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Coronary Artery Disease

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PATHOGENESIS OF CORONARY ARTERY DISEASE

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To

Harold Brunn, M.D., and Elise Haas, whose efforts were responsible for the creation of the Harold Brunn Institute

PREFACE

Although coronary artery disease has been, and will continue to be, much written about, I believe that perhaps I will be able to say at least a few new things that might be of value to both the investigator and the practitioner in the field. I believe this chiefly because few other investigators have had the opportunity to spend half the day in the experimental laboratory working with animals and the remaining half day with patients suffering from coronary heart disease. Complementing laboratory with clinical activities for approximately three decades has given me certain perspectives concerning experimental as well as clinical data, which I could then correctly delineate. For example, if in the morning in the laboratory I peered through the microscope at the dense hard scar seriously occluding a diseased human coronary artery, then in the afternoon in my office, I could not seriously believe that my patient's thickened coronary arteries could be cured simply by his ingestion of unsaturated fats.

This conjunction of laboratory investigation with consultation practice keeps me constantly aware that coronary artery disease not only devours our laboratory animals but devastates the lives of so many human subjects. Therefore, I scrutinize each patient with this disorder, not just to confirm the sometimes isolated results I might have obtained in the laboratory, but to glean from his statements, from his actions, and from his physiological and chemical data any new clue that might be brought to the experimental laboratory. Basically, laboratory data are important for their relevance to the human situation.

Finally, no investigator having the direct responsibility for the care of seriously ill patients ever allows himself to forget that the pathogenesis of coronary artery disease is probably a multifaceted phenomenon. Fortunately, this concept prevails in our laboratory at the Harold Brunn Institute.

I should like to pay my thanks to my professional associates, Drs. Ray H. Rosenman, Sanford O. Byers, Shirley St. George, Felix Pearl, Laurence Rivkin, Leland Felton, and G. J. Van den Bovenkamp and above all to technicians Clarence Omoto, Warren Hayashi, and Marshon King who were responsible for obtaining most of the laboratory data present in this monograph. I should also like to express my gratitude to my secretary, Mrs. Vernice Carroll, whose truly remarkable administrative capacities have freed so many of us over this past decade for direct work in the laboratory. Finally, I should like to acknowledge my very deep indebtedness to Jerome M. Rosefield whose aid has been of incalculable benefit in the execution of some of the clinical studies described in this monograph.

I should like to point out that all of the original experimental studies in which I participated, and whose results are alluded to in this book, were aided by the National Institutes of Health, National Heart Institute Grants HE 00119 and HE 03429.

MEYER FRIEDMAN

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CONTENTS

I

EXPERIMENTAL STUDIES

1 DESCRIPTION OF THE NORMAL CORONARY ARTERY

Before the intimate structure of the normal coronary artery is described, perhaps it would be expedient to describe several phenomena relevant to the human coronary artery that frequently escape the conscious attention of even veteran investigators in this field.

First, the human coronary artery differs from that of many mammals in that a considerable portion of its proximal segment usually courses upon the surface of the myocardium rather than in the cardiac musculature itself. In other words, the coronary artery of most animals is sheathed in muscle, whereas a goodly length of human coronary arteries is covered only by connective tissue, i.e., pericardium.

Second, the coronary artery, although possessing an anatomic structure essentially similar to the remaining arteries of the body, nevertheless is subjected to an entirely different milieu. This milieu is one in which a contracting, shortening, and turning heart effects twisting, compressing, and distorting of the coronary artery approximately 100,000 times a day, without a single respite during an entire lifetime. Undoubtedly other arteries elsewhere also are subjected to forces besides the chronic one of systolic and diastolic displacement, but such forces are not incessantly applied as they are to the coronary arteries. Do these stresses injure the coronary artery and, if so, how frequently? We now have no way of determining this point and, as a consequence, we are a bit too inclined to overlook the probability that such stresses are regularly and frequently damaging the coronary vasculature. But much of the data concerning the pathogenesis of coronary artery atherosclerosis simply become inexplicable unless we assume that such injury and sequential repair is constantly occurring.

