DISSEMINATED INTRAVASCULAR COAGULATION AND STROKE

A Thesis
Submitted for partial fulfilment of M.Sc. Degree
In Neuropsychiatry

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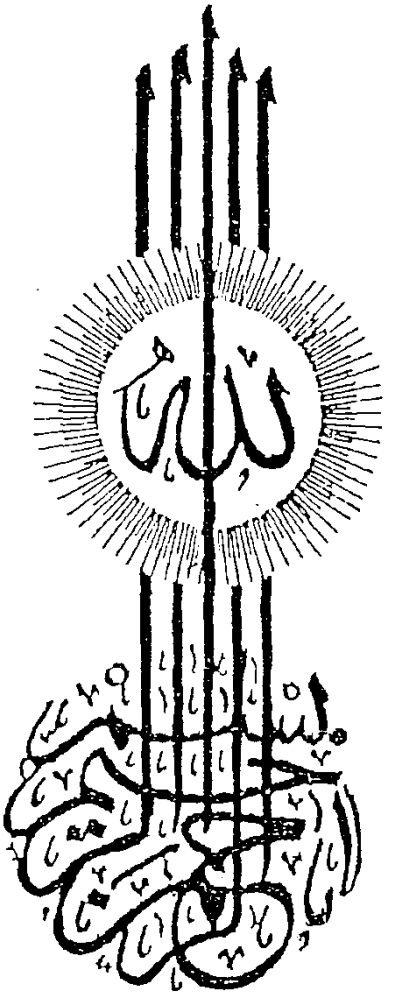

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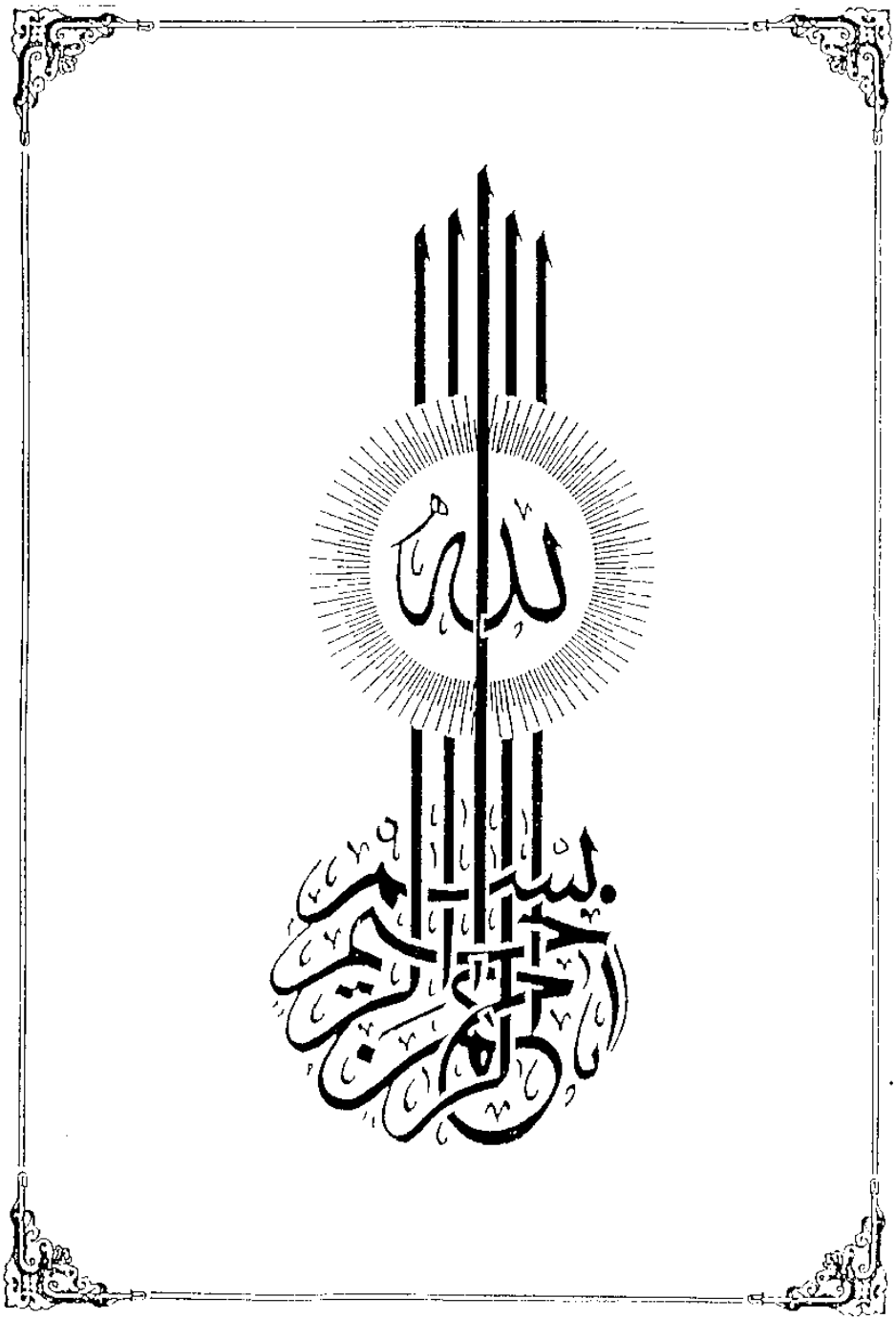

