STUDY OF THE COAGULATION MECHANISM IN DIFFERENT TYPES OF HAEMOLYTIC ANAEMIAS

THESIS

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of M.D. in Paediatrics

By

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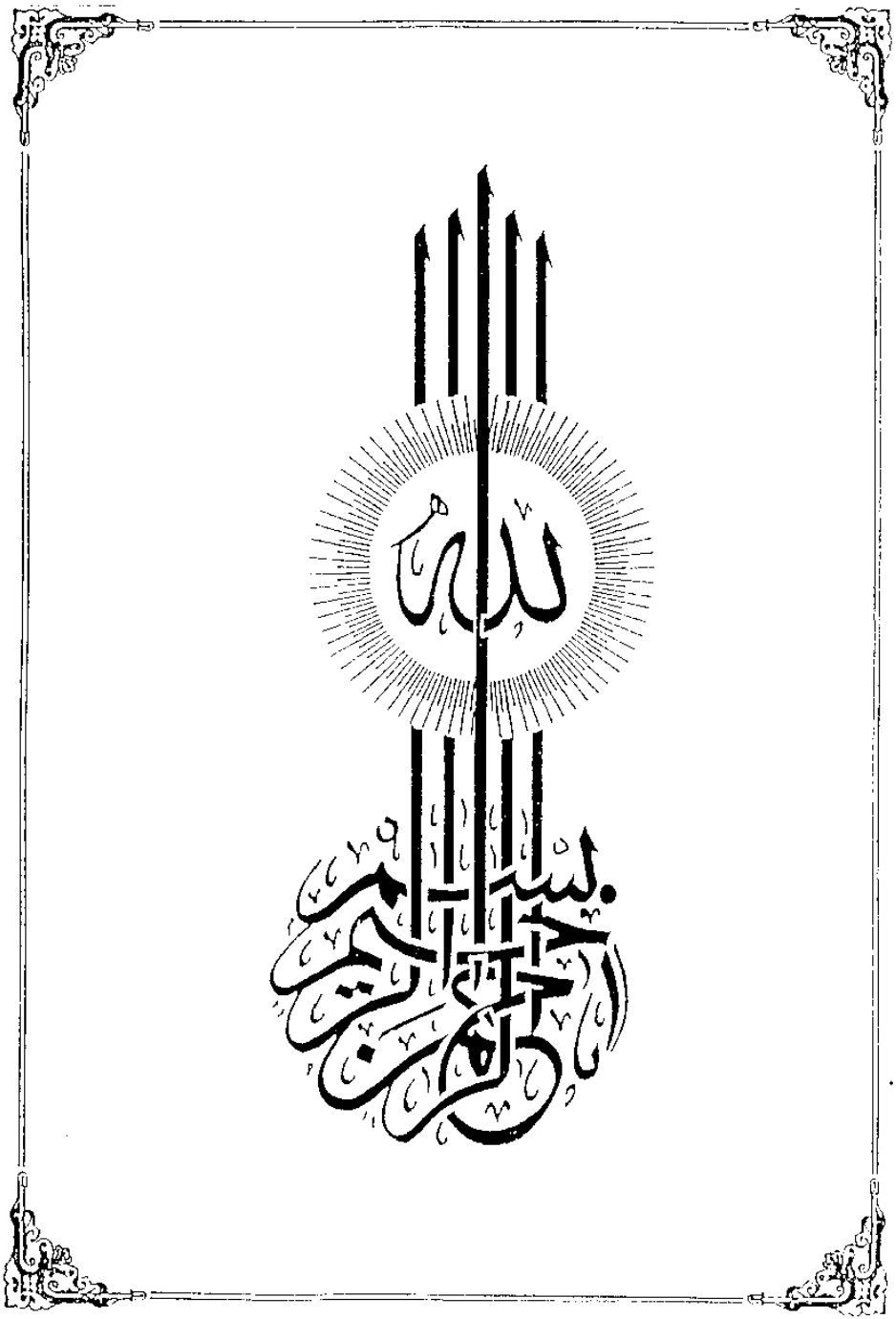

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INTRODUCTION
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INTRODUCTION AND AIM OF THE WORK

There are accumulating evidences pointing to the frequency of disturbed coagulation in different types of haemolytic anaemias. Thirty five years ago it was found by Evans and Duane that acquired haemolytic anaemia may present with purpura and bleeding tendency. On the other hand, some haemolytic syndromes are known to initiate a state of disseminated intravascular coagulation (Reid and Nkrumah, 1972). It has been found that infusion of haemolysate into dogs produced hypercoagulability, frequently followed by consumption coagulopathy. The latter phenomenon was much more prominent when depression of the reticulo-endothelial (RE) system was induced by carbon or splenectomy (Rabiner and Friedman, 1968).

