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Reaction of the Aortic Wall of the Rabbit after Superficial, Longitudinal, Mechanical Trauma*

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Die Reaktion der Aortenwand des Kaninchens nach oberflächlicher mechanischer Längsverletzung

Zusammenfassung. Die Innenflächen von Kaninchenaorten wurden durch mechanische longitudinale Traumen oberflächlich verletzt, um ein hämodynamisches Trauma nachzuahmen. Die Reaktion der Arterienwand auf das Trauma wurde nach verschieden langen Intervallen lichtmikroskopisch untersucht. Eine Reihe von Veränderungen repräsentierte eine Heilungsreaktion der Aortenwand, die zur Wiederherstellung der aortalen Innenauskleidung führte. Die reparativen Vorgänge waren charakterisiert durch Vermehrung und Einwachsen der angrenzenden Endothel- und glatten Muskelzellen sowie durch eine Verdoppelung der Elastica interna. Es resultierte eine subendotheliale Verdickung, die die darunterliegende Region vor der mechanischen Belastung bewahrte. Nach einer ruhigeren Phase von 2 Wochen Dauer nahm die subendotheliale Verdickung wieder ab, nach 8 Wochen war sie kaum noch wahrnehmbar.

Ähnliche Veränderungen an den Arterien junger Menschen, die von anderen Autoren beschrieben wurden, machen es wahrscheinlich, daß es sich bei den mitgeteilten Veränderungen um einen physiologischen Reparationsmechanismus handelt. Es kann angenommen werden, daß die in der Humanpathologie beobachtete progressive Intimaverdickung nach wiederholter oder andauernder hämodynamischer Belastung eine ähnliche Gewebsreaktion darstellt. Die Beziehung zwischen progressiver Intimaverdickung sowie akuter Beschädigung und der Entwicklung der Atherosklerose kann durch Störungen des Reparationsmechanismus erklärt werden.

Summary. To imitate hemodynamic trauma the lumenal surface of the rabbit aorta was injured superficially by longitudinal mechanical trauma. The reaction of the artery wall was studied by light microscopy after different time-intervals. A series of changes that followed represented repair reactions leading to restoration of the wall. These changes were characterized by (i) the reconstitution of injured parts by multiplication and ingrowth of surrounding endothelial cells and smooth muscle cells, and (ii) reduplication of the internal elastic membrane and a subendothelial thickening which apparently relieved the underlying injured region from mechanical strain. After a more static phase of two weeks the subendothelial thickening decreased and was barely detectable after 8 weeks.

Similar changes in the arteries of young humans as reported by others, suggest that the changes represent physiological repair. It is postulated that the progressive intimal thickening in man may be due to a similar response to repeated or continuous hemodynamic strain, and that the relation of progressive intimal thickening and acute injury to the development of atherosclerosis may be explained by disturbance of the reparative reaction.

A multifactorial cause of atherosclerosis seems now to have been established (CONSTANTINIDES, 1965). Evidence for hemodynamic mechanical trauma as

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one of these factors has been presented in a series of studies (cf. DUNCAN, 1963; ADAMS, 1964; TEXON, 1967). However, little is known about the sequential stages of the arterial wall response to trauma. The paucity of information is especially apparent regarding the reaction after experimental trauma imitating hemodynamic trauma, i.e. selective injury to the inner surface of the artery wall.

The scope of the present study was to design an experimental technique by which a controlled, superficial injury could be induced to the lumenal surface of the rabbit aorta and to study the sequential stages of the arterial wall reaction after such trauma.

Materials and Methods

Twentytwo country-bred albino rabbits of both sexes, weighing between 2.7 and 4.4 kg, were obtained from the same source. They were fed *ad libitum* on standard rabbit diet (AB Teknosan, Malmö, Sweden) with addition of fresh vegetables.

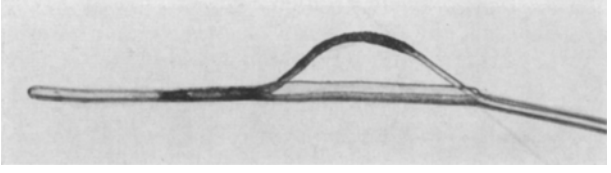


Fig. 1. Distal end of the instrument used for the production of injury to the inner surface of the aorta in the living rabbit. For details see text (Materials and Methods)

Damage to the inner surface of the aorta was done by means of the following instrument (Fig. 1): in a 35 cm long Nylon catheter with an outer diameter of 1.0 mm (Portex, Vena Cava Catheter, "Pink", Portland Plastics Ltd., Huthe, Kent, England) an 0.8×13 mm slot was made 1 cm from the distal end. Along a 9 mm segment of a Perlon fishing line with a diameter of 0.45 mm industrial diamonds (Quintus diamonds, 100/120 mesh; Asea Diamond Division, Stockholm, Sweden) were glued on half of the surface. The diamonds, covered with glue, had their outer points exposed by polishing off superfluous glue after drying. The Perlon line was introduced into the catheter with the diamond covered part in the slotted part of the latter. The line's position was fixed by gluing its distal non-diamond bearing portion 5 mm beyond the slot in the catheter. The distal opening of the catheter was closed by heating, yielding a smooth, spherical surface. At the other end, the line protruded 10 cm from the proximal end of the catheter. The diamond covered part protruded from the slot when the line was pushed into the catheter (Fig. 1). The diamond covered part could again be withdrawn into the catheter by pulling the line.

