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THE REACTION PRODUCED IN THE PULMONARY ARTERIES BY EMBOLI OF COTTON FIBERS*

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In the routine examination of sections of lungs from necropsies over a period of 20 years, we have observed, as an incidental finding in 6 cases, foreign bodies in the smaller branches of the pulmonary arteries. These foreign particles were slender and had a faintly greenish tinge; they did not stain with the dyes used in routine histologic preparations and were doubly refractive. They did not cause thrombus formation. The foreign bodies usually lay against the intimal surface of the artery and in some instances a few large mononuclear cells and several multinucleated giant cells of the foreign body type had collected about them (Fig. 1).

When the histories of these patients were studied, there was one feature common to all: Each had received either one or more intravenous injections of physiologic saline or glucose solution or blood transfusions, within a period of not more than 10 days prior to death. The foreign particles were considered to be fragments of cotton that were contained in the solution injected and that had come either from the gauze through which the solution had been filtered, or from particles of a cotton stopper that adhered to the mouth of the flask.

To test the correctness of the impression that these foreign particles were cotton fibers and to study in detail the lesions that might be produced by them in the pulmonary arteries, the following experiments were performed.

PROCEDURE AND METHODS

A small mass of cotton, either absorbent or nonabsorbent, was immersed in physiologic saline solution and cut into very minute fragments. These were of such a size as to be readily drawn into a syringe through a no. 19 gauge hypodermic needle. Each cubic centimeter of saline solution contained approximately 0.02 cc. of cotton fibers. The physio-

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logic saline solution containing the cotton fibers was then sterilized in the autoclave at a pressure of 15 lbs. for 30 minutes.

Sixty-two adult albino rats were used in the experiment. Under ether anesthesia, an iliac vein was exposed, and approximately 1 cc. of the saline solution with the suspended cotton fibers was injected. When the injection did not proceed rapidly, it was found that the fibers had settled and jammed the plunger of the syringe. When this occurred another injection was made into the other iliac vein. There were no untoward effects from the injections and each animal appeared normal as soon as it recovered from the anesthesia. Rats in groups of 3 to 5 were sacrificed at varying intervals, some at the end of 24 and 48 hours and others at approximately weekly intervals thereafter for the first 2 months and at longer intervals between the third and sixth months.

At necropsy, 3 or 4 specimens of tissue were obtained from the lungs of each animal; these were fixed in Zenker's solution without the addition of acetic acid or formalin, and in 10 per cent formalin solution. Three to 5 sections were cut from each paraffin-impregnated block of tissue. In some instances, the block was sectioned serially. The routine stains were hematoxylin and eosin, and Weigert's stain for elastic tissue counterstained with hematoxylin and eosin. Occasionally, Wilder's silver stain counterstained with azocarmine-aniline blue was used.

Results

Some of the animals were injected with absorbent cotton, others with nonabsorbent cotton. The changes observed were the same, and a single description of the results will suffice for both groups. Before discussing the results it is necessary to review briefly the structure of the pulmonary artery of the rat.

The first branches of the pulmonary artery to enter the various lobes of the lung have walls of uniform thickness, the media being well developed. In the branches of medium size, the wall of the artery often undergoes an abrupt change in thickness, owing to a sudden thinning of the media. This change may involve both sides of the vessel as seen in longitudinal or tangential section, although in many the thinning of the media is restricted to a segment of the wall. From these vessels of medium size, branches are at times given off abruptly at right angles. The arterioles have walls of uniform width. The precapillary branches consist of endothelium, a single layer of elastic tissue, and adventitia.

The injected cotton fibers were lodged chiefly in the arterioles and in the precapillary branches. At the end of 24 hours many of the cotton

fibers were found in apposition to the endothelium and without any reaction about them. In other instances, large mononuclear cells were densely packed about the cotton fibers, and about some of these vessels were collections of similar cells (Fig. 2). These large mononuclear cells completely filled the lumina of the precapillary branches. The elastica was stretched and often ruptured at one point, permitting the mononuclear cells within the lumen to stream through and merge with any cells that had collected about the vessel. No multinucleated cells were present nor was there any thrombus formation. Forty-eight hours after the injection, most of the cotton fibers were surrounded by large mononuclear cells, among which multinucleated giant cells had made their appearance (Fig. 3). These granulomata often distended the lumina of the precapillary branches of the artery and arterioles to many times the original diameter. The elastica was stretched and in the smallest branches was ruptured, permitting the cell mass to move outward (Fig. 4). The surrounding tissue often appeared compressed and pushed aside by the cells as they passed outward from the lumen. Occasional mitotic figures were seen in the large mononuclear cells of the granuloma.

In the animals sacrificed during the first and second weeks after injection, the alterations had progressed further. Cotton fibers lying in the granulomata were carried outward as the cell mass moved through the gap in the elastica and came to lie well beyond the original limits of the vessel wall. At other times, when the elastica ruptured immediately beneath the particle of cotton, the cotton was carried outward at the rounded apex of the granulomatous mass of cells as they pushed from the lumen into the surrounding tissues. This was seen especially well in the precapillary branches. As the cell mass moved outward, a lumen began to appear again in the vessel. Sometimes the granuloma was being covered over by endothelial cells.

Cotton fibers, which had lodged in the portions of the arterial tree where the vessels had thick muscular walls, provoked a granuloma in some instances. At other locations the cotton was being covered by a few endothelial cells. Granulomata occasionally were seen in some of the large branches of the artery, as in an animal sacrificed at the end of 11 days. They partially filled the lumen and were covered by endothelial cells (Fig. 5).

As early as 11 days, the Wilder azocarmine-aniline blue preparations demonstrated numerous fibrils in the granulomata; some of these were argyrophilic, others were stained blue. The argyrophilic fibrils were more abundant in those granulomata that contained mainly large mono-

nuclear cells, and were much less numerous in those composed predominantly of multinucleated giant cells.

Sometimes a cotton fiber became lodged in a muscular artery in such fashion that one end was pointed directly against the wall; in those instances it could be readily seen that the fiber was beginning to penetrate the wall of the vessel.

As early as 4 weeks after injection, granulomata were found that lay entirely outside arterioles and small arteries. The opening through which the granuloma passed to the perivascular tissue had been filled with fibrous tissue in which, in many instances, delicate new elastic fibrils had been laid down. The inner surface of this new tissue closing the gap was covered with endothelium. The lumen of the vessel again was patent (Fig. 6). The passage of the granuloma through the vessel wall was not accompanied by hemorrhage.

