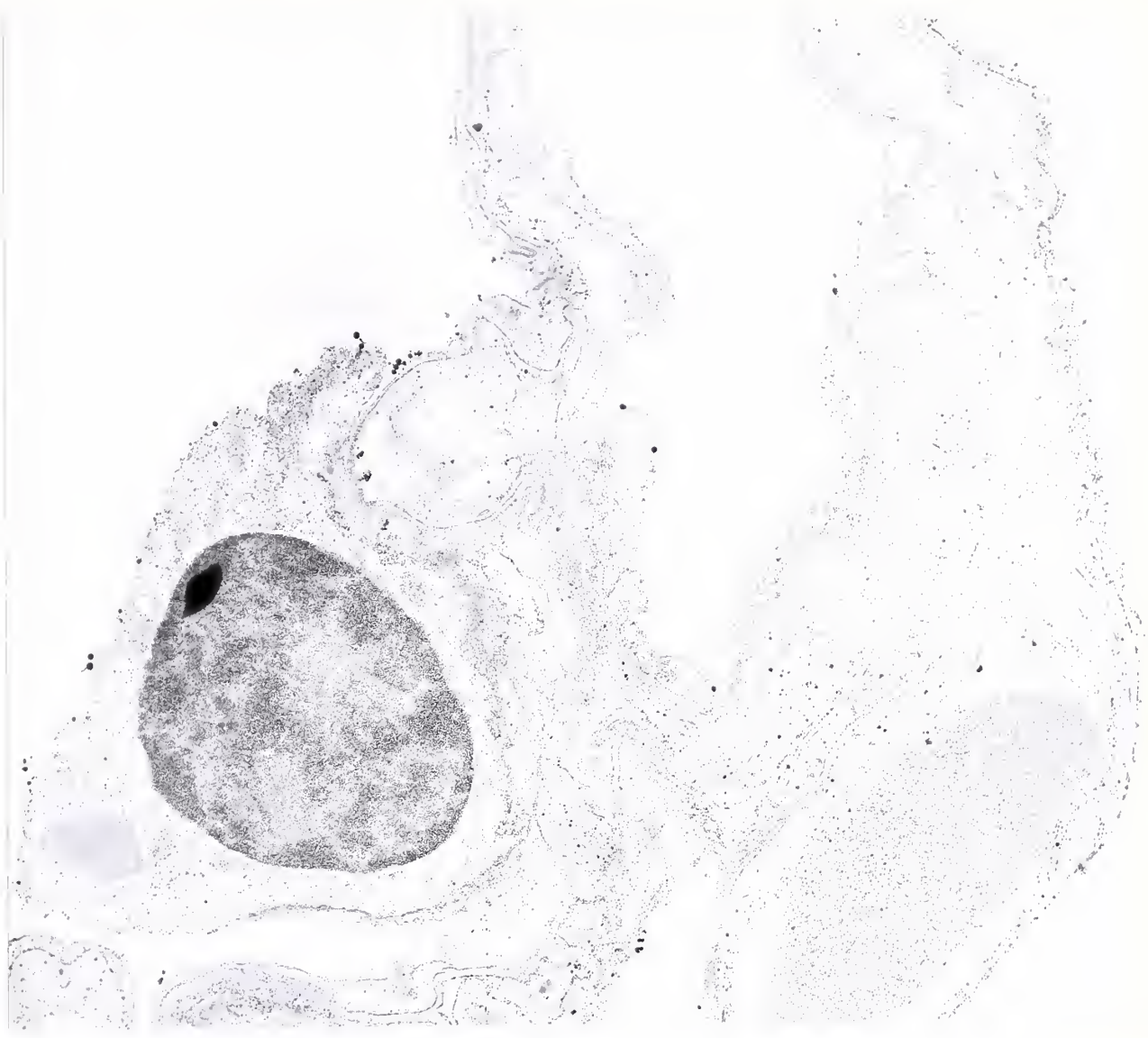

Figure 18: A low magnification view in a shocked dog, showing peri-capillary, edema-fluid-containing spaces associated with disruption of the collagen (3+ disruption). There is a generalized increase in the number of small electron-dense deposits (2+ interstitial sodium). A type II pneumocyte is seen in the lower left corner. The granules here are not empty, but there is apparent blunting of the epithelial microvilli. (Experiment #1. Magnification: X7,920).

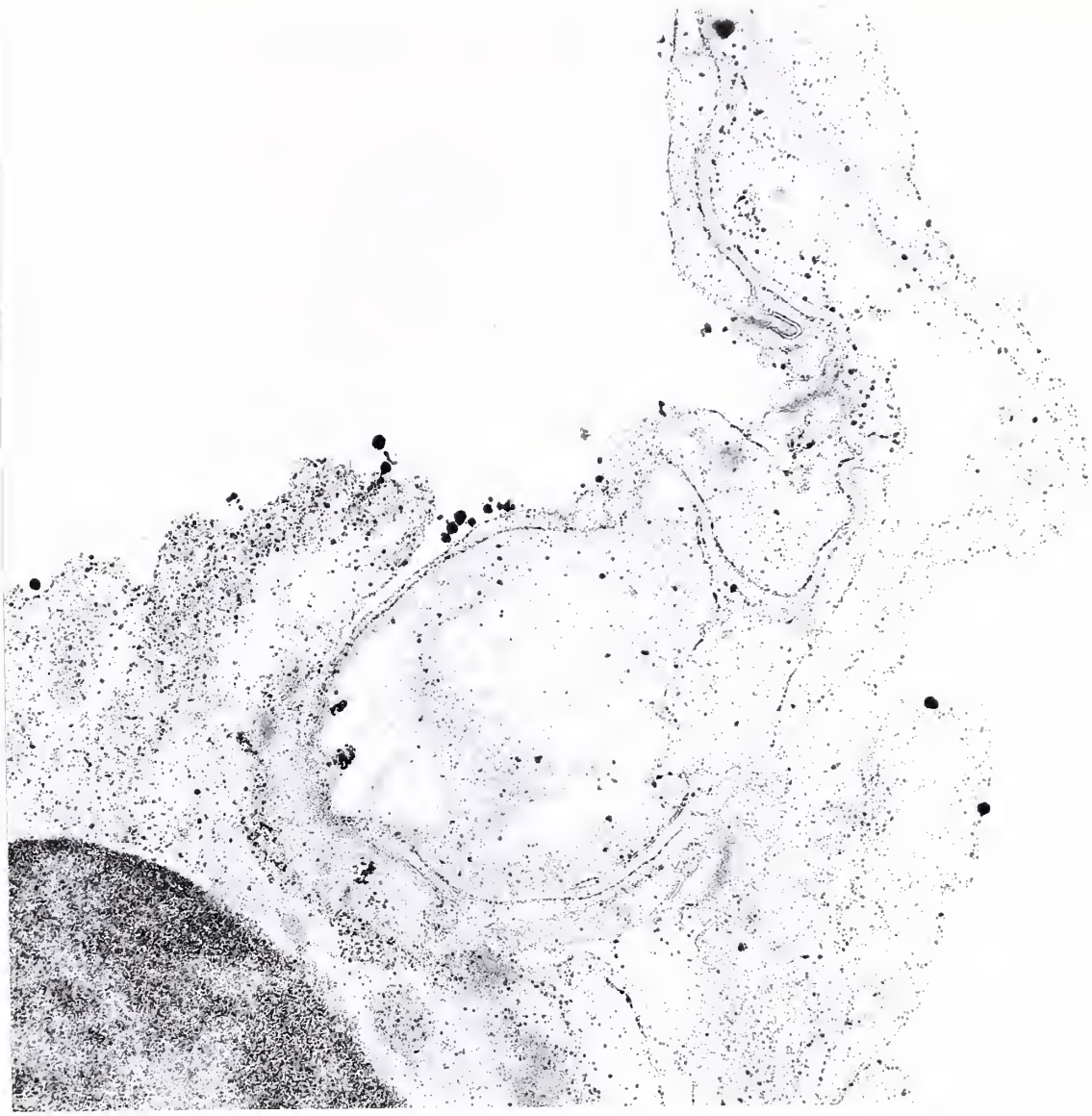

Figure 19: A higher magnification of Figure 18, showing peri-vascular edema, disruption of collagen, and generalized increase in small deposits in more detail. (Experiment #1. Magnification: X16,320).

