STUDY OF FIBRINOGEN AND FIBRINOLYTIC ACTIVITY AS WELL AS THE CORTISOL BLOOD LEVEL IN PATIENTS UNDER PROLONGED CORTICOSTEROIDS THERAPY NAMELY BRONCHIAL ASTHMA AND RHEUMATOID ARTHRITIS

THESIS

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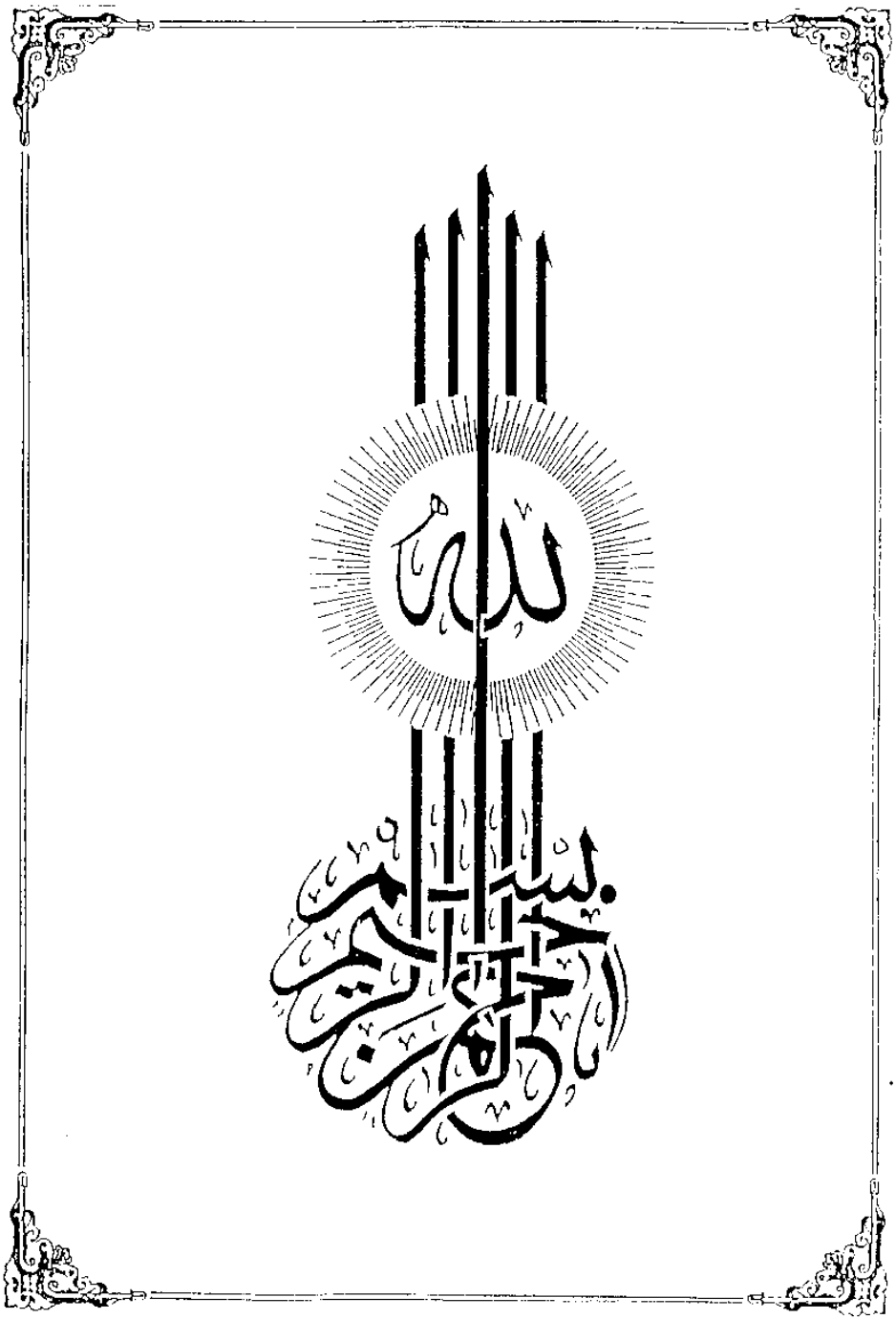

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CONTENTS

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LIST OF ABBREVIATIONS

AMCA : Tranexamic acid or Para amino methyl cyclohexane carboxylic acid.

C D : Cotton dust.

D I C : Disseminated Intravascular Coagulation.

EACA : Epsilon - Aminocaproic acid.

EDTA : Dipotassium salt of ethyline diamine tetraacetic acid,

ELT : Euglobulin lysis time.

ESR : Erythrocyte sedimentation rate.

FDP : Fibrin degradation product.

H D : House dust.

LSU : Luminating standard unit.

MES : 2N morpholine ethane - sulphonic acid.

MM : Mixed moulds.

MP : Mixed pollens.

