THE UPTAKE OF COLLOIDAL THORIUM DIOXIDE BY THE ARTERIAL LESIONS OF CHOLESTEROL ATHEROSCLEROSIS IN THE RABBIT

Its Significance in Relation to Pathogenesis *

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Although other theories have been proposed and supported by various authors,[1] it has been generally accepted for many years that the nutrition of the inner layers of arterial walls is provided by fluid derived from the plasma, which permeates the intima from the lumen and seeps through the arterial wall to be drained off by the venules and lymphatics of the outer layers. While this is a perfectly logical idea, confirmatory experimental evidence is virtually confined to observations on the permeation of colloidal dyes through the intima from the lumen of the aorta.[2] As a corollary to this concept it has been assumed also that the lipids that accumulate in the intima in atherosclerosis are derived from the nutritive fluid that filters through it from the lumen. Indeed, this is one fundamental assumption on which is based the imbibition or infiltration theory of the pathogenesis of atherosclerosis as propounded by Ribbert,[3] Aschoff,[4] Anitschkow,[5] and others. However, the form in which lipids enter the intima, their mode of transit through the lining endothelium, and the manner of their progressive aggregation in the subendothelial layer of the intima are problems yet to be elucidated.

It appeared to us that additional evidence bearing on these questions might be accumulated by the use of identifiable colloidal materials other than dyes and by the study of their entry into preformed experimental atherosclerotic lesions, as well as their behavior when introduced into the circulation of animals with normal arteries. Some years ago, Plewes[6] observed the presence of thorium dioxide in the foam cells of an aortic atherosclerotic plaque at necropsy in a patient in whom thorotrast had been used for diagnostic purposes. This suggested the possibility that thorotrast might be a suitable agent for such experimental studies. These studies have now been in progress for several years and some of our observations have been reported briefly elsewhere.[7]

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Materials and Methods

In an initial experiment, 15 young adult rabbits were fed for 2 to 3 months on a diet containing corn oil and cholesterol, the latter in a dose of 0.6 to 0.8 gm. daily. This procedure led to the development of hypercholesterolemia and moderately severe atherosclerosis of the aorta. At the end of the period of cholesterol feeding, colloidal thorium dioxide in the form of warmed thorotrast* was injected intravenously into each rabbit in a dose of 2 to 3 cc. per kg. of body weight. The animals were killed at intervals of from 5 minutes to 4 days after the injection of thorotrast. Six rabbits that had not been fed cholesterol were injected with colloidal thorium dioxide in the same manner and were killed at times ranging from 30 minutes to 12 hours following injection. Careful necropsy examinations were carried out on all animals and the organs and many cross sections of the aorta were subjected to microscopic examination in paraffin sections and in frozen sections stained for fat.

Forty-six young adult white rabbits were employed in a second experiment. Five of these animals were not fed cholesterol but were injected intravenously one, two, or three times with thorotrast in the same dose as before at intervals of 24 hours; and were killed 24 hours after the last injection. The remaining 41 rabbits were fed 1 gm. of cholesterol mixed with 92 gm. of rabbit chow and 7 gm. of corn oil daily for 5 days each week. Samples of serum taken at the beginning and at the end of each experiment were analyzed for their content of cholesterol, lipid phosphorus, and fatty acids of neutral fat. Twenty-four hours before the animals were to be killed each was injected intravenously with 3 cc. of warm thorotrast per kg. of body weight. Blood specimens, taken at random times following the injection of thorotrast, were collected from the ear opposite that into which the material was injected and were allowed to clot. The clots were then fixed in formol-saline solution, embedded in paraffin, sectioned, stained, and examined microscopically for the presence of thorium dioxide. The animals were killed in small groups at weekly intervals after from 1 to 8 weeks of cholesterol feeding. Their organs and multiple blocks of aorta were examined microscopically in paraffin sections and in frozen sections stained for fat.

Observations

With one exception, the aortic intimas of the total of 11 control animals that had not been fed cholesterol did not contain microscopically visible amounts of thorium dioxide. The exception occurred in a

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patch of thickened, fibrotic intima that covered an area of spontaneous calcific sclerosis in the media of the aorta. In this location only, the lining endothelial cells were seen to contain fine granules of thorium dioxide. The endothelial cells were somewhat swollen but otherwise were of normal appearance. The endothelial cells covering another similar lesion in the aorta of another animal, however, showed no thorium in the plane of the microscopic section.

