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.