Editorials

Current Trends in Atherosclerosis Research

DURING the past two decades the field of arteriosclerosis has expanded tremendously; not only in terms of growing interest and expanding research but also in understanding the nature of the process. We recognize today that atherosclerosis is the hub of the arteriosclerosis problem. Once it is conquered, a tremendous dent in morbidity and mortality rates will follow, and the average life span will be greatly lengthened.

Let us see wherein this progress lies. It lies first of all in rejection of the view that arteriosclerosis is merely aging which is inevitable and irreversible and, more important, it lies in the acceptance, instead, that it is a disease which is reversible and, we are convinced, preventable. Basically, it is a metabolic disorder involving lipid-cholesterol-lipoprotein metabolism. The theory upon which the work of the Michael Reese group is based considers that, when dealing with population groups, altered lipid-cholesterol-lipoprotein metabolism is engendered by a luxus of calories, lipid and cholesterol in the diet over the life span. This acquired rich and unbalanced diet, particularly in the sedentary, with its high fat content influences the metabolism of lipid-cholesterol-lipoprotein and so sets the background for the ready genesis of atherosclerosis in the population. Deficiencies of some vitamins and amino acids may accelerate atherogenesis. Certain diseases, habits, stresses, genetic traits and local factors, such as vascular trauma and vascular infections, may act as triggers in individual cases. Hypertension, too, is an accelerator of atherosclerosis. But basic to all of these triggers and accelerators, in most cases at least, is the dietary pattern over the life span, consisting of an excess of calories, lipid and cholesterol. There is no doubt that atherosclerosis develops more readily in certain abnormal blood vessels than in normal ones, but we hold the view that it depends here too on the character of the lipid-cholesterol-lipoprotein metabolism.

On this basis further studies must be directed along three principal lines, namely: (1) clinico-pathologic, (2) epidemiologic and (3) experimental. The first two supply the background of atherosclerosis; they pose the problems to be tested. In the experimental studies we put questions derived in this way and seek to obtain answers concerning etiology, pathogenesis, treatment and prophylaxis. After detailed analysis and adequate confirmation in the animal, we are prepared to verify our concepts by cautious probes in man. This has been the modus operandi of the work of our group in the last two decades. It is my considered judgement that only by such a broad perspective can the problem of arteriosclerosis be conquered. This approach, plus care in designing the research program and care in interpreting its results, will avoid fruitless, as

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contrasted with useful, bickering and "theorizing" (and "idle speculation") which divert so much energy from the primary task of filling in gaps in our knowledge.

The study of atherosclerosis brings together investigators from many disciplines and points up the trend toward narrow specialization which has crept into medical science recently. Appreciation of the views of persons from other disciplines and understanding of the methodologies and "jargon" of the multiplicity of disciplines essential for understanding atherosclerosis will go as far as any single ordinary discovery in accelerating our conquest of this disease. It definitely points up the need of overcoming the defects inherent in excessive specialization without loss of its benefits. Group research is one answer; a group which combines many talents can accomplish much, when supplemented by brilliant individualistic effort. Who amongst us knows which bit of knowledge or, more likely, which combination from many disciplines will unlock the closets where the solutions of atherosclerosis are hidden? It follows, therefore, that we desperately need a meeting of minds, a return to broader perspectives in science, a counterbalance to the trend to specialization in research.

Clinicopathologic studies have had a dominant role in atherosclerosis for many years, they helped define the correlation of this vascular disorder with other human diseases. Morphologic pathology has been useful in this regard when it recognized that its examination revealed only the anatomic character of this vascular process. From the anatomic examination one can only conjecture the dynamic biochemical, biophysical and physiologic processes which, over the lifetime of the deceased, led to the necropsy findings. The findings at autopsy must not be mistaken for the living process.

Clinical studies have been useful too in outlining the manifestations and sequelae of atherosclerosis, as well as the circumstances under which they become apparent. A moment's reflection will convince one that there is a vast domain of subclinical atherosclerosis that cannot now be definitely revealed by present methods of clinical study. Clinical manifestations and sequelae must not be confused with the disease itself, and procedures affecting the former must not be wrongly interpreted as necessarily reflecting effects upon the basic pathogenesis of the disease itself. The value of alleviating detrimental manifestations and of avoiding unwanted sequelae is obvious, but this does not necessarily mean getting to the bottom of the problem. Tests, even elaborate ones, and the factors altering the tests, do not necessarily reveal the pathogenesis, treatment or prophylaxis of the disease. It is not from the manifestations nor from the sequelae that the answers will come, but only from an understanding of the total organism in its environment on the one hand, and the biologic process in living cells on the other. And, by the way, it is necessary to remind oneself constantly, over and over again, that changes in the blood do not always reflect the changes occurring within the living cells, nor the adaptations of the entire organism.

