would be great difficulty in distinguishing between malarial aortitis and nodular sclerosis from other causes.

Experimentally aortitis has been produced by the injection of various microbes—B. typhosus, B. diphtheriæ, streptococcus, etc.—sometimes with and sometimes without previous traumatism to the artery by means of a probe inserted through the carotid. The French especially have been interested in this work (Gilbert and Lion, Therèse, Crocq, Pernice, Boinet and Romary). In some cases the lesions were vegetative, in others gelatinous plaques due to endarterial proliferation resulted. Infiltrations about the vasa vasis were often present. Nodular thickenings are described by Boinet and Romary as following the injection of toxins, of lead, urate of soda, and phloridzin, with or without preceding injury. In their later stages the lesions would be identical with nodular arteriosclerosis.

Metastatic abscesses in the walls of arteries are rare. Virchow observed one in the beginning of the pulmonary artery; and Eppinger describes an abscess, the size of a walnut, in the posterior wall of the aorta just distal to the origin of the left subclavian artery. Andral describes a case of multiple abscesses, of the size of hazelnuts, in the wall of the aorta, but there is some doubt as to the real nature of this case. Spengler describes an abscess in the wall of the aorta just above the semilunar valves.

Consecutive Exudative and Suppurative Angeiitis.—While blood-vessels possess considerable resistance against the invasion of suppuration from without, so that in large abscesses it is not unusual to find the vessels wholly freed from the surrounding tissue and bathed in pus, yet periarterial and periphlebitic infiltration and proliferation are common consecutive lesions. This occurs in the vessels at the base of the heart in acute exudative pericarditis, pleuritis, and mediastinitis; the adventitia is then the seat of an œdematous, sero-purulent, and purulent infiltration. And suppurative and necrotic processes around blood-vessels may extend not to the adventitia only, but also to the media and the intima, causing necrosis of the epithelial lining and secondary thrombosis. In this way also may develop suppurative thrombo-arteritis and thrombo-phlebitis. The weakening of the wall of arteries caused by the purulent disintegration of the media sometimes results in another form of aneurismal dilatation—erosion aneurism produced by a kind of hernia of the inner coats at the point of least resistance. This result of consecutive peri- and mesarteritis is especially frequent in the branches of the pulmonary artery that are exposed upon the floor and the trabeculæ of phthisical cavities. The aneurismal bulging takes place upon the side of the artery that is least supported by surrounding tissue, namely, that toward the lumen of the cavity. Frequently an obliterating thrombosis prevents the formation of aneurism and removes the danger of hemorrhage under these conditions. Suppuration in a wound, or in an amputation stump, may destroy the granulation tissue formed by the intima in the process of definitive closure of an artery, cause purulent disintegration of any thrombus present, and thus give rise to the much-dreaded secondary hemorrhage of the preaseptic times.

Colin and Flexner describe instances of perforation of the inferior vena cava in amœbic abscess of the liver.

On subsidence of acute inflammatory lesions of this nature, vascular granulation appears in the walls of the vessel, producing more or less extensive fibrous thickening of the various coats with narrowing of the lumen; in case thrombosis has taken place, the substitution of the thrombus by connective tissue may cause occlusion of the vessel. Terminal fibrous changes of this kind do not differ histologically from the lesions of many primarily productive forms of angeiitis.

Productive Angeiitis.—Inflammation of blood-vessels resulting in the production of new tissue is a frequent form In productive or obliterating endarteritis and endophlebitis there occurs a proliferation of the cellular elements of the intima, which leads to thickening of the intima, eccentric narrowing of the lumen, and eventually to complete occlusion. This process is observed under a variety of conditions. The occlusion after birth of the ductus arteriosus and the umbilical vein and arteries is accomplished by the formation of connective tissue by the intima; as the pressure of the blood in these vessels fails, a degree of contraction ensues that favors the filling of the vasa vasorum; in the narrowed lumen a small thread-like thrombus may form which is finally substituted by fibrous tissue. Similar changes occur in occlusion following ligature, and in the narrowing of the lumen of vessels the capillary bed of which has been restricted (amputations, indurative processes in the lungs, etc.). In these conditions there is usually atrophy of the media. A ligated vessel may be occluded by intimal proliferation without thrombosis taking place; in many cases a thrombus forms, which is then replaced by granulation tissue. In the old and feeble, especially when the arteries are sclerotic, the intima may have lost its power of proliferating and then there is danger of secondary hemorrhage.