Third, an artery responds to almost any sort of physical or chemical injury to which it may have been exposed with a hyperplasia or replication of its surviving or still-intact remnants. Thus whether the injury is induced by transplantation,[745] by needle puncture,[367,656] by freezing,[156,434,781] by heat,[152,153,154] by exposure to electron irradiation,[514] by induced hypertension,[741] by cholesterol infiltration,[30] or by pressor amines,[233] the typical response of the tunic[152] affected is a hyperplastic one. Moreover, it is only when an artery is involved in an autoimmune, toxic, or infectious process that this essentially hyperplastic or replicative phenomenon is also accompanied by blood-derived inflammatory cells.

Fourth, and perhaps most important of all, each of an artery's three tunics (i.e., the intima, media, and adventitia) responds in its *own characteristic manner* to a given injury. For far too long, an artery has been generally considered as a homogeneous tissue in its pathogenic responses, despite the fact that not only anatomic studies but also pathologic data have clearly indicated that the various arterial tunics may differ from each other almost as much as renal tubular epithelium differs from glomerular endothelium. In short, contiguity of tissues does not ensure their homogeneity.

THE TUNICA INTIMA

The intima of the normal coronary artery is similar to that of most other arteries in the body. In the normal adult animal, the intima is extremely thin and consists almost exclusively of endothelial cells, most of which directly abut[98] upon the internal elastic lamina or are separated from the latter by an actual or potential subendothelial space (Fig. 1-1). Although it is true that an occasional spindle cell[201] or unidentifiable mononuclear cell[619,620,764] or a smooth muscle cell[66,620,762] might lie in this subendothelial space between endothelial cell and internal elastic lamina, such cells are quite rare[201] and may directly derive from the tunica media via traumatically induced or naturally occurring fenestrations of the elastic lamina.[764] For all practical purposes then, the normal intima is only a layer of endothelial cells lying upon a network of closely knit elastic fibers separating it from the tunica media. Accordingly the terms "intimal thickening," "intimal sclerosis," etc., can be used correctly only to describe some sort of tissue which usually appears to lie internal to, or upon, the internal elastic lamina but which may have had its cellular provenance from some other than coat the original intima.

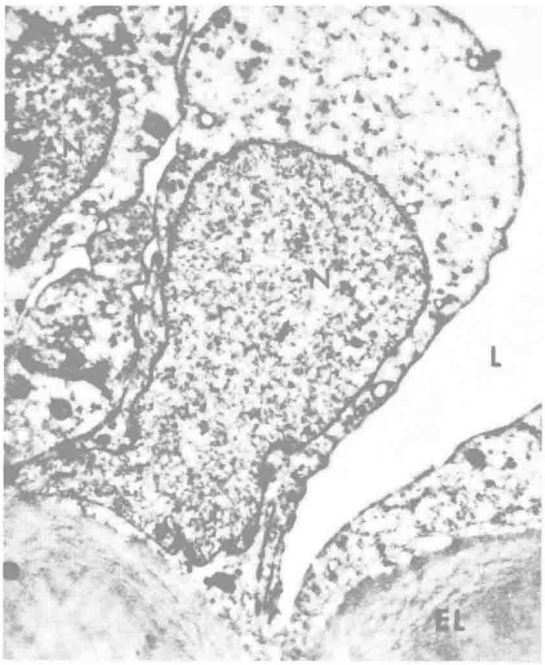

Fig. 1-1. Normal endothelium of rabbit artery (×13,000). (EL, internal elastic lamina; L, lumen of artery; N, nucleus of endothelial cell). Note that these endothelial cells rest *directly* upon the internal elastic lamina. (Electron microphotograph reproduced with permission of the editors of the American Journal of Pathology and R. C. Buck, the author, from R. C. Buck, The Fine Structure of the Aortic Endothelial Lesions in Experimental Cholesterol Atherosclerosis of Rabbits, *American Journal of Pathology*, (34:897, 1958.)

