HEMODYNAMIC BASIS OF ATHEROSCLEROSIS

with Critique of the Cholesterol-Heart Disease Hypothesis

Second and Expanded Edition

Meyer Texon, M.D.

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Hemodynamic Basis of Atherosclerosis
with Critique of the Cholesterol-Heart Disease Hypothesis - Second and Expanded Edition

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To my wife, Ami
To Stephen Texon
To Sylvia and Thomas S. Rogers
To my grandchildren,
Raphael Samson Texon
Robert Samuel Rogers
Jessica Lauren Rogers
Jason Benjamin Rogers

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FOREWORD
TO THE SECOND EDITION

Dr. Meyer Texon has made many important contributions to the pathogenesis of atherosclerosis. He has dedicated his unusual scientific abilities to studying the role of hemodynamics in the production of atherosclerosis. His insights are unique and his data are very pertinent. A lifetime of biomedical research is presented in a lucid and convincing manner in this second edition of *Hemodynamic Basis of Atherosclerosis.*

In the development of atherosclerosis there are many factors that contribute to the ultimate lesions which cause major circulatory problems. These factors include metabolic pathways which result in cellular, subcellular and molecular changes. Different cells participate in forming the lesions which include mononuclear cells which are blood monocytes, endothelial cells and platelets. The products of these cells and the lipids contribute importantly to the aberrations.

What has been generally neglected in studying the pathogenesis of atherosclerosis are the physical factors of the circulation and in particular the structure of blood vessels and the effects of the forces of blood flow on the structure of the layers of tissues that form blood vessels. We pay a great deal of attention to physical factors which affect the structures and functions of our anatomy in producing abnormalities. Thus, much interest is spent on muscles, joints and skin but little on the physical forces of dynamic systems such as the circulation.

Included in the pathogenesis of atherosclerosis are the physical forces. Hydromechanics are a major component of the circulation. These mechanics are influenced by the gross structure of the circulatory system. Atherosclerosis is more common in segments of the circulation which have particular relationships to large and medium sized blood vessels. It is quite likely that physical forces contribute significantly to the lesions.

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PREFACE
TO THE SECOND EDITION

During the last 15 years the need for a second edition of this work has become increasingly necessary for several reasons.

Firstly, a basic understanding of the cause, nature, and natural course of atherosclerosis is not sufficiently recognized or understood by the general public and by many physicians.

Secondly, in spite of numerous epidemiological studies, lipid research studies and clinical trials there is still no unequivocal scientific evidence that reduction of cholesterol levels or any of its fractions by diet or drugs influences the pathological process or lowers the risk of atherosclerotic vascular disease in the total population. Critical analysis of these studies reveals statistical flaws, improperly drawn conclusions, and unwarranted extrapolations. Statistical associations per se do not constitute scientific proof of causal relations, and statistical significance does not always correlate with clinical significance. Questions are answered not by authority but by experiment. One crucial experiment can demolish all statistics and speculation. Yet, the National Institutes of Health, the American Heart Association, the National Cholesterol Education Program, the media, the drug companies, the food industry and others in the medical establishment are "selling" the American people this medical fallacy, claiming to relate diet and cholesterol in a causative sense to coronary heart disease.

Thirdly, ongoing studies of blood flow patterns, vascular geometry, and the endothelium have established the effect of the laws of fluid mechanics—hemodynamics—as the primary causative factor in the localization, inception and progressive development of atherosclerosis.

The time has come to change course and to place the cholesterol-heart disease hypothesis in a holding pattern while more promising directions for atherosclerosis research—hemodynamic, molecular, cellular, immunological, and

heredity—are explored.

We may look forward to the control or modification of blood velocity and other relevant hydraulic conditions that cause atherosclerosis.

We may also look forward to control or modification of the response of the endothelium at the cellular level to the hydraulic factors that cause atherosclerosis. We may then retard the development of atherosclerotic vascular disease and consequently extend the human life span.

Meyer Texon, M.D.

ACKNOWLEDGMENTS
TO THE SECOND EDITION

Major funding for my basic research in hemodynamics and atherosclerosis since its inception in 1955 was provided by the Fan Fox and Leslie R. Samuels Foundation, New York, for which I am deeply grateful.

I am also deeply appreciative of the encouragement I received from my peers and the many researchers who recognize the validity of the hemodynamic basis of atherosclerosis while noting the lack of conclusive evidence to support the Diet-Cholesterol-Heart Disease Hypothesis.

Once again I express thanks and gratitude to my wife, Ami, whose sustained interest in my research helped me challenge conventional wisdom by applying the principles of logic and scientific findings to establish scientific proof and truth.

Finally, I want to thank the publishers and their editors Jung Ra, Daniel Fitzsimons, and Conor Ivory for their helpful suggestions and whole-hearted cooperation .

