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بسم اللّه الرحمن الرحيم

مركز الشبكات وتكنولوجيا المعلومات

قسم التوثيق الإلكتروني

Salwa Akl

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم باللّه العظيم أن المادة التي تم توثيقها وتسجيلها

علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

Salwa Akl

بعض الوثائق الأصلية تالفة
وبالرسالة صفحات لم ترد بالأصل

A COMPARATIVE STUDY OF THE EFFECTS OF EPIDURAL VERSUS GENERAL ANAESTHESIA ON COAGULATION, FIBRINOLYSIS AND THE OUTCOME AFTER MAJOR SURGERY

THESIS

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In

Anaesthesiology

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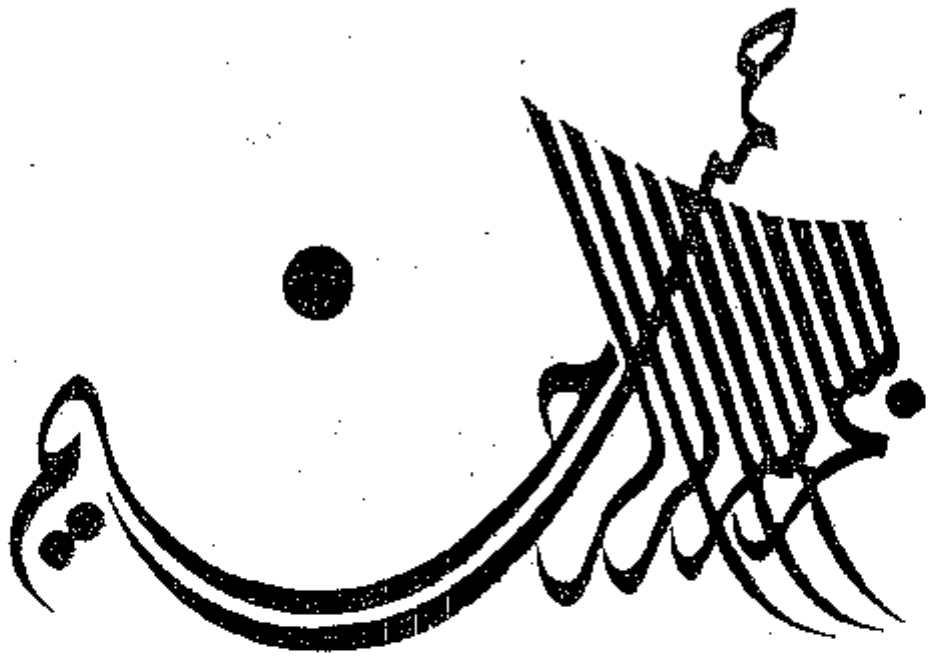