PPP : Platelet poor plasma.

PRP : Platelet rich plasma.

RBCs : Red blood corpuscles.

SCT : Serial clot thin time.

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INTRODUCTION AND AIM OF THE WORK

It is a well known fact that corticosteroids are a very useful and effective weapon in the management of many medical problems. Nevertheless, there use is marked by many hazards and complications which may amount to very distressing biological changes. Most of these complications are gross enough to be discovered with relative ease.

On the other hand, some of these ill effects are imposed on special organs and tissues and the biological abnormality in such cases cannot be detected on clinical grounds alone. These alterations are mainly found in the blood and body fluids and they sometimes may pass unnoticed except if specific investigations were carried-out. Among these, are the alteration in the blood fibrinolytic mechanism and plasma cortisol level.

Fibrinolytic mechanism, is the most important guard against haemostatic abnormalities. It is thought that under normal conditions, fibrinogen is constantly transformed into fibrin, and this fibrin is laid down on the

endothelium of the blood vessels, where it gives further strength to them, thus preventing spontaneous blood loss. Meanwhile this fibrin is subjected to a continuous process of removal by the fibrin dissolving mechanism i.e. fibrinolysis. In other words, there is a balance between fibrinogenic versus fibrinolytic mechanism.

This balance is responsible for the presence of the normal haemostasis. Dysequilibrium between these two opposing mechanisms result in either a tendency to blood loss or a tendency to thrombosis. (Salzman and Britten, 1965).

Since corticosteroids are known to affect different parameters of haemostasis (Corrigan, 1970), it can be inferred that the prolonged use of these drugs can result in some abnormalities in the fibrinolytic mechanism.

Thus, this work is interrested in the discovery of the possible alterations in the fibrinolytic mechanism as a result of prolonged use of corticosteroids.

To achieve this aim, patients with rheumatoid arthritis and patients with allergic bronchial asthma,

needing prolonged corticosteroid therapy were chosen to be studied before and after treatment. The relation between the, changes in endogenous cortisol level in the plasma and exogenous corticosteroid intake is another point of study in the present work. Any correlation between the different aspects of the study will be found out.

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FIBRINOLYSIS

Fibrinolysis can be defined as the enzymatic liquifaction of blood or fibrin clot (Fearnley, 1971). The invivo function of the fibrinolytic system is the removal of unwanted fibrin deposits or fibrin once it has served its purpose in, for example, healing and inflammation. Fibrinolysis may also be regarded as the physiological antagonist of coagulation, and blood may be considered as a tissue of the body which can exist in the fluid or the gel phase depending upon the balance between coagulation and fibrinolysis. Unless the coagulation system is checked by the fibrinolytic system, the clotting mechanism would solidify the whole circulating blood within a few minutes (Macfarlane, 1972).

Normally there is a physiological balance between coagulation and fibrinolysis. An imbalance in one direction might lead to haemorrhage (coagulation defect or excessive fibrinolysis) - while the reverse situation (hypercoagulability or defective fibrinolysis) might predispose to thrombosis (Salzman and Britten, 1965).

Normally there is a continous process of deposition and removal of fibrin on and from the vessel wall (Astrup, 1956; Jensen, 1956).

Historical Perspective:

The earliest known published observation on fibrinolysis is that of John Hunter, who in 1794 recorded the liquid nature of blood in cases of sudden death. He also observed that, the same occurs in animals killed by lightenig or electricity (McNicol and Douglas, 1972).

Green in 1887, noted that when fibrin prepared from ox blood had dissolved when incubated in saline, it could not be clotted again by thrombin. He also observed that clots prepared from human blood obtained by cupping, occasionally dissolve within 24 hours. He made the fundamental observation that once fibrin was dissolved, it could not be clotted by thrombin. Dastre in 1893 named this process, "Fibronolysis". (McNicol and Douglas, 1972).

In 1903, Delezenne and Pozerski observed that, serum became proteolytic when shaken with chloroform.

Hedin, in 1904 discovered spontaneous fibrinolytic activity in stored solution of blood globulin.

Since that time, it became known that the agent responsible for fibrinolysis could be concentrated in the euglobulin fraction of serum.

In 1933, Tillet and Garner, reported that, rapid lysis had occurred in plasma clots incubated with extract of beta haemolytic streptococci.

The streptococcal extract was originally assumed to contain proteolytic enzyme specifically adapted for fibrinogen and fibrin and hence was designated "Streptolysin".

In 1941, Milstone reported that, streptococcal extract has no hydrolytic effect on purified fibrinogen, but the fibrinolytic activity did occur if a small amount of the serum fraction containing globulin was added to the mixture of streptococcal extract and fibrinogen.

Kaplan and Christensen, 1944 clarified this observation. They showed that the streptococcal factor was an activator for the enzyme precursor present in the euglobulin fraction of human blood plasma or serum.

