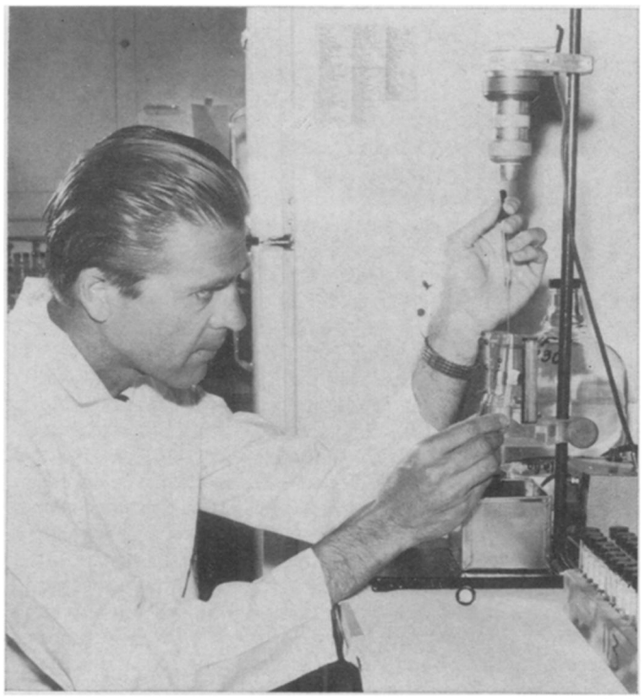
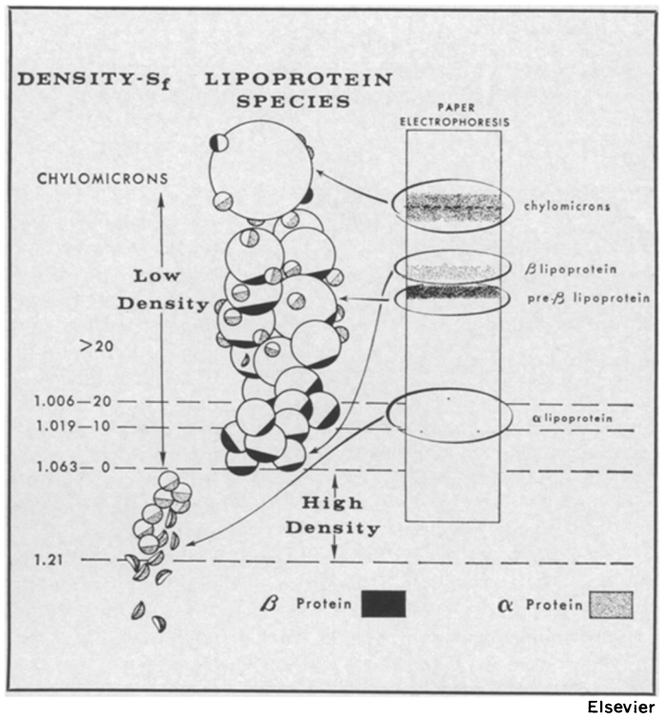


LRL



Elsevier

Advances in lipoproteins

Current research may lead to early diagnosis of vascular disease

by Jay Chamblin

The most direct cause of impaired heart function is the decline or sudden failure of coronary circulation.

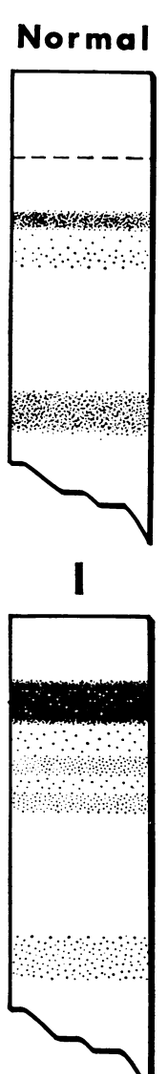
Many factors, such as age, sex, high blood pressure, cigarette smoking, reduced exercises, stress and obesity contribute to a process whereby healthy, resilient coronary arteries become narrowed, brittle and hardened, with an accompanying loss in circulatory efficiency. This is atherosclerosis, the underlying problem in most heart disease. And other crippling diseases may be added which are either the direct result of, or complicated by, atherosclerotic arteries elsewhere in the body; kidney disease, stroke, hypertension and many less clearly defined health problems.

Heart disease is the leading cause of premature death in the U.S. today. And to deal with it, last-ditch efforts such as organ transplants and artificial organs are no substitutes for early diagnosis, control or prevention of vascular disease.

Recently, at the annual meeting of the National Academy of Sciences, two symposia were presented in tandem. They represented these polar approaches to disease: last-ditch surgery and prevention-oriented research.

Photos: NIH, Karger

Nichols (top) and Gotto: working on the functions and characteristics of the different species of lipoproteins; electrophoresis patterns (right) identify a normal test pattern and one type of genetic abnormality.

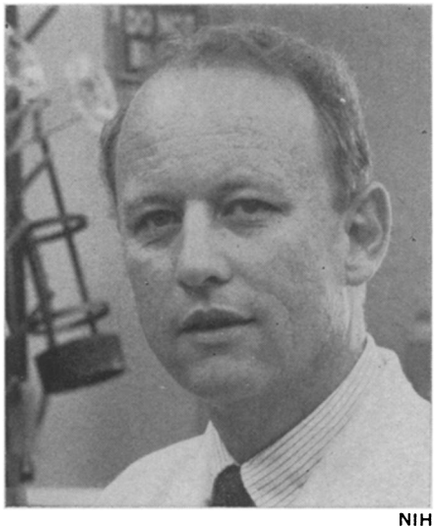


At the well-attended morning symposium, Dr. Norman Shumway and four colleagues held forth on organ transplantation. The press conference which followed lasted several hours into the afternoon.