FOREWORD
TO THE FIRST EDITION

Claude Bernard wrote, "We are all fallible when facing the immense difficulties presented by investigation of natural phenomena." It is evident that some are more fallible than others. It is also evident that some branches of medical research offer more difficulty than others in avoiding fallibility.

Knowledge essential for effective clinical practice has not been easy to acquire. Only patients can instruct physicians; but where observations cannot be made on patients, recourse must be had to studies on other species. Such studies are based on animals living free in nature or, more usually, restricted in captivity. The overwhelming majority of the studies are artifactual, particularly when carried out on caged mammals. The studies involve inducing infections, toxic states, or nutritional disorders under conditions presumed to resemble those that occur in human disease, but they clearly never resemble them closely.

Although today we consider bedside teaching essential, there was no formal clinical teaching anywhere on the European continent, except at Leiden, until 1745. In that year (many of the Leiden faculty had moved to Vienna), ward rounds were begun in Vienna under van Swieten. Kanilfeld began this kind of teaching at Pavia in 1780, von Plenciz at Prague in 1781, Frank at Gottingen in 1784, and Hufeland at Jena in 1793. De Rechefort, who should be remembered for having introduced electroshock in the treatment of depression, is known for having originated clinical teaching in France around 1780. The rich early history of bedside teaching in Great Britain revolves mainly about the great hospital medical schools, starting with Guy's in 1723. Unlike the medicine throughout much of Europe, German medicine remained tied to dogmas until beyond the middle of the nineteenth century, except for the teaching by Frank at Gottingen and Hufeland at Jena.

Despite the growth of interest in bedside medicine in most of Europe, its teaching was inexact and ill-directed until the remarkable developments of the post-Napoleonic years at Paris and the corresponding period at Vienna. The discovery of percussion by Anenbrugger in Vienna and its promotion by Corvisart in France was followed by the discovery of auscultation by Laennec and the subsequent growth of physical diagnosis under the French physicians Louis, Bayle, and Andral, the last of whom brought the microscope and the chemistry laboratory into the service of bedside medicine. Physical diagnosis reached new heights a little later under Skoda in Vienna.

Despite these notable advances, clinical medicine could not develop assurance by bedside studies alone. It was not until Bichat and Cruvilhier in France, and later Rokitansky in Vienna, gave bedside observation the support of pathological anatomy that clinical medicine reached greatness. Bedside medicine and postmortem anatomy fed each other's growth and development, a symbiosis that unfortunately has been lost sight of in recent decades. (The close relation between pathology and medicine was recognized at Harvard as recently as 1912, when Henry Christian went from hospital pathologist to Hersey Professor of the Theory and Practice of Physic at Harvard and Physician-in-Chief of the Peter Bent Brigham Hospital.)

Gross pathology could not, however, establish etiology (except in trauma) and was also deficient in elucidating progressive states of disease. The development of pathological histology and bacteriology in the second half of the nineteenth century helped in these directions, for these disciplines remained basically patient oriented. Nevertheless many erroneous ideas resulted from the artifacts inherent in their use. The development of physiology and physiological chemistry, largely in Germany, also began slowly to enter the picture, but their influence on bedside medicine was for years small and their contributions were intermingled with some very stubbornly maintained erroneous theoretical formulations.

Among the interesting findings in chemistry was one made in 1903 by Winterstein, one of the great chemists of the time. He showed that there was no such thing as pure cholesterol more than a day or two old, when made pure it changed quickly to several dozen other compounds. This has been repeatedly verified since that time. A decade later the Russian Anitshkow stated that when he fed cholesterol to rabbits they developed atherosclerosis and that the dietary cholesterol caused the atherosclerosis; his report was received in some quarters with astonishment but for the most part only with indifference. This error was resurrected two decades later in the United States. Timothy Leary's monograph on atherosclerosis (Arch Pathol 17:434, 1934) praised the Russian theory and presented in its support a series of important-sounding irrelevancies, embel-

lished with some gross errors. He wrote:

> Any metabolic agent capable of producing atherosclerosis must have been an article of diet from early times, since atherosclerosis has been found in mummies. The substance is a necessary part of every animal cell, forming, from Starling's concept, the stable groundwork of the cell cytoplasm. As far as anyone knows no cholesterol is synthesized by the human body. All of the supply is ingested. The most urgent demands for it come at times of most rapid cell formation. Egg yolk is intended for the embryo. Milk is intended for the infant. It is interesting to note that Wells, in his "Outline of History," records that it was relatively late in the evolution of primitive man that he developed what Wells calls "the rather unnatural use of animal's milk as food." The high blood cholesterol found in pregnant women marks the mobilization of this substance for the needs of the fetus in utero. Man is the only animal that ingests eggs and milk* throughout its lifetime. Man is also the only animal, as far as is known, which dies in early life from coronary sclerosis, and which acquires atherosclerosis almost universally in advanced life.

