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Arteriosclerosis of the Mesenteric Arteries of Rats with Renal Hypertension

Electron Microscopic Observations

Masamichi Aikawa, MD and Simon Koletsky, MD

SEVERAL REPORTS ON ATHEROSCLEROSIS of hypertensive human and experimental animal models studied by electron microscopy have been published recently.[1-5] However, these studies emphasize the morphology and development of atheromata. Since the accumulation of lipid droplets distorts the cellular structure of the vascular wall, the direct effect of high blood pressure on the artery often has been overlooked. On the other hand, electron microscopic studies of arteriosclerosis with minimal atheroma formation are scanty when compared with those of atherosclerosis. Furthermore, the studies on arteriosclerosis without atheroma are concerned mainly with the arterioles and small arteries.[6-9] It is known that arterioles respond, morphologically, in a somewhat different manner from the major arteries in hypertension.

The present study deals with the development of arteriosclerosis in the mesenteric arteries of rats with renal hypertension. In the course of the hypertensive state these vessels frequently develop a nodular type of arteriosclerosis that is characterized by proliferative, degenerative and exudative lesions but is not accompanied by accumulation of fat in significant degree. Atherosclerosis is not observed either spontaneously in the normal rat or in the hypertensive rat, probably be-

From the Department of Pathology, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106.

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Address for reprint requests: Dr. Masamichi Aikawa, Department of Pathology, Case Western Reserve University, School of Medicine, Cleveland, Ohio 44106.

cause the laboratory diet generally used for this animal is very low in fat content.

The purpose of this study was to elucidate the sequence of lesions that characterize the development of arteriosclerosis as a response of the vascular wall to sustained elevation of intraluminal blood pressure. Particular emphasis was placed on low-power magnification electron microscopy in order to study the overall morphologic alteration of the artery and to better correlate the changes with those observed with the use of light microscopy. In addition, the vascular lesions produced by hypertension were compared with the general cell response to injury.

Materials and Methods

Two-month-old Sprague-Dawley rats weighing about 200 g each were used. Hypertension was produced in 25 rats by constricting the abdominal aorta between the ostia of the left and right renal arteries.[10] Seven normal rats were used as controls. The blood pressure of the hypertensive rats was measured by cannulating the brachial artery with a No. 50 polyethylene catheter, which was connected to an Hg manometer. The animals attain hypertensive levels (>150 mmHg) within a few hours and the high blood pressure is then sustained. After 1 week the pressures varied from 170 to 230 mmHg. The rats were fed Purina chow (less than 5% fat) and received tap water *ad libitum* for drinking. The hypertensive and control rats were sacrificed at intervals from 6 weeks to 5 months after hypertension was induced.

At sacrifice, the animals were perfused with a fixative through the thoracic aorta at a pressure 10–20 mmHg higher than the blood pressure. The fixative consisted of 2.5% glutaraldehyde, 4% sucrose and 0.05 M phosphate buffer. After perfusion, cross sections were taken from the distal portion of branches of the mesenteric artery (200–300 μ in diameter) and were placed in the fixative for at least 1 hour. The tissue was then washed in 0.05 M phosphate buffer for 30 minutes and postfixed in 1% OsO_4 for 1 hour. The dehydration was carried out in an ascending concentration of ethanol and the tissue was finally embedded in Epon 812. The sections were cut with a Porter-Blum MT-2 ultramicrotome and were placed on Formvar-covered single-hole copper grids. They were stained with 1% uranyl acetate and lead citrate and were examined with the Siemens Elmiskop 1A and 101 electron microscopes.

Observations

Normal Structure of the Mesenteric Artery

Though electron microscopic observations of the morphology of the mesenteric artery of rats was previously described,[11] the normal structure of the vessel is essential in order to understand the arterial lesions produced by hypertension. Hence the structure of the mesenteric artery will be described briefly with a particular emphasis on the structure of the organelles that are altered as a result of hypertension.

The mesenteric artery of the rat has three distinct layers: intima, media and adventitia (Fig 1). The intimal layer consists of a layer of

endothelial cells, a narrow subendothelial region and an internal elastic lamina (Fig 2). The endothelial cells are fusiform in shape and the central part protrudes into the lumen, due to the presence of a large nucleus (Fig 2). When the mesenteric artery is contracted, the endothelial cell is often cuboidal and bulges prominently into the lumen.

The cytoplasm of the endothelial cell contains mitochondria, endoplasmic reticulum, ribosomes, vesicles and caveolae, a few electron-dense bodies, and scattered microtubules (Fig 2). Endothelial vesicles and caveolae are observed along the plasma membrane facing the lumen as well as along the basal and lateral sides. Each vesicle and caveola measures about 700 Å in diameter and its matrix is generally electron translucent, though the inner surface is covered with fuzzy material.

Each endothelial cell is in close proximity with the next. Usually, two adjacent endothelial cells are separated by a narrow space of 200 Å and occasionally they are bridged by tight junctions (Fig 2); the cytoplasmic processes between two cells often interdigitate. The subendothelial region between endothelial cell and internal elastic lamina is narrow and contains fine fibrils 200–250 Å in width. The internal elastic lamina is uniformly electron transparent, zigzag in appearance and not surrounded by a definite limiting membrane. There are randomly distributed fenestrae along the internal elastic lamina, through which a few fibrils extend between intima and media.

The medial layer is the thickest layer of the mesenteric artery and consists mainly of 4–5 layers of smooth muscle cells (Fig 1), which are seen in thin section to run perpendicularly to the long axis of the artery (Fig 1).

The smooth muscle cell is spindle shaped with a thicker middle portion, which contains a large nucleus and cytoplasmic organelles (Fig 3). An electron-opaque basement membrane 60 mμ thick, composed of fine filaments, surrounds the cell (Fig 3). The smooth muscle cell is surrounded by a unit membrane, which shows small invaginations forming vesicles. Along the inner surface of the plasma membrane are several electron-dense poorly demarcated structures of pyramidal shape (Fig 4), which are referred to as dark bodies,[12] into which myofilaments often extend (Fig 4). Numerous myofilaments occupy most of the cytoplasm except in the perinuclear region; in general they run parallel to the long axis of the cell (Fig 3).

The cytoplasmic organelles, such as mitochondria, Golgi complexes, endoplasmic reticulum and ribosomes, are observed mainly around the perinuclear region and less frequently along the plasma membrane

(Fig 3). The intercellular space separating each smooth muscle cell is electron transparent and a few bundles of fibrils 250 Å in width, reported to be elastic fibers, are often seen.

The adventitial layer is separated from the media by an external elastic lamina and is composed mainly of fibroblasts and bundles of collagen fibers (Fig 1). The fibroblasts show abundant endoplasmic reticulum and ribosomes. Collagen fibers are occasionally seen extending from the cytoplasm of the fibroblast to the intercellular space. Each fiber measures about 500 Å in width and shows prominent striations perpendicular to its long axis. The external and internal elastic lamina are similar in morphology; fenestrae are occasionally observed in both.

Morphologic Changes in the Mesenteric Arteries of Hypertensive Rats

The changes in the mesenteric arteries of rats can be divided into four types according to a developmental sequence and in order of increasing severity. These are (1) arterial hypertrophy, (2) arterial hyperplasia, (3) arterial degeneration and associated fibrosis and (4) fibrinoid necrosis.

Arterial Hypertrophy

Hypertrophic alterations of various cell components usually occur in the early stage of hypertension. The endothelial cell becomes cuboidal and the nucleus appears to be enlarged with irregular contour. The cytoplasmic organelles increase in number. Numerous endothelial vesicles are seen along and near the plasma membrane at both luminal and basal sides (Fig 5–7). These vesicles often contain electron-dense material (Fig 7). The mitochondria appear to increase in number, although their size is unchanged. Frequently centrioles, which are rare in the control group, are seen in these cells (Fig 6). The subendothelial region and internal elastic lamina show the same appearance as in the control group.

The smooth muscle cells in the media show an increased number of cytoplasmic organelles (Fig 5). The mitochondria increase in number and rough-surfaced endoplasmic reticulum is more abundant (Fig 5). The microtubules, which are rarely observed in the control group, are seen often in the perinuclear region of the hypertensive animals. Several Golgi complexes are present (Fig 5, 8 and 9) and increased numbers of small vesicles are seen around them (Fig 8). The myofilaments are dispersed in different directions. The dense bodies of the smooth muscle cell increase in number and size. More vesicles contain

electron-dense material. The outline of the smooth muscle cell becomes irregular and shows invaginations and protrusions. The basement membrane surrounding each smooth muscle cell reveals foci of detachment from the plasma membrane of the smooth muscle cell (Fig 9), which creates a narrow electron-transparent space between the basement membrane and the smooth muscle cells. The intercellular space is wider than that of the control group.

No morphologic changes are apparent in the adventitia.

Arterial Hyperplasia

The endothelial cells remain as a single layer (Fig 10) and do not undergo proliferative change. No mitotic figures are observed in these cells. The internal elastic lamina occasionally shows fragmentation and fraying (Fig 11) and at times becomes electron opaque.

In the hyperplastic stage, the most prominent changes occur in the media layer. The latter becomes thickened and may consist of six to ten or more layers of smooth muscle cells (Fig 10) as compared to four or five in the control animals. Each smooth muscle cell still contains abundant cytoplasmic organelles as in the hypertrophic cell. Apparently as the result of mitotic activity, two nuclei are often present in a smooth muscle cell. The intercellular space of the media increases its width and contains collageneous fibers and fibrils (Fig 10).

As the number of the smooth muscle cells increases, some migrate into the intima through fenestrae of the internal elastic lamina (Fig 11 and 12). Such migration also occurs through fragmented portions of the internal elastic lamina. As the migration progresses, the subendothelial space becomes widened and is occupied by a large number of smooth muscle cells (Fig 13 and 14). The migration of smooth muscle cells is accompanied by collagenous fibrils, which tend to surround the muscle fibers (Fig 13 and 14).

The adventitia shows an increased number of fibroblasts and collagenous fibers, which in places extend to the medial layer through the fenestrae of the external elastic lamina.

Arterial Degeneration and Fibrosis

In this stage, the endothelial cell shows degenerative changes. The mitochondria are swollen and myelin figures are often observed in the cytoplasm. Occasionally, large vacuoles are present. As in the early stage, endothelial vesicles are abundant.

The internal elastic lamina at this stage show fragmentation and fraying and in some sections is more electron opaque. Because of its

fragmentation and disintegration, the demarcation between intimal and medial layers is not clear in some regions.

Prominent changes in the media are enclosure of the smooth muscle cells by abundant collagen fibers and fibroblasts in the intercellular space (Fig 15–17). The shape of the smooth muscle cell becomes more irregular, and the cells are widely separated by the fibrous tissue (Fig 22). Also noted are occasional smooth muscle cells with an electron-dense cytoplasmic matrix (Fig 19) in which mitochondria are prominent. In these cells, individual myofilaments can hardly be distinguished.

Some smooth muscle cells often contain large vacuoles (Fig 18) and osmiophilic bodies (Fig 20) while the others show uniformly dense cytoplasm (Fig 19); two nuclei are frequently present in one cell. Myofilaments are disoriented and dense bodies are often observed.

Collagen fibers approach the thickened basement membrane of the smooth muscle cell (Fig 23 and 24) and this often gives the appearance of fraying out of the basement membrane. The fibroblasts are numerous and collagen fibers are abundant. The external elastic lamina is fragmented.

Collagenous fibers in the intercellular space appear to be derived by extension from the adventitia into the media through the fenestrae or fragmented foci of the external elastic lamina (Fig 20). Thus the collagenous fibers are more abundant near the adventitia.

The fibroblasts in the tunica adventitia are irregular in shape and contain many cytoplasmic organelles. Dividing fibroblasts are seen occasionally (Fig 21). Bundles of collagen fibers are numerous and their appearance is the same as that of the control group.

Fibrinoid Necrosis

Fibrinoid necrosis is usually observed in the vessels of rats that had severe renal hypertension (200 mmHg or above) of relatively short duration. The endothelial cells now appear more hypertrophic than in the early stage of arteriosclerosis. The endothelial cell often contains uniformly electron-opaque globules, which measure up to 1.5 μ in diameter, surrounded by a unit membrane (Fig 25). Similar electron-opaque components are seen in the intercellular space between two endothelial cells (Fig 26). These are also noted in the inpocketing of the basal side of the plasma membrane, as it is being discharged into the subendothelial region (Fig 26). After such discharge, the electron-opaque material is no longer surrounded by a membrane, but instead lies in the subendothelium and appears to be intermingled with the fibrous tissue.