Productive Thrombo-Arteritis.—The presence in an artery of a thrombus, whatever the cause of the thrombosis may have been, or of an embolus, is sooner or later followed by reactive changes on the part of the vessel wall, which result in the production of a vascular granulation tissue, provided destructive infection does not occur. The plug becomes infiltrated with leucocytic phagocytes and with fibroblasts. The amount of new tissue and the rapidity with which it is formed will depend more or less upon the age of the patient and upon the previous condition of the walls of the artery in question. The vessels of the aged, the walls of aneurisms and of sclerotic arteries are often so changed and degenerated that but slight or no reactive proliferation takes place under conditions that in young healthy arteries are followed by vigorous growth of new tissue. The vessels present in the new tissue result in part from ingrowth of vascular sprouts from the vasa vasorum, in part from the epithelial cells of the intima. In case the lumen of the artery is but partially occluded, then the tissue replacing the thrombus or embolus gives rise to various forms of intimal thickening—flattened elevations, projecting ridges and bands, cord-like networks. Complete occlusion of the artery may be followed by cicatricial obliteration of the lumen, or the new tissue may be so traversed by vascular spaces that the continuity of the lumen in some measure is restored. (For further details concerning connective-tissue substitution of thrombi, see article on *Thrombosis.*)

In the healing of wounds of arteries and veins a thrombus composed of blood plates and of fibrin first forms, which is subsequently replaced by new fibrous tissue.

Productive Thrombo-Phlebitis.—Productive inflammatory changes occur in the walls of veins after thrombosis. The process pursues the same general course as thrombo-arteritis. It is observed especially in the periuterine veins, the veins of the lower extremities, the pelvic veins, and the sinuses of the dura, which constitute those parts of the venous system that are most frequently the seat of thrombosis. The residues of connective-tissue replacement of a venous thrombus may be fibrous bands coursing across the lumen, the interior of the vein resembling that of a dural sinus, more diffuse intimal thickenings, and great shrinking of the part of the vein involved with complete obliteration of the lumen. Such changes may occur also in the larger veins, such as the venæ cavæ. I refer with more detail to occlusion of the superior vena cava in the section devoted to tumors of the vessels.

Obliterating Endophlebitis of the Hepatic Veins.—An obliterating, proliferative phlebitis occurs in the main stems of the hepatic veins. This process has recently been studied by Chiari. In seven cases collected by Chiari there were periphlebitic proliferative processes or thrombosis followed by productive thrombo-phlebitis. Chiari describes three instances of an apparently primary obliterating phlebitis of the main stems of this vein, which on account of the resulting circulatory disturbances became the cause of death. The endophlebitic process was situated in the proximal portions of the veins with peripheral extension in one case. The tendency to obliteration was marked, leading to mechanical obstruction and fateful secondary thrombosis. The

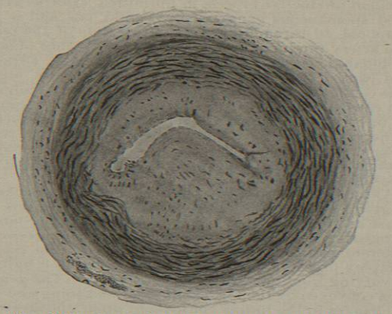

FIG. 627.—Obliterating Endarteritis in Chronic Salpingitis. Hæmatoxylin and eosin. × 100.

condition is undoubtedly a peculiar one, possibly of syphilitic origin; in one case it was associated with similar changes in the coronary arteries.

Consecutive Productive Angeiitis.—Inflammation, acute and chronic, generally takes place in the walls of all arteries that lie in tissue the seat of inflammatory processes. In this case cellular infiltration and proliferation extend into the vessel wall from without inward, and all the coats may in time become fibrous; the thickening of the intima caused by the proliferation of fibroblasts and the formation of new fibrous tissue is generally pronounced and complete obliteration of the lumen may take place. In many instances the formation of fibrous tissue in the intima of vessels in organs the seat of chronic fibrous processes is undoubtedly in some measure the result also of obliteration of portions of the capillary districts of the vessels (Thoma), the resulting narrowing of the lumen partaking of an adaptative nature—a localized form of secondary angeio-sclerosis. Changes of this general character are seen in chronic interstitial inflammations and fibrotic processes in the parenchymatous organs, as in interstitial nephritis, orchitis, etc. (Fig. 627). They are well marked in the specific granulomatous processes, and the resulting arterial lesions need not always necessarily present any specific characteristics. The acute stages can be studied nicely in the pial arteries in tuberculous leptomeningitis. There is leucocytic infiltration of the adventitia, extending into the media and intima; the wandering cells are seen making their way between the fibres of the media and through the fenestrations of the internal elastic coat, the nuclei being drawn out long so as to pass through narrow spaces; the elastic coat at times becomes broken through by the cells which may accumulate under the epithelium; simultaneously fibroblasts appear, especially in the subepithelial layers of the intima (see Tuberculous Arteritis) (Fig. 628). Similar changes of a more chronic but non-specific character are seen also in the walls of arteries and veins in chronic tuberculous areas and cavities in the lungs. Great narrowing of the lumen and even closure may result from the newly formed fibrous tissue in the intima. Quite similar changes occur in syphilitic lesions, and it is probable that an isolated, primary, histologically non-specific, productive endarteritis is often caused by syphilis. In productive endarteritis of whatever cause, fibrillar connective tissue interspersed with elastic elements is formed in the intima. At times a distinct, new, elastic membrane develops; it is generally thinner than the original elastic layer, the general course of which it imitates, and it forms the inner boundary of the new, greatly narrowed lumen. But the process is not thereby brought to a standstill, as new fibrous tissue may again form and completely occlude the vessel.

