ALPHA-1-ANTITRYPSIN IN HEPATOMEGALY WITH EMPHYSEMA

THESIS

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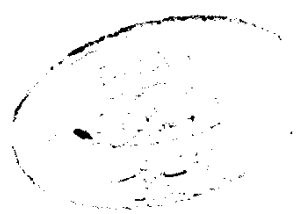

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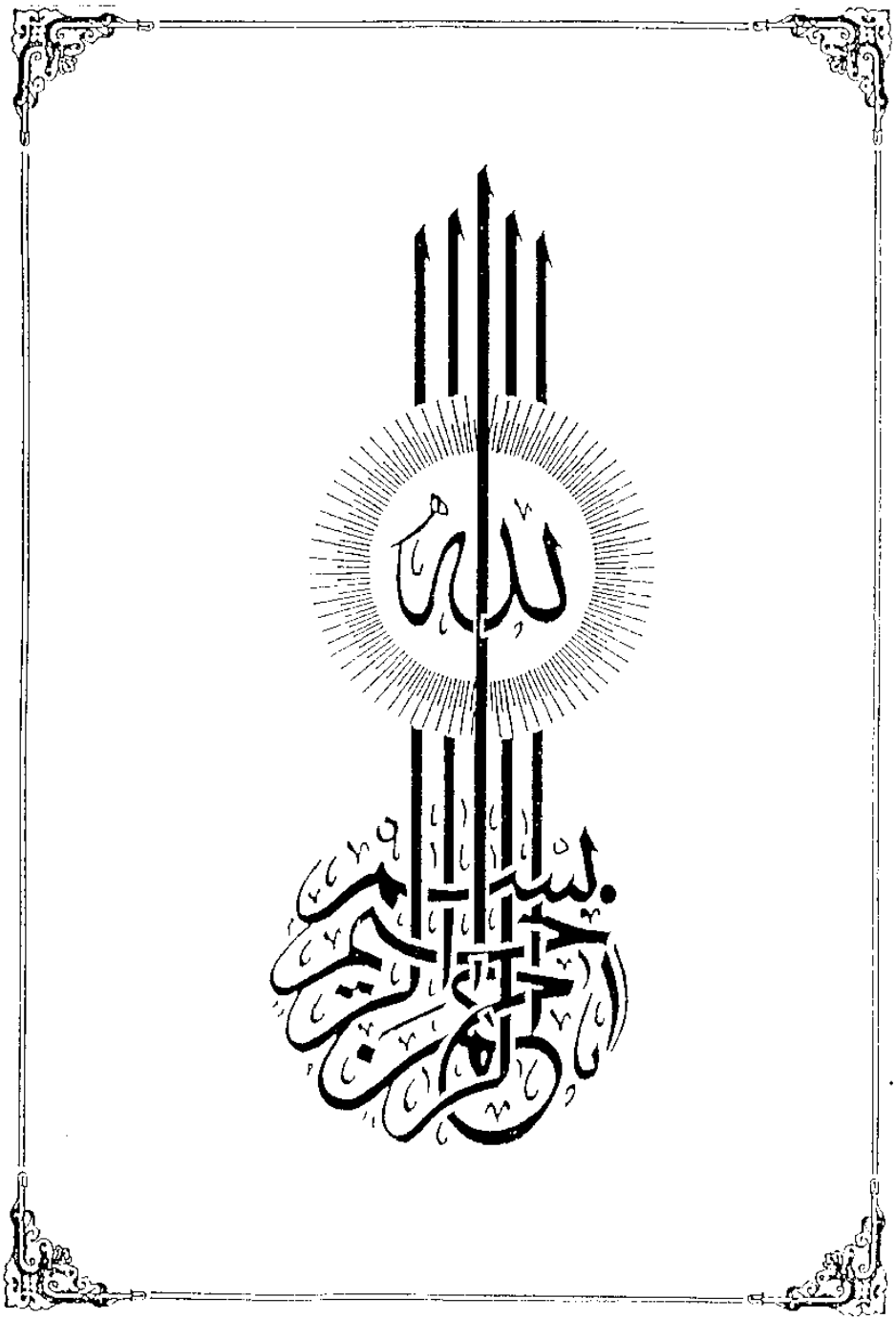

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Alpha-1-antitrypsin is a plasma protein comprising 80 - 90 % of alpha-1-globulin. Its function is protective through antiproteolytic activity. Deficiency of alpha-1-antitrypsin is inherited as a recessive character. This deficiency presents either as neonatal hepatitis or with obstructive airway disease in early adult life (Gray and Howorth, 1980).

In emphysema, alpha-1-antitrypsin deficiency was reported (Eriksson, 1965). Hepatomegaly is also common in emphysema.

The aim of this work is to find wether there is a relationship between alpha-1-antitrypsin deficiency and hepatomegaly in emphysema with consideration that emphysema may be complicated by cor pulmonale which causes right sided heart failure leading to liver congest' n.

REVIEW OF LITERATURE

ALPHA-1-ANTITRYPSIN (A1AT)

** Function and chemical structure

Opie in 1905, was perhaps the first to draw attention to the occurence of proteases and protease inhibitors in inflammatory exudates. Purified Alpha-1 proteolytic inhibitor from human plasma was shown to inhibit the pancreatic enzymes trypsin and chymotrypsin (Laurell& Jeppsson, 1975).