In the next developmental stage the electron-opaque material is observed in the deeper layer of the subendothelium (Fig 27). In some areas, the less electron-dense material appears to be incorporated into the electron-dense crystalloid material (Fig 28).

The electron-dense crystalloid material, when seen by higher magnification, shows a distinct transverse striation of 300 Å periodicity and another linear structure of similar periodicity enclosing a 60° angle with the former (Fig 29). These crystalloid materials are mainly observed in the subendothelial layer; however, they are also present in the medial layer. The adventitia and media at this stage show numerous granulocytes in the intercellular space and between the collagen fibers (Fig 30).

Discussion

Previous studies of the arterial lesions in animals with experimental hypertension have emphasized two main alterations, namely an increase in vascular permeability [9, 13, 14] and changes involving the medial smooth muscle cells.[9, 15, 16] Increased permeability may be due to separation of the intercellular junctions of endothelial cells, perhaps as a result of stretching of the vessel due to increased intramural pressure,[17] or to degenerative changes in the lining endothelium that facilitate the passage of materials from the bloodstream into the vascular wall. Another possibility is an increased number of endothelial vesicles and caveolae, which are thought to be partially responsible for transport of materials from the lumen to the vascular wall.[18] These types of lesions were observed in the present study. Separation of the endothelial cell junctions was especially prominent in instances where fibrinoid material was present in the vessel wall.

Several investigators have reported the accumulation in the vascular walls of hypertensive animals of injected carbon particles [9] and horseradish peroxidase [13] in greater amounts than were observed in normotensive controls. Increased vascular permeability in hypertensive animals has also been demonstrated with the use of radioactively tagged proteins.[17] Substances like these seem to accumulate in the vessel wall with greater facility in the presence of injury secondary to high blood pressure. The latter not only enhances vascular permeability but in addition injures the cellular components of the vessel wall either mechanically and/or by altering their metabolism; as a result, the vessels are more likely to accumulate substances from the circulating blood.

Esterly and Glagov [14] observed blood cells, macrophages and cell fragments in the intimal layer of the renal arteries of rats rendered

hypertensive by administration of deoxycorticosterone and salt and interpreted these as evidence of increased vascular permeability. Such cells were not observed in the mesenteric arteries of the hypertensive rats in our study. Perhaps they accumulate more readily in the renal arteries since the renal vascular tree is generally believed to be more sensitive than other vessels to injury from prolonged high blood pressure. However Wiener *et al*[9] reported that the pancreatic and mesenteric arteries of rats with renal hypertension were permeable to colloidal particles of carbon and plasma fibrinogen as well as to erythrocytes and platelets.

Geer *et al*[15] observed that the medial layer of the pancreaticoduodenal arteries of hypertensive rats contained interstitial collections of osmiophilic material, which was usually associated with smooth muscle degeneration. Gardner and co-workers[16] reported the presence of osmiophilic particles within the cytoplasm of the vascular smooth muscle cells of the arterioles of rats with adrenal regeneration hypertension. Similar observations were made in the present study. Whether such substances represent accumulation of lipid material derived from the bloodstream or whether they represent a metabolic alteration of the vascular smooth muscle cells is not certain. The arteries that are damaged as a result of high blood pressure may take up more nutrients from the bloodstream in order to support the increased metabolic requirement of the hypertrophic and hyperplastic cell components of the vascular wall. Since the rat does not possess vasa vasorum,[19] it would appear that for this animal the likely route for vessels to receive nutritive materials is by way of the luminal side; and in hypertensive animals they are received in increased amounts as a result of enhanced permeability and perhaps also because of increased filtration pressure.

In this study, the degenerative alterations observed in the endothelial cells of the mesenteric arteries were similar to those described by Wiener and co-workers.[9] They noted swelling of cytoplasmic organelles, increased electron density of cytoplasm, numerous cisternae of rough-surfaced endoplasmic reticulum and the presence of many nonmembrane-associated ribosomes. In addition, the hypertrophied endothelial cells in the early stage of the vascular lesion in our hypertensive rats frequently showed an increased number of endothelial vesicles. The latter suggests augmented uptake, by these cells, of materials in the bloodstream, thus confirming an increase in vascular permeability.

Proliferation of vascular smooth muscle in the medial layer of the arteries of hypertensive animals has been reported by several investi-

gators [7, 10] and was a prominent feature of our study. The proliferative change was associated with an increased number of binuclear smooth muscle cells but no mitotic activity was observed even when there was a marked increase in the number of smooth muscle cells. However increased mitotic activity of vascular smooth muscle cells of the aorta of cholesterol-fed swine was reported recently by Florentin and co-workers,[20] who suggested that the cholesterol itself might have provided the stimulus for increased mitosis.

Marked proliferation of smooth muscle cells was reported by Koletsky and co-workers [10] in normotensive animals fed a high-fat diet; the resulting lesions were morphologically indistinguishable from those that occurred much more rapidly in hypertensive animals on the same high-lipid intake. Thus smooth muscle cell proliferation is not dependent on high blood pressure and it probably represents a nonspecific reaction to various types of injury, one of which is the presence of abnormal amounts of certain metabolites. Smooth muscle cell hyperplasia with inclusion of these cells in the intimal layer was reported in rats given serial infusions of angiotensin.[21] Wellman and Volk [22] observed migration of smooth muscle cells into the subendothelial space, through the fenestrae of internal elastic lamina, during the development of atherosclerosis of the coronary arteries of normotensive rats with hypercholesterolemia. Proliferation of medial smooth muscle in hypertensive rats is associated with similar penetration of these cells into the subendothelial space.[7, 23] Such cells probably represent the myointimal cell, which is believed to play an important role in the genesis of atherosclerosis.

Proliferation of the smooth muscle of the mesenteric arteries of the renal hypertensive rats in our study was associated with the presence of microtubules and an increased number of cytoplasmic vesicles in these cells. We are unaware that the presence of such microtubules has been described in the normal smooth muscle cell. Although the function of microtubules is not clear, their function may be contractile in nature and thus they might play a role in vascular contraction or serve as supporting structures providing cellular rigidity.[24] The small cytoplasmic vesicles occur mainly along the plasma membrane and while their function is unknown, they possibly serve to transport nutrients in a way similar to pinocytic vesicles.

The degenerative changes observed in smooth muscle cells in our study include increasing density of the cytoplasmic matrix, swollen mitochondria, vacuolization, appearance of osmiophilic bodies and disorientation of myofilaments. The presence of such changes in the

markedly thickened media of the mesenteric arteries supports the view that the hyperplastic change may result from the fact that there is insufficient nutrients to provide for the enhanced metabolic needs that accompany proliferation of the cells. The degenerative lesions may be a requirement for the subsequent accumulation of lipid, and then for the formation of atheromatous plaques. However the latter apparently occur only if the animals are fed a high-fat diet.[10]

Several investigators [25, 26] have expressed the view that the collagen fibers or fibrous tissue that develops within the media of the arteries of hypertensive animals originates from the smooth muscle cells. An alternative view, which we are inclined to favor, is that the fibrous tissue is derived, at least in large part, from the adventitia. Collagen fibers often appear to extend into the media from the adventitia and, especially in the early stage of hypertension, occur in that part of the media in proximity to the adventitia. The production of fibrous tissue in the media and then in the subendothelial area may represent a healing process that results in a loss of elasticity.

Summary

Electron microscopic observations on the mesenteric artery of rats with renal hypertension were made. The arterial lesions have been divided into four classes: (1) arterial hypertrophy, (2) arterial hyperplasia, (3) arterial degeneration and fibrosis and (4) fibroinoid necrosis.

Arterial hypertrophy is characterized by the appearance of hypertrophic endothelial and smooth muscle cells, and arterial hyperplasia by thickening of the medial layer with the presence of several layers of smooth muscle cells. Migration of smooth muscle cells was noted from the medial layer to the subendothelium through fenestrae or fragmented foci of the internal elastic lamina.

Arterial degeneration is delineated by degeneration of the endothelial cells and smooth muscle cells. The endothelial cells show swelling of cytoplasmic organelles. The degenerative changes of smooth muscle cells include increasing density of the cytoplasmic matrix, swollen mitochondria, vacuolization, appearance of osmiophilic bodies and disorientation of myofilaments. Concomitantly, the collagen fibers increase within the medial layer. Each smooth muscle cell becomes irregular in shape and is finally obliterated by fibrous tissue. The extensive fibrosis of the mesenteric artery appears to be the end stage of the sclerotic artery produced by long standing hypertension. Fibrinoid necrosis is characterized by deposition of electron-dense crystal-

loid materials in the vascular wall. Prior to their occurrence, electron-opaque granular materials are seen in the endothelial cells and appear to be discharged into the subendothelium. These apparently become incorporated into the crystalloid material.

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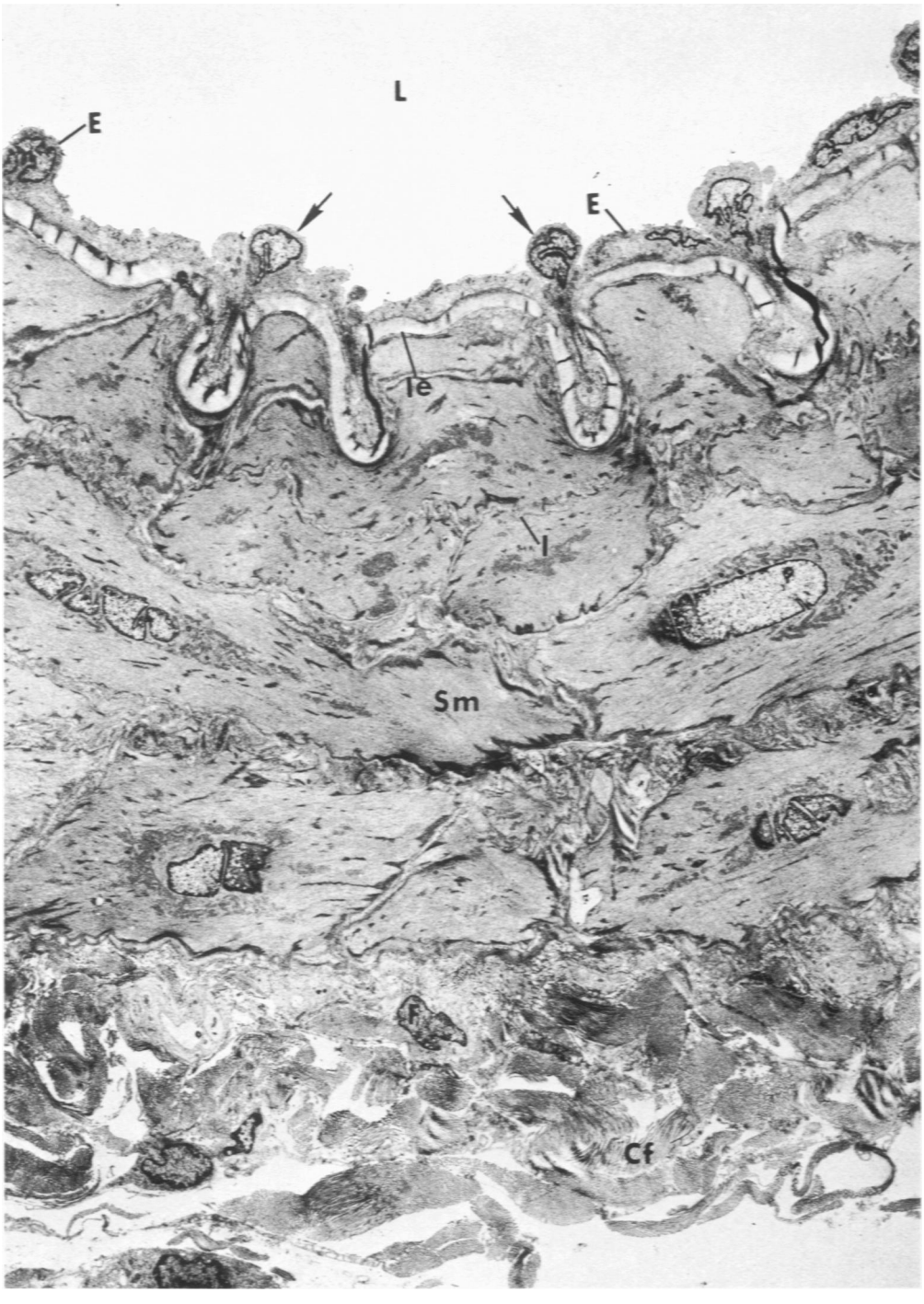
Legends for Figures

