An Etiologic Concept of Atherosclerosis
Based on Study of Intimal Alterations
after Shock

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On the basis of analysis of the bibliography of animal experiments and of anatomic observations on
autopsy and surgical material from infants and adolescents who experienced shock, a new concept
of atherogenesis is formed. Changes in osmotic pressure, plasmatic dysestasis and hypalbuminemia
cause hydropic swelling of the intimal endothelial cells followed by increased permeability.
Seepage of plasma through injured endothelium results in edema and hyaline-mucoid change of the
subintimal ground substance. Lipoproteins are broken down and most of the foreign matter is
resorbed. Lipids, namely cholesterol, remain in the subintima, act as irritants and initiate the
alterations known as atherosclerosis.

VOLUMINOUS writing on the histo-
genesis of atherosclerosis has accumu-
lated. For almost half a century, practi-
cally all attention has been focused on lipid
deposits in the blood vessels. The reason for
this trend lies in the finding of lipid matter in
atherosclerotic vessels, namely in atheroma,
and in the successful production of atheroscle-
rosis by feeding cholesterol to rodents. A
thorough search of the literature leads to a
number of articles and notes—often hidden in lengthy
German essays—commenting on hyalinosis as
preceding lipodosis of the inner layers of arteries.
The expression “hyalinosis” is used for want of a
better term: the true nature of the protein or
protein-like material (albumin, globulin, lipo-
protein, glucoprotein, mucoprotein, poly-
uronide, hyalin, amyloid?) present in the sub-
intimal ground substance is not yet known.

Edema of the inner layers of the vascular
wall was first observed in 1856, by Virchow.1
He thought that the bulging of the intima is
due to increased cell size caused by intracellular
edema. Twenty years later, Koester2 and Trom-
petter3 described edema (Quellung) of the in-
timal ground substance. They assumed that the
fluid arrived in the intima through the vasa
vasorum. (The older authors did not differen-
tiate between intima and subintima but
spoke of superficial and of deep layers of the
intima, respectively.) Voigt4 stated that

mucoid quelling or hyaline degeneration was a
common finding in human blood vessels. Tor-
horst5 discussed “mucinosis” of the pulmonary
arteries. He was the first to hint that the ma-
terial deposited in the intima might originate
from the blood stream.

On the basis of these reports, a discussion
ensued about whether or not edema and mucoid
change of the intima precede lipodosis. Ribbert6
gave the sequence of events as follows: (a) in-
creased blood pressure, (b) imbibition by the
vessel wall of plasma through pressure, (c) pre-
cipitation of proteins, (d) drainage of fluid by
lymphatics, and (e) fatty metamorphosis to follow the hyalinosis. Aschoff7,8,9 subscribed to the
theory of imbibition of lipids. He thought that
hyalinosis and lipodosis develop simultane-
ously because blood plasma contains proteins as
well as fats. Rössle10 objected to the concept of
imbibition (Einpresse) of lipids. He claimed that
penetration (Eindringen) of proteins initi-
ates the vascular damage. Schürmann and Mac-
Mahon11 studied extensively the nosogenesis
of malignant nephrosclerosis. They chose the term
“dysoria” to explain functional damage to the
endothelial blood-tissue barrier with subsequent
increase in subendothelial mucoid ground sub-
stance of renal arterioles and capillaries. More
recently, Meyer12 applied the term “plasma-
pheresis” to characterize the process by which
plasma seeps through a supposedly intact endo-
thelium into the subintimal layer of the aorta.
He compared the process to the formation of an
exudate, or rather insudate, in which fine molecular noneagulable protein particles are dispersed. Unfortunately, Meyer reverts to Virchow's misconception that edema is always indicative of inflammation. Virchow\(^1\) spoke of "chronic deforming endarteritis"; Meyer\(^2\) concluded that "atherosclerosis is a reactive, productive, inflammatory, chronic process with tendency to recurrence." Certainly, atherosclerosis can develop on the basis of inflammation, arteritis. But this is an exception and not the rule.