Surgical procedures were carried out under sodium pentobarbital anesthesia and aseptic conditions. The proximal part of the right superficial femoral artery was exposed. The catheter was then introduced through a slit into the artery and advanced to reach the upper part of the descending thoracic aorta. The diamond covered part of the instrument was then brought into slight contact with the aortic wall (perceived as a slight resistance against push) and longitudinal damage created by pulling the whole instrument approximately 20 mm distally. The diamond covered part was then retracted into the catheter and the instrument pulled distally about 20 mm. Other lesions were then produced by repeating this procedure until the catheter window appeared in the femoral artery. In some animals transverse damage was also induced by rotating the instrument in a short segment in the lower thoracic aorta and lower abdominal aorta to enable comparisons between longitudinal and transverse damage in the same animal (to be reported separately). The catheter was then withdrawn and the artery ligated.

The animals were killed after different time intervals after the induction of trauma; two rabbits after 24, 48 hours and after 2, 3, 4, and 8 weeks; three rabbits after 1 week and one rabbit after 16 weeks. Four sham operated animals were killed by pairs after 24 hours and 2 weeks. The aortas of two unoperated animals were investigated. When the animals were killed the following procedure was followed. A midline incision was made under sodium pentobarbital anesthesia and a catheter introduced into the ascending thoracic aorta through the left ventricle. The animal was perfused through this catheter with Ringer's solution at a pressure of 100 mm mercury until the venous return to the heart was clear (usually 5—6 min). The aorta and common iliac arteries were rapidly dissected out, avoiding stretching and direct touching, brought into ice-cold Ringer's solution, opened, mounted flat, and fixed in a neutralized solution of 1% calcium acetate in 10% formalin. In one control rabbit and one rabbit a week after induction of damage the Ringer perfusion was followed by fixation *in situ* with the above mentioned formalin solution under 100 mm mercury pressure.

Staining and Histochemical Methods. Frozen sections and paraffin sections were prepared from damaged segments from both thoracic and abdominal aorta. The frozen sections were stained for lipid with oil red 0 as described by LILLIE (1944). The paraffin sections were stained with Goldner's modification of Masson's trichrome stain (ROMEIS, 1948) combined with Gomori's aldehyde-fuchsin stain for elastic tissue (GOMORI, 1950). In addition, damaged segments were cut out *en bloc*, and stained for lipid as described above or with Weigert's resorcin fuchsin — van Gieson stain in combination with iron hematoxylin. After removal of the adventitia and outer media the material was then mounted as a surface preparation.

Due to the small optical contrast of the different components of the inner aortic surface in the whole unstained preparation, it was necessary to briefly stain the fixed whole aorta in Mayer's hemalum to recognize the damaged areas in the 24 hour and 4 day animals.

Results

No complications were encountered after the operations. The wounds healed *per primam.*

Characteristics of the Injury. The direct effects of the instrument after 24 hours observed in surface preparations were loss of endothelium in areas of varying size (see below) and within such areas crescent-shaped or oval defects of the internal elastic membrane with long axes of about 20 to 250 μ oriented perpendicularly to the long axis of the vessel (Fig. 2). Usually, 1—3 such defects were found in a damaged segment (Fig. 2a). In some cases, the array of defects within such a segment was interconnected by a longitudinal rift (Fig. 2b). Three types of defects of the internal elastic membrane were observed: (i) total defects, where continuity of the membrane was broken and the lumenal part of the innermost lamella of the media was exposed (Fig. 2b, c); (ii) subtotal defects, in which a thin continuous residual sheet of the internal elastic membrane formed the bottom of the defect (Fig. 2d); and (iii) areas with the internal elastic membrane heavily wrinkled (Fig. 2e). Loss of endothelium was found over and around such defects (Fig. 2). The extent of endothelial loss varied from just the damaged areas of the internal elastic membrane to the entire vessel surface in the segment of damage. In some damaged areas, partially torn off endothelium was observed as long flaps. The media was not affected directly by the cutting action of the instrument as judged from the continuity of the constituents in the innermost lamella, even beneath total defects of the internal elastic membrane.

Macroscopic Changes after Injury. No thickening of the aortic wall was observed with the unaided eye until after two weeks. At this stage, longitudinal, ridge-like thickenings protruding into the lumen were found at the levels in the aorta where damage had been induced. The length of the thickenings varied from 5 to 20 mm.