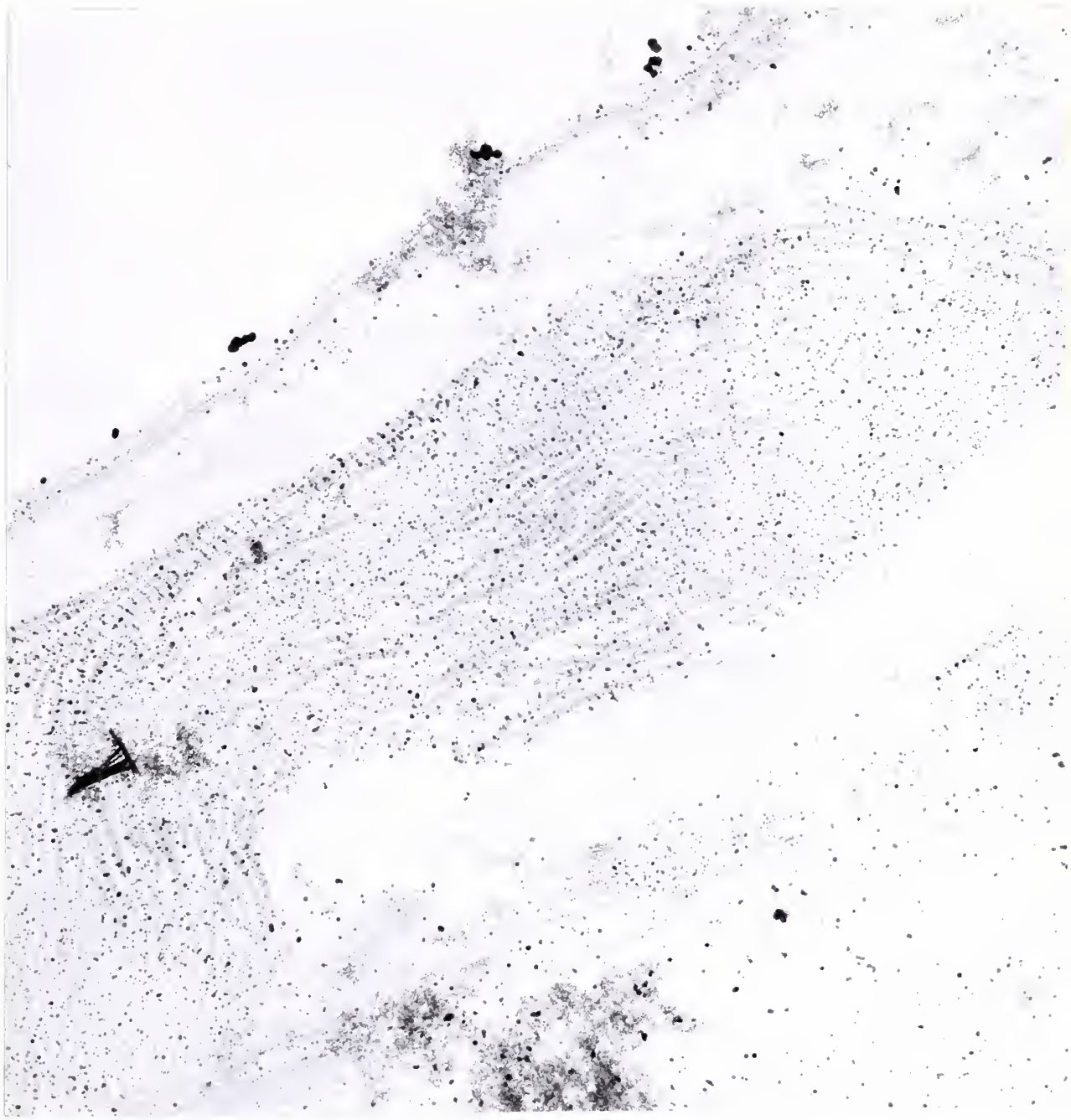

Figure 20: A high magnification view of the interstitium in a shocked dog. There are edema-fluid-containing spaces although the collagen bundles are not disrupted. There seems to be an increase in the number of small electron-dense deposits, particularly over the collagen fibers (2+ interstitial sodium).
(Experiment #3. Magnification: X30,000).

Figure 21: A very high magnification of a type II pneumocyte of a shocked dog. The granules are not empty, and there is apparent blunting of microvilli. Large sodium deposits can be seen near the cell surface. (Experiment #13. Magnification: X48,000).