In the first experiment, the 15 cholesterol-fed rabbits showed prominent atherosclerotic lesions of the aorta at necropsy. Some of these contained particles of thorium dioxide. No thorium was seen in the aortas of those animals killed within 10 minutes following the injection of thorotrast, but it was found in trace amounts in the atherosclerotic lesions of some of the rabbits killed 20 minutes after injection. In animals killed 3 hours after injection the substance could be seen as rather coarsely aggregated granules, while in those animals killed 24 hours after receiving thorotrast the particles of thorium dioxide were often densely clumped in those cells in which it was present. Thorium was not found in the aortic atherosclerotic lesions of every animal killed from 20 minutes to 3 hours after injection but it was invariably present in animals killed 12 hours or longer after injection. It was present in areas where atherosclerotic lesions occurred but was absent from the intervening areas that were not involved by atherosclerosis. It was found in both the lining endothelial cells and in the foam cells of the atherosclerotic lesions.

The thorium dioxide as observed in the histologic sections had the characteristic bronze, metallic appearance and agglomerated, particulate form that has been described by other authors.[8,9] In the lining endothelial cells the granules lay in the cytoplasm and were usually minute (Figs. 1 and 2). The endothelial cells containing thorium were always more swollen than their neighbors and were often ovoid. Endothelial cells containing thorium, sometimes in rather large amounts, were often numerous and prominent over the atherosclerotic lesions. Much larger amounts of thorium eventually accumulated in the globular foam cells that composed the bulk of the atherosclerotic lesions (Figs. 1, 2, and 3), but its earliest appearance in these cells was in the form of minute granules scattered through the cytoplasm. With the passage of succeeding hours the aggregates of thorium became progressively coarser and more numerous. Thorium was also found in small amounts in some of the fibroblastic cells in atherosclerotic lesions that contained them. Granules of thorium were not observed in the intercellular ground substance except in a few microscopic preparations and then in circumstances in which it was impossible to be sure that

the granules had not been artificially displaced from neighboring cells.

The distribution of thorium among the cells of the atherosclerotic plaques was generally irregular. It was observed to occur in single, isolated, lining endothelial cells, in small groups of them or in many adjacent endothelial cells always in relation to atherosclerotic lesions. Sometimes the subjacent foam cells or fibroblasts contained thorium and sometimes they did not. Aggregates of thorium dioxide were seen in lipid-filled foam cells beneath endothelial cells that were free of the substance (Fig. 3) and the reverse was also true. Single foam cells and groups of adjacent foam cells were observed to contain the material while other cells between them contained none (Figs. 2 and 3). In some early lesions all of the foam cells in a single section were completely filled (Fig. 1).

In spite of the general irregularity of distribution, it was noted that granules of thorium dioxide were accumulated first and most abundantly in the layers of foam cells closest to the endothelial surface rather than in those closest to the media (Figs. 2 and 3). In sections of the aortas of 4 animals the thorium dioxide was found to have accumulated most abundantly at the periphery of many of the atherosclerotic plaques, both in endothelial cells and in foam cells rather than at random over their surfaces (Fig. 4). For several animals longitudinal sections of the aorta were made after the proximal end had been marked for identification by injecting India ink into the adventitia. In no case was it apparent that the proximal part of an atherosclerotic plaque had accumulated significantly more or less thorium dioxide than the distal part. The distribution of thorium appeared to be fairly uniform around the whole periphery of such plaques and was absent only in the depths of their central areas.

Mitotic figures similar to those described and illustrated in a previous publication[10] were seen in the foam cells, both in cells that contained thorium and in cells that did not. In addition, one endothelial cell that contained a few minute particles of thorium was found with a mitotic figure in anaphase (Fig. 5). No instance of mitosis in an endothelial cell was encountered in our previous study of mitotic activity in the lesions of experimental cholesterol atherosclerosis.

No thorium was found in the smaller arteries of other organs and tissues except in the coronary arteries of one animal in which two small atherosclerotic plaques showed the presence of thorium granules in endothelial and foam cells in a distribution similar to that observed in the aortic lesions. The distribution of thorium dioxide in the additional organs examined was similar to that described by other

authors.[8,9] In those animals that had been fed cholesterol, thorium was found in abundance in the lipid-filled reticulo-endothelial cells of the liver, spleen, and other organs.

