CHRONIC PULMONARY EMPHYSEMA (AN EXPERIMENTAL STUDY)

II. Spontaneous Pulmonary Emphysema in Rabbits

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During attempts to produce chronic vesicular pulmonary emphysema experimentally in rabbits, it became obvious that emphysema occurred spontaneously in these animals. While this is probably known to individual workers, no record of such lesions could be found apart from Zahn's personal statement to Kläsi,[1] in 1886, that emphysema occurred spontaneously in old rabbits. For this reason, an account of the lesions and of certain associated inflammatory alterations will be given.

Material and Methods

The description which follows is based on the study of the lungs of 155 rabbits of various ages and breeds.

The lungs were removed and gently inflated through the trachea by Bouin's fluid at a head of pressure not exceeding 18 inches until expansion, as judged by inspection, was complete. The trachea was then tied and the lungs stored in 10 per cent formol-saline. Two blocks were taken routinely, one from an upper lobe including the anterior margin near the apex and the other at random from a lower lobe. Additional blocks were taken when necessary. The blocks were vacuum embedded in paraffin at -250 mm. of Hg.

Ordinary thin sections were not employed regularly. The optimum thickness for a thin section was found to be 20 μ, but even this was too thin for the study of emphysematous lesions and the elastic fibers. Therefore, thick sections of 100 μ were cut in every case. To prepare thick paraffin sections, it is advisable to embed in slightly softer wax than normally used. Curling of the thick sections can be prevented by holding down the leading edge. The sections were mounted in the usual way on albuminized slides.

Sections from each block were stained by hemalum and eosin and by Hart's modification of Weigert's resorcin-fuchsin elastic tissue stain,[2] omitting the final alcoholic rinse and counterstaining directly in saturated aqueous picric acid for 15 to 30 seconds. Gram's or Giemsa's stains were employed in examinations for organisms.

It might be thought that overenergetic tracheal inflation of isolated lungs could produce appearances similar to those of emphysema. Preliminary investigations showed that this was not the case. It should also be noted that these procedures did not increase the number of alveolar pores.

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Macroscopic Appearance

The lesions of naked eye dimensions fall into two main groups: congenital anomalies and acquired lesions.

Congenital Anomalies

Presence of a Left Middle Lobe. A complete left middle lobe was present in 20 per cent of cases; in 17 per cent the lobe was absent. The remaining cases showed some degree of partial separation of the left middle lobe. This is important only if a minimal degree of separation simulates a marginal lobule, one of the lesions to be described below.

Crenation of the Sharp Margins. Some degree of crenation of the sharp margins was present in 75 per cent of the lungs. This should not be confused with emphysema.

Smooth Pleural Clefts of Developmental Origin. In 33 per cent of cases, smooth regular developmental clefts in the pleura occurred in the lower lobes on the lateral diaphragmatic margin. Identical clefts occurred at various sites in other lobes in 7 per cent of cases. These clefts are of no importance, being unassociated with any emphysematous lesions.

Acquired Lesions

Marginal Lobules and Pleural Fissures. The name "marginal lobule" has been given to a lesion occurring on the sharp margins of the lungs. Some of these are nonemphysematous (Fig. 1). Many, however, resemble the large hypertrophic bullae of human emphysema (Fig. 2).

Nonemphysematous lobules are simply portions of a sharp margin partially isolated by fissures or depressions in the pleura above and below the lobule. They are overexpanded, and the curved free margin is sharp. Grossly emphysematous marginal lobules appear as striking, rounded, frequently predunculated, bullous structures of various sizes. The lobules are seen only on the sharp margins, most frequently on the anterior-medial margins of the upper or middle lobes. They may be single or multiple (Fig. 3) and vary in diameter from a cm. or less to 4 cm. Not all marginal lobules are emphysematous, but in general the more prominent the lobule the more emphysematous, and vice versa.

Pleural fissures may be present on the medial or lateral aspects of the lungs. They may be associated with marginal lobules or may occur independently. When both are present in the same lobe they may be quite separate; or the fissures may be continuous with the pleural depressions that isolate the lobules from the parent margin. Their irregu-

larity easily distinguishes fissures from smooth developmental pleural clefts. Marginal lobules and pleural fissures are both the result of inflammation.

Vesiculation. Macroscopic emphysematous lesions other than marginal lobules also occur on the sharp margins of the lungs. These are comparable with nonpedunculated marginal bullae seen in man and appear as tiny vesicles, like dewdrops or froth. The term vesiculation has been adopted for these lesions. This occurs most commonly at the apex or on the anterior margins of the upper lobes. The lesion is rarely seen in other sites. It may be associated with marginal lobulation (Fig. 4). The vesicles rarely exceed 1 mm. in diameter.

It is important to note that vesiculation is always a manifestation of underlying microscopic emphysema, whereas a marginal lobule may be nonemphysematous.

Generalized Emphysema. While the presence of generalized emphysema may occasionally be suspected on macroscopic examination, it can only be established, with certainty, microscopically.

Microscopic Appearance

Normal Histologic Structure

Most of the description which follows is based upon the appearances in thick section, as this enables the alveolar walls and the lesions to be studied in 3 dimensions (Fig. 5).

General. There is no material difference between the histologic arrangement of the rabbit lung and the human lung. However, all structures are more delicate in the rabbit, and nowhere is interstitial fibrous tissue conspicuous. Only one order of respiratory bronchiole can be detected and this is inconstant. The terminal bronchiole (nonrespiratory) can be regarded as communicating directly with the alveolar ducts. As in man, there is usually a single order of alveolar ducts which communicate directly with the atria, which in turn lead into the alveolar sacs. The term atrium will not be used, as it is doubtful if this can be regarded as a separate structure in the rabbit. The following terminology will be employed: terminal bronchiole, alveolar ducts, alveolar sacs, alveoli.

Alveolar Pores. The alveolar pores (pores of Kohn) have been discussed in a preceding article.[3] For the present, it is sufficient to state that in thick sections, small oval or rounded fenestrations, easily distinguishable from irregular artificial tears can be seen in the side walls and bases of the alveoli. Although pores are not visible in every alveolus and vary considerably in numbers, they have been seen in every rabbit lung in this series (Figs. 6 and 7). They are very infrequent in very young rabbits and increase in numbers with aging.

Elastic Tissue. The elastic tissue links bronchi, blood vessels and pleura with the alveolar framework of the lung (Fig. 8). The bundles of the alveolar elastica are in continuity with those of other structures and may be divided roughly into 3 main types.

"Thick": Large bundles of fibers that run round the mouths of alveoli, outlining the lumens of the alveolar ducts and sacs (Fig. 9). The component fibers of these bundles rearrange themselves and run down, mainly in the corners of the alveoli, as the medium bundles, to cross and rearrange themselves at the bottom of the alveolus (Fig. 10). The rearranged fibers, then, run onward as medium bundles, in the corners of the contiguous alveoli which belong to the neighboring alveolar sac or duct to continue laterally and circumferentially at the mouths of these alveoli as part of the thick bundles which outline this alveolar duct or sac.

