THE MORPHOLOGIC ELEMENTS IN THE EARLY LESIONS OF ARTERIOSCLEROSIS *

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Although some of the early focal intimal thickenings of the aorta commence as minute accumulations of lipids, other early lesions develop by a different mechanism. It was found that not all develop as lipid-rich lesions, nor do they all progress to a stage of atheroma. More advanced and even old lesions, although quite prominent, can be almost completely devoid of lipid. Therefore, the term "arteriosclerosis" instead of "atherosclerosis" is preferred.

The material for this study was selected on the basis of gross appearance. The lesions considered to be early appeared grossly as (1) circumscribed and diffuse glassy translucent elevations; (2) white opaque elevations (plaques); (3) small red mural thrombi; or (4) yellow dots and streaks. In addition, one group of lesions was included even though they were so small that they represented a chance observation. These were not visible grossly and were discovered accidentally on microscopic examination; they were also considered to represent early alterations.

The staining and other technical procedures were carried out as described in another publication.[1] From a total of 148 aortas, 470 sections were examined: 56 represented fatty dots and streaks; 129 were gelatinous elevations; 5 were small, just visible thrombi; and 13 were small, grossly invisible thrombi. The white opaque elevations (plaques) will be dealt with in a subsequent publication.

RESULTS

Gelatinous Elevations

The basic change, whether circumscribed or diffuse, consisted of an edematous swelling of the intima. This was caused by "insudation" of serum or plasma into the intima. In the swollen intima the 2 to 3 layered pattern described previously[2] was frequently distorted or no longer discernible. The various components of connective tissue, such as collagen, elastic fibers, and ground substance, and cellular elements,

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as well, had undergone lysis. In sections stained with toluidine blue, the metachromasia normally present in the intima was diminished and at times absent, indicating a diminution, "dilution," or perhaps depolymerization of acid mucopolysaccharides (AMP). In sections in which the AMP were stained with Alcian blue, such as pentachrome I or II[3] or Alcian blue-PAS-orange G, a decrease of Alcian blue-positive substance was noted. In milder lesions the elastic and collagen fibers were separated by the swollen ground substance (Fig. 1). Occasionally this change was confined only to the connective tissue layer of the intima (Fig. 2). In more pronounced lesions the 2 or 3 layered pattern described in the normal intima[2] was often completely wiped out (Fig. 3). Although some fibrin could often be demonstrated in milder lesions, insuded threads of fibrin constituted an almost constant finding in more advanced lesions. The fibrin was present in the form of threads and stellate structures (Fig. 4), sometimes conglomerating to form clumps, and at times a meshwork, in which entrapped red cells were frequently noted (Fig. 5). Occasionally the serofibrinous insudate caused not only separation, but also swelling of collagen fibers (Fig. 6). Lipids could be demonstrated in the insudate at times. Whether the lipid had been present at the site of the lesion before the insudation had taken place, or whether it was a component of the insudate, could not be determined. The fat was present extracellularly in dispersed or finely granular form, or as intracellular lipid (Fig. 7).

Fatty Dots and Streaks

Microscopically, the small yellow dots were found to be comprised of accumulations of foam cells, located either beneath the endothelium (Fig. 8) or somewhat deeper in the intima (Fig. 9). Larger accumulations of foam cells corresponded to typical grossly visible yellow streaks. The largest streaks were formed by confluence of numerous foam cells (Fig. 10). Despite the marked accumulation of lipids seen in some lesions (Fig. 11), there was neither increase of connective tissue nor reactive fibrosis in response to the deposition of lipids. If such fatty lesions were covered by a fibrous cap, the origin of the latter could always be traced to recent or old mural thrombi.[4-8]