In the second experiment, there were 17 animals that failed to show any evidence of aortic atherosclerosis either on gross examination or in the sections studied microscopically. The majority of these animals had been fed cholesterol for periods no longer than 3 weeks. Nevertheless, in 4 of these rabbits that had been fed cholesterol for 1 week and in which the level of serum cholesterol had risen to three to five times the normal value, small granules of thorium dioxide were found in several slightly swollen aortic endothelial cells. In one animal fed cholesterol for 3 weeks the total cholesterol content of the serum reached 1240 mg. per cent. The aorta presented a normal intima in microscopic sections except that particles of thorium were found in a number of swollen endothelial cells. The same was true of one other rabbit fed cholesterol for 8 weeks, during which time the total serum cholesterol rose to only 280 mg. per cent. The remaining 11 rabbits in this group exhibited neither aortic atherosclerosis nor particles of thorium dioxide in the intima of the aorta. Five of these animals were moderately hypercholesterolemic but 6 were only mildly hypercholesterolemic or showed normal levels of cholesterol in their sera when they were killed.

Six rabbits that were fed cholesterol for 3 to 8 weeks showed only very slight microscopic changes in the aorta consisting of localized areas of swelling of endothelial cells and of the subendothelial layer of the intima without histologically demonstrable fat. Thorium dioxide in minute granules was present in some of these swollen endothelial cells. The remaining 18 rabbits presented microscopic or gross atherosclerotic lesions of the aorta. In early microscopic lesions in which subendothelial foam cells contained easily demonstrable lipids, granules of thorium dioxide were present in the overlying endothelial cells and in the foam cells. More advanced atherosclerotic plaques presented the appearances detailed in preceding paragraphs.

One hundred and six samples of peripheral blood, taken from 30 minutes to 24 hours after the injection of thorotrast, were examined in paraffin sections of clot. All but two showed granules of thorium dioxide. In various samples the substance was found free in the plasma or contained in polymorphonuclear leukocytes and in monocytes. Various combinations of these extracellular and intracellular situations were observed. Accumulations of thorium dioxide in polymorphonuclear leukocytes never amounted to more than a few granules scattered

in the cytoplasm, but in monocytes the numbers of granules ranged from a few to numbers so large as to fill the cytoplasm and to distend the cell to a large size. These large cells showed no vacuolation of their cytoplasm or any other evidence of lipid content. Monocytes filled to capacity with thorium granules were rare in specimens collected from 30 minutes to 8 hours after the injection of thorotrast. In blood samples obtained from 18 to 24 hours after injection, monocytes well filled with thorium granules were far more numerous.

Discussion

The results of these experiments show a consistent uptake of intravenously injected colloidal thorium dioxide in atherosclerotic lesions by the foam cells lying in the layer nearest the lumen. These cells accumulated thorium earlier than the deeper ones and always in larger quantities. Indeed, in advanced lesions the foam cells nearest to the media contained no thorium at all and the deposit was confined to the foam cells nearer the lining endothelium. These observations clearly imply entry of the colloidal thorium dioxide from the arterial lumen through the lining endothelial membrane and not from the vasa vasorum. This in turn substantiates the theory that other colloidal substances, including those of lipid character, enter the intima from the lumen through the endothelium and accumulate in atherosclerotic lesions. While the observations in these experiments do not demonstrate the passage of thorium dioxide from the lumen into the normal parts of the intima, neither do they deny the possibility of such an occurrence. It may be merely that the substance passes through the normal intima without accumulating there in visible amounts. Nevertheless, the permeation of colloidal thorium from the lumen into established atherosclerotic plaques is entirely in harmony with the concept of normal nutrition of the intima by infiltration of nutritive fluid from the lumen.

It is of interest that many of the foam cells of the atherosclerotic lesions, though already well filled with lipids, avidly accumulated particles of thorium dioxide in great numbers and in a very short time. This suggests a remarkable degree of functional activity on their part. There is no reason to doubt that they could increase their accumulations of lipids just as rapidly as they took up thorium if lipid substances were presented to them at the same rate and in suitable form. In view of this potential acquisitive activity, it is not apparent why individual foam cells, unlike their neighbors equidistant from the endothelium, failed to take up any thorium, unless it is assumed that their

position was by chance such as to exclude thorium dioxide from contact with them or else that the functional potential of the foam cells varies from time to time.