Fig 1.—Low-magnification electron micrograph of mesenteric artery from control rat. Layer of endothelial cells *(E)* surrounds lumen *(L)*. Since this artery is contracted, some of endothelial cells bulge toward lumen *(arrows)*. Internal elastic lamina *(Ie)* is wavy in appearance because of contracted status of artery. Four to five layers of smooth muscle cells *(Sm)* are seen in tunica media. Each smooth muscle cell runs parallel to luminal surface. Narrow intercellular space *(I)* is observed between smooth muscle cells. Tunica adventitia is composed of bundles of collagen fibers *(Cf)* and fibroblasts *(F)*. × 3000.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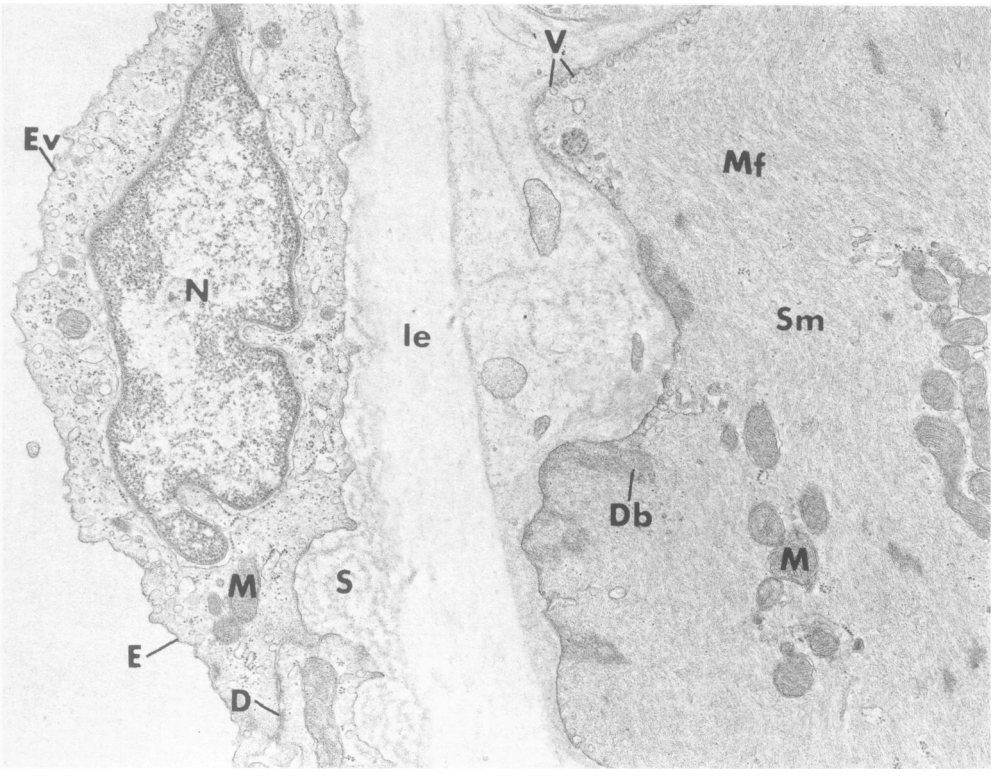

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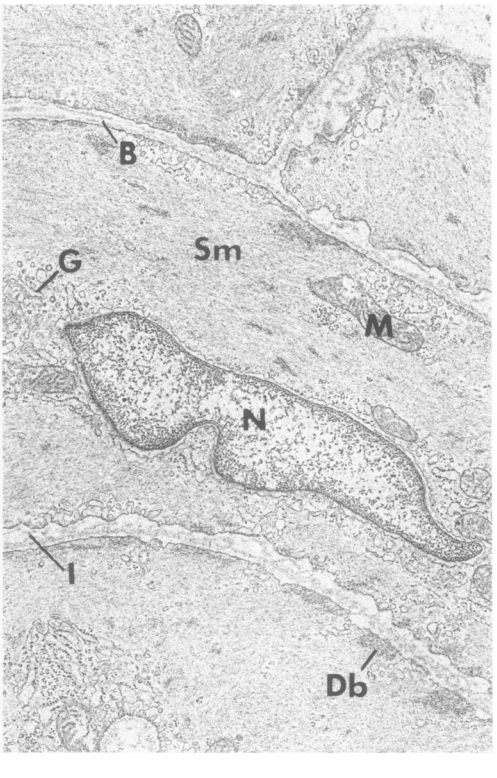

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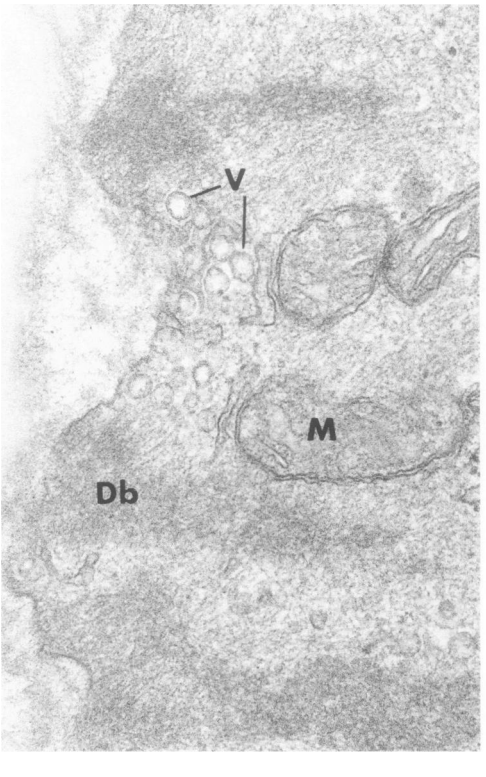

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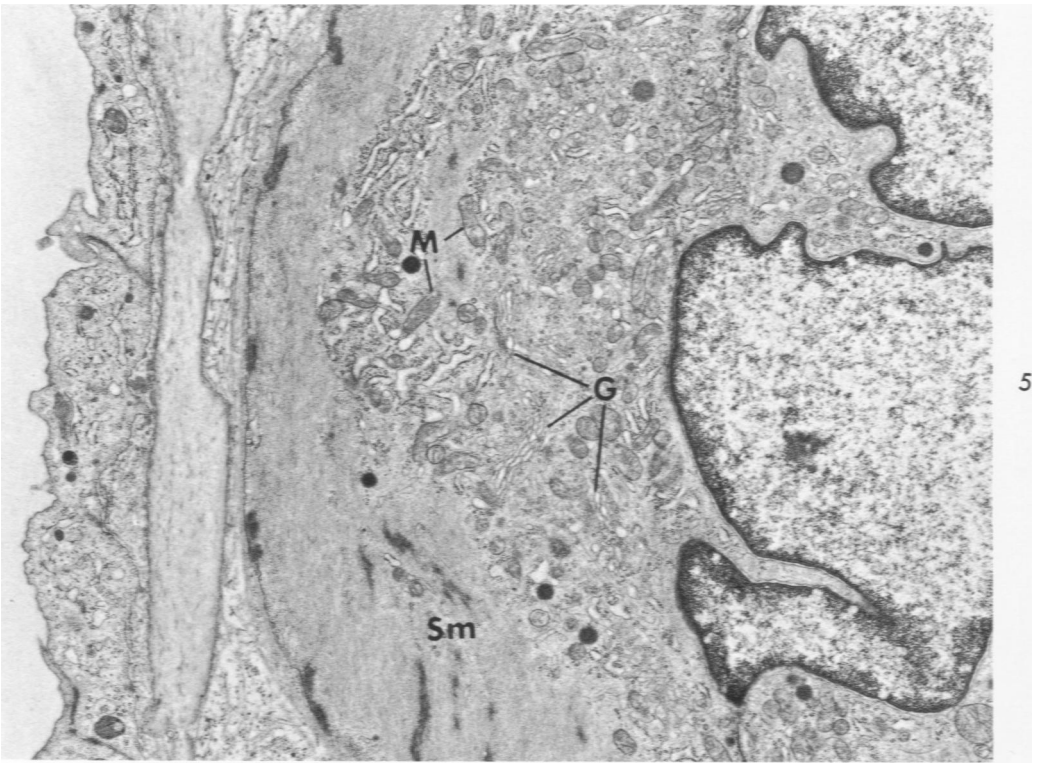
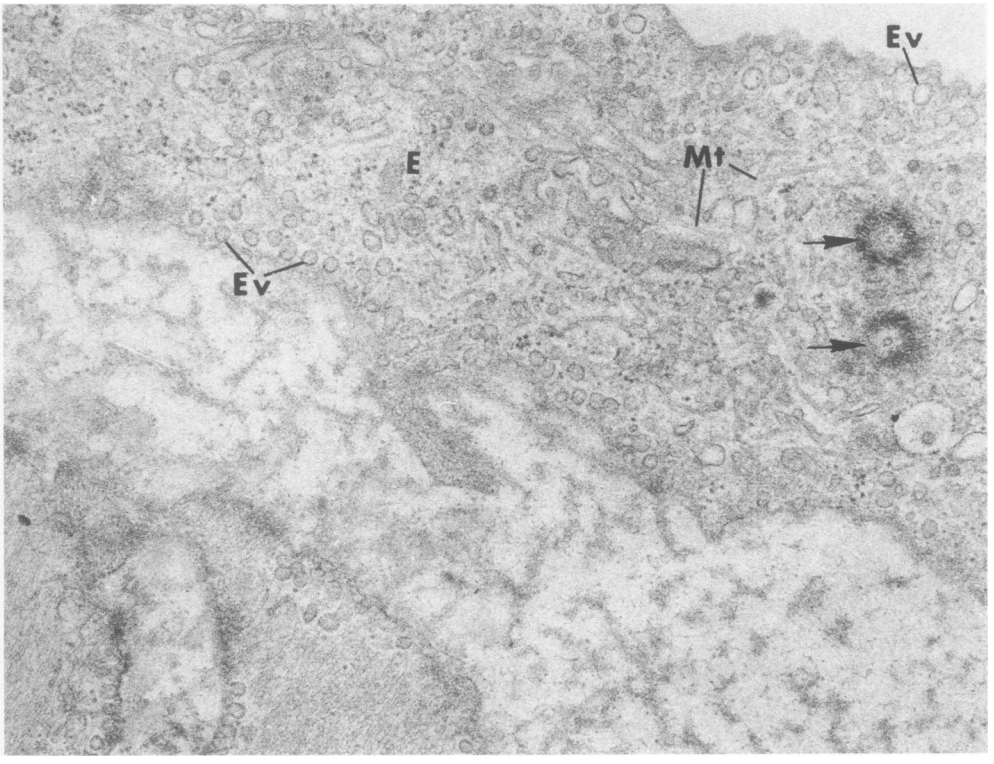


Fig 5.—Portion of hypertrophic mesenteric artery from hypertensive rat. Hypertrophic changes are primarily seen in smooth muscle cell *(Sm)*. Hypertrophic smooth muscle cell possesses abundant mitochondria *(M)*, Golgi complexes *(G)*, endoplasmic reticulum, and ribosomes (compare with Fig 2). Location of these organelles extends from perinuclear region to area near plasma membrane. × 14,000.

Fig 2.—Higher-magnification electron micrograph showing endothelial cell *(E)*, an internal elastic lamina *(Ie)* and portion of smooth muscle cell *(Sm)* of mesenteric artery of control rat. Endothelial cell is fusiform in shape and nucleus *(N)* is located centrally. Mitochondria *(M)*, endoplasmic reticulum, ribosomes, and endothelial vesicles *(Ev)* are seen in the cytoplasm. Desmosomes *(D)* are observed at junction of two endothelial cells. Subendothelial space *(S)* contains fine fibrils. Internal elastic lamina *(L)* is electron translucent. Portion of smooth muscle cell shows mitochondria, myofilament *(Mf)*, dense bodies *(Db)* and vesicles *(V)*. × 16,000.

Fig 3.—Portion of tunica media (control). The smooth muscle cell *(Sm)* possesses nucleus *(N)*. A few mitochondria *(M)*, endoplasmic reticulum, ribosomes and Golgi apparatus *(G)* are present in perinuclear region as well as along plasma membrane. Rest of smooth muscle cell is occupied with myofilaments, which merge into dense bodies *(Db)*. Each smooth muscle cell is surrounded by basement membrane *(B)*. Intercellular space *(I)* is narrow. × 12,000.