The fibrous perivascular changes that develop in connection with productive angeiitis of diffuse character lead to obliteration of the perivascular lymph spaces and serious obstruction of the lymph flow, which in some tissues, as for instance the brain, may produce grave disturbances of the function and the structure of the special cells.

Acute endarteritis may in time give rise to fibrous nodules upon the intima and to more diffuse thickening. Fenger describes an extensive polypoid fibrous endarteritis of the pulmonary artery associated with valvular endocarditis. The polypoid outgrowths, which almost close the lumen, sprang from the deeper layers of the intima. Willigk described numerous, small pedunculated vegetations. Eriksen noted large radiating scars, producing annular stricture, in the stem of the pulmonary artery, and Willigk found a stenosis of the right pulmonary artery, the lumen being reduced to a diameter of 2 mm.

Goebel describes a local endarteritis that gives rise to small elevations in the intima. The process involves only the intima. The resulting thickenings are based upon the elastic coat and are composed of a network of fibrillæ and elastic elements apparently splintered off from the elastic layer; the nodules are partly vascular. As they become polypoid, thrombosis may result and cause gangrene, which was the case in an instance of spontaneous gangrene in a child, one and a half years old, that forms the basis for his study. Goebel found similar nodules in medium-sized arteries in three of twenty children examined for this process. The cause is obscure; possibly some form of traumatism may be the underlying condition. Syphilis was excluded. It may be added by way of suggestion that a local toxic or infectious endarteritic process might result in such elevations.

Elastic Fibres in Endarterial Proliferations.—The newer methods of staining elastic fibres, elaborated by Tänzer and Unna and by Weigert, have resulted in the demonstration that they are present to a greater extent in the endarteritic proliferations than was formerly thought. Langhans believed that the pre-existing elastic layer—the elastica interna—underwent hypertrophy. Heubner found that in arteriosclerosis the inner layer of the elastica becomes granular, and that in the later stages of the disease four to eight or more elastic bands appeared in the thickening of the intima; in syphilis a new elastic membrane formed near the lumen in the quiescent stages; Heubner derived the new elastic elements from the epithelial cells. Wendeler pointed out that in syphilis each period of growth in the intima closes by the formation of an elastic membrane. Dmetrieff shows that in arteriosclerosis the newly formed elastic fibres in the intima

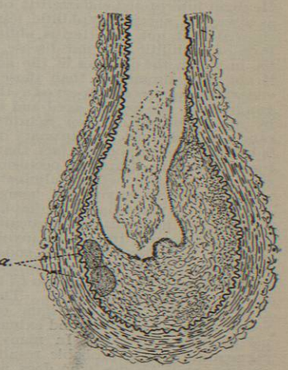

FIG. 628.—Chronic Endarteritis in Chronic Tuberculous Meningitis. *a*, Blood spaces. × 150 diameters.

have the same general course as the fibres of the media (see Fig. 629). Jores holds that elastic fibres are formed in two ways: the one is due to the splitting up of the internal elastic layer into several lamellæ, some of which may appear as quite independent bands. This process occurs especially in arteriosclerosis and probably to some extent under normal conditions. But the new formation of fine fibres is by far the most important. Jores favors the theory that these fibres are formed by the secretory activity of the young connective-tissue cells, although it cannot be said that the origin of elastic elements from chemical changes in the collogenous intercellular substances has been wholly disproved. In intimal proliferations Weigert's elastic-fibre stain shows that the new fibres appear first as finer granular lines that surround the cells as a fine network. The epithelial cells do not seem to play any part in this process, inasmuch as elastic fibres never appear between the individual epithelial cells, but are always confined to the subepithelial layers. From observations on ligated vessels Jores found that new elastic fibres are formed more numerously in vessels subjected to the pressure of the circulating blood than in parts enclosed between two ligatures or in vessels the seat of thrombo-arteritis. Hence he regards the new formation of elastic fibres as distinctly compensatory in character. The cells in intimal proliferations are gifted with greater powers to form elastic fibres, directly or indirectly, than the cells of the media.

Malkoff and Gardner hold that the elastic fibres develop in the outer layers of the cell bodies.

In typical endarteritis obliterans there is not much change in the elastic elements, which maintain the same relation in endarteritis obliterans as in productive thrombo-arteritis. In arteriosclerosis, on the other hand, the intimal thickening occurs in layers separated by elastic fibres (Falta).

