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Department of Pathology, Columbia University, New York, N.Y. 10032

A tentative molecular-biological hypothesis for arteriosclerosis*)

H. Kaunitz

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I.

Inasmuch as the complications of arteriosclerosis are the most frequent causes of death in the industrialized world, studies of its etiology have been the subject of intense interest. In humans the condition is morphologically characterized by the occurrence of atheromata in specific arteries and by myocardial infarctions. At present the majority of the examiners believes that arteriosclerosis is a disease induced by disturbances of lipid metabolism (cholesterol) and other risk factors ("multifactorial" disease).

The "lipid theory" is mainly based on these undisputed observations. 1) The developed atheroma contains large amounts of cholesterol; 2) there is a positive correlation between elevated serum cholesterol and triglycerides and the incidence of myocardial infarctions; 3) congenital (and other) hyperlipidimias are associated with vascular lesions; 4) feeding of cholesterol to some species (especially rabbits) leads to vascular deposits of cholesterol (so-called "experimental atherosclerosis").

Innumerable papers have been published in which the attempt has been made to prove that arteriosclerotic lesions are induced by infiltration of the arterial wall by cholesterol. The theory seemed to be shaken by the observation that high-density serum lipoproteins (HDL) containing about 20 % of cholesterol showed a negative correlation with the incidence of myocardial infarcts. But the low-density serum lipoproteins (LDL) containing 50 % cholesterol are positively correlated with infarctions; now they have become the culprits.

Gradually, a number of facts have been clear which are hardly compatible with the lipid theory. The exogeneous cholesterol (present in the nutrition) and the endogeneous cholesterol (mainly produced by liver and intestines) are in homeostatic equilibrium (1, 2); the daily turnover is about 2000 to 3000 mgs regardless of the amount present in the diet. This is one of the reasons why the Food & Nutrition Board of the National Academy of Sciences does not attribute importance to the cholesterol content of the diet (3).

*) Read on the occasion of receiving the Alton-Bailey award of the North Central Section of the American Oil Chemist's Society.

Early atheromatous lesions show normal lipid content compared with the surrounding tissue (4, 5); later a tissue develops similar to that seen in various granulomatous lesions consisting of large amounts of cholesterol, collagen, polysaccharides, calcium and other minerals. In lesions such as the tubercle and the gumma, this tissue has protective properties, and takes part in the repair process. It is probable that this tissue has similar properties in arteriosclerosis (6).

Experiments feeding animals cholesterol have little value since atheromata and myocardial infarctions are not observed; in contrast to humans cholesterol deposits are present in all organs; finally the diets are entirely unphysiological.

Concerning the relation of hyperlipidimias to arteriosclerosis, familial hypercholesterolemia is usually cited as the paradigm of a hyperlipidemia inducing arteriosclerotic lesions. However, some authors believe that the vascular lesions in familial hypercholesterolemia differ from those seen in arteriosclerosis; in other hyperlipidimeas it is by no means sure whether the hyperlipidemias are a cause or a consequence of the condition (7).

The lipid theory cannot explain why the atheroma and the myocardial infarctions are observed only in humans; why the lesions occur only in certain parts of the arterial bed (aorta, coronaries, brain and leg arteries); why the lesions show spotty distribution and why the lesions (although in some fashion present throughout life) induce clinical symptoms at a "programmed" time. Reduction of serum cholesterol by dietary or other means has no influence on the course of the disease. Altogether the lipid theory is probably obsolete.

The assumption that arteriosclerosis is a "multifactorial disease" may be derived from a misunderstanding. The theory is based on the fact that environmental factors such as smoking or over-eating or such conditions as hypertension and diabetes are unquestionably associated with more advanced stages of the lesions. However, the same is true for other specific diseases. For instance, tuberculosis is trongly influenced by climatic and nutritional factors but it is not a multifactorial disease. Most of the so-called risk factors merely modify the intensity of the basic lesions, while elevated levels of serum cholesterol are not a risk factor at all, but are a consequence of the condition.

II.