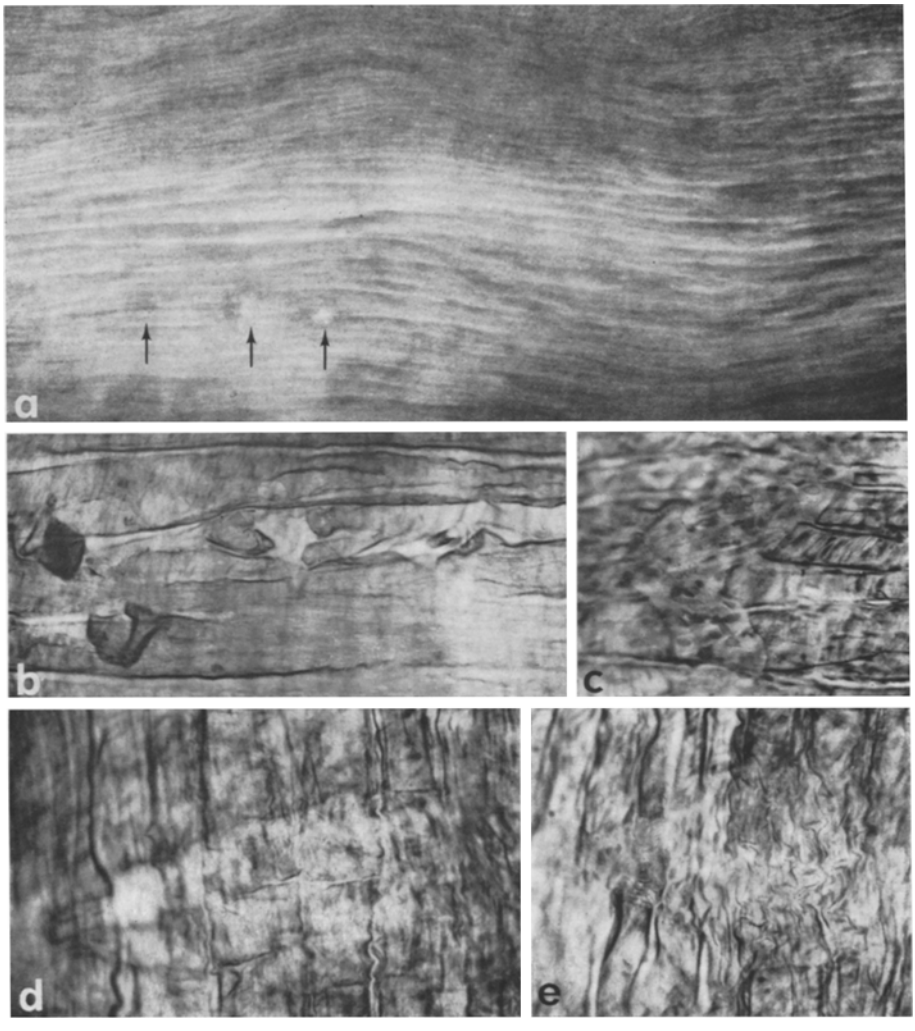


Fig. 2a—e. Direct effects of the instrument on the inner aortic surface as seen in surface preparations. a Injured segment 24 hours after damage. The white area is devoid of endothelium. At arrows small defects of the internal elastic membrane. Parallel ridges and furrows are due to contraction of the vessel wall. They run in longitudinal direction and make possible optical cross-sections in surface preparations; cf. Figs. 3b—f and 6b (Mayer's hemalum; × 50). b Multiple total defects of the internal elastic membrane, some of which are interconnected by rifts, in injured segment 24 hours after damage. The region is devoid of endothelium (× 215). c Crescent-shaped, total defect of the internal elastic membrane 4 days after injury. The defect is partially re-endothelialized (× 225). d Subtotal defect of the internal elastic membrane (lighter area) with a thin residue of the membrane at the bottom of the defect. Preparation one week after injury (× 240). e Subtotal defect (left, middle) and wrinkled area (right middle) of the internal elastic membrane in injured sector 24 hours after damage (× 245). b—e Weigert's resorcin-van Gieson-Htx stain

After 3 weeks similar but higher longitudinal ridges were found. By 4 weeks their heights were reduced, and after 8 weeks no thickening of the wall could be observed.