Edema and hyaline-mucoid alterations are seen as elevated, white or pale yellow streaks and patches upon the cusps of the mitral valve, in the aorta and also in smaller vessels of children and young adults. They may be present in the inferior vena cava. The impression that such alterations are absent or rare in adults is erroneous. It is due to the fact that pathologists are satisfied with gross observations and only seldom study microscopically the intimal patches. The alterations are easily missed unless one examines a multitude of gross lesions which differ but slightly in appearance and selects also seemingly normal sectors of various blood vessels for histologic study.

The discussion as to whether juvenile and senile plaques are fundamentally different or whether they are part of the same disease process has not yet been closed. Stumpf\(^3\) examined 84 aortas: 35 from babies less than a year old, 35 from children below 15 years, and 14 from juveniles less than 20 years old. He observed in over one-half of all vessels gross patching of the aorta and, microscopically, loosening of the ground substance of the intima. About two-thirds of his patients had died of chronic infections and about one-third of the children with aortic lesions had died of acute infections. He held chronic infection to be the causative factor for vascular changes. From the study of aortas from 644 persons below the age of 16 years, Schmidtmann\(^4\) arrived at a similar conclusion but singled out tuberculosis as an etiologic factor. Zinserling\(^5,\)\(^6\) described hyalinosis, lipidosis and calcinosus in the aorta of 12 persons aged from 14 to 36 years. He found\(^7\) analogous lesions in the aorta of dogs. The three phenomena were held to be inde-
visceral vessels. Recently, Baker and Selikoff demonstrated cholesterol in hyalinized renal arterioles. Similar results might be expected from study of cerebral and splenic vessels. Hyalinosis seems to precede the deposit of lipids, regardless of the caliber of the diseased blood vessel. The etiology of alterations of various vessels seems also to be the same. Schürmann and MacMahon mentioned a great number of bacterial, serologic and inorganic toxins as possible damaging agents of renal capillaries and arterioles.

The theory that bacterial toxins play a role in the development of atherosclerosis received support from experimental data. Klotz produced noninflammatory intimal lesions by intravenous injection of typhoid bacteria. Saltykov injected rabbits with cultures of staphylococci and produced alterations in the aorta and large vessels. He believed that mucoid matter is formed locally, within the vessel wall. Anitschkow, from observations on rabbits, arrived at the conclusion that mucoid matter enters the vessels from the blood stream, together with lipids. Rinehart and Greenberg pointed out the similarities of mucoid intimal alterations in pyridoxine deficient monkeys and in juvenile human atherosclerosis. Rinehart and Abul-Haj identified abundant mucopolysaccharides in the subintima, by histochemical reactions.

Many of the conclusions reached by the investigators whose works were cited above are equivocal. Their observations are, by and large, correct. Illustrations in many of the quoted papers are inferior and lack details. Thus, it is, for example, impossible to check on Meyer's impression that the intimal endothelium covering a mucoid aortic defect is intact. Still, clarification of this particular question is of utmost importance for the understanding of atherogenesis.

Material and Methods

In performing necropsies on children and adolescents, we gained the impression that atherosclerotic plaques are more common and more numerous in youngsters who had died suddenly or after only a brief hospital stay than in other groups of juveniles. (Patients with lipid nephrosis form an exception.) Many of the young people who had been well prior to terminal hospitalization had grossly visible plaques in the aorta and in other blood vessels, as well.

These observations prompted a careful review of case histories, necropsy protocols, reports on surgical specimens and of tissue sections. Only such postmortem material was selected for this study when necropsy was performed within three hours after death. In many instances, additional tissue blocks were processed and special stains for mucin, neutral fat and cholesterol were applied.