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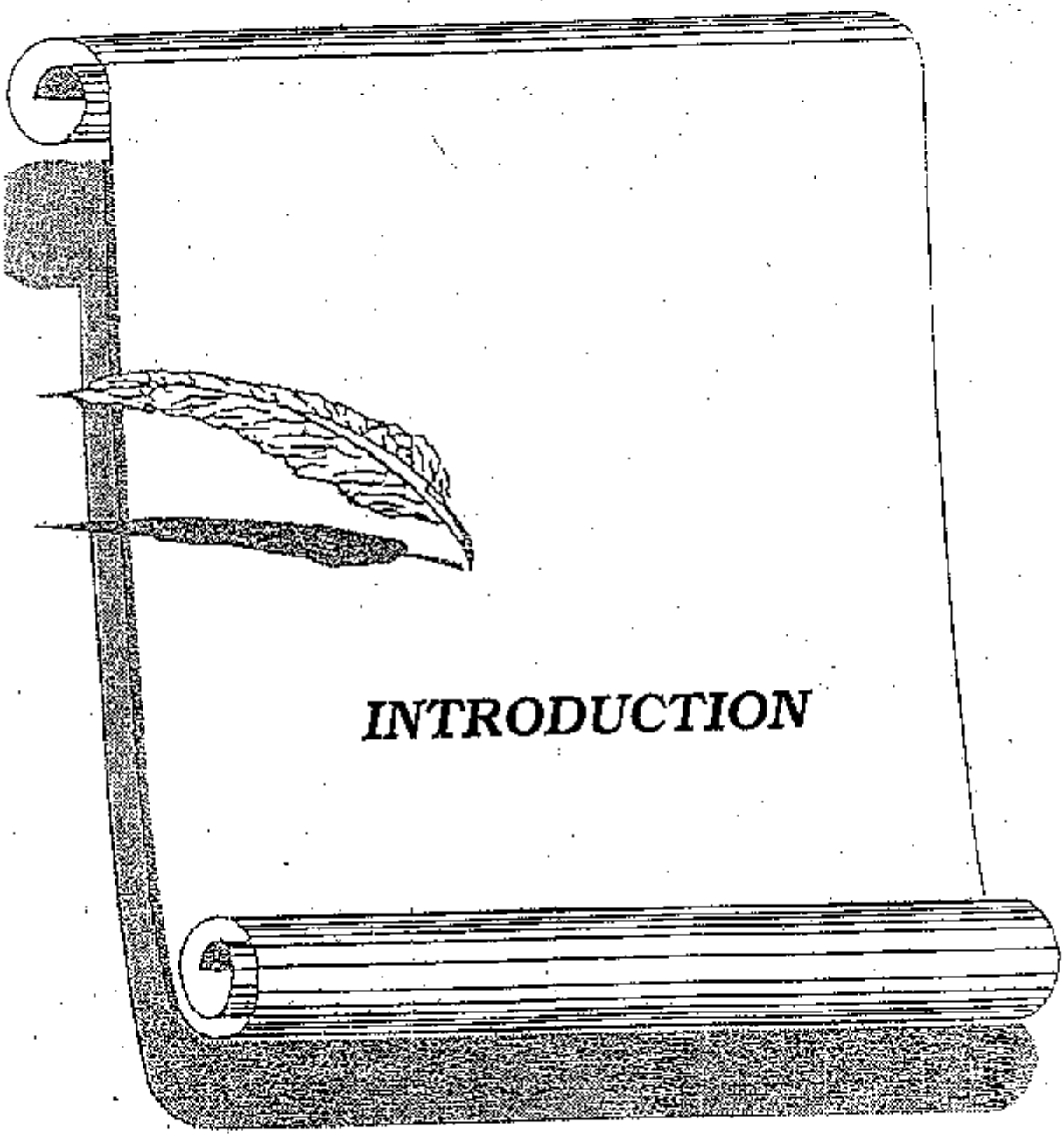