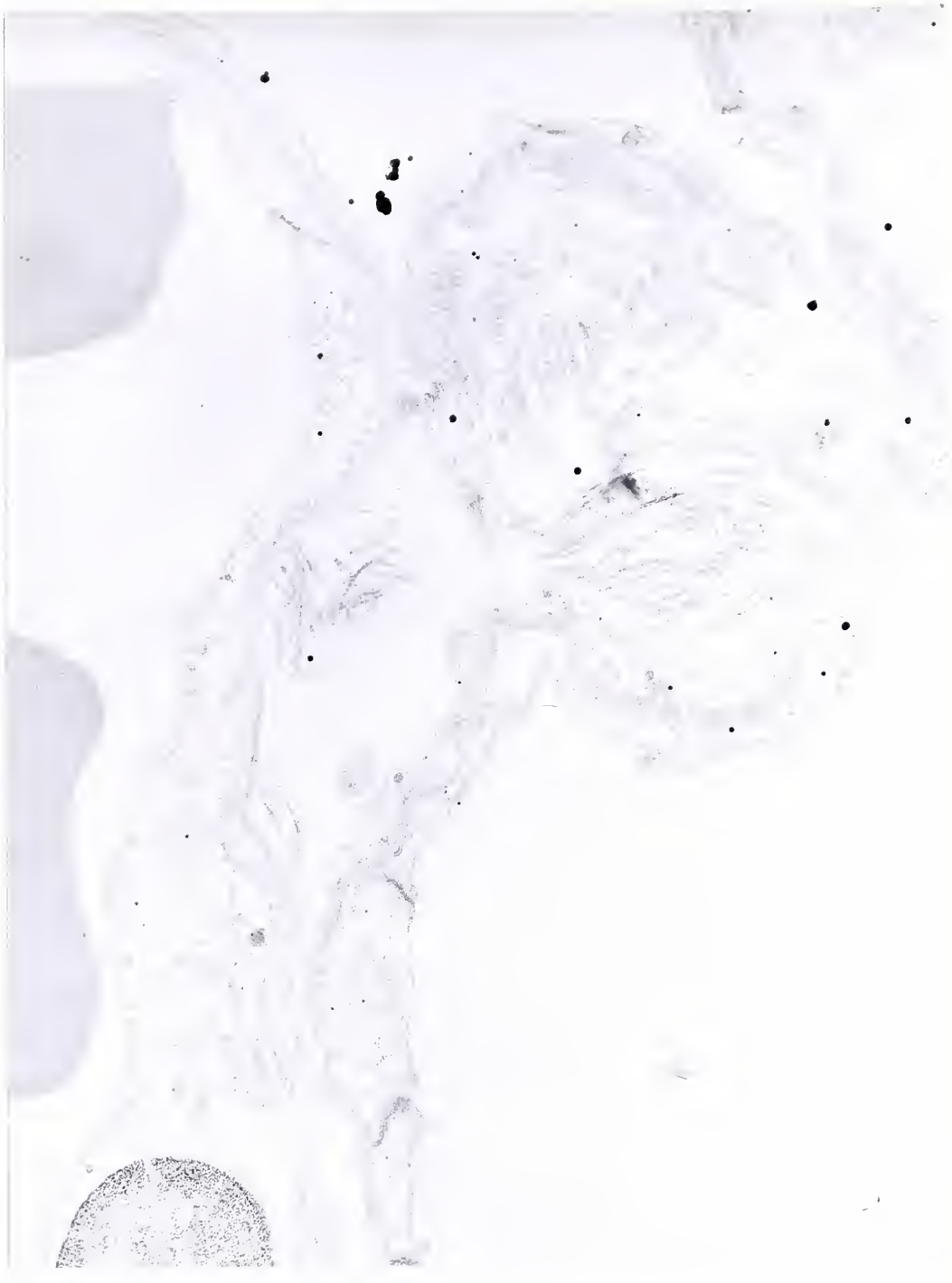

Figure 22: A low-magnification view of the disrupted interstitium in a Group D dog (recipient of shock plasma). Peri-vascular clear spaces are seen around disrupted collagen fibers (3+ interstitial disruption). There does not seem to be any increase in interstitial sodium (1+ sodium). The endothelial vesicles to the left of the picture do not appear to be increased. (Experiment #2. Magnification: X13,440).

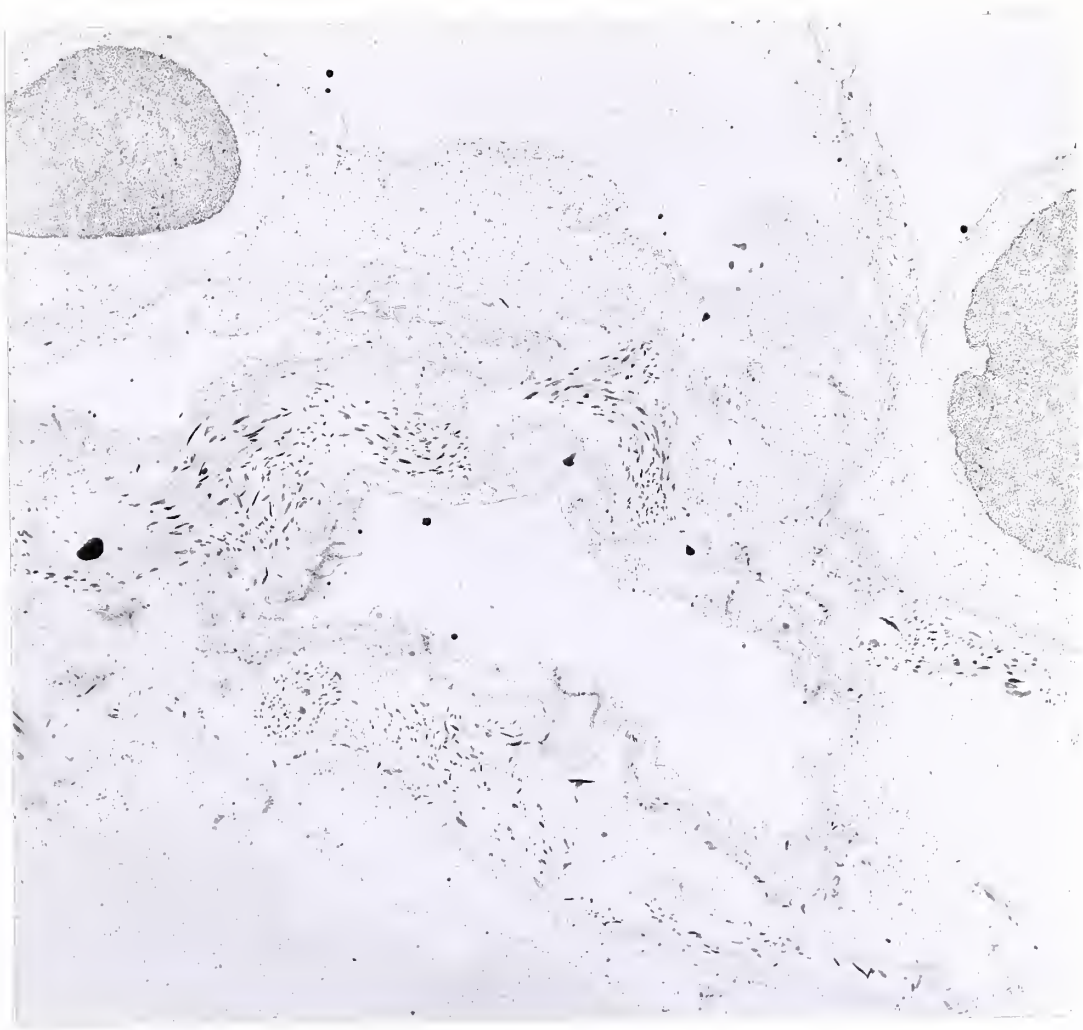

Figure 23: A low-power view of the interstitium of a dog which had received shock plasma (Group D). The collagen bundles look fairly well preserved, although there is an edema fluid-containing, clear space in the lower right corner (2+ interstitial disruption). There are crystal-like deposits over the collagen bundles, which may or may not represent sodium. A type I pneumocyte is seen in the mid-right field, and an endothelial cell is present in the upper left corner. Endothelial vesicles do not appear to be increased in number.
(Experiment #14. Magnification: 9,360).