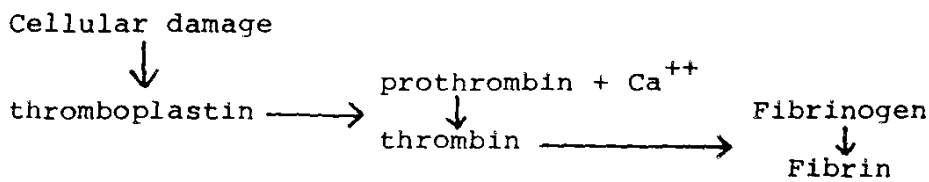
This work is intended to study the coagulation mechanism in different types of haemolytic anaemias aiming to detect the presence of coagulopathy and to identify the exact nature of this disturbance and the possible underlying factors. This may be of value in the prevention and treatment of such hazardous complication.

REVIEW OF LITERATURE

BLOOD CLOTTING MECHANISMS

The blood is in dynamic equilibrium between fluidity and coagulation. This balance must be precisely maintained to assure that exsanguination does not follow trivial trauma or that spontaneous thrombosis does not occur.

Morawitz (1905) put a theory of blood coagulation which remained unchanged for 50 years. This postulated the existence of four factors, thrombokinase, prothrombin, fibrinogen and ionized calcium. Following tissue damage thromboplastin enters the blood and reacts with prothrombin in the presence of calcium to form thrombin which in turn reacts with fibrinogen to form insoluble threads of fibrin. The essential feature of this theory was the existence of separate inactive entities which could be triggered into sequential, two stage reaction by the appearance of an activator released by cellular damage



In 1935, Quick introduced his one stage prothrombin time test. The test was based on the four factors theory that if three factors i.e thromboplastin, fibrinogen and

calcium were present in adequate amount the clotting time would reflect the concentration of the remaining factor, prothrombin.

BLOOD COAGULATION:

The plasma proteins or (factors) involved in blood coagulation were given Roman numericals in the order in which they were discovered. These numericals therefore do not depict the position of the respective coagulation factor in the sequence of reactions that lead to formation of a fibrin clot.

Several additional factors have been recognized in recent years, which have not been assigned Roman numericals by the international committee on nomenclature in the early 1960s (Graham et al, 1983).

Table I lists the various plasma proteins involved in blood coagulation process and their functions.

Table I: Plasma proteins involved in blood coagulation.

Plasma clotting factor		Function in coagulation process
Symbol	common name	
I	Fibrinogen	Soluble fibrinogen polymerized to insoluble fibrin clot following proteolysis by thrombin (11a)
II	Prothrombin	Precursor of the protease 'Thrombin(11a)', converted to thrombin by Xa (plus va, Ca^{2+} and phospholipid)
V	Accelerator globulin (AcG); labile factor	Precursor of Va, substrate for 11a and Xa, Va serves as "co-factor" with Xa to accelerate conversion of 11 to 11a
VII	Proconvertin, serum prothrombin conversion accelerator (SPCA); stable factor	serves as first component of "extrinsic" pathway to activate X to Xa and requires the presence of "Tissue factor", substrate for 11a, Xa, X11a, Kallikrein and X1a
VIII	Antihemophilic factor (AHF) or globulin (AHG)	Precursor of VIIIa serves as "co-factor" with IXa (in presence of Ca^{2+} and phospholipids) in conversion of X to Xa in the "intrinsic" pathway.

Table I: (Continued)

Plasma clotting factor		Function in coagulation process
Symbol	common name	
IX	Plasma thromboplastin component (ptc); Christmas factor	Precursor converted to the protease IXa by XIa + Ca^{2+}; IXa (+ VIIIa; Ca^{2+}, phospholipid) converts X to Xa; IX is also substrate for VIIa and Xa.
X	Stuart factor	Precursor of the protease Xa, which plays a central role in intrinsic and extrinsic pathways for conversion of II to IIa; substrate for IXa and VIIa.
XI	Plasma thromboplastin antecedent (PTA)	Precursor of protease (XIa), which converts IX to IXa; substrate for XIIa.
XII	Hageman factor	First component of "intrinsic" pathway; activated by "surface" and/or Kallikrein to form XIIa, which in turn activates XI to XIa.
XIII	Fibrin-stabilizing factor (FSF); fibrinoligase.	Converted to transglutaminase (XIIIa) by thrombin (IIa); causes covalent cross-linking of fibrin polymers.