This restatement of Anitshkow's theory evoked even less approval, if that is possible, than the first. Leary, like Anitshkow, ignored the fact that what he fed was a mixture of two or three dozen compounds and not cholesterol per se. The journalistic tone of his concluding statements and his grossly inadequate understanding of nutrition and biochemistry evoked scorn as often as indifference.

We know that much of the cholesterol in the blood and tissues is synthesized in the body, some of it in the blood vessels themselves. Today we also know that cholesterol purified every day before being administered to animals does not cause atherosclerosis and that oxides that form when cholesterol is exposed to air for a time do. The recent review by Mann (N Eng J Med 297:644-650, 1977) should dispose of the diet-cholesterol theory of atherosclerosis. It probably will not; the "mysterious viability of error" commented on by Francis Bacon in 1605 can be counted on to prevail in official dicta for years to come. The notion has become a petrifact, a word used by Spengler to describe stubbornly defended error. It may never be demolished, however strong the evidence against it. The petrifact has continually received vociferous support in irresponsible statements by journalists and spokespeople for foundations and official agencies. These statements maintain that high dietary cholesterol intakes in the industrialized nations have initiated an explosive worldwide epidemic of heart disease. Statements of this sort are reprehensible (however, unintentionally so). Although the number of cases of coronary heart disease has increased in this century, A. E. Harper (J Nutr Ed 9:154, 1977) has shown that when the statistics

*The popularity of milk is far from new. It should be remembered, for instance, that Clement of Alexandria (third century A.D.) called the Christians *galaktophogoi*. For a discussion of the symbolism of milk in Christian dogma, see Eisler, R. Orpheus the Fisher. London: Watchkins, 1921, p. 62 et seq. [footnote added].

are corrected for the aging of the population, there has been no increase in the disease. In fact, there has been a steady decrease that started long before significant numbers of the susceptible population began to be concerned about the notion that cholesterol in the diet causes atherosclerosis.

How can errors due to indifference to artifactual factors be avoided? History provides the answer to this question. Physicians since the time of Bonet and, more strikingly, of Morgagni have used postmortem examination of their patients as a first step in clinical investigations because the examination of patients dead reveals more than the examination of patients living. Meyer Texon has used this approach and thereby provided us with a mass of unselected postmortem material on the subject. The demonstrated occurrence of the atherosclerotic lesions at bends, branchings, bifurcations, and fixed points of arteries—all areas of distorted blood flow—calls attention to the primary role of hemodynamic factors in the genesis of atherosclerosis. (An observant naturalist might have reached the same conclusion, having been struck by the fact that the only place the carp develops significant atherosclerosis is at a bend of 135° in its aorta. This experiment of nature should not have been so long ignored.) Although the ways in which hemodynamic forces stimulate the smooth muscle cells of the media to increase in number, rearrange themselves, and migrate remain incompletely defined, it must be concluded that the development of atherosclerosis is a hemodynamic phenomenon. The next step, already initiated by Texon, is the experimental production of atherosclerosis in various species according to the principles expanded in this book. After that, attempts can be made to mitigate these effects.

Meyer Texon's book, as a nonartifactual study of human atherosclerosis, stands out as a basic text of all research on the subject.

Mark D. Altschule, M.D.
Harvard Medical School

PREFACE
TO THE FIRST EDITION

In 1954 I wrote a book entitled *Heart Disease and Industry* (Texon, 1954), which consisted of my clinical experience with 100 consecutive workmen's compensation cases of individuals who claimed that their heart disease was related in a causative sense to industrial conditions or incidents as described. In 78 of the 100 cases the diagnosis included arteriosclerotic heart disease due to coronary atherosclerosis (Texon, 1959). After critical analysis of the pertinent factors and findings in these cases, I concluded that coronary atherosclerosis occurs in the working population in the same manner that it occurs in the entire population.

The compelling conclusions were also drawn that the radix malorum is atherosclerosis which frequently pursues its natural course to produce myocardial infarction as a result of progressive coronary occlusive atherosclerotic disease, and that atherosclerosis is not significantly influenced by external factors such as rest, exertion, emotional stress, or nonpenetrating chest trauma. I recommended that a nonoccupational accident and sickness disability benefits insurance law be applied to heart disease so that all questions of time, place, and causal relation could be eliminated (Burchell, 1966). In 1954, after presenting a paper on heart disease and industry at the Second World Congress of Cardiology and the American Heart Association in Washington, D.C., I was invited by Dr. Paul D. White to become a member of the Committee on the Effect of Strain and Trauma on the Heart and Great Vessels of the American Heart Association, serving as a member of the subcommittee on physiology and pathology. In order to study coronary heart disease firsthand, I became a member of the Department of Forensic Medicine at the New York University Medical Center and an Assistant Medical Examiner of the City of New York, under the direction of Dr. Milton Helpern, the late Professor and Chairman of the Department of Forensic

Medicine and Chief Medical Examiner of the City of New York.

