CHAPTER IV

DISCUSSION

The liver has unequivocally been shown to synthesize albumin, prealbumin, α_1-acid glycoprotein, haptoglobin, α_2-macroglobulin, Gc-component, transferrin, high and low-density lipoproteins. Studies with radioactive-labeled amino acids also point to the liver as the problem source of ceruloplasmin (Lang and Renschler, 1958; Hochwald et al., 1961) and possibly of hemopexin (Hochwald et al., 1961). The predominate role of the liver in the synthesis of plasma protein is illustrated by the classical experiments of Miller and his associates (Miller et al., 1951; Miller and Bale, 1954).

Plasma is a complex mixture of compounds of which proteins form the major macromolecular component. The precise number of proteins in plasma has not been determined finally, although in 1966 Schultze and Heremans listed almost two hundred recognizable immunologically distinct entities or enzymatic activities. This list excluded the different individual antibodies that form the immunoglobulin population.

Polyacrylamide gel electrophoresis (PAGE) and rocket-immunoelectrophoresis are sensitive methods for human plasma protein separation. The protein patterns in the gel were identified according to Felgenhauer (1970) and Albraham et al., (1970). Bands produced by

PAGE, such as prealbumin, α_1-acid glycoprotein, albumin and transferrin form a single peak and are determined directly. About 90 per cent of the first post-albumin peak contain Gc-globulin, α_1-antichymotrypsin and α_1-β glycoprotein. The second post-albumin peak consisted mainly of α_2 HS-glycoprotein and 4, 6S-glycoprotein. Hemopexin and then ceruloplasmin migrated directly in front of transferrin and the haptoglobin zone becomes unclear (Schultze and Heremans, 1966, Felgenhauer, 1970; Hoffmeister and Schuett, 1972; Pongpaew et al., 1975).

In sera from patients with primary liver cell carcinoma, certain changes in concentrations of the normal constituent proteins have been shown by PAGE: prealbumin, albumin and transferrin fractions are decreased. In patients with other liver diseases such as amoebic liver abscess, cirrhosis, cholangiocarcinoma and carcinoma of the head of pancreas prealbumin, albumin and transferrin are decreased as well. These changes have been reported by Schaffner et al., 1962, as being characteristic in liver diseases. Damage to liver parenchymal cells may result in a decrease of serum protein synthesis and a change in protein metabolism.

Prealbumin decreased significantly in all liver diseases ($P < 0.01$) because it is the most sensitive indicator of the impaired liver function (Haellen and Laurell, 1972).

Comparison of albumin in various liver diseases showed that for patients with amoebic liver abscess and cirrhosis the albumin

level were significantly lower than in patients with primary liver cell carcinoma ($P < 0.05$). The albumin concentration in patients with amoebic liver abscess was significantly lower than in patients with cholangiocarcinoma as well.

Transferrin was reported to be increased in iron deficiency anemia and during pregnancy, but it is decreased in hemolysis, liver diseases, nephrosis and inflammation. (Mandel, 1959; Rentsch et al., 1974). It was found that if transferrin is high and iron is low, there is a lack of iron. Whereas, if both are low there might be inflammation or neoplasia. This study indicated that the concentration of transferrin decreased significantly in amoebic liver abscess, cirrhosis, cholangiocarcinoma, carcinoma of the head of pancreas and primary liver cell carcinoma ($P < 0.01$). The transferrin levels in sera from patients with primary liver cell carcinoma were significantly higher than those in the sera from patients with amoebic liver abscess, cirrhosis, cholangiocarcinoma and carcinoma of the head of pancreas ($P < 0.01$).

α_2 HS-glycoprotein was reported to be decreased in cancer (Schultze and Heremans, 1966; Synder and Ashwell, 1971). Significant decrease of α_2 HS-glycoprotein was found in all liver diseases studied in this investigation ($P < 0.01$). α_2 HS-glycoprotein levels were significantly lower in patients with amoebic liver abscess, cirrhosis of the liver and cholangiocarcinoma ($P < 0.01$) than in

patients with primary liver cell carcinoma. A significant decrease of α_2 HS-glycoprotein was found in patients with amoebic liver abscess when compared with patients with carcinoma of the head of the pancreas ($P < 0.01$ - "T-test").

Elevated hemopexin levels occur in various forms of cancer (Korinek, 1969; Braun and Aly, 1971; Manual et al., 1971). Whether this elevation is an early or late manifestation has not been ascertained. Very high hemopexin levels were encountered in patients with fast-growing melanomas. In the case of severe liver diseases, hemopexin levels decline presumably because of decreased synthesis rather than hemolysis.

