MORE THAN A CENTURY has elapsed since the thrombogenic origin of atherosclerosis was first proposed. In the Manual of Pathological Anatomy (1841-1846), Rokitansky stated that atherosclerosis consists of an "excessive formation and deposition of the lining membrane of the artery derived from the mass of the blood, and at the same time constitutes hypertrophy of this membrane." "The deposit is an endogenous product derived from the blood and for the most part from the fibrin of the arterial blood" and "increases in thickness by addition of new strata." He also recognized vascularization, atheromatous softening, hemorrhage, and calcification and regarded them as secondary processes.

Virchow rejected this thesis, as Morgan pointed out, essentially because the rate of regeneration of endothelium and elastic tissue was not appreciated. Accordingly, it was impossible for him to visualize that organization of a mural deposit is associated with an enveloping growth from the adjacent tissues which effects its incorporation into the intima. Virchow's professional stature was so great that his views prevailed and the thrombogenic thesis was and remained virtually eclipsed for a century until Duguid, Professor of Pathology, University of Durham, England, revived and elaborated upon it.

Careful study of the microscopic structure of intimal lesions in human coronary arteries and aortas convinced Duguid that fibrous thickening results from a vascular organization of mural thrombi. "It is not suggested that all atherosclerosis is thrombotic in origin for there are fatty changes to be found in the young aorta which are undoubtedly the outcome of other processes but it can be shown that most of the features we regard as characteristic of the advanced atherosclerosis including fibrous thickening, hyaline and fatty degeneration, atheromatous softening and vascularization of the intima, can be the products of mural thrombi." A number of workers have subsequently confirmed these observations using electron microscopy and fluorescein-labeled antifibrin antibodies, as well as more conventional histologic technics applied to human tissues. It seems clear then that thrombosis must be recognized as a factor in the development of atherosclerosis. Indeed, Duguid regards arterial narrowing as a fairly sure sign of preceding thrombosis. His opinion is based on the premise that a pure degenerative process in the arterial wall could only lead to dilatation.

Occlusive thrombosis of a major coronary artery has been identified as the cause of serious clinical heart disease for at least two generations. During this period deaths from coronary artery disease have risen steadily in
the U.S.A., England, and the Scandinavian countries. While the progressive change in the mortality rate has generally been attributed to an increasing severity of intimal disease, Morris' studies of postmortem records suggested instead that arterial thrombosis had increased in frequency but that there had been no change in the severity of atherosclerosis despite a tenfold increase of deaths from ischemic heart disease.

Experimentally, too, Hartroft and Thomas had found a dichotomy between the occurrence of intimal lesions and the development of occlusive thrombosis in rats. Whether these are comparable situations is questionable. In man, a sizable proportion of myocardial infarcts are unassociated with an occlusive coronary artery thrombosis. Moreover, it is doubtful that valid quantitative comparisons of intimal disease can be made from conventional autopsy protocols. To contend that there may be an augmented clotting tendency and frequency without attendant change in intimal disease is an apparent contradiction, not only of Duguid’s hypothesis, but of the findings of comparative geographic studies. These have demonstrated that thromboembolic disease is frequent in a population severely afflicted with atherosclerosis, whereas it is a rarity in a population not similarly involved.

The proposal of a direct relationship between intimal disease and the occurrence of thrombosis does not deny that some coagulative disturbance may have contributed to the complication as well as to the underlying intimal disease. Indeed such a premise seems essential to explain the parallel relationship between severe atherosclerosis and the incidence of thromboembolism, a process that is basically and initially venous.

Almost invariably, complicating arterial thrombi in atherosclerosis involve diseased areas in which the lesions are usually advanced in character. Exceptionally the intimal disease is relatively slight and occlusions have formed despite an intact endothelium. On the basis of this and other circumstantial evidence, as well as their demonstrated anticoagulant potency, it has been proposed that the acid mucopolysaccharides of the vessel walls, which are most abundant in the intima, contribute to the anticoagulant properties of its lining. Since atherosclerosis is associated with a loss of these materials on the luminal surface of many of the lesions, there seems to be an adequate explanation for the positional relation of thromboses. More insidious evidence of focal loss of clot-inhibiting potency is afforded by the demonstration of mural deposits of fibrin on the surface of lipid streaks, a form of intimal lesion often accorded little significance, except as a precursor of more advanced forms. Similar deposits are not observed over perfectly normal intima.

It has been suggested that the fibrinolytic system normally compensates for the continuous intravascular formation of fibrin from its short-lived precursor, fibrinogen. Abnormal deposits (or thromboses) may therefore be a consequence of reduced fibrinolytic activity, or of hypercoagulability, or of both. Numerous studies have attempted to ascertain whether, and to what extent, changes in the blood coagulation or fibrinolytic systems may participate in the development of atherosclerosis and of its complications. The results have been inconsistent, varying from MacDonald’s conclusion that increased coagulability of the blood is present in patients with ischemic heart disease to the negative report of a study comparing the Bantu with the South African white. Merskey and his associates found no evidence to show that “the comparative immunity of the Bantu to severe atherosclerosis and to clinical heart disease is due to a lesser coagulability of the blood.” Moreover, they could not confirm other studies relating accelerated coagulation or retarded fibrinolysis to dietary lipemia.

A number of inherent difficulties confront the investigator interested in making an accurate appraisal of the presence or absence of a coagulative disturbance in atherosclerosis. It seems likely that some of the disparate reports reflect a lack of uniform recognition of these problems. There is the technical matter...
of making estimations at the most insensitive portion of the blood-clotting activity curve. The selection of a suitable control group for comparison is a serious problem. It is fallacious, for example, to assume that absence of clinical symptoms is synonymous with absence of coronary intimal disease.

In interpreting his findings, the investigator must be alert to the possibility that he may be demonstrating secondary rather than primary changes or that some coincident condition or circumstance may be causally related to his findings. Finally, he must be cautious and judicious in evaluating the significance of his observations. Poole has emphasized that clotting in the test tube is not synonymous with thrombosis in blood vessels. It was he who also indicated that while an accelerated viper-venom clotting time with lipemia might be of great significance to individuals who, having consumed a fatty meal, were unfortunate enough to be bitten by an appropriate snake, it has very little to do with the much more prevalent problem of intravascular coagulation in atherosclerosis.

Ira Gore

Fredrick J. Stare

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IRA GORE and FREDRICK J. STARE

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