Endothelial Changes Induced by Arterial Spasm

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Prolonged arterial constriction can cause damage to the artery itself. The purpose of this study was to define the intimal changes. Two muscular arteries of the rat were studied by electron microscopy 15 minutes to 7 days after L-norepinephrine had been dripped over the vessels. Endothelial damage was caused by the tight folding of the internal elastic lamina, which mechanically squeezed the cells. As the artery relaxed, the endothelium showed gaps, patches of thinned cytoplasm, and many adhesions between cells on opposite sides of intimal folds. The adhesions involved whole cells or cytoplasmic bridges stretched across the intimal "valleys." They were present up to one day; later they seemed to snap and disappear without causing further cellular damage. A survey of the literature shows that such adhesions can also develop in collapsed arteries postmortem. They explain the endothelial "bridges" previously described by others as a normal intimal structure. (Am J Pathol 1981, 102:346–358)

IT HAS LONG BEEN KNOWN that prolonged arterial constriction can occur as a pathologic event[1,2] and cause tissue damage through ischemia.[3-7] More recently it has been realized that it can also injure the artery itself. We have studied—by light and electron microscopy—the cellular changes in the wall of a muscular artery induced to contract by a normally occurring molecule, L-norepinephrine. Damage was found both in the intima and in the media; this paper will deal with the intimal changes.

In presenting our experiments we have chosen the word "spasm" to describe arterial constriction. Like other terms inherited from ancient medicine, "spasm" is difficult to define. It certainly overlaps with the physiologic event of vasoconstriction, but it is currently used where there is an implication of abnormality, as in "posttraumatic spasm" (a similar loose distinction exists between "contraction" and "cramp"). This use is consecrated by time: in the Hippocratic books, "spasmós" is always a pathologic event.[8] Since our findings concern arterial contraction associated with arterial damage, the choice of "spasm" seems appropriate.

Materials and Methods

We used 20 male Wistar rats (Charles River Breeding Laboratories, Wilmington, Mass) weighing 225–400 g. To induce spasm we dripped 0.2 ml L-norepinephrine (Levophed Bitartrate [Winthrop] USP 0.2%, diluted 1:10 in 0.9% NaCl) over the operating field, exposing the chosen artery. This dilution corresponds to a 1 mM solution of L-norepinephrine. Although a vascoconstrictor effect can be obtained with a micromolar solution, we used a higher concentration because the drug was applied to the fascia over the artery and had to diffuse through this membrane. We chose two muscular arteries of different caliber and easily exposed with a minimum of trauma: the saphenous artery, and its distal branch, known as medial tarsal artery.[9]

The rats were anesthetized with ether. The skin of the right leg was shaved, and a longitudinal incision was made on its inner aspect. The fascia was loosened, exposing the saphenous and medial tarsal arteries, and norepinephrine was dripped over them. Their contraction was observed for 3–4 minutes with a surgical microscope (Applied Fiber Optics, Southbridge, Mass). The edges of the cut were then approximated with Michel clips and the rats were allowed to survive for 15 minutes, 30 minutes, 1, 2, or 24 hours, or 7 days. For some 1- and 2-hour experiments, thorium dioxide (Thorotrast, Fellows Testagar, Detroit, Mich) was injected intravenously 10 minutes before the animal was killed. The same surgical protocols were followed for

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sham operated animals, except that 0.9% NaCl was dripped over the vessels, instead of L-norepinephrine. In 2 rats the drug was dripped over the artery 3 times at 6-hour intervals, and the animals were sacrificed 12 hours after the last treatment. All animals were killed with an overdose of ether, then perfused with glutaraldehyde 3% (in 0.1 M cacodylate buffer) via an 18G needle inserted into the thoracic aorta. The fixative was infused at room temperature at a pressure of 110 mm Hg. The jugular veins were opened for outflow. After 20 minutes of perfusion[10] the saphenous and medial tarsal arteries were dissected out, immersed in fixative, cut into 1-mm segments, and allowed to fix further for a total of 5 hours. The tissues were left overnight in 0.1 M cacodylate buffer at 4 C, postfixed in 1.3% osmium tetroxide in 0.2 M collidine buffer for 2 hours at 4 C, dehydrated in graded alcohols, and embedded in Epon 812 (Ladd Research, Burlington, Vt). One-micron sections were cut with glass knives and stained with toluidine blue for light microscopy. Thin sections were cut with a diamond knife on an LKB Ultrotome III, mounted on uncoated copper grids, stained with uranyl acetate and lead citrate, and examined with a Philips 301 electron microscope.

Results

In the description that follows it is assumed that the degree of contraction of the artery is well expressed in cross-sections by the shape of the internal elastic lamina (IEL), which is flat in the expanded state, folded in the contracted.[11,12] In contracted arteries, the intimal depressions between folds will be referred to as valleys, the humps between them as ridges.

Control Animals

The saphenous and medial tarsal arteries are muscular, with a thick IEL and 6–7 or 3–4 layers of smooth muscle cells, respectively. The IEL was smooth or slightly wavy; the endothelium was unremarkable.

Spasm

Under the surgical microscope, the artery was well visible next to the parallel vein; the L-norepinephrine drip caused no immediate change in the caliber of the vein, whereas the artery rapidly faded out of sight; it became visible again as a thin streak after 15–30 minutes. After Epon embedding, different blocks of the same artery showed that contraction had occurred all along the vessel but in varying degree; the relaxation was also uneven. Thus the sequence of events described below cannot be strictly timed; the best guide to the condition of spasm was the shape of the IEL.

15 and 30 Minutes

In the most spastic segments, the endothelial cells facing each other in the valleys were squeezed together; this caused some nuclei to be deformed into a dumbbell shape (Figure 1). Often the squeeze was so tight that no endothelial cytoplasm was visible between the apposed surfaces of the IEL (Figure 2). The portion of endothelial cytoplasm that remained free of compression (toward the lumen) showed several characteristic changes (Figure 1): most common were concentric whorls of membranes, and sometimes typical myelin figures. The endothelial cells atop the ridges were very tall, as described by others.[11] Here and there the endothelium was lifted by large, clear vacuoles, which often coincided with fenestrae in the IEL. Some of these vacuoles were characteristic of myoendothelial hernias.[13] Adhering to the endothelial surface were occasional platelets and white blood cells.

