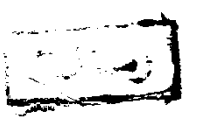
PLASMA FIBRONECTIN CONCENTRATIONS IN PATIENTS WITH ACUTE VIRAL HEPATITIS

THESIS

Submitted in Partial Fulfilment for the Master Degree in Tropical Medicine (M.Sc.)



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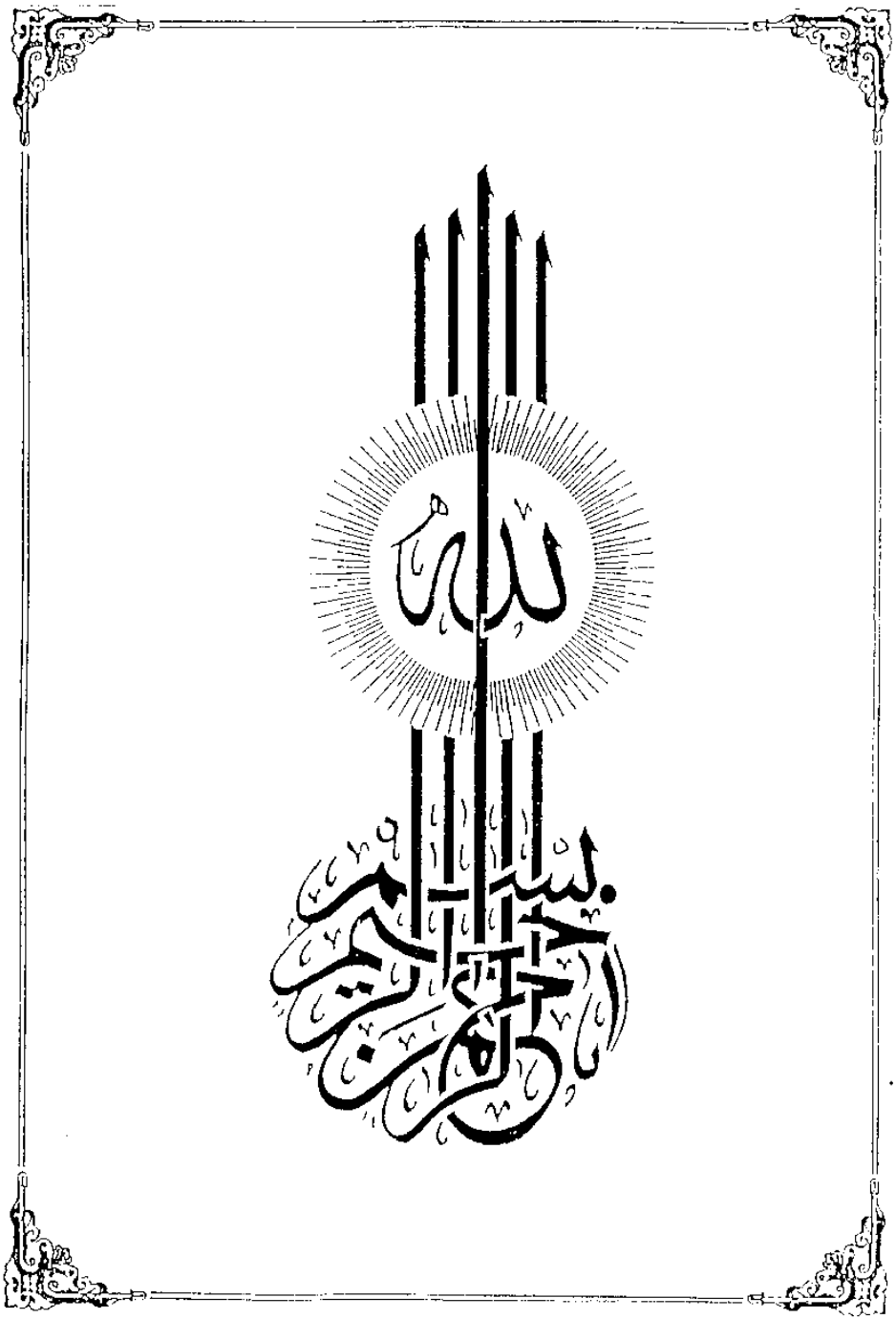
قالوا

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا

إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة (الآية ٣٢)



THE RESEARCH OF TODAY.

THE MEDICINE OF TOMORROW.

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INTRODUCTION

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*Fibronectin (cold insoluble globulin) is a high molecular weight glycoprotein found both in an insoluble form in connective tissue, blood vessel walls and basement membranes and in a soluble form in extracellular fluids (**Yamada et al. 1978**).*

*Mesenchymal cells, including fibroblasts and vascular endothelial cells, are considered the main sites of synthesis of fibronectin (**Wartrovaara et al., 1974**). Cultured rat hepatocytes have also been demonstrated to synthesize and excrete fibronectin (**Voss et al., 1979**).*

*Consequently, parenchymal liver disease may lower plasma fibronectin either due to decreased synthesis or due to increased consumption of fibronectin. Repair processes following liver disease involve both proliferation of parenchymal liver cells and formation of fibrosis by mesenchymal cells. these repair processes may also influence plasma fibronectin concentration. So far the problem has received little attention (**Matsuda et al., 1982**), (**Pot et al., 1980**) and needs more study to be clarified and solved.*

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The concentration of plasma fibronectin in normal subjects and in various diseases have been determined in several laboratories **(Ganrot et al., 1972; Fyrand et al., 1976).**

However some of the data reported are contradictory and inadequate for final conclusions to be drawn **(Ne et al., 1981).**

The object of the present study was to elucidate the plasma fibronectin level changes in patients with acute viral hepatitis.