Slides from 96 consecutive necropsies on patients aged from 6 weeks to 22 years were studied. Among these patients there were 31 who had died either from violence or unexpectedly. They were between 9 weeks and 22 years old. Tissues removed from 13 young patients who experienced shock, for example, due to perforation of the appendix, were examined. This surgical material was compared with 60 analogous specimens removed under less dramatic conditions. In both groups, the youngest patient was 4½ months old and the oldest was 23 years. Finally, the large vessels and organs of 21 patients aged between 60 and 95 years were searched for comparable vascular alterations. These patients had died from various ailments but all had experienced terminal traumatism, such as a major surgical operation, or shock, for example, from paralytic ileus. All these old persons had clinical and anatomic evidence of marked atherosclerosis.

Observations

To avoid tedious abstracts of case histories and repetitious descriptions of gross and microscopic observations, six representative cases are hereby illustrated. Cases 1, 2, and 3 form a sequence depicting the evolution of vascular alterations. Case 4 is shown as an example of comparable histologic findings in surgical specimens and also to counteract the argument that disruption of the intimal endothelium might be a postmortem change. (Where such is the case, the endothelium, or large portions of it, is lifted up in toto and not individual endothelial cells.) Cases 5 and 6 are presented to support the
statement that vascular lesions in the young and old have basically the same character.

Case 1. A 9 week old baby (R. S.) fell from a high bed two and one-half hours before admission. The child was dead on arrival at the hospital and necropsy (A-50-108) was performed promptly. The baby was well developed and normally nourished.

It had been well up to the time of the accident. Extensive bilateral subarachnoidal hemorrhage with molding of the brain was found at autopsy. Grossly, the aorta appeared normal. Microscopically, vascular lesions were present in the aorta, periaortic artery, pulmonary and bronchial arteries. Lesions might have been present in other visceral vessels but were not found in the sections viewed. (See figs. 1 and 2.)

Case 2. A 15 year old boy (W. M.) was pinned against the wall of a house by an automobile back-}

ing out of a garage. The boy was riding a bycycle. He was taken to the hospital, infused with plasma and whole blood; his wounds were treated surgically. He died 23 hours after admission and autopsy (A-50-110) was performed two hours after death. Numerous, extensive lacerations of the perineum, the scrotum, urinary bladder, multiple compound fractures of the pelvis and both legs, and severe pulmonary edema were found on necropsy. Numerous plaques were present in the ascending aorta, even more in the abdominal aorta, and also in the inferior vena cava. Microscopically, alterations were

![Aorta (X 130) of case 1. Severe laceration of the intimal endothelium. Disruption of the cell membranes, loss of nuclei of the endothelial cells. Intracellular edema. Interstitial edema of the sub-intimal ground substance. Increased metachromasia (by special stains) of the edematous tissues. Positive reactions for fat and for cholesterol (by special stains) confined to the edematous areas. The edema stops at the media. (Intimal-subintimal layer is rather narrow in an infant of this age.)](image1)

![Periaortic artery (X 550) of case 1. Hydropic swelling of endothelial cells. Adventitial edema.](image2)

seen in the aorta, vena cava, and in pulmonary arteries. (See figs. 3, 4, and 5.)

Case 3. A 22 year old woman (C. D.) died during labor from excessive blood loss due to fibrinopenia. This primigravid, primiparous woman received infusion of 500 cc. of plasma and transfusion of 3000 cc. of whole blood. (Fibrinogen was not available.) The patient had been well before and during pregnancy. Necropsy (A-50-29) was performed two and one-half hours after death. The pertinent findings were severe anemia, generalized visceral edema, and terminal infarction of the myocardial septum due to anoxia. Numerous plaques were present throughout the aorta. The microscopic picture of the
vascular lesions differed from that of other patients in the series: the process was more advanced. (See fig. 6.)

Case 4. A 41\(\frac{1}{2}\) year old girl (R. M.) experienced rupture of a gangrenous appendix. At surgical operation performed 19 hours after perforation, localized peritonitis was found. Recovery from shock and operation was uneventful. Examination of the surgical specimen (SJ-51-43) confirmed the clinical diagnosis. Microscopically, alterations were seen in a periappendiceal artery. (See fig. 7.)

