

## PLASMA PROTEINS AND SERUM LIPOPROTEINS IN RELATION TO CARDIOVASCULAR DISEASE

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ULTRACENTRIFUGAL and electrophoretic technics provide means of characterizing, quantitating, and isolating proteins and lipoproteins of body fluids and tissues. Through investigation of plasma proteins and lipoproteins in experimental animals, in normal human beings of different racial and age groups, and in patients with various metabolic diseases before and after treatment, some understanding of the factors involved in maintaining normal plasma protein and lipoprotein patterns has been obtained.

The plasma protein fractions resolved by free-moving boundary or paper-electrophoretic technics at pH 8.6 are conventionally designated in the order of decreasing mobility: albumin,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ,  $\phi$ , and  $\gamma$ -globulins. All serum cholesterol is found in the lipoproteins that are fractions of the  $\alpha$ - and  $\beta$ -globulins. The  $\alpha$  and  $\beta$  lipoproteins have been extensively studied by ultracentrifugal technics.<sup>1</sup>

In some species atherosclerosis can be produced readily, while other species are resistant to the disease. A comparison of the serum lipoprotein patterns and cholesterol concentrations among various species showed that, in the dog, in which atherosclerosis is produced with difficulty, a large part of the lipid is found in the  $\alpha$ -lipoprotein, while the  $\beta$ -lipoprotein concentration is low.<sup>1</sup> The rat, which has a low concentration of serum cholesterol and of  $\alpha$ - and  $\beta$ -lipoproteins, is also resistant to development of atherosclerosis. The serum lipoprotein pattern of swine has some characteristics similar to that of the human, with relatively high concentrations of  $\beta$ -lipoprotein and of low-density  $\beta$ -lipoprotein. Swine is a species in which atherosclerosis occurs spontaneously. The lipoprotein patterns of various strains of miniature swine fed the same diet, have been found to be different. The  $\beta$ -lipoprotein fractions were significantly higher in *short-fat* than in *long-lean* animals. The genetic factor is thus of basic importance in determining the lipoprotein pattern. It establishes characteristic patterns not only for a given species, but also for strains within a species.

The stability of the lipoprotein patterns of normal individuals was demonstrated when serum lipoprotein and cholesterol concentrations were determined yearly for seven years on a group of 107 Cleveland executives at the time of their annual physical examinations. Those persons who had low serum cholesterol and lipoprotein concentrations at the time of the initial examination, consistently had low values on succeeding determinations, while those with high concentrations were usually high on repeated studies.<sup>2</sup> While the lipoprotein pattern of a specific individual is relatively stable over a period of years, the concentrations of serum cholesterol and lipoprotein increase slowly both in men and in women between the ages

of 20 and 50 years, when they level off in men, but continue to increase in women, so that the concentrations of cholesterol and  $\beta$ -lipoprotein are characteristically higher in women more than 60 years of age than in men.<sup>3\*</sup> The serum lipoprotein pattern both of young and of older women showed a significantly higher concentration of  $\alpha$ -lipoprotein and  $\alpha/\beta$  ratio than was found in sera of men. The incidence of atherosclerosis and coronary heart disease is greater in men than in women.

Since atherosclerosis is rare in some races and commonly is found in patients with certain metabolic diseases, a comparison was made of serum cholesterol concentrations and protein and lipoprotein patterns of Indians, normal white persons residing in the Cleveland area, and patients with metabolic diseases, to determine whether or not differences in the protein and lipid patterns could be associated with incidence of atherosclerosis. Sera of Navajo and Peruvian Indians, groups in which atherosclerosis and coronary heart disease are rare, had significantly higher concentrations of  $\gamma$ -globulin, and lower concentrations of serum cholesterol and  $\beta$ -lipoproteins than sera of Cleveland-area white persons of similar age. The  $\alpha$ -lipoprotein concentration of the Indians was similar to that of the Clevelanders, so that the  $\alpha/\beta$  ratio of the Indians was significantly higher than of the Cleveland white subjects.

