# Fibrinolytic Inhibitors in Bilharzial hepatic disease



*Thesis*

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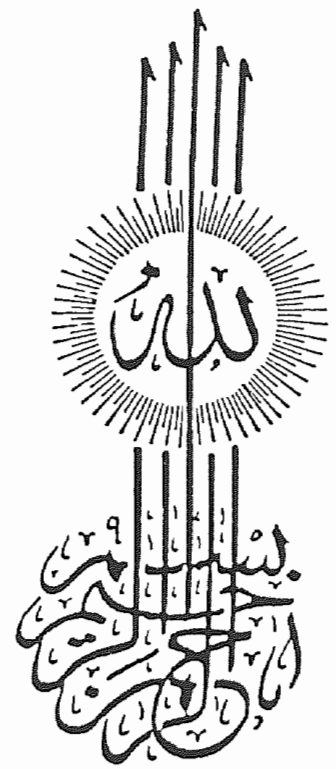

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
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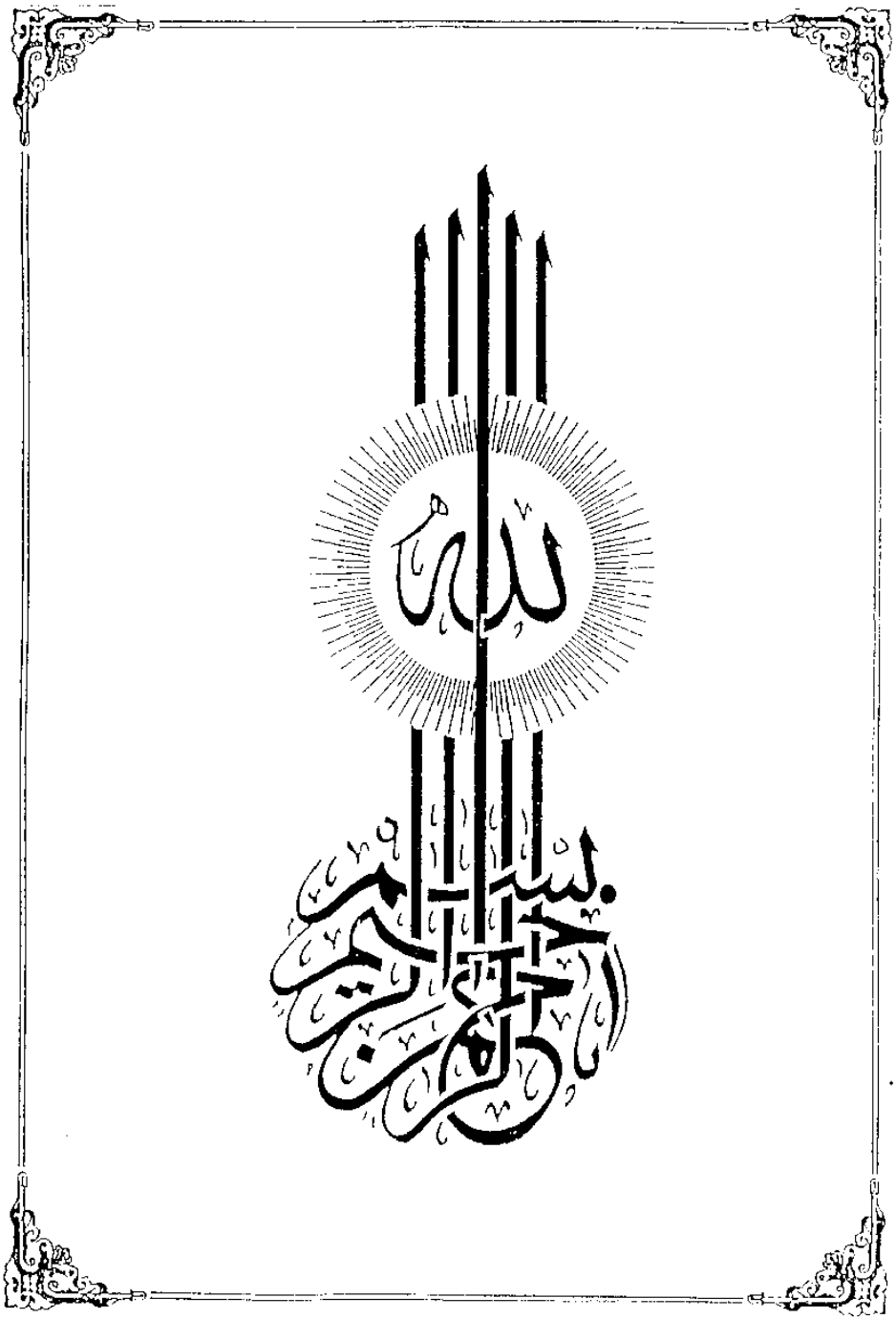

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# INTRODUCTION

# AND

# AIM OF THE WORK

# INTRODUCTION

Multiple abnormalities of bleeding and coagulation parameters have been found in patient with liver disease, the severity of the acquired abnormalities depends to a large extent upon the degree of hepatocellulor damage (Deutch 1965 and Donaldson et al, 1969).