The serum concentration of A1AT in a healthy person is 180 - 280 mg./dl. (Kueppers & Black, 1974). A1AT accounts for approximately 90% of the protease inhibitor activity of normal plasma (Gitlin & Gitlin, 1975).

* Chemical structure

A1AT is a glycoprotein which has a molecular weight of 55,000 Daltons (Crawford, 1973). This glycoprotein consists of a single polypeptide chain of about 415 amino acids residues (Laurell & Jeppsson, 1975).
Galactose, mannose, N-acyl glucosamine, N-acyl neuraminic acid, acetyl hexosamine and sialic acid comprise the 12% carbohydrate portion (Kueppers & Black, 1974).
On routine protein electrophoresis, it is the predominent glycoprotein responsible for the alpha-1 globulin band, a relative absence of which is the easiest way to screen for

a severe deficiency state (Myerowitz et al., 1972).

* Biological function

Kueppers et al., in 1964, have shown that A1AT can inhibit proteases from human granulocytes including an elastase and a collagenase. These enzymes are probably major contributors to tissue destruction during an inflammatory process (Ohlsson & Olsson, 1973).
All the above mentioned enzymes are firmly bound and inactivated by A1AT in an immediate reaction with a molar ratio of 1:1 as was first shown by Bundy & Mehl, in 1959. They stated that the mechanism of blocking of the active site is largely unknown.

A1AT reaction with the protease implies formation of complexes with covered active sites of the enzymes. The complexes are stable on electrophoresis, pH 9 to 5, and have an electrophoretic mobility intermediate to that of the reactants. The mobility of the enzyme-inhibitor complex increases suddenly on supersaturation with trypsin. The stability of the complexes on chromatographic and electrophoretic separation is an indication of the firmness of the linkage, but the reaction is reversible(Ohlsson, 1971 a).

Ward & Talamo in 1973, observed that sera from patients with A1AT deficiency also have low levels of"chemo-

tactic factor inactivator". So far, nothing indicates that this factor is identical with A1AT. Perhaps both defects are interrelated in a more indirect way. In the absence of this inactivator, more granulocytes may remain at the site of inflammation for a prolonged period, which may lead to excess local proteolytic activity.

In 1974, Heck and Kaplan showed that A1AT inhibits plasma thromboplastin, by such an action A1AT could influence clotting.

Inhibition of microbial enzymes such as Aspergillus oryzae protease has been observed (Bergkvist, 1963). The A1AT binding provides a mechanism for enzyme destruction. Complexes between the enzyme and A1AT are normally not detectable in plasma (Laurell & Jeppsson, 1975).

In acute pancreatitis A1AT complexes appear in the exudate from the pancreas and in ascitic fluid, but they disappear during the draining of the fluid through the lymphatic system (Laurell & Jeppsson, 1975). Granulocytal protease A1AT complexes have been detected in ascitic fluid in acute peritonitis, in cerebrospinal fluid during leukocytosis (Laurell & Jeppsson, 1975), in the synovial fluid in arthritis (Shtacher et al., 1973) and in abscesses (Ohlsson, 1973).

Protease inhibitors can inactivate synovial cell enzymes and so limit their inflammatory action. A1AT def-

iciency ought to facilitate the development of inflammatory joint diseases or delay its resolution (Buisseret et al., 1977).

The occurence of A1AT in extrahepatic sites may be important, since certain protease inhibitors inhibit the growth of tumour cells or inhibit the process of transformation (Schnebli, 1974). The increased level of protease activity in malignant cells might be due to deficiency of protease inhibitors in these cells (Schnebli et al., 1972).

** Alpha-1 Antitrypsin in Human Macrophages

A1AT was first demonstrated in human alveolar macrophages by Cohen in 1973, by means of an immunofluorescence technique. He noted that intensity of fluorescence declined over 72 hours and interpreted this finding as evidence that macrophages had taken up plasma A1AT which was then gradually lost from the cells. Preliminary studies have suggested that A1AT is a useful immunohistochemical marker of histiocytes (monocytes/macrophages) and malignant tumours derived from them (Isaacson et al., 1981).

In normal tissues, while certain non-lymphoreticular cells such granulocytes may contain A1AT, the macrophages are the only lymphoreticular cells in which A1AT was consistantly demonstrated. To confirm the reliability of A1AT as a marker of histiocytes, Isaacson et al., in 1981, studied a wide variety of benign and malignant lymphoreticular

cells and tissues that have been stained by immunoperoxidase technique for A1AT and positive staining was found to be confined to histiocytes.

Immunodiffusion, isotope labelling and isoelectric focusing studies performed on cell lysates confirmed that +ve staining shown by monocytes and histiocytes is due to presence of A1AT identical with serum A1AT and that this material is synthesized by these cells rather than taken up from their environment. Thus we can state with confidence that the presence of A1AT in cytoplasm of malignant lymphoreticular cells, seen by +ve immunoperoxidase staining for A1AT, is a reliable indicator of their true histiocytic derivation or origin (Isaacson et al., 1981).