1 and 2 Hours

The spasm had begun to relax; thus the valleys were somewhat wider and open to the lumen. Several changes appeared in the endothelial cells that had been squeezed: *a*) *thinning*, often to 1000 and even 500 Å (Figures 3–7); *b*) *gaps*, 0.5 to 1 mμ in width (when Thorotrast had been injected intravenously, these gaps were often marked by particles) (Figure 5); *c*) *adhesions* between cells on opposite sides of a valley. These adhesions appeared in the form of bridges stretched across the valley (most were fine strands, single or multiple, 300–500 Å in diameter, cut longitudinally or more often obliquely) (Figures 3 and 5). In some cases a whole cell was involved in the adhesion, as shown in Figure 3, where an endothelial cell has its footing on one side of the valley, while its apical portion is attached to the opposite side. A few adhesions included an intracellular junction (Figure 4). Adhesions were often multiple across a single valley, creating complex patterns (Figures 3 and 7). Small islands of endothelial cytoplasm that appeared suspended over a valley ostensibly corresponded to sections of adhesions not entirely contained within the plane of section (Figure 7). Some pictures suggested that the adhesion had snapped (Figure 8). Occasional adhesions were filamentous and very thin, on the order of 100 Å.

24 Hours and 7 Days

The endothelium was similar to that of sham-operated control animals, except for the presence of a few

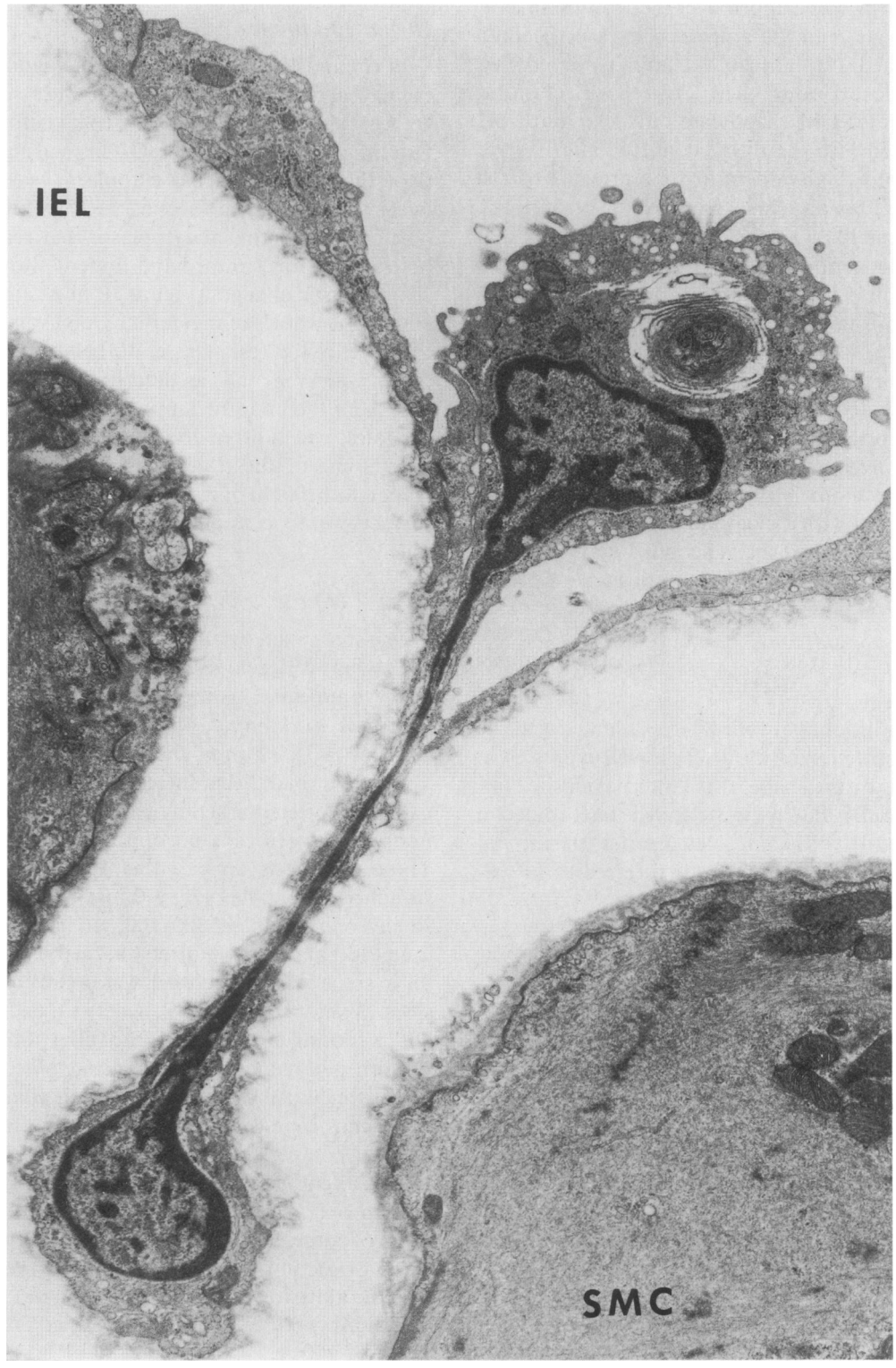


Figure 1—Saphenous artery, 1 hour after norepinephrine. An endothelial cell and its nucleus are squeezed between tight folds of the internal elastic lamina (*IEL*). Whorls of membranes are formed in the apical cytoplasm. *SMC* = smooth muscle cell. (×15,400)