The nature of haemostatic defects in liver disease is complex including dereased synthesis of coagulation factors (Rappaport, 1961), defects of fibrin polymerization (Alkajersig et al , 1962) and increased fibrinolysis (Hersh et al., 1987).

α2-antiplasmin , α2 macroglobulin and α1-antitrypsin act as fibrinolytic inbibitors, the major inhibitor of plasmin in blood is α2-antiplasmin that inactivates plasmin rapidly and irreversibly by forming a covalent bond (Lijmen and Collen, 1985).

α1 antitrypsin acts as slow inhibitor forming irrerversible complex with plasmin which is rapidly removed from the circulation (Robbin, 1982 one/ Rimon et al., 1966).

The fibrinolytic inhibitors α2-antiplasmin and α1-antitrytsin are synthesized by the liver (Kelly et al., 1987) and low level of α2-antiplasmin may be found in cirrhosis or hepatic failure (Aoki and Yamanaka, 1978).

Congenital absence of α2-antiplasmin is associated with severe life long bleeding diathesis (Aoki, et al., 1979) and partial deficiency has been found in families with a mild or moderate bleeding tendency (Klaft et al., 1982).

Several people who were evaluated for unexplained chronic bleeding disorders have subnormal α2-antiplasmin level with otherwise normal screening test of coagulation.

Using the presence of severe α2-antiplasmin deficiency as an indication for therapy, Epsilon aminocaproic acid adiminstration was associated with cessation of life threatening bleeding (Williams, 1989).

## AIM OF THE WORK

The aim of this work is to study the changes in the levels of both α2-antiplasmin and α1-antitrypsin in different stages of bilharzial hepatic disease.

# REVIEW

# OF

# LITERATURE

## BLOOD COAGULATION CASCADE

(Figure 1)

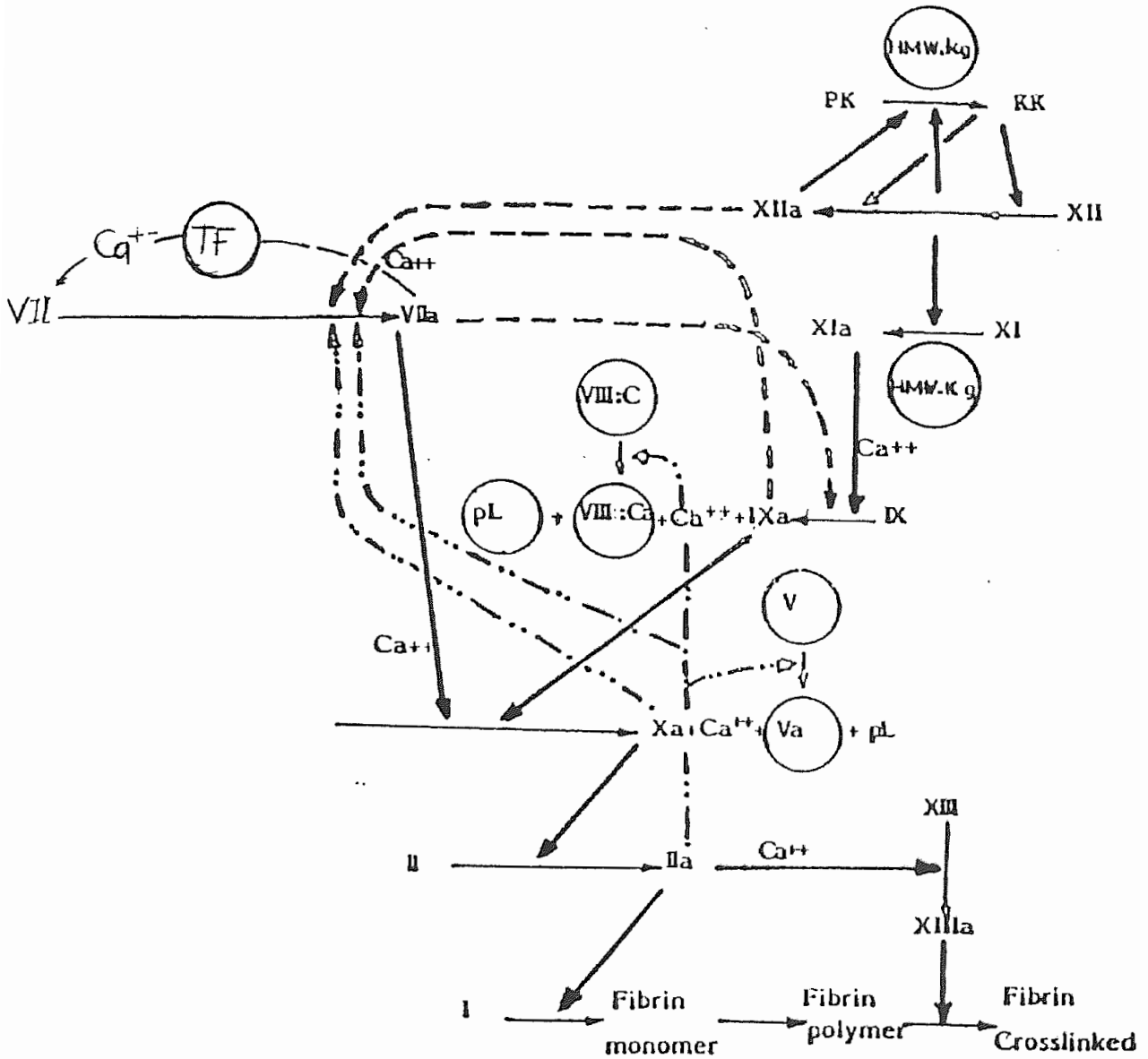
The coagulation mechanism is composed of a series of reactions which function as a biological amplifier. This view was enunciated independently by Macfarlane (1964) and Davie & Ratnoff (1964) and termed the cascade hypothesis.