INTRODUCTION

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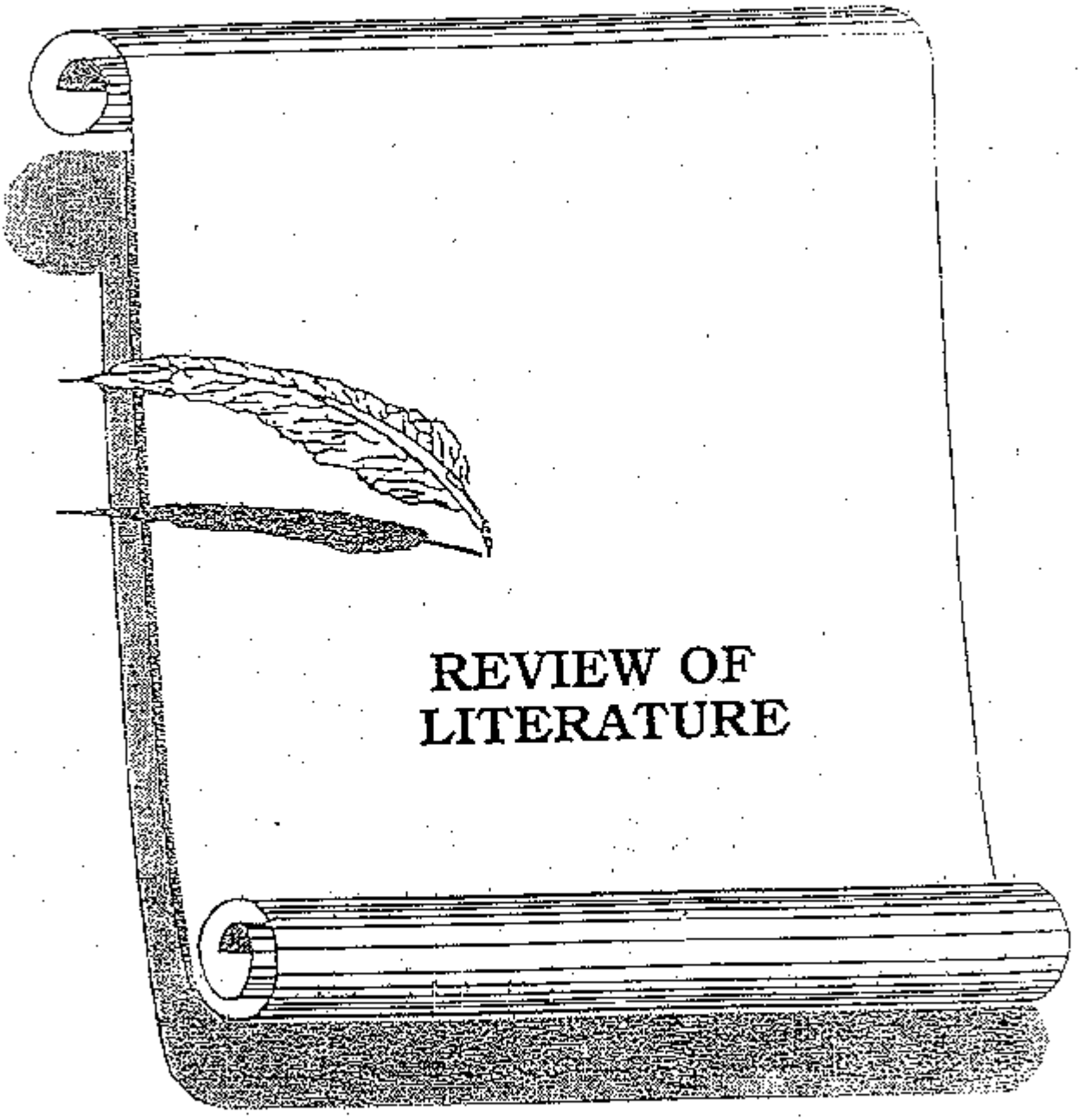
Perioperative changes in haemostasis have been hypothesized to explain the high frequency of deep venous thrombosis and pulmonary embolism after surgery. Increased concentrations of coagulation factors, decreased concentrations of coagulation inhibitors, enhanced "in vitro" fibrinolysis have been reported postoperatively, suggesting a "hypercoagulable state" [1].

Teleologically, an increased tendency for blood to coagulate after tissue trauma can be viewed as adaptive; however, in patients with peripheral vascular lesions, these haemostatic changes have the potential to increase the likelihood of arterial thrombotic complications i.e. limb loss. Evidence linking postoperative hypercoagulability with arterial thrombotic complications was reported. The observed reduction in postoperative vascular graft occlusion in patients receiving anticoagulants provides further support for etiologic role of hypercoagulability in this event [2].

Investigators long have been interested in identifying anaesthetic regmins that modulate the stress response to surgery. Regional anaesthesia (RA) has been reported to reduce perioperative morbidity when compared with general anaesthesia (GA) [3].