Obliterating Endarteritis and Spontaneous Gangrene.—The occurrence of obliterating endarteritis in an independent, primary form has not been established upon a satisfactory basis. Its occurrence as a secondary process in indurative processes, in the organization of thrombi, and as the result of consecutive and specific arteritis is generally recognized since Friedländer, in 1876, first called especial attention to endarteritis obliterans. Heubner interpreted endarteritis of the cerebral vessels as always a specific syphilitic lesion, but Baumgarten showed that not endarteritis obliterans is the specific form of syphilitic vascular disease, but gummous arteritis, in which the changes in the adventitia are equally if not more prominent than those in the intima. The endarteritis obliterans observed as the case of spontaneous gangrene in the middle-aged and the young is regarded by von Winiwarter, von Schrötter, Borchhardt, and others as a distinct and primary disease. This opinion is based largely upon the fact that premonitory symptoms, indicative of gradual occlusion of the arteries, may exist a long time before culminating in gangrene, the more prominent symptoms being pain, cyanosis, and coldness. In some cases the complex of symptoms called by Charcot "intermittent claudication" has been present. The arteries more frequently involved are those of the foot, leg, and forearm. The endarteritis, which is described as typical, with vascularization of the new tissue in the intima and reduplication of the elastic coat, begins in the peripheral branches. The adventitia may be greatly thickened, and in some cases the neighboring veins and nerves were found extensively involved in the perivascular sclerosis. In many cases thrombosis or pigmentation, the probable result of thrombosis, was present, and Thoma, who does not believe there is a special form of obliterating endarteritis, holds that the endarteritic changes in this form of gangrene result from the replacement by connective tissue of thrombi in sclerotic vessels. Zoege von Manteuffel claims that the gradual occlusion is brought about by the deposition and organization of successive layers of parietal thrombi in primarily sclerotic arteries. Von Recklinghausen describes hyaline thrombi in the smaller arteries of limbs the seat of spontaneous gangrene. Haga regards endarteritis thrombotica as syphilitic. Hoegersted and Nemsen find that parietal thrombi in sclerotic arteries may result in occlusion and constriction of the vessels. Falta has described cases of gangrene in old people as due primarily to arteriosclerosis associated with an apparently independent productive process in the intima. Goebel attributed spontaneous gangrene in a child, one and a half years old, to thrombosis at the bifurcation of the popliteal artery produced on account of the presence of small globular elevations composed largely of elastic elements and caused by a local endarteritis of obscure origin. The conditions that may produce spontaneous gangrene not caused either by embolism and secondary thrombosis or by arteriosclerosis and thrombosis are consequently rather complicated. Undoubtedly many instances result from arterial thrombosis secondary to the endarterial inflammatory changes that occur in various infectious diseases (see *Gangrene*).

Angiosclerosis.—*Definition.*—It is quite impossible to give a comprehensive definition of angiosclerosis, because as at present used this term, and the more common term arteriosclerosis, undoubtedly include processes of different nature. Angiosclerosis is, to say the least, a complex process that appears under different conditions in varying stages and varying distribution. The general idea conveyed by the term is fibrous thickening and other changes in the intima consequent upon changes of a degenerative nature in the media of arteries and veins. When the process affects arteries, and that is by far its more prominent, more important, and more frequent localization, it is known as arteriosclerosis; and sclerotic changes in veins constitute phlebosclerosis. In cases of diffuse sclerotic changes in the vessels both arteries and veins are often involved, but the arterial changes are the more conspicuous both from the clinical and from the anatomical points of view.

The term arteriosclerosis was introduced by Lobstein over fifty years ago; he regarded the process as the result of nutritive disorders in the vessel wall incident to age and use. The word atheroma is used by some as almost synonymous with arteriosclerosis, but in reality atheroma is applicable only to certain late stages of the process, as it affects the aorta and its large branches. In the text-books of pathological anatomy of fifteen to twenty years ago arteriosclerosis is described generally under the heading endarteritis chronica deformans s. nodosa, and phlebosclerosis is mentioned sometimes as endophlebitis chronica deformans s. nodosa; these terms were introduced by Virchow; they are now rarely used. Other quite synonymous names are arteriocapillary fibrosis, introduced by Gull and Sutton, and arteriofibrosis. Since Thoma's epochal investigations, the terms arteriosclerosis, phlebosclerosis, and angiosclerosis are used quite universally. Atheroma should not be used as synonymous with arteriosclerosis.

Pathogenesis and Histogenesis.—Through the investigations and theories of Thoma and his students, angiosclerosis, in some of the phases of its genesis, has been placed upon the same basis as certain processes that occur in the vessels, especially the arteries, under normal physiological conditions.