Similar alterations were found in the vast majority of appendixes with perforation. The oldest patient in this group was a 23 year old woman. Her appendix was removed 24 hours after perforation. There was prolonged shock and recovery was slow. Hydropic swelling was present in several arteries within the appendiceal serosa.

Case 5. A 19 year old boy (W. R.) fell backward on the roller-skating rink, three days prior to admission and five days before death. He had been well until the accident. He was admitted with headache and vomiting, became unconscious and developed convulsions. On admission, his cerebrospinal fluid was bloody. His total blood cholesterol equaled only 80 mg. per 100 cc., and the ratio of free to total cholesterol was normal, determined by the Schoenheimer-Sperry method. At necropsy (A-49-43), the salient findings were excessive cerebral hemorrhage, internal hemocephalus, subarachnoidal hemorrhage, and pulmonary edema. Numerous plaques were present throughout the aorta and in the coronary arteries. [See figs. 8 and 9 (to be compared with fig. 10).]

Case 6. A 65 year old man (T. G.) experienced a cerebrovascular accident at the age of 59. Atherosclerosis was diagnosed clinically and confirmed by opthalmoscopy. For about a year, the patient had had complaints which, on his first visit to the clinic, prompted study for esophageal carcinoma. The diagnosis of gastric adenocarcinoma, grade III, was
made from esophageal biopsy. The patient died three days after surgical exploration. His total blood cholesterol was 180 mg. per 100 cc.; the ratio of free to esterified cholesterol was normal. At necropsy (A-51-47), extensive gastric carcinoma involving the proximal half of the stomach was found. The neoplasm extended subepithelially to the esophagus and had metastasized to the liver and the regional lymph nodes. There was severe generalized atherosclerosis. (See fig. 10.)

Figure 10, compared with figure 9, shows less metachromasia, more severe sudanophilia, about an equal amount of cholesterol, no polarizing material in either aorta. There is greater loss of cells and there is intense neoformation of connective tissue fibers. Demarcation of alterations against the media is not as sharp. Still, basically, the histologic picture is the same as that of "juvenile" atherosclerosis.

DISCUSSION

Gross and/or microscopic vascular alterations were found in all our patients who had experienced shock. Of the many investigators who described juvenile atherosclerosis but two reported aortic and mitral plaques in young persons who died after brief illness and in children who died of burns or of intoxication. Most authors named acute or chronic infectious diseases, namely tuberculosis, as atherogenic. Our investigation did not include patients who died of infections. Thanks to medical progress, little material is available for such study. If contagious diseases were responsible for initial vascular damage the incidence of atherosclerosis should steadily diminish. On the other hand, bacterial toxins were successfully used to produce intimal alterations in animals. A common denominator was found by Selye who classified trauma, hemorrhage, burns, infections and many other factors as "alarming stimuli."
In no single person who had died without having been exposed to shock were comparable vascular alterations found, in our series. In none of the surgical specimens removed were the blood vessels altered except in those of patients who had experienced severe or prolonged shock. The dividing line between the two groups of patients was clear-cut.

The importance of studying visceral vessels microscopically and of examining sections from various sectors of large vessels must be stressed. Frequently, hydropic swelling of the intimal endothelial cells of arterioles and small arteries represents the only abnormal finding. Of course, the thickness of the subintima of these vessels is negligible in comparison with that of the aorta and therefore edema and hyalinosis is not as impressive in the visceral vessels as in the aorta or vena cava. For similar reasons, comparison of experimental atherosclerosis in rodents with human atherosclerosis is difficult. In animals, hydropic swelling of the intima results, accord-
whole vascular system subsequent to injury of the intima seems to be an additional feature of shock.

It might be suggested that plasmatic dyscolloidity as such suffices to produce vascular damage through pressure changes. Anitschkow, Okunoff, and Zinserling demonstrated that bile pigment and colloidal dyes injected into the blood stream of various animals appear promptly in the vascular subintima in the same sectors of the aorta in which cholesterol deposits are found upon feeding. The phenomenon has been confirmed by Pollak and Wadler who injected intravascularly colloidal graphite and sodium stearate into rabbits. Hypoalbuminemia of shock represents another factor in the development of vascular damage: it is responsible for the pressure change and it facilitates precipitation of hydrophobic colloids, such as cholesterol. According to Pollak, albumin is the best stabilizer of cholesterol sols.