Some granulomata were partly within the lumen and partly outside in the surrounding tissue (Figs. 7 and 8). The granuloma then assumed a shape somewhat like that of a dumbbell, with the narrow portion filling the opening in the wall of the arteriole or small artery. In this circumstance, the surface of the portion of the granuloma within the lumen was covered with endothelium. As the granuloma reached the tissue outside the vessel, the cells composing it were less densely packed; it appeared to have expanded. Serial sections often disclosed that granulomata apparently lying outside the vessel still had a small portion plugging a gap in the wall. Also it was obvious that the opening originally had been larger and that after the major portion of the granuloma had passed through, the gap in the wall was being filled in with new fibrous tissue (Figs. 9 and 10).

When the granuloma had formed in a larger artery, it was clearly seen that the cotton fiber was slowly penetrating the wall, often accompanied by a giant cell. Although the elastica interna had ruptured, the granuloma had not yet begun to move outward from the lumen.

Twenty-four animals were allowed to live from 2 to 6 months after injection. Cotton fibers were found in arteries indenting the wall and pushing the elastica interna outward; sometimes these fibers were incompletely surrounded by giant cells, in other instances they had been covered by connective tissue and endothelium. Other cotton fibers near the periphery of the lung were in the alveolar septa, bulging the septal wall inward into the alveolar space, or a pointed end of a fiber projected into the alveolus; a few were found in alveolar spaces, lying within giant cells that also contained anthracotic pigment (Fig. 11). This was

seen as early as 7 weeks after the injection. It was not possible to identify accurately the vessel in which the fiber had lodged because the lumen was reopened and the wall reconstituted after the fiber had escaped.

Numerous granulomata had passed from vessels into the adjacent tissue. As in the animals that were sacrificed in less than 2 months, these granulomata were composed of loosely arranged giant cells. Among them were occasional giant cells holding anthracotic pigment. A few vessels were found in which granulomata had remained in the lumina. These granulomata were reduced chiefly to compact masses of connective tissue which were covered by endothelium and incompletely or completely filled the lumina. Other granulomata had not yet entirely penetrated the vessel wall; a small portion of the cell mass still filled the narrow gap through which the major portion of the granuloma had passed.

Some examples were noted in which a granuloma lay near two arterioles. Each arteriole had a repaired defect in its wall adjacent to the granuloma that appeared to be too large to have been formed in a vessel of that size. It seems reasonable to assume that in these circumstances a small granuloma moved outward from each arteriole and by chance merged to form a single large one.

Restoration of the walls of the vessel, at the gaps through which granulomata had moved to the adjacent tissue or were in the process of escaping, was found in various stages regardless of the length of time the animals were allowed to live (2 to 6 months). There was a growth of connective tissue at the margin of the gap in the vessel wall. This new connective tissue seemingly formed a close-fitting collar about the granuloma as it passed outward; when the last trailing attenuated portion of the granuloma emerged, the gap was closed by connective tissue. Prior to this, endothelium had covered the surface of the hindermost part of the granuloma before it had entered the gap in the vessel wall. Thus the defect was repaired and no blood escaped from the lumen (Figs. 9 and 10).

As early as 2 months after injection certain cells, which had a distinctive appearance and staining reaction, were noted in the connective tissue filling the defect in the vessel wall. These cells resembled in all respects the smooth muscle cells of the media of the vessel (Fig. 12). Mitotic figures have not been found among the muscle cells of the media at the margin of the defect.

Some of the scars in the vessel walls were devoid of elastic tissue;

others contained delicate elastic fibrils (Fig. 6). In yet other vessels, an elastic tissue strand, as heavy as the original elastica interna, had been laid down and often joined the original elastica at a distance from the outwardly turned ends at the site of the rupture in the vessel wall (Fig. 12).

Granulomata occasionally were found in the largest branches of the artery within the lung. They were closely adherent to the intima over a considerable area and were covered with endothelium. In these vessels the granulomatous mass remained within the lumen and underwent organization.

Never did the partial or complete occlusion of the lumen of any of the branches of the pulmonary arteries lead to infarction of the lung.

Discussion

As might have been anticipated, the introduction of cotton fibers through a vein produced foreign body granulomata in branches of the pulmonary arteries. At first, the cells that collected about the particles of cotton resembled in every way large mononuclear wandering cells. These cells most probably were derived from the large mononuclear cells of the blood. Mitotic figures were seen in some of these collections of cells, indicating that cell proliferation was in progress within the granuloma. Very quickly, there appeared multinucleated giant cells among the cells collected about the cotton. The formation of the giant cells was probably similar to that described by Lewis,[1] following the inoculation of tubercle bacilli into hanging-drop preparations of blood.

The granulomata in the precapillary branches of the artery filled and distended the lumen of the vessel. In these branches the granulomata appeared to be under pressure; the elastica was stretched and ruptured within 24 hours. The granuloma then seemed to spring sharply outward into the surrounding tissue and carried with it the cotton fiber or fibers.

Granulomata in the arterioles and medium-sized arteries also distended the lumina of these vessels. The elastica interna was stretched and finally ruptured. It was very obvious that the rupture of the wall of the medium-sized artery occurred in that portion where the media had abruptly become thinner (Figs. 7 to 10).

As to the manner in which the granulomata escape from the vessels, there are two possibilities. The first of these is that the media and adventitia tear following the rupture of the internal elastica; the other possibility is that the cotton fiber penetrates the wall and gradually passes through, the cells of the granuloma following in the wake of the cotton

fiber. Both of these methods occurred. Granulomata were found emerging through a gap in the vessel wall, and the only cotton that could be discovered in serial sections was in the center of the granuloma. Other lesions were seen in which the cotton was penetrating the vessel wall, and cells comprising the granuloma were following it.

Regardless of the manner in which the vessel wall is damaged, once the gap in the wall has been formed, the granuloma moves outward into the surrounding tissue. One can only surmise what forces the granuloma outward. In the precapillary branches the mass of cells is so crowded together that the lumen is distended, and when the elastica is ruptured, the cells adjacent to the gap emerge through it. The gap, furthermore, is enlarged by the retraction of the elastica when it ruptures.

The passage of the granuloma through the walls of the arteries and arterioles with their muscular media is not so simple as in the precapillary branches. The arteries of medium size and the arterioles are distended by the granulomata. Once a defect is made either by tearing or penetration of the wall by the cotton particles, the cells of the granuloma move into the gap. The granulomata are under the constant pressure of the blood in the pulmonary vascular tree, and, in addition, the heightened pressure during systole probably stretches the hole in the wall and forces the forward portion of the granuloma further into the defect, thus widening and deepening it. When the defect involves all layers of the vessel, the granuloma begins to emerge to the outside and pushes ahead of it the surrounding loose tissue. With each cardiac systole more of the granuloma is forced outward until all of it has emerged from the vessel. Probably the blood pressure within the precapillary branches also plays a part in the passage outward of the granulomata. It is not clear what part the movement of the lung during respiration may play in the process.