REVIEW OF LITERATURE

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HAEMOSTASIS

Normal haemostasis is a balance between maintaining the fluidity of the blood in normal intact vasculature and the restriction of blood loss from damaged blood vessele this equilibrium is dependent on the presence of activating and inhibiting processes with regulatory positive and negative feedback pathways.[4]

The three equally important anatomic compartments of haemostasis are the, ***platelets*** which must be normal in both number and function,***blood proteins,*** which include procoagulants, anticoagulants, fibrinolytic protcins, and the ***vasculature***, which remains the "last frontier" and most poorly understood with respect to disorders of haemostasis. It should be emphasized that these three compartments are intricately interrelated. Disturbance of these delicately balanced interrelationships may lead to serious clinical consequences. [5]

Vascular function and Haemostasis :

Normal vascular morphology is comprised of three discrete layers: intima, media, and adventitia. The ***intima*** consists of a monolayer of nonthrombogenic endothelial cells and an internal elastic membrane. The ***media*** consists of smooth muscle cells, the size of the media will vary depending on the type (arterial or venous) and size of the vasculature. The ***adventitia*** is comprised

of an external elastic lamina or membrane and supportive connective tissue.[6,7,8]

Endothelial sloughing may be induced by a wide variety of insults (triggers), including acidosis, hypoxia, endotoxin, circulating antigen-antibody complexes, and many others (Fig. 1). [9,10]

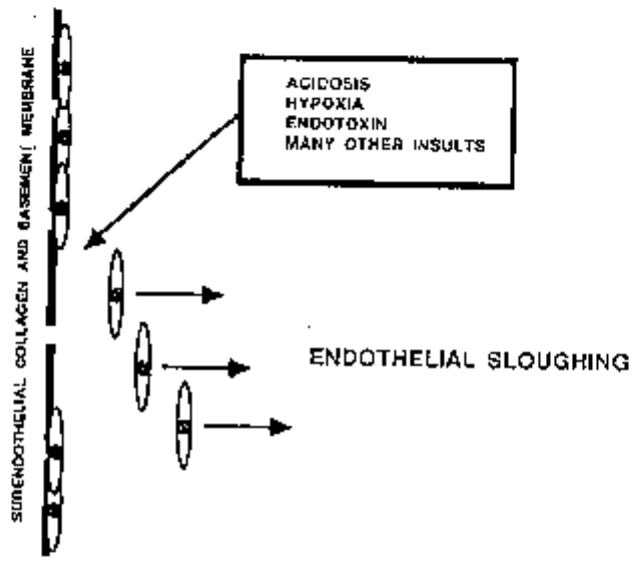

Fig (1): Endothelial sloughing and exposure of blood to subendothelial collagen and basement membrane.[5]

The frist event that occurs after endothelial sloughing, with the subscquent exposure of subendothelial collagen and basement membrane, platelets are immediately recruited to "fill" this endothelial gap (Fig. 2).[5,11,12]

Both subendothelial collagen and subendothelial basement membrane recruit platelets, with the goal being to form a primary haemostatic plug, thereby stopping blood from leaving the vascular compartment. As the primary haemostatic plug is formed, subsequent reparative events ensue: smooth muscle or

other cells from the media differentiate, migrate through the internal elastic membrane, and then differentiate into new nonthrombogenic endothelial cells. [5]

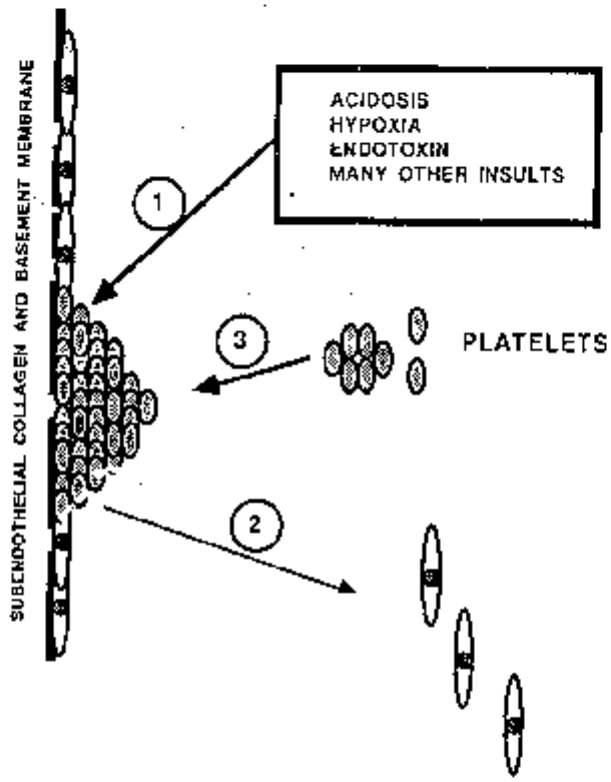

Fig (2) : Platelets filling endothelial gaps. [5]