"Medium": These have been described as deriving from the thick bundles. In addition to running directly down in the corners of the alveolus, fibers or fiber bundles run off from the main medium bundles and course obliquely across the alveolar walls. They may be very thin indeed, but always run right across the alveolar walls to reunite with the main system of medium or thick bundles.

"Fine": These bundles are usually, but not always, as thin as the thinnest of the medium bundles. Some of the fine bundles are derived from the medium type, some from the elastica of the terminal arterioles, while others have no demonstrable connection with the remainder of the elastica. Many of the fine bundles are remarkably tortuous. They terminate in relation to the capillaries by a fanning out of their individual fibers over the capillary wall. The fine bundles are extremely scanty and not constantly demonstrable. They are more plentiful in old than in young rabbits. There is no regular spatial relationship between any of the elastic bundles and the alveolar pores. Occasionally, however, a bundle may run around the margin of a pore.

The arrangement is essentially the same as that described in man by Eppinger [4] in 1876, and Orsós [5,6] in 1907 and 1936, but the fine fibers are much scantier in the rabbit than in man.

Pathologic Histology

The congenital anomalies are, *per se,* associated with neither emphysema nor any specific alterations in lung architecture. They will not be discussed further. The acquired lesions will be discussed under the following headings: Inflammatory lesions; marginal lobules and pleural fissures; emphysema.

Inflammatory Lesions. These consist of a subacute or chronic interstitial pneumonia which was present in 84 per cent of cases. Usually

the inflammation is very trivial and consists of minute focal areas of hypercellularity in the alveolar walls or perivascular connective tissue. These occur in all parts of the lungs, but frequently only one or two foci are present in any given section. They consist of an interstitial infiltration by mononuclear cells and occasional lymphocytes. In larger lesions there is extreme and obvious interstitial infiltration associated with alveolar catarrh and occasional small areas of frank alveolar consolidation. The exudate, in these cases, mainly consists of mononuclear cells with occasional giant cells and scanty lymphocytes. Polymorphonuclear cells rarely are seen except when necrosis of the exudate occurs. The lumens of bronchi are not involved except in the largest consolidated areas. Examination of all the more active lesions in Gram or Giemsa stained sections revealed no organisms. No further bacteriologic studies were carried out.

Where the lesions are of minor or moderate severity, there is no obvious change in lung architecture beyond the thickening of the alveolar septums by the infiltration (Fig. 11). Severe lesions affect the architecture in two ways. Firstly, there is a shortening and thickening of the alveolar septums in the inflammatory focus, and secondly, there is actual destruction of lung tissue due to necrosis in larger lesions.

Marginal Lobules and Pleural Fissures. The lesions seen in marginal lobules are twofold: firstly, those concerned with the formation of the lobule itself, and secondly, the development of emphysema in the lobule. The emphysema will be described later. Both the lobules and fissures result from the interstitial pneumonia described above. The architectural deformity caused by severe subpleural lesions pulls down the pleura and forms the fissure (Fig. 12). If this happens at the sharp margin of the lung, the fissure partially cuts off a portion of the sharp margin to form a marginal lobule. In early cases, marked interstitial pneumonia is present at the base of the lobule (Fig. 13), but at this stage there is no dilatation of alveoli or emphysema within the lobule. In time, the causative inflammatory changes become inconspicuous. Fibrosis is not a prominent feature and usually there is only slight residual thickening of the shortened septums. When emphysema develops in these marginal lobules, it does so subsequently, and bears no relation to the degree of activity of the inflammatory changes.

Emphysema. The microscopic changes of emphysema are everywhere the same, differing only in grade of severity. However, it is convenient to classify the lesions according to distribution as follows:

I. Marginal emphysema.
   (A) Vesiculation
   (B) Emphysema in marginal lobules

II. Generalized emphysema.

I. Marginal emphysema. The term vesiculation has been retained to distinguish between local foci of emphysema confined to the sharp margins of the lungs, but not within a marginal lobule, from emphysema within these lobules. Either type of marginal emphysema may occur independently or in the same lung, and either or both may be associated with generalized emphysema.

The earliest microscopic alterations comprise a group of events. There is dilatation of the alveolar sacs and of the alveoli, with widening of the mouths of the latter. The dilatation is readily appreciated in the marginal lesions where the rest of the lung acts as a control. At the same time, structures indistinguishable from the alveolar pores are much more numerous in the dilated area. In addition to an increase in the numbers of "pores," there is a definite increase in their size (Fig. 14). It is not possible to determine whether the dilatation of alveoli and alveolar sacs or the increase in the number of the "pores" comes first, as the two phenomena are always seen together.

The next change is a progressive enlargement of the "pores" until adjacent pores merge to form larger gaps in the alveolar walls, causing a striking fenestrated appearance (Figs. 15 and 16). As the fenestration develops, the alveolar septums become lower and lower and finally disappear completely, leaving the alveolar sac as a simple expanded vesicle. Simultaneously, fenestration occurs in the alveoli subtended by the alveolar ducts and also in the boundaries between neighboring alveolar sacs. Extension of the process leads to the fusion of contiguous alveolar sacs to form a larger single vesicle communicating with the dilated fenestrated remains of the alveolar duct and presenting macroscopically as vesiculation (Figs. 17 and 18).

In vesiculation the changes rarely develop beyond this point. In marginal lobules, however, fenestration progresses until the whole lobule consists of a very few large vesicles imperfectly divided from each other by sheets and strands of fenestrated residual lung tissue (Figs. 19 and 20). The bullous spaces communicate with the terminal bronchioles.

During the process of fenestration, the capillary bed is gradually obliterated. An appearance of stretching or narrowing of a capillary can sometimes be seen. Such a stretched capillary may be the only observable structure separating two pores which are on the point of fusing. Finally, the only capillaries which remain are those in the residual sheets and strands of lung tissue which course across the emphysematous vesicles.

In the earliest lesions no change which precedes the appearance of fenestration can be detected in the elastica. The elastic bundles bear no

constant relationship to the fenestrations (Fig. 21), and while bundles may run round the margins of fenestrae, there is no evidence that the fenestrations are the result of rupture or other observable change in the elastica. Changes in the fine bundles are very difficult to assess because of the extreme scantiness and variable staining properties of these elements. They usually vanish, but even in severely fenestrated walls, occasional fine bundles persist in the residual tissue (Fig. 22). No statement can be made as to the mode of disappearance of the fine bundles apart from an impression that they may retract and fuse with the medium bundles.

Initially the medium bundles show no change (Fig. 22), but later they may be displaced by the enlarging fenestrations (Fig. 23). This leads to fusion of some of the medium bundles with each other so that fewer but thicker bundles now run across the alveolar wall. There is no sign of obvious rupture of these or other elastic bundles; but when careful search is made, occasionally, near a fenestration, the continuity of one of the finest of the medium bundles becomes interrupted and the ends appear to be retracted (Fig. 24). It is only when artifact can be excluded that such appearances can be accepted as a genuine lesion. It must be emphasized that changes indicative of rupture are rare, and there is no suggestion of widespread loss or rupture of the medium fibers.