Reparative processes begin quickly with the proliferation of fibroblasts. These form a collar about the column of cells of the granuloma and appear to fit snugly about it. Endothelial cells cover the surface of the granuloma and separate it from the circulating blood. When the last portion of the granuloma passes through the intima, the continuity of endothelial surface has been restored. As rapidly as the last part of the granuloma penetrates the media, connective tissue cells fill the gap behind it. When the granuloma finally has passed entirely through the wall, the defect has been filled with connective tissue. It would thus appear that the emergence of the granuloma to the tissues outside the vessel is comparatively slow and affords ample time for restoration of the wall.

The granuloma, or portion of it lying outside the vessel, has a much

less compact structure. The giant cells are more loosely arranged and the cell mass occupies a greater space than it did in the lumen of the vessel. This is very likely due to the fact that it is now no longer confined to a restricted space in the lumen of the vessel nor subjected to the pressure of the blood within the vessel. Also, additional giant cells are formed from the tissue wandering cells that are attracted by the presence of the foreign body. That some of the cells come from the surrounding tissue is evidenced by the anthracotic pigment to be seen in an occasional giant cell; similar pigment has not been found in any cell in a granuloma within the lumen of a vessel except when rupture of the vessel wall has occurred. The presence of anthracotic pigment within the cells in the lumen is a rare occurrence (Fig. 13).

The movement of the cotton fibers does not cease when the granuloma reaches the tissues around the vessel. Long, slender, pointed particles of cotton are to be seen pushing inward the wall of a nearby alveolus, or the naked end of such a fiber projects into the alveolar space. Moreover, tiny fragments of cotton that have escaped through the wall of a precapillary branch of the artery ultimately are found within a giant cell in an alveolus. Probably the constant expansion and contraction of the lung is responsible for the movement of the cotton fibers in the tissue after they have escaped from the vessels.

The compact granuloma within the lumen of the vessel, even in its earliest stages, is impervious to the entrance of blood. Red blood cells and hemosiderin are not found within it. That there is no hemorrhage as the granuloma passes from the vessel is due to the fact that the cell mass acts as a tightly fitting stopper in the defect in the vessel wall. Furthermore, the quick covering of the granuloma with endothelial cells shuts it off from contact with the blood. In addition, the passage of the granuloma to the outside tissues is seemingly slow and reparative processes have sufficient time to keep the margins of the gap tightly closed about the emerging granuloma and to fill the space behind it. After the granulomata have escaped from the vessels, the lumina are again patent.

The restoration of the continuity of the wall of the vessel is complete as soon as the granuloma has passed through it. At first the defect is filled with connective tissue covered with endothelium. Soon delicate elastic fibrils are noted in this scar tissue. Later a more compact strand of elastic tissue is found either incompletely or entirely spanning the area filled with scar tissue. Often this new elastica joins the original ruptured

elastica interna at a distance from its outwardly turned ends. Further changes take place in the scar that fills the defect in the vessel wall. As early as 2 months after injection of the cotton, plump cells having the morphologic and tinctorial properties of smooth muscle cells are distinguishable among the connective tissue elements of the scar. It is not likely that these come from the smooth muscle of the media for no evidences of proliferation of this muscle are to be found. The formation of muscle is most probably due to metaplasia of fibroblasts and is quite analogous to the familiar formation of smooth muscle about the vessels in an organized, canalized thrombus.

The collateral circulation was adequate to prevent infarction of the lungs in the experimental animals; in those instances in which cotton fibers were found in human pulmonary arteries, there was only very slight reduction of the lumina and no infarcts had resulted.

The lack of thrombus formation about the cotton fibers when they lodge within the lumen of the vessel is a striking feature, true in both the experimentally injected animals and in the human cases.

No report of cotton fibers in the pulmonary arteries of the human nor of any experiments in which cotton fibers have been experimentally injected into the venous circulation of animals could be found in the literature. Flory[2] reported the formation of granulomata about cholesterol injected into the pulmonary arterial circulation of rabbits. His experiments were of short duration and no description was given of any movement of the granulomata through the walls of the arteries.

Summary

Cotton fibers accidentally introduced into the pulmonary arterial circulation of the human provoke a foreign body reaction. When cotton fibers are injected into the iliac veins of rats and lodge in the pulmonary arteries, foreign body granulomata are formed. These granulomata in the larger branches of the arteries undergo organization. In arteries of medium size, arterioles, and precapillary branches, the granulomata distend the lumina and often escape through defects in the walls. The defect in the vessel wall is produced by penetration of the cotton fiber through it and also by actual tearing of the wall. The gap is at first filled with fibrous tissue; later some smooth muscle and frequently a new elastica interna are formed. The scar is covered by endothelium. The lumen is again patent after the granuloma has escaped. Some of the cotton fibers ultimately come to lie in alveolar spaces and are surrounded

by foreign body giant cells. There is no thrombosis nor hemorrhage associated with these granulomata, nor does the process lead to infarction of the lungs.

REFERENCES

1. Lewis, M. R. The formation of macrophages, epithelioid cells and giant cells from leucocytes in incubated blood. *Am. J. Path.*, 1925, 1, 91–100.
2. Flory, C. M. Arterial occlusions produced by emboli from eroded aortic atheromatous plaques. *Am. J. Path.*, 1945, 21, 549–565.

DESCRIPTION OF PLATES

The cotton fibers do not stain. In some of the photomicrographs they show faintly in the granulomata; in others, seemingly empty spaces in the granulomata indicate the size and location of the cotton fibers.

PLATE 86

FIG. 1. Cotton fibers in a pulmonary artery of a child, 14 months of age, who had been given a blood transfusion. The cotton is surrounded by giant cells. Hematoxylin and eosin stain. × 390.

FIG. 2. Rat, 24 hours after injection. Cotton fiber in a precapillary branch of a pulmonary artery, surrounded by large mononuclear cells. The vessel is distended, the elastica has ruptured. Hematoxylin and eosin and Weigert's elastic tissue stains. × 660.

