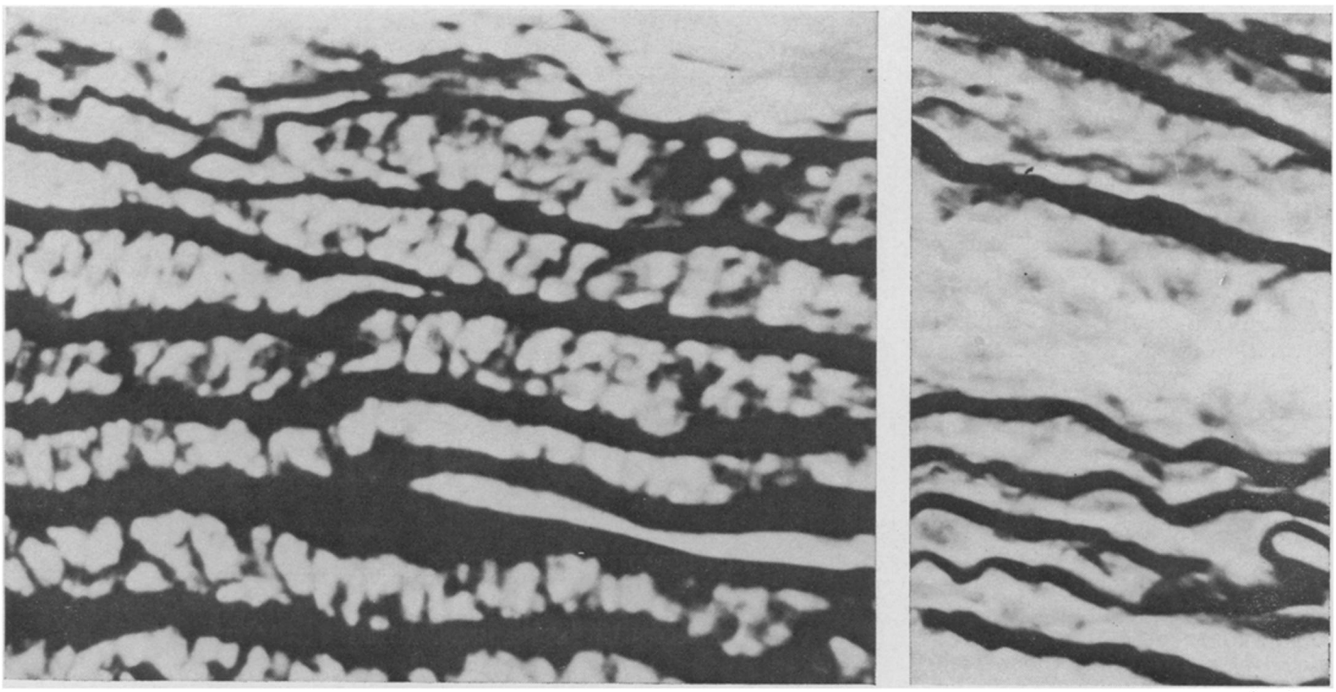


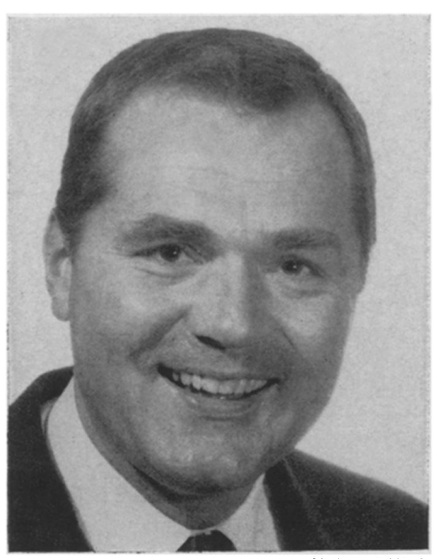
Sandberg

Molecular comparison of healthy tissue and disrupted elastin from the aorta of a copper deficient rat (right).

ATHEROSCLEROSIS

Progress through fluid dynamics

Stress on blood vessel walls may be the reason for build-up of disease-causing plaques



Univ. of Utah

Sandberg: Data are far from complete.

by Barbara J. Culliton

Ever since atherosclerosis was first described as a disease in the 19th century, scientists have alternately focused their attention on the blood vessel wall and the content of blood as the primary cause. In the early 1900's, a number of treatises attacked the problem by examining the physical properties of blood flow and their effect on the vascular wall. Then during the last two decades, during which lipid chemistry emerged as a dominant area of research, emphasis turned to the role of fats in the blood. At the American Heart Association's 1969 meeting on atherosclerosis, for example, 51 of 57 scientists presented papers dealing with lipids.

Certainly investigators in the 1970's will continue to look at lipids as they attempt to explain the processes by which plaques build up on and block blood vessels. But there are signs that the pendulum will swing back once again to the vessel wall. Among those researchers favoring this swing are members of a team of scientists at the University of Utah in Salt Lake City. Their approach combines molecular biology and physics.

Vascular degeneration, Utah's Dr. Keith Reemtsma believes, begins with molecular changes in the connective tissue of the blood vessel wall, particularly in the protein elastin. These changes are associated with alterations in physical properties of the wall, possibly triggered by patterns of blood flow. The clinical manifestations of atherosclerosis, such as plaque build-up, may be later responses to these vessel wall disturbances.

Blood vessel walls consist primarily of collagen, smooth muscle cells and elastin. Dr. Lawrence Sandberg, also of Utah, who has recently isolated for the first time a precursor or subunit of elastic fiber, proposes a tentative explanation of how disruptions in the elastic fiber occur and how they constitute the molecular basis of atherosclerosis. He did the work with Dr. Norman Weissman and Donald Smith.

