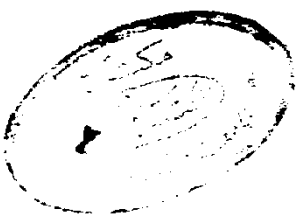
A REVIEW OF "THROMBOLYSIS IN INFANCY AND CHILDHOOD"

THESIS

Submitted in Partial Fulfilment for the Degree of Master in Pediatrics



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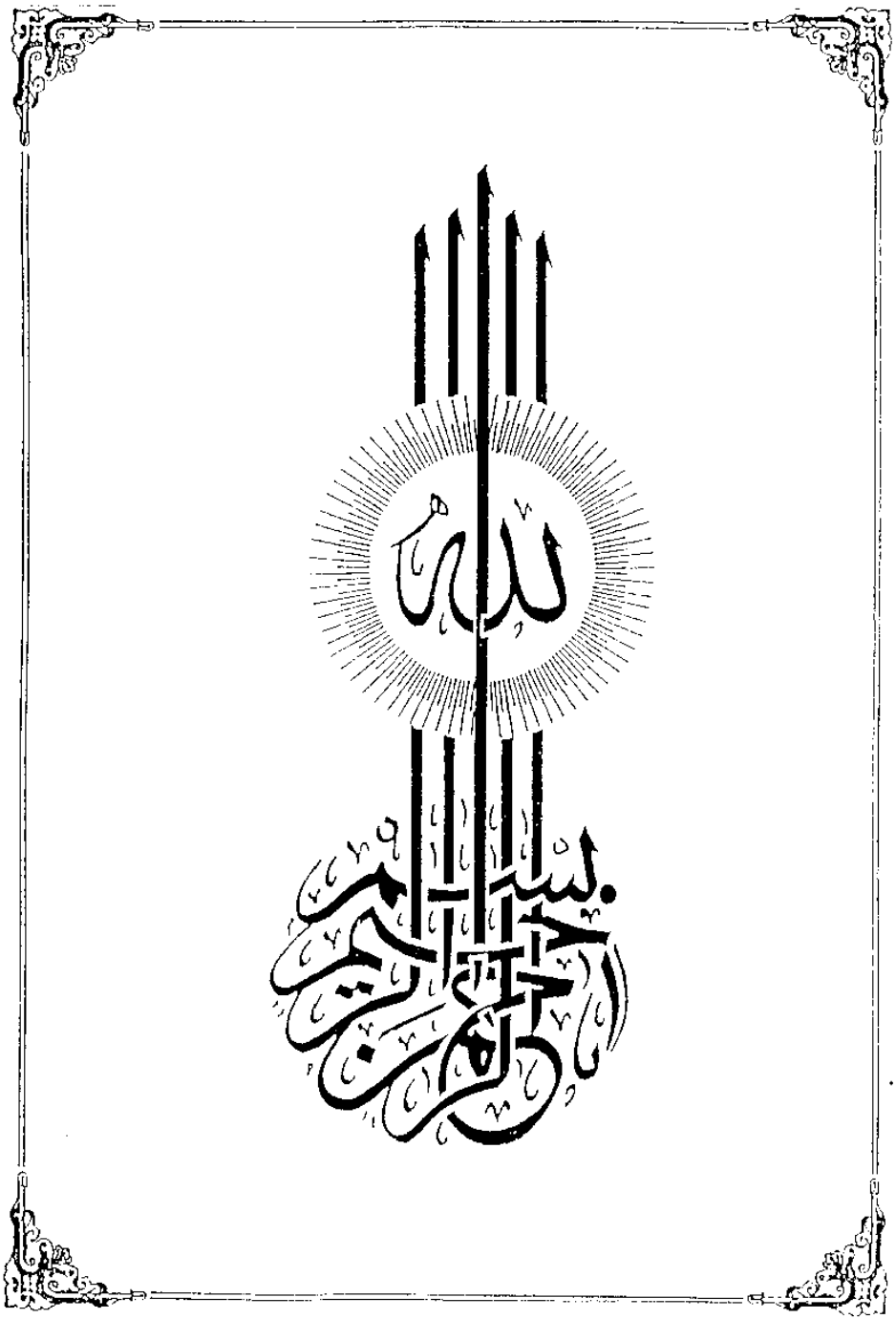

C O N T E N T S

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INTRODUCTION

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In the blood there is a delicate balance between the fluidity of blood on one hand and clotting on the other hand.