Fig 4.—Higher-magnification photomicrograph of the smooth muscle cell showing a few vesicles *(V)*, mitochondria *(M)* and dense bodies *(Db)* near plasma membrane. × 45,000.



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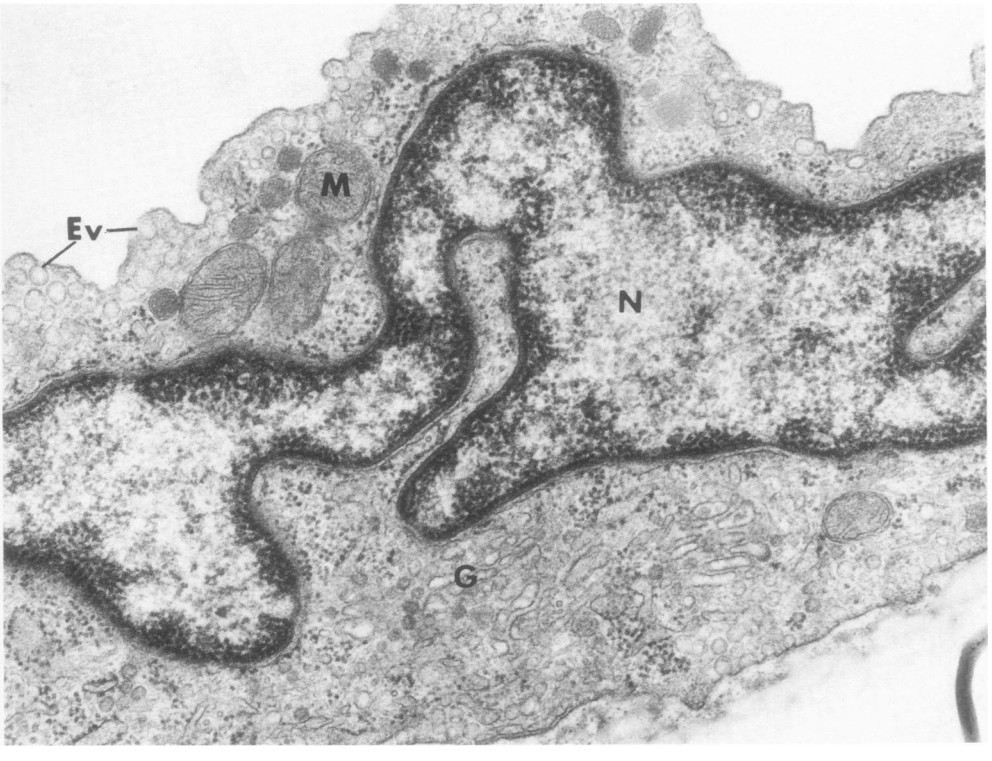

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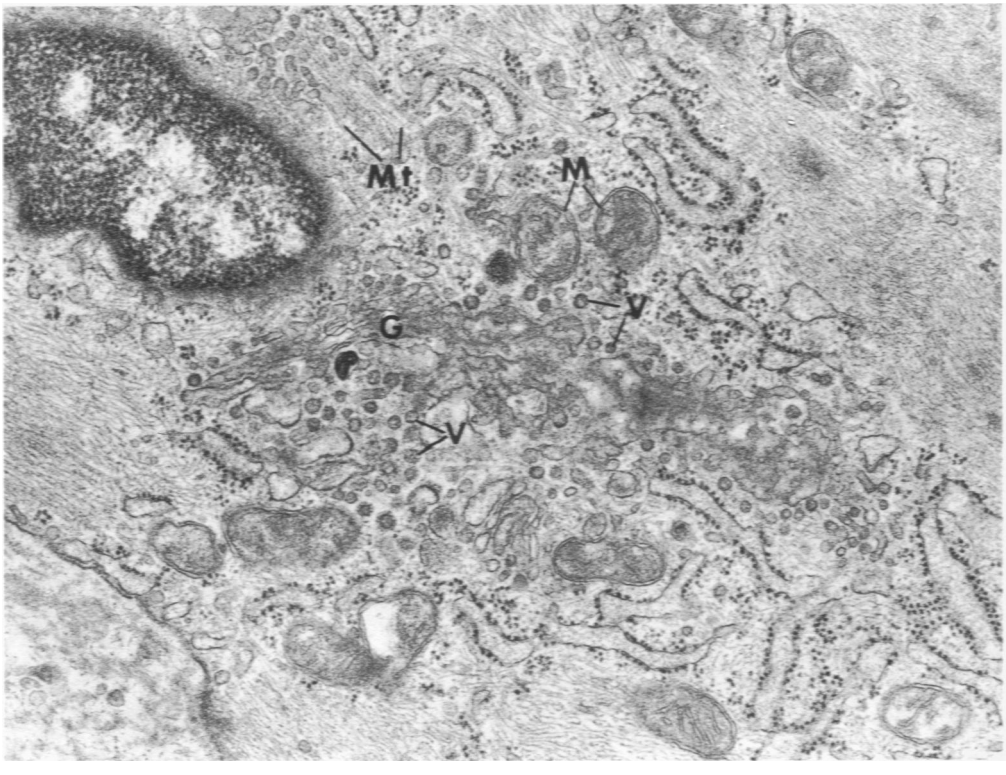


Fig 8.—Higher-magnification photomicrograph of hypertrophic smooth muscle cell. Large Golgi complex *(G)* is associated with numerous vesicles *(V)*. Also seen in cytoplasm are several mitochondria *(M)*, dilated endoplasmic reticulum, ribosomes, microtubules *(Mt)* and myofilaments. × 29,000.

Fig 6.—Hypertrophic endothelial cell *(E)* showing abundant endothelial vesicles *(Ev)*, two centrioles *(arrows)*, and microtubules *(Mt)*. × 27,000.

Fig 7.—Another example of hypertrophic endothelial cell. Nucleus *(N)* becomes irregular in shape. Abundant endothelial vesicles *(Ev)*, Golgi complex *(G)* and mitochondria *(M)* are seen. × 31,000.

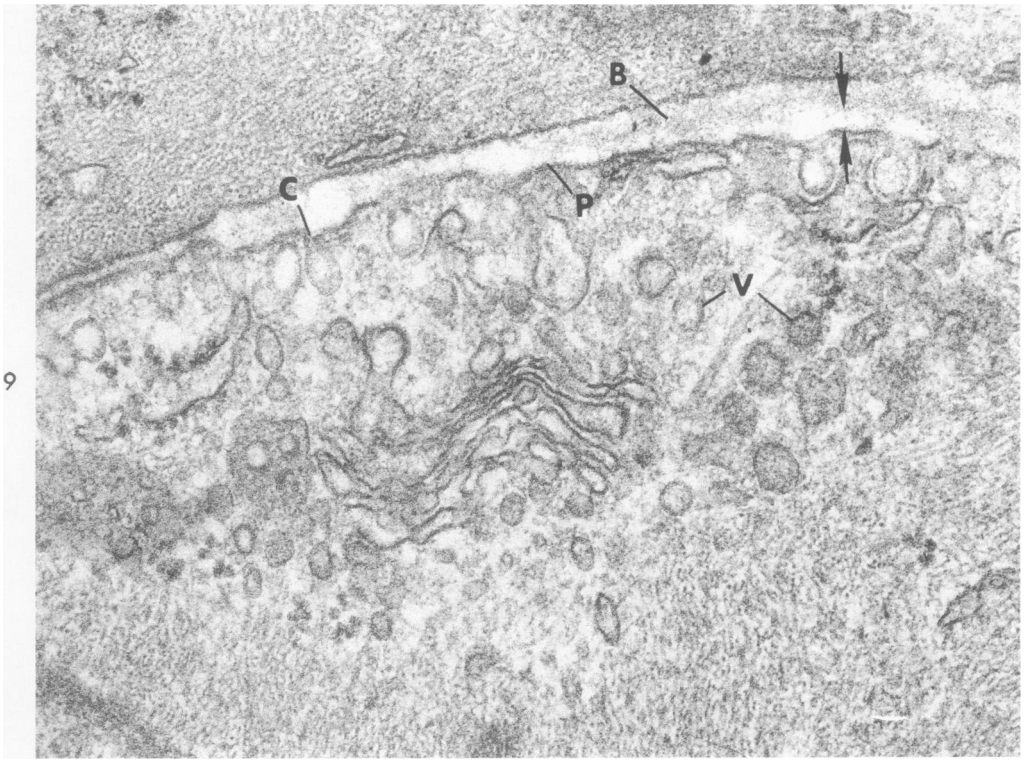
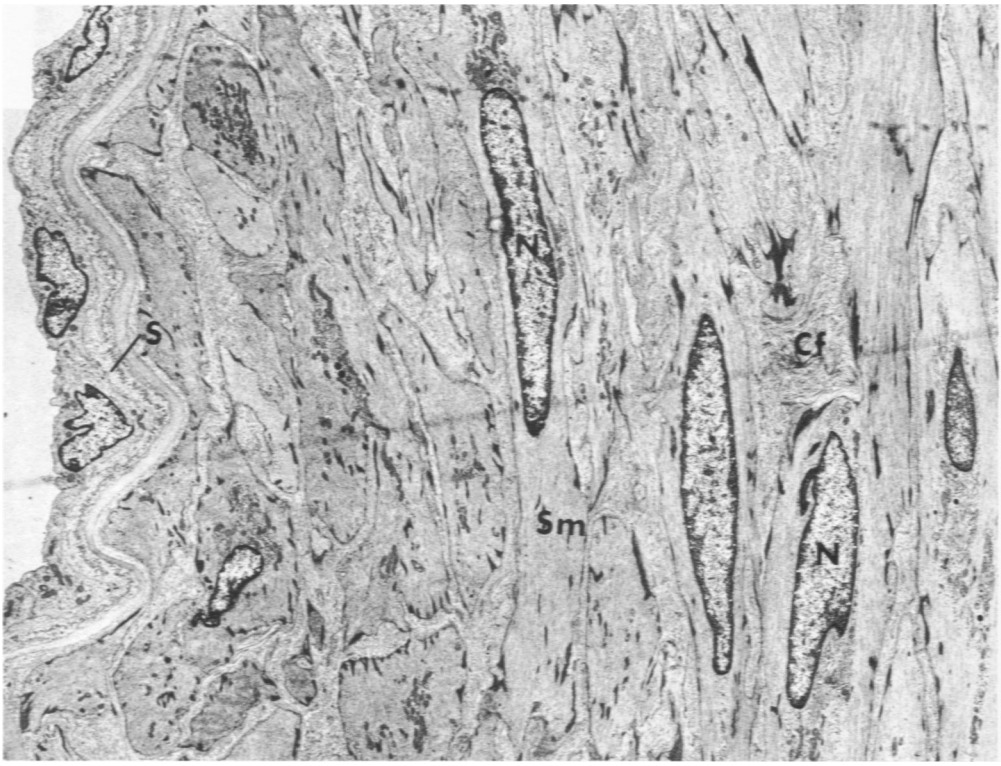


Fig 9.—Another example of hypertrophic smooth muscle cell showing cytoplasm near plasma membrane *(P)*. Vesicles *(V)* and caveolae *(C)* increase in number as compared with control group (compare with Fig 4). Each vesicle is coated with fuzzy material. Basement membrane *(B)* is partially separated from plasma membrane *(arrows)* and also shows foci of discontinuities. × 64,000.

Fig 10.—Lower magnification of hyperplastic mesenteric artery of hypertensive rat. Hyperplastic changes are mainly seen in tunica media, which shows eight to ten layers of smooth muscle cells *(Sm)*. Nucleus *(N)* of smooth muscle cell is larger than that of control group (compare with Fig 11). Subendothelial space *(S)* is wider as compared with control group and contains fibrillar material. Moderately increased amount of collagen fibers *(Cf)* is seen in intercellular space. × 2800.

Fig 11.—Portion of hyperplastic mesenteric artery. Internal elastic lamina *(Ie)* is split *(arrow)* in one area. Small portion of smooth muscle cell *(Sm)* is extending from tunica media to subendothelium *(S)* through fenestra *(F)* of internal elastic lamina *(thicker arrow)*. × 13,000.