The concentration of hemopexin in this study was shown to be significantly lower only in patients with cholangiocarcinoma when compared with controls ($P < 0.01$). Hemopexin concentrations were significantly lower in patients with cholangiocarcinoma than in patients with amoebic liver abscess or primary liver cell carcinoma ($P < 0.01$). In patients with cirrhosis of the liver and carcinoma of the head of the pancreas hemopexin levels were significantly lower than in patients with amoebic liver abscess and primary liver cell carcinoma ($P < 0.05$).

There was no significant difference of Gc-globulin in liver diseases in this study, although it has been reported that Gc-globulin decreased in severe liver diseases (Schultze and Heremans, 1966).

Haptoglobin, α_2-macroglobulin, ceruloplasmin and α_1-acid-glycoprotein belong to the acute-phase reactants (Aronson et al., 1972; Koj, 1974). They increase rapidly during infections. For this reason the controls under investigation were chosen carefully.

Haptoglobin, a fast reacting protein, will increase during the infection process (Anastassea et al., 1972; Giblett, 1974; Koj, 1974). Inflammation and neoplasia also cause an increase in haptoglobin (Aly and Braun, 1974). Minchin et al., 1970 indicated significant increase of haptoglobin in serum of patients with tuberculosis. High serum levels of haptoglobin were found by Schuett and Hoffmeister in 1971 in various inflammatory lung conditions and bronchial neoplasms. They indicated that the serum haptoglobin concentration was significantly lower in patients with various inflammatory lung conditions than in patients with bronchial neoplasms. They suggested haptoglobin as a useful tool in the early diagnosis of carcinoma of the lung. The haptoglobin concentration is usually elevated in the blood of patients with infectious diseases, cancer, leukemia, as well as after surgery and burns (Jayle and Moretti, 1962; Owen and Smith, 1964; Wiedermann et al., 1966; Dobryszycka et al., 1969; Werner, 1969). Haptoglobin is also regarded as a very sensitive indicator of disease persistence.

In this study, significantly higher levels of haptoglobin were found in patients with amoebic liver abscess, obstructive jaun-

dice (including cholangiocarcinoma and carcinoma of the head of the pancreas) and primary liver cell carcinoma ($P < 0.01$). The marked increas in haptoglobin levels was noticable in amoebic liver abscess and primary liver cell carcinoma (three and two times of controls respectively). Significantly higher amounts of haptoglobin were found in patients with amoebic liver abscess than in patients with cirrhosis of the liver, cholangiocarcinoma, primary liver cell carcinoma ($P < 0.01$) or carcinoma of the head of the pancreas ($P < 0.05$). Haptoglobin may be a useful tool for differentiation of liver diseases.

α_2-macroglobulin is an acute-phase reactant which shows elevated levels in acute infection and other stressful situations such as trauma. One of the functions of α_2-macroglobulin may be the binding and clearance of proteolytic enzymes (Ohlsson, 1974). α_2-macroglobulin concentration in normal male serum is between 150 to 350 mg/100 ml and it is increased in liver diseases, nephrosis and diabetes (Schultze and Heremans, 1966). According to this study α_2-macroglobulin increased significantly in amoebic liver abscess, cirrhosis of the liver, cholangiocarcinoma ($P < 0.01$) and carcinoma of the head of the pancreas ($P < 0.05$). Furthermore, α_2-macroglobin levels than in patients with cirrhosis of the liver were significantly higher in patients with amoebic liver abscess, cholangiocarcinoma and primary liver cell carcinoma ($P < 0.01$) and in patients with carcinoma of the head of the pancreas ($P < 0.05$).

Ceruloplasmin transports copper in plasma. It is reported to increase in diseases such as carcinoma, myocardial infarction and in liver diseases (Wewalka, 1969; Pineda et al., 1972).

Significant increase of ceruloplasmin levels in this study occurred in patients with cholangiocarcinoma, primary liver cell carcinoma ($P < 0.01$) and in patients with carcinoma of the head of the pancreas, cirrhosis of the liver ($P < 0.05$, $P < 0.025$ respectively-"T-test"), but not in patients with amoebic liver abscess.

Another acute-phase reactant protein studied was α_1-acid-glycoprotein. This protein is reported to be increased in malignant neoplasms, chronic inflammatory conditions and rheumatoid arthritis (Schultze and Heremans, 1966). This study indicated that only patients with amoebic liver abscess showed significant increase in α_1-acid-glycoprotein. Perhaps this is secondary to the fact that PAGE was used to separate α_1-acid-glycoprotein, whereas the more sensitive rocket immuno-electrophoresis was employed for separation of other acute-phase reactants.

In summary, increases in acute-phase reactant or fast-reacting proteins i.e. haptoglobin, α_2-macroglobulin, and ceruloplasmin may be helpful in the differentiation of liver diseases.

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