The clotting mechanism guards against the danger of haemorrhage, while vascular damage is remedi by the deposition of platelets and fibrin on the vessel wall. If this deposition becomes excessive, the circulation is progressively obstructed and eventually completely occluded by thrombus.

The balance mechanism guards the body against the two hazards of thrombosis and hemorrhage. (Walter and Israel, 1974).

In the normal physiologic state the fluidity of the circulating blood is maintained by an optimum velocity of the blood flow, the ratio between the cellular and plasma components of the blood providing a normal viscosity, the integrity of the endothelial covering of the blood vessels as well as other several protective defences against thrombosis.

The triggers of both platelet aggregation and coagulation are separated from blood plasma by being

concealed either in the subendothelial tissue or within the blood cells. If the trigger of platelet aggregation is relieved, the aggregates tend to break up and disperse, because of subsequent degradation of ADP by plasma. The platelets then acquire a temporary refractoriness to reaggregation (Holmsen and Rozenberg, 1971). If coagulation is triggered, the plasma is provided with protective inhibitors which neutralise activated clotting factors at all stages of the clotting process. If fibrin nevertheless is formed, the fibrinolytic system is automatically activated by the release of activators from the vascular endothelium. Finally and just as important, all products of coagulation are very effectively removed by the reticuloendothelial system. (Owren, 1973).

Haemostasis is principally mediated by interplay of blood vessel walls, platelets and specialized plasma factors. Plasma factors in turn consist of coagulation factors directly involved in fibrin clot formation, natural inhibitors of coagulation and fibrinolysis and fibrinolytic factors involved in clot removal (McMillan, 1978).

From a clinical point of view abnormalities of any of these three components of the plasma phase are ultimately expressed in a given disorder of coagulation. These disorders are arbitrarily divided into two major categories :-

(1) Decreased activity of one of more coagulation factors i.e. "hypocoagulable", or coagulation deficiency disorders.

(2) Normal or increased activity of one or more coagulation factors i.e., "hypercoagulable" or thrombotic disorders.

(Hilgartner and McMillan, 1978)

Most studies and research work were concerned with the coagulation deficiency disorders, however thrombotic disorders revealed to be more common. With the development in thrombosis research which has been very fast in the past quarter century there is subsequent development in antithrombotic therapy.

The aim of this work is to discusss the following points :-

- The normal physiological capacity of the fibrinolytic process in preserving the patency of the blood vessels and its potential role in the removal of thrombi and intravascular fibrin deposits in patients with thromboembolic disorders.
- The prothrombotic state.
- A survey of the recent development in antithrombotic therapy as regards antiplatelet therapy, anticoagulant therapy with emphasis on augmenting fibrinolytic activity by thrombolytic agents.

Historical Aspects

The evolution of concepts about blood coagulation began with the discovery of Malpighi in 1666 that a solid substance of a blood clot after thorough washing proved to be a meshwork of white strands and not whole of blood as previously presumed. Morawitz in 1905 proposed a simple and definitive scheme of coagulation, based on four coagulation factors which are, as recognized in order, fibrinogen, prothrombin, tissue thromboplastin, and ionic calcium. Conclusive identification of factor V was made by Owren in 1947, and the discovery of factor XIII was by Laki and

Lorand in 1948. From then untill 1960, six additional clotting factors involved in prothrombin conversion were discovered and ultimately assigned the following Roman numerals in the order of their discovery;factors VII, VIII, IX, X, XI and XII.

(Hilgartner and McMillan, 1978)

From many years it has been known that human blood possesses fibrinolytic activity. Hunter in 1794 recorded that the blood does not clot in animals killed by lightening or electricity or in animals which were made to run very hard,and killed in such a state. This phenomenon was partly explained by Morawitz in 1906 who noted that the blood from victims of sudden death contained no fibrinogen and could destroy the fibrinogen and fibrin of normal blood. Denis in 1838 reported that the blood clots obtained in wet cupping redissolved in less than a day. Dastre in 1893 during the course of phlebotomy in dogs, found reduced yields of firin which he attributed to its destruction by a process which he named "fibrinolysis", and Hedin in 1904 observed spontaneous fibrinolytic activity in the globulin fraction of ox blood. The main outline of present knowledge of spontaneous fibrinolytic