REVIEW OF LITERATURE

FIBRONECTIN

Introduction

The term fibronectin describes a family of structurally and immunologically related high molecular weight glycoproteins that are present on many cell surfaces, in extracellular fluid in connective tissues, and in most basement membranes. Interaction with certain discrete extracellular substances, such as glycosaminoglycans (e.g. heparin) fibrin, and collagen and with cell surface structures seem to account for many of its biologic activities, among which are regulation of cell adhesion, spreading and locomotion **(Mosesson et al., 1980).**

Prior to the sugession of the name "fibronectin" the protein in its various forms had been designated by a variety of terms including: Cold insoluble globulin (Clg) **(Morrison et al., 1948),** *Antigelatin factor* **(Wolff et al., 1967).** *Opsonic protein* **(Saba et al., 1970),** *Large external transformation sensitive protein (LETS)* **(Hynes et al., 1974)** *soluble fibroblast antigen (SF-antigen)* **(Rouslahti et al., 1974),** *cell surface protein (CSP)* **(Yamada et al., 1974),** *Galactoprotein a* **(Gahmberg et al., 1974),** *Z* **(Blumberg et al., 1975),** *cell adhesion factor (CAF)* **(Pearstein et al., 1976),** *and cell spreading factor* **(Grinnell et al., 1976).**

At present, there appears to be widespread recognition of the need for a single general designation for all forms of

the protein as well as general acceptance of the term "fibronectin". The word itself was created to emphasize the propensity of the protein to bind to fibrous proteins like collagen and fibrin (fibra, fibre, and necrete, to bind) in certain instances, such as for descriptive clarify, it is useful to apply a name other than fibronectin **(Mosesson et al., 1980).**

Historical Events (1948-1975):

The name "cold-insoluble globulin of plasma" stems from the report in 1948 by Morrison et al., who described a protein component of fibrinogen containing fractions that was cold-insoluble and, unlike fibrinogen, was not thrombin coagulable. Cold-insoluble globulin (Clg) displayed a more rapid anodal electrophoretic migration rate and higher sedimentation coefficient than did fibrinogen. Later, physicochemical analyses reported in 1955 by **Edsall et al. (1955)** *led to the suggestion that Clg was a modified dimer of fibrinogen. Shortly thereafter,* **Smith and Von Koff (1957)** *described a protein with properties similar to those of Clg that they had found in a heparin-induced cold precipitate of either normal or pathologic plasma.*

subsequent clarification of a patient presenting with a chronic intravascular coagulation syndrome secondary to an occult neoplasm **(Mosesson et al., 1968).** *The illness was characterized by the persistence of pathogenic cold-induced plasma*

precipitate termed "cryofibrinogen". The solubilized cryofibrinogen was partially coagulable by thrombin, thus proving that fibrinogen was present. Another major component resembling Clg was also found in the fractions and was shown to be immunochemically identical with a normal serum protein unrelated to fibrinogen. Follow-up investigations by ***Mosesson and Umfleet (1970)*** *presented a method for isolation and purification of Clg and provided clear evidence that it was unique and major plasma protein (300 ± 10 ug/ml)*

In the early 1970s, a number of investigations had focused on the changes that occured in cell surface proteins of fibroblasts as a consequence of transformation by oncogenic viruses. Particular attention was paid to a large external transformation. Sensitive glycoprotein (LETS) of molecular weight 250,000 ***(Ruoslahti et al., 1973), (Yamada et al., 1974), (Gahmberg et al., 1974), (Blumberg et al., 1975)*** *that was released from the fibroblast cell surface into the culture medium* ***(Ruoslahti et al., 1973; Rouslahti et al., 1974),*** *the report by Ruoslahti that Clg was antigenically identical to LETS brought to light the uniquessness of fibronectin as both a cell surface matrix protein and a blood protein and has stimulated numerous investigations on all forms of the protein* ***(Mosesson et al., 1980).***

Distribution and Biologic Activities of Tissue forms of Fibronection:

In addition to being synthesized by fibroblasts, fibronectin is also produced by astroglial cells ***(Vaheri et al., 1976).*** *Schwann cells* ***(Kurkinen et al., 1979),*** *endothelial cells,* ***(Birwell et al., 1978)*** *chondrocytes* ***(Hassell et al., 1978)*** *myoblasts* ***(Chen et al., 1977)*** *certain epithelial cells* ***(Chen et al., 1977; Crouch et al., 1978; Oberly et al., 1979)*** *including those derived from carcinoma cell lines* ***(Zetter et al., 1978, Smith et al., 1979).*** *Peritoneal macrophages have also been reported to synthesize and secrete fibronectin* ***(Johansson et al., 1979)*** *although* ***Pearlstein et al. (1978)*** *did not find the protein on the surface or within resident or activated peritoneal macrophages.*