My duties as a Medical Examiner included investigations at the scene of death in the many and varied circumstances that come under the jurisdiction of the Medical Examiner's office. My duties also included the pathological examination of hearts and coronary arteries of individuals of all ages who had died of heart disease as well as those who had died of other causes. I visited the laboratories of Dr. Stanley Durlacher in New Orleans and Dr. James Paterson in London, Ontario to observe their methods of tissue preparation and examination. I spent long sessions in discussions with Dr. Paul D. White, Dr. Howard Sprague, and others on the committee. My studies at the autopsy table included blood vessels in all areas of the circulation—gross observations, microscopic sections, innumerable serial sections, varied histological staining techniques, and photographs of both gross and microscopic specimens. The basic pathological findings in the atherosclerotic lesions were identified as progressing from the earliest intimal thickening to the occlusive plaque, including the variations resulting from fibroblastic proliferation, lipids, intramural hemorrhage, and thrombosis.

In pondering the bewildering mass of clinical and pathological data (Rindfleisch, 1872), I found atherosclerosis in both men and women, in relatively young as well as elderly persons, in hypertensive as well as normotensive persons (Moyer, 1971), and in lean as well as obese individuals. Notwithstanding available studies of the statistical association of atherosclerosis with lipids, diet, age, sex, hypertension (Brest and Moyer, 1974), race, occupation, smoking (Astrup and Kjeldsen, 1974), nutritional status, trace elements, enzyme systems (Zemplenyi, 1974), hormones, and emotional stress, my data indicated that the causal relation of these factors, either singly or in any combination, to atherosclerosis was not thereby proved or demonstrated. A statistical association per se does not constitute scientific proof of a causative mechanism. I became convinced that the primary causative factor or mechanism for atherosclerosis is a common denominator operating in all cases and that it determines the presence as well as the absence of atherosclerosis in all cases and in any given case.

In the fall of 1955, all the parts of the puzzle fell into place when I attempted to explain the localization of the atherosclerotic plaque. I returned to the autopsy specimens and reviewed my data from the standpoint of the laws of fluid mechanics in relation to the forces generated by flood flow, with emphasis on the biologic response of vessels with various geometric vascular configurations and different patterns of blood flow.

The puzzle was solved. I found that atherosclerosis occurs at the segmental zones of diminished lateral pressure produced by the forces generated by the

flowing blood. I accumulated more specimens to demonstrate the lesions at zones of curvature, branching, bifurcation, tapering, and external attachment. In December 1955, after completing the routine autopsy work of the day, I presented my findings to Dr. Helpern and the staff at an informal conference. I emphasized and demonstrated the hydraulic conditions and the basic laws of fluid mechanics that are relevant to the development of atherosclerosis. I was encouraged to continue accumulating more specimens and anatomical proof for the hemodynamic basis of atherosclerosis. In April 1957 I presented the concept in the Ether Dome of the Massachusetts General Hospital at Medical Grand Rounds with an introduction by Dr. White. The first publication (Texon, 1957) appeared in March 1957. In 1958 the research was awarded the Hektoen Silver Medal of the American Medical Association for an exhibit at the annual meeting held in San Francisco.

The relation of the laws of fluid mechanics to human circulation and in particular to the development of atherosclerosis was becoming increasingly apparent. I consulted with Dr. Richard Skalak, James Kip Finch Professor of engineering mechanics and Chairman of the Department of Civil Engineering and Engineering Mechanics at Columbia University. Mathematical analysis of blood flow and computer studies of velocity, wall shear stress were instituted for various patterns of flow. Localized areas of diminished lateral pressure in the theoretical models uniformly correlated with the localization of atherosclerotic lesions found in the human circulatory system.

It occurred to me that if a normally straight vessel were altered to become a curvature with other conditions held constant, additional support for the hemodynamic basis of atherosclerosis could be achieved. I then consulted with Dr. André Cournand and was referred to Dr. Jere R. Lord, Jr., who in turn referred me to Dr. Anthony M. Imparato. The surgical competence of Dr. Imparato led to a series of experiments in which atherosclerotic changes were produced in dogs by surgical alteration of their vascular configurations.

The hemodynamic basis of atherosclerosis has become a subject for reports, papers, chapters, meetings, and symposia both in this country and abroad. This book is the record and product of my research effort in identifying the effect of the laws of fluid mechanics as the primary causative factor in the development of atherosclerosis.

Meyer Texon, M.D.