Knowledge of the individual components and reactions has greatly expanded during the succeeding years and additional factors were identified (Prekallikrein and high molecular weight kininogen).

Contact Activation System (Intφinsic Pathway) :

The contact system is composed of factor XII (Hageman factor), prekallikrein, high molecular weight kininogen (HMWK) and factor XI, the interaction of which results in the conversion of factor XII to factor XIIa which in turn activates factor XI to XIa. The latter then proteolytically activates factor IX to factor IXa, which in the presence of factor VIIIa, $Ca^{++}$ and phospholipid vesicles or membranes activates factor X and leads to the formation of prothrombinase complex which consists of factors Va (a cofactor), Xa (an enzyme), $Ca^{++}$ and membranes. This complex converts prothrombin to thrombin, which leads to clot formation (Nemerson Y., 1988).

## COAGULATION PATHWAYS. INITIATION AND REGULATION




——→ Transformation of precursors into active species.

——→ "Forward" reactions of classical extrinsic, intrinsic and common pathway.

– – – → Positive feed back reactions.

– – – → Reacctions between components of classical extrinsic and classical intrinsic systems.

Fig. (1) : Clot promoting reactions of the extrinsic and intrinsic systems, Positive feedback reactions and linkages between both coagulation systems. (Lammle et al., 1985).

Extrinsic coagulation mechanism

This requires a tissue factor which gains access to the blood only when tissue is damaged. It is initiated by the formation of a complex of the tissue factor with factor VII. Factor VIIa in the presence of tissue factor and calcium is capable of activating factor X and in addition can activate factor IX (Zur & Nemerson, 1980). So in tissue factor (TF) initiated coagulation, factor Xa is generated directly by the action of the TF: VIIa complex and indirectly by the activation of factor IX; the instantaneous concentration of factor Xa is determined by the summation of the two pathways (Nemerson, 1988).