The idea has been proposed by Leary[11] and elaborated by Gordon[12] that the foam cells of atherosclerotic lesions have their origin as cells of the reticulo-endothelial system in the spleen, liver, lungs, or elsewhere which become loaded with lipids *in situ* and later migrate by way of the blood stream to invade the arterial intima by penetrating the endothelial lining. According to this hypothesis, the lipid content of the atherosclerotic lesions is brought in from a distance by this kind of intracellular transport. Our observations indicate that this is not true of thorium dioxide. Thorium granules accumulated in large numbers in the lipid-filled reticulo-endothelial cells of the cholesterol-fed rabbit in the spleen, liver, and elsewhere, but the thorium-containing cells found in the circulating blood were free from cytoplasmic vacuolation or any other sign of the presence of lipid. In this respect they differed completely from the reticulo-endothelial cells of the liver and spleen and also from the foam cells of the atherosclerotic lesions, all of which contained thorium granules and abundant lipids. No cells were found in the circulating blood that could account for the intracellular transport of thorium from the reticulo-endothelial system to the aortic intima during the relatively brief period when large amounts of thorium were being accumulated in the aortic lesions.

To the extent that an analogy can be drawn between the behavior of lipids in the blood stream and of intravenously injected colloidal thorium dioxide, it is apparent that our observations are in conflict with Leary's[11] hypothesis. More direct evidence that this theory is not valid is provided by the experiments of Simonton and Gofman[13] and of Harris,[14] who labelled the reticulo-endothelial cells of rabbits with identifiable materials before and during cholesterol feeding. Ultimate examination of the atherosclerotic lesions that developed during the experiments showed that no significant migration of the labelled reticulo-endothelial cells into the lesions had occurred, though the lesions contained abundant lipid-filled foam cells.

The accumulation of thorium in the lining endothelial cells overlying atherosclerotic lesions was an entirely unexpected finding. Thorium did not accumulate in the normal aortic endothelium of control rabbits injected with thorotrast. This is in conformity with the observations of Efskind[15] who found that thorium dioxide did not appear in the lining endothelium of the arteries of normal rabbits after intravenous injection of thorotrast. In our experiments the aortic endothe-

lium of cholesterol-fed rabbits also was free of the substance except in swollen endothelial cells that lay in most instances in relation to obvious atherosclerotic lesions. It seems apparent, therefore, that the ability of lining endothelial cells to take up and aggregate colloidal thorium dioxide into microscopically visible particles is an acquired characteristic that develops during the course of cholesterol feeding. Its development is regularly accompanied by some degree of swelling of the endothelial cells in question.

In one control animal not fed cholesterol, swollen endothelial cells lying over a spontaneous calcific lesion of the media also exhibited the capacity to accumulate thorium. Accordingly, it is impossible to regard this manifestation of altered function on the part of the endothelial cells as a specific effect of cholesterol feeding. Indeed, this observation suggests the possibility that the lining endothelial cells may undergo the observed morphologic and functional changes during cholesterol feeding simply because of the accumulation of lipid deposits beneath them which displaces the endothelial cells lumenward. This process might be thought of as providing a mechanical or chemical stimulus that causes alteration of cellular form and function.

While this seems a perfectly plausible explanation of the relation between the morphologic and functional alterations of lining endothelial cells and the intimal or medial lesions that lay beneath them, it is equally possible that the localization of the lipid deposits in the arteries of the cholesterol-fed rabbits may have been determined by the prior occurrence of functional changes in the lining endothelium in certain localized areas. Although our experimental observations do not demonstrate such a property, it is quite conceivable that swelling of endothelial cells and their acquisition of the ability to aggregate colloidal thorium dioxide may be accompanied by an increase in their permeability. This not only might be expected to favor the entrance of lipids into the intima in the affected areas but might even be a *sine qua non* to the process of lipid deposition. It appeared highly important, therefore, to determine if possible whether the acquired changes in the lining endothelial cells of the aorta preceded or followed the first appearance of lipid deposits in the arteries of cholesterol-fed rabbits.

