Serum Lipoprotein Patterns in Liver Disease (34886)

N. M. Papadopoulos and M. A. Charles

Division of Biochemistry, Walter Reed Army Institute of Research; and Department of Medicine, Walter Reed General Hospital, Walter Reed Army Medical Center, Washington, D. C. 20012

Alterations of serum lipid concentrations in human liver disease, accompanied by changes of lipoproteins have been reported by several investigators (1–7). The very low density (VLD) or pre-beta-lipoproteins are formed in the liver and their determination in serum is of special interest in liver abnormalities. Paper electrophoresis, usually employed for the fractionation of serum lipoproteins does not detect clearly pre-beta-lipoproteins in normal serums and its application in the study of hypopre-beta-lipoproteinemias is unsatisfactory.

An agarose gel electrophoretic technique, recently reported (8), for the determination of serum lipoprotein patterns, consistently detects the pre-beta-lipoprotein band as well as additional zones in the pre-beta area. This technique has been applied to human liver disorders in order to study the effect of the liver abnormality on the serum lipoprotein pattern. Reported herein are the prospective observations noted in portal cirrhosis, viral hepatitis, and biliary cirrhosis.

Experimental Methods. Three representative categories of liver disease were selected in these studies, namely, eight cases of advanced portal (Laennec's) cirrhosis, eight cases of viral hepatitis, and three cases of primary bilary cirrhosis. Diagnoses were established by clinical evaluation, histologic examination of biospy specimens, and biochemical methods. Each of the portal cirrhosis and viral hepatitis patients were attended by one of the authors. Venous blood was obtained after an overnight fast, allowed to clot, and serum was separated by centrifugation. Only fresh specimens were analyzed. The lipoprotein patterns were developed by the agarose gel electrophoretic method recently reported (8). Inadvertently the destaining part of the procedure was omitted from the previous description of the method; destaining was accomplished by two washings of the stained slices in 50% ethanol. Along with the lipoprotein analysis, cholesterol and triglycerides were also determined in each sample as described in the same paper (8).

Results. Serum lipoprotein patterns representative of the three conditions studied are shown in Fig. 1. A normal control is included for comparison. The portal cirrhosis pattern is characterized by a strong beta-lipoprotein band, a very weak alpha zone, and absence of the pre-beta zone. All of the samples studied gave consistently the same pattern. The values of the cholesterol and triglyceride determinations were lower than normal in most but not all of the cases. In primary bilary cirrhosis the pattern showed a densely staining beta-band; a pre-beta zone was detected in all of the specimens analyzed. Of the two alpha-bands the density of one was increased and the other was weakly stained or absent. Cholesterol was elevated in these cases and the triglyceride levels were in the normal range. In viral hepatitis, serial determinations of serum lipoprotein patterns showed that during the first week of the acute phase of the disease, the pre-beta- and alpha-lipoproteins disappeared and only one wide intensely stained beta migrating zone was detected, as shown in Fig. 1. During the second week of the acute phase the pre-beta- and alpha-bands began to reappear and normal patterns were reestablished in the recovering cases without complications. The cholesterol and triglyceride analyses during the same period gave values within a broad normal range; small changes were attributable to diet variations.

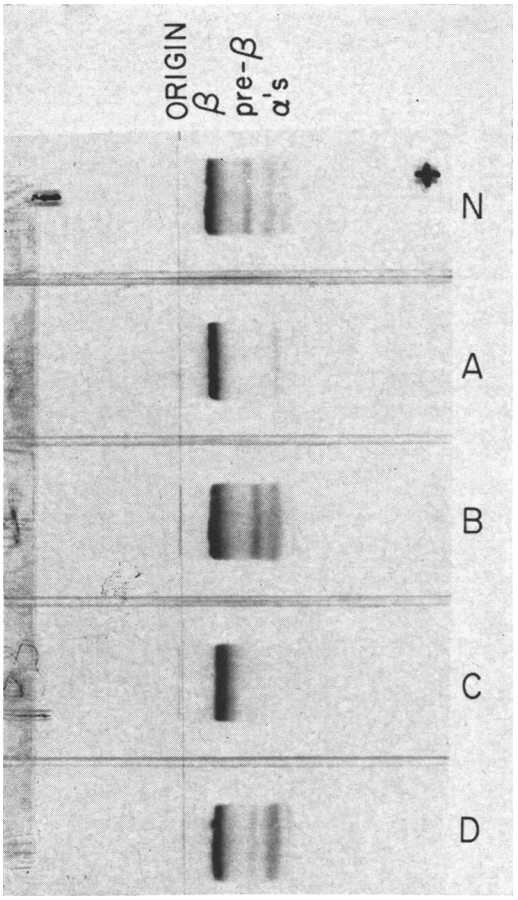

FIG. 1. Serum lipoprotein patterns by agarose gel electrophoresis from a normal (N) subject and from patients with: A, Laennec's cirrhosis; B, primary bilary cirrhosis; C, viral hepatitis during the acute phase; and D, the same patient during the recovery phase.