The cells composing the intima of most normal animals form a continuous layer and possess a pleomorphic type of nucleus and a cytoplasm rich in vesicular or tubular structures but poor in mitochondria and Golgi membranes.[98] These cells typically have a few cytoplasmic filaments but do not exhibit the electron-dense bodies and basement membrane possessed by smooth muscle cells.[314,620] It would appear that most endothelial cells, besides allowing the diffusion of various gaseous and solid ions and molecules, also are capable, either by phagocytic or by pinocytic means, of removing various macromolecules and particles present in blood flowing past them[98] or from the fluid bathing them in tissue culture studies.[468]

The endothelial cells of the intima have been observed to multiply by mitotic division in both in-situ[554,653,742] and in-vitro studies.[468] Although Altschul,[17,19] on the basis of his morphologic studies, and Lewis,[508] on his tissue culture observations, believed that endothelial cells could give rise to smooth muscle cells, Koide et al.[468] never observed such transition in their own culture studies of tissue taken from either normal or atherosclerotic intimas, nor have any other observers recorded this phenomenon. It is the writer's opinion that this does not occur. Similarly, it is very unlikely that a smooth muscle cell ever can give rise to an endothelial cell because no such transformation has been observed either in the intact artery or in tissue culture studies.[468]

The normal intima, almost everyone agrees, derives its gaseous and solid nourishment

from and only from the luminal blood, primarily by processes of diffiusion, but, as mentioned above, various nondiffusible substances also are capable of uptake by the endothelial cells.

Finally, and perhaps of considerable importance for the succeeding discussion of the involvement of the intima in the atherosclerotic process, endothelial cells (or cells thought to be endothelial in nature) in tissue culture, unlike spindle or smooth muscle cells, exhibit the capabilities of becoming both pleomorphic[469] and ameboid in movement.[468]

THE TUNICA MEDIA

The tunica media of the aorta and also of the coronary artery contains three different types of cells, two different kinds of fibers, a ground substance containing the preceding cellular and acellular elements, and in its middle and outer portion a probable network of capillaries.

The most prominent cell is of course the smooth muscle cell, which is approximately five times as long as it is wide. The cell has its greatest diameter in its midportion wherein a nucleus (also elongated) is situated and tends to taper at both ends. It thus resembles and is frequently called a spindle cell. It is easily recognized and identified if scrutinized with the electron microscope because of its possession of myofilaments, dense bodies, and basement membrane.[314,620]

As already mentioned, whereas there is some evidence that an endothelial cell may give rise to a smooth muscle cell, there is no evidence whatsoever that the bulk of smooth muscle cells present in the media derives from the living endothelial cells. Also no valid documentation exists to suggest that a mature muscle cell can give rise to additional new muscle cells. Rather it would seem that some species of precursor cell (a specialized form of fibroblast?) exists in the media which is capable of evolving into a mature smooth muscle cell. At this time, no histologic differentiation has been made between those muscle cells of the media making up the "tension muscle" fascicles of the arterial wall[44] and those composing the "ring muscle" fibers[241] except that the former appear to be attached to the elastic fibers.

Fibroblasts and macrophages are the remaining two types of cells that are present in the tunica media. The fibroblasts probably are not totally similar, at least not in their potential capabilities. Thus it seems that the elastic fibers are derived from some form of fibroblast in the media,[485] but the collagen fibers also appear to be derived from fibroblasts.[44] This family of medial fibroblasts also appears to be responsible for the formation of the mucoid ground substance in which all fibers are embedded. The presence of macrophages is rarely detected in the normal tunica media, but since they can be seen in a media that is diseased, it has been assumed that they probably existed therein prior to the disorder. It is of course possible that these cells entered the media only after the latter's receipt of an injury.

Elastic fibers, as mentioned above, appear to be derived from fibroblasts and are composed of fibrils chiefly containing the very durable, water-insoluble, acid- and alkali-resistant elastin.[485] These fibrils exhibit neither organization nor orientation in the fiber,[485] a fact which probably accounts for the great extensibility but limited tensile strength of the elastic fiber.[44] The fibers lie directly over each other, forming fenestrated membranes to which muscle fibers of the tension type are attached.[44] There is a particular aggregation of these elastic fibers at the inner and outer limits of the media forming the internal and external elastic laminae respectively. Usually the internal appears as the most prominent of the two membranes.