In the shadow of that, the second symposium, on plasma lipoproteins, was attended by a handful of mostly elderly academy members silently drawing on pipes. The speakers, on the other hand, were mostly young scientists.

But if a long-range answer to cardiovascular disease develops, it is more likely to come from lipoprotein research than from transplantation of organs.

. . . lipoprotein



NIH

Fredrickson: 10 abnormal genotypes.

Lipoproteins are microscopic particles, composed of lipid (fat) and protein molecules, present in all tissues of the body. The protein faction serves as carrier in transporting different kinds of fat and cholesterol, in the manner of a tour guide, through the maze of blood vessels, lymph channels and intercellular spaces to where they are needed for energy, tissue-building or storage in adipose tissue.

"It is clear," says Dr. Alexander V. Nichols of the University of California at Berkeley, "that man has a most effective carrier system for the transportation of fats via plasma to metabolizing tissue sites." But, as efficient as it may be under normal conditions, when it ceases to function normally, it can produce atherosclerosis. And despite recent progress and some developing utility as a diagnostic tool, the role of lipoproteins in atherosclerosis is still little understood.

Lipoproteins were first isolated from horse serum more than 40 years ago, but it was not until 1950 that scientists working under Dr. John W. Gofman at Berkeley established a link between them and cardiovascular disease. Although a window was opened then to new investigative challenges, original expectations for immediate medical application proved too optimistic. But dividends are now beginning to appear in improved methods of testing for disorders of the body's fats and refined research techniques in studying their relationship to vascular and associated diseases.

Chemically, lipoproteins can be separated into four major groups, based on their lipid-to-protein ratios. Because of the relatively low specific gravity of fat, high lipid ratios produce particles of lower density, and those particles which have proportionately more protein show densities that are relatively higher.

In order of increasing density, the four primary groups are designated as chylomicrons, very low-density lipoproteins, low-density lipoproteins and high-density lipoproteins.

Dr. Antonio M. Gotto Jr. of the National Heart Institute in Bethesda, Md., is working on the chemical definition of serum low- and high-density lipoproteins, and has succeeded in refining the analysis of both the fat portions and protein carriers of the lipoprotein complex. With these important elements now available in greater purity for separate investigation, their roles in fat metabolism have come under close scrutiny.

Berkeley's Dr. Nichols, studying the functions and interrelationships of different kinds of plasma lipoproteins, finds that fats are conveyed through the blood stream primarily by two kinds of protein carriers: the proteins found in the low-density and high-density particles. These two proteins carry the fats, phospholipids and cholesterol, which are important structural compounds used in building cell walls, membranes and much of the important machinery of the cell. The fats related to energy production and storage in fatty tissues are transported by the same two kinds of proteins, but the resulting particles are larger and of lower density. They are the pair with lowest densities.

To apply these insights into how fats and cholesterol are shuttled through the body, scientists at the National Heart Institute have developed a test which will provide important information about how much and what kinds of lipoproteins are present in the blood. Links can be established between test results and abnormal conditions.

One method for testing and studying the physiology of fats is paper electrophoresis, a method for separating molecules according to their mobility in an electric field.

With practice, scientists say, a technician can learn to segregate most of the plasma samples into normal and abnormal categories simply by looking at the electrophoretic patterns on a paper strip. Lipoproteins migrate at specific rates and distances depending on the kind of particle.

Lipoprotein paper electrophoresis is already being used in clinics throughout the U.S. Its value is its increased sensitivity and greater specificity in detecting problems in the lipid transport and metabolic activities than has been possible by testing for a single blood component, for example, cholesterol.

Complicating the understanding of atherosclerosis has been the question of cholesterol. There has been much evidence to support the idea that high concentrations of cholesterol in the plasma causes atherosclerosis. But the evidence is far from clear. Dr. Michael DeBakey of the Baylor University College of Medicine, Houston, Texas, reported as long as five years ago that of 1,700 patients with atherosclerotic disease, 1,326 had normal cholesterol levels. There is even some evidence from animal studies that a sudden reduction in the kinds of dietary fat which lower cholesterol levels in the blood may aggravate existing atherosclerosis (SN: 12/30/67, p. 634).

Dr. Donald S. Fredrickson is working with an unusual group of patients at the National Heart Institute who have hereditary abnormalities of plasma lipid concentrations. "Some of the more obvious genetic determinants" of lipoprotein disorders, says Dr. Fredrickson, "can be illustrated by certain genetic abnormalities." He has discovered at least 10 such abnormal genotypes, some of whose lipoproteins are high, some low, and certain groups whose lipid disorders are associated with arterial disease.

From electrophoretic studies, the mutant lipid patterns, as well as abnormal lipid patterns from individuals with secondary lipid irregularities, group themselves into five basic different characteristic patterns. The groups are generally classified as variations of the disease, hyperlipoproteinemia.

The type I hyperlipoproteinemia pattern demonstrates high concentrations of chylomicrons many hours following a meal. Normally, chylomicrons, which carry dietary nutrient fats from the intestine to tissues for energy production, clear the blood stream within a couple of hours after a meal. Type I patterns are usually specific for hereditary defect, although a few other conditions such as severe diabetes or acute alcoholism may underlie the abnormality. No increase in atherosclerosis is associated with type I, and it is treated with dietary restriction of fat.

How successful the application of this research will be in reducing the incidence of cardiovascular disease, only time can tell.

"It may be as long as three years, or as short as one year," says Dr. Robert I. Levy of the National Heart Institute. Dr. Levy recommends that every male between 25 years and 35 years old should be tested. He says the test has just begun to reach the physicians, and more are ordering clinical lipoprotein tests routinely all the time.

"We are trying to eliminate the shotgun approach to this area of medicine," says Dr. Levy. ◇