Initially and even in grossly fenestrated alveoli, the thick bundles show no change. There is no hint of rupture. Instead, as the alveolar septums are destroyed, the thick bundles become augmented by the addition of other bundles, displaced in the process of fenestration, and look thicker than corresponding bundles in less fenestrated areas. Both the thick and medium bundles appear to be responsible for the maintenance of relatively normal architecture even in markedly fenestrated areas. However, as fenestration proceeds, all the elastic bundles are displaced toward the periphery and remain intact in the rim of tissue that separates the alveolar sac from its neighbor. In this tissue there is an increased number of thick and medium bundles per unit area while the bundles are thicker and compounded of more component fibers than normal.

With the retraction and loss of the alveolar septums, the bundles no longer run in 3 dimensions from the mouth of one alveolus to cross at the base and then on, upwards, to the mouths of the alveoli of the adjacent alveolar sac. They are now rearranged in a simpler, virtually two-dimensional network that outlines the simple ovoid vesicle of the emphysematous alveolar sac. The individual fibers of the bundles redistribute themselves at the crossing points in the network as did the medium bundles at the base of a normal alveolus. At the same time, the

alveolar ducts also lose their alveolar septums, and an identical re-arrangement of the elastica takes place at this level (Fig. 25). As the marginal lesions develop, the spatial re-arrangement continues, re-duplicating the changes just described at the level of alveolar sacs and ducts. There is no evidence that rupture plays a part in the development of even the largest bullous lesions (Fig. 26).

II. Generalized emphysema. This may be present with or without either of the two types of marginal emphysema. The changes in generalized emphysema are the same as in the marginal forms, but differ in the extent to which they develop. Thus, the destruction of the alveolar walls by fenestration usually is only partial in the deeper parts of the lungs, and there is preservation of the outlines of alveolar sacs and ducts without the formation of large vesicles.

In the least severe examples there is fairly widespread fenestration of alveolar walls which, however, may be patchy in distribution, leaving areas of alveolar tissue that are within normal limits (Figs. 27 and 28). The fenestration increases in severity and extent until it is widespread and obvious in nearly every part of the lung (Fig. 29). In such cases the solidity of the alveolar walls, as seen in thick sections, is lost, and the lung is converted into an open network (Figs. 30 and 31). The remains of the capillary bed run in the strands of residual alveolar tissue.

In the absence of normal lung in the same section to serve as a control, it is not easy to assess dilatation of the alveoli and alveolar sacs. Nevertheless, the appearances give the impression of distention. Occasionally, in the subpleural regions or in relation to larger bronchi or blood vessels, there is loss of alveolar septums or even fusion of alveolar sacs. When a sharp margin is involved, vesiculation is produced. It must be emphasized that it is essential to employ thick sections for the certain diagnosis of generalized emphysema, especially in the less severe grades in which there may be no obvious alteration in architecture in thin sections. In the more severe grades, even in thin sections, gaps begin to appear in the line of the alveolar septums.

The changes in the elastica are the same in generalized as in marginal emphysema. There is merely loss of the fine bundles and re-arrangement and fusion of some of the medium bundles. Only rarely is there evidence of rupture of some of the thinnest medium bundles. Usually the thick and most of the medium bundles remain apparently unchanged and, unless there is loss of alveolar septums, they do not show the peripheral displacement seen in the more advanced marginal lesions. Indeed, the thick and medium bundles appear largely to be responsible for the maintenance of the reasonably intact architecture of the lung. A lung showing considerable fenestration in the hemalum-eosin stained section may

show little obvious change in the elastic fibers (Figs. 32 and 33). However, when areas of gross and minor fenestration in the same section are compared, it is seen that the thick and medium bundles in the grossly fenestrated areas are thicker, due to displacement and fusion of some of the bundles in the course of fenestration. As in the marginal lesions, signs of rupture of fibers are very inconspicuous, and there is no evidence of any degenerative change in the elastica.

Incidence, Pathogenesis and Nature of the Lesions

The description is based on the study of the lungs of 155 rabbits which have been divided into 4 groups:

Group A: Normal rabbits known to be between 5 and 11 weeks old.

Group B: Rabbits which have been sacrificed in the course of experiments unconnected with the respiratory system.

Group C: Normal rabbits known to be over 2½ years old.

Group D: Rabbits sacrificed in the course of acute experiments involving thoracotomy or direct puncture of the heart.

The rabbits in groups B and D were adults of miscellaneous ages, apparently between 9 and 18 months old, but their exact ages were not known. Groups A and C were collected to collate the incidence of the lesions with age.

Congenital Anomalies

These are unimportant except for the possible confusion with emphysematous lesions. The overall incidence has already been given.

Acquired Lesions

The incidence of the individual lesions is shown in Tables I and II. It should be noted that, in Table II, some of the lungs included in the nonemphysematous column had marginal lobules which did not show emphysema microscopically.

Marginal Lobules. The incidence of marginal lobules ranged between 15 and 44 per cent in the various groups, with an overall incidence of 25 per cent. Inflammatory changes were present in all the lobules, and the appearances left no doubt that these lesions were of inflammatory origin. The figures show that of a total of 38 cases of marginal lobules, only 25 showed emphysema in the lobules microscopically. This supports the view that the lobules are first formed by inflammatory alterations and subsequently develop emphysema. This increasing incidence in the older ager group suggests that age plays a part in the development of emphysema in marginal lobules.

The present material provides no direct evidence as to how the

emphysema develops, but there appear to be two main possibilities. Firstly, the anatomic connection which remains between the lobule and the parent lung may be such that normal (or abnormal) ventilation of the lung causes abnormal distention of the lobule. Secondly, the inflammatory lesions themselves may so alter the nutrition or tensile strength of the lobule that even normal respiratory distention causes the emphysema. Naturally both these factors could operate together.

Theoretical considerations apart, marginal lobules are a frequent, naturally occurring lesion. Furthermore, these lobules so commonly become emphysematous in animals with otherwise normal lungs that

TABLE I

INCIDENCE OF MACROSCOPIC LESIONS

Group	No. in group	Macroscopic lesions		
		"Normal"	Marginal lobule	Vesiculation
A	20	17 (85%)	3 (15%)	0 (0%)
B	96	76 (79%)	18 (19%)	6 (6%)
C	21	12 (57%)	9 (43%)	7 (33%)
D	18	9 (50%)	8 (44%)	4 (22%)
Totals	155	114 (74%)	38 (25%)	17 (11%)

TABLE II

INCIDENCE OF MICROSCOPIC EMPHYSEMA

Group	No. in group	Nonemphysematous	Emphysematous		
			Marginal lobule	Vesiculation	Generalized
A	20	20 (100%)	0	0	0
B	96	78 (81%)	11 (11%)	8 (8%)	8 (8%)
C	21	8 (38%)	8 (38%)	7 (33%)	11 (52%)
D	18	11 (61%)	6 (33%)	4 (22%)	1 (6%)
Totals	155	117 (75%)	25 (16%)	19 (16%)	20 (13%)

marginal emphysema of this type cannot be considered significant in the experimental production of emphysema.