Damage to the endothelial cells facilitates seepage of blood plasma into the subintima. This results in intercellular edema and loosening of the ground substance. The process is characterized by increased metachromasia. Sometimes, intimal "cysts" are formed. Intra-cellular edema causes swelling of the cells. Their nuclei become round, spheric, and later undergo karyolysis and disappear. The edema and hyalinitosis causes thickening of the subintima. The edema stops abruptly at the media. Elastic fibers of the lower subintima become fragile and disappear. So do collagen and hyaline trabeculae. In the next phase, the reactive process of the mesenchyme takes place: hyalinitosis is followed by neoformation of connective tissue, and at the same time lipophages appear. Then, the intima proper becomes fibrosed and thickened.
Thus, the initial damage to the endothelium becomes obscured. (Compare fig. 10.) By this time, the plasma has been resorbed and only coarse particles of lipoproteinid complexes are left behind. The results of histochemical reactions for neutral fat and for cholesterol which are found extracellularly in exactly the areas which correspond to the imbibition by plasma are held confirmative for our concept. The absence of cholesterol esters can be demonstrated by the lack of polarizing material. This is further supportive evidence. Faber pointed out that a breakdown of lipoproteins in the tissues apparently is due to action of heparin. Cholesterol is first liberated and then locally esterified. Within the lipophages, cholesterol esters can be demonstrated. Cholesterol esters act as a local irritant. They initiate the process known to us as atherosclerosis. The interplay of physicochemical forces and morphologic alterations discussed by us represents the overture to atherosclerosis.

Most recently, Gianni arrived at very similar conclusions by using an investigative approach comparable to ours. He studied autopsy material and performed animal experiments with intravascular injection of cholesterol sols. He subscribes to the concept of insudation of plasma which initiates endothelial and mesenchymal subendothelial changes. He recognizes four different types of anatomic alterations depending upon the composition of the effused plasma (plasma poor in protein and lipids causing edema, plasma rich in various lipids initiating atherosclerosis, plasma rich in glucoproteins with subsequent mucinosis, and plasma with abundant fibrin causing fibrinoid degeneration of the inner vascular layers.) This classification seems too hypothetical. Gianni's correlation of the appearance of atherosclerosis after infectious diseases, in neoplastic diseases and in diabetes complicated with infectious disease follows the line of thought of other authors cited.

Physical forces within the blood stream, such as differences in local pressure, and the rate of flow determine the localization of plaques, together with structural factors, such as the elasticity, or the branching of vessels. Anatomic differences between vessels of various caliber and between arteries and veins are largely responsible for the fate of alterations. In the large arteries, the media represents, for a certain period at least, a barrier for the resorption of material deposited in the subintima. The lack of vasa vasorum in the inner layers represents another unfavorable factor for resorption.

![Fig. 10. Aorta (X 130) of case 6. Section through plaque. Marked thickening of intima and subintima. Interstitial edema with "cyst" formation. Cysts mostly located in the deeper layers. Severe loss of nuclei. Increased metachromasia; positive stains for fat and cholesterol but no polarizing material seen. Neoformation of connective tissue of subintima and also of the intima proper, the latter obscuring the endothelial layer and any endothelial damage which might have been present before. (Compare with fig. 9.)](http://circ.ahajournals.org/ctx/asst/fig/10.jpg)
ously damaged will be more susceptible to repeated insults. Also, repair will be progressively poorer.