It was in the hope of determining this point that our second experiment was carried out in which the rabbits were fed cholesterol for brief periods, given an intravenous injection of thorotrast, killed 24 hours later, and their aortas subjected to microscopic examination. In some of these animals fed cholesterol for periods as short as 6 days, granules of thorium dioxide were found in small groups of swollen

endothelial cells that were encountered in otherwise normal areas of the intima which lacked any trace of lipid deposit. This observation gives clear proof of the rapid acquisition of altered properties on the part of the endothelial cells within a very short period of cholesterol feeding. However, it is impossible to be sure that lipid deposits, though not demonstrable in the sections examined, did not exist in close proximity but outside the plane of the section. Wherever the smallest definite lipid deposit was found in the intima, the overlying endothelial cells had already acquired a slightly swollen appearance and the ability to take up and aggregate the intravenously injected colloidal thorium dioxide. Nevertheless, the use of cross sections of the aorta that were not serial sections rendered it impossible to conclude with certainty that the described morphologic and functional alterations of the lining endothelial cells preceded the first appearance of lipid deposits in the intima.

We are convinced that the conventional method of examining histologic cross sections of arteries lacks sufficient precision for the microscopic study of the very earliest changes of atherosclerosis such as those with which we are dealing here. This conviction is fully confirmed by preliminary observations already made, employing a method that we have devised and described elsewhere[16] which permits the microscopic examination of large areas of the arterial intima from its surface. By this method the topographic relationship of endothelial cells containing granules of thorium dioxide to deposits of lipids in the underlying intima can be readily demonstrated in a single preparation. Further studies employing this technique may settle some of the questions to which our present observations do not provide final answers.

It seems remarkable that lining endothelial cells of the arteries in cholesterol-fed rabbits should take up and accumulate colloidal thorium dioxide injected into the circulation when they show no tendency to accumulate lipid materials in appreciable amounts. Of course, the two kinds of substances are quite different in chemical constitution and very different in physical state as well. The lining endothelium must be, or must become during cholesterol feeding, permeable to both, since both must pass through the endothelial membrane to accumulate in the foam cells that lie beneath. It is all the more remarkable, therefore, that some of the thorium should be arrested and aggregated in the endothelial cells while quantities of lipid materials pass through the membrane leaving scarcely a trace in the lining endothelium. This fact is a fortunate one, however, for it has permitted in these experiments a clear demonstration (for the first time, so far as we are aware)

that a localized change in the biologic properties of lining endothelial cells develops in close association with the first appearance of lipid deposits in the intima of the aorta in cholesterol-fed rabbits.

Since thorotrast has been employed as a radiologic contrast medium, it seemed worth while to determine whether the quantities of thorium dioxide that accumulated in the experimental atherosclerotic lesions were sufficient to throw the lesions into contrast in roentgenograms. Though the quantities of thorium present in some of the lesions appeared under the microscope to be considerable, we were unable to demonstrate corresponding shadows in roentgenograms when aortas containing well developed lesions infiltrated with thorium dioxide were opened and laid flat on the photographic plate during a suitable exposure to x-ray beams of appropriate quality.

Summary and Conclusions

Colloidal thorium dioxide in large quantities was injected intravenously into normal rabbits and into rabbits that had been prepared by the previous feeding of cholesterol for from 1 week to 3 months. The animals were killed 5 minutes to 4 days following the injection of thorium dioxide. The aortas and other tissues were subjected to a searching microscopic examination for the presence of the characteristic granular aggregates of thorium dioxide.

It was observed that thorium dioxide did not accumulate in the normal arterial endothelium and intima of normal rabbits nor in the endothelium or intima of normal appearance that lay between atherosclerotic lesions in the aortas of cholesterol-fed rabbits. However, thorium dioxide accumulated rapidly and consistently in some of the endothelial cells and in superficially situated foam cells that constituted the principal cells of both small and large atherosclerotic lesions.

The observations clearly imply the entry of the colloidal thorium dioxide from the arterial lumen through the lining endothelial membrane and not from the vasa vasorum. The permeation of the substance into established atherosclerotic lesions is consistent with the concept of normal nutrition of the intima by perfusion of fluid from the vascular lumen and substantiates the theory that other colloidal substances, including those of lipid character, enter the intima from the lumen through the endothelium to accumulate in atherosclerotic lesions.

To the extent that lipids in the blood and intravenously injected colloidal thorium dioxide may be assumed to behave similarly, the observations deny the hypothesis that the foam cells in atherosclerotic

plaques have their origin as lipid-filled reticulo-endothelial cells in the spleen, liver, and lungs that subsequently migrate in the blood stream with their contained lipid to invade the intima (Leary's hypothesis).