Vesiculation. In contrast to marginal lobulation, vesiculation was always a naked eye manifestation of an underlying microscopic emphysema. As in the case of marginal lobules, age appeared to be an important factor. Occasionally vesiculation was the only emphysematous lesion, but more often it was merely the local accentuation of generalized emphysema.

Minute foci of interstitial pneumonia were found in the area of vesiculation in 17 of the 19 cases, but in most instances the anatomic deformity of the lung framework, seen in the case of marginal lobules,

was absent. Nevertheless, in one or two cases there was a suggestion that vesiculation might result from local deformity of architecture, and it is possible that, in some cases at least, vesiculation may have a pathogenesis similar to marginal lobulation.

Generalized Emphysema. The different age incidence is striking. No generalized emphysema was found in the young rabbits of group A. The incidence was 8 per cent in the miscellaneous adults of group B, and 52 per cent in the old rabbits in group C. The present series does not include any animals known definitely to be between the ages of 9 and 18 months, but it is believed that most of the miscellaneous adults were between these ages. Experience with a group of 25 rabbits, known to be under 18 months old, showed a similarly low incidence of generalized emphysema.[7]

Age could operate in two ways in determining the increased incidence of generalized emphysema. Firstly, the emphysema might be a simple senile manifestation, and secondly, it might be the result of other causative factors which had to be operative over a long period of time, producing the lesions. Obviously a combination of senile changes and other factors could produce the lesions.

There was no sign of bronchial disease, *per se,* and there were no detectable differences in the elastica of the young and old rabbits except that this tissue was more prominent in the older animals. Thus, it appeared that the only lesion likely to be responsible for the development of generalized emphysema was the interstitial pneumonia. Therefore, the material was analyzed to see if there was any correlation between the two lesions.

The interstitial pneumonia has been classified on an arbitrary plus basis. It must be emphasized that the lesions graded as 1 or 2 plus were of very minor severity and that even the most severe lesions, in general, retained their patchy nature. The degree of generalized emphysema has also been graded on a plus basis; details of this will be given in the next article of this series.[7]

Table III shows that there is no correlation between the total incidences of generalized emphysema and of interstitial pneumonia in the various groups. While there was a somewhat lower incidence of the severest grades of interstitial pneumonia in the young rabbits of group A which had no generalized emphysema, there was no significant difference in the incidence of these lesions in the other groups. Thus the severity of the inflammation bore no direct relationship to the incidence of generalized emphysema. Table IV shows that the total incidence of the 3 plus inflammatory lesions was the same in the emphysematous and the nonemphysematous cases while there was little correlation between the

degree of inflammation and the degree of emphysema. The results do not suggest a direct relationship.

Histologically, there was no direct relationship between the foci of interstitial pneumonia, which were essentially of a trivial patchy nature, and the generalized emphysema. Nor was there any relationship between alveolar catarrh and emphysematous fenestration.

It is concluded that the relationship, if any, between interstitial pneumonia and generalized emphysema is indirect; perhaps disturbance in respiratory dynamics is the mechanism involved, e.g., excessive sneezing. Regardless of the pathogenesis, the significant fact is that after the

TABLE III

INCIDENCE OF GENERALIZED EMPHYSEMA AND INTERSTITIAL PNEUMONIA

Group	No. in group	Generalized emphysema, total incidence	Interstitial pneumonia				
			Total incidence	Degree			
				o	+	++	+++
A	20	o	16 (80%)	4 (20%)	11 (55%)	4 (20%)	1 (5%)
B	96	8 (8%)	79 (82%)	17 (18%)	37 (39%)	29 (30%)	13 (14%)
C	21	11 (52%)	20 (95%)	1 (5%)	6 (29%)	11 (52%)	3 (14%)
D	18	1 (6%)	16 (89%)	2 (11%)	6 (33%)	4 (22%)	6 (33%)

TABLE IV

DEGREE OF GENERALIZED EMPHYSEMA AND INTERSTITIAL PNEUMONIA

Degree of generalized emphysema	No. of cases	Degree of interstitial pneumonia			
		o	+	++	+++
o	135	24 (18%)	54 (40%)	38 (28%)	19 (14%)
+	10	o	3	6	1
++	6	o	2 (30%)	4 (50%)	o (20%)
+++	4	o	1	o	3

age of 2½ years, over 50 per cent of rabbits may be expected to have some degree of generalized emphysema as a naturally occurring lesion. The significance of this in the assessment of results in experimental emphysema is obvious.

Influence of Acute Operative Procedures. The rabbits of group D, which were miscellaneous adults, died during or within a few hours of operations on the thorax. Nearly all of them had tachypnea. Table II shows that the incidence of emphysematous lesions did not differ significantly from that in the other adult groups.

Nature of the Emphysematous Process

It has been convenient to subdivide the various emphysematous lesions according to their distribution, and this subdivision, especially in the case of marginal lobules, gives a partial indication of the nature of

the pathogenic factors involved. However, in spite of differences in distribution, the fundamental microscopic lesions in all the subdivisions were identical in character, differing only in the degree of their development.

In the previous section of this article it is shown that the classic descriptions of the changes in human chronic vesicular emphysema[3] are identical to the basic lesions in the rabbit. Hence, the rabbit can be accepted as a suitable animal for the experimental study of chronic emphysema. The lesions, as seen in thick sections, do not suggest that chronic emphysema results from tearing of the lung tissues. In addition, there is no evidence that rupture of the elastica is a primary, or even an important factor in the genesis of the lesions. Loss of alveolar tissue, including capillaries, in the course of fenestration appears to be the essential lesion of chronic emphysema. It is very difficult, morphologically, to regard fenestration as a purely mechanical effect, and it seems much more reasonable to consider it as a manifestation of tissue atrophy.

Summary

An account has been given of the types of spontaneous chronic vesicular emphysematous lesions and associated inflammatory changes found in the lungs of 155 rabbits.

The emphysematous lesions and the elastica were studied in paraffin sections 100 μ thick. The microscopic appearances of all types of emphysema were essentially the same and consisted of the development of progressive fenestration of the alveolar walls leading to destruction of the walls. The elastic tissue showed no changes which antedated the appearance of fenestration and seemed to be the most resistant component of the alveolar framework. The appearances are considered to be the result of an atrophy of the alveolar walls.

The following types of chronic emphysematous lesions have been distinguished:

(I) Generalized emphysema: This can only be diagnosed, with certainty, microscopically. It is not the direct result of inflammatory changes, but there may be an indirect relationship. The incidence of generalized emphysema is nil in young rabbits but rises to over 50 per cent in rabbits over 2½ years old. Various acute operative procedures did not influence the incidence of generalized emphysema.