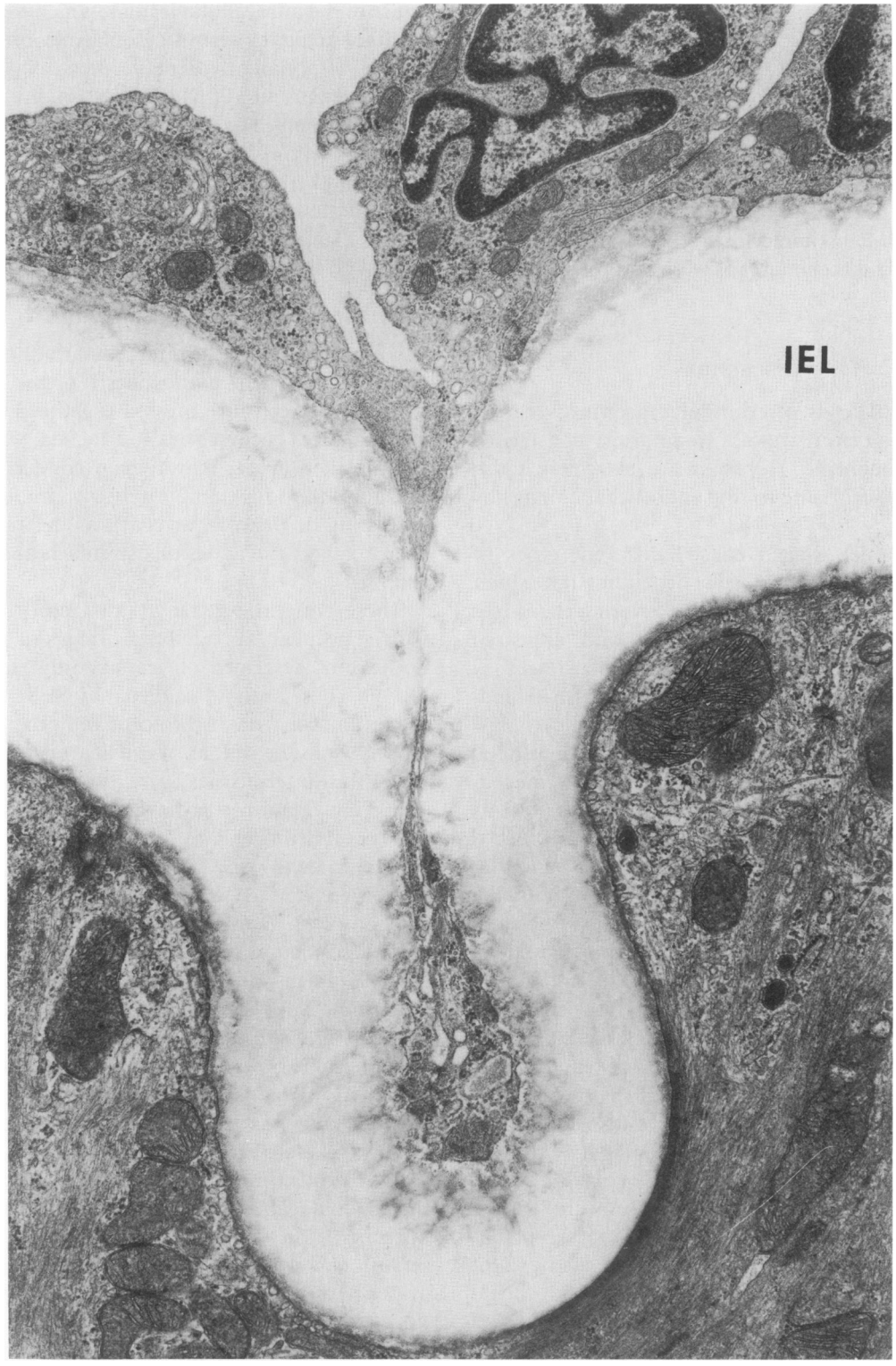


Figure 2—Saphenous artery 15 minutes after norepinephrine. The endothelial layer is so tightly squeezed between folds of the internal elastic lamina (*IEL*) that no trace of cytoplasm is visible. (×24,600)

adhesions and of phagosomes filled with amorphous material at 24 hours.

12 Hours After Repeated Spasm

The intima was wavy; adhesions were present (Figures 7 and 8). About a fourth of the endothelial cells were slightly thicker than normal and contained unusual amounts of rough endoplasmic reticulum and ribosomes, as seen in regenerating cells.[14] A few endothelial cells also contained phagosomes filled with electron-dense material (Figures 9 and 10). Occasional small intercellular gaps were also found (Figure 11).

Discussion

The intimal folds of contracted arteries were observed over a century ago.[15] In an artery constricted by L-norepinephrine, the folds are extremely tight; thus it is not surprising to find endothelial damage by squeezing.

In our model, spasm caused different types of changes in the endothelial cells, depending upon their location along the intima. Those covering the ridges became—as expected—much taller and appeared "perched atop the folds"[11]; in three dimensions they presumably formed a thin ridge of cytoplasm extending the intimal fold toward the lumen. The cytoplasmic abnormalities that they sometimes developed (Figure 1) could conceivably arise by three mechanisms: The most likely is *forced cytoplasmic flow*, as might occur if a part of a cell's cytoplasm were pinched in a valley and squeezed upward; we have seen milder examples of such flow in contracting endothelial cells.[16] *Trauma* by exposure to increased velocity of flow in the stenotic vessel has been postulated by others.[17-20] The answer must wait until the endothelial changes due to increased velocity of flow are better defined. *Direct injury* by Levophed can be ruled out. Presumably the drug affected the entire length of the artery; yet the spasm was segmental, and the endothelial changes also had a segmental distribution.

Cellular Damage

Cellular damage in the valleys took several forms. The squeezing illustrated in Figure 2 is self-explanatory; in three dimensions, the result of such a tight squeeze should be an interruption in the endothelial layer. In fact, endothelial gaps were common (Figures 3-6, 9, and 11); in some cases they were clearly intercellular, but one could well imagine that the squeeze would not necessarily fall at an intercellular junction; thus it is possible that endothelial "perforations" or "wounds" also occur. We plan to settle this question with future studies by scanning electron microscopy (SEM). Lesser degrees of squeezing are probably the cause of the intracellular lesions, which we called—for want of a better term—cytoplasmic bruises—small masses of apparently denatured cytoplasm that later became engulfed in phagosomes (Figures 9 and 10).

We had expected to see platelets adhering to the subendothelium in relation to the gaps.[21,22] At the 1-hour and 2-hour stage we did see small thrombi or isolated platelets adhering to the surface (Figure 6); it is possible that some platelets were washed away during the 20-minute perfusion-fixation.

Formation of Endothelial Adhesions

Unexpected were the intercellular adhesions across the valleys. Their pathogenesis seems straightforward: if two cells are pressed together long enough, their surfaces become focally attached; when they are again pulled apart, they remain connected by cytoplasmic adhesions (more rarely by tenuous adhesions consisting of the cellular coat); as the artery relaxed even further, the adhesions stretched and eventually snapped.