Christensen and MacLeod in 1945 named the streptococcal activator, streptokinase.

The active proteolytic enzyme was designated "plasmin" or "fibrinolysin" (Christenson and McLeod, 1945) and the enzyme precursor present in the beta

globulin fraction of plasma as "plasminogen "or" profibrinolysin" (Christon sen, 1945).

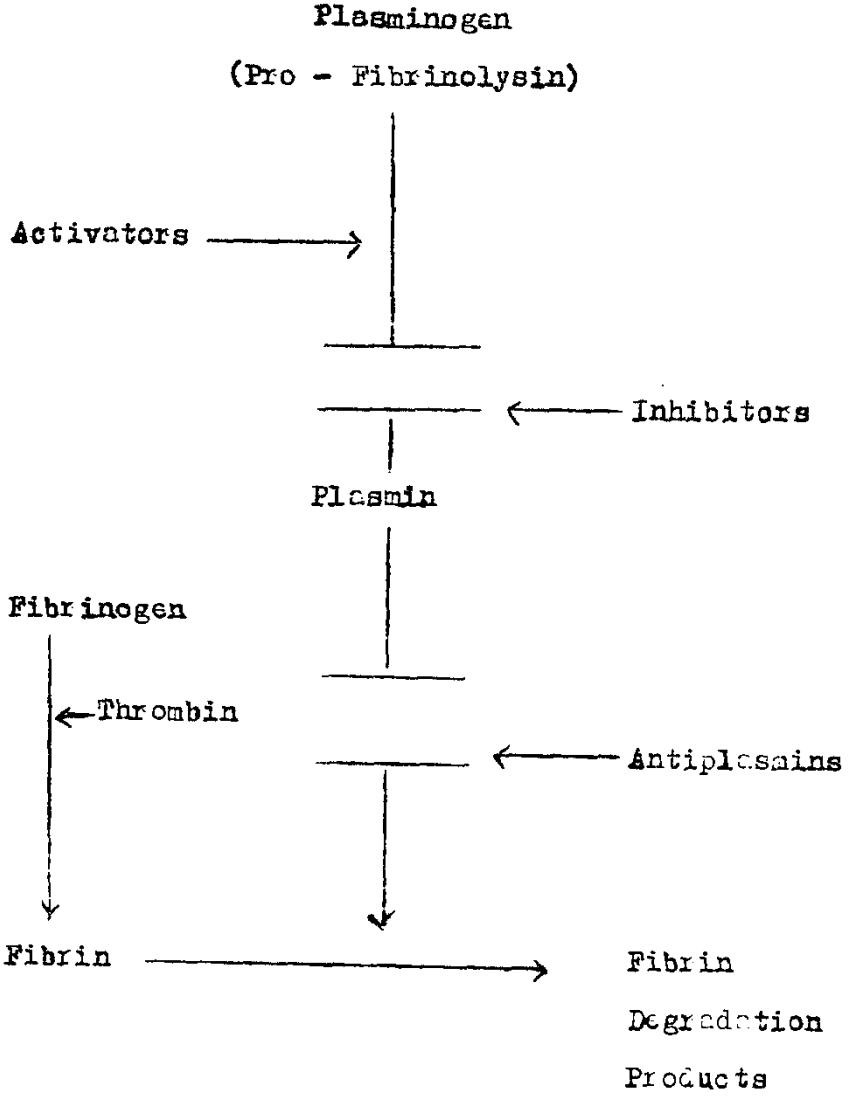
Plasmin is capable of digesting fibrin as well as fibrinogen and other coagulation factors, proaccelerin (factor v), antihaemophilic globulin (Factor VIII), prothrombin (Factor II) and it can also digest Christmas Factor (Factor IX), (Cliffton, 1957).

Active plasmin is normally inactivated when formed in the blood by antiplasmin (McNicol and Douglas, 1964).

There is evidence that there is a proactivator present in the blood which needs to be activated to produce the activator of plasminogen.

So we can visualize the fibrinolytic system to be composed of:

1. Proactivator.
2. Activator.
3. Plasminogen.
4. Plasmin.
5. Antiplasmin.
6. Activator inhibitors.



A simplified scheme of fibrinolysis
Quoted from (Porter G.H., 1967).

Proactivators.

The proactivator, is a protein which can be isolated from human plasma.

Greig and Cornelius (1960), . suggested that it is activator which is bound to inhibitor, the inhibitor is a cholesterol or a lipoprotein containing cholesterol.

Kline and Fishman, 1957 considered it to be the human plasminogen.

Some activators such as streptokinase and lysokinase do not activate the plasminogen directly, they first react with the proactivator and then activate plasiminogen (Mullertz and Lassen, 1953; Painter and Charles, 1962).

Plasminogen Activators

Plasminogen can be activated either spontaneously or by substances called activators. They are either exogenous or endogenous:

I . Endogenous activators: are present in :

1. Plasma and serum (circulating activators),