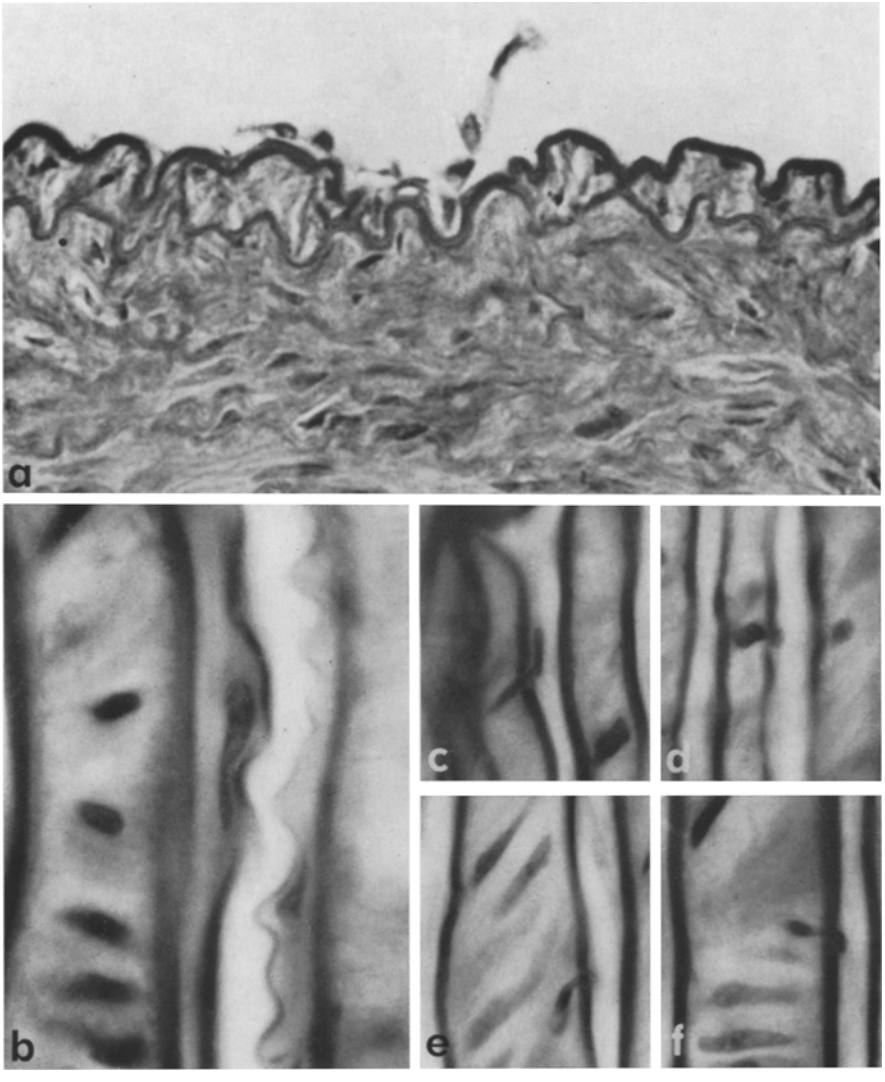


Fig. 3a—f. Injured aortic segments 24 hours after damage. a The internal elastic membrane is denuded and duplicated except for region with small endothelium residue (centre). Cross-section. (Goldner's trichrome — Gomori's aldehyde fuchsin stain; × 500). b—f Duplications of the internal elastic membrane with interposed smooth muscle cells (b) and smooth muscle cell nuclei located in pores of the internal elastic membrane (c—f) as seen in longitudinal ridges in surface preparations; cf. Fig. 2a, text. (Weigert's resorcin fuchsin-van Gieson-Htx stain; b × 2,400; c, f × 1,640; d, e × 1,280)

Microscopic Changes after Injury. Numerous mitotic figures appeared from 24 hours to 1 week in the *endothelium* surrounding the damaged areas (Fig. 4). The regenerating endothelium was irregular and consisted of cells of varying size and shape. Most defects were partially covered with endothelium by 4 days (Fig. 2c) and completely covered after 1 week.

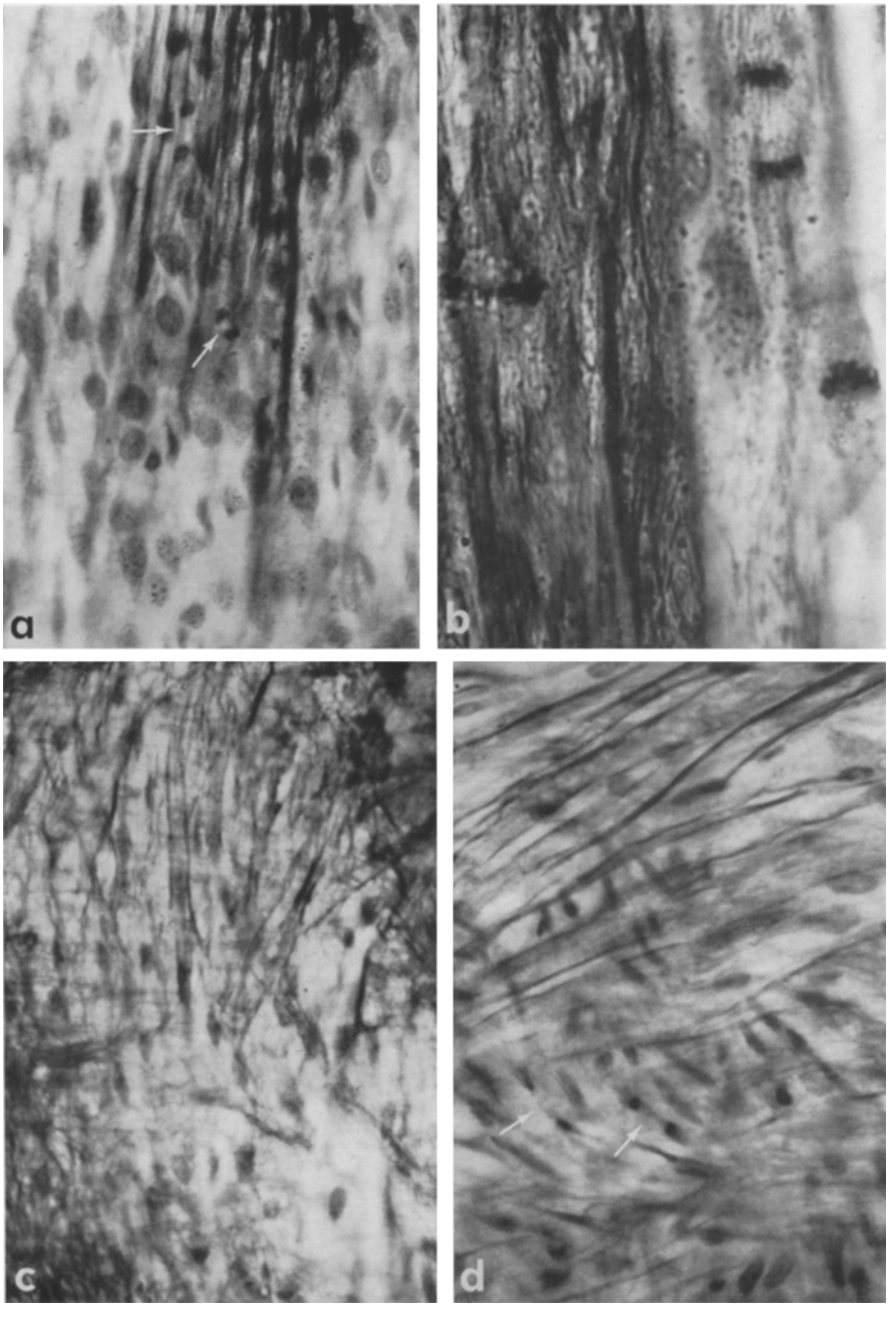


Fig. 4a—d. Injured aortic segments 4 days after damage. Surface preparations. a, b Regeneration of endothelium. a Dark part (upper, middle) represents area with duplications of the internal elastic membrane. The surface is covered with endothelium with exception for the central part of area with duplications (top, middle). Slightly behind the edge of the endothelium mitotic figures are seen in endothelium cells (arrows). b Region with duplicated internal elastic membrane (left half of figure) and transition to single membrane (right).