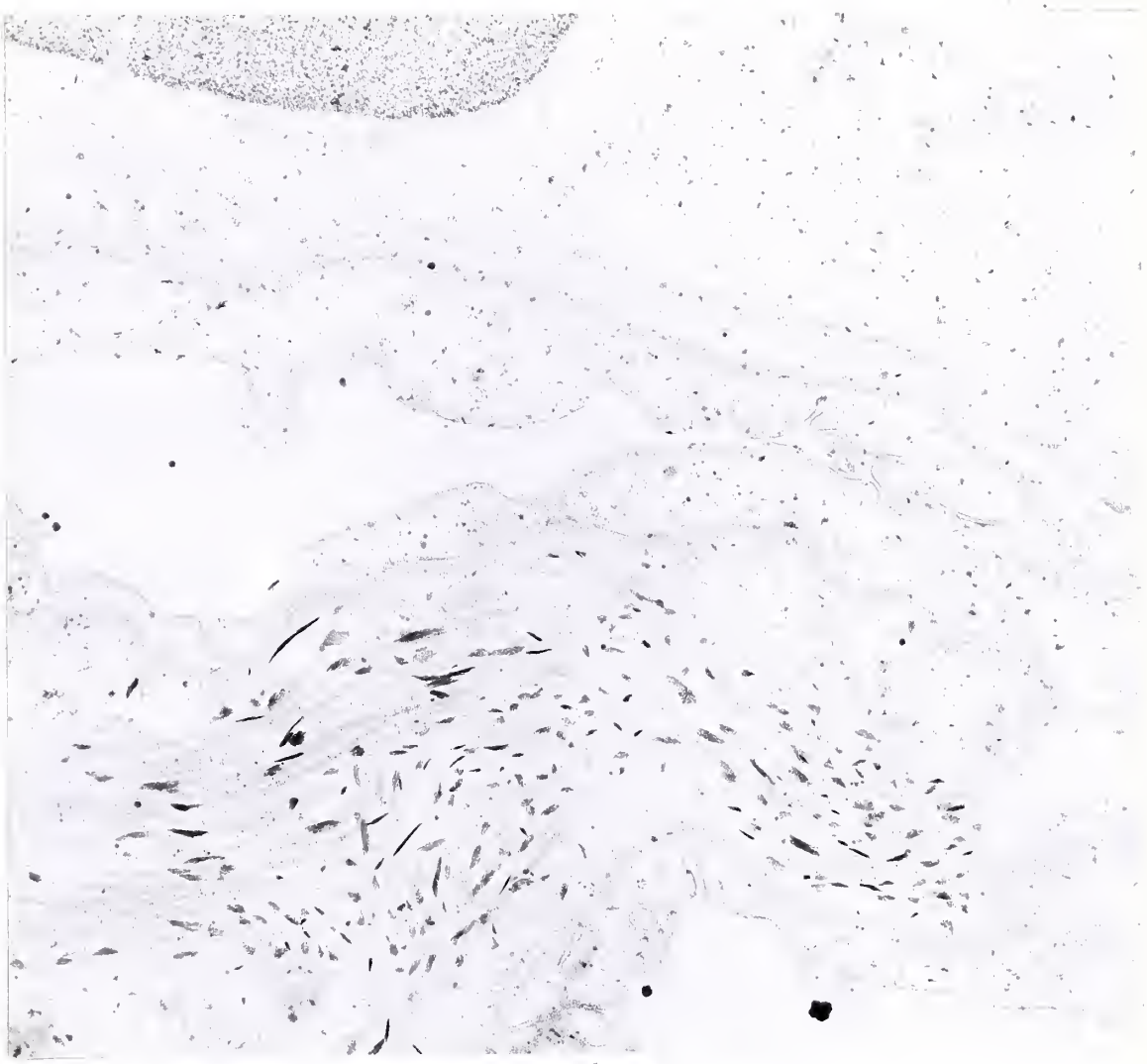

Figure 24: A higher magnification of Figure 23, showing the crystal-like materials over the collagen fibers in more detail.

The small, round electron-dense deposits purported to represent sodium are sparsely seen in this field (1+ interstitial sodium). No obvious edema is observed.

(Experiment #14. Magnification: X24,000).

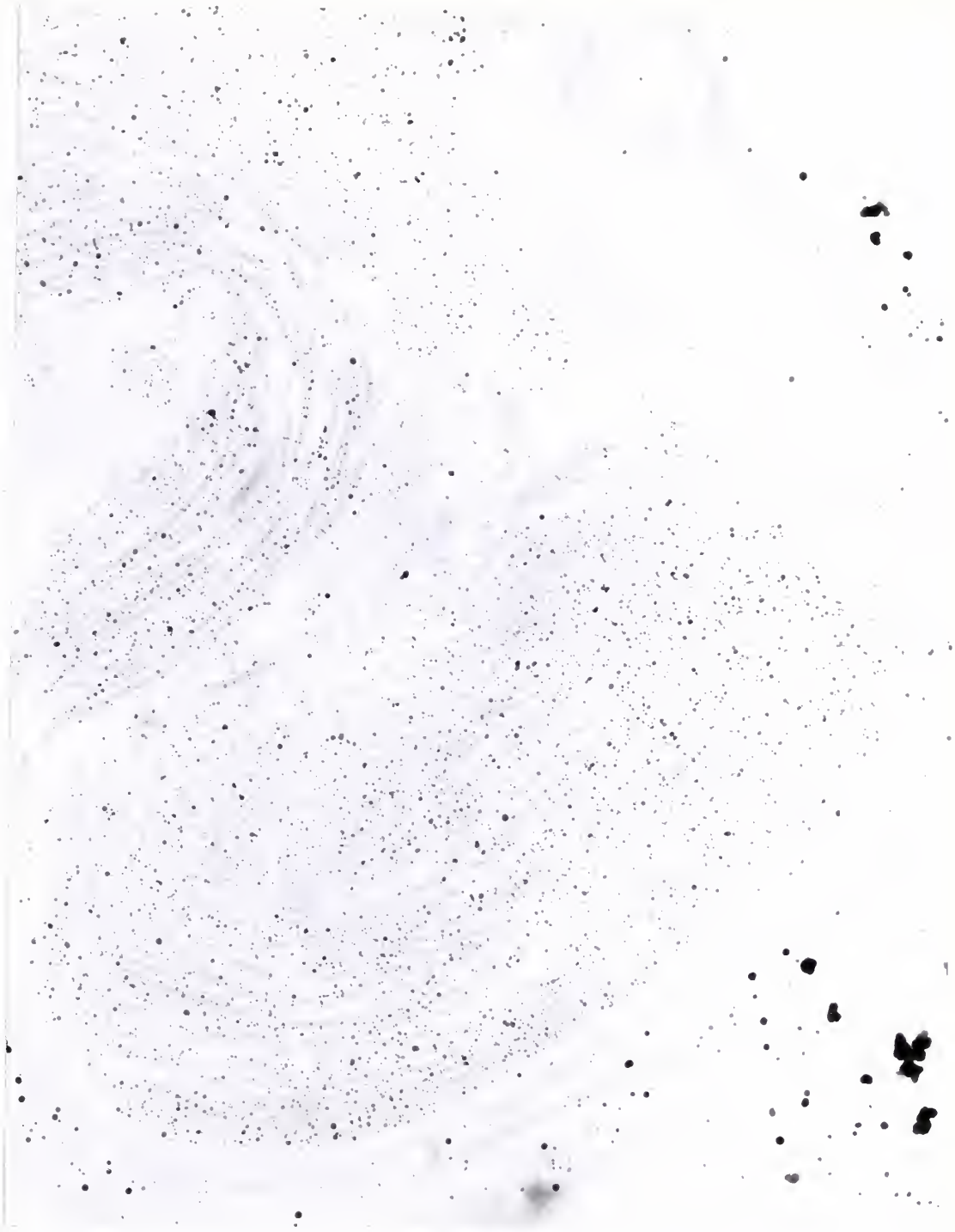

Figure 25: A high magnification view of the interstitium of a Group D dog (recipient of shock plasma), demonstrati somewhat disrupted collagen fibers, clear spaces, and moderate amount of interstitial sodium (2+ sodium). A few large aggregates of sodium pyroantimonate are seen in the lower right corner.
(Experiment #9. Magnification: X24,000).