Discussion. Most of the lipids in serum are transported in the form of lipoproteins. A major portion of these lipoproteins is formed in the liver. The determination of serum lipoprotein patterns is a better index of liver abnormalities than determination of lipids alone. There is no uniform agreement in the literature (1–4, 9) on the serum levels of cholesterol and triglycerides in parenchymal liver disease; variations of concentrations of the same constituents were also found in our studies. Conversely, the characteristic elevation of serum concentration of unesterified cholesterol in subjects with obstructive liver disease was confirmed by our finding of a moderate increased level of cholesterol in all the biliary cirrhosis cases studied.

The results presented here in which patterns are characterized by the absence of pre-beta-lipoproteins in portal cirrhosis, presence of pre-beta-lipoprotein in primary biliary cirrhosis, and absence of pre-beta- and alpha-lipoproteins during the first week of the acute phase of viral hepatitis were consistently the same for each condition in all of the cases studied. This information is a useful aid in the differential diagnosis of liver diseases. It also indicates that the capacity of the hepatocyte to form alpha- and pre-beta-lipoproteins is greatly diminished in parenchymal liver disease whereas this impairment is not significant in obstructive liver disease. Whether the impaired formation of these lipoproteins in the liver is due to decreased synthesis of the apoproteins or interference with the conjugation process of lipids and apoproteins or both remains to be elucidated.

It is interesting to note that the beta-lipoprotein zone was always present in all the conditions studied. It is known that this lipoprotein is formed in the liver as well as in the intestine. Whether this lipoprotein originates from the liver, the intestine, or both, in these conditions remains to be elucidated. An abnormal lipoprotein with beta mobility has been recently been reported in obstructive liver disease (9).

In these patients with liver disease, the serum lipoprotein patterns differed markedly from the patterns found in serums from patients with atherosclerotic heart disease and related conditions. In a previous report (10), it has been shown that portal cirrhosis and hepatitis gave characteristic protein patterns, by agar gel electrophoresis, which were different from other pathological conditions. The combined determination of protein and lipoprotein patterns together with other related tests such as immunoglobulin analysis, provide a useful biochemical system for the study and differentiation of liver diseases. It has now been extended to include other diseases of the liver such as chronic active hepatitis, Wilson's disease and sarcoidosis.

Liver diseases cause variable degrees of

alterations of serum pre-beta- and alpha-lipoproteins. The detection of small changes of these lipoproteins by the agarose gel electrophoretic technique enables the physician to follow the course of the disease and seek an explanation of the mechanism of the disease.

Summary. An agarose gel electrophoretic technique which clearly detects and sharply resolves serum lipoproteins has been applied to the determination of serum lipoprotein patterns in liver diseases. The patterns obtained are characterized by presence of beta-, absence of pre-beta-, and trace of alpha-lipoproteins in portal cirrhosis; presence of beta-, pre-beta-, and alpha-lipoproteins in primary biliary cirrhosis; a densely stained beta- and absence of pre-beta- and alpha-lipoproteins in viral hepatitis during the first week of the acute phase and reappearance of pre-beta- and alpha-lipoproteins after 2 weeks in the recovering cases without complications. These data provide information on the variable nature and for differential diagnosis of these conditions.

We acknowledge the technical assistance by Mr. J. A. Kintzios.

1. Man, E. B., Kartin, B. L., Durlacher, S. H., and Peters, J. P., J. Clin. Invest. **24**, 623 (1945).

2. Kunkel, H. G., and Slater, R. J., J. Clin. Invest. **31**, 677 (1952).

3. Eder, A. H., Russ, M. E., Rees, R. A., Willber, M. M., and Barr, D. P., J. Clin. Invest. **34**, 1147 (1955).

4. Phillips, G. B., J. Clin. Invest. **39**, 1639 (1960).

5. Levy, R. I., Lees, R. S., and Frederickson, D. S., J. Clin. Invest. **45**, 63 (1966).

6. Smith, S. C., Scheig, R. L., Klatskin, G., and Levy, R. I., Clin. Res. **15**, 330 (1967).

7. Switzer, S., Gastroenterology **53**, 790 (1967).

8. Papadopoulos, N. M., and Kinzios, J. A., Anal. Biochem. **30**, 421 (1969).

9. Deidel, D., Alaupovic, P., and Frurman, R. H., J. Clin. Invest. **48**, 1211 (1969).

10. Papadopoulos, N. M., and Kintzios, J. A., Proc. Soc. Exp. Biol. Med. **125**, 927 (1967).

Received Mar. 26, 1970. P.S.E.B.M., 1970, Vol. 134.