The physiological paradigm of angiosclerosis is seen in the changes that take place in the aorta immediately after birth. At birth there is no connective tissue in the intima of the aorta. Immediately after birth the circulation in the umbilical arteries ceases; a part of the territory of the aorta is cut away, the aorta is now too large in comparison with the area it supplies with blood, and the circulation in it becomes slower. Under these circumstances connective tissue develops in the intima of that part of the aorta between the ductus arteriosus and the hypogastric arteries, and in this way its lumen is reduced to a size commensurate with the rate of blood current best suited to the needs of the tissues for nourishment. Later in life similar changes occur normally in the carotid, for instance, because from the eighth to the tenth year the growth in strength of this artery does

not keep pace with that of other vessels; hence it dilates, its lumen becomes so large that slowing of the circulation takes place, and new tissue develops in the intima until the current reaches the normal flow (Sack). Similar changes take place in arteries after amputation and in arteries whose capillary area is destroyed by disease. The connective-tissue formation in these cases is therefore spoken of as compensatory, calculated to reduce the lumens of the arteries to their proper size.

From these and other observations the general theory is deduced that every slowing of the blood current in the arteries and veins of man that is not completely and at once remedied by a proportionate contraction of the media, leads to a new growth of connective tissue in the intima, which narrows the lumen of the affected vessel, and thus restores the normal swiftness of the blood current more or less completely (Peabody). It may be said here that the compensating endarteritis is regarded as the result of mechanical and chemical changes that occur in and about the cells of the intima of the part of the artery affected; it is not claimed that the compensating proliferation is distinctly and purely teleological in its nature. In order to explain the new growth in the intima, Thoma has elaborated a rather complex theory according to which the irritation produced by the abnormal conditions upon the vaso-motor nerves connected with Vater-Pacini's corpuscles in the adventitia, leads to functional disturbances and hyperæmia of the vasa vasorum and eventually to new tissue in the intima. But intimal thickening occurs in vessels that have no vasa vasorum when the current is supposed to be slower than normal.

The origin of the new tissue in the intima is traced partly to the epithelial cells (Baumgarten, Thoma), partly to the connective-tissue cells in the subepithelial layer. The latter are probably the more important factors in the process. Ingrowth of connective tissue from the media and of vessels from the vasa vasorum is also mentioned as possible by some writers.

The weakening of the wall and consecutive local or general dilatation that gives rise to compensatory thickening in the intima are regarded as the result of wear and tear, of strain, of heightened intravascular pressure, and of toxic and infectious influences. These factors may operate singly or in combination. The obliteration of capillary areas and the narrowing of smaller, peripheral vessels are also held to induce thickening in the intima of the larger vessels because of the relative abnormal wideness of their lumens under these circumstances, but here it is manifestly difficult to determine the primary events in the process.

Thoma showed by physical tests upon the iliac arteries that weakening and dilatation of the arterial walls may occur in the early stages of arteriosclerosis without evident structural changes in the vascular tunics being present. Other investigators describe structural changes, especially in the elastic elements, that surely give rise to loss of strength and elasticity in the arteries affected.

Weiszmann and Neumann, Zwingmann, and others described tears in the elastic lamellæ and granular disintegration of the elastic fibres of the aorta in arteriosclerosis. Manchot observed similar changes in the aorta in the wall of aneurisms. Eberhardt was inclined to attribute the changes described as artefacts due to the use of alcohol not wholly free from water in the staining method then employed, in which fuchsin was the principal ingredient. Eberhardt found, however, that the changes described occurred to a slightly greater extent in the elastic lamellæ and fibrous network of the artificially distended than in the non-distended carotid artery.

Hilbert found that tears or transverse ruptures of the internal elastic coat occur at all ages in the arteries near the heart (aorta and carotids); in youth they are rare in the external iliacs, but after the fourth decennium they are frequent here also. In the renal and similar arteries ruptures are rare at all ages. Internally to the ruptures may be one or more layers of evidently modified or new elastic fibres. In the iliacs he noted a marked separation or splintering of the internal elastic layer in aortic insufficiency. The ruptures that he describes are attributed to momentary increase in the blood pressure under sudden physical exertion or mental excitement. They occur also in hypertrophy of the left ventricle and in cases of probable diminished resistance on account of nutritive disturbances. Sclerosis and aneurisms may result.

By means of more improved technical methods, Dmitrijeff has recently studied the changes in the elastic elements of the arterial wall in arteriosclerosis. He finds that the principal change in the media is a granular disintegration of the elastic fibres, which begins first in the inner parts of the media in the network between the elastic lamellæ. The granules appear in chains, and stain, some well, some poorly, with acid orcein. Later, changes appear in the lamellæ, which stain irregularly and break up into irregular pieces. The chemical nature of the elastic elements changes in some way and they become basophilous; Unna's modified elastin, elacin, is present. These are the earliest changes in the vessels and occur especially in advancing years; Dmitrijeff found them also in the aorta of an eight-year old child that died from scarlet fever. At the same time nodules or more diffuse thickenings appear in the intima, composed of fibrous tissue and new elastic elements arranged either as lamellæ or as networks of fine elastic fibres; this new formation easily undergoes degeneration (atheromatous changes), so that in arteriosclerosis there is degeneration of and new formation of elastic fibres. Foci of inflammation and proliferation in the adventitia and the media also lead to destruction of the elastic fibres in their vicinity. Peri-arterial and mesarterial inflammatory infiltrations about the vasa vasorum were regarded as of great importance by Köster, Huchard, and others. The etiology of such foci is probably to be sought in toxic and infectious influences. Martin and other French writers go so far as to advocate that the degenerative (atheromatous) changes in the large arteries are the result of sclerosis of the vasa vasorum.