ACKNOWLEDGMENTS
TO THE FIRST EDITION

In the preparation of this book, I have received help from many sources. It is a pleasure to acknowledge the initial research grant-in-aid of the National Heart Institute in 1958 (H-3590). I wish to express my sincerest thanks and gratitude to The Fan Fox and Leslie R. Samuels Foundation for the major financial support of this work by establishing The Fan Fox and Leslie R. Samuels Cardiovascular and Hemodynamics Laboratory in the Department of Forensic Medicine at the New York University Medical Center. In this laboratory additional pathological findings and correlations confirmed the original work and led ultimately to the publication of this volume. Additional financial aid in support of this research effort was provided by the Swift Newton Research Fund, the Dr. and Mrs. Henry Raphael Gold Research Fund, the Metzger-Price Research Fund, the Alan W. and Therma E. Jones Research Fund, the Emanuel Frank Foundation, the Mark Lipsky Research Fund, and the Harry A. Kurnitz Research Fund.

I am especially appreciative of the encouragement and help I received from the late Dr. Milton Helpern, Professor of Forensic Medicine at New York University Medical Center and Chief Medical Examiner of the City of New York, who witnessed the beginnings of this research effort and generously provided source material and advice. Because he was a recognized authority in pathology, his scientific endorsement and agreement with my findings were most supportive. I am deeply indebted to Anthony M. Imparato, M.D., Professor of Surgery at New York University Medical Center, for his cooperation in the experimental dog preparations. His surgical competence in altering vascular configurations provided a basic scientific support for causally relating blood flow patterns to the localization of atherosclerotic lesions.

To Richard Skalak, Chairman and James Kip Finch Professor of Civil Engineering and Engineering Mechanics at Columbia University, I express my warm-

est thanks for his deep interest and help by applying his expertise in fluid mechanics, computer science, and mathematical analysis to identify various patterns of flow with respect to velocity, shear stress, and wall pressure. My glass model hydraulic systems and pathological specimens provided data that uniformly correlated with his theoretical mathematical computations.

To Mark D. Altschule, M.D., Professor Emeritus of Medicine at Harvard Medical School, I owe a great deal. His rare combination of wisdom, satire, and wit pervaded many discussions we held regarding this research. From the outset we agreed that scientific truth must be stated without equivocation and without regard to its effect upon any interested parties.

To my colleagues Dr. Yong-Myun Rho, Deputy Chief Medical Examiner, Dr. Dominick J. DiMaio, Chief Medical Examiner, retired, and Dr. Elliot M. Gross, Chief Medical Examiner of the City of New York, as well as Dr. Sidney Weinberg, Chief Medical Examiner of Suffolk County, I want to express my sincere thanks for their cooperation and encouragement, especially while the data from human pathological specimens, glass hydraulic models, and experimental vascular preparations in dogs were being correlated in my hemodynamics laboratory.

For the scientific line drawings, I am indebted and deeply obligated to the late Sol Nodel who graciously applied his talent as an artist and illuminator. To my sister, Frances C. Texon, who passed away while this book was in its later stages of completion, I owe thanks for her many expressions of devotion. She continued in the family tradition of solidarity and encouragement fostered by my late parents Morris David Texon and Eva Texon.

Mary Cahibbo, my secretary, deserves special thanks for her invaluable help, diligent efforts, and devotion. She not only typed the many drafts and the original manuscript of this book but also tended to the myriad of secretarial details at every stage of my research, lecturing, and publications over the many years, while at the same time helping me in my busy practice of medicine and cardiology.

To my beloved wife, Ami, who shared in all the problems that beset a practicing physician and researcher, I express thanks and deep gratitude that can hardly compensate for her love, patience, understanding, tolerance, unfailing encouragement, and sustained interest during the more that two decades of research effort that culminated in this publication.

Finally, I want to thank the publishers for their many courtesies and wholehearted cooperation.

Meyer Texon, M.D.

HEMODYNAMIC BASIS OF ATHEROSCLEROSIS

1

INTRODUCTION

Modern medicine uses basic scientific facts established by many disciplines. Physicists, chemists, and engineers have frequently applied their special knowledge to medical research and have thus contributed to advances in clinical medicine. This crossing of lines that arbitrarily divide the sciences enriches both the donor and recipient disciplines. Such a cross-fertilization occurs when the laws of fluid mechanics are applied to the natural conditions in the circulatory system and to the nature and development of atherosclerosis.

Application of the laws of fluid mechanics to the natural conditions in the circulatory system reveals a rational and demonstrable basis for the localization, inception, and progressive development of atherosclerosis. Atherosclerosis does not occur at random locations. It occurs uniformly at specific sites of predilection that can be precisely defined, predicted, and produced by applying the principles of fluid mechanics. The areas of predilection for atherosclerosis are consistently found to be the segmental zones of diminished lateral pressure produced by the forces generated by the flowing blood. Such segmental zones of diminished lateral pressure are characterized by curvature, branching, bifurcation, tapering, or external attachment. Serpentine flow in relatively straight vessels may also produce sites of diminished lateral pressure. Although these anatomic configurations occur in many variations of geometry, their common feature is a pattern of blood flow conducive to the production of localized areas of diminished lateral pressure. This is the initial stimulus. Atherosclerosis may therefore be considered the reactive biologic response of blood vessels to the effect of the laws of fluid mechanics, namely, the diminished lateral pressure generated by the flowing blood at sites of predilection determined by local hydraulic specifications in the circulatory system.