(II) Emphysema in marginal lobules: Marginal lobules are formed by inflammatory deformity of the sharp margins of the lungs. Initially, the lobules are not emphysematous but become so subsequently. This type of emphysema should be disregarded in assessing the results of attempts to produce experimental emphysema.

(III) Vesiculation: These minute marginal emphysematous lesions usually constitute merely a local accentuation of generalized emphysema. But some examples may be the result of local inflammatory changes as in the case of marginal lobules. Therefore, caution is needed in the assessment of the significance of vesiculation in the experimental production of emphysema.

The associated inflammatory lesions were those of a subacute or chronic interstitial pneumonia, the causative organism of which was not identified.

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Legends for Figures

All microscopic sections have been cut at 100 μ unless otherwise stated. Except where indicated, photographs were prepared from sections stained with hemalum and eosin.

Fig. 1. Small nonemphysematous marginal lobule. × 1.

Fig. 2. Large emphysematous marginal lobule. × 1.

Fig. 3. Multiple emphysematous marginal lobules. × 0.6.

Fig. 4. Vesiculation at apex of lung. × 3.7.

Fig. 5. Normal rabbit lung in a thick section, showing alveolar ducts and surface view of intact alveolar septums. × 30.

Fig. 6. Alveolar pores in a young rabbit. × 480.

Fig. 7. Alveolar pores in an old rabbit. × 480.

Fig. 8. A general view of the lung elastica. Elastic tissue stain. × 60.

Fig. 9. "Thick" elastic fiber bundles outlining alveolar ducts and sacs. Elastic tissue stain. × 120.

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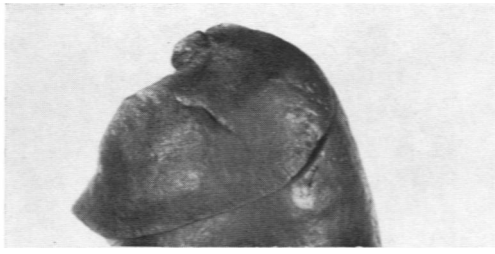

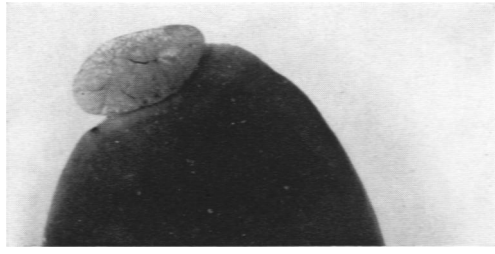

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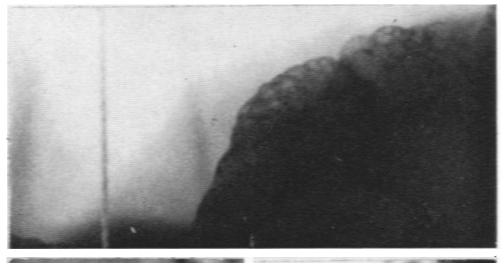

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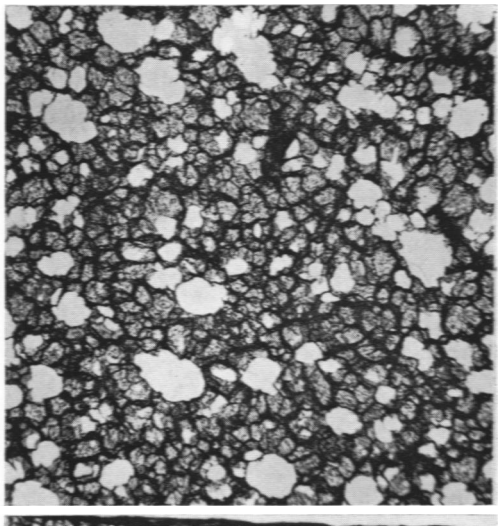

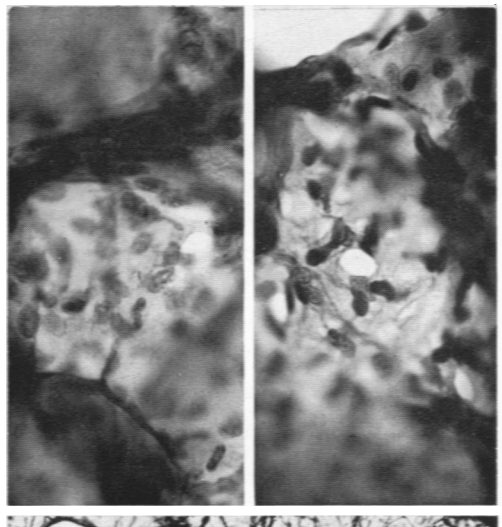

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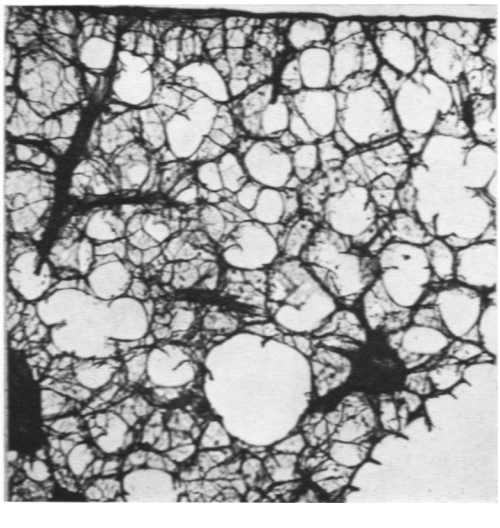

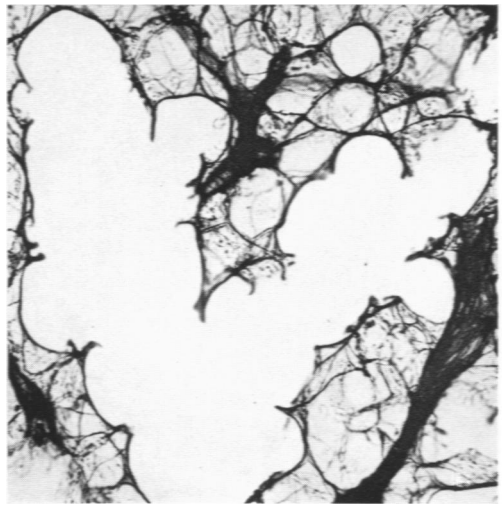

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FIG. 10. "Medium" elastic fiber bundles crossing and undergoing re-arrangement at the bottom of an alveolus. Elastic tissue stain. × 480.

FIG. 11. Subpleural interstitial pneumonia producing thickening of alveolar septums but no obvious architectural deformity. Section cut at 20 μ. × 60.

FIG. 12. Formation of a pleural fissure by contracture and deformity of underlying parenchyma due to interstitial pneumonia. Section cut at 20 μ. × 30.