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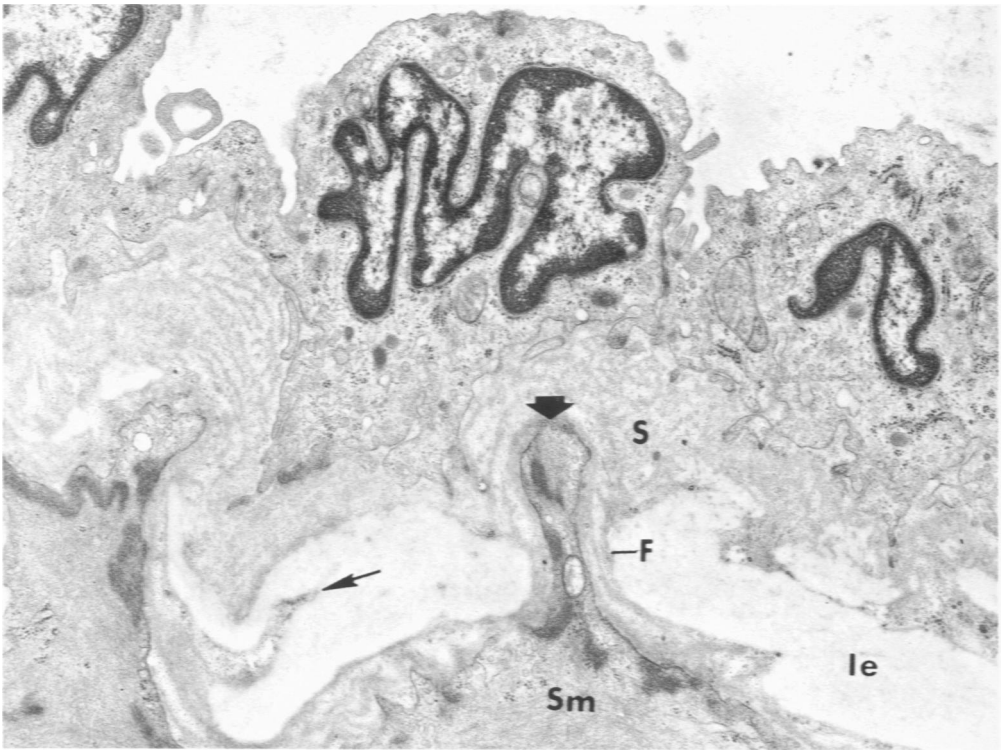

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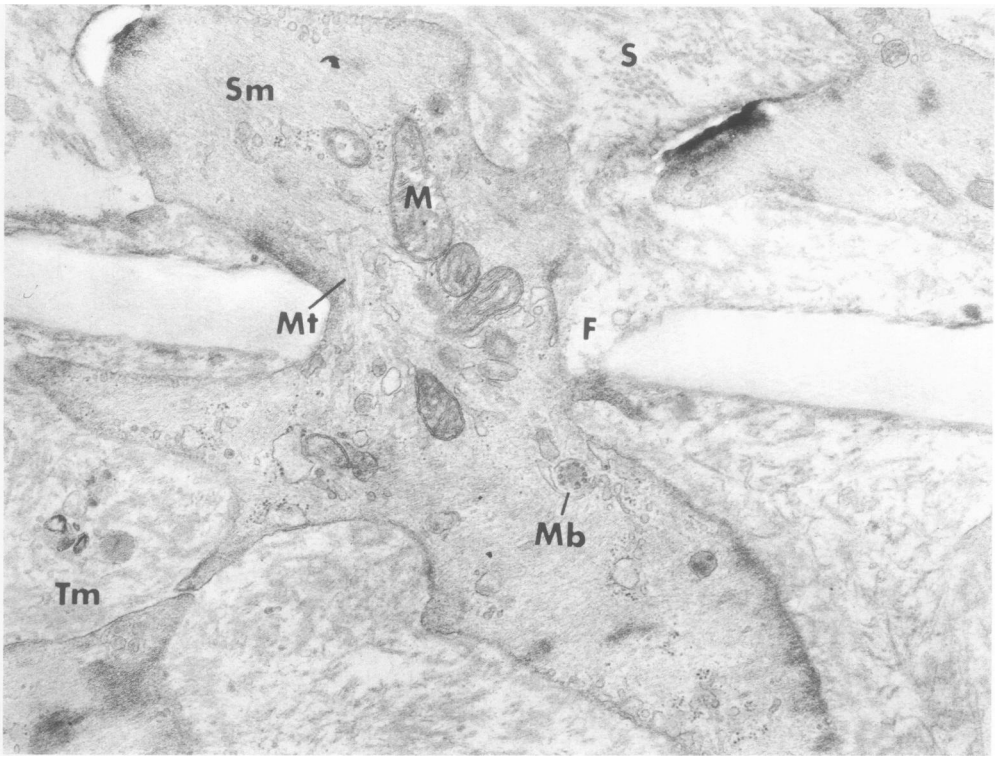
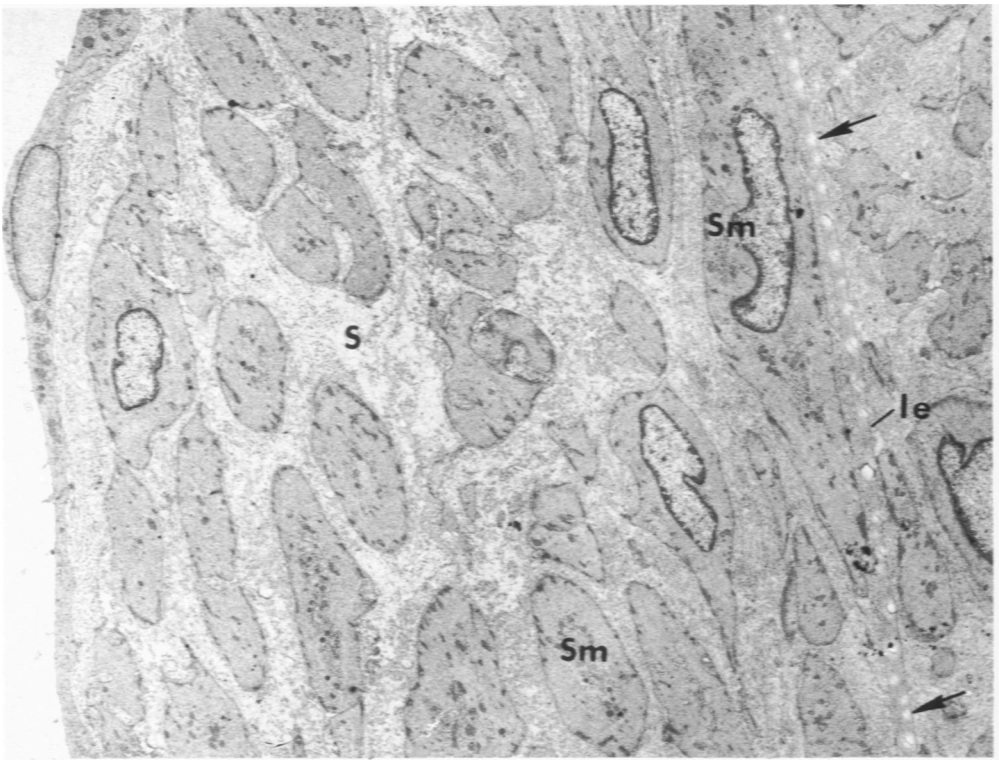


Fig 12.—Portion of hyperplastic mesenteric artery. Smooth muscle cell *(Sm)* is located at fenestra *(F)* of internal elastic lamina, extending from tunica media *(Tm)* to subendothelial space *(S)*. Smooth muscle cell possesses mitochondria *(M)*, myofilaments, microtubules *(Mt)*, vesicles, endoplasmic reticulum, and ribosomes. Also present are two multivesicular-like bodies *(Mb)*. × 18,000.

Fig 13.—Lower-magnification electron micrograph of hyperplastic mesenteric artery. Subendothelial space *(S)* is widened and possesses numerous smooth muscle cells *(Sm)*, which are not located close to each other as seen in tunica media. Instead, loosely packed fine fibrils are present between smooth muscle cells. Small electron-transparent areas *(arrows)* on internal elastic lamina *(Ie)* are artifacts. × 26,000.

Fig 14.—Higher-magnification photomicrograph of hyperplastic mesenteric artery. Smooth muscle cells *(Sm)* are present in tunica media *(Tm)* as well as in subendothelium *(S)*. Internal elastic lamina *(Ie)* is electron opaque. × 18,000.



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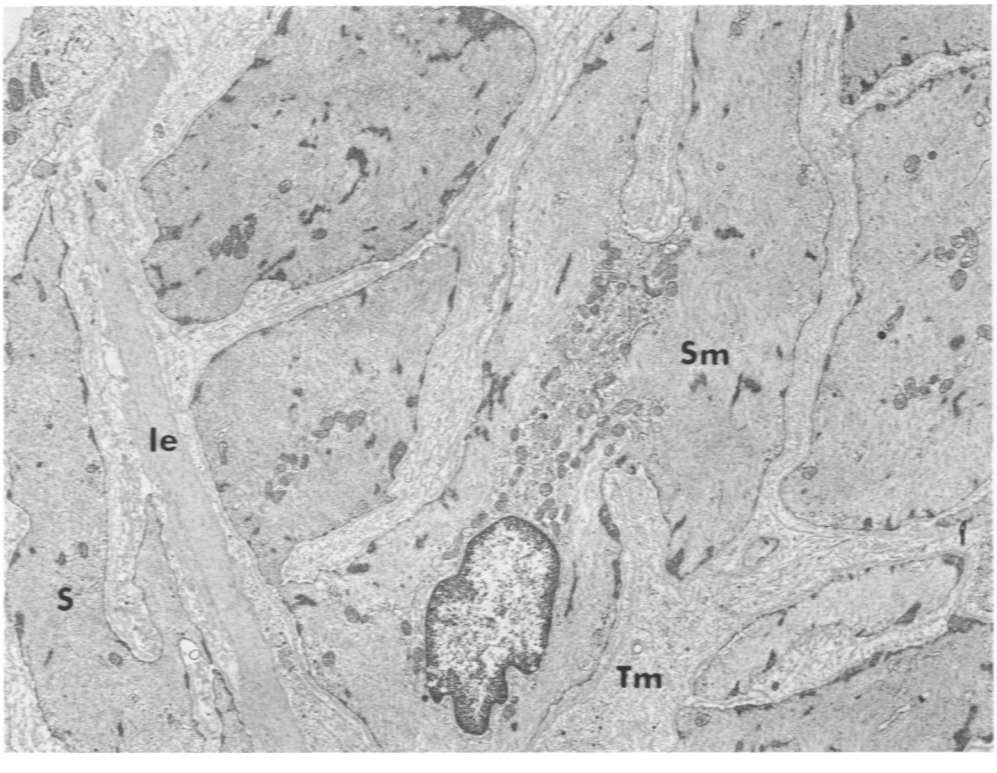