Malkoff, from the experimental study of the effects of crushing and stretching of the carotid artery, concludes that injuries of various kinds produce changes in the walls of the arteries that render the wall less resistant and dilatations are produced; but after a time the lumen may be narrowed again by a growth of connective tissue and elastic elements in the intima and also in the media; the lumen may become even narrower than before the injury. The experiments were not extended over a period of time sufficient to disclose the ultimate results.

But in angiosclerosis the compensatory proliferation of new tissue in the intima is sooner or later followed by more pronounced degenerative changes. The new tissue is not able to maintain its integrity in the face of the constant strain of the intravascular pressure and of the inadequate facilities for nutrition. Hyaline and fatty changes take place in the deeper layers of the intimal thickening and in the inner layers of the media. Complete disintegration into fatty and granular débris mixed with cholesterin tablets and crystals of fatty acids give rise to smaller and larger foci of softening that have been termed atheromatous abscesses. By extension the overlying tissue may be destroyed, and defects arise in the intima—"atheromatous ulcers"—upon the rough surface of which fibrin may be deposited. Petrification often takes place in the degenerated tissue and calcareous plates and irregular masses form in the intima and inner layers of the media. True bony tissue has also been found to develop. It is to this degenerative stage of arteriosclerosis, which is seen best in the aorta and its larger branches, that the term atheroma is frequently applied. In advanced cases the sclerotic, degenerative, and petrifying changes are present in varying degrees and produce great deformity, unevenness, and changes in the normal color of the intima and irregular dilatations of the vessels. The relation of arteriosclerosis to

aneurism and of phlebosclerosis to varicosity of the veins is elaborated under these respective headings.

Etiology.—The etiological relations of angiosclerosis are ill defined. So far it has not been possible to produce experimentally sclerosis of vessels of animals comparable to the human disease, except possibly the gelatinous nodules in the aorta that French investigators describe after the introduction of bacteria and of toxic substances with or without preceding injury to the intima; these nodules resemble the lesions of nodular arteriosclerosis. Angiosclerosis is rarely observed in animals; it has been seen mostly in old cattle and in old horses.

According to Edgren's statistical study of arteriosclerosis, syphilis, alcoholism, and old age are the predominating factors in its production. Henschen, in his criticism of Edgren's work, points out that the source of the material for such studies must be carefully scrutinized because conclusions based upon the presence of arteriosclerosis in the inmates of institutions that harbor especially syphilitics, alcoholics, or old people naturally will be one-sided and misleading. Such studies usually take no note of the form of arteriosclerosis present.

Angiosclerosis occurs so commonly in advanced years that it is generally regarded as a sort of involutional change; this is true especially of the senile form of arteriosclerosis. It is thought that the media gradually loses its elasticity; dilatation and the formation of more or less new tissue in the intima followed by degeneration take place. According to Thoma a moderate degree of thickening of the intima is frequent after the thirty-sixth year, especially in the peripheral arteries.

The period of life at which a well-marked arteriosclerosis appears and the extent that it may assume are dependent upon the natural, inborn resisting power of the muscular and elastic elements of the arterial wall and upon the amount of wear and tear to which the vessels are subjected. The tendency seen in certain families to the early development of arteriosclerosis is explained as due, at least in part, to an inherited weakness of the arterial walls. This theoretical conclusion has received as yet no confirmation in the form of demonstrable anatomical deviations from the normal in the structure of the arteries of such individuals. On the other hand, there are cases recorded in the literature of centenarians with smooth and normal vessels.

Changes similar to arteriosclerosis have been described in the vessels of children and young persons. Von Schrötter enumerates several recorded instances; Young described sclerosis of the temporal artery in a child of fifteen months; Meigs of the left coronary artery in a child of five months; Gee described aneurisms of the coronary arteries and atheromatous changes in the aorta in a child of seven years that died from dropsy and pneumonia following scarlet fever; and Chiari observed sclerosis of the aorta with typical histological changes in a boy of thirteen years, the disease being attributed to abuse of tobacco and alcohol. Seitz found seventeen cases of arteriosclerosis between ten and twenty-seven years of age out of one hundred and forty-eight cases of arteriosclerosis examined post mortem. Durante has described an instance of calcification of the inner layers of the tunica media of the pulmonary artery and the aorta in a prematurely born infant that lived only a few days. He regards this as an example of a congenital atheroma. The parental history of the infant was unknown; death resulted from peritonitis due to infection of the navel.

It is of course doubtful whether the sclerotic changes in the vessels of children and young persons depend upon a general primary weakening and loss of elasticity and contractility of the media. Special toxic and infectious influences may be at work in such cases, the sclerosis being the result of inflammatory and other lesions in the media.