In a few cases, where the loss of endothelium had obviously been widespread, denuded areas were observed after 1 week (Fig. 2d). After two weeks all damaged segments were covered by endothelium.

Fragmentation of the *internal elastic membrane* and/or the formation of multiple sheets of elastic tissue attached to the membrane was observed in the affected areas 24 hours to 4 weeks after injury (Figs. 3a, b and 8).

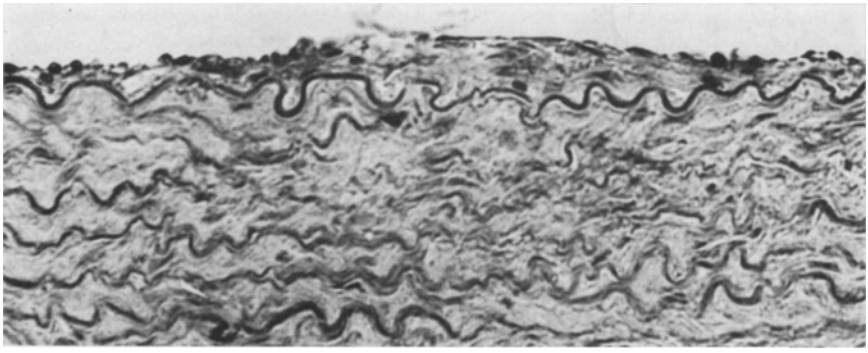
The number of superimposed internal elastic membrane sheets varied. In some lesions four sheets were seen. Between the sheets smooth muscle cells were arranged in a palisade-like fashion. Mitotic figures appeared in the smooth muscle cells between the elastic sheets from 24 hours to one week after the damage. Scattered or ribbon-like accumulations of collagen on both sides of the internal elastic membrane were regularly observed after 4 days (Fig. 5).

Smooth muscle cells partially located in pores in the internal elastic membrane appeared 24 hours after injury (Fig. 3c—f). Networks or parallel ribbons of smooth muscle cells were observed 4 days after injury between endothelial cells and the internal elastic membrane in areas surrounding defects of the internal elastic membrane (Fig. 4c). *Subendothelial smooth muscle cells* were also seen in sections of damaged areas. After one week such cells appeared as a continuous stratified subendothelial thickening 2—3 cell layers thick (Fig. 5). After 2 and 3 weeks the height of the subendothelial smooth muscle cell thickenings in most cases equalled that of the media (Figs. 7, 8). In the basal part of these thickenings the cells were longitudinally arranged; in the middle part they were arranged as concentric palisades; and in the lumenal part as one or two layers of transversely aranged cells beneath the endothelium. Sheets or fibers of elastic tissue were found between the palisades and their component cells (Figs. 7, 8). The cellular organization of the intimal thickening was essentially the same after 4 weeks. The depth of the thickening was reduced and the majority of the cells showed a transverse arrangement. After 8 weeks the lesions could not be detected macroscopically. However, in surface preparations or serial sections at levels where damage had been induced, defects of the internal elastic membrane were found (Fig. 9). In a few occasions a low subendothelial thickening covered the defects (Fig. 9). The areas were covered with endothelium.

Mitoses were occasionally found in subendothelial smooth muscle cells after 1, 2, and 3 weeks.

Signs of degeneration of the *media* varied to a great extent from 24 hours to one week. In some damaged areas, the smooth muscle cells were apparently intact, even in the uppermost lamella underlying total defects of the internal elastic membrane. In other damaged areas with endothelial loss or subtotal damage of the internal elastic membrane the number of smooth muscle cells and elastic fibers or sheets in the innermost media lamellae was markedly decreased (Fig. 5). The depth of medial cell loss did not exceed 4 lamellae. Frequent smooth muscle

Three mitotic figures in endothelium cells. c Network of smooth muscle cells overlying the internal elastic membrane. d Changes in media. The focus is at the innermost media lamella. A strand of smooth muscle cells (centre) projects from encompassing normal media (base of figure) into injured media devoid of cells. Mitotic figures are present in the strand (arrows). (Weigert's resorcin fuchsin-van Gieson-Htx stain; a × 512; b × 1,760; c × 1,360; d × 530



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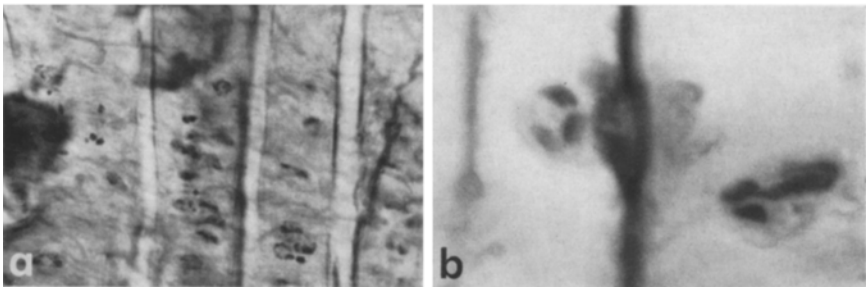