The collagen fibers which abound in the media of all arteries, also as mentioned above, are derived from fibroblasts. But it is doubtful whether the latter are the same cells that also produce elastic fibrils. Unlike the elastic fibers, collagen fibers possess very limited extensibility but far more tensile strength. They form the tissue that most surely preserves the essential integrity of the arterial wall. It is these fibers too that, when necessary, substitute for frayed elastic fibers and degenerated

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smooth muscle cells.[562] It is of course axiomatic that the contractility and extensibility of an arterial vessel is inversely proportional to the degree of such collagen replacement of the original components of the vessel wall.

The ground substance in which these cellular and acellular elements of the media lie consists essentially of two mucopolysaccharides.[375] One of these, chondroitin sulfate, probably serves to cement the collagen fibers to each other; the other, hyaluronic acid, is believed[375] to act as a lubricant for the movement of these same fibers.

It is uniformly agreed[319,463,492,553,853] that the outer two-thirds of the media is supplied with capillaries emanating chiefly from the vessels of the tunica adventitia but that the inner third of the media, like the intima, receives its nourishment directly from the vascular lumen. If, however, the artery becomes severely *enough* sclerosed, all these same investigators again agree that the inner portion of the artery wall also will receive capillaries derived from the adventitial vasa vasorum.

There is no evidence at this time[44] that there are functioning lymphatic vessels in the tunica media of even the largest blood vessels. The tunica media however is furnished with a relatively rich nerve supply.[71,476] These autonomic nerve fibers apparently enter the media along with the vasa vasorum and form an intricate plexus which covers the entire muscular coat and also extends between the individual muscle fibers to terminate apparently within the cytoplasm of the muscle cells.

THE TUNICA ADVENTITIA

This tissue, totally sheathing the tunica media with its mass of blood and lymphatic vessels, autonomic nerves, fibroblasts, mature connective tissue cells, and occasional fat cells enmeshed loosely in a network of collagen fibers, serves chiefly as the source of blood-borne nourishment and neurogenic communication to most of the media. But in addition, this tissue also serves as an ever-vigilant "sentinel" to promote the immediate movement into the media of fibroblastic tissue with its own accompanying capillary blood supply whenever the tunica media and probably the tunica intima have sustained a derangement too great for their own in situ resolution or repair. Perhaps no more reliable principle concerning the reaction of an artery to injury exists than the following one: Whenever the structure or the nourishment of any part of the tunica media is seriously deranged, cellular and capillary ingrowth immediately ensues from the adventitia. Such ingrowth can and frequently does extend to and involve even the intima.

2 INDUCTION OF VARIOUS TYPES OF EXPERIMENTAL ATHEROSCLEROSIS

THE REQUISITE ROLE OF CHOLESTEROL IN EXPERIMENTAL ATHEROSCLEROSIS

Almost all forms of experimentally induced atherosclerosis require the ingestion of some cholesterol (with or without the concomitant feeding of fat) if regular, reproducible lesions are to be obtained. Although scattered reports[181,757,884] have appeared suggesting that the ingestion of certain kinds of fat alone may induce atherosclerotic lesions, major opinion[465,768] favors the dietary inclusion of cholesterol as an essential requisite for the occurrence of significant atherosclerotic lesions.

In other words, before the discovery of the hypercholesteremic and atherogenic properties of ingestion of cholesterol in the rabbit,[31,814] no truly adequate or satisfactory model for the study of experimental atherosclerosis existed in the laboratory. Since this epochal discovery, many other species also have been found to be quite susceptible to cholesterol feeding, hypercholesteremia and atherosclerosis following in its wake. Thus, chickens,[175,803] certain genetically susceptible pigeons,[135] dogs,[758] monkeys,[155,565] guinea pigs and hamsters,[18,338] and baboons[769] also exhibit varying degrees of hypercholesteremia when cholesterol is added to their diet. The rat however is notoriously resistant to the development of both hypercholesteremia and atherosclerosis despite the fact that it has been reported[528] to exhibit occasionally small, spontaneously arising atherosclerotic lesions. However, even when huge amounts of cholesterol and fat are fed to this species, leading to extreme degrees of hypercholesteremia, the structure of its coronary arteries still remains essentially unaffected[793] although the lumen of some of these vessels may be occluded by thrombi. This failure of even the severely hypercholesteremic rat to exhibit significant atherosclerosis actually furnishes the investigator a clue to one of the prime factors underlying the atherogenic process—a clue which will be discussed fully below.