Atherosclerosis occurs more frequently in myxedematous patients and in diabetics than in the normal population. A study of the plasma protein pattern of patients with myxedema (1944) showed high  $\beta$ -globulin and low albumin concentrations. It was suggested that the high  $\beta$ -globulin values possibly were due to increased concentrations of lipoproteins. When methods for measuring the lipoproteins subsequently were developed, they were employed and high concentrations of  $\beta$ -lipoproteins in the sera of patients with myxedema were found.<sup>4</sup> The concentrations of these lipids decreased after administration of thyroid hormone. Similarly, high  $\beta$ -globulin and low albumin concentrations were found in the plasma of patients with uncontrolled diabetes, and also in the plasma of patients with well-controlled diabetes but with vascular complications. A study of the serum lipoproteins of patients with diabetes for 10 years or longer showed higher mean concentrations of cholesterol and  $\beta$ -lipoproteins than in normal subjects, and high  $\alpha$ -lipoprotein of concentrations in middle-aged men and women with so-called "brittle diabetes." In general, vascular complications occur more frequently in stable than in brittle diabetics.

The serum lipoprotein patterns of patients with early or mild essential hypertension varied only slightly beyond normal range, but the patterns of severe or malignant hypertensives showed increased concentrations of  $\beta$ -lipoproteins.<sup>5</sup> The electrophoretic protein patterns of essential hypertensive patients, also, were nearly

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\*Findings of a cooperative study of lipoproteins and atherosclerosis, by Lena A. Lewis, Frederick Olmsted, Irvine H. Page, of The Cleveland Clinic Foundation; Eleanor Y. Lawry, George V. Mann, Frederick Stare, of the Harvard School of Public Health; Martin Hanig, Max A. Lauffer, of the University of Pittsburgh; Tavia Gordon, Felix E. Moore, of the National Heart Institute.

normal, while those of malignant hypertensives showed decreased concentration of albumin and increased concentration of  $\beta$ -globulin. Studies on dogs with experimental hypertension showed that the serum electrophoretic protein and lipoprotein patterns were normal in animals with neurogenic hypertension, while those with renal hypertension showed increased concentration of  $\gamma$ -globulin, and when malignant hypertension occurred the concentrations of  $\beta$ -globulin and  $\beta$ -lipoprotein also were increased.

Extremely abnormal plasma protein and lipoprotein patterns were frequently observed in patients with renal disease, and in animals with experimental nephrosis. The plasma albumin and  $\gamma$ -globulin concentrations were decreased, and usually there was a greatly increased concentration of  $\alpha_2$ - and  $\beta$ -globulins. The lipoprotein pattern showed increased concentrations of all classes of lipoproteins, but chiefly in the  $\beta$ -lipoproteins. While the serum cholesterol and lipoprotein concentrations increase in animals with renal disease, changes in blood lipid concentration are not dependent upon the presence of the kidney. Studies carried out on nephrectomized dogs maintained by peritoneal dialysis showed increased concentrations of cholesterol and  $\beta$ -lipoproteins, and often slightly decreased concentrations of  $\alpha$ -lipoprotein.

The high concentrations of serum cholesterol and lipoproteins, and the low concentrations of  $\gamma$ -globulin found in patients with primary renal disease, contrast with the low concentration of lipoproteins and high globulin concentration found in patients with multiple myeloma. The sera of patients with myelomatosis had low concentrations of cholesterol,  $\alpha$ - and  $\beta$ -lipoproteins, and even when renal involvement occurred the concentrations were not greater than normal. The concentrations of serum globulins,  $\beta$ ,  $\gamma_1$  or  $\gamma_2$ , were, however, high in myeloma sera.<sup>6</sup>