Elastin is not a newly identified protein. But it was only seven years ago

that researchers began to learn about its molecular structure.

Elastin molecules, relatively large proteins, are joined together to form stretchable vascular tissue by an unusually stable, unique type of chemical bond. These intermolecular linkages, named desmosine links, are built of an amino acid synthesized only in elastic tissue. The links require copper for their formation.

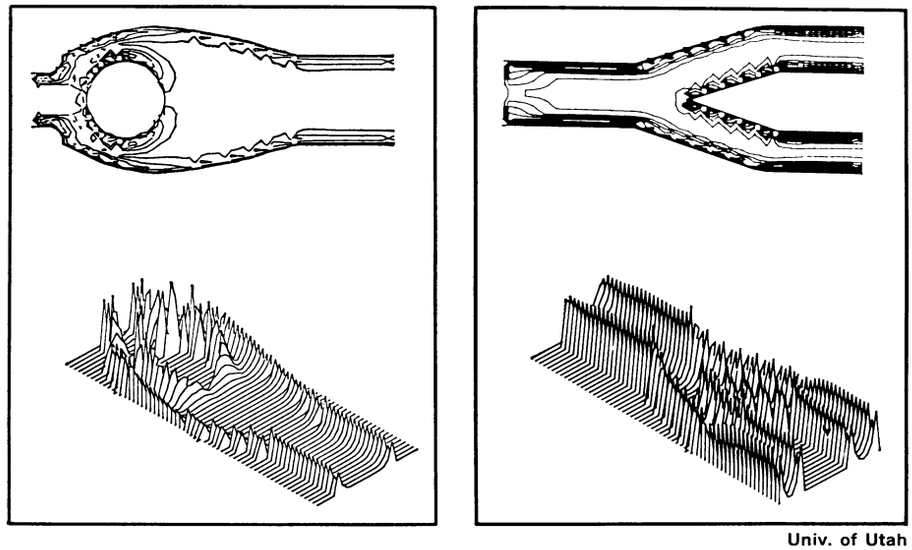
In normal animals, these firm links are quickly formed whenever a free precursor molecule is available, and isolation of that precursor is next to impossible. Swine bred in the Utah mountain area to be deficient in copper provided Dr. Sandberg with a way around the problem. Because of the copper deficiency these animals are unable to form desmosine links.

Using these animals as a source of supply, Dr. Sandberg reports isolation of the precursor molecules, subunits of elastic tissue. Called tropoelastin, each subunit is built of 800 amino acid molecules that may constitute a spherical protein. At no less than six positions on the surface of the sphere, he believes, there are amino acid units that act like prongs and can form the desmosine links, knitting the tropoelastins into complex elastic fiber. Encased within the individual spheres are amino acid configurations that expand and contract in response to pressure, giving vessels their elasticity.

According to Dr. Sandberg's hypothesis, chemical or mechanical stress may occasionally disrupt the spherical configuration of tropoelastin molecules enabling amino acid units in the interior to protude from the protein surface. These molecular units, unlike those meant to be on the surface, have a strong affinity for lipids and attract these fats in the blood, thereby initiating the process of plaque build-up on the vessel wall.

The hypothesis, Dr. Sandberg maintains, fits with known associations between vascular degeneration and aging. In the first place, the synthesis of elastic fiber for vessel walls essentially stops at puberty. Therefore, breaks in its molecular structure cannot be repaired by adults, and the accumulation may account for the gradual build-up of plaque and onset of atherosclerosis.

In addition, he observes, while it is difficult to isolate intact tropoelastin molecules from man, it is possible to detect broken fragments of these molecules, generally seen in higher quantities in aged than in younger individuals. "One therapeutic approach to atherosclerosis," he speculates, "is the stimulation of tropoelastin synthesis in adults. However, we will have to learn a great deal more about what is happening before we can even begin to consider this."



Univ. of Utah

Heart valves and blood stream junctures are displayed by computer graphics.

Assuming that this explanation of blood vessel degeneration and plaque build-up is correct—Dr. Sandberg stresses that, at present, his data are far from complete—scientists are working to determine the kinds of stresses that can cause breaks in vessel tissue. The first place to look is at the flow properties of blood continuously coursing through the vessels.

Physicist Harvey H. Greenfield of Utah has recently launched computer studies which he hopes will show areas of particular stress and define their causes—pressure, vibration and velocity. Applying principles of fluid dynamics to blood flow, he is attempting to construct a mathematical model that simulates various conditions of the circulatory system.

"Wind tunnel experiments," he says, "have shown that a fluid behaves in a series of fairly regular changes when flowing around a fixed object in a stream." A blood vessel is a stream. Fixed objects within it include heart valves, natural or artificial, clumps of plaque on a vessel wall, and even the corners blood must turn as it moves from main arteries into side branches of the vascular tree.

Dr. Greenfield constructs mathematical models of these various situations, taking into account the shape and location of the obstacle and the dynamics of fluid flow around them. Simulation is then carried out by a computer attached to an optical display system. From this he gets graphic computer drawings indicating changes in flow patterns.

Though the system, intended to predict areas of stress and characterize the nature and strength of that stress, is still in preliminary stages of development, there is evidence that it will be useful. From clinical experience and observation, surgeons can identify certain areas in the vascular tree that appear to be particularly susceptible to plaque formation. One of these is the juncture in the main aorta in the abdomen where it branches into two large arteries descending into each leg.

Greenfield: Applying fluid dynamics.

In the future, Dr. Greenfield says, efforts will be directed toward studying flow patterns in other vessels and toward designing computer models of other physiologic circumstances—particularly the influence of blood flow patterns on alterations in pulse rate, blood viscosity or thickness and the elastic properties of vessel walls themselves. □