FIG. 13. Nonemphysematous marginal lobule, showing interstitial pneumonia at the base of the lobule. × 7.5.

FIG. 14. Emphysematous alveolar septum, showing abnormally large and numerous fenestrations otherwise indistinguishable from alveolar pores. × 480.

FIG. 15. Marginal emphysema, showing obvious fenestration. × 60.

FIG. 16. A normal portion of the lung shown in Figure 15. × 60.

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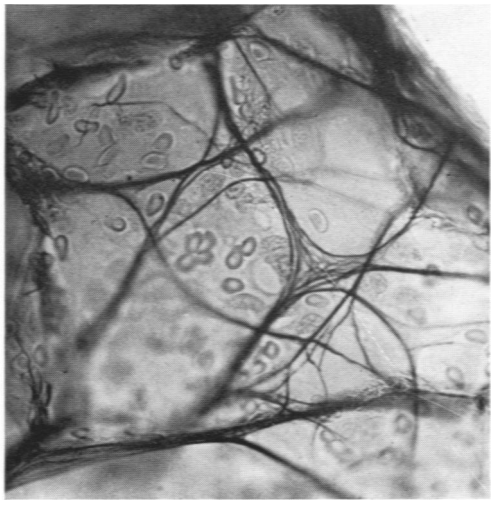

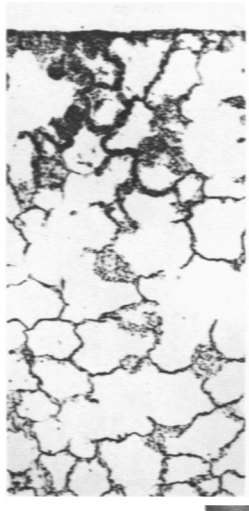

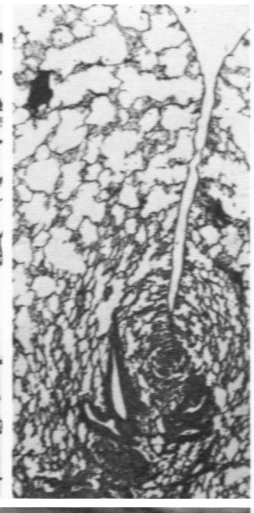

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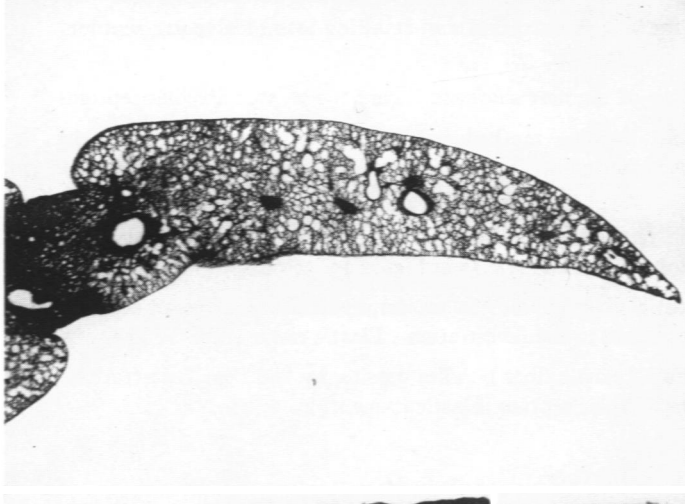

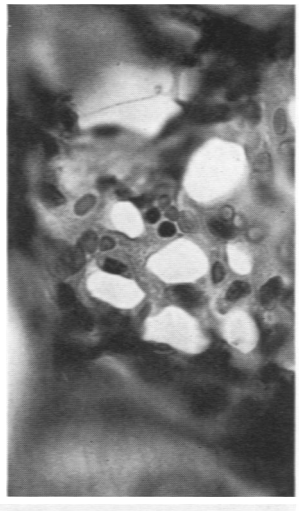

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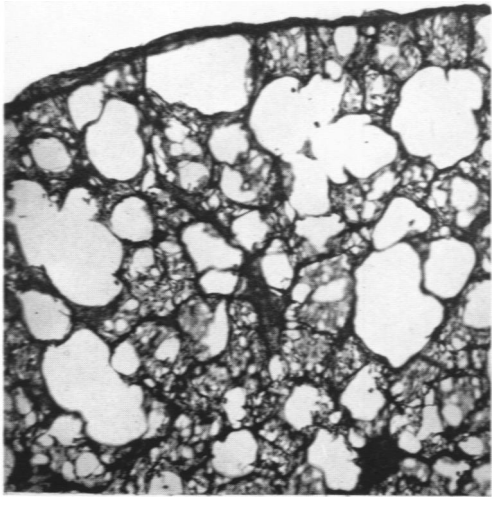

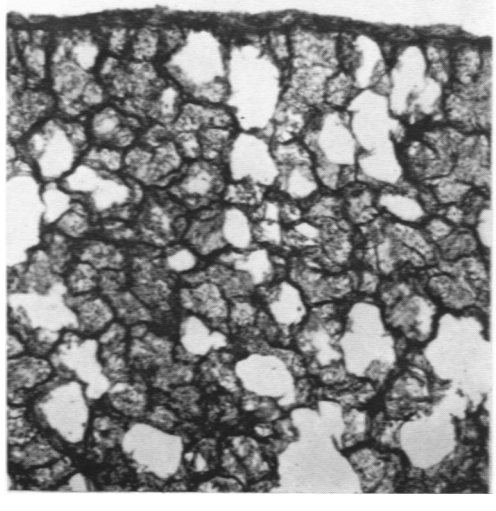

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FIG. 17. Vesiculation, showing fenestration and resulting loss of alveolar septums from alveolar ducts and sacs. × 30.

FIG. 18. A normal portion of the lung shown in Figure 17. × 30.

FIG. 19. Marginal lobule, showing marked emphysema. Fenestration has led to fusion of adjacent ducts and sacs. The remainder of the lung outside the lobule is normal. × 7.5.

FIG. 20. Fenestration in remaining septums between alveolar ducts in an emphysematous marginal lobule. Same lobule as in Figure 19. × 60.

FIG. 21. "Medium" elastic fiber bundles in an emphysematous alveolar septum. The bundles are not related to the fenestrations. Elastic tissue stain. × 480.

FIG. 22. Normal "medium" elastic fiber bundles passing by and near fenestrations in an emphysematous alveolar septum. Elastic tissue stain. × 480.