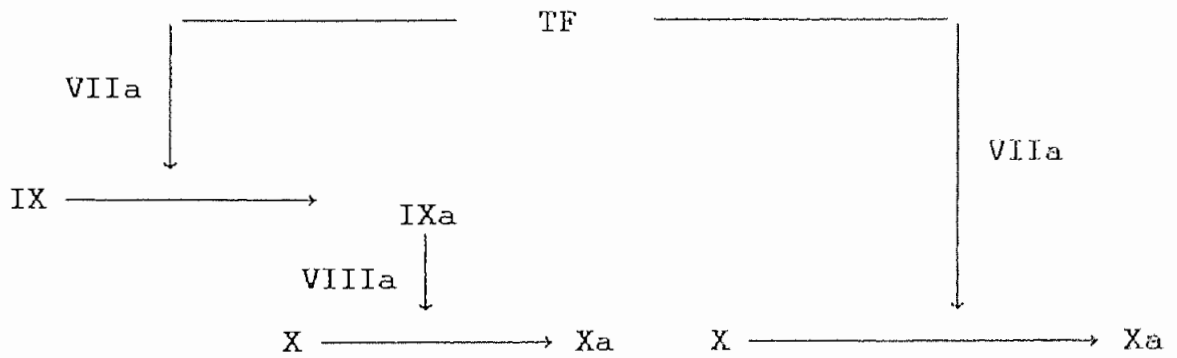



Figure (2) : Tissue factor-initiated coagulation (Nemerson, 988 : Tissue factor and haemostasis).

In TF - initiated coagulation one can imagine the following events : an injury either physical or chemical, disrupts the endothelium and pertubs cell surfaces, thereby making TF available and allowing blood to contact subendothelial tissues, which leads to the formation of a TF : VII complex, which then generates activated factor X, which inturn actalyzes the conversion of factor VII to its two chain derivative VIIa thereby resulting in an increase of some 100 fold in coagulation activity (Nemerson Y, 1988).

Endothelial regulation of TF and protein C :

Under normal circumstances the endothelium is probably inert with respect to coagulation. However upon exposure to agonists such as interleukin I, tumour necrosis factor and endotoxin, TF activity appears on the surface of the cells (Bevilacqua et al., 1985; Nawroth & Stern, 1966).

Because it has been shown that protein synthesis is required for this process, it is unlikely that induction of TF is involved in haemostasis. However, the fact that, for example, bacteria are frequently encapsulated in fibrin suggests that interleukin I or endotoxin may promote local TF synthesis. Likewise, if the endothelium is exposed to promoters of TF synthesis, it is also possible that these cells could be rendered thrombogenic. If this were the case, one could envision stimulated endothelium being responsible

for initiating thrombosis formation. A particular appealing finding in this regard is the demonstration that as TF is "up regulated", the expression of thrombomodulin is "down regulated" (Moore et al., 1987).

If the above phenomenon occurs in vivo, then stimulation of endothelial cells could promote coagulation by TF and inhibit the anticoagulant effects of protein C through suppression of thrombomodulin (Nemerson, 1988).

Protein C deficiency had been studied in liver cirrhosis with bleeding oesophageal varices by Sallam et al., 1992. they found that cirrhotic patients with bleeding oesophageal varices showed the lowest level of protein C in their plasma. They concluded that the striking decrease of protein C in all cirrhotic patients, and specially those with bleeding oesophageal varices, may reflect a compensatory and prophylactic mechanism by which protein C is markedly decreased to re-establish a balance between coagulation system on one side and the anticoagulant, fibrinolytic system on the other.

Fibrin Formation :

The conversion of soluble circulating fibrinogen into a network of fibrin at the site of injury provides stability to the haemostatic plug of platelets. The fibrinogen molecule is a dimer with two identical halves consisting of polypeptide chains (Aα, Bβ , ) which are connected by disulphide

pridges. Disulphide bonds also join the two half molecules. It is now generally accepted that the molecule has elongated nodular structure, the model originally described by Hall & Slayter (1959).

Thrombin first attacks the Aα chain of fibrinogen cleaving the bond between arginine and glycine (Arg 16-Gly 17) to release fibrinopeptide A. The remainder of the monomeric molecule (fibrin I) undergoes polymerisation to form a two-stranded structure termed a protofibril which was identified by Ferry in 1952 (Derek & Bruce 1985).

Following the formation of the protofibril, thrombin cleaves the bond between arginine and glycine in the Bβ chain to release fibrinopeptide B, a step which allows lateral association of the protofibrils to form thicker fibrin fibres (Blomback et al., 1978).The concept of a two-stage removal of fibrinopeptides has been supported by kinetic analysis of the sequential nature of release (Higgins et al., 1983).

The production of stabilized fibrin of high tensile strength involves the formation of convalent bonds between adjacent fibrin monomers. This is achieved through the action of factor XIII (Fibrin stabilizing factor) which circulates in plasma in the form of an inactive zymogen. The activation of plama factor XIII needs thrombin and calcium ions. The result of activation is the production of separate (a) and (b) subunits. (Derek & Bruce 1985).