Grossly Invisible Fibrin Thrombi

This group of early alterations was discovered accidentally, no lesion being visible in the gross. While in large mural thrombi, described elsewhere,[5,6] most of the blood constituents could be demonstrated, these small lesions proved to be recent mural thrombi composed of fibrin and platelets (Fig. 12). The fibrinous nature could be well dem-

onstrated with the phosphotungstic acid hematoxylin stain, in which a meshwork of fibrin was manifest in the less dense parts. Despite extension of some thrombi over relatively large areas (Fig. 13), the underlying intima showed no morphologic alterations. Some small mural thrombi, however, covered an intima which was the seat of insudation and swelling as described above (Fig. 14). When such thrombi had been present for some time, the fibrinous material appeared as acidophilic bands. Endothelium usually covered the thrombi, incorporating them into the wall of the aorta. The fate of mural thrombi will be discussed in a subsequent paper.[6]

Small Fibrin Thrombi, Barely Visible Grossly

This last group of early lesions revealed a composition similar to the one just described; i.e., they consisted of fibrin and platelets. At times, however, some other constituents of the blood, such as red blood cells, could also be demonstrated.

Discussion

Insudative lesions in the intima of the aorta were first described by Ribbert in 1904.[9] Despite a clear demonstration, these observations were neglected. In 1942 Bredt,[10] stimulated by Klinge's studies in rheumatic aortitis,[11] examined the lesions in pulmonary arteries and described swelling of the intima as the earliest visible change in arteriosclerosis of that vessel. Similar alterations were found in the aorta by Holle.[12] Meyer[13] was the first to describe fibrinous insudation occurring predominantly in the distal parts of plaques. This was believed to cause further progression of the plaques. Meyer used the term "insudation" in the belief that he was dealing with an inflammatory exudate in the sense of Virchow, who referred to arteriosclerosis as "*endarteritis chronica deformans.*"

We have adopted the term "insudate"[14] as proposed by Meyer in order to emphasize the fact that the protein-rich material is deposited *into* the substance of the intima. Whether this represents an inflammatory process is presently undetermined. If we accept Rössle's[15] concept of serous inflammation, during the course of which lysis of connective tissue elements may be encountered, in contradistinction to noninflammatory edema, then the lesion in the aortic intima is of inflammatory nature. Whether the lipid material found in these lesions has been deposited into the intima along with serum or plasma, or whether it had been there previously, could not be determined in our studies.

An interesting aspect of the early lesions in which the lipids were a

predominant feature was the lack of a reactive fibrosis. It is generally believed that the fibrosis occurring in arteriosclerosis represents a reaction to the lipid pool. We could find no evidence for this hypothesis in our studies. If there was any fibrosis present, its origin from fibrinous material was always evident. These fibrin or fibrin-platelet thrombi, usually found on the surface of an intima, showed some degree of alteration such as serous or serofibrinous insudation or deposition of lipids. In some cases, however, the intima was unaltered. Submicroscopic changes of the intima may have preceded the deposition of mural thrombi. We are thus in partial agreement with Rokitansky,[16] Clark, Graef and Chasis,[17] and contemporary British investigators,[18-21] that arteriosclerosis may develop as a result of thrombotic encrustation. However, this is only one way in which this complex lesion has its inception. The other two demonstrable mechanisms are serous or serofibrinous insudation and deposition of lipids.

Summary

The structure of lesions which appeared to represent the earliest alteration in the development of arteriosclerosis has been described and the gross and microscopic features correlated.

Corresponding to the gelatinous translucent elevations, a swelling of the intima and insudation of serum and fibrin with or without lipids were noted. The microscopic counterpart of the yellow dots and streaks was an intracellular accumulation of lipid material. A remarkable observation was the absence of reactive fibrosis in fatty lesions. An incidental feature was the existence of small mural fibrin thrombi deposits, not only on altered but also on morphologically unaltered intima.

These observations clearly indicate that the early focal lesions of arteriosclerosis in the aortic intima have at least 3 distinct patterns in their structural and chemical composition. It is not possible from these observations to determine whether further evolution of the 3 lesions may lead to a common end stage.