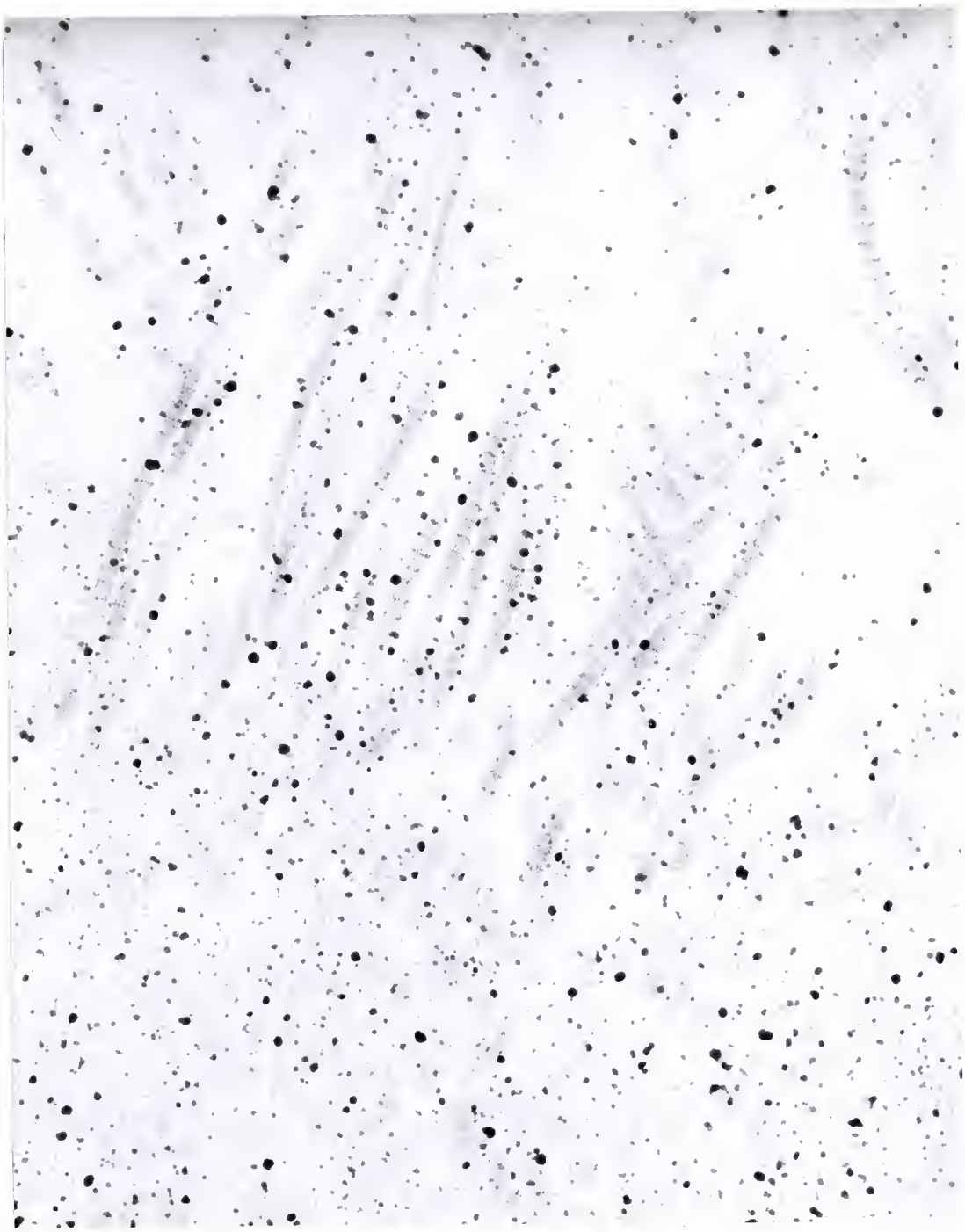

Figure 26: A very high magnification view showing disrupted collagen fibers and moderate increase in sodium deposition in a Group D dog that had received shock plasma. (3+ interstitial disruption and 2+ interstitial sodium).
(Experiment #9. Magnification: X48,000).

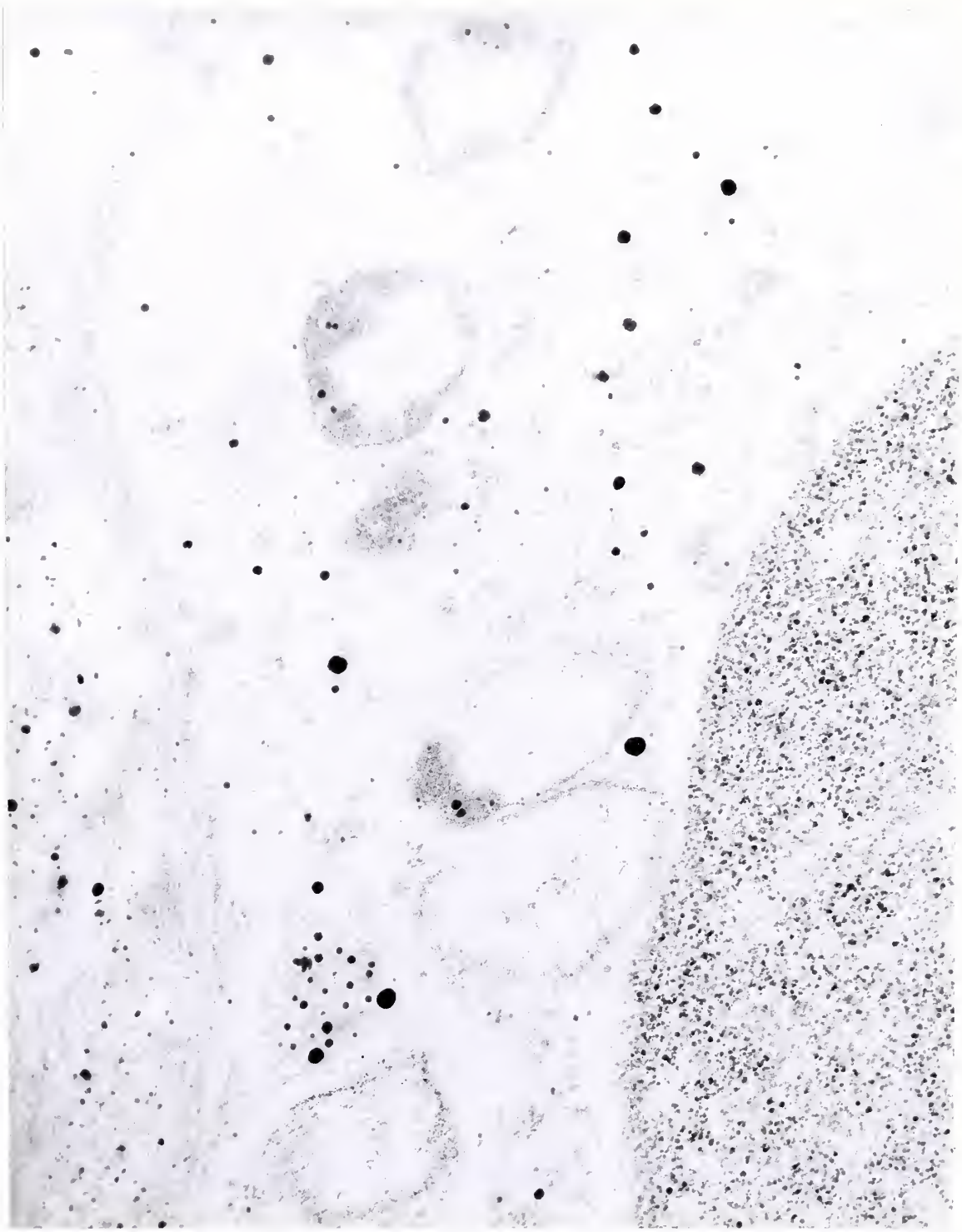

Figure 27: A very high magnification view of part of a type II pneumocyte in a Group D dog (recipient of shock plasma). Some of the intracytoplasmic granules are empty. (Experiment #9. Magnification: X48,000).