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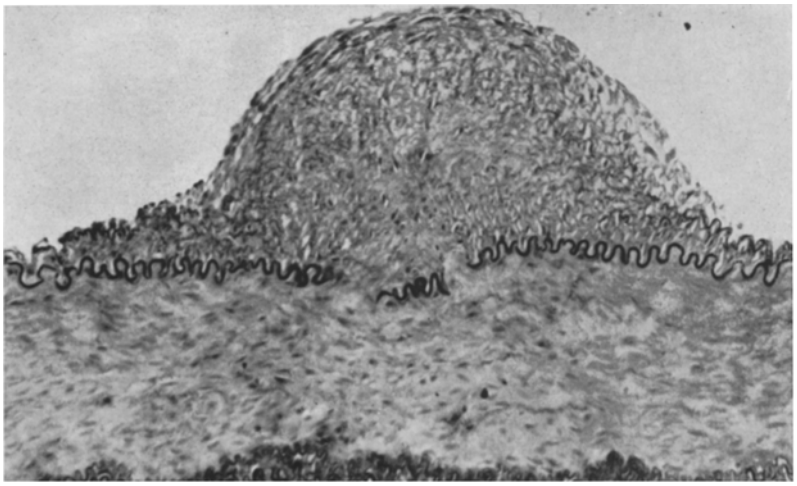
Fig. 5. Injured aortic segment 1 week after damage. A subendothelial thickening 2—3 cell layers of height has formed. The thickness and intensity of stain of the internal elastic membrane varies and the patterns of elastic tissue of the four innermost media lamellae is distorted. The thin, light zone underlying the internal elastic membrane was stained as collagen. Cross-section (Goldner's trichrome-Gomori's aldehyde fuchsin stain; × 190)

Fig. 6a and b. Invasion of neutrophil leukocytes in injured aortic wall as seen in surface preparations 24 hours (a) and 1 week (b) after damage. a Numerous leukocytes are present in the innermost media lamella. Some leukocytes show signs of degeneration. The media tissue in focus is devoid of smooth muscle cells. The same segment as in Fig. 2b but focused at innermost media lamella. b Leukocyte in lumenal furrow (left), in pore of the internal elastic membrane, and in the media (right) indicating migration of leukocytes through the membrane (Weigert's resorcin fuchsin-van-Gieson-Htx stain; a × 430; b × 2,400)

Fig. 7. Cross-section of injured sector 2 weeks after damage. The subendothelial thickening shown formed a ridge parallel to the length axis of the vessel, 15 mm in length. A reduction of the height of the media as suggested by this section was not observed in the majority of specimens (Goldner's trichrome-Gomori's aldehyde fuchsin stain; × 210)

Fig. 8. Cross-section of injured sector 3 weeks after injury stained for elastic tissue. The elastic fibers or sheets are oriented in concentric planes attached to the internal elastic membrane lateral to the injury (Weigert's resorcin fuchsin stain; × 170)

Fig. 9. Cross-section of injured segment 8 weeks after damage. Endothelium and a low subendothelial thickening cover the discontinuous internal elastic membrane. The gross structure of the media is restored; cf. media as shown in Fig. 5 (Weigert's resorcin fuchsin-van Gieson-Htx stain; × 360)



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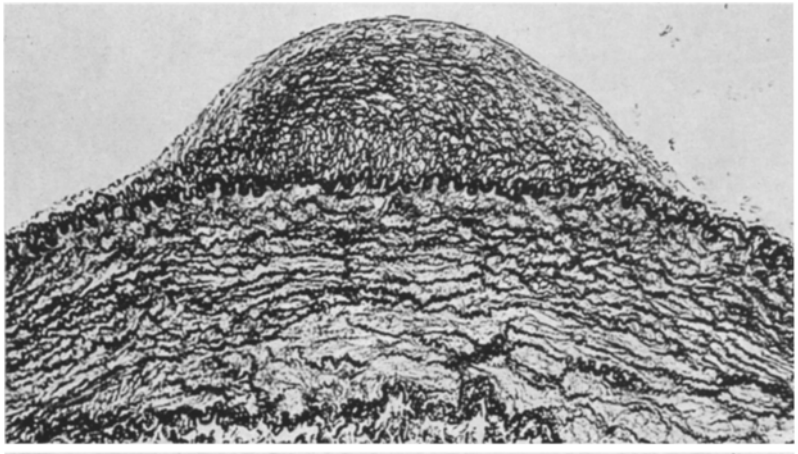

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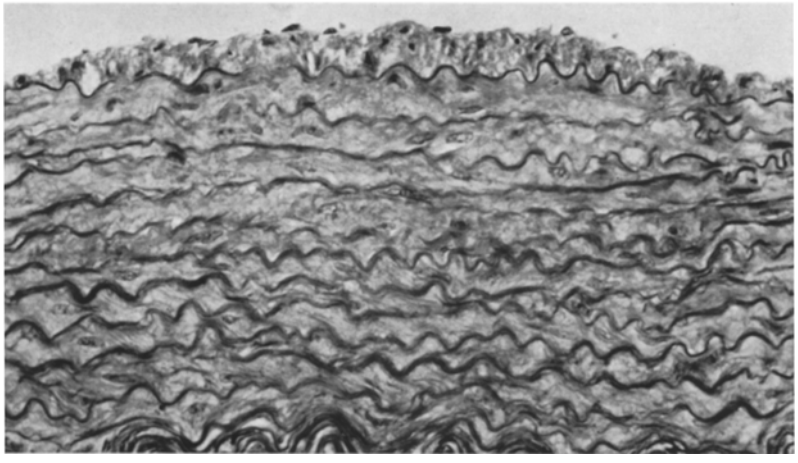