Some investigators have protested the use of the cholesterol-fed rabbit as a laboratory model for the study of the causes and the pathogenesis of human atherosclerotic lesions. They have pointed out that such animals usually have exhibited not only a very high level of serum cholesterol (i.e., values frequently higher than 1,000 mg of cholesterol/100 ml of serum) but also an excess deposition of cholesterol in almost all tissues besides the arteries. These same investigators also have pointed out that the common complications of the human atherosclerotic plaque, such as intercurrent hemorrhage, mural thrombosis, calcification, ulceration, and final thrombotic occlusion with infarction, rarely occur in the experimentally induced plaque.

At first glance these objections to the use of dietary-induced atherosclerosis as a working tool in the laboratory to investigate all the ramifications of the human atherosclerotic lesion seem formidable ones. However, such objections may be more relevant in respect to our present methods of working in the laboratory than actually demarcating the ex-

perimental from the human lesion. For example, most investigators prefer to induce atherosclerotic lesions quickly, and knowing quite well that one of the factors influencing the rate of growth of these lesions is the height of the serum cholesterol, they purposely seek to elevate the serum cholesterol of their animals as high and as rapidly as they can, thus reaching levels far higher than those observed in most human subjects and also leading to a relative "cholesterol saturation" of the animal's extravascular tissues. But atherosclerosis nevertheless can be induced in laboratory animals, as Malinow et al.[529] and also Beckel[53] demonstrated, even though they reduced the amount of dietary cholesterol ingested so greatly that the average serum cholesterol of the animals never exceeded that found in the average human subject. If investigators would be willing or patient enough to wait for even the fraction of the time it takes the human individual to develop significant lesions in order to obtain animal lesions, we might easily manage to do the latter without inducing a monstrous degree of hypercholesteremia.

In regard to the remaining objections cited above, it should be pointed out that if our total experience with human atherosclerosis were confined to children and adolescents, we also would be constrained to believe that the plaque seen therein, like that of the cholesterol-fed rabbit, never is subject to internal hemorrhage, grossly detectable intercurrent mural thrombosis, calcification, ulceration, or occlusive thrombosis with infarct formation. Our present methodology then in reproducing animal lesions after only several months of experimental feeding could well be responsible for some of the curious and rather inexplicable cul-de-sacs with which investigators are confronted.

Although it would seem obvious, indeed common sense, to the beginning student in this field to believe that the excess cholesterol found in the plaque of the cholesterol-fed animal originally came from the cholesterol ingested in the diet, this fact had to be and perhaps is still being confirmed. Of course, from the time that Anitschkow and Chalatow[34] first announced the atherogenic potential of dietary cholesterol, almost all researchers believed that it was the absorption, transportation, and seepage into the arterial wall of this ingested cholesterol that initiated and promoted the growth of the atherosclerotic lesions which were observed. However, when it was discovered that both normal and atherosclerotic arterial tissue could synthesize cholesterol[711,727] and phospholipid,[600,868] suspicions naturally arose that perhaps, even in the cholesterol-fed animal, the cholesterol present in its plaques might have arisen because of excessive in situ synthesis. However, it was demonstrated long ago by Hueper[417] and by Duff et al.,[204] and again more recently by Biggs and Kritchevsky[67] and Dayton[182] that the excess cholesterol present in the plaque of the rabbit fed excess dietary cholesterol derives from the latter and is not manufactured in situ.

It has been particularly unfortunate that, because the animal and human body synthesize cholesterol so readily and in daily amounts that far exceed the usual dietary intake of this sterol, a goodly number of investigators still remains unconvinced that dietary cholesterol, particularly in the human subject, carries much atherogenic potential. This is especially odd because some of these very same investigators, although eschewing the possible pathogenicity of chylomicronous cholesterol (i.e., dietary cholesterol in plasma transit), nevertheless differentiate the pathogenic properties of cholesterol carried in the α-lipoprotein from those of cholesterol carried in the lower-density β-lipoproteins.