Research reports from this laboratory beginning in 1957 have described the prerequisite hydraulic conditions and the basic laws of fluid mechanics that are relevant to the development of atherosclerosis in the circulatory system (Texon, 1957, 1967). The hemodynamic mechanism for the localization, inception, and progressive pathological changes that characterize atherosclerotic lesions has also been described (Texon, 1963). Similarly, characteristics of blood flow in arteries (Rubinow and Keller, 1966), flow patterns, and certain theoretical calculations have been identified (Fry, 1969; Reemtsma et al., 1970; Texon, 1971). In addition, hemodynamically induced atherosclerotic lesions in dogs have been produced by the surgical alteration of vascular configurations under controlled conditions (Gyurko and Szabo, 1969; Imparato et al., 1961; Texon et al., 1962). The naturally and experimentally produced lesions in dogs and the naturally occurring lesions in humans have been illustrated and analyzed both pathologically and mathematically (Texon, 1972, 1976). The atherosclerotic changes are demonstrated consistently to result from the same specific stimulus—the diminished lateral pressure—as determined and produced by the characteristics of flowing blood and the local hydraulic specifications.

Variations as well as similarities in the severity of atheroslcerosis in different individuals and in different locations in the circulatory system of the same individual are principally caused by differences as well as similarities in local hydraulic specifications (Texon, 1974). The velocity and pattern of blood flow, the caliber of the lumen, and the anatomic configuration are of importance. A biologic factor must also be considered, namely, the local reparative reaction or pathophysiological response of the intima to the diminished lateral pressure generated by the flowing blood. It is here that the nature and degree of atherosclerotic change may be modified or influenced by differences in tissue structure and differences in cellular response arising from genetic and species characteristics (Texon, 1974).

The roles of associated or contributory factors (Werko, 1976) such as age, sex, race (Keys, 1970; Robertson et al., 1977a,b; Tillotson et al., 1973), heredity, diet (Yudkin, 1957), nutritional status, habitus, lipid metabolism (Roberts et al., 1970, 1973), cholesterol (Billings, 1962; Garrett et al., 1964; Page, 1977; Talbott, 1961), obesity, drugs, trace elements (Schroeder, 1974), associated diseases, enzyme systems (Zemplenyi et al., 1963), hormones, hypertension (Hollander, 1976; Oberman et al., 1969), occupation, and emotional stress (Friedman and Rosenman, 1974; Friedman et al., 1973) require reevaluation as secondary or modifying factors. Not one of these factors is always present (Rosenman and Friedman, 1971); nor is any particular combination present as a common denominator, *sine qua non*, or as a primary factor responsible for causing atherosclerosis. None of these factors can create or cause atherosclerosis. Atheroscle-

rosis is found in both men and women, in the relatively young and in the elderly, in hypertensive (Kannel et al., 1976; Moser and Goldman, 1967) as well as in normotensive persons, and in lean as well as in obese individuals. Notwithstanding available studies of the statistical association of atherosclerosis with lipids (Fredrickson et al., 1967; Kannel and Gordon, 1971), diet age, sex, race, occupation (Stamler et al., 1960), hypertension (Chapman and Massey, 1964; Pickering, 1974), smoking, and emotional stress (Jenkins, 1971; Russek, 1967), proof of the causal relation of these factors (Corday and Corday, 1975; McMichael, 1976) to atherosclerosis is not thereby proved or demonstrated. A statistical association per se does not constitute scientific proof of a causative mechanism. A primary causative factor or mechanism for atherosclerosis must be a common denominator operating in all cases so that it determines the presence as well as the absence of atherosclerosis in every case.

The mechanical factors involved in atherosclerosis can be more easily defined. The localized decrease in static pressure at zones of predilection produces, in effect, a local suction action or tensile stress upon the intima at some phase of pulsatile flow in the cardiac cycle. The intima is subjected to the lifting or pulling effect of the flowing blood upon the endothelium and subjacent cells. The response is a local biologic change, a reparative or reactive thickening which results from the proliferation of endothelial cells (Altschul, 1954, Haust, 1976), fibroblasts and smooth muscle cells.