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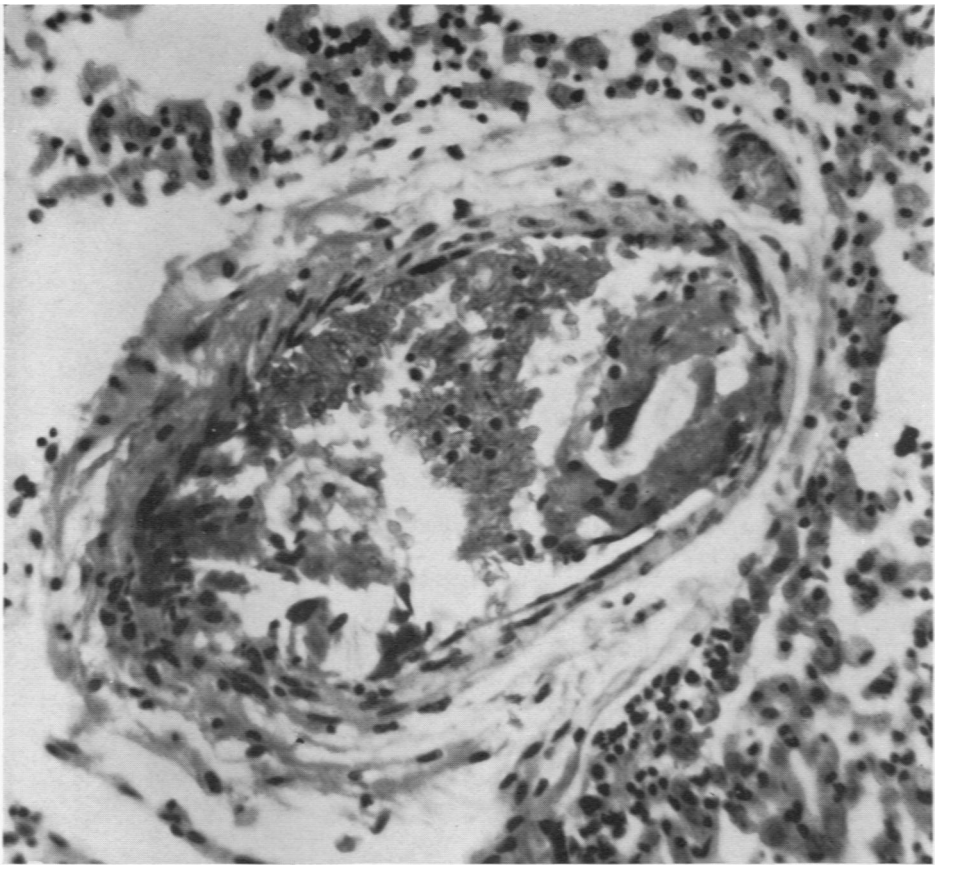

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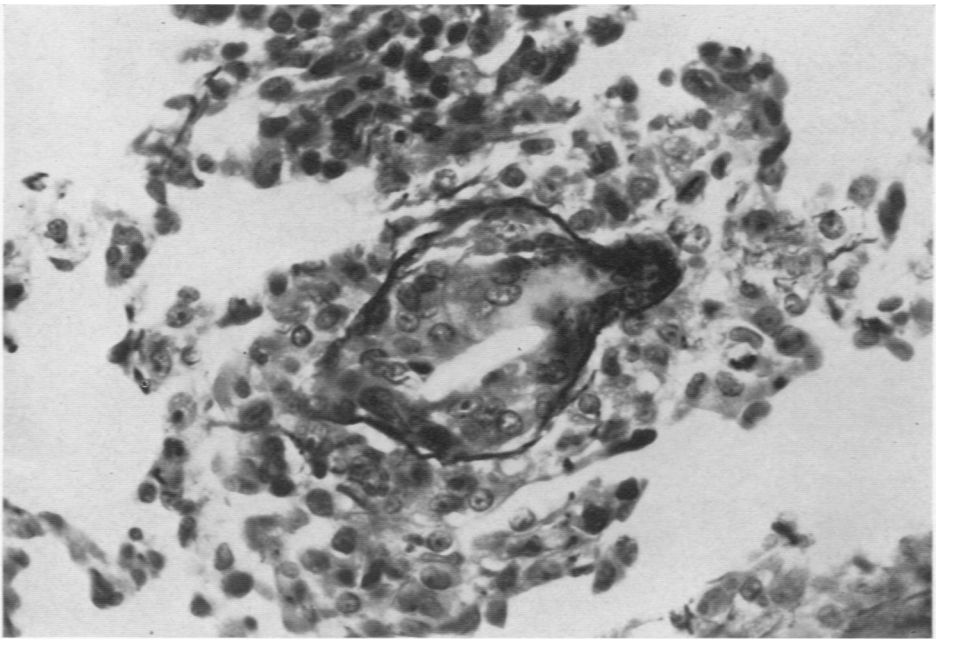
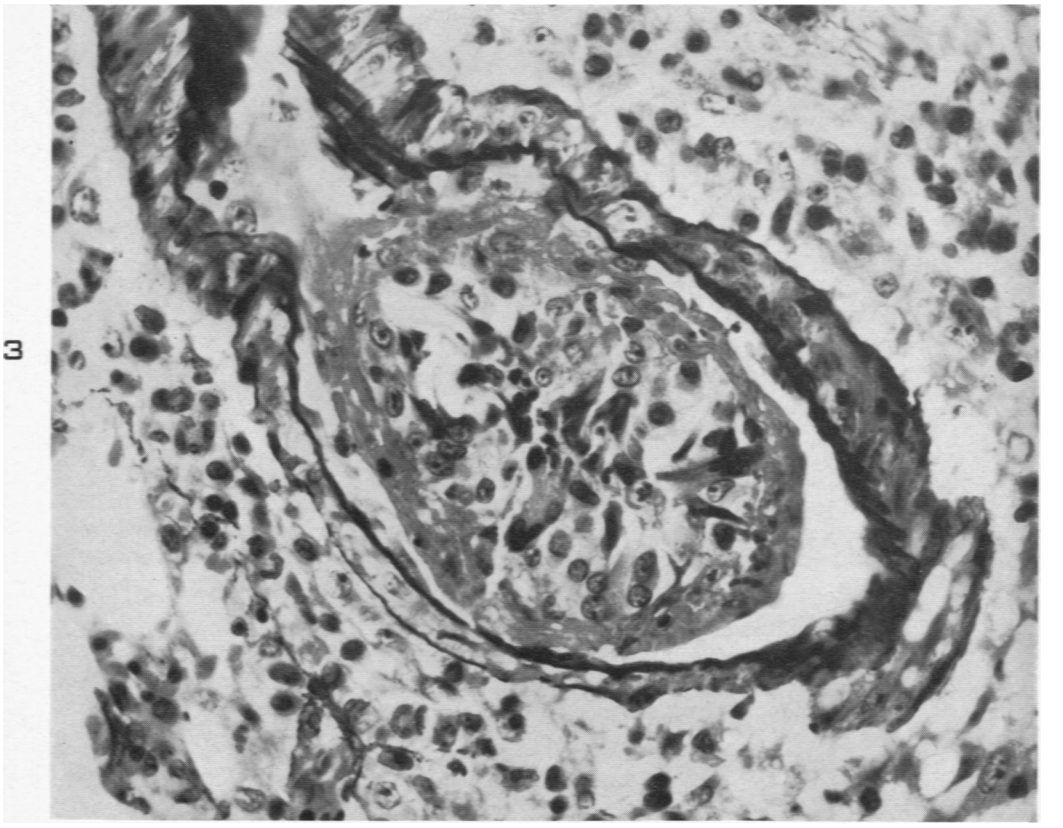


Von Glahn and Hall Pulmonary Emboli of Cotton Fibers

PLATE 87

FIG. 3. Rat, 48 hours after injection. Granuloma in a pulmonary artery of medium size. Cotton is seen near the center of the granuloma. The lumen is distended. Hematoxylin and eosin and Weigert's elastic tissue stains. × 660.