REFERENCES.

(1) Attar,S.M.A., Tingey,H.B., McLaughlin,J.S., Cowley, R.A.: Bradykinin in Human Shock. Surg Forum 18:46, 1967.

(2) Aviado,D.M.: Adenosine Diphosphate and Vasoactive Substances. J Trauma 8:880, 1968.

(3) Back,N., Wilkens,H., Steger,R.: Proteinases and Proteinase Inhibitors in Experimental Shock States. Ann NY Acad Sci 146:491, 1968.

(4) Baird,J.N.,Jr., Thompson,R.L., DeVoe,K.: Shock Lung. Am J Obstet Gynecol 115:538, Feb 1973.

(5) Barkett,V.M., Coalson,J.J., Greenfield,L.J.: The Early Effects of Hemorrhagic Shock on the Surface Tension Properties and Ultrastructure of Canine Lungs. Johns Hopkins Med J 124:86, Feb 1969.

(6) Barkett,V.M., Coalson,J.J., Greenfield,L.J.: Effects of Pulmonary Denervation on Canine Lung Stucture and Surfactant after Hemorrhagic Shock. J Trauma 11:248, 1971.

(7) Blaisdell,F.W.: Respiratory Insufficiency Syndrome: Clinical and Pathological Definition. J Trauma 13:195, 1973.

(8) Blaisdell,F.W., Lim,R.C.,Jr., Stallone,R.J.: The Mechanism of Pulmonary Damage Following Traumatic Shock. Surg Gynec Obstet 130:15, 1970.

(9) Blaisdell,F.W., Schlobohm,R.M.: The Respiratory Distress Syndrome: A Review. Surgery 74:251, 1973.

(10) Bryant,L.R., Trinkle,J.K., Dubilier,L.: Acute Respiratory Pathophysiology after Hemorrhagic Shock. Surgery 68:512, 1970.

(11) Buckberg,G.D., Lipman,C.A., Hahn,J.A., Smith,M.J., Henessen,J.A.: Pulmonary Changes following Hemorrhagic Shock and Resuscitation in Baboons. J Thorac Cardiovasc 59:450, 1970.

(12) Bulger,R.E.: Use of Potassium Pyroantimonate in the Localization of Sodium Ions in Rat Kidney Tissue. J Cell Biol 40:79, 1969.

(13) Burford,T.H., Burbank,B.: Traumatic Wet Lung. Observations on Certain Physiologic Fundamentals of Thoracic Trauma. J Thorac Surg 14:415, 1945.

(14) Campbell,G.S., Haddy,F.J., Adams,W.L., Visscher,M.B. Circulatory Changes and Pulmonary Lesions following Increased Intracranial Pressure, and the Effect of Atropi on Such Changes. Amer J Physiol 158:96, 1949.

(15) Chien,S., Dellenback,R.J., Usami,S., Burton,D.A., Gustavson,P.F., Magazinovic,V.: Blood Volume, Hemodynamic and Metabolic Changes in Hemorrhagic Shock in Normal and Splenectomized Dogs. Am J Physiol 225:866, Oct 1973.

(16) Chien,S., Gregersen,M.I.: Determination of Body Fluid Volume, in: Physical Techniques of Biological Research, edited by W.L.Nastuk. New York: Academic, 1962, vol 4, pp. 1-105.

(17) Chryssanthou,C.: The Possible Implication of a Humoral Smooth Muscle Acting Factor (SMAF) in Shock.

Mt Sinai J Med NY 41:260, 1974.

(18) Cleghorn,R.A.: Studies of Shock Produced by Muscle Trauma. II. Pathological Changes in Various Tissues. Canad J Res. Sect E. 24:155, 1946.

(19) Clermont,H.G., Adams,J.T., Williams,J.S.: The Effect of Cross Circulation in Hemorrhagic Shock. Surg Gynec Obstet 135:593, Oct 1972.

(20) Collings,J.A.: The Causes of Progressive Pulmonary Insufficiency in Surgical Patients. J Surg Res 9:685, 1969.

(21) Cook,W.A.: Experimental Shock Lung Model. J Trauma 8:793, 1968.

(22) Cottrell,T.S., Levine,O.R., Senior,R.M., Wiener,J., Spiro,D., Fishman,A.P.: Electron Microscopic Alterations at the Alveolar Level in Pulmonary Edema. Circ Res 21: 783, 1967.

(23) Crowell,J.W.: Oxygen Transport in the Hypotensive State. Federation Proc 29:1848. 1970.

(24) Daicoff,G.R., Chavez,P.R., Anton,A.H., Swenson,E.W.: The Hemodynamic Effects of Serotonin in Pulmonary Embolism. Presented at the 48th Annual Meeting of the American Association of Thoracic Surgery, Pittsburg, April 24, 1968.

(25) Daniels,C., Stein,A.A., Moss,G.S.: The Shock Lung Syndrome: Anemia as a Predisposing Factor. Surg Forum 24:1, 1973.

(26) Darby,T.D., Watts,D.T.: Acidosis and Blood Epinephrin

Levels in Hemorrhagic Hypotension. Amer J Physiol 206: 1281, 1964.

(27) Davis,H.A.: Pathology of Dehydration Shock. Arch Surg 42:939, 1941.

(28) Desai,J.M., Kim,S.I., Monks,J., Shoemaker,W.C.: Sequence of Hemodynamic Events after Gradual Prolonged Hemorrhage. Physiologist 10:155, 1967.

(29) Eaton,R.M.: Pulmonary Edema: Experimental Observation Dogs following Acute Peripheral Blood Loss. J Thorac Surg 16:668, 1947.

(30) Farrell.G.L., Rosnagle,R.S., Rauschkolb,E.W.: Increased Aldosterone Secretion in Response to Blood Loss. Circ Res 4:606, 1956.

(31) Fegler,J., Banister,J.: Congestive Atelectasis in Lungs of Rabbits and Other Animals Subjected to the Action of Low Barometric Pressure. Quart J Exper Physiol 33:291, 1944-1946.

(32) Fishman,A.P.: Shock Lung: A Distinctive Non-Entity. Circulation 47:921, May 1973.

(33) Fishman,A.P., Pietra,G.G.: Handling of Bioactive Materials by the Lung. Part II. New Engl J Med 291: 953, 1974.

(34) Fukuda,T.: Endogenous Shock-Inducing Factor in Canine Hemorrhagic Shock. Nature 205:392, 1965.

(35) Fulton,R.L.: Adsorption of Sodium and Water by Collagen during Hemorrhagic Shock. Ann Surg 172:861, 1970

(36) Gilbert,H.C., DasGupta,T.K., Cochin,A., DeWoskin,R..

Newson,B., Moss,G.S.: Factors Affecting Interstitial Sodium Transport in Primate Lung. Surg Forum 24:10, 1973.

(37) Gilbert,R.P., Hinshaw,L.B., Kuida,H., Visscher,M.B.: Effects of Histamine, 5-Hydroxytryptamine and Epinephrine on Pulmonary Hemodynamics with Particular Reference to Arterial and Venous Segment Resistances. Am J Physiol 194:1, 1958.

(38) Glenn,T.M., Herlihy,B.L., Lefer,A.M.: Protective Action of Protease Inhibitor in Hemorrhagic Shock. Arch Int Pharmacodyn Ther 203:292, Jun 1973.

(39) Gomez,A.C.: Pulmonary Insufficiency in Non-Thoracic Trauma. J Trauma 8:656, 1968.