With continuing blood flow, progressive changes occur *in situ* (Duguid and Robertson, 1957). These may include elastic tissue changes, cellular infiltration, collagen deposition, lipid changes, calcification, and vascularization. The pathological processes inherent in atherosclerosis may be stationary for long periods of time or slowly progressive. Relatively quick or sudden changes (Friedman et al., 1973) may also occur. Ulceration of an atherosclerotic plaque may result from lifting off or shearing off of the superficial layers. Blood elements (Mustard and Packham, 1975) may form a thrombus at the raw or ulcerated surface. The thrombus (Spaet et al., 1974) may enlarge to a partially occlusive or totally occlusive degree by the accretion of additional blood elements. The progressive pathological process of encroachment on the lumen produces occlusive changes of all degrees. These changes are the result of the biologic or cellular response to the continuing mechanical stresses at segmental zones of the intima as determined by the flowing blood and local hydraulic specifications.

In summary, all of this laboratory's data from human specimens, model hydraulic systems, the laws of fluid mechanics, and the experimental production of hemodynamically induced arterial lesions in dogs support the hemodynamic basis of atherosclerosis and compel the conclusion that the effect of the laws of fluid mechanics—vascular dynamics—is the primary causative factor in the localization, inception, and progressive development of atherosclerosis.

2

FLUID MECHANICS— HEMODYNAMICS AND VASCULAR DYNAMICS

The flow of rivers and streams in their boundaries, the flight of airplanes, insects, and birds, the movement of ships in the water or fish in the depths, and the circulation of the blood in our arteries and veins are all varied expressions of the laws of fluid mechanics. Everywhere in this domain the laws of fluid mechanics must control.

The hemodynamic basis of atherosclerosis was first developed by correlating atherosclerotic lesions found at autopsy with their anatomical localization as determined by the laws of fluid mechanics. The forces and principles involved are directly comparable to those that prevail in all hydraulic systems with due regard to the characteristics of flowing blood and the local hydraulic specifications.

The motion of fluids may be streamline or turbulent. In a streamline or laminar flow, the fluid moves in definite layers or smooth paths. In turbulent motion the fluid moves in an eddying mass, and at a given point the velocity varies irregularly from instant to instant. At a low velocity the motion of fluid is usually laminar. As the velocity increases the laminar motion breaks down and becomes turbulent (Stehbens, 1960). Because blood flow is laminar or streamline in all the smaller blood vessels, their pressure-flow relations can be analyzed with considerable mathematical precision. In the larger arteries, some

turbulence exists and some differences from laminar flow may be expected. However, the significant features of low pressure areas occur in both laminar and turbulent flow.

When lines of flow converge there is a tendency toward stability or streamline flow. Flow in tubes with converging boundaries or narrowed lumina is characterized by an increase in velocity and a decrease in static or lateral pressure (Schultz, 1972). The decrease in lateral pressure is predictable in an inviscid fluid on the basis of Bernoulli's theorem, which states that the sum of the pressure and the square of the velocity times $\rho/2$ is constant for any two points of flow on the same streamline

$$P_1 + \tfrac{1}{2}\rho V_1^2 = P_2 + \tfrac{1}{2}\rho V_2^2 \tag{1}$$

The effect of gravity is neglected in this equation since gravity is not expected to have any significant influence on the distribution of the reduction in local pressure referred to in this presentation.

Regions of low pressure can readily be identified in a variety of local situations (Figures 1, 2, 3, 4, 5 and 6):

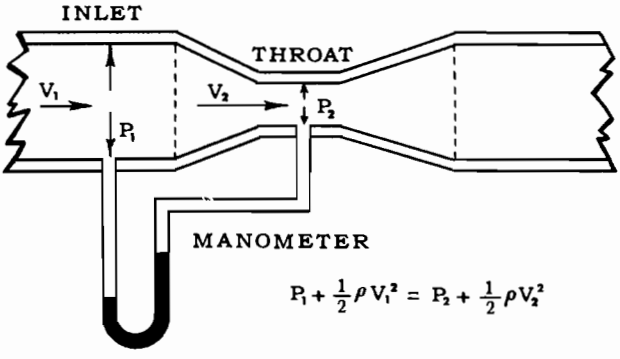

FIGURE 1. Venturi meter and Bernoulli's equation. Flow in a tube with converging boundaries causes the lateral pressure to be reduced at the narrow portion where the velocity is increased. Bernoulli's theorem states that the sum of the pressure and the square of the velocity times $\rho/2$ is constant if fluid flows from point 1 to point 2 on the same streamline. From Texon (1957). Copyright 1957, American Medical Association.

1. Fluid in a venturi meter, as in a tube or vessel with converging boundaries, causes the lateral pressure to be reduced at the narrow portion where the velocity is increased .
2. In curvilinear motion the lateral pressure is increased along the outer wall and decreased along the inner (convex) wall by virtue of the effective centrifugal force.