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Acknowledgement

It gives me a great pleasure to express my deepest gratitude to Prof. Dr. Mohamed Hasan El Banoby, Professor of Neurology, Ain Shams University for his generous help, sympathetic support and valuable supervision.

I am deeply grateful to Prof. Dr. Mohamed Osama Abdulghani, Assistant Professor of Neurology, Ain Shams University for his valuable guidance, close supervision and encouragement.

Special thanks goes to Dr. Samia Ashour, Assistant Professor of Neurology, Ain Shams University, and the Director of the Stroke Unit, Ain Shams Specialized Hospital, for her kind help and assistance during the work.

Finally, I wish to express my sincere thanks and deep appreciation to all the staff members of the Neurology Department, Ain Shams University, also all the staff members of the Stroke Unit in Ain Shams Specialized Hospital.

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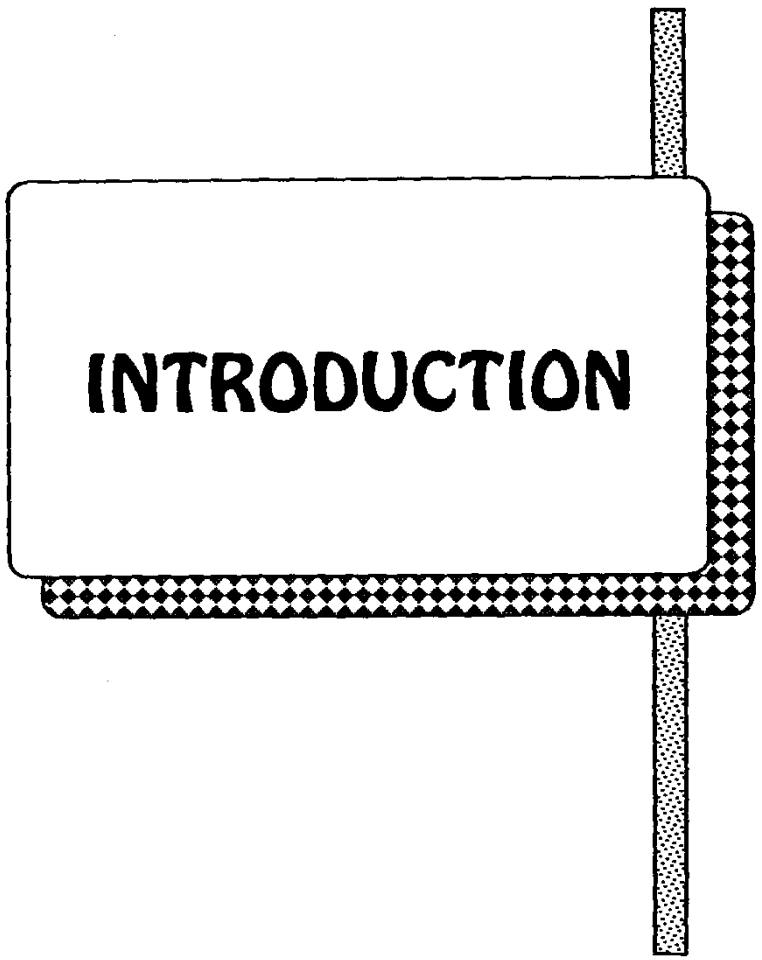

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INTRODUCTION

It was found that patients suffering from acute completed stroke with persistent neurological deficit, show some haemorheological changes in the form of significant increase in the fibrinogen level and marked spontaneous platelet aggregation (Abdulghani, 1986).

Disseminated intravascular coagulation (DIC) can be defined as evidence of activation of the coagulation mechanism resulting in proteolysis of fibrinogen by thrombin and plasmin and an acute thrombocytopenia (Hart and Hallenborg, 1992). Data indicate that fibrinogen plasma levels are strongly correlated to the thrombin activation in plasma (Ceriello et al, 1994). Plasmin is the key enzyme of the fibrinolytic pathway (Collen and Lijenen, 1991). Plasmin can result in inactivation of protein C at certain concentration in invitro incubation. Attenuation of the anticoagulant properties of protein C would favour thrombin generation and lead to an imbalance between clot formation and clot dissolution, thus facilitating thrombin generation (Katalin et al, 1994).