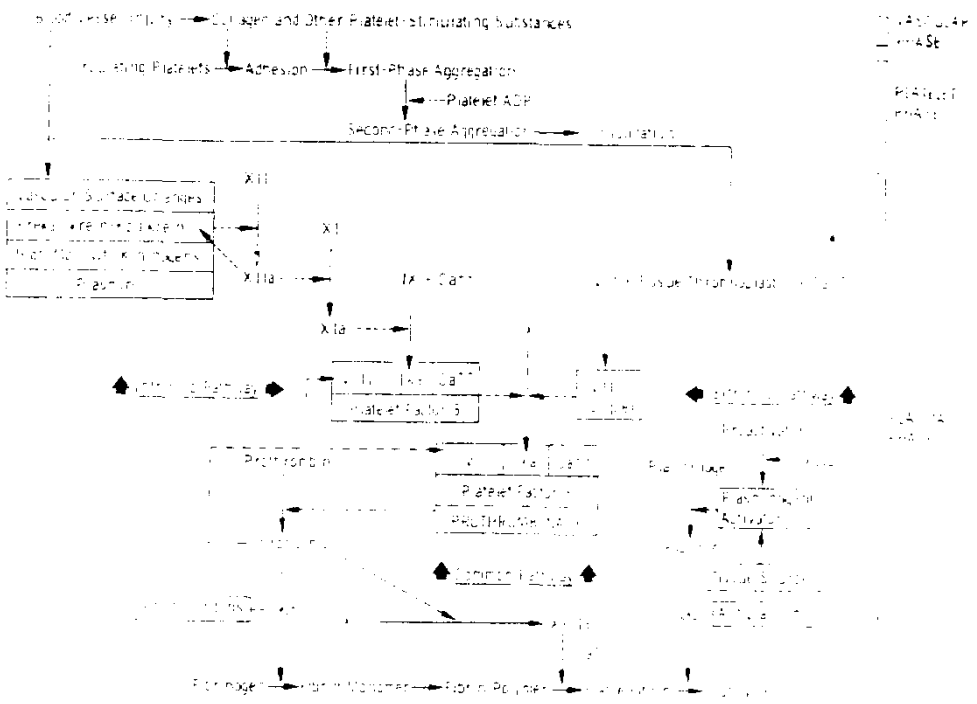
activity in blood was finally obtained by Macfarlane in 1937 who showed that in man surgical operations could provoke fibrinolytic activity in the blood.

Towards the end of the nineteenth century knowledge was also accumulating on methods by which lytic activity might be induced in vitro. Denys and Marbaix in 1889 found that proteolytic and fibrinolytic activity could be induced in serum by treatment with chloroform, and Delezenne and Pokerski in 1903 showed that this action of chloroform was probably due to removal of inhibitors of fibrinolysis. Wolf in 1908 considered that the lysis of blood clots was the end result of the coagulation process and, like coagulation, was due to activity of proteolytic enzymes. Opie and Barker in 1907 found that the proteolytic activity induced by chloroform treatment of serum was in the globulin fraction, as were the factors responsible for spontaneous activity.

The fundamental advance in knowledge of fibrinolytic mechanisms was made by Tillet and Garner in 1933, they found that the culture media of certain strains of haemolytic streptococci contained a

substance, now called streptokinase, capable of producing rapid lysis of human blood clots. Milstone in 1941 reported that this streptococcal product could not lyse purified human fibrin, but if traces of euglobulin of human serum were added lysis readily occurred. Christensen in 1945 found that this effect of the euglobulin fraction of human serum was due to the presence of an inactive substance now named plasminogen, which is converted to the active proteolytic enzyme plasmin by a variety of activators, of which streptokinase is one. The terms plasminogen and plasmin were suggested by Christensen and Macleod in 1945. (McNicol and Davies, 1973).

REVIEW OF LITERATURE



Concept of hemostasis in 1978. Solid lines represent transformation, broken lines action.

(McMillan, 1978)

HAEMOSTASIS IN INFANCY AND CHILDHOOD

Haemostasis may be defined as the sum total of those specialized functions within the circulating blood and its vessels that are designed to stop haemorrhage. It is principally mediated by interplay of blood vessel walls, platelets and specialized plasma factors.

As a result of vascular injury vasoconstriction occurs and is mediated by serotonin released from platelets and by vasoactive peptides related to the activation of factor XII. The platelets adhere to the exposed collagen, aggregate as a result of release of ADP and ADP and then consolidation of the platelet plug takes place by deposition of fibrin within it. This is followed by clot retraction for which platelets are necessary. At the same time coagulation proceeds through the intrinsic and extrinsic pathways.

In the intrinsic pathway, injury-induced vessel surface changes leads to sequential activation of factors XII, XI and IX, activated factor IX interacts with factor VIII, platelet factor 3 and calcium for activation of factor X.