(40) Green,H.D., Bergeron,G.A., Little,J.M., Hawkins,J.E. Evidence from Cross-Transfusion Experiments that No Toxic Factor is Present in Ischemic Compression Shock Capable of Inducing a Shock State in Normal Dogs. Am J Physiol 149:112, 1947.

(41) Gump,F.E., Mashima,Y., Jolgenson,S., Kinney,J.M.: Simultaneous Use of Three Indicators to Evaluate Pulmonary Capillary Damage in Man. Surgery 70:262, 1971.

(42) Hanzlik,P.J., Karsner,H.T.: Anaphylactoid Phenomena. J Pharm Exp Ther 23:173, 1924.

(43) Hardaway,R.M., James,P.W.,Jr., Anderson,R.W., Bredenberg,C.E., West,R.L.: Intensive Study and Treatment of Shock in Man. JAMA 199 :779, 1967.

(44) Harkins, H.N.: Recent Advances in the Study and Management of Traumatic Shock. Surgery 9:231, 1941.

(45) Hashimoto,E.: Lung Lesion Produced by Materials Released from Superior Mesenteric Vein after Superior Mesenteric Artery Occlusion. Jap Circ J 35:1071, Sep 1971

(46) Hedden,M., Miller,G.J.: Mendelson's Syndrome and Its Sequelae. Canad Anaesth Soc J 19:351, 1972.

(47) Henry,J.N., McArdle,A.H., Scott,H.J., Gurd,F.N.: A Study of the Acute and Chronic Respiratory Pathophysiology of Hemorrhagic Shock. J Thorac Cardiovasc Surg 54:666, 1967.

(48) Hurtado,A., Kaltreider,N., Mc Cann,W.S.: Respiratory Adaptation of Anoxemia. Am J Physiol 109:626, 1934.

(49) Jenkins,M.T., Jones,R.F., Wilson,B., Moyer,C.A.: Congestive Atelectasis: Complication of Intravenous Infusion of Fluid. Ann Surg 132:327, 1950.

(50) Keller,C.A., Schramel,R.J., Hyman,A.L., Creech,O.,Jr: The Cause of Acute Congestive Lesions of the Lung. J Thorac Cardiovasc Surg 53:743, 1967.

(51) Kho,L.K., Shoemaker,W.C.: Cardiorespiratory Changes in Acute Hemorrhage. Surg Gynec Obstet 124:826, 1967.

(52) Kim,S.I., Shoemaker,W.C.: Role of the Acidosis in the Development of Increased Pulmonary Vascular Resistance and Shock Lung in Experimental Hemorrhagic Shock. Surgery 73:723, May 1973.

(53) Komnick,H., Komnick,U.: Elektronen mikroskopische Unter suchungen zur Funktionellen Morphologie des Ionentransportes Experimenteller Nachweis der Transport-

wege. Z Zellforsch Mikrosk Anat 60:163, 1963.

(54) Kusajima,K., Wax,S.D., Webb,W.R.: Microcirculation in the Reimplanted Lung in Hemorrhagic Shock. Surg Forum 24:3, 1973.

(55) Laennec,R.T.H.: De l'Auscultation Mediate ou Traite du Diagnostic des Maladies des Poumons et du Coeur, Fonde Principalement sur ce Nouveau Moyen d'Exploration. Paris, 1819.

(56) Lefer,A.M., Martin,J.: Role of Kinins in Hemorrhagic Shock. Fed Proc 28:272, 1969.

(57) Lewin,D.: The Use of Phenoxybenzamine and Propranolol in Shock Lung. Yale Thesis, 1974.

(58) Lewin,I., Weil,M.H., Shubin,H., Sherwin,R.: Pulmonary Failure Associated wiyh Clinical Shock States. J Trauma 11:22, 1971.

(59) Maire,F.W., Patton,H.D.: Neural Structures Involved in the Genesis of "Preoptic Pulmonary Edema", Gastric Erosions and Behaviour. Amer J Physiol 184:345. 1956.

(60) Mallory,T.B., Brickley,W.: Pathology with Special Reference to Pulmonary Lesions. Ann Surg 117:865. 1943.

(61) Martin,A.M.,Jr., Soloway,H.B., Simmons,R.L.: Pathologic Anatomy of the Lungs following Shock and Trauma. J Trauma 8:687, 1968.

(62) Mc Caa,R.E., Mc Caa,C.S., Cowley,A.W.,Jr., Ott,C.E. Guyton,A.C.: Stimulation of Aldosterone Secretion by Hemorrhage in Dogs after Nephrectomy and Decapitation. Circ Res 32:356, Mar 1973.

(63) McKay,P.A., Kumpress,J.H., Finlayson,N.H., Hampson, L.G.: Hypoxemia and Atelectasis in Experimental Hemorrhagic Shock: Its Decrease by Periodic Hyperinflation of Lungs. Can J Surg 12:357, 1969.

(64) Mc Namara,J.J., Molot,M.D., Stremple,J.F.: Screen Filtration Pressure in Combat Casualties. Ann Surg 172:334, 1970.

(65) Meyers,J.R., Moyer,J.S., Baue,A.E.: Does Hemorrhagic Shock Damage the Lung? J Trauma 13:509, 1973.

(66) Mills,M.: The Clinical Syndroma. J Trauma 8:651, 196

(67) Moore,F.D., Lucas,J.H.,Jr., et al. Post Traumatic Pulmonary Insufficiency. W.B.Saunders, 1969.

(68) Moss,G.S., DasGupta,T.K., Newson,B., Nyhus,L.M.: Morphologic Changes in the Primate Lung after Hemorrhagic Shock. Surg Gynec Obstet 134:1. 1972.

(69) Moss,G.S., DasGupta,T.K., Newson,B., Nyhus,L.M.: Effect of Hemorrhagic Shock on Pulmonary Interstitial Sodium Distribution in the Primate Lung. Ann Surg 177:211, 1973.

(70) Moss,G.S., Staunton,C., Stein,A.A.: Cerebral Hypoxia as the Primary Event in the Pathogenesis of the "Shock Lung Syndrome". Surg Forum 22:211, 1971.

(71) Moss,G., Staunton,C., Stein,A.A.: Cerebral Etiology of the "Shock Lung Syndrome". J Trauma 12:885, 1972.

(72) Moss,G.S., Stein,A.A.: Shock Lung: Anemia as a Predisposing Factor. Am J Surg 126:419, Sep 1973.

(73) Moutier,F.: Hypertension et Mort par Pulmonaire

Aigu chez les Cranioencephaliques. Presse Medicale 26:108, 1918.

(74) Moyer,C.A., Morgraf,H.W., Monafo,W.W.: Burn Shock and Extravascular Sodium Deficiency. Treatment with Ringer's Solution with Lactate. Arch Surg 90:799, 1965.

(75) Nachman,R.L., Webster,B., Ferris,B.: Characterizatio of Human Platelet Vascular Permeability-Enhancing Activit J Clin Invest 51:549, 1972.

(76) Nash,G., Bleunerhasset,J.B., Pontopiddan,H.: Pulmonary Lesions Associated with Oxygen Therapy and Artificial Ventilation. New Engl J Med 276:368, 1967.

(77) Olcott,C.IV, Reichgott,M., Robinson,A.J.: Bradykinin Production in Patients with Intravascular Coagulation. Circulation 46 (suppl II):199, 1972.