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[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Edematous swelling of the ground substance with separation of the formed connective tissue elements of the intima. Trichrome stain. × 110.

FIG. 2. Edematous swelling of the connective tissue layer of the intima, due to insudation of serum, causing "lysis" of acid mucopolysaccharide (AMP) and cells. Pentachrome I stain. × 100.

FIG. 3. Marked intimal swelling associated with decreased staining of AMP and lysis of formed connective tissue elements and cells. The normal 3 layered pattern, which was present in the adjacent normal intima, has been eradicated. Pentachrome I stain. × 30.

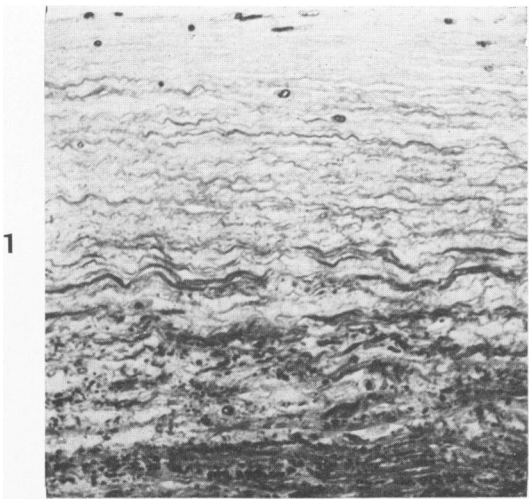
FIG. 4. Serofibrinous insudate of intima. The serous fluid seen as homogeneous gray material (light bluish-pink in sections) and the fibrin as black (intensely red in sections) threads, stellate structures, and clumps. Heidenhain's azan stain. × 200.

FIG. 5. Dense meshwork of fibrin with entrapped red cells in a serofibrinous insudate. Phosphotungstic acid hematein stain. × 450.

FIG. 6. Argentophilia of collagen fibers in a gelatinous plaque of the intima. The serous fluid between the fibers is seen as a homogeneous gray material. Gomori's silver impregnation. × 200.

FIG. 7. Intracellular lipid seen as varying-sized black clumps and extracellular lipid in the form of granular material deposited along the elastic fibers. Carbowax section; Fettrot and hematoxylin stains. × 250.

FIG. 8. Accumulation of foam cells below the endothelium. Hemalum, phloxine, and saffron stains. × 100.



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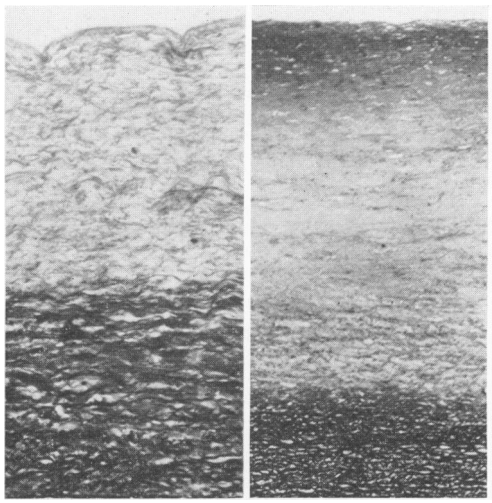

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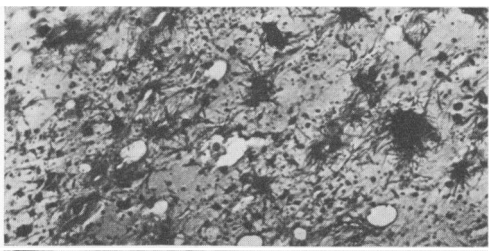

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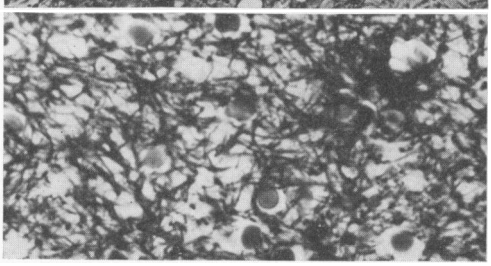