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During a research on neurosurgical patients including those with intracerebral haemorrhage, subarachnoid haemorrhage and those with cerebral infarction or embolism it was observed that disseminated intravascular coagulation or its preparatory states were induced by severe brain damage, infections, failure of other organs, shock and others (Kameyama et al, 1992).

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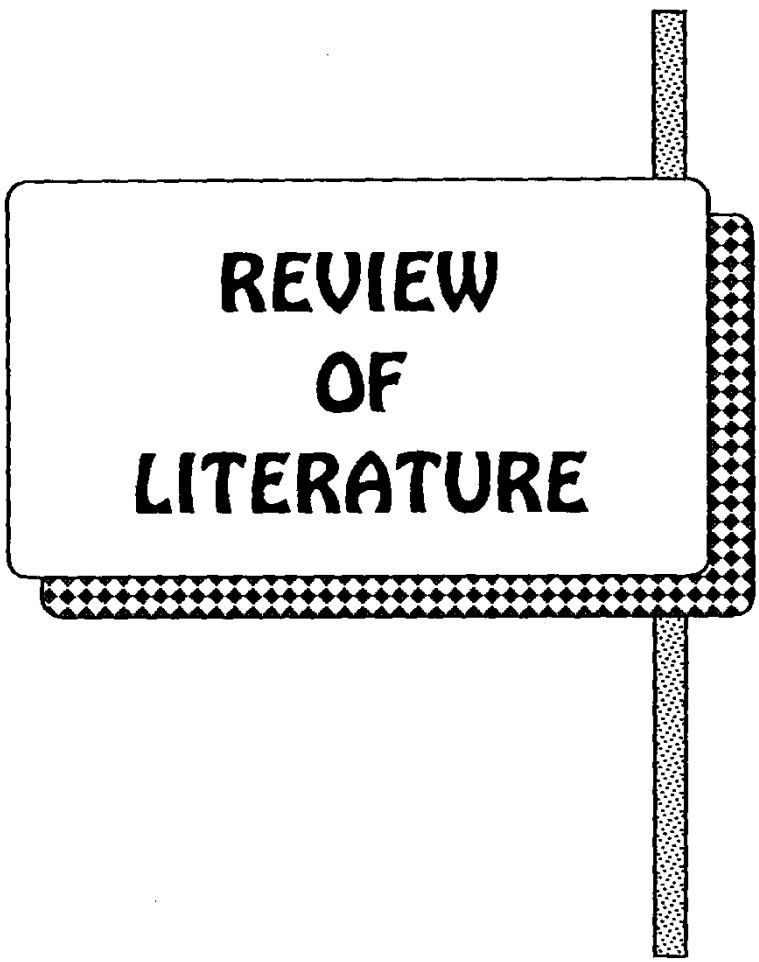

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Blood Vessel Wall

Atherosclerosis

Atherosclerosis is a special type of thickening and hardening of medium-sized and large arteries that accounts for a large proportion of heart attacks, cerebral ischaemia, numerous instances of peripheral vascular disease, and most aneurysms of the lower abdominal aorta (Ross and Glomset, 1979; and Wissler, 1984).

Atherosclerotic vascular alternations are promoted by several risk factors. Four of these are nowadays generally regarded as risk factors of the first order, i.e those pathogenetically active on their own; namely hyperlipoproteinaemia, hypertension, diabetes mellitus and smoking (Leiss and Bergmann, 1985).

Furthermore, it has been suggested by pathological studies that, besides age, hypertension and diabetes mellitus again proved to be major factors for the development of arteriosclerosis (Lechner et al, 1986 a). In 1992 Marmot and Poulter, studied the risk factors for stroke and they mentioned

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that serum cholesterol, blood pressure, over weight, fibrinogen, diabetes, and diet habits are risk factors. Moreover, they commented that serum cholesterol concentration is strongly related to death from non haemorrhagic stroke.