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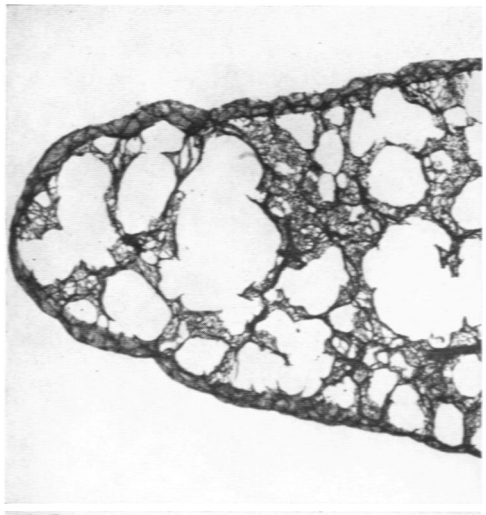

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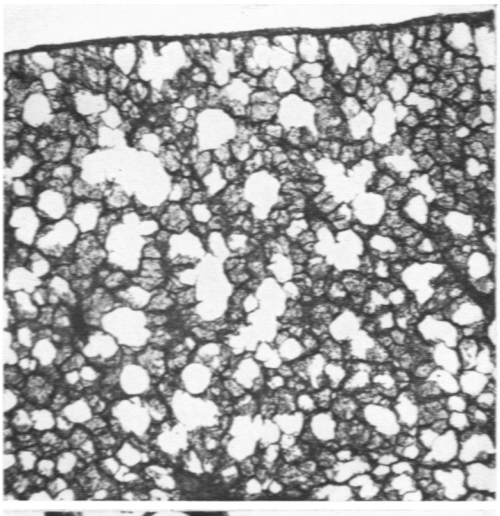

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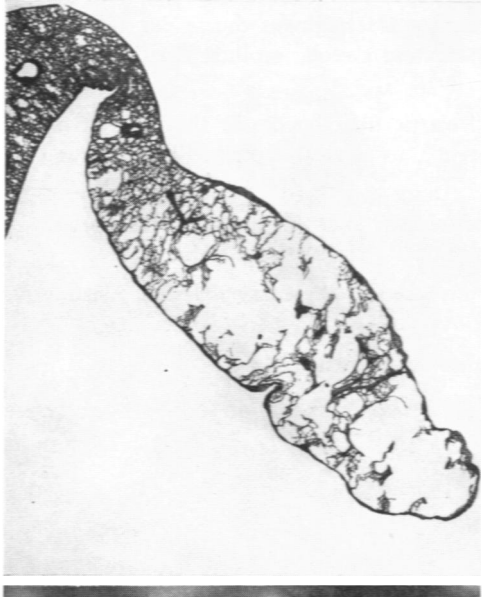

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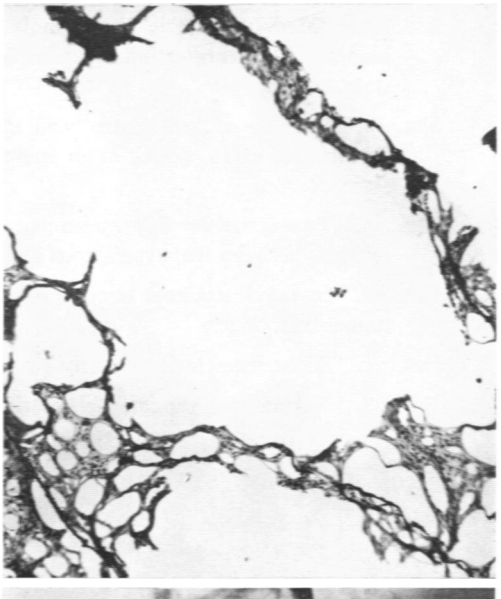

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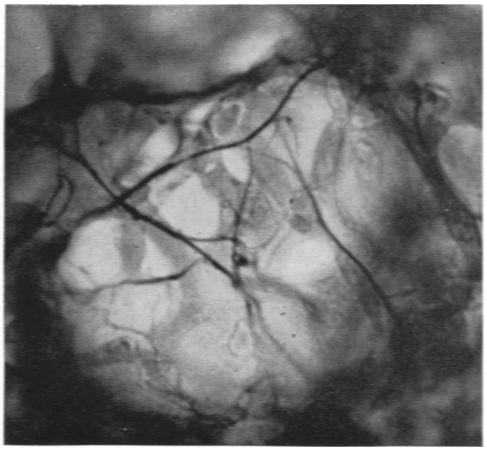

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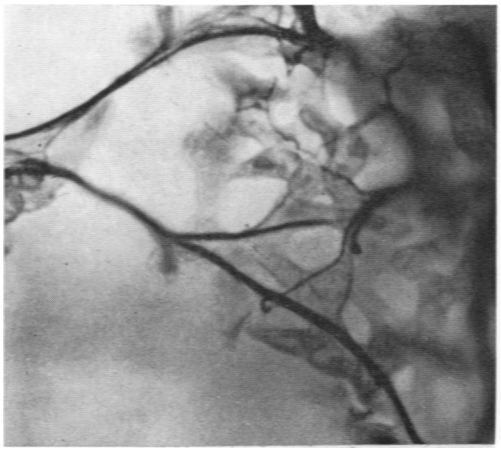


FIG. 23. "Medium" elastic fiber bundle running a serpiginous course due to displacement by fenestration in an emphysematous alveolar septum. Elastic tissue stain. × 480.

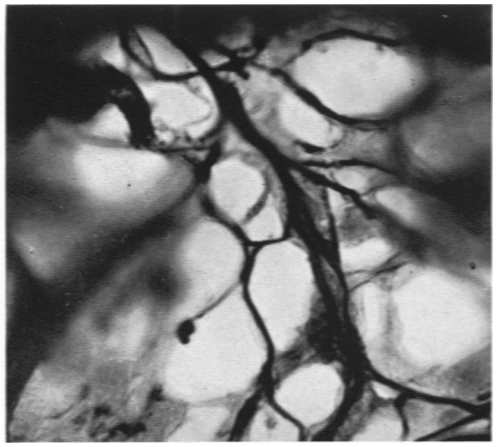
FIG. 24. Rupture of a delicate "medium" elastic fiber bundle to the right of a fenestration at 12 o'clock in an emphysematous alveolar septum. Elastic tissue stain. × 480.

FIG. 25. Two-dimensional arrangement of elastic fiber bundles in fenestrated septums between emphysematous alveolar ducts. Elastic tissue stain. × 120.

FIG. 26. Intact elastic fiber bundles in an advanced emphysematous lesion. Elastic tissue stain. × 120.

FIG. 27. Slight fenestration in early generalized emphysema. × 60.

FIG. 28. Normal lung for comparison with Figure 27. × 60.