FIG. 4. Rat, 48 hours after injection. Granuloma in precapillary branch of pulmonary artery. The granuloma has distended the lumen and is passing outward through a wide gap in the vessel wall, where the elastica has ruptured. A cotton fiber is near the center of the granuloma. Hematoxylin and eosin and Weigert's elastic tissue stains. × 660.



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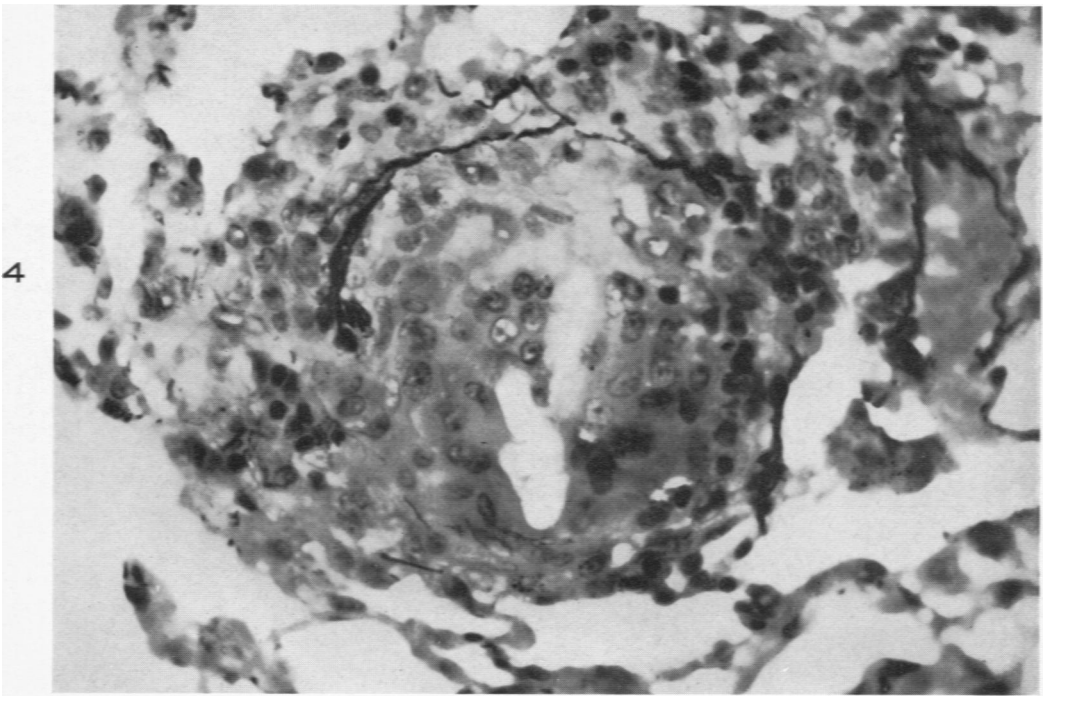

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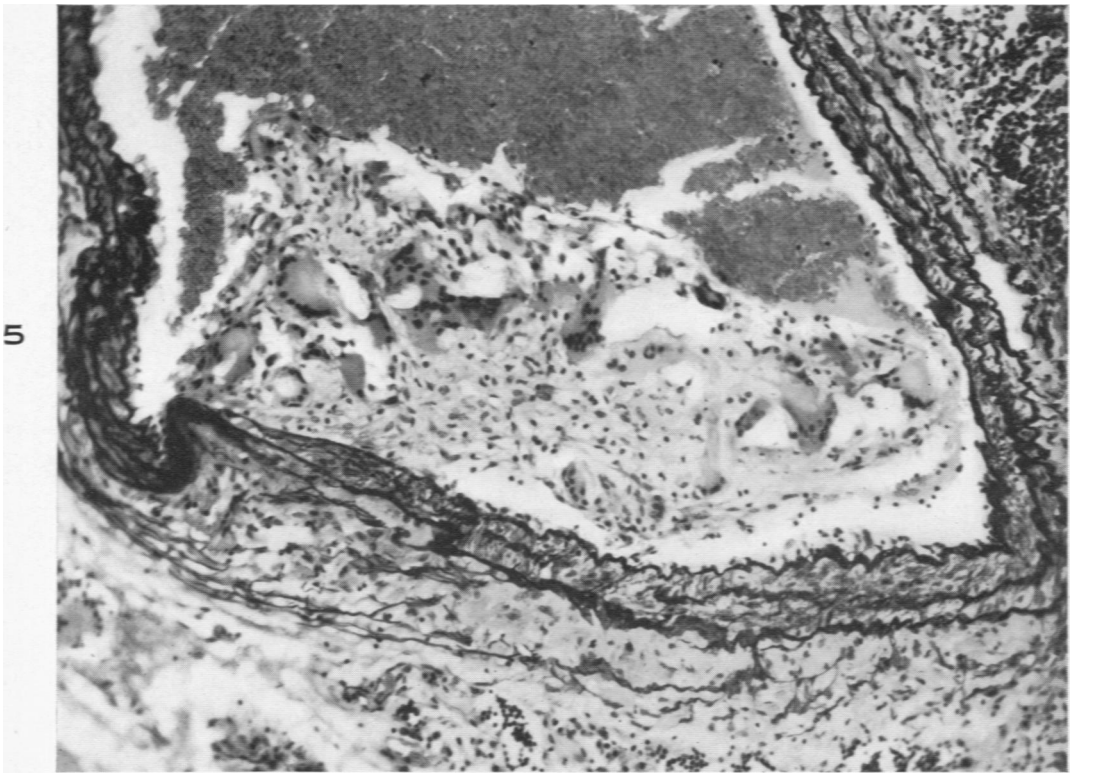
PLATE 88

FIG. 5. Rat, 11 days after injection. Granuloma with many fragments of cotton in large branch of pulmonary artery. The surface of the granuloma is covered by endothelial cells. Hematoxylin and eosin and Weigert's elastic tissue stains. × 190.

FIG. 6. Rat, 4 weeks after injection. Granuloma lying entirely outside medium-sized branch of pulmonary artery. The defect in the vessel wall is closed by fibrous tissue in which are delicate elastic fibrils. Lumen is again patent. Hematoxylin and eosin and Weigert's elastic tissue stains. × 390.