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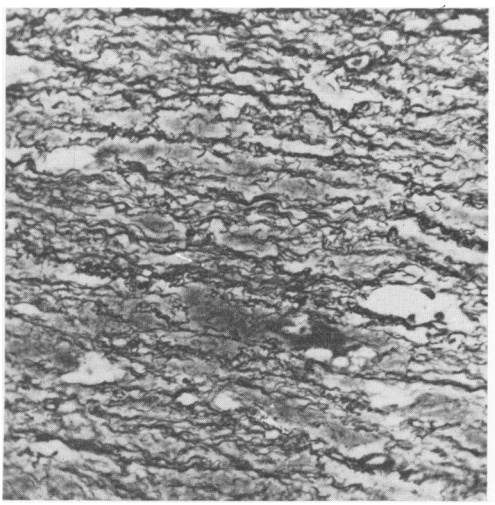

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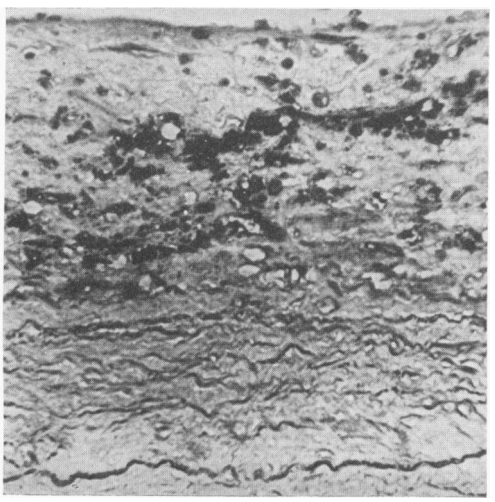

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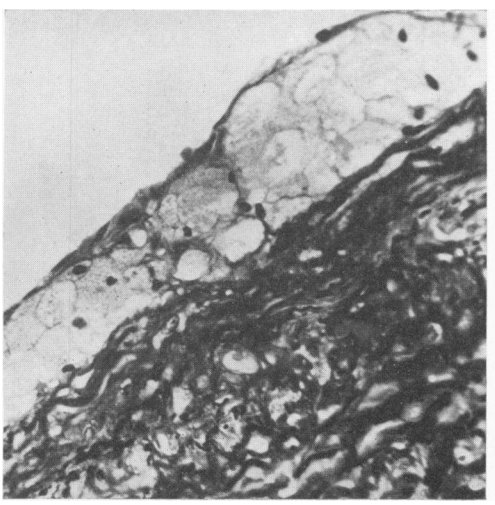

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FIG. 9. A row of foam cells in the intima representing a small dot in the gross. Pentachrome II stain (elastica omitted). × 250.

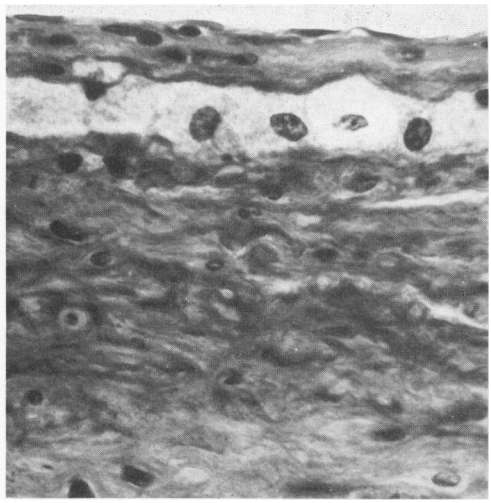
FIG. 10. Numerous lipophages forming a fatty streak. Note slight bulging of the intima. Carbowax section; Fettrot and hematoxylin stains. × 250.

FIG. 11. Numerous lipophages in the upper part of the intima and extracellular lipids forming an early atheroma at the base of the intima. Carbowax section; oil red O, Alcian blue, and hematoxylin stains. × 250.