Actually cholesterol when added to the diet in such small amounts that it doesn't elevate the plasma cholesterol[529] still will induce spontaneous atherosclerosis and also lead to marked intensification of the lipidization taking place in experimental thromboatherosclerosis.[273] No observations so clearly point to the probable differences in atherogenic potential existing between dietary cholesterol and that endogenously synthesized as those describing the fate of cholesterol when it is injected in the crystalline or chylomicronous form and when it is injected in soluble lipoprotein form.[114,410] Thus lipoprotein cholesterol, whether injected into subcutaneous tis-

sue or into arterial tissue, unlike crystalline or chylomicronous cholesterol, quickly disappears and is noninflammatory. That various forms of cholesterol may vary (depending upon their physicochemical state) in their period of residence in arterial tissue should occasion no surprise. For example, after the brilliant studies of Faires and McCarty[235] we accept the fact that, whereas sodium urate exists in both an amorphous and microcrystalline state, it is only the presence of the latter in a joint that induces acute gout. Moreover, although a relatively large amount of amorphous urate elicits little joint reaction, very small amounts of this same chemical when injected into a joint in its microcrystalline state create an inflammatory havoc. Similarly, I am proposing that the daily exposure of arterial tissue to relatively small amounts of cholesterol barely suspended in a chylomicronous mass is far more atherogenic than far larger quantities of the same substance when it travels in blood relatively securely bound to various phospholipid-triglyceride-protein molecules having considerable solubility. This belief is not founded upon the ease with which a centrifuge separates chylomicronous cholesterol from lipoprotein cholesterol but upon the above-cited tissue studies. They demonstrate that once chylomicronous cholesterol escapes into the wall of an artery, it persists immeasurably longer and creates more damage in that tissue than do most forms of lipoprotein cholesterol (including even the cholesterol enmeshed in some classes of β-lipoprotein).

Now after these preliminary and rather general remarks, a more specific account of various types of experimentally induced atherosclerosis will be given.

SIMPLE DIETARY INDUCTION OF ATHEROSCLEROSIS IN THE RABBIT: The Classical and Standard Model of Experimental Atherosclerosis

THE PATHOGENESIS OF THE VERY EARLY PLAQUE

More than 50 years have elapsed since Anitschkow and Chalatow,[34] discovered that the (cholesterol-fed) rabbit easily became hypercholesteremic, even atherosclerotic. Moreover, with the possible exception of the fowl, no animal responds to dietary cholesterol so invariably and relatively so consistently with both a plasma elevation of cholesterol and the appearance of intimal lesions as does the rabbit. And in this era in which rapid developments and results are desired, it can be easily understood that these propensities of the rabbit strongly favor its employment. Sometimes, a slightly cynical observer might be tempted to believe that this rapidity of pathologic development has so intrigued us that we prefer the rabbit for our approach to the study of the human disease despite the fact that this animal differs radically from the human subject, not only in its metabolic disposition of exogenously derived cholesterol but also (and in perhaps very important respects) in its vascular reaction to cholesterol therein. Indeed it is a still undecided question (and one which may take a few decades to answer) whether a study of this animal's dietary-induced atherosclerosis is diverting us from the true pathways whereby human atherosclerosis may be totally understood and combated. Even if this is true or partially true, it seems reasonable enough to believe that at least some facts having possible relevance to the human situation may be obtained. I cannot help but wonder though, if, instead of the rabbit, Anitschkow and Chalatow had attempted to feed the cat, for example, excess cholesterol, whether we now would be so presently intrigued with this sterol.

Within a week, the rabbit given a daily ration of 1 to 2 Gm of cholesterol (usually together with an unsaturated fat) exhibits a five- to tenfold increase in its serum cholesterol. Sometime between 4 and 10 weeks of continued feeding, the serum cholesterol reaches an average of 1,000 to 3,000 mg/100 ml of serum, where it more or less remains if the special diet is continued. If the special diet however is discontinued, the serum cholesterol does not immediately fall. Usually it requires 3 to 6 months[268] to return to a normal value due to the continued entrance of the excess cholesterol stored in various extravas-

cular tissues (e.g., the liver). But during this waning phase of hypercholesteremia, excess cholesterol is still capable of entering a previously established plaque. Failure to realize this last fact in the past has led to misinterpretations of the intrinsic lipid metabolism of such a plaque.[148]

The excess cholesterol present in the serum of the cholesterol-fed rabbit is carried[424] mostly in a moderately low-density lipoprotein (S_f 10–30), and although such serum may appear quite turbid at times during the cholesterol feeding regimen, its average triglyceride content is rarely elevated significantly.