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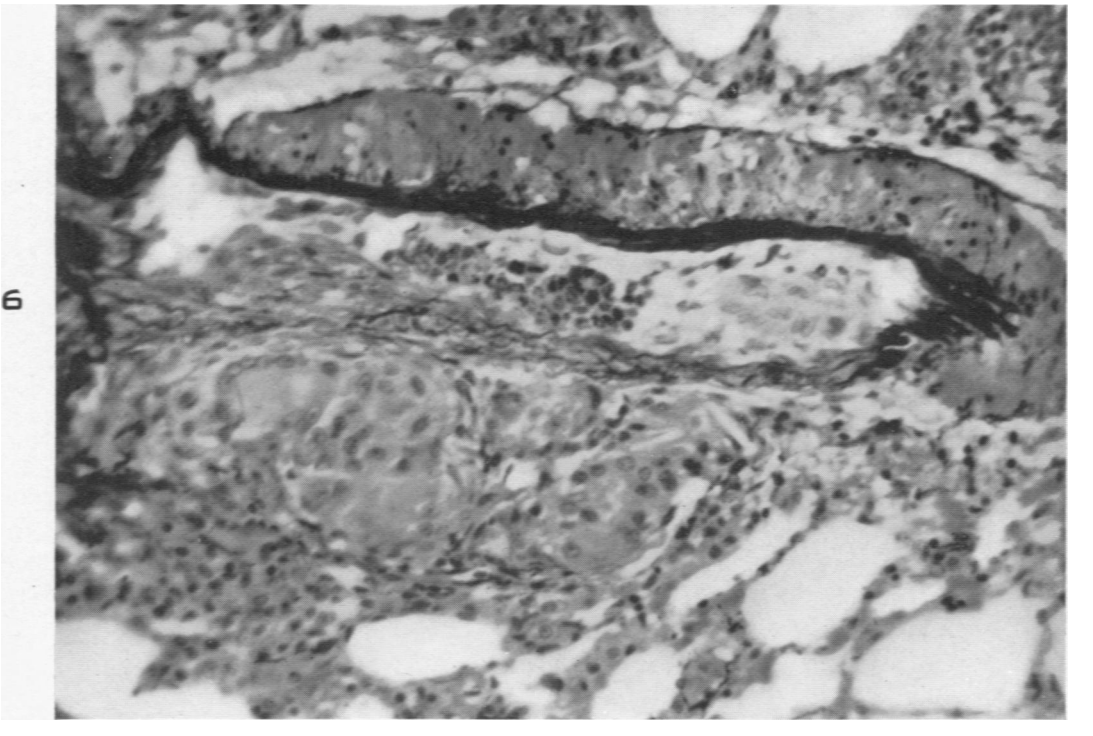

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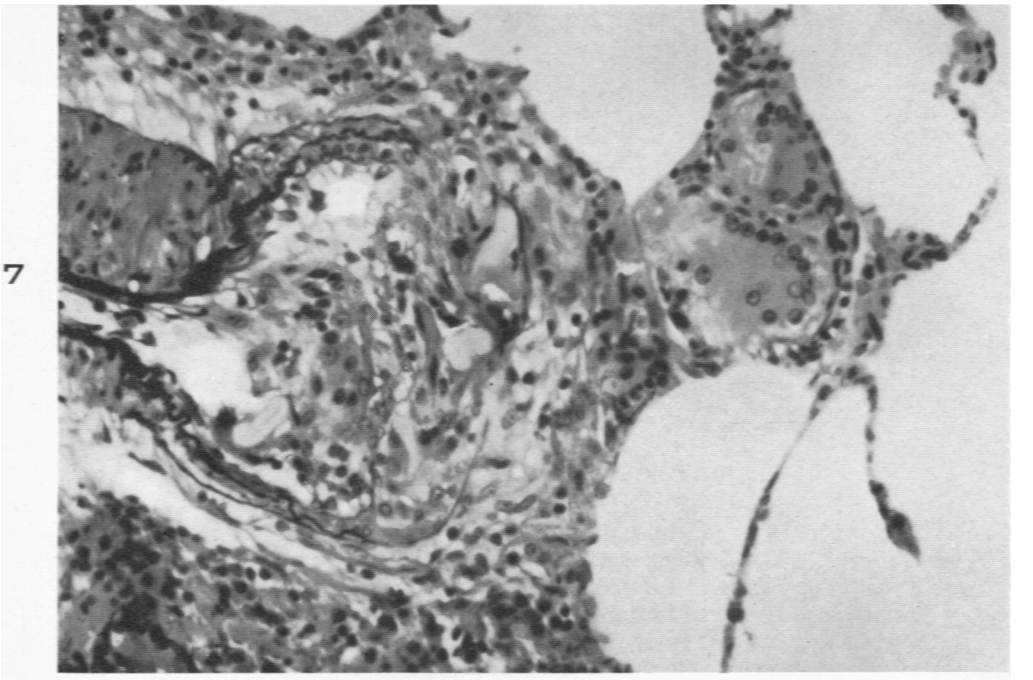
PLATE 89

FIGS. 7 and 8. Rat, 11 days after injection. Granulomata in medium-sized branches of pulmonary artery. The granulomata are passing outward through defects in walls of vessels. In Figure 7 it is to be noted that rupture of the vessel occurred in a normally thinner portion of wall. Hematoxylin and eosin and Weigert's elastic tissue stains. × 390.