The acquisition by endothelial cells of the ability to accumulate thorium dioxide during cholesterol feeding appeared to be a non-specific effect possibly due to some mechanical or chemical stimulus or to a local alteration in cellular and intimal permeability. An attempt was made in short-term cholesterol feeding experiments to determine whether lining endothelial cells of the rabbit's aorta acquired the ability to take up and aggregate colloidal thorium dioxide prior to or after the first appearance of lipid deposits in the intima. This question could not be resolved, but it was shown that this change in the biologic properties of lining endothelial cells occurred at a time at least as early as the earliest appearance of lipid deposits in the subendothelial layer of the intima as seen in histologic cross sections of the aorta stained for fat. The possible significance of these observations on the altered behavior of the arterial endothelium in relation to the pathogenesis of experimental cholesterol atherosclerosis in the rabbit is discussed.

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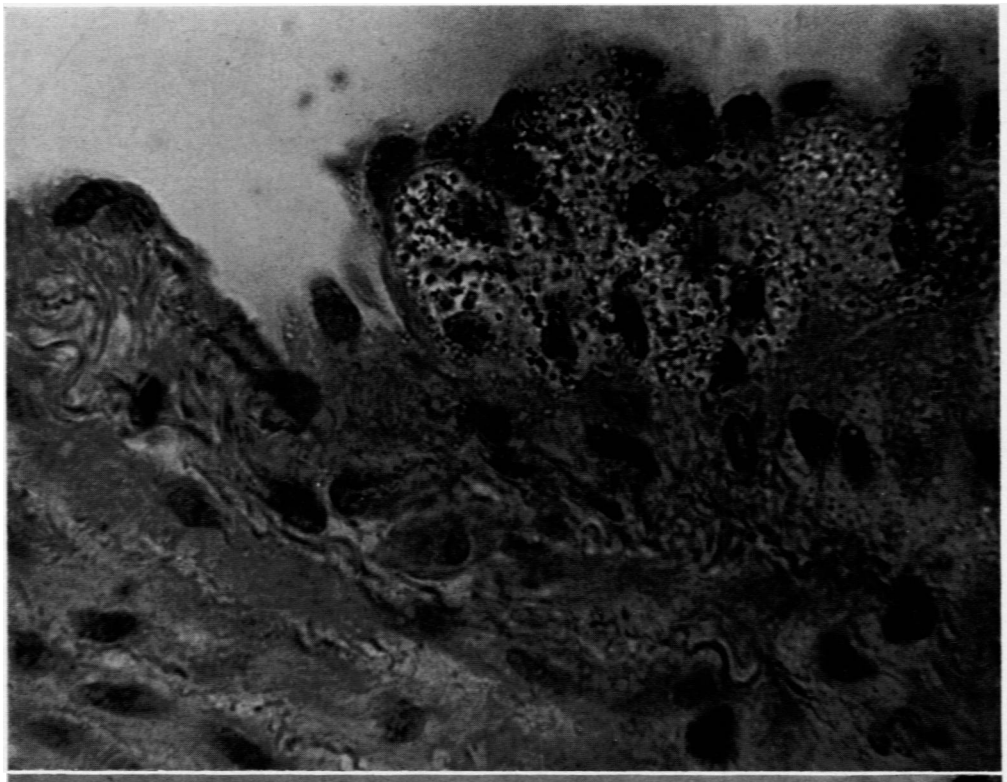
LEGENDS FOR FIGURES

FIG. 1. A small atherosclerotic lesion of the aorta. The swollen endothelial cells on its surface contain small, dark granules of thorium dioxide. Fine and coarse granular aggregates of the same material are accumulated in the cytoplasm of the lipid-filled foam cells that constitute the lesion. A clear halo can be seen around some of the granules. Zenker-formol fixation. Hematein-phloxine-saffron stain. × 900.

FIG. 2. A large atherosclerotic lesion of the aorta containing several layers of cells. The endothelial cells are somewhat swollen and small granules of thorium dioxide are seen in some of them. The foam cells immediately subjacent to the endothelium contain much thorium dioxide while those that lie deeper and closer to the media contain little or none. Zenker-formol fixation. Hematein-phloxine-saffron stain. × 900.