The revolutionary development in molecular biology during the past decades have introduced new concepts about the aging processes[1]). Since the relation of arteriosclerosis to aging phenomena has been emphasized, at least since Virchow (8), it may be rewarding to ask whether the chemical and structural changes known to exist in aging arteries are sufficient to explain arteriosclerotic lesions, or whether arteriosclerosis encompasses features which necessitate the assumption that it is a disease sui generis. The high lipid values of arteriosclerotic tissues are by no means specific for this condition but are found in aging tissues in general. This has been

[1]) Dr. Maria Huryn of the "Human Health Science Libraries" of Columbia University conducted a routine computer search of publications about the relation of DNA changes to aging processes. She found between 1971 and 1980 479 publications (in English and German).

demonstrated in studies of serum cholesterol levels in older people (9), in analyses of "bulk" tissues (skin adipose and connective tissues [10]) and particularly in analyses of normal human aorta at various ages (11).

The question of whether the human arteriosclerotic lesions can be fully understood as part of the normal aging process or whether additional factors suggest a more specific disease has been discussed at length. Blumenthal (12) believed it to be essentially a consequence of aging, while Bierman (13) is more in favor of a specific disease process. One of his arguments is the fact that animals although exposed to the same environmental conditions do not develop the morphological signs of the human condition. However, this argument is by no means convincing because aging processes in humans and animals differ sharply (e.g. in their life span). The observation that arteriosclerosic symptomatology varies greatly in different human populations can be explained by genetic and environmental modifications of the lesion. Such biological variability does not require the assumption of a disease. Altogether it seems permissible to conclude that the arteriosclerotic lesion is essentially part of the normal aging processes.

Burnet and White (14) believed that aging processes must be related to changes in the cell nucleus, and later Hayflick (15) expressed the current feeling that "changes occurring in the genetic program of individual cells seem to be the most tenable hypothesis to explain fundamental causes of aging".

Even an abbreviated review of the ideas which have been developed about the relationship of aging to changes in the genetic material would exceed the limits of this discussion. A summary of the various "genotropic" theories of aging prepared by G. M. Martin (16) is shown in table 1.

Table 1. George M. Martin; Advances in Pathobiology V. 7, p. 6, (1980); reproduced with the permission of the author and the Thieme-Stratton publishers.

Selected genotropic theories of aging

I. Theories emphasizing modifications in gene structure:
   - A. Intrinsic mutagenesis
   - B. Protein synthesis error catastrophe (via abnormal DNA polymerase)
   - C. Cross-linking and free radicals
   - D. Autoimmunity (mutational or recombinational origin)
   - E. Slow virus (mutational or recombinational origin)

II. Theories emphasizing modifications in gene expression:
   - A. Neuroendocrine clocks, including the pituitary "death hormone" hypothesis
   - B. Progressive transcriptional repression
   - C. Isoenzyme shifts
   - D. Allelic exclusion
   - E. Codon restriction, including theory of tRNA hypomethylation
   - F. Specific post-translational midifications of protein
   - G. Alterations in protein turnover
   - H. Terminal differentiation
   - I. Autoimmunity ("unmasking" of antigens)
   - J. Slow virus (derepression)

For the clinician, the relations to autoimmunity and extrachromosomal subcellular organisms are particularly interesting.

Aging is associated with drastic immunological changes (17, 18). On the one hand the lymphocytes undergo changes which reduce their immunological competence. On the other hand, all tissues show changes which make it difficult for the immune system to recognize them as self. The tissues may be changes by "intrinsic mutagenicity". The altered DNA probably induced the formation of deficient proteins which have antigen-like character; these could provoke antibody formation, and chronic inflammatory changes. It is not unreasonable to assume that changes of this sort play an important part in the development of aging phenomena including the arteriosclerotic lesions.

One of the main discoveries of molecular biology is the demonstration that the genome contains independent (or semi-independent) organisms. In Novick's (19) words, the cell is "an ecological niche occupied by a variety of subcellular, submicroscopic organisms – organisms whose structure and reproductive dynamics are so profoundly different from those of cellular forms that they should probably be assigned to a new taxonomic kingdom". In addition to "slow viruses" (Gaydusek (20)), plasmids (Lederberg (21)) and virons (Diener (22)) have been described (the latter two predominantly in prokariotic cells). The appearance of these organisms in the cell can be traced to the constant exchange of genetic materials between cells ever since they came into existence (Archer (23)). This process is one of the fundamental forces in evolution.

The extrachromosomal organisms show enormous variability and specificity; some authors have suggested that they could be responsible for organ specificity of the lesions, and their programmed appearance. This theory is supported by the fact that slow viruses are ubiquitous; they are the product of host-virus interaction formed by evolutionary processes (Burnet (24)). They may have incubation periods of several decades, at the end of which clinical symptoms may appear.