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Figs. 7—9

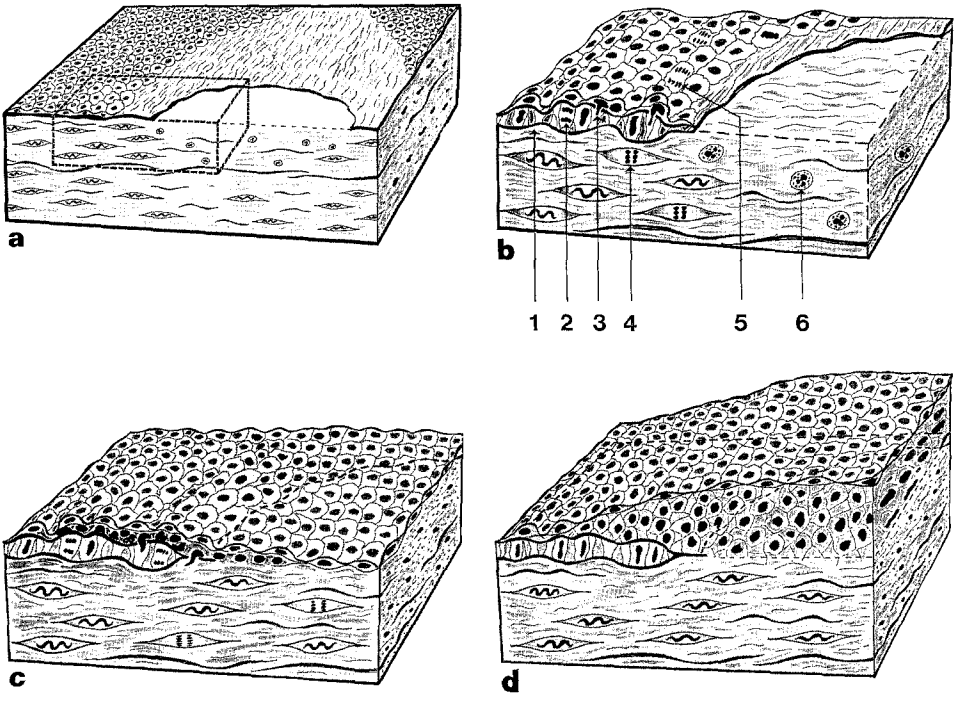

Fig. 10a—d. Scheme depicting the main changes in the aortic wall at varying times up to 2 weeks after injury. a Immediate changes in injured sector are loss of endothelium, of the internal elastic membrane, and of smooth muscle cells in innermost media lamellae. Only the two innermost media lamellae are shown. The dashed portion is shown in b—d. b Changes 24 hours after injury are fragmentation and/or duplication of the internal elastic membrane (*1*); multiplication of smooth muscle cells located between the internal elastic membrane sheets (*2*), in media (*4*), and of endothelium cells (*5*); location of smooth muscle cells in pores of the internal elastic membrane (*3*); and invasion by neutrophil leukocytes (*6*). c 4 days after injury numerous mitotic figures are found in smooth muscle cells encompassing and projecting into injured media; a subendothelial network of smooth muscle cells is present. d 1—2 weeks after injury a subendothelial thickening has formed and the gross structure of the media is restored. For functional aspects of changes see Discussion

cell mitoses were observed in strands of remaining smooth muscle cells in such areas and in the normal media encompassing the damaged media (Fig. 4d) at all stages from 24 hours to 1 week of recovery. From two weeks after the damage the gross structure of the media was restored (Figs. 7—9).

Varying numbers of neutrophil leukocytes appeared on the surface of the damaged areas, in the duplications, and in the damaged parts of the media 24 hours after injury (Fig. 6). They seemed to be more numerous in connection with total internal elastic membrane damage than in less severely damaged areas. Leukocytes with signs of degeneration were frequent. No leukocytes were observed after two weeks post-damage. Deposits of blood constituents on damaged areas were very rare. In all specimens studied three minute aggregates and three small areas with mononuclear cells were found in the vicinity of injuries by 24 hours and 4 days.

No lipid accumulation was discerned in the intima or the media at any stage after induction of the damage nor in the unoperated or sham operated animals. No alterations similar to those described after induction of damage were found in the unoperated or sham operated animals in the portion of the aorta studied with the exception of the presence of scattered foci of fragmentation and/or duplication of the internal elastic membrane predominantly confined to branch points of the aorta. The duplications differed from those of the experimental animals in the following respects. They were covered by endothelium, no mitotic figures were seen in their containing cells, and they were not associated with defects of the internal elastic membrane.

A schematic illustration of the main changes after injury is given in Fig. 10.

Discussion

Reaction to Injury. Injury to arteries has been induced experimentally by a variety of means, e.g. heat, freezing, tearing, scratching the inner surface with a needle pierced through the wall, ligation, clamping, injection of chemical irritants, exposure to X-rays, and distension by means of a balloon catheter (for reviews and references see ADAMS, 1964 and FRENCH, 1966). Control of the depth of the trauma does not seem to have been possible with these techniques. GUTSTEIN and coworkers (1963) and LA TAILLADE *et al.* (1964) induced a more selective type of mechanical trauma in rabbit aorta by the action of a barbed needle introduced through the femoral artery. However, they state that the depth of the damage could not be exactly controlled. Data on detailed sequential changes were not reported.