If this is one-time events, a normal reparative process is completed. It should be noted, however, that forming the primary haemostatic plug may constitute an overwhelming event leading to a large platelet/ fibrine thrombus, and impedance of blood flow with resultant end-organ damage via ischaemia. [5]

Another event that may occur when endothelial sloughing and damage occurs atherosclerotic plaque formation (Fig.3).[5,13,14,15,16]

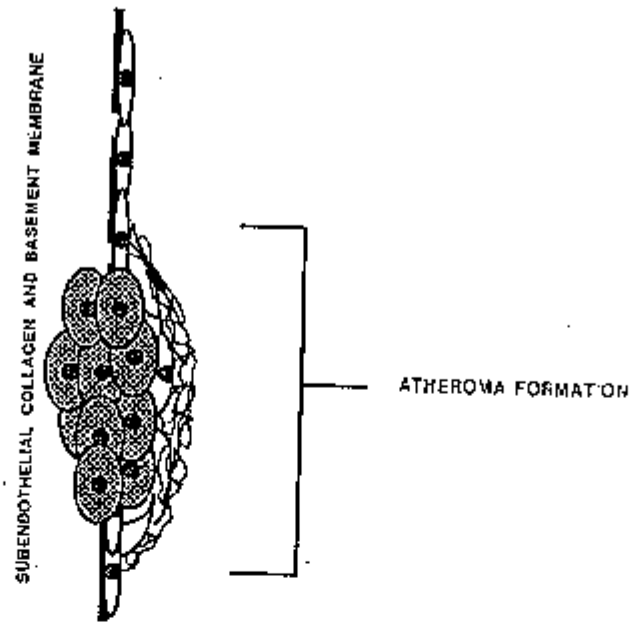

Fig (3): Endothelial sloughing and atheroma formation.[5]

If this occurs repeatedly in the same area over a protracted period, then as smooth muscle or other cells differentiate and migrate into the intima, compounds are released that attract macrophages, which then ingest cholesterol and other materials and atherosclerotic plaque eventually develops.[5,17] All these potential events are summarized in (Fig.4).

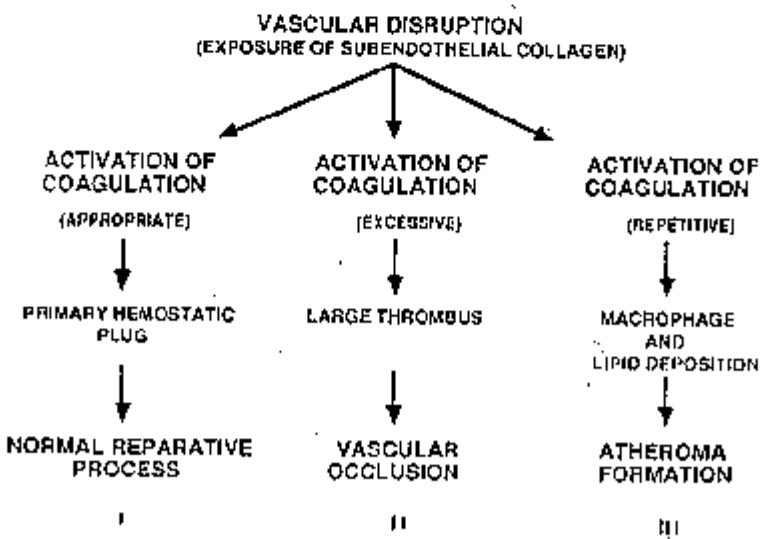

Fig (4): Vascular damage and consequences (endothelial-cell sloughing). [5]

Permeability, fragility, and vasoconstriction are properties of the vasculature. [5] and are summarized in (Fig 5) .