It should be mentioned at this point that the excess cholesterol occurring in the serum of the cholesterol-fed rabbit (quite early in the feeding regimen) begins to "leak out" of the blood vessels. This phenomenon for example can easily be seen by inspection of the iris of such an animal. As early as 3 weeks after the addition of cholesterol to the diet, iridic exudates of lipid cholesterol (see Figs. 2-1*A* and *B*) already begin to appear.[260] This same phenomenon of cholesterol leakage[114] also takes place in samples of rapidly growing connective tissue placed in the abdominal cavity of a hypercholesteremic rabbit. Thus it appears quite likely that throughout the entire body of such an animal, excess cholesterol is leaving the bloodstream very early and in increasingly greater amounts to accumulate in such disparate organs, for example, as the liver and the heart. It is doubtful however that such excess deposition of cholesterol takes place in the brain of the hypercholesteremic rabbit.

The deposition of such leaked cholesterol also takes place in the walls of the blood vessels of the hypercholesteremic rabbits and can easily be detected in scattered portions of the thoracic segment of the aorta 21 to 28 days after cholesterol feeding. Leakage usually first occurs in this region primarily because it is this segment of the aorta which has been demonstrated[267,606,641] to be most permeable to colloidal substances present in the luminal blood.

Almost all investigators[30,20,254,355,505a,619,720,764] agree that the internal elastic lamina is involved in the beginning vascular lesion of the cholesterol-fed rabbit. In this connection quite recently, Kramsch et al.[473] observed that, after injection of labeled cholesterol, the latter preferentially accumulated about or upon the elastic membranes of the arterial wall. Indeed Parker[619] thought he could detect morphologic changes in the structure of this membrane 24 hours after cholesterol had been added to the diet, but this has been denied by other electron microscopists[762] and was not noted, or at least not reaffirmed, by Parker himself in a later study.[620]

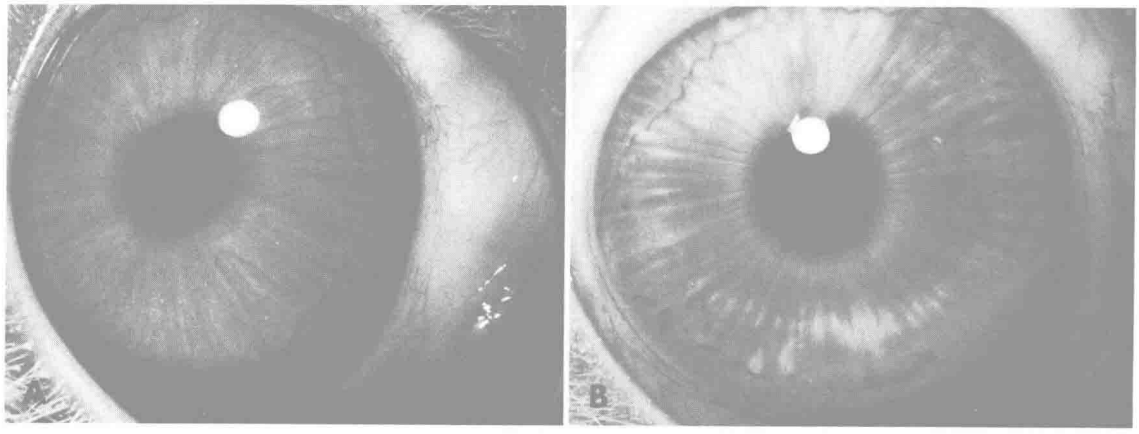

Fig. 2-1. *A.* Iris of normal rabbit. *B.* Iris of rabbit fed excess cholesterol for 28 days. The iridic extravasation of excess cholesterol/lipid substances (cotton-wool-like white areas) along the course of the iridic vessels can be seen. (*Figure 2-1A is reproduced from the American Journal of Physiology,* 197:842, 1959, *with the permission of the editors.*)