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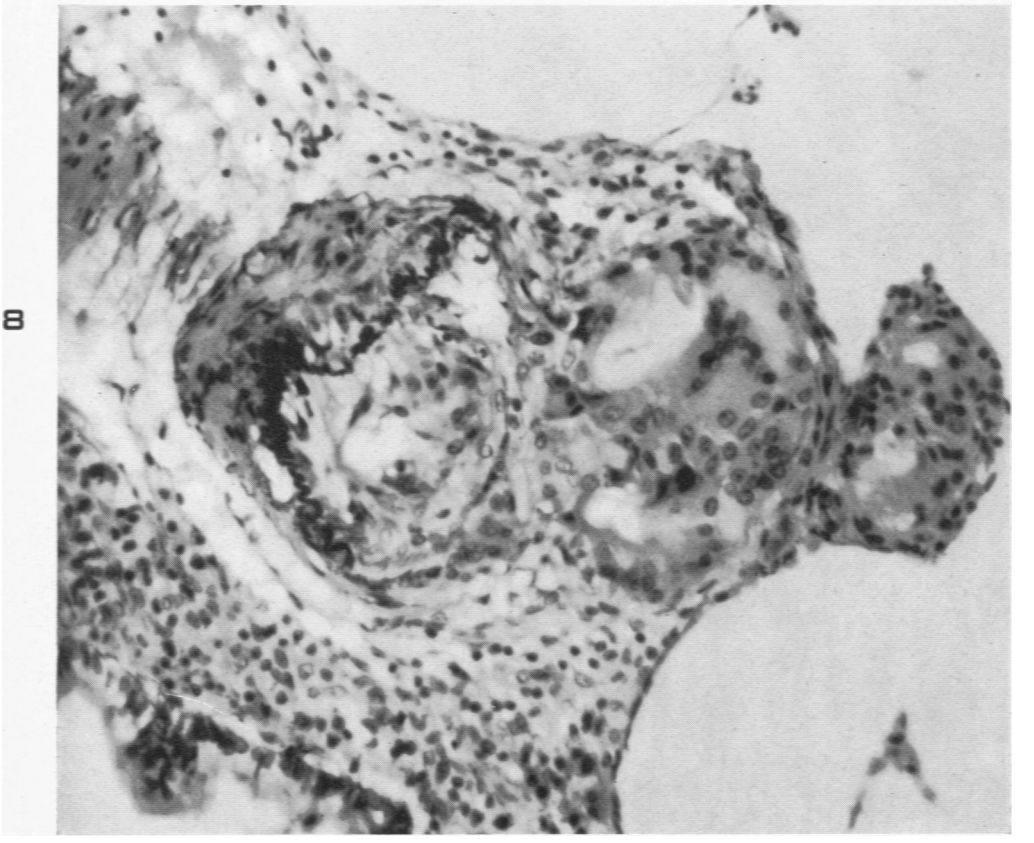

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PLATE 90

FIGS. 9 and 10. Rat, 2 months after injection. Medium-sized branch of pulmonary artery. In Figure 9 the granuloma appears to be entirely outside the vessel and the defect in the wall closed completely by fibrous tissue. Figure 10 is from another of the serial sections through the granuloma. The last portion of the granuloma has just emerged from lumen and is covered by endothelium. The rupture occurred in the normally thinner portion of the vessel wall. Hematoxylin and eosin and Weigert's elastic tissue stains. × 280.

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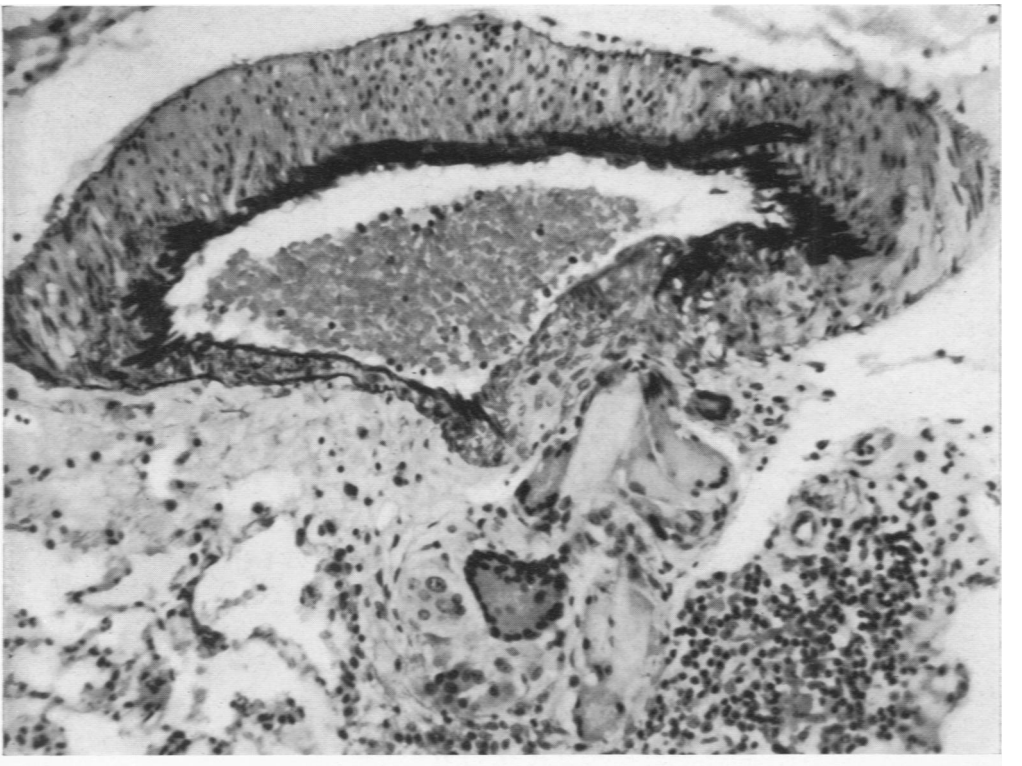

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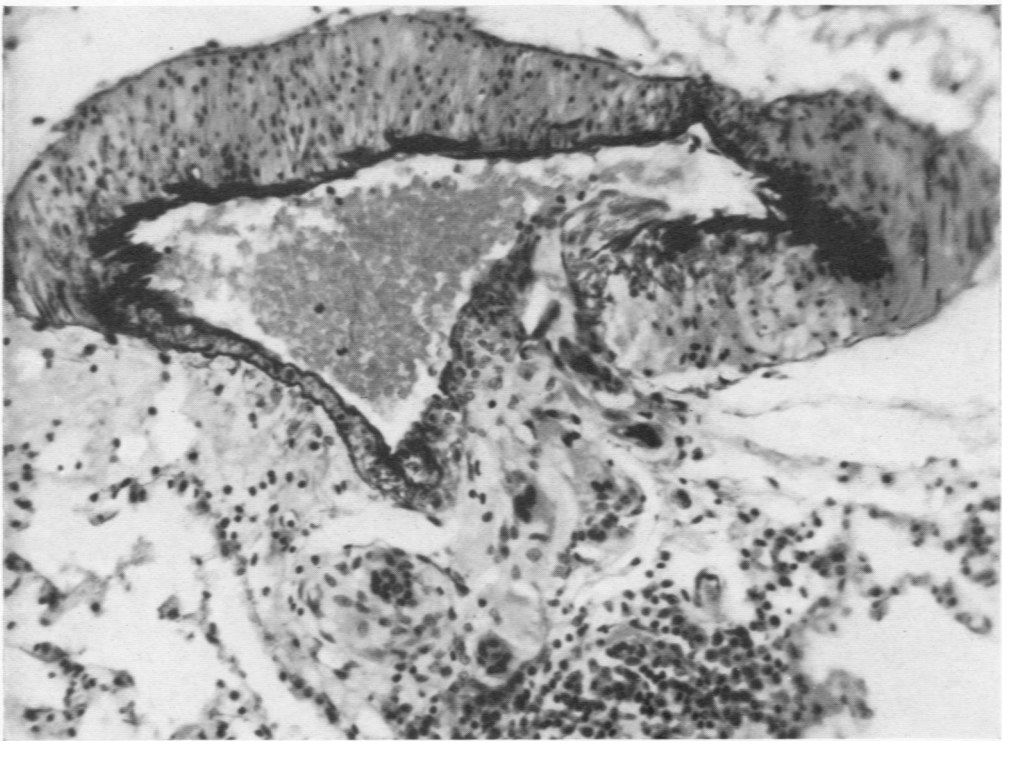

PLATE 91

FIG. 11. Rat, 2 months after injection. A small piece of cotton in an alveolus. The cotton is surrounded by a giant cell containing anthracotic pigment. In a nearby septum there are two pieces of cotton, each with a giant cell, near two precapillary branches of an artery. Hematoxylin and eosin stain. × 588.