These adhesions offer a satisfactory explanation for the peculiar "intercellular bridges of vascular endothelium" described 11 years ago by Shimamoto et al.[23-29] These authors studied—by SEM and TEM—the intimal surface of the aorta and other large arteries and veins, as well as of the heart, in rabbit and in man (the latter tissues were obtained at autopsy). Perfusion-fixation was never used. The intima was always marked—as may be expected—by deep longitudinal folds; by SEM, transverse or oblique connections were noticed between the folds, suggesting at low power a ladderlike effect. These connections were described as long and short bridges, measuring —in the aorta—5-10 μ in length and 2-6 μ in thickness (the published micrographs suggest thinner segments). Transmission electron microscopic (TEM) examination showed that the "bridges" contained organelles.[26] Thus we can exclude that these authors were seeing fibrin filaments. It was speculated that the bridges were physiologic structures with the function of protecting the regular arrangement of endothelial folds and also of preventing the excessive opening of the intracellular junctions.[28] Similar observations were reported recently[30] and interpreted as evidence of endothelial damage preceding disintegration.

As regards length, thickness, and fine structure, the "bridges" described by Shimamoto et al are compatible with all our observations. Missing in the above description are only the finest adhesions that we have seen (Figure 5); since their diameter can be as small as

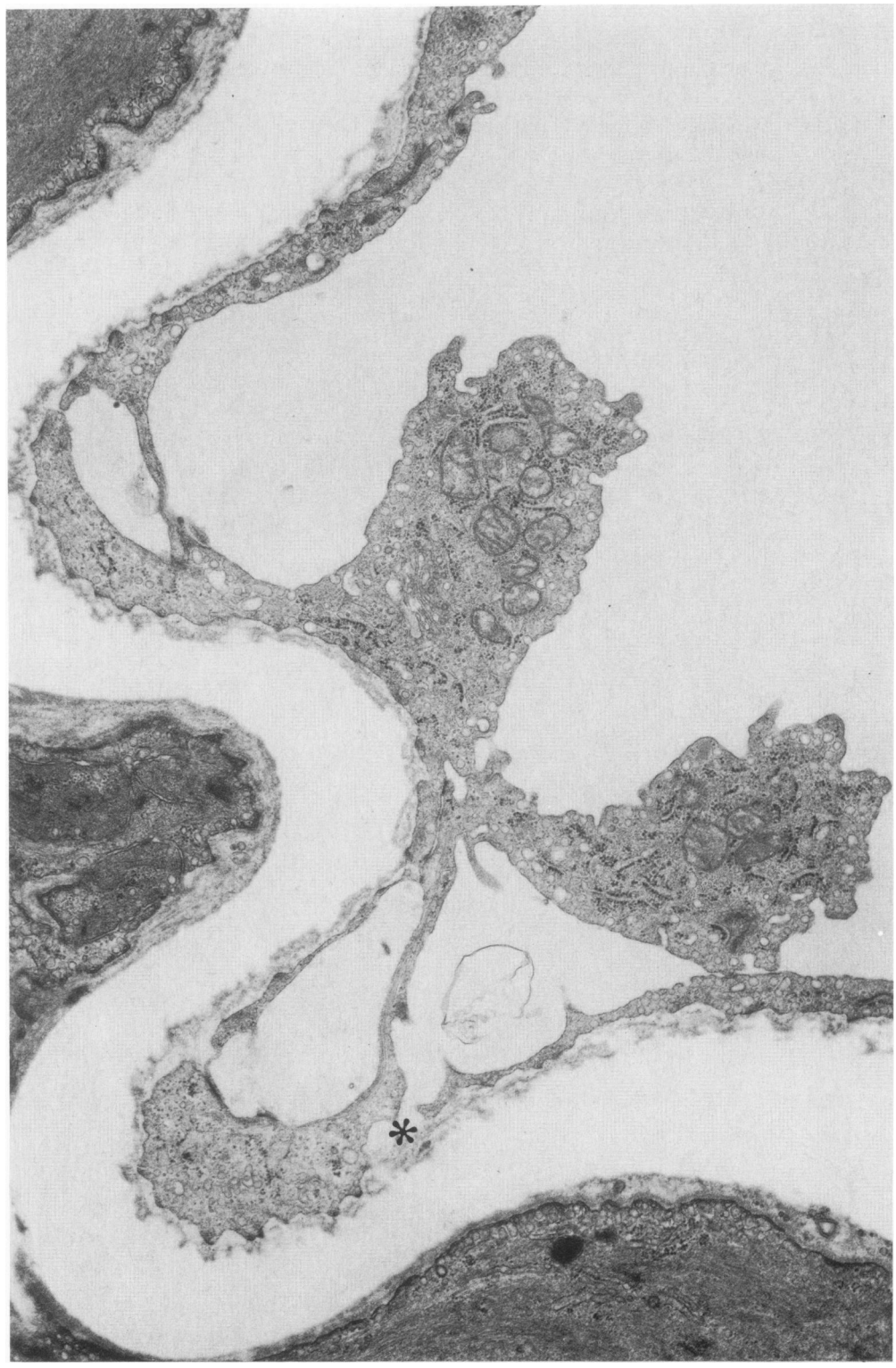


Figure 3—Saphenous artery 15 minutes after norepinephrine. Multiple endothelial adhesions are seen in an artery that has just begun to relax. One adhesion (*bottom right*) consists of a whole endothelial cell bridging a valley. Note endothelial gap (*). (× 16,000)

0.05 μ, they may have been destroyed in preparing the surface for SEM. However, very fine "bridges" (on the order of 0.1 μ in thickness) were noticed in a recent SEM study[31] aimed at verifying the effect of intraluminal fixation pressure on the shape of the intimal surface. Carotid arteries of the dog were excised and *thereafter* fixed at pressures varying from 0 to 100 mm Hg. At 40 mm Hg the intima was still heavily folded; filamentous "bridges" were seen stretching across the valleys. They were interpreted as anchors reinforcing