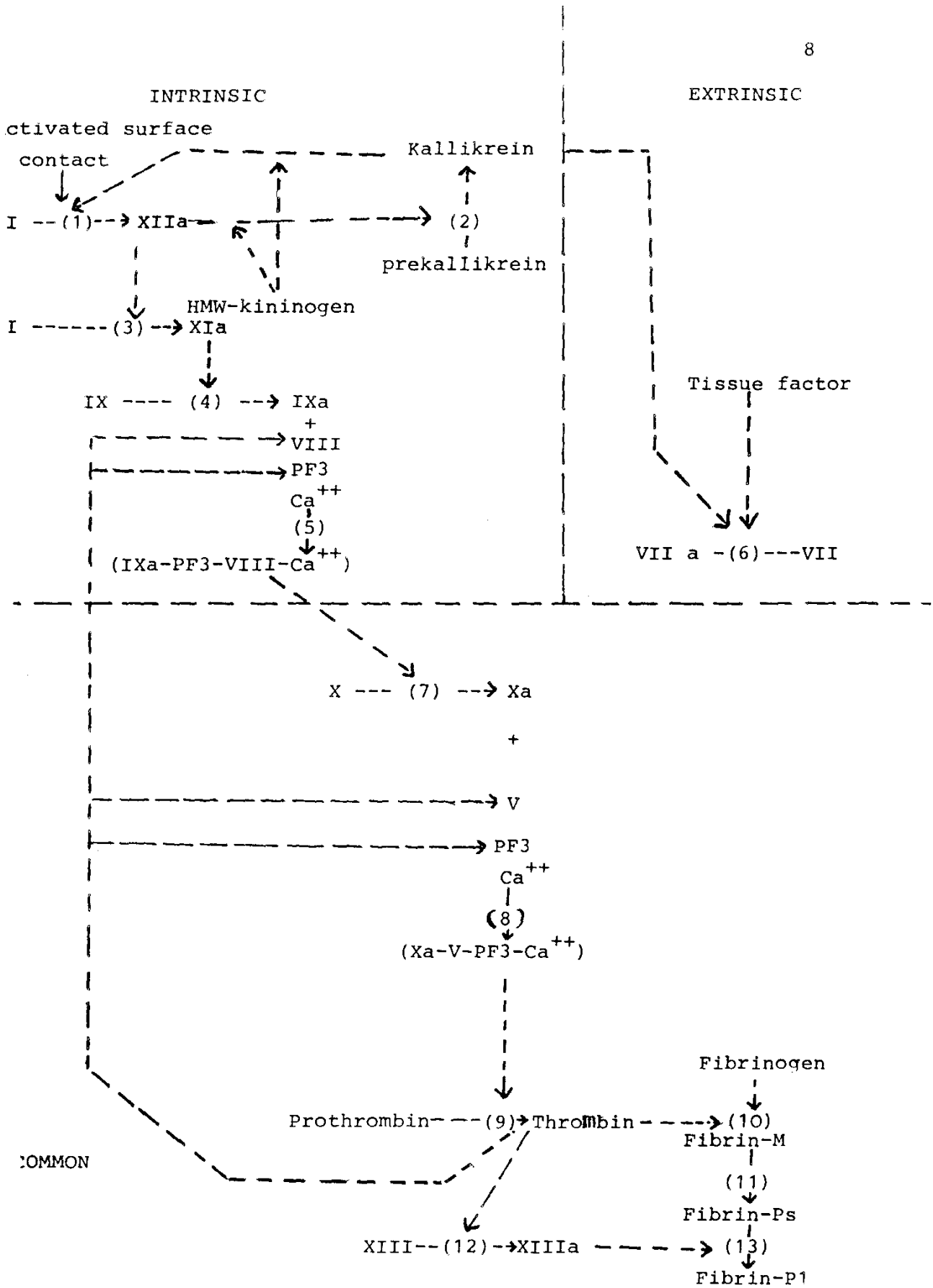
Table I: (Continued)

Plasma clotting factor		Function in coagulation process
Symbol	common name	
-	Prekallikrein; Fletcher factor	Converted to the protease kallikrein by XIIa; Kallikrein also activates XII to XIIa and high-molecular weight kininogen to "kinins".
-	High-molecular weight kininogen; Flaujeac-Fitzgerald-Williams factor	Precursor of plasma kinins (e.g. bradykinin); also acts with IIa and kallikrein to activate XI to XIa
-	Protein C	Inactivates Fs. V and VIII and endothelial cofactor.

(Graham et al, 1983)

PHYSIOLOGY OF BLOOD COAGULATION

Early recognition that blood coagulation involved enzymatic processes eventually led to the "Cascade" or "Waterfall" hypotheses almost simultaneously but independently proposed in 1964 by Davie and Ratnoff and by Mac Farlane. Coagulation is perceived as a sequence of closely coupled reactions in which coagulation factors circulating as inactive enzyme precursors are converted into active enzymes, each factor acting first as substrate and then as enzyme. The sequence of steps in the formation of a fibrin clot has been linked to an electronic amplification system, in that small amounts of enzyme are capable of activating large amount of substrate in each successive step of the sequence. (Esnouf and Mac Farlane,1968). A schema of the original "Cascade" (modified to include more recent information" is illustrated in Fig. (1). In this schema coagulation is activated via 2 different pathways, an intrinsic system, initiated by contact activation involving factor XII, fletcher factor, Williams factor, factors XI, IX, VIII and phospholipid (platelet factor 3), and an extrinsic system, triggered by tissue factor activation of factor VII. Both pathways feed into a common pathway involving factor X, V, platelet factor 3, prothrombin and fibrinogen (Wintrobe et al, 1981).



. (1) Modified schema of water fall "hypothesis of coagulation mechanism. (Wintrobe, 1981).