(78) Ratliff,J.L., Fletcher,J.R., Hirsch,E.F., Kopriva,C. The Mechanism of the "Lung Lesion" in Shock, in The Fundamental Mechanisms of Shock, p.203. edited by Hinshaw,L.B., Cox,B.G. Plenum Press, New York, London. 1972.

(79) Ratliff,N.B., Wilson,J.W., Hackel,D.B., Martin,A.M. The Lung in Hemorrhagic Shock.II: Observations on Alveol and Vascular Ultrastructure. Am J Path 58:353, 1970.

(80) Ravin, H.A., Schweinburg,F.B., Fine,J.: Host Resistance in Hemorrhagic Shock. XV. Isolation of Toxic Factor from Hemorrhagic Shock Plasma. Proc Soc exp Biol Med (NY) 99:426, 1959.

(81) Schweinburg,F.B., Shapiro,P., Frank,N., Fine,J.: Host Resistance in Hemorrhagic Shock. IX: Demonstration of Circulating Lethal Toxin in Hemorrhagic Shock. Proc Soc exp Biol Med 95:646, 1957.

(82) Sealy,W.C.: The Lung in Hemorrhagic Shock. J Trauma 8:774, 1968.

(83) Sealy,W.C., Ogino,S., Lesage,A.M., Young,W.G.,Jr.: Functional and Structural Changes in the Lung in Hemorrhagic Shock. Surg Gynec Obstet 122:754, 1966.

(84) Shires,G.T., Carrico,C.J., Canizaro,P.C.: Shock. W.B.Saunders Co., Philadelphia, London, Toronto, 1973.

(85) Shoemaker,W.C.: Physiological Mechanisms in Clinical Shock, in The Fundamental Mechanisms of Shock, p.57. ed. by Hinshaw,L.B., Cox,B.G. Plenum Press, New York, London. 1972.

(86) Shubrooks,S.J., Schneider,B., Dubin,H., Turino,G.M.: Acidosis and Pulmonary Hemodynamics in Hemorrhagic Shock. Am J Physiol 225:225, Jul 1973.

(87) Simeone,F.A., Witoszka,M.M.: The Central Nervous System in Experimental Hemorrhagic Shock. Am J Surg 119:427, 1970.

(88) Soma,L.R., Neufeld,G.R., Dodd,D.C., Marshall,B.E.: Pulmonary Function in Hemorrhagic Shock: the Effect of Pancreatic Ligation and Blood Filtration. Ann Surg 179:395, Ap 1974.

(89) Spath,J.A., Gorczynski,R.J., Lefer,A.M.: Pancreatic Perfusion in the Pathophysiology of Hemorrhagic Shock.

Am J Physiol 226:443, Feb 1974.

(90) Stallone,R.J., Herbst,H.H., Cafferata,H.T., Blaisdell,F.W., Murray,J.F.: Pulmonary Changes following Regional Ischemia: Response to Treatment. Am Rev Resp Dis 98:144, 1968.

(91) Staunton,C., Stein,A.A., Moss,G.: Cerebral Etiology of the Respiratory Distress Syndrome: Universal Response, with Prevention by Unilateral Pulmonary Denervation. Surg Forum 24:229, 1973.

(92) Sugg,W.L., Webb,W.R., Ecker,R.R.: The Prevention of the Lung Lesions Secondary to Hemorrhagic Shock. Surg Gynec Obstet 127:1005, 1968.

(93) Sugg,W.L., Craver,W.D., Webb,W.R., Ecker,R.R.: Pressure Changes in the Dog Lung Secondary to Hemorrhagic Shock: Protective Effect of Pulmonary Reimplantation. Ann Surg 169:592, 1969.

(94) Sugg,W.L., Webb,W.R., Nakae,S., Theodorides,T., Gupta,D.N., Cook,W.A.: Congestive Atelectasis: An Experimental Study. Ann Surg 168:234, 1968.

(95) Sukhnandan,R., Thal,A.P.: The Effects of Endotoxin and Vasoactive Agents on Dibenziline-Pretreated Lungs. Surgery 58:185, 1965.

(96) Swank,R.L., Hissen,W., Bellman,J.H.: 5-Hydroxytryptamine (Serotonin) in Acute Hypotensive Shock. Am J Physiol 207:215, 1964.

(97) Sykes,M.K.: Respiratory Disturbances in Shock, in Conference on Shock, p.27, edited by Ledingham,I McA,

Mc Allister,T.A. C.V.Mosby Co, St Louis, 1972.

(98) Teplitz,C.: The Ultrastructural Basis for Pulmonary Pathophysiology following Trauma; Pathogenesis of Pulmonary Edema. J Trauma 8:700, 1968.

(99) Torack,R.M., LaValle,M.: The Specificity of the PyroAntimonate Technique to Demonstrate Sodium. J Histochem Cytochem 18:635, 1970.

(100) Veith,F.J., Hagstrom,J.W.C., Nehlsen,S.L., Karl,R.C Deysine,M.: Functional, Hemodynamic, and Anatomic Changes in Isolated Perfused Dog Lungs: the Importance of Perfusate Characteristics. Ann Surg 165:267, 1967.

(101) Veith,F.J., Hagstrom,J.W.C., Panossian,A., Nehlsen,S.L., Wilson,J.W.: Pulmonary Microcirculatory Response to Shock, Transfusion, and Pump Oxygenator Procedures. A Unified Mechanism Underlying Pulmonary Damage. Surgery 64:95, 1968.

(102) Veith,F.J., Panossian,A., Nehlsen,S.L., Wilson,J.W Hagstrom,J.W.C.: A Pattern of Pulmonary Vascular Reactivity and Its Importance in the Pathogenesis of Postoperative and Posttraumatic Pulmonary Insufficiency. J Trauma 8:788, 1968.

(103) von Haam,E., Frost,T.T.: Changes in Parenchymatous Organs Produced by Artificially Produced Fever. Proc Soc Exp Biol Med 42:99, 1939.

(104) Weaver,D.O., Henson,C.C., Crowell,J.W., Arelger,R. Brunson,J.G.: Structural Alterations Produced in Dogs in Sublethal Hemorrhagic Shock. Arch Path 93:155, 1972.

(105) Webster,M.E., Clark,W.R.: Significance of the Callicrein-Callidinogen-Callidin System in Shock. Am J Physiol 197:406, 1959.

(106) Westerfeld,W.W., Weisiger,J.R., Ferris,B.G.,Jr., Hastings,A.B.: The Production of Shock by Callicrein. Am J Physiol 142:519, 1944.

(107) Wiggers,C.J.: Physiology of Shock. New York: Commonwealth Fund, 1950.

(108) Willwerth,B.M., Crawford,F.A., Young,W.G.,Jr., Sealy,W.C.: The Role of Functional Demand on the Development of Pulmonary Lesions during Hemorrhagic Shock. J Thorac Cardiovasc Surg 54:658, 1967.

(109) Wilson,J.V.: The Pathology of Traumatic Injury. Baltimore, the Williams and Williams Co., 1946.

(110) Wilson,J.W., Hackel,D.B.: A Unified Mechanism Producing a Microcirculatory Pulmonary Lesion in Response to Hemorrhagic Shock, Transfusion, and Pump Oxygenator Procedures. Anat Rec 160:452, 1968.

(111) Wilson,J.W., Ratliff,N.B., Hackel,D.B.: The Lung in Hemorrhagic Shock.I: In Vivo Observation of Pulmonary Microcirculation in Cats. Am J Path 58:337, 1970.

*****END*****

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

Madeleine A Cirello	12/13/76
NAME AND ADDRESS	DATE