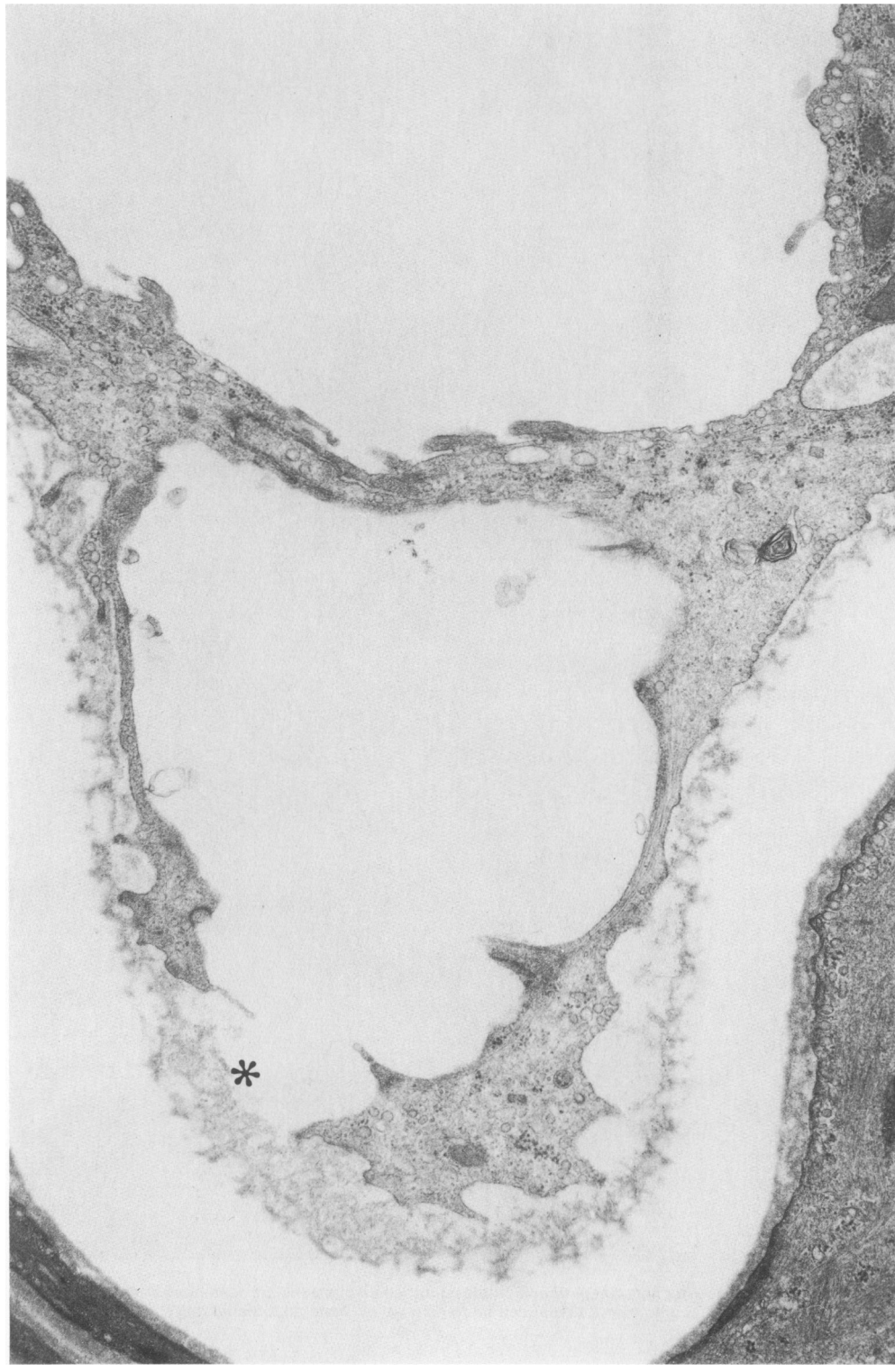


Figure 4—Saphenous artery 15 minutes after norepinephrine. Two consequences of spasm in a valley that has just started to recover from being squeezed; an adhesion between endothelial cells and a gap (*). Note an intercellular junction in the adhesion. (× 19,200)

the attachment of the endothelium to the intimal surface.

In support of our interpretation—whereby the "bridges" described by the two groups above are the same as our endothelial adhesions—is one significant fact: in both sets of experiments[23-29,31] the artery was allowed to collapse before fixation. We can assume that the intima became folded, and that adhesions developed across the valleys. Then, as the arteries were partially distended during fixation, the adhesions