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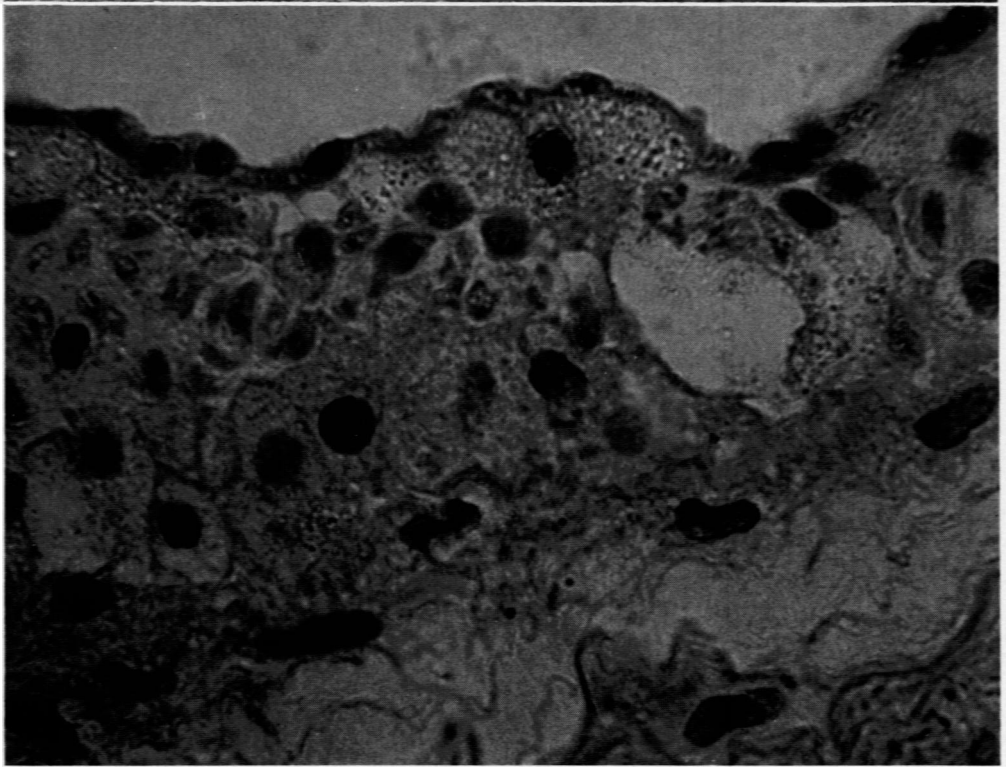

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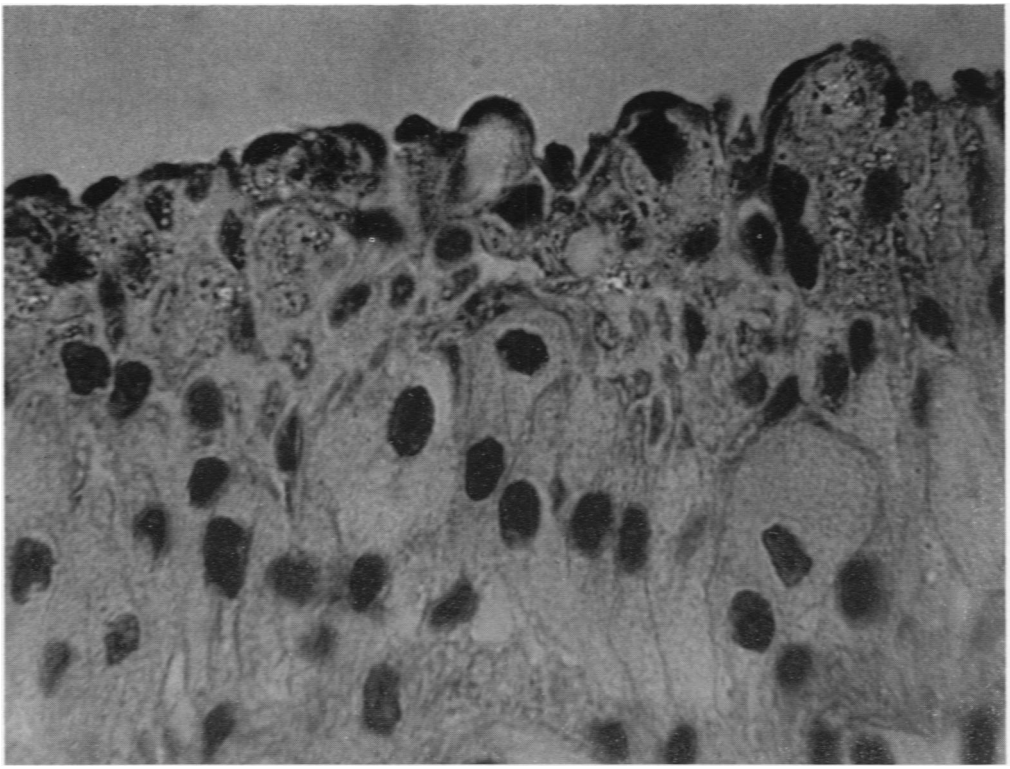
FIG. 3. A large atherosclerotic lesion of the aorta. Thorium dioxide granules are not visible in the endothelial cells and the latter are not swollen. Some of the subjacent foam cells contain granules of thorium while immediately neighboring cells do not. The deeper layers of cells are free. Zenker-formol fixation. Hematein-phloxine-saffron stain. × 900.