FIG. 12. Small mural platelet-fibrin thrombus on the surface of unaltered intima. Trichrome stain. × 250.

FIG. 13. Small mural thrombus covering the intima over a large area. Intima shows no morphologic alteration. Phosphotungstic acid hematoxylin stain. × 150.

FIG. 14. Mural thrombus seen as a black streak on top of an intima showing insudative changes. Endothelium partly covers the thrombus, representing the first step in its incorporation into the vessel wall. Phosphotungstic acid hematoxylin stain. × 250.



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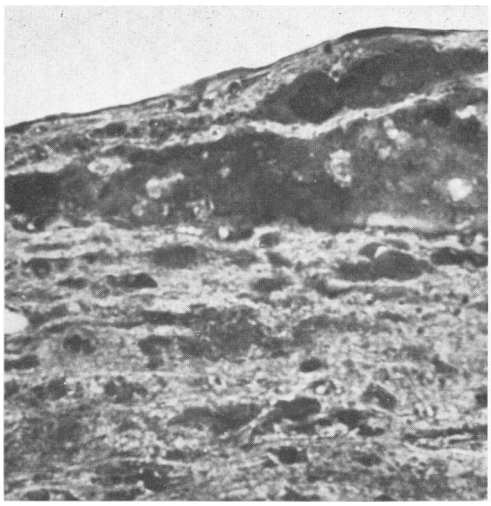

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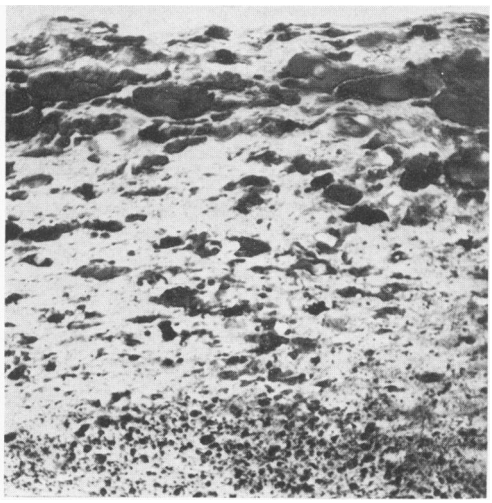

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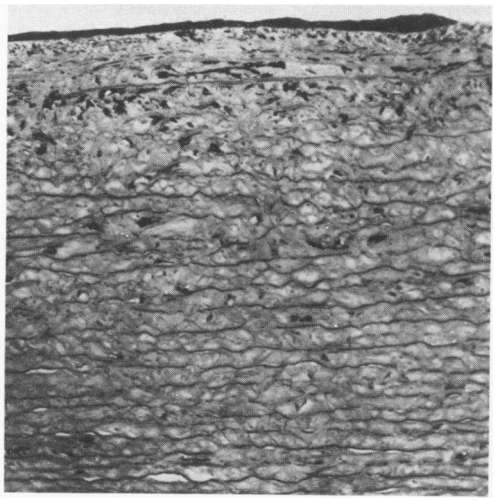

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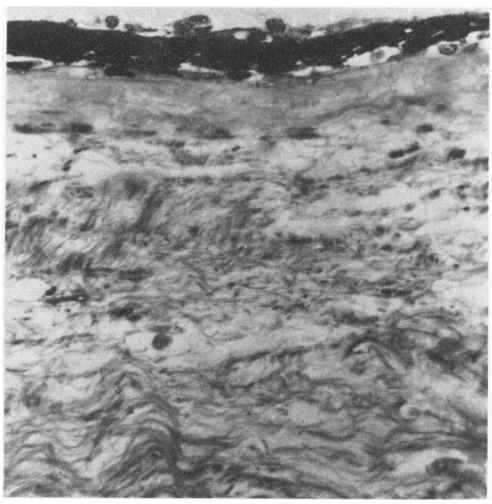

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