III.

If one accepts the premise that arteriosclerosis is part of the aging process, an explanation of its pathogenesis on the basis of the mechanisms discussed can be attempted. The increased lipid values are at least partly related to the lipid changes observed in aging tissues. The composition of the arteriosclerotic lesion suggests on the one hand the presence of autoimmune processes and on the other hand indicates that (similar to granulomatous tissues) the lipid accumulation is part of the adaptive processes developed in response to the molecular-biological changes temporarily counteracting the destruction of the vascular wall. The organ specificity and the programmed appearance of the clinical symptoms can be explained by the action of the extrachromosomal organisms of the genome. These processes may be supported by the unfaithfulness of DNA transcription with advancing age.

This sketchy attempt to find an approach to the understanding of the symptomatology of arteriosclerosis on the basis of age-related molecular-biological phenomena suggests that arteriosclerosis is part of the normal

human evolution. Inasmuch as the belief is widespread among biologists that all structures developed in normal evolution confer advantages to the species ("teleonomy" (25)) one may ask about the deeper meaning of arteriosclerosis for man.

The continuing evolution of the species is possible only if old individuals are removed in order to create living space for those in their reproductive years. Therefore, aging must be considered to be a necessary adaptive phenomenon. Population growth in the industrial societies is mainly controlled by two mechanisms, namely malignant growth and arteriosclerosis. In that death from arteriosclerosis is probably preferable to that from cancer, arteriosclerosis may confer advantages even to the individual.

Summary

In view of the fact that complications of arteriosclerosis are the most frequent causes of death in industrialized societies, its etiology is of enormous interest. The widely held lipid theory (detrimental effects of cholesterol) has been attacked because it cannot account for such facts as the homeostatic relationship of endogenous and exogenous cholesterol; for the "normal" cholesterol content of the early atheroma; for the distribution of the lesions, their spotty occurrence and their "programmed" appearance. Arteriosclerosis is part of the normal processes of aging which are related to molecular-biological changes. Autoimmune processes and the effects of extrachromosomal organisms of the genome (viruses, plasmids, viroids) are clinically of interest. Arteriosclerotic lesions are probably influenced by autoimmune processes; the variability and specificity of the non-chromosomal organisms may explain the location of the lesions; the end of the incubation period of the organisms may be responsible for the programmed appearance of clinical symptoms. The lipid changes are probably part of the adaptive mechanisms counteracting the rapid destruction of the vessels following the DNA alterations. Arteriosclerosis is part of normal evolution.

Zusammenfassung

Im Hinblick darauf, daß Komplikationen der Arteriosklerose die häufigsten Todesursachen in den Industrieländern sind, ist ihre Ätiologie von enormer Bedeutung. Die weit verbreitete Lipidtheorie (besonders die Annahme von cholesterinbedingten Schäden) kann nicht aufrechterhalten werden, da sie viele Tatsachen nicht erklären kann. Hierher gehören z. B. die homöostatische Beziehung zwischen exogenem und endogenem Cholesterin; der „normale" Cholesteringehalt des frühen Atheroms; die charakteristische Verteilung der Läsionen sowie das sozusagen „programmäßige" Auftreten der klinischen Veränderungen. Arteriosklerose ist ein Teil der normalen Altersprozesse, die mit Veränderungen des Genoms einhergehen. Von klinischem Interesse sind dabei besonders Autoimmunprozesse und Veränderungen der extrachromosomalen Organismen des Genoms (Viren, Plasmide, Viroide). Die spezifischen Effekte dieser Organismen könnten die charakteristische Verteilung der arteriosklerotischen Läsionen erklären, und das Ende ihrer Inkubationszeit könnte vielleicht für das mehr oder weniger programmäßige Auftreten der klinischen Komplikationen verantwortlich sein. Die Lipidveränderungen sind wahrscheinlich ein Teil der Adaptionsvorgänge, die der rapiden Zerstörung der Gefäße nach dem Auftreten der DNS-Veränderungen entgegenwirken. Arteriosklerose ist ein Teil der normalen Evolution.

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Author's address:

Dr. Hans Kaunitz, Columbia University, 630 West 168 Street, New York, N.Y. 10032