Since both plasminogen activator inhibitor type 1 (PAI - 1) and tissue plasminogen activator (tPA) are secreted from the vascular endothelium (Ridker et al, 1994), it is possible that concentrations of these fibrinolytic factors increase in response to prevalent atherosclerosis, endothelial damage or both, even among symptom free individuals. This hypothesis is further supported by findings that tPA activity and PAI-1 production are higher in atheromatous arteries than in normal blood vessles (Ridker et al, 1994)

It has been reported that in prospectively collected blood samples, high concentrations of endogenous tissue-type plasminogen activator (tPA), the primary mediator of intavascular fibrinolysis, among apparently healthy men are strongly associated with the risk of future myocardial infarction (Ridker et al, 1993). On the basis of this, it has been postulated that activation of the endogenous fibrinolytic system occurs several years before vascualr occlusion and that

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extent of this activation may serve as a marker for preclinical atherosclerosis. With cross sectional data, others found that tPA antigen concentrations correlate with carotid atherosclerosis (Salomaa, 1993). Some groups have suggested that the circadian variation of stroke may be related partly to cyclical changes in tPA activity (Ridker et al, 1994).

The term atherosclerosis is used to describe pathological changes taking place in arteries under the influence of risk factors, such as constriction of the lumen and thickening and loss of elasticity of the vascular walls. The most important stages of atherosclerosis can be understood after remembering that in arteries of all sizes, the transected wall shows three major microscopic layers; the intima, the media, and the adventitia (Wissler, 1984). The intima is formed of endothelium, basement membrane, an occosional smooth muscle, myointimal cells, a few collagen and/or elastic fibres, and an infrequent blood derived mononuclear cells. The multilayered cushion of myointimal cells formed in arteries at all ages in human may be a pathological finding (Wissler, 1984). The media is formed by multiple layers of smooth muscle cells (SMC). At present, both circumstantial evidence and careful invitro studies of the arterial (SMC) indicate that it can

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synthesize collagen, elastin and glycosaminoglycans. It now appears likely that relationships between cells, collagen, and elastin in the media are orderly designed, permitting the strength and relative inflexability of collagen to interact in the best possible way with elastin (Glagov, 1979). The (SMC) probably acts as a major monitor of this adaptability (Abdulghani, 1986). The pathogenesis of atherosclerosis begins with a lesion of the endothelium, that is to say local morphological or functional damage to the innermost tissue layer (endothelium), which removes the natural barrier between the blood stream and subendothelial layers. Hyperlipoproteinaemia is another risk factor responsible for an increased frequency of endothelial defects (Fagiotto et al, 1984). Following damage to the endothelial cells, the penetration of lipoproteins and macrophages is considerably facilitated. At first, reversible deposits are formed (the so-called fat layers), a process that begins already in childhood. In the neighbourhood of the lesion the endothelial production of prostacyclin, which acts as an antiaggregator and vasodilator, is reduced (Eldor et al, 1982). Platelets collect at the site of defect and their aggregation increases. On aggregation the platelets are stimulated to release thromboxane A_2, which acts as an aggregator and

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vasoconstrictor. At the same time the platelets release growth factors, which stimulate diffusion of vascular wall smooth muscle cells from the media into intima and their proliferation in the intima. Low density lipoproteins (LDL) likewise promote the migration and proliferation of smooth muscle cells (Ross, 1981). The muscle cells and macrophages that have diffused into the intima accumulate cholesterol and degenerate into foam cells. As the plaque ages, calcium compounds may be deposited, and scar tissue or necrotic foci may be formed. The growth of the plaque may last several years, and slowly leads to a reduced perfusion by narrowing the lumen. The danger is that a thrombus may form in the plaque region in a few minutes and leads to total occlusion of the vessel. In the presence of hyperlipoproteinaemia, the risk of thrombus formation is greater, since the blood viscosity (Leonhardt and Arntz, 1977) and the tendency towards platelet aggregation are higher (Hassal et al, 1983).

Lechner et al (1986 a) reported that haemorheological disturbances increase with arteriosclerotic lesions of cerebral vessels. While hyperviscosity may be found in 35% of patients with normal vessel system, it is detected in as many as 70 - 80% of patients displaying arteriosclerotic lesions with high degrees

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of stenosis or even occlusion as determined by angiography. Damage of the vessel wall is considered a necessary precondition for the pathophysiological development of rheological disorders.

Leitinger et al (1994) found in their in-vitro studies on the influence of prostaglandin on oxidation of human low density lipoproteins (LDL), that prostaglandins produce oxidative modification of the LDL particles and through this modification prostaglandins can affect the development and progression of atherosclerosis.

Endothelial cell

Ulutin (1991) stated that there is an increasing evidence that the endothelial cell (EC) is involved in numerous physiological and pathological processes in the vascular system as well as in the haemostatic mechanism. The importance of the EC being increasingly recognized. The EC has a strong antithrombotic action due to the substances it contains and synthesizes. It has been demonstrated that the functions are reduced in pateints with atherosclerosis and there is no doubt that the EC constitutes the most important "key cell" together with changes in the vascular wall in the development of

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