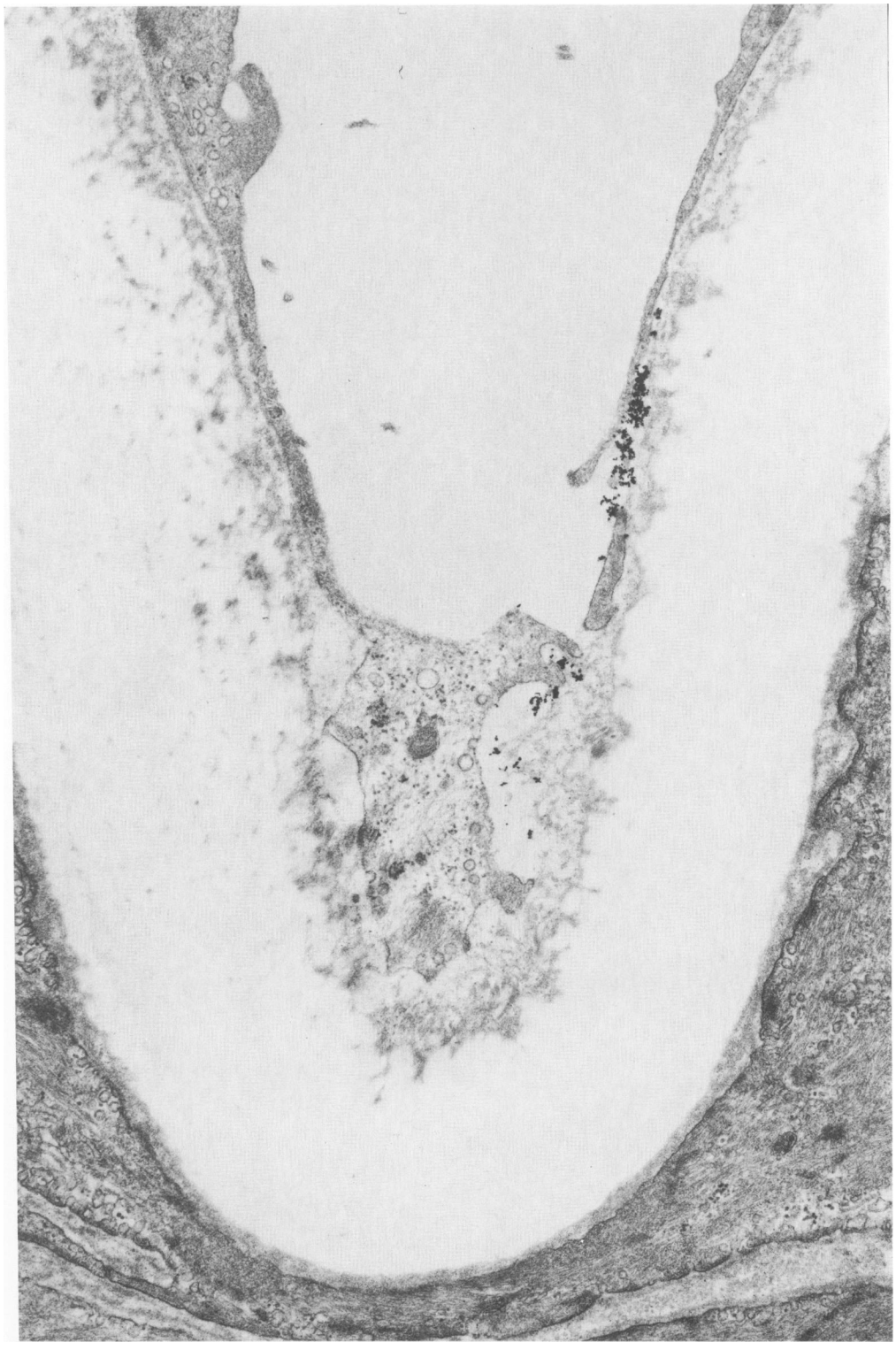


Figure 5—Saphenous artery 1 hour after norepinephrine and 10 minutes of Thorotrast. Valley after a squeeze: the endothelium is extremely thin; at *right*, two gaps, partly labeled by Thorotrast. (× 19,200)

stretched out as filaments. Thus, under the conditions of those experiments, they represented an experimental artifact, or, better, an artificially produced cellular effect. Surely they are not physiologic structures, as stated again in a recent atlas.[32]

Our findings suggest that the adhesions (under the conditions of our experiments) can last up to one day and that they snap easily, causing no further cellular damage. It remains to be seen what may happen if the process is repeated many times.

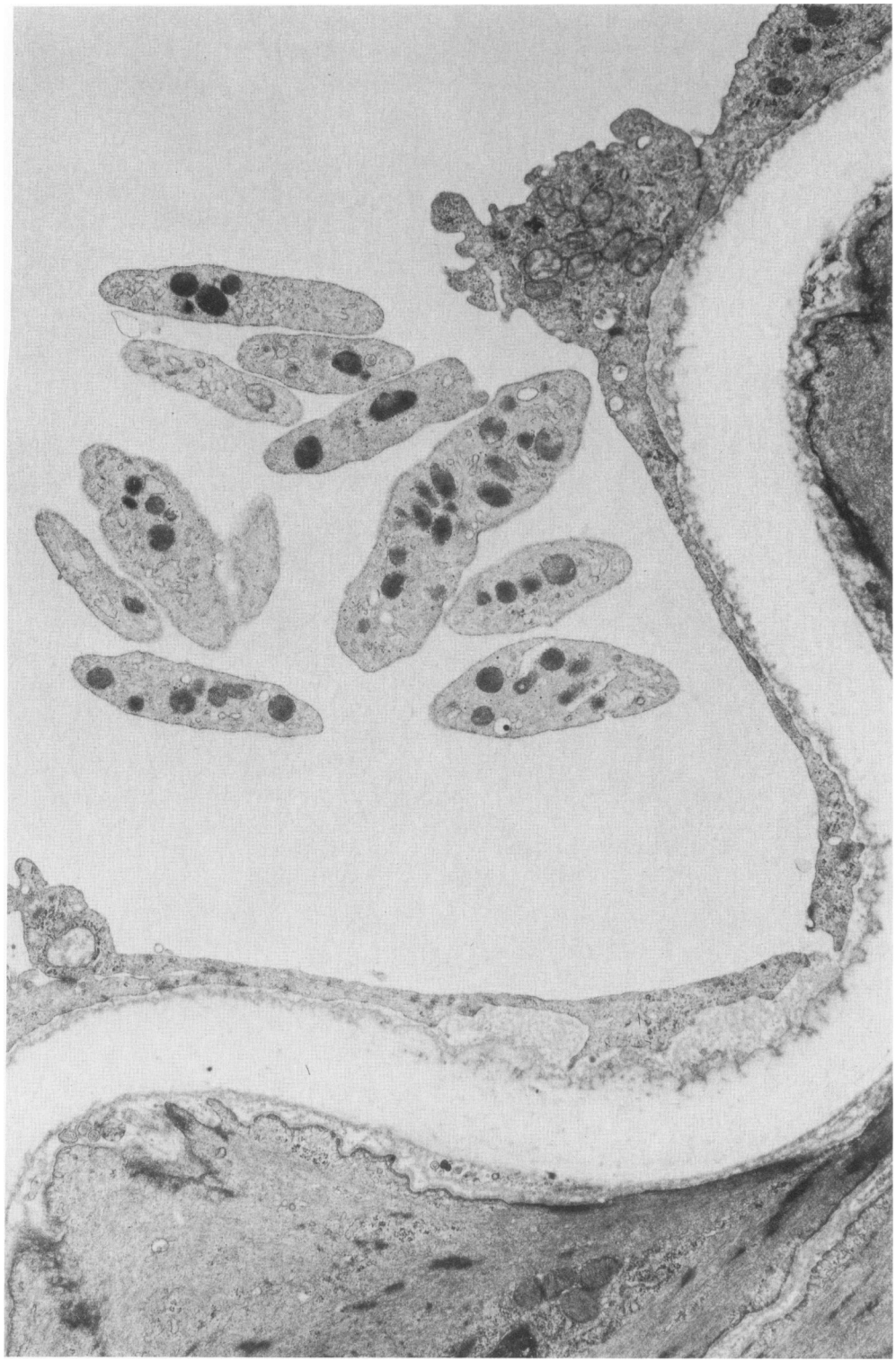
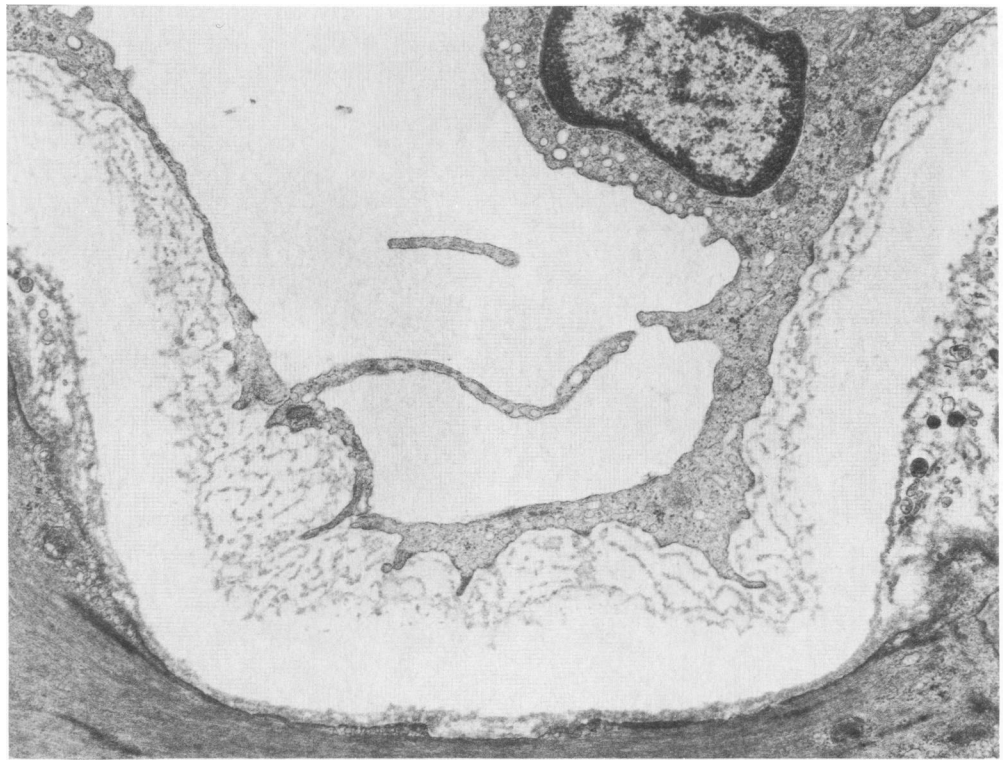