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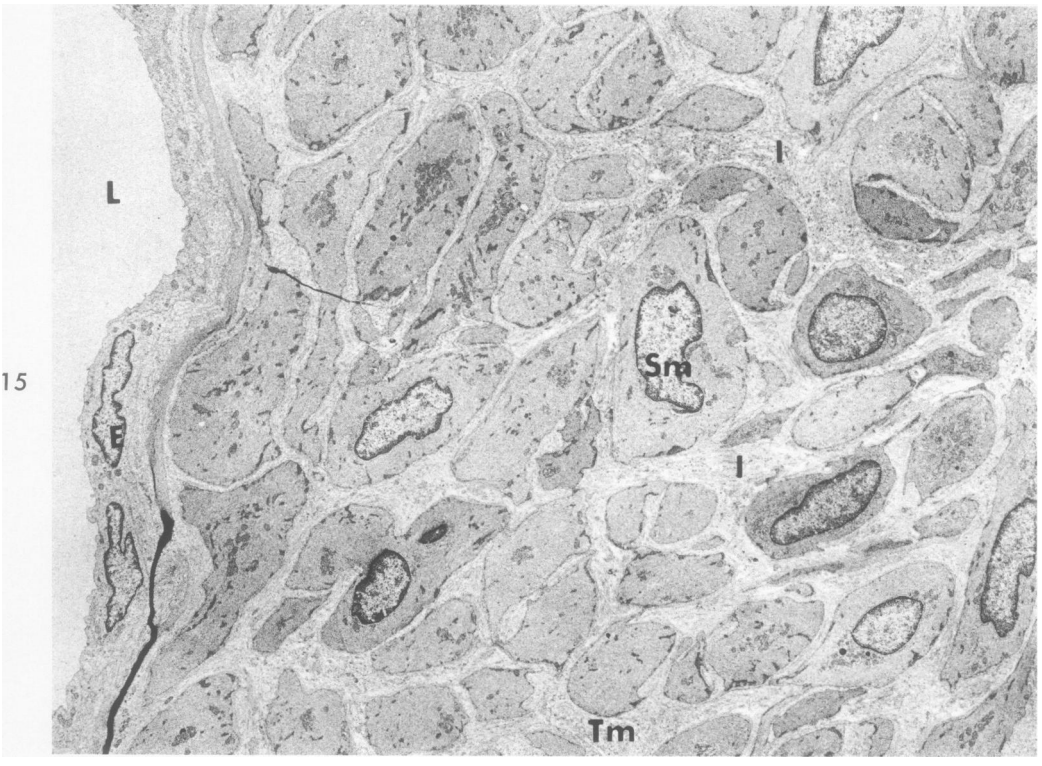
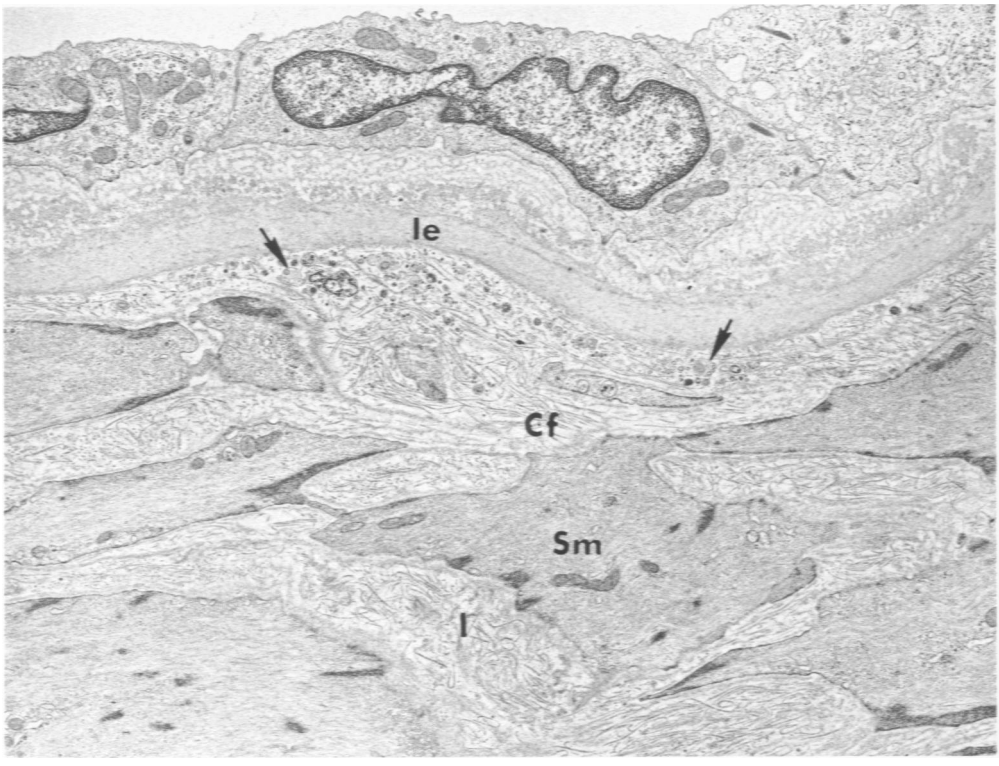


Fig 15.—Low-magnification photomicrograph of hyperplastic mesentery artery that is now in the transitional stage to become sclerotic or fibrosed artery. Though numerous smooth muscle cells *(Sm)* are present in tunica media *(Tm)*, each cell is irregular in shape due to increasing amounts of collagenous fibers in the intercellular space *(I)*. × 2700.

Fig 16.—Higher-magnification photomicrograph of fibrosing mesenteric artery. Intercellular space *(I)* of tunica media is widened and contains disoriented bundles of collagen fibers *(Cf)*. Smooth muscle cells *(Sm)* are irregular in shape and somewhat obliterated. Also present in intercellular space are vesicles and granules *(arrows)*. Internal elastic lamina *(Ie)* is electron opaque and is fraying out into subendothelium *(arrow)*. × 8000.

Fig 17.—Portion of tunica media. Collagen fibers *(Cf)* are abundant in intercellular space and are obliterating smooth muscle cells *(Sm)*. Cell with large nucleus *(N)* seen in right upper side of this photograph appears to be fibroblast *(Fb)* producing collagen fibers. × 7000.



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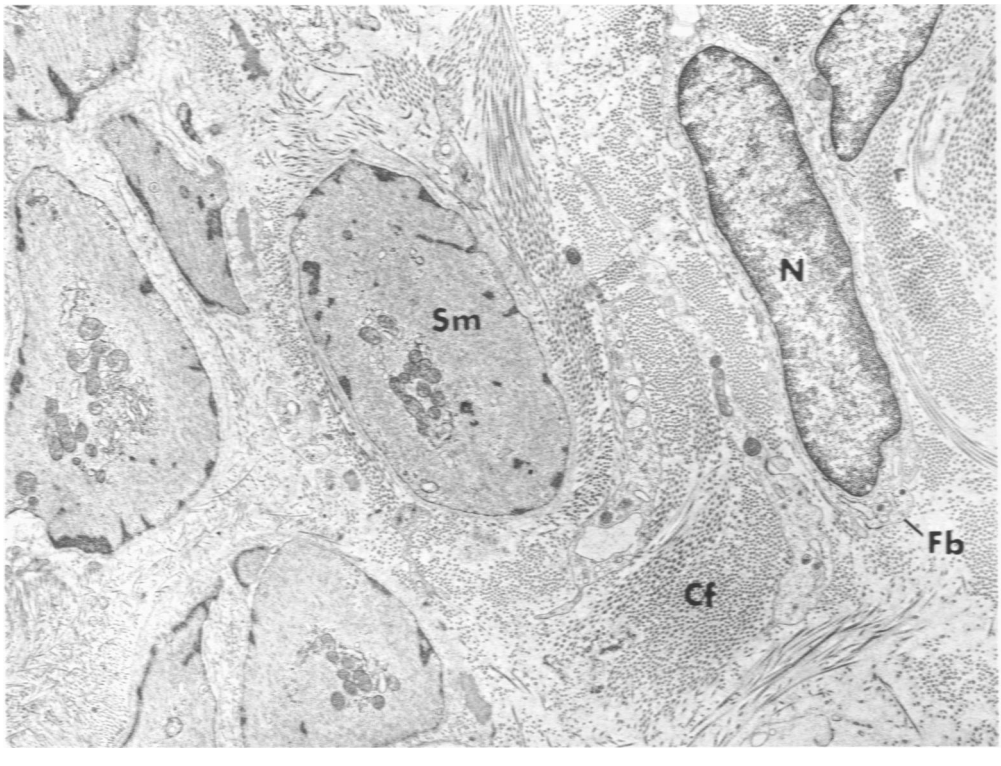

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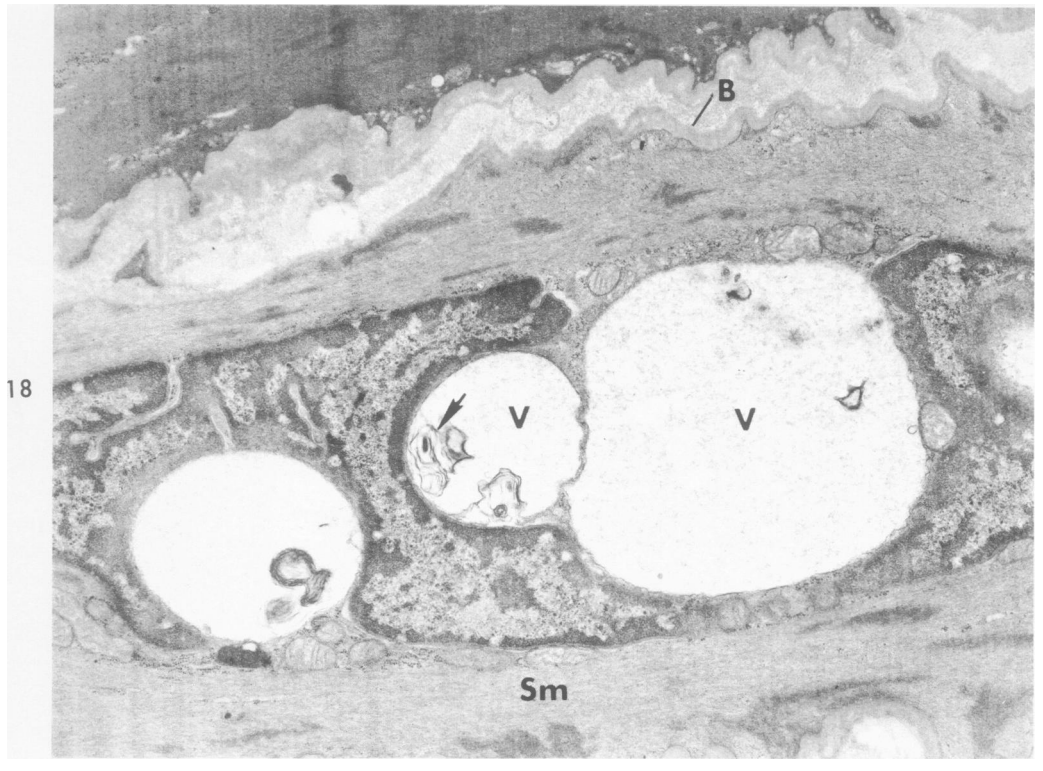

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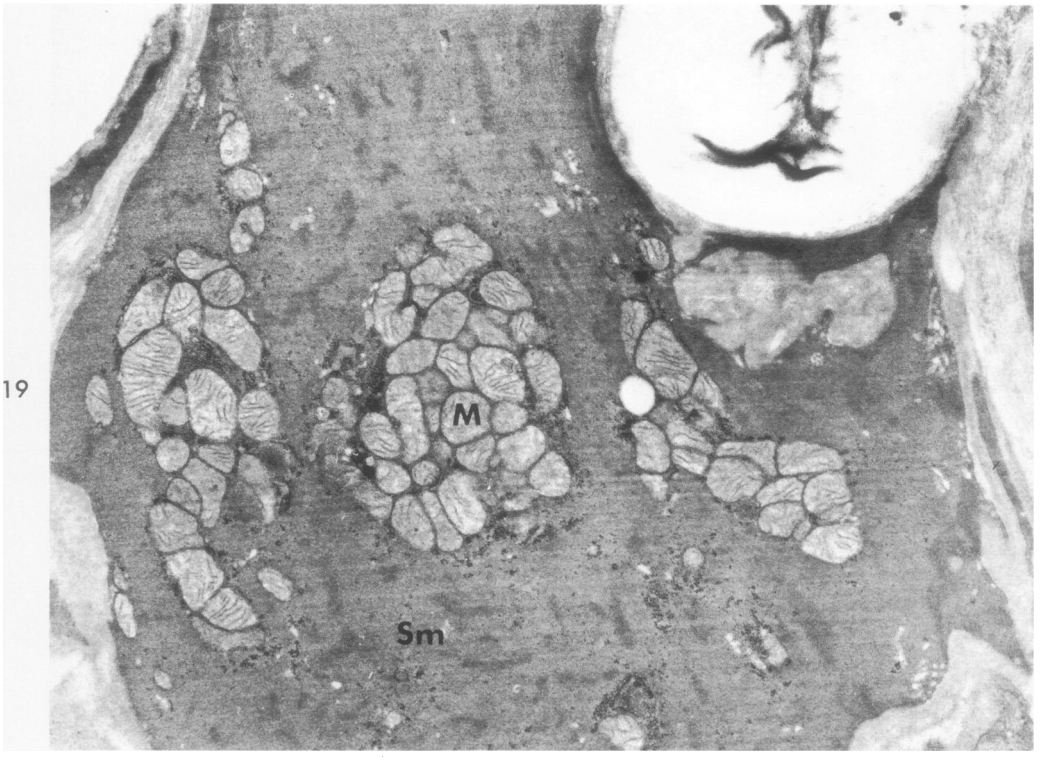