Statistics show that men are more frequently affected with angiosclerosis than women. Edgren's statistics give twenty-one per cent. of arteriosclerosis in women and seventy-nine per cent. in men. Arteriosclerosis apparently develops later in life in women than in men.

Chronic intoxications and infections of various kinds are regarded generally as playing an important part in the etiology of angiosclerosis, but so far it has not been possible to make any etiological subdivisions of the disease. Among the intoxications those due to alcohol, lead, and gout are of the first importance. Tobacco is regarded by clinicians as not entirely free from deleterious action upon the arteries; Huchard thinks it exercises a special influence upon the coronary arteries. The precise mode of action of these substances can hardly be more definitely specified than that under the toxic influences degenerative changes and weakening develop in the arterial wall, especially the media. Martinotti claims to have produced changes in the renal and cerebral arteries resembling arteriosclerosis by the injection of camphor, alcohol, and turpentine.

Of the chronic infections syphilis is the most important. Edgren places syphilis first in the etiology of arteriosclerosis, which when due to syphilis tends to appear rather early in middle life. Arteriosclerosis upon a syphilitic basis does not appear to present any special features (see Syphilis of the Vessels, page 105).

Infectious diseases in general appear to exercise a harmful influence upon the muscular and elastic parts of the walls of blood-vessels. Reference has already been made to the toxic and infectious forms of angeiitis and to the production of gelatinous plaques in the aorta by the injection into animals of bacteria and toxins. The closure of the vasa vasorum by inflammatory changes in the adventitia and the outer layers of the media would surely interfere with the proper nutrition of the inner layers of the wall. Thoma has shown that the strength of the arterial wall suffers in diseases of the most various kinds.

The overfilling of the vascular system due to excessive eating and drinking and the increased pressure and strain upon the arteries in muscular work constitute another group of causes (Osler). According to Huchard and Edgren arteriosclerosis is inseparably connected with the pathogenesis of increased pressure. The relation of angiosclerosis to the intravascular pressure is seen in the distribution of the disease in the vascular system.

Arteriosclerosis sustains a double relation to renal disease. An existing sclerosis of the renal and peripheral arteries may interfere with the nutrition of the renal parenchyma to a degree that parenchymatous degeneration and connective-tissue overgrowth result. On the other hand, a primary interstitial nephritis by raising arterial pressure may lead to connective-tissue growth in the intima.

The Forms of Arteriosclerosis.—There is some confusion in the classification of arteriosclerosis. The various anatomical forms often are found connected by transitional stages. Thoma recognized two main forms, diffuse or secondary, nodular or primary. The former he regarded as due mainly to primary changes in the peripheral vessels and the capillaries and as consecutive to the increased peripheral resistance. The latter he regarded as the result of primary changes of a degenerative nature in the media, and as localized especially in those regions where the pulse wave is high and strong. Councilman holds that the diffuse form is a distinct disease associated with widespread changes in the media, and he distinguished a third form, the senile arteriosclerosis, in which the lesions are mainly degenerative, compensatory thickening in the intima being but little marked.

Senile Arteriosclerosis.—In this form the process is largely one of degeneration and calcification with but little thickening in the intima. It represents the general atrophy and degeneration of senility as they affect the arteries when even connective tissue has lost much of its power of proliferation. In this form the heart is not always hypertrophied; atrophy of internal organs may be marked. The aorta and its larger branches are dilated irregularly, tortuous and elongated, the walls in general thinner than normal, stiff, and covered by calcareous plates or the seat of cavities containing grayish-yellow, grumous material—the detritus of degenerated, necrotic

muscular and fibrous tissue. The cavities are sometimes called atheromatous abscesses; frequently the thin internal membrane is ruptured and rough spots and areas arise ("atheromatous ulcers") in the floor of which calcification may take place or thrombotic material accumulate. In typical cases the aorta and other large vessels are changed into rigid calcareous tubes, the inner surface being rough, frequently fissured, and covered by fibrinous masses. The intima has lost its glistening appearance. The resulting deformities of the affected vessels certainly warrant the name arteritis deformans which Virchow applied to the disease.

The relations of senile arteriosclerosis to thrombosis, senile gangrene, cerebral softening, and other consecutive changes in the body are discussed fully elsewhere.

Diffuse Arteriosclerosis.—This is the more important form, and in it the lesions are widely distributed, embracing all the arteries of the body. As pointed out by Councilman, contrary to the senile sclerosis, the subjects of diffuse arteriosclerosis are generally in the prime of life.

In twenty-seven cases of this disease studied by Councilman, the youngest, a negro, gave his age as twenty-three; the oldest was sixty. Most of the cases ranged between forty and forty-five; fourteen were white and thirteen colored. The negro seems disposed to this disease.