Figure 6—Saphenous artery 15 minutes after norepinephrine. There is a microthrombus in a valley, which has just undergone a tight squeeze (note abnormally thin endothelium and gap at right). The reason for this thrombosis is morphologically not apparent. (× 12,200)



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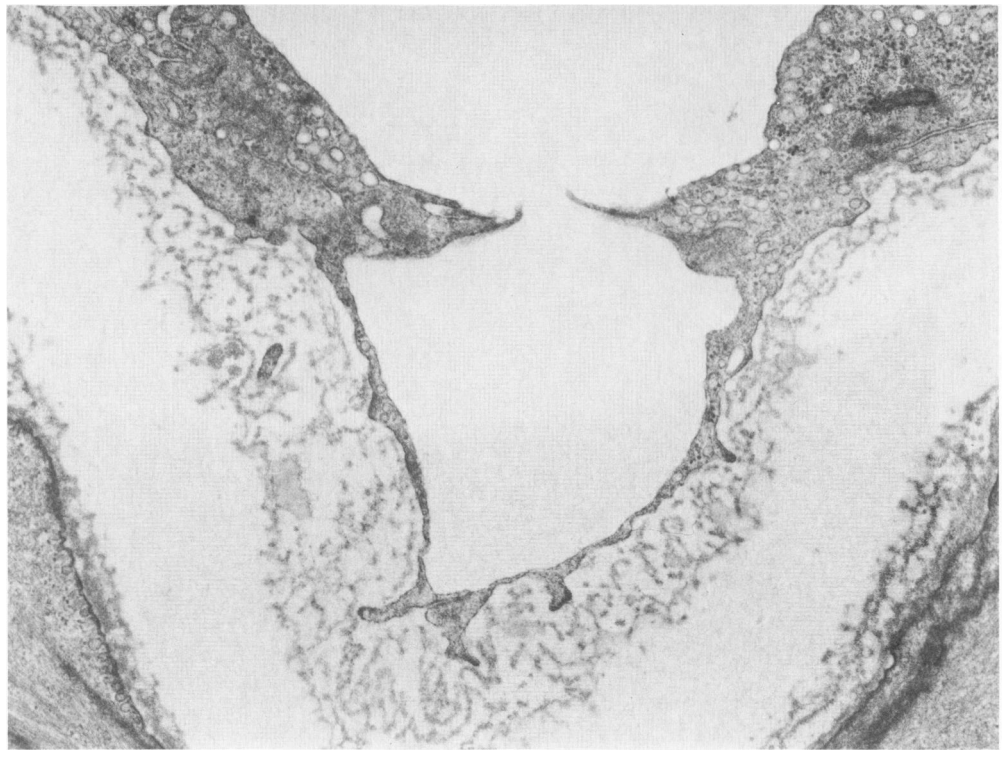

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Figure 7—Medial tarsal artery perfused 12 hours after 3 exposures to norepinephrine. Two common aspects of endothelial adhesions: *below*, a thin strand of cytoplasm crossing a valley; *above*, a fragment of cytoplasm apparently suspended over a valley (an adhesion cut obliquely). (× 15,400) **Figure 8**—Medial tarsal artery perfused 12 hours after 3 exposures to norepinephrine. In this valley, two endothelial cells had become attached by a cytoplasmic bridge that appears to snap as the spasm relaxes. Note extreme thinness of the endothelial cytoplasm, presumably a result of compression. (× 19,200)