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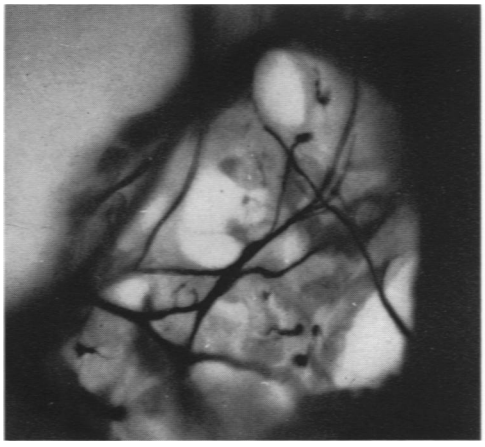

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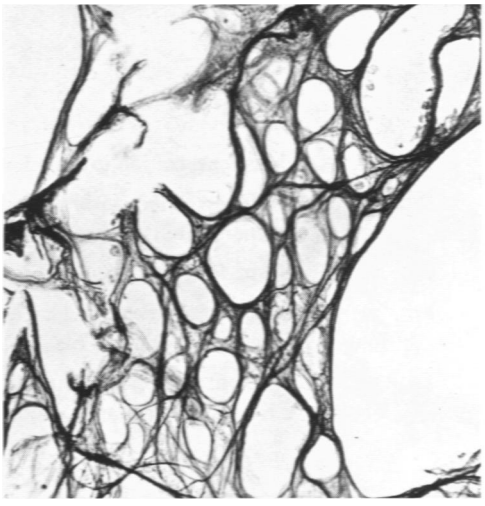

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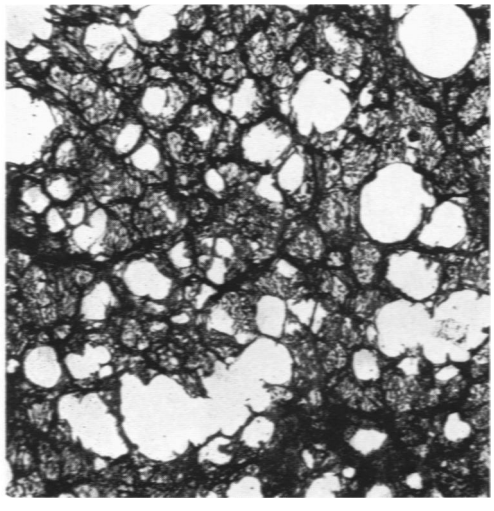

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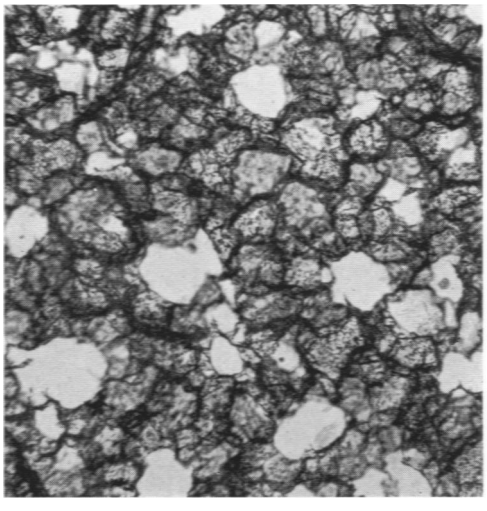

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FIG. 29. Obvious fenestration in a moderately severe generalized emphysema. × 60.

FIG. 30. Gross fenestration with virtual destruction of alveolar septums but retention of general architecture in very severe generalized emphysema. × 60.

FIG. 31. Detail of fenestration. Same lung as in Figure 30. × 120.

FIG. 32. General arrangement of elastica in severe generalized emphysema. Same lung as in Figures 30 and 31. Elastic tissue stain. × 60.

FIG. 33. General arrangement of elastica in a normal lung for comparison with Figure 32. Elastic tissue stain. × 60.

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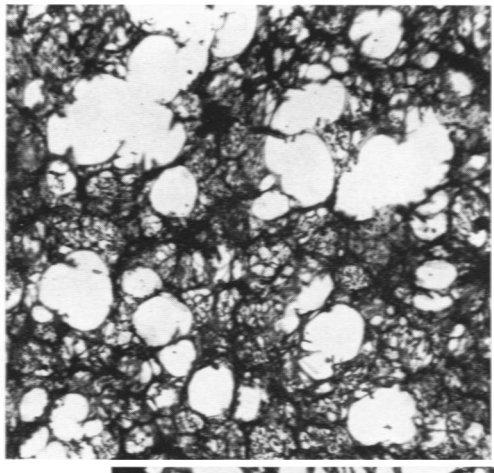

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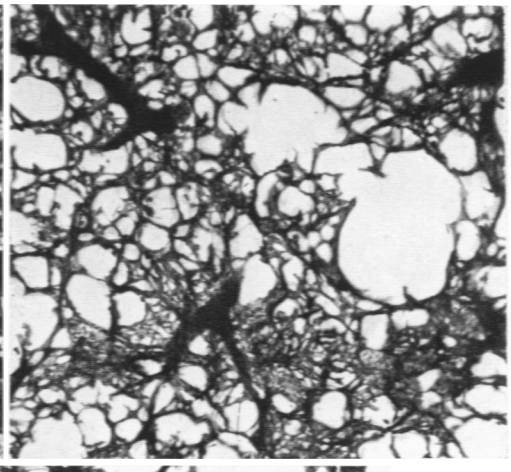

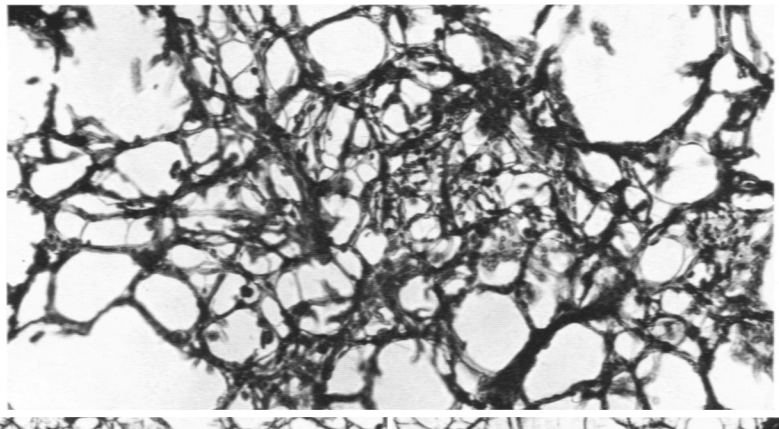

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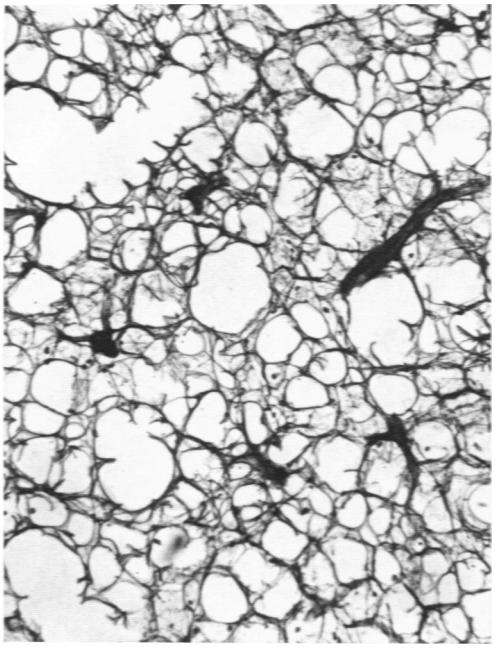

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