In this disease there is a typical pathological picture. Most of the subjects who come to autopsy are strongly built, well-nourished, muscular individuals. As a rule, there is no œdema either of the face or of the lower extremities. When œdema is present it comes on in the last few days or weeks of life. Heart hypertrophy is always present and may reach an extreme degree. In two of Councilman's cases in which there were no valvular lesions whatever, the heart in one weighed 850, and in the other 820 gm. The average weight was over 400 gm. The myocardium is firm and dark. Close examination often shows some degree of fibrous myocarditis, this depending on the degree of involvement of the coronary arteries in the general trouble. The heart hypertrophy may be confined to the left ventricle, but in most cases it is always associated with so much dilatation that the right ventricle also becomes hypertrophied. The dilatation may be so excessive as to affect the integrity of all the valves. Anatomical lesions of the valves are usually absent. There may be some extension of the aortic disease to the aortic valves or to the aortic segment of the mitral valve, but the thickening so produced is not generally sufficient to interfere with the functions of the valves. The supposed inflammatory changes in the myocardium described by Buhl and referred to by Thoma were not found by Councilman. The most marked changes are found in the aorta and the large arteries given off from this. The large arteries are more or less dilated, the dilatation in some cases starting in the aortic orifice and extending throughout the aorta and large arteries. This dilatation is seldom symmetrical throughout, but in addition to the general dilatation there may be here and there mere local dilatations.

The branches of the arch are sometimes relatively more dilated than the aorta. There is elongation of the vessels as well. The aorta makes lateral curves and the normal curves of other arteries are greatly accentuated. In addition to the dilatation there is a general diffuse thickening of the arteries, which is often relatively greater in arteries the size of the radial than in the large vessels. In the large arteries the intima is roughened by projecting elevations, which are frequently distinguished by differences in color and consistency. They may be of a pearly, transparent color and very hard, in both color and consistency similar to cartilage. They may be of an opaque, whitish-yellow color, and the centre soft and pultaceous. On incising such places a soft, white, mortar-like mass escapes. We may find irregular, ragged excavations, often covered with fibrin, showing that the softening has extended through the intima of the vessel during life. Similar areas of softening and degeneration may be found in the diffusely thickened intima. There may be more or less calcification which is usually confined to the projecting elevations, but this never reaches the same extent here as in the senile form. There are frequently longitudinal folds and puckering of the intima as though due to the contraction of the vessel after death.

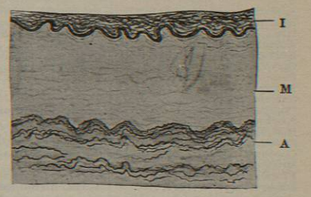

FIG. 629.—Diffuse Arteriosclerosis. Renal artery. Weigert's elastic-fibre stain. I, Intima with new elastic fibres; M, media, the seat of hyaline degeneration; no elastic elements; A, adventitia with increased number of elastic fibres. × 150.

The two essential alterations are various degenerative changes in the media and a growth of tissue in the intima. The degenerations in the media are shown in various ways. Sections of the fresh artery show some fatty degeneration, but this does not play the chief part. The most common change seems to be necrosis and hyaline degeneration (Figs. 629 and 630). The muscle cells lose their nuclei and the whole muscular coat is changed into a solid homogeneous mass. The elastic fibres between the muscle laminæ are frequently broken up and disappear; these changes probably appear early in the process. In some sections of the dilated carotid, for instance, the media as such may not be recognized, the whole artery being changed into a dense, thick mass of sclerosed connective tissue. This atrophy of the media is always best marked opposite the points of greatest thickening of the intima. The tissue composing the thickened intima consists of thick layers of dense connective tissue, which not only in consequence of the poor nutrition which it has, but also in consequence of the pressure to which it is subjected, is particularly prone to degenerative changes. The tendency to degenerative changes, however, is not so marked here as it is in the senile form.

This diffuse arteriosclerosis that Councilman describes agrees best with the form which Thoma has described as secondary arteriosclerosis, and in which he considers

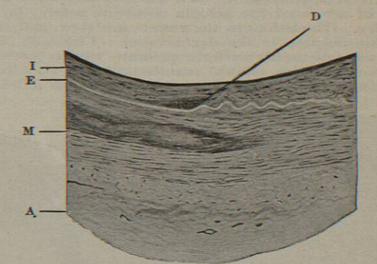

FIG. 630.—Sclerosis of Anterior Tibial Artery. Gangrene of foot from thrombosis. I, Fibrous intima; E, elastic lamina; M, media with hyaline degeneration and calcification; A, adventitia; D, beginning degeneration in intimal thickening. Hæmatoxylin and eosin. × 100.

that the changes in the large arteries are due to the resistance to the blood circulation that the diseased small arteries cause. In a paper on the conditions of the vessels in Bright's disease, which preceded his publication on the arteries, Thoma shows that there is an opposition to the passage of the blood, which is due primarily not to a narrowing of the calibre of the vessels by the thicken-