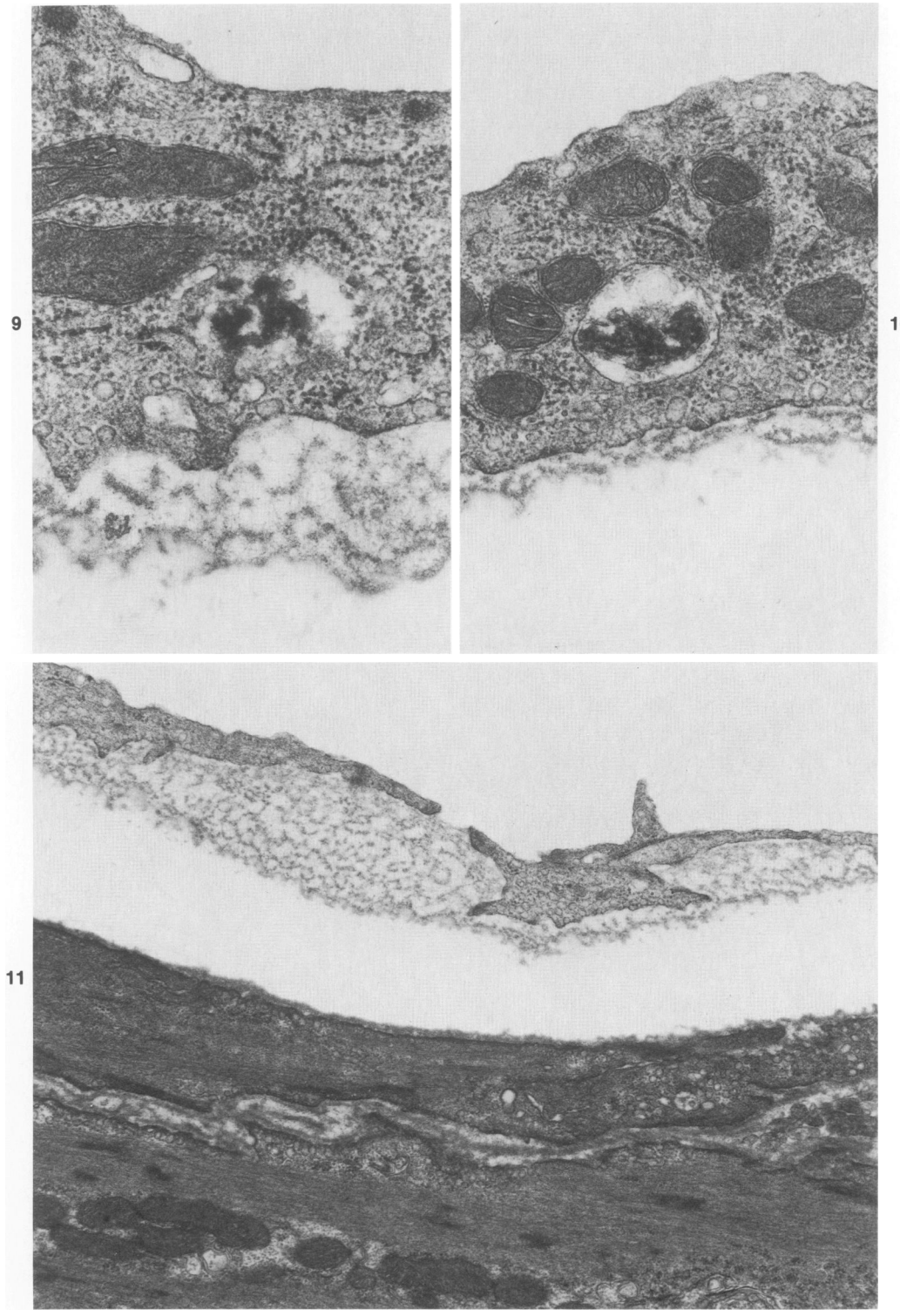

Figure 9—Medial tarsal artery 12 hours after 3 exposures to norepinephrine. There is a small mass of apparently denatured cytoplasm ("bruise") in an endothelial cell. (× 42,500) **Figure 10**—Saphenous artery 12 hours after 3 exposures to norepinephrine. There is a "cytoplasmic bruise" engulfed in a phagosome. (× 40,500) **Figure 11**—Saphenous artery perfused 12 hours after 3 exposures to norepinephrine. A gap between two endothelial cells persists in a relaxed segment of the vessel. (× 15,400)

The process of endothelial adhesion may well be significant in chronic arterial spasm, since the number of adhesions is very large. Although the material of Shimamoto et al is different from ours, it offers an order of magnitude as to the frequency of the adhesions: the estimates for the aorta (limited to the larger "bridges" as seen by SEM) was on the order of 1000–4000/sq mm.[24]

Previous Studies on Intimal Damage by Spasm

We know of a single paper that described endothelial damage induced by arterial spasm as seen with the light microscope.[33] Altschul studied the central ear artery of the rabbit after needle puncture; he found that the nuclei of the endothelial cells were squeezed out of the valleys and piled up onto the ridges, where they could be seen for as long as 24 hours. Some nuclei appeared damaged. The "squeezing out" of the nuclei occurred also after lethal intravenous injections of adrenaline. Other vessels did not show these effects "with similar clarity"; however, this study is important because it suggests that a recent episode of spasm might be diagnosed even postmortem by demonstrating rows of endothelial nuclei piled up along the ridges.

The model of spasm that has received most attention in recent years is the spasm of cerebral arteries after subarachnoid hemorrhage, both in man[3,4,34] and in experimental animals.[35–40] In patients who died 4 weeks or more after the episode of bleeding, histologic studies of neighboring arteries showed intimal proliferation interpreted as a response to "either mechanical or anoxic damage to the intima" caused by the spasm itself.[41] In the basilar artery of the dog, 3 to 7 days after subarachnoid injection of autologous blood, Tanabe et al[40] found "endothelial cells detached from each other" with leukocyte sticking; at 1 month the endothelium was again normal.

Spasm produced by several means in the basilar artery of monkeys and cats induced endothelial changes and thrombosis, visible 15 minutes and 2 hours later by SEM; the changes were attributed to "hemodynamic or other factors related to arterial stenosis"[17] or to shear stress.[18,42,43] Other studies were done on coronary arteries of the dog, constricted by partial ligature or by electrical stimulation; SEM 30 minutes later showed "endothelial craters and balloons," desquamation, and platelet attachment; the damage was attributed to increased shear stress.[19,20] It cannot be excluded that shear stress contributed to the endothelial damage consecutive to arterial spasm; however, this must remain purely hypothetical, whereas the damage caused by intimal folding (as illustrated herein) is evident. In our experience, increased shear stress produces one type of endothelial injury that can be considered almost specific, ie, focal erosions of the endothelial cell surface.[44] This was never observed in our spastic arteries, nor was it mentioned by the authors quoted.

Kobori et al[45] studied the lesions in mesenteric arteries of the rat caused to contract with methoxamine hydrochloride (10 mg/ml). They described necrosis and desquamation of endothelial cells, followed by thrombosis. Endothelial pinching and adhesions were not mentioned. Since the arteries thus treated went on to become completely necrotic and became surrounded by "neutrophils, plasma cells and lymphocytes," the role of spasm *per se* in these experiments is difficult to interpret. In our model, 7 days after spasm, the arteries were indistinguishable from normal, except for minimal, ultrastructural residual damage (occasional medial vacuoles).

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