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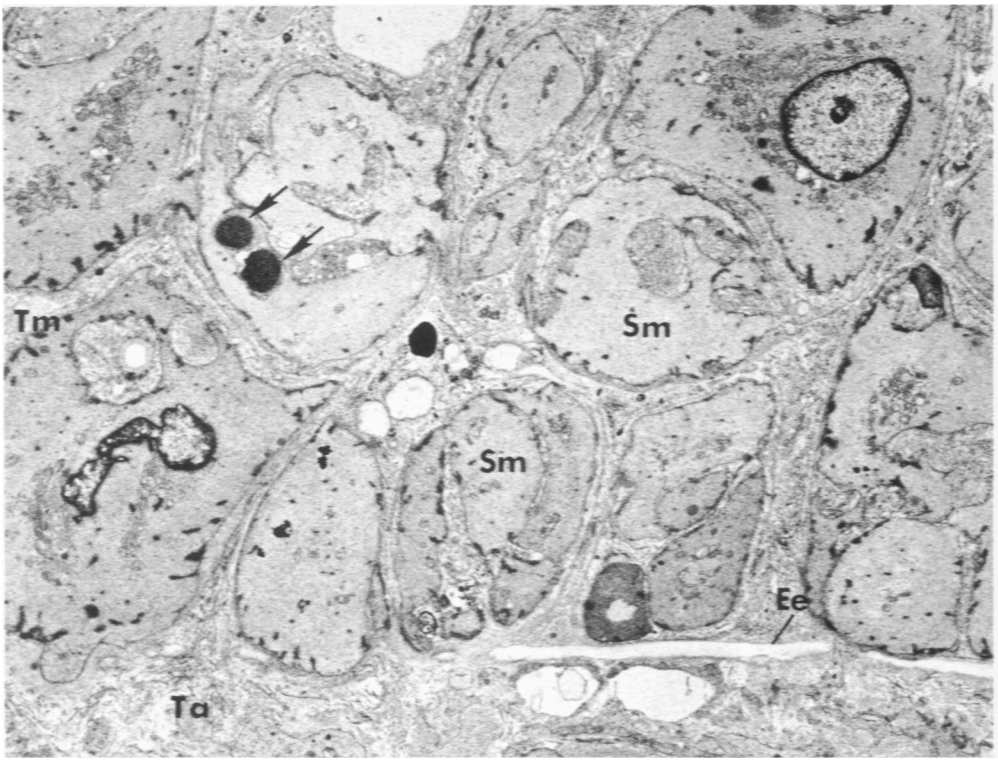
Fig 18.—Sclerotic mesenteric artery showing degenerated smooth muscle cells *(Sm)*. Large vacuoles *(V)* are present in cytoplasm and contain fragments of membrane *(arrow)* as well as fine granular material. Thick basement membrane *(B)* is prominent. × 12,000.

Fig 19.—Another example of degenerated smooth muscle cell *(Sm)*. Cytoplasm becomes darkened and myofilaments cannot be identified. Mitochondria *(M)* are moderately swollen and stand out in darkened cytoplasm. × 15,000.



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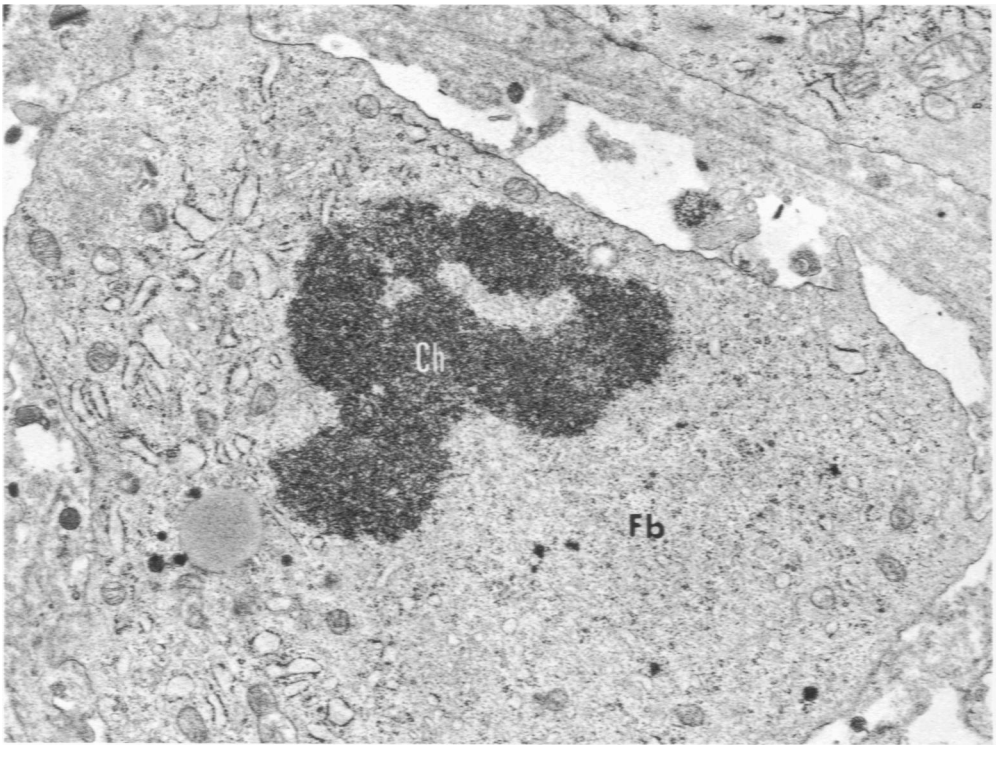

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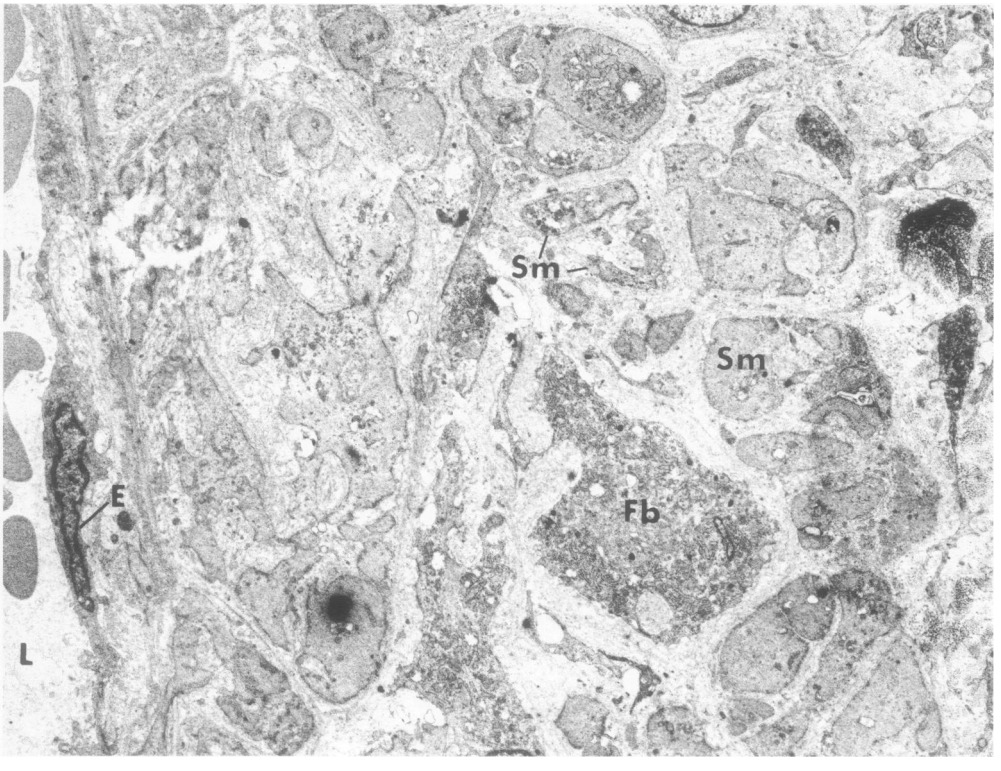
Fig 20.—Fibrosing mesenteric artery of hypertensive rat. External elastic lamina *(Ee)* has partially disappeared and collagen fibers are extending from tunica adventitia *(Ta)* to tunica media *(Tm)*. Smooth muscle cells *(Sm)* are obliterated by collagen fibers and become irregular in shape. Smooth muscle cell contains two osmiophilic bodies *(arrows)*. × 3000.

Fig 21.—Fibroblast *(Fb)* in process of mitosis in tunica media. Chromosomes *(Ch)* are evident. × 15,000.



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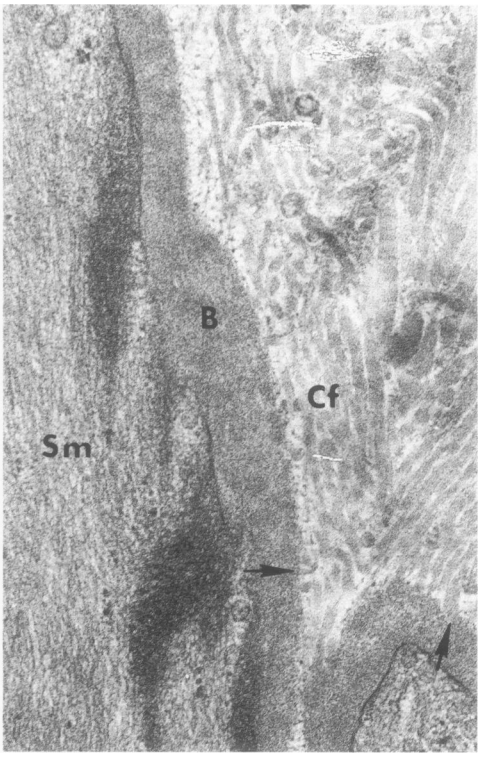

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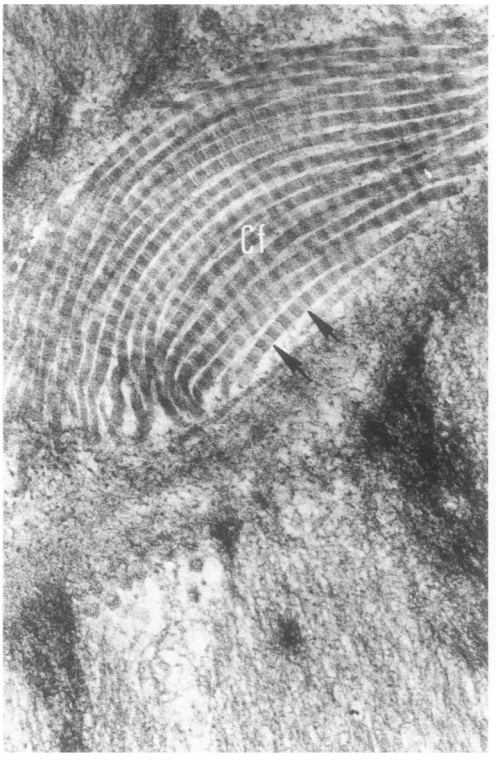

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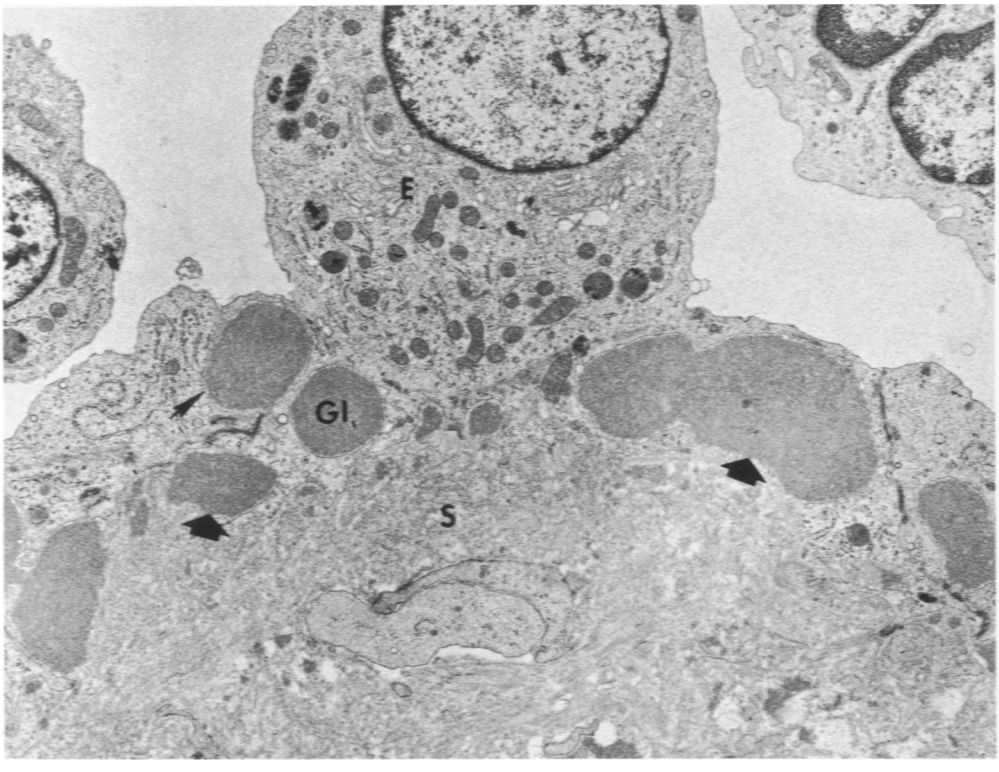