The initial defects noted in the internal elastic lamina are its swelling, changes in tinctorial qualities, fraying, and fragmentation.[202,355,720,764] The nature of the swelling is not known, and it has variously been considered to be due to penetration therein of lipid (cholesterol extravasated from the blood serum[764]) or even accumulation therein of mucopolysaccharide substances.[321,590,873] Indeed Gero et al. concluded that such excess mucopolysaccharide led to excess retention of lipid—a finding however not able to be confirmed by Böttcher et al.[79] I suspect that such swelling and also the later deterioration of the elastic lamina is due to excess penetration of free cholesterol, a phenomenon that would not be identified by Sudan staining.[698] However, once the endothelial cells become detached from the internal elastic lamina, the material lying between them usually takes the Sudan stain. In such areas too the underlying internal elastic lamina is badly damaged.

Concomitant with or even preceding these changes in the internal elastic lamina, swelling and some deposition of lipid cholesterol is observed in the endothelial cells.[202,355,619,764] Because very few investigators had performed serial-section and time-phase studies of the very early plaque (i.e., 21 to 28 days after institution of the cholesterol feeding regimen), the exact precedence or sequence of endothelial, subendothelial, and elastic laminar involvement had not been determined.

These latter types of studies however have been performed recently in our laboratory and the results obtained[254] allow one to determine this sequence. Thus when a series of very young aortic plaques measuring 0.5 mm in diameter or less together with a circumferential segment of grossly appearing, normal intima was serially sectioned, the youngest or least-developed portion of the plaque was observed at the latter's periphery where the lesion "melded" into the surrounding still-intact intima. In these sites, the first signature of the atherosclerotic process was the deposition of lipid/cholesterol (as determined by Sudan IV) in, above, or below the first elastic lamina (see Figs. 2-2*A* and *B*). Such deposition was not accompanied necessarily by any apparent gross change in the lamina itself or in the endothelial cells (and certainly not in the underlying medial cells). But as more central and presumably older sections of the lesion were viewed, not only did the internal elastic lamina become even more severely encumbered with lipid cholesterol, but also it showed (see Fig. 2-3*A*) morphologic and tinctorial aspects of deterioration and frank fracture. Moreover, the endothelial cells (whose cytoplasm normally on cross section is barely detectable, cf. Fig. 2-2*A*) became swollen and engorged with identical sudanophilic debris (see Fig. 2-3*B*).

At the central portion of the lesion itself (see Figs. 2-4*A*, *B*, and *C*), the elastic lamina,

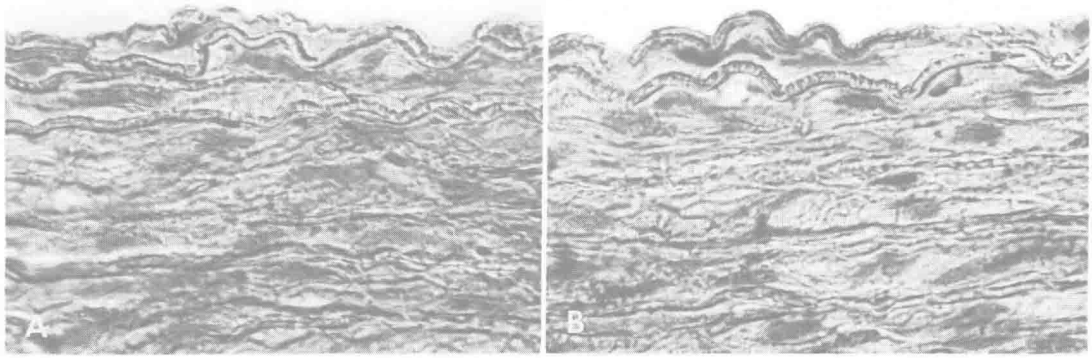

Fig. 2-2. Sections of aortas of normal rabbit and rabbit fed excess cholesterol for 21 days (Sudan IV, (×400). *A*. Aorta of normal rabbit. *B*. Aorta of rabbit fed excess cholesterol for 21 days. Here, beginning, minute accumulations of excess sudanophilic substances (black) can be seen lying beneath the internal elastic lamina and the second elastic lamina.

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