FIG. 4. Photomicrograph illustrating the peripheral margin or shoulder of an atherosclerotic lesion of the aorta. The lesion is several cell layers in thickness toward the left hand side but only one cell thick on the right. This thinner portion is covered by a partly detached film of clotted blood. The subjacent endothelial cells are swollen and contain granules of thorium. The underlying foam cells contain much thorium dioxide that is visible even at this relatively low magnification. The cells that constitute the thicker and more central part of the lesion contain only small amounts of the material or none at all. Zenker-formol fixation. Hematein-phloxine-saffron stain. × 210.

FIG. 5. Photomicrograph illustrating an endothelial cell in mitotic division. The division is in anaphase. The cell cytoplasm contains granules of thorium. To the right, immediately under the endothelium, is a foam cell containing much thorium dioxide. Formol-saline fixation. Hematoxylin and eosin stain. × 1100.



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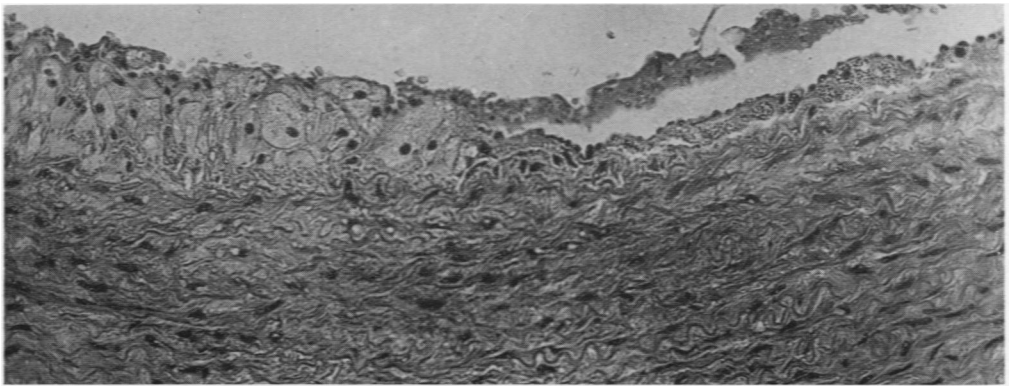

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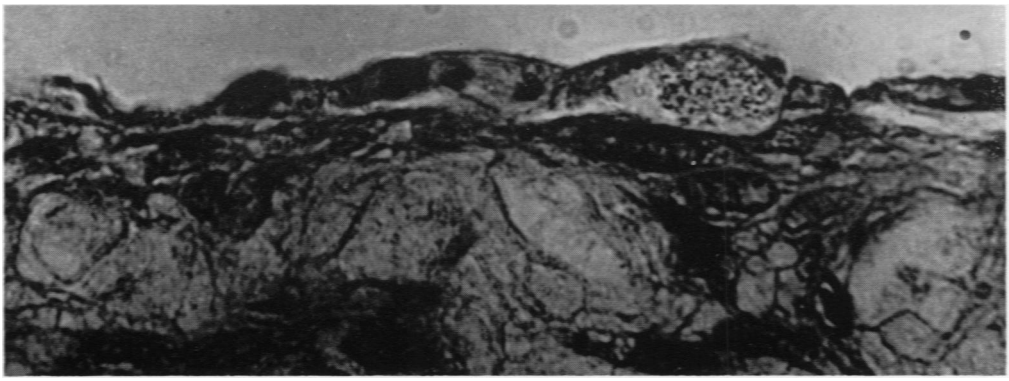

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