A great deal of information is obtainable from the study of man in his natural environment by methods which have proven so effective in the infectious and contagious diseases and which have been fruitful in the science of ecology as far as plants and animals below man are concerned. Man is of different ethnic origins, of two sexes and of various ages. In the world today, and even in the U. S. A., man's environment is extremely variable as regards climate, occupation, mores, diet and other stresses. This too is true of earlier periods of man's existence. Some of this data can be procured from available archeologic and, anthropologic studies. More can be gotten, especially in recent years, from vital statistics, death certificates and census figures. Field studies need to be developed. A concerted attack in an expanding amount needs to be developed to pluck out the information buried in these rich sources of data. This will depend on correlations of differences obtained. By going from the study of the individual to that of large groups and by using the statistical approach based on probabilities, we may be able to derive as exact mathematic leads to
the factors resulting in atherosclerosis, as is derived by the physicist and chemist when dealing with populations of molecules in different environments. Of course, epidemiology applied to atherosclerosis is a young and virgin field. But it is vigorous and already has made important contributions. The information available has pitfalls for the unwary. But with time, diligence and skill, these can be recognized and discounted. Concentration by properly trained scientists in this underdeveloped discipline should change the trickle to a veritable bonanza of new, needed, vital information, from which questions can be put to the experimentalists to get answers from their animal studies.

The Experimental Approach

The greatest impetus to the problem of atherosclerosis has come recently from the experimental approach in the animal laboratory. This type of approach has three fundamental advantages: (1) The experiment can be designed to answer specific questions. (2) Controls can be run to exclude extraneous influences and, by using large enough samples and by random selection of "aliquots," statistically significant changes can be distinguished from sampling errors. (3) The lesions of atherosclerosis themselves can be studied in all its stages, rather than some secondary manifestation or sequela or a presumed associated index.

It goes without saying that experiments must be properly conceived and executed. A mass of information can come from properly conducted animal experiments such as concern: (1) the role of dietary and other ingested materials, (2) the effect of various microorganisms resident in the gastrointestinal tract, (3) the influence of hormones and other humoral and neurogenic regulators of bodily function, (4) the intermediary metabolism of lipid, cholesterol and phospholipids, their kinetics, energetics and enzymology, (5) the biology and metabolism of the blood vessels, (6) the transport of fatty substances in the blood and tissues, etc.

Much information has already been gained but many gaps remain and new problems have arisen as old ones were solved. Thus, the revelation of differences in biologic response of different arterial beds, as for example between the coronary arteries and the aorta, has posed the problem of the cause of this difference. Many findings in man, especially as to sex, have been confirmed and analyzed in animals and new insight into its mechanism obtained. The role of age and species differences has received growing attention. Some therapeutic and prophylactic potentialities have been revealed so that some investigators may feel that animal experimentation has all the answers to atherosclerosis. Far from it. The mere fact that species differences do exist demand that all animal observations of significance must be reexamined in the species we are interested, in man. Otherwise ghosts may be created which fade in the piercing light of clinical experience.

Summary

Obviously, crystallization of information concerning atherosclerosis will come only by the proper free interplay and adequate fusion of the three major approaches to the problem, epidemiologic, clinical and experimental. We are getting to our goal—but we have not reached it yet. We have a motif, the life span unbalanced luxus diet, rich in calories, fats and cholesterol. We must look into other aspects, as for example: (1) the causes for localization of lesions in particular sites, (2) the causes for intimal ulceration, (3) the influence of hemorrhage and thrombosis, (4) the influence of physical and psychic stresses. These are, as it were, decorations to beautify the motif, they must not be mistaken for the motif itself.

We have come a long way along the road to the solution of the problem of atherosclerosis in the last two decades. The goal is dimly glimpsed through the haze ahead. But we are not there yet, considerable labor on the part of many, carried out in a truly scientific atmosphere still lies ahead. But the reward will more than repay the effort still to be employed.

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