In patients with cirrhosis of the liver the concentrations of serum cholesterol may be increased. The lipoprotein patterns showed increased concentrations of  $\beta$ -lipoprotein, and an abnormal  $\alpha$ -lipoprotein spectrum. In terminal hepatic disease the concentrations of cholesterol and all lipoprotein fractions were unusually low.<sup>4</sup> The electrophoretic plasma protein patterns of patients with cirrhosis showed low albumin concentration and increased concentrations of  $\beta$ -,  $\delta$ - and  $\gamma$ -globulins. A decrease in the concentration of all serum lipoproteins and cholesterol was observed in hepatectomized dogs 16 hours after operation, which indicated that normal concentrations of cholesterol and lipoproteins could not be maintained in the absence of the liver.

The incidence of atherosclerosis and coronary artery disease is high in patients with primary disturbances in lipid metabolism. The lipoprotein pattern may show one of three types of abnormality.<sup>5</sup> In the patient with primary hypercholesteremia the lipoprotein pattern was characterized by a high concentration of  $\beta$ -lipoproteins; the  $\alpha$ -lipoprotein concentration was normal or decreased. The lipoprotein pattern of the patient with hyperglyceridemia showed greatly increased concentration of the chylomicron type of lipoprotein, and a low concentration of  $\beta$ - and  $\alpha$ -lipo-

proteins. The third type of lipoprotein abnormality has been termed "mixed hyperlipemia" and was characterized by increased concentrations of all fractions in the  $\beta$ -lipoprotein spectrum, while the  $\alpha$ -lipoprotein concentration was normal or was decreased. Treatment of these patients with low-fat or vegetable-oil food patterns significantly decreased the serum cholesterol concentration and improved the lipoprotein pattern. Even when the serum cholesterol concentration reached normal, the lipoprotein patterns were not entirely normal. The hyperglyceridemic's pattern showed a low concentration of  $\beta$ - and  $\alpha$ -lipoproteins, and the hypercholesteremic's pattern had a higher than normal  $\beta$ - and often a low  $\alpha$ -lipoprotein concentration. The beneficial effects resulting from the diets were maintained for as long as four years.

The serum cholesterol and lipoprotein concentrations of experimental animals can also be greatly altered by diet. High concentrations of serum and hepatic lipids were produced in rats by feeding diets containing high concentrations of coconut oil or soya oil, and higher concentrations were obtained when cholesterol was also added to the diet. Studies to determine whether or not exercise could influence serum and tissue lipid concentrations showed that exercise was effective in reducing serum total lipid and cholesterol concentrations in rats in which the concentrations were high from high-fat intake, but did not modify the normal concentrations of rats fed chow diets.

Short-time cigarette smoking, which may be considered a type of stress, caused no significant change in the concentrations of serum cholesterol or of lipoproteins. The roles that the central nervous system and the pressor hormones play in the regulation of lipid metabolism and blood lipid concentrations are being explored.

### Summary

The genetic factor plays an important part in determining the serum lipoprotein pattern. The concentrations of the various lipoprotein fractions, however, are modified by age, sex, hormones, and diet. A high concentration of serum cholesterol and low-density lipoproteins is associated with a greater frequency of atherosclerosis in the human being and greater ease of experimentally producing the disease in animals. The plasma protein and lipoprotein patterns of patients with mild essential hypertension are nearly normal, but the patterns of malignant hypertensive patients show a decreased albumin, increased  $\beta$ -globulin, low-density  $\beta$ -lipoprotein and  $\beta$ -lipoprotein and cholesterol concentrations. Low concentrations of serum cholesterol are frequently associated with high concentration of  $\gamma$ -globulin (in normal Indians and in patients who have myelomatosis), and high concentrations of cholesterol and  $\beta$ -lipoproteins may be accompanied with low  $\gamma$ -globulin concentration (as in nephrotics). The plasma albumin concentration is frequently decreased in patients with diseases in which abnormal lipoprotein concentrations occur.

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