Aschoff\textsuperscript{7,8} stated that atherosclerosis is a pathologic process superimposed on a physiologic aging process. He also pointed out\textsuperscript{49} that affinity to lipids increases with aging of the blood vessels. Björling\textsuperscript{49} studied the morphologic, tinctorial and chemical properties of vascular ground substance. He found an increased metachromasia, that is, an increase in mucoid tissues, in atherosclerotic and syphilitic aortas. Of great interest is the observation of Steinbiss.\textsuperscript{49} Medial alterations analogous to those obtained on treatment with epinephrine were produced by feeding animals dried organs. Addition of vegetables to the animal protein diet resulted in marked metachromasia of the lower subintimal layers and in a microscopic picture similar to that of experimental cholesterol atherosclerosis. Schultz\textsuperscript{48} proved that metachromasia of the ground substance increases with age but found that this process is greatly enhanced by atherosclerosis. The affinity to lipids increases parallel with metachromasia. Solowijew\textsuperscript{44,48} confirmed these observations. In our study, lipids could be demonstrated only in the atherosclerotic sectors.

Certainly all tissues change with age. There is anatomic and chemical aging. The acidity of tissues increases with age; this favors the precipitation of cholesterol. Throughout life, calcium accumulates in the vascular media. Aging of tissues is reflected in blood chemical changes. With advancing age, there is hypoalbuminemia, relative hyperbeta globulinemia, a tendency to hypercholesterolemia, a decrease in blood lipase and other enzymes. All these changes are part of the terrain for atherogenesis. Normal aging should therefore be considered in the discussion. Physiologic and pathologic aging can hardly be separated. Oversimplification of the problem of atherosclerosis should be avoided.

The question of identity of juvenile and adult or senile atherosclerosis is closely linked to the question of the degree to which hyaline-mucoid changes are reversible. Hueck\textsuperscript{47} thought that the lesions seen in children might, but need not, lead to adult atherosclerosis. Saltykow\textsuperscript{49} believed, on the basis of statistics, that juvenile lesions represent the initial stage of adult atherosclerosis. Lubarsch\textsuperscript{49} spoke of the identity of alterations in young and old. Schmidtmann\textsuperscript{14} subscribed to the same concept because of lack of evidence that juvenile lesions are reversible. Aschoff\textsuperscript{49} considered lesions in children reversible but spoke of them as the “presclerotic phase” of atherosclerosis. Our own observations on human and animal material suggest that the fate of initial, that is edematous-hyaline-mucoid alterations depends upon the localization and the extent of the injury and also upon repetition of episodes of dyscolloidity and insults to the blood vessels.

Our concept helps to explain the episodic character of atherosclerosis and the progress of the disease with advancing age. Are we reverting to the abandoned theory of “wear and tear”?” The very occurrence of juvenile atherosclerosis repudiates this theory. When we assume that atherosclerogenesis is initiated by “shock” we remain at a safe distance from the “wear and tear” theory. With the usage of the less definitive term “stress” we approach the “wear and tear” theory which implies inevitability of an aging process. Though neither shock nor stress can be entirely avoided, our efforts to mitigate or arrest atherosclerosis need not be futile. We might succeed in strengthening the intimal endothelium. We might attempt to prevent formation of lipoprotein complexes or to break down these molecules. By increasing the serum albumin level, we can stabilize the plasma colloids. We can avoid excessive deposit of irritating material, namely cholesterol, through reduction of the blood cholesterol level. The future might bring other and more effective preventive measures.

**Summary**

1. A gross and microscopic study of autopsy and surgical specimens from infants, children, adults and from old persons who experienced shock is presented. The observations are compared with material from patients not exposed to shock.
2. In all persons exposed to shock, hydropic
swelling of the intimal endothelial cells of vessels of various caliber was seen.

3. On the basis of an analysis of the bibliography and of original observations, a new concept of the etiology of atherosclerosis is formed.

4. It is being suggested: (a) that physicochemical disturbances of plasma colloids in shock initiate hydropic swelling of the intimal endothelial cells followed by increased permeability; (b) that seepage of plasma through the defective endothelium causes edema and hyaline-mucoid change of the subintima; and (c) that, after the breakdown of lipoproteins and resorption of most of the foreign material, lipids, namely cholesterol, remain in the subintima where they act as irritants and initiate the alterations which are generally known as atherosclerosis.

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