FIG. 12. Rat, 3 months after injection. Granuloma lying entirely outside medium-sized artery. A defect in the wall of the artery is filled by fibrous tissue in which are cells identical with smooth muscle. New elastic tissue joins the ruptured original elastica at a distance from the outwardly turned ends. Rupture occurred through a normally thinner portion of vessel wall. Hematoxylin and eosin and Weigert's elastic tissue stains. × 588.

FIG. 13. Rat, 8 days after injection. Granuloma in a precapillary branch of artery. The lumen is greatly distended. The elastica has ruptured in two places and the granuloma is escaping through a wide gap in the vessel wall. Anthracotic pigment occurs in two of the giant cells. Hematoxylin and eosin and Weigert's elastic tissue stains. × 588.

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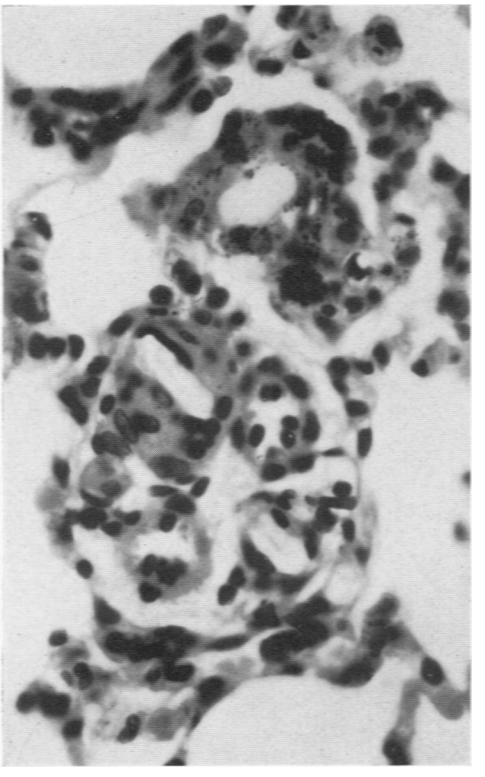

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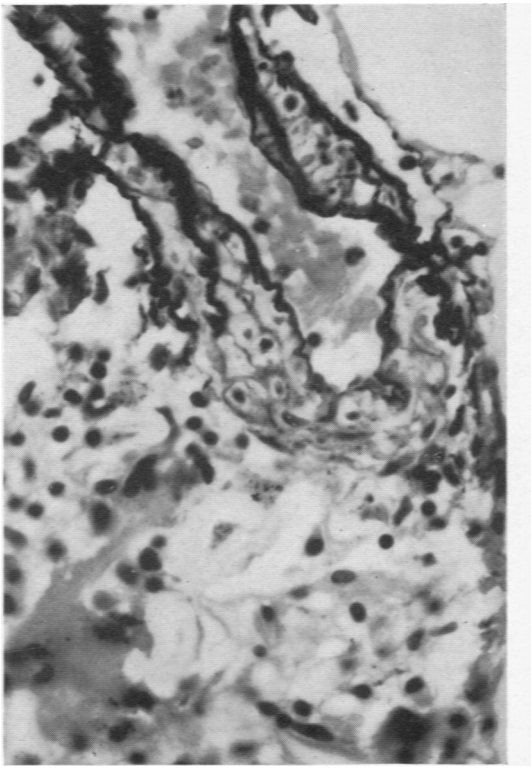

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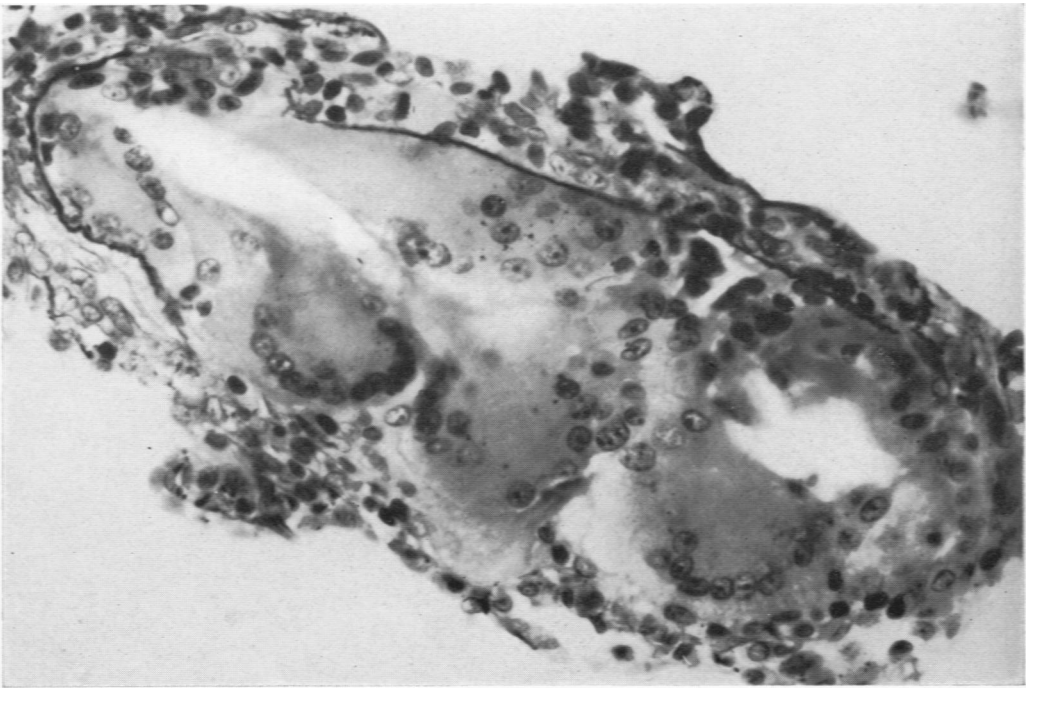

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