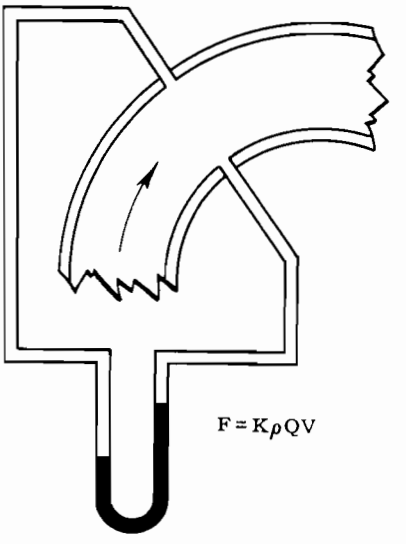

FIGURE 2. Elbow flow meter and force equation. In curvilinear motion, the lateral pressure is increased along the outer wall and decreased along the inner wall, owing to the effective centrifugal force. From Texon (1957). Copyright 1957, American Medical Association.

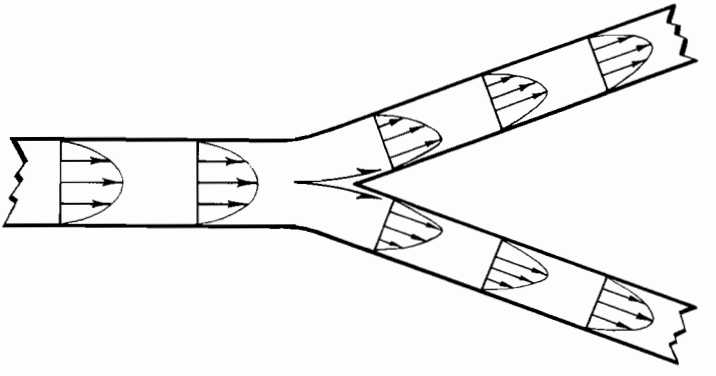

FIGURE 3. Velocity distribution for streamline flow along a tube and bifurcation. The velocity of flow at a cross section of a tube increases from the wall toward the center. Division of the axial stream results in a relative increase in velocity near the wall just downstream of the bifurcation due to the local curvatures required of the streamlines. From Texon et al. (1960). Copyright 1960, American Medical Association.

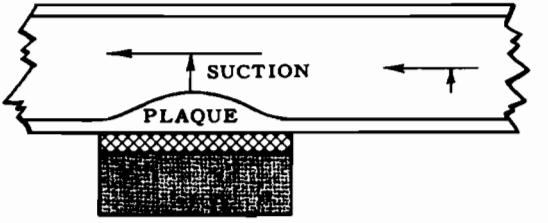

FIGURE 4. Effect of diminished lateral pressure at zone of external attachment. From Texon et al. (1963).

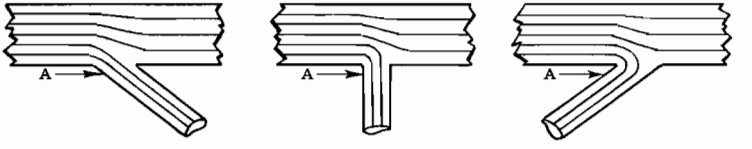

FIGURE 5. Flow patterns at sites of branching. Points "A" are low pressure areas. From Texon et al. (1963).

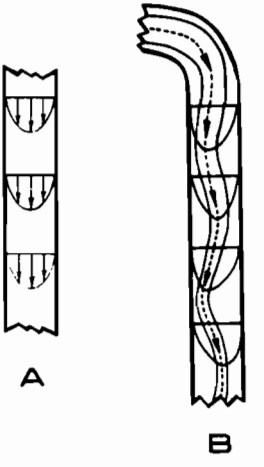

FIGURE 6. Velocity distribution along a tube for laminar flow (A) and serpentine flow (B). From Texon, *Bulletin*, New York Academy of Medicine 62.875-880 (1986) with permission.

3. The velocity of flow at a cross section of tube increases from the wall toward the center. Division of the stream at a site of bifurcation results in a relative increase in velocity and a decrease in lateral pressure at the medial walls due to the local curvatures required of the streamlines.
4. At areas of external attachment, a relative diminution in lateral pressure is developed by the fixation that resists any tendency of the flowing blood to move the wall of the vessel inward toward the more central streamlines.
5. At sites of branching, the flow patterns vary but tend to develop a low pressure region on the proximal wall of the branch and distal wall of the main stem. The zones of low pressure in a branching pattern are determined by the local hydraulic specifications, which include velocity of flow, angle of branching, ratio of diameter of main stem to diameter of branch, and shape of the ostial orifice.
6. Serpentine Flow in a relatively straight vessel also produces segmental zones of diminished lateral pressure.

These anatomic patterns occur in various combinations and in many variations of geometry. In each instance low pressure zones are produced as a common feature in accordance with the laws of fluid mechanics. The sites of predilection for atherosclerosis are uniformly found to be precisely those locations characterized by a relative reduction in lateral pressure.

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