In the majority of these studies signs of degeneration of elastic components and smooth muscle cells and a subsequent thickening of the intima were observed after injury. The origin of the cells of the thickened intima is not clear and it has been suggested that they arise alternatively from endothelial cells, blood cells, multipotent cells in the subendothelial space, or media smooth muscle cells (cf. FRENCH, 1966). Smooth muscle cells with an intermediate position between media and intima located in gaps in the internal elastic membrane have been found in different types of intimal thickening. This suggests a migration of smooth muscle cells from media to the subendothelial space (BUCK, 1961, 1963; FRENCH *et al.*, 1963; PARKER *et al.*, 1963; HOFF and GOTTLOB, 1968). The frequent occurrence of such cells from 24 hours after injury in the present study and the subsequent formation of a subendothelial network or parallel ribbons of smooth muscle cells constituting the first stage of the developing intimal thickening lend considerable support to this suggestion. The high rate of cell multiplication (often 2—3 mitoses/high power field) in the innermost media lamellae as observed seems to constitute a source of such migratory cells.

The fact that few mitoses were observed in subendothelial smooth muscle cells suggests that the main source of the cellular component in the thickened intima is cells from the inner media, although multiplication of subendothelial cells may contribute.

The reendothelialization of the defects in the present study seems to have occurred more rapidly than in previous investigations. This discrepancy may be explained by the small size of the defects created in the present study.

A conspicuous change after injury was the formation of multiple sheets of elastic tissue attached to the internal elastic membrane. The space between the sheets contained smooth muscle cells. Formation of elastic tissue by these cells is indicated by the fact that the elastic tissue in such areas exceeded by far that of the parent membrane. That smooth muscle cells in the adult animal have capacity to form elastic tissue has also been demonstrated by HAUST and MORE (1967) under other experimental conditions.

Pathophysiological Aspects. Essential features of repair in other tissues as invasion by leukocytes, cell division and migration, and synthesis of fibrous components (EDWARDS and DUNPHY, 1958) were also found to be characteristic of repair in the arterial wall. However, the hyperplastic characteristic exhibited by the formation of a marked subendothelial thickening may be a feature specific for repair of the arterial wall. The subendothelial thickening seems to have at least two functions. The elastic component of the thickening is oriented in concentric planes attached to the internal elastic membrane lateral to the damage (Fig. 8). It is likely that the elastic and collagen components of the subendothelial thickening serve a function of relieving the underlying damaged area from tangential strain.

The change of the geometry of the arterial wall due to the formation of a subendothelial thickening has the effect of reducing the tangential wall tension in the thickened sector. The tangential wall tension is expressed by the Frank-Laplace equation (FRANK, 1920).

$$T = \frac{R \cdot P}{H}$$

where T is the tangential wall tension, R the radius of the vessel, P the distending pressure, and H the wall thickness. It can be seen that the increase of wall thickness and the decrease of radius due to the presence of the subendothelial thickening both will reduce the tangential wall tension in the thickened sector, i.e. the damaged area.

It is known that rupture of wounds not followed by resuturation retards healing. In analogy, it is plausible that the subendothelial thickening may protect the damaged sector from rupture and, thus, serve as an important component of repair in the artery wall.

The aim of the present study was to follow the changes in the artery wall after superficial, artificially induced injuries, intended to imitate injury which might occur naturally due to hemodynamic factors. That the arterial wall is subjected to increased hemodynamic strain at certain sites of the arterial tree is suggested by studies of hydrodynamics, the geometry of the arterial tree, the physical properties of the arterial wall, blood pressure and flow. Sites where increased hemodynamic strain due to turbulence, viscous drag or suction effects is likely to occur are bifurcations, branchings, bendings, and constrictions (MCDONALD, 1960; STEHBENS, 1959; TEXON, 1967; ATTINGER, 1964). It should also be pointed out that an injury may not only be caused by increased hemodynamic strain. A decrease of the resistance of the artery wall to mechanical strain may also lead to injury.

That the experimentally induced defects in the present study may closely imitate naturally occurring ones is suggested by the frequent occurrence of similar

defects in human coronary arteries of young individuals (WOLKOFF, 1923; BORK, 1926; EHRICH *et al.*, 1931; MOON and RINEHART, 1952; MOON, 1957; JAFFE, 1967). The earliest changes were beading, fraying, or complete disruption of the internal elastic membrane, features which also characterize the experimental injury. As after experimental injury, a thickening of the intima followed which has been considered to be a manifestation of a generalized and basic mechanism of tissue reaction to injury (MOON, 1957). It, therefore, seems reasonable to propose that the reaction after injury studied in the present work may be a physiological repair mechanism of the artery wall.

Relation to Atherosclerosis. The intimal thickening following acute injury was reversible. It is possible that repeated or continuous trauma can cause sustained intimal thickening. Therefore, the progressive intimal thickening present in man and in certain other species may be caused by repeated or continuous mechanical insufficiency of the arterial wall.

Both acute injury and the progressive intimal thickening are related to atherosclerosis. It is well documented that arterial injury favours the development of dietary-induced atherosclerosis and it has been suggested that the progressive intimal thickening is pathogenetically related to atherosclerosis (for review see ADAMS, 1964). It is suggested that the relationship between acute arterial injury and progressive intimal thickening to atherosclerosis may both be explained by disturbance of the repair reaction leading to atherosclerosis.

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