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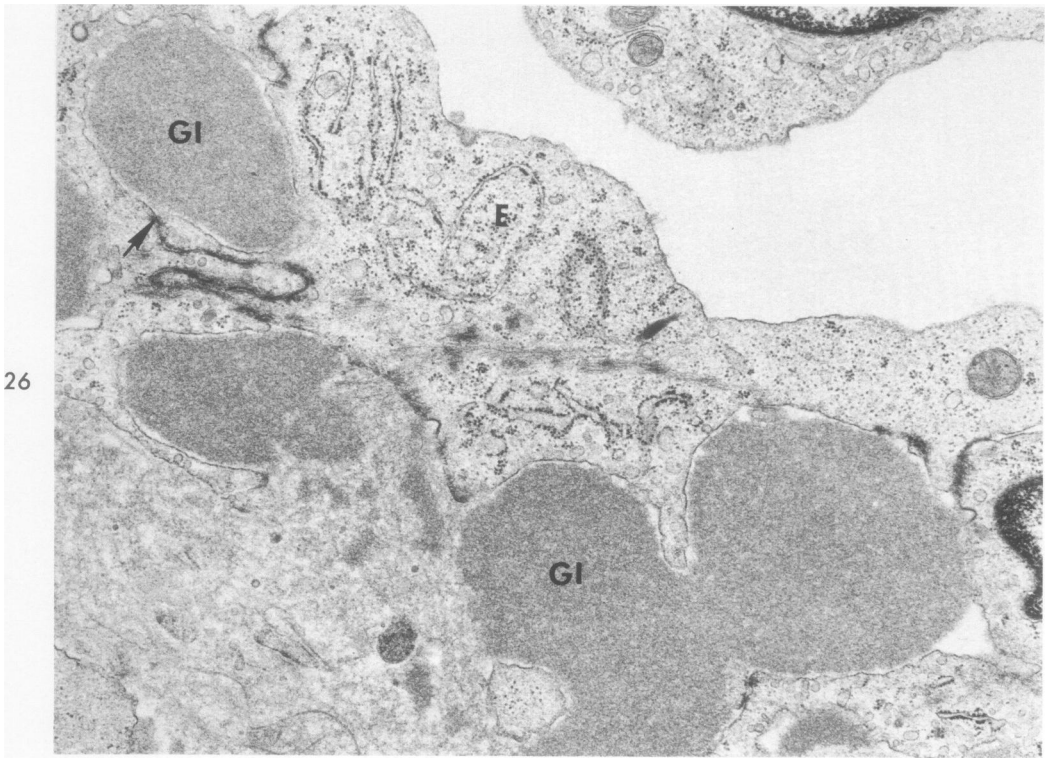
Fig 25.—Portion of tunica intima from mesenteric artery with fibrinoid necrosis. Electron-opaque globules *(Gl)* are present in endothelial cell *(E)* as well as in intercellular space between two endothelial cells *(arrow)*. Also, similar globules are seen in subendothelial space *(S)*, indicating transfer of globules from endothelial cell to subendothelial space *(thick arrows)*. × 9000.

Fig 22.—End stage of sclerotic mesenteric artery. Tunica media is largely replaced by fibrous tissue and fibroblasts *(Fb)*. Smooth muscle cells *(Sm)* are markedly obliterated by fibrous tissue. × 3200.

Fig 23.—Higher magnification photomicrograph of sclerotic vessel. Smooth muscle cell *(Sm)* is surrounded by thickened electron-opaque basement membrane *(B)*. In some areas, collagen fibers *(Cf)* merge into basement membrane *(arrows)*. × 53,000.

Fig 24.—Another example of sclerotic vessel showing collagen fibers *(Cf)* with transverse striation *(arrows)*. × 55,000.



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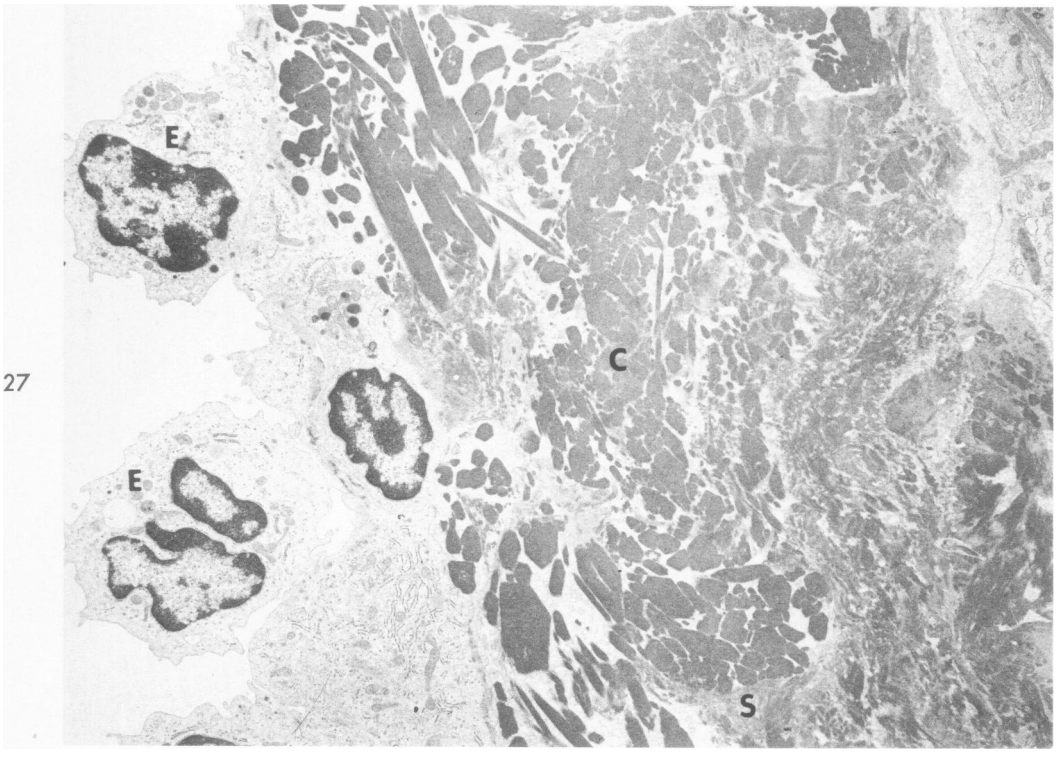

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Fig 26.—Higher-magnification electron micrograph showing electron-opaque globules *(GI)* in intercellular space *(arrows)* of endothelium *(E)* and subendothelium. Globule is finely granular. × 16,000.

Fig 27.—Mesenteric artery with fibrinoid necrosis. Electron-dense crystalloid materials *(C)* are mainly present in subendothelial space (S). × 4500.

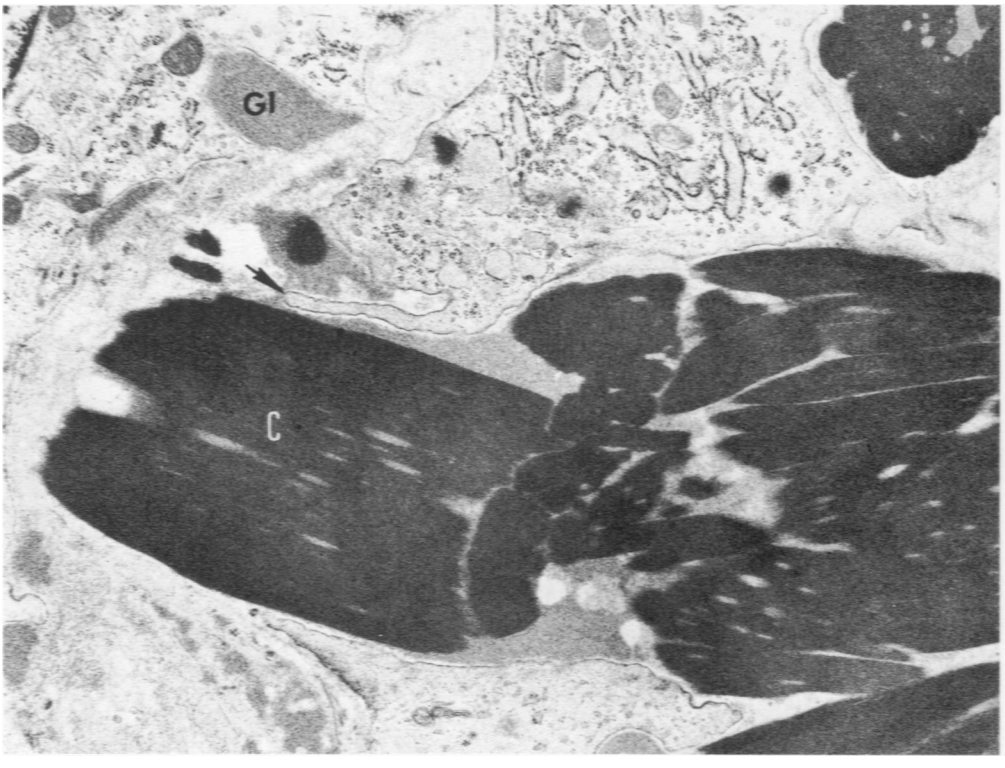

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Fig 28.—Electron-opaque globules *(GI)* apparently migrate into deeper layer of mesenteric artery and merge into more electron-dense crystalloid material *(C) (arrow)*. X 12,000.

Fig 29.—Higher-magnification photomicrograph of crystalloid material shown in Fig 28. It shows regular striation and periodicity. × 34,000.

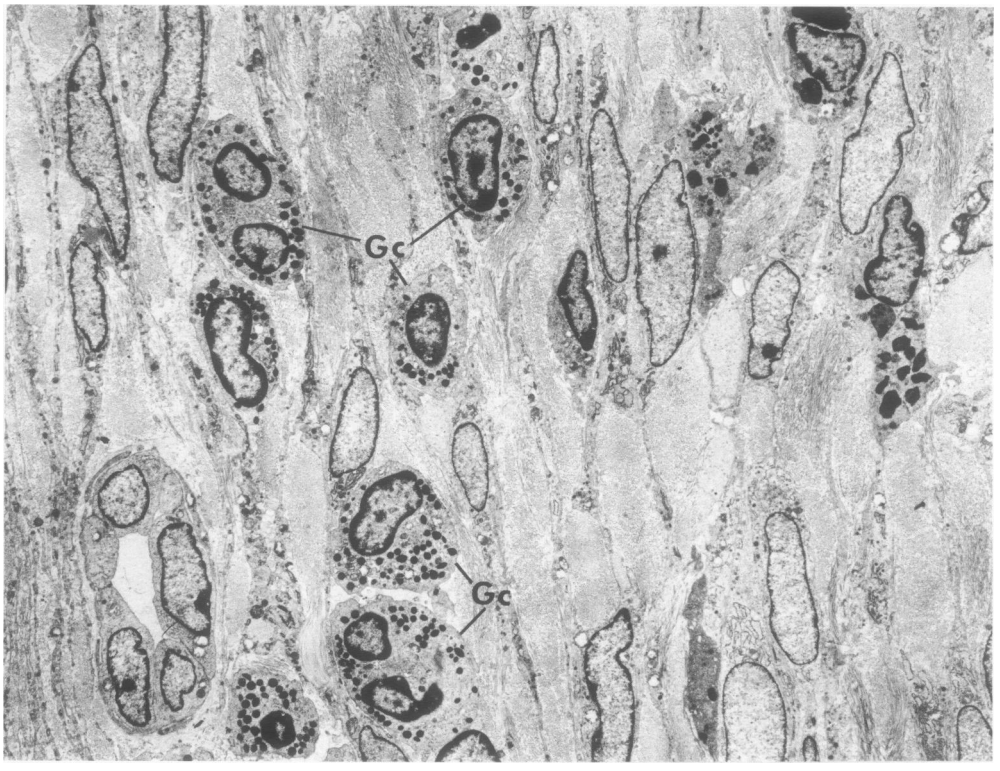

Fig 30.—Low-magnification micrograph of tunica adventitia from mesenteric artery with fibrinoid necrosis. Tunica adventitia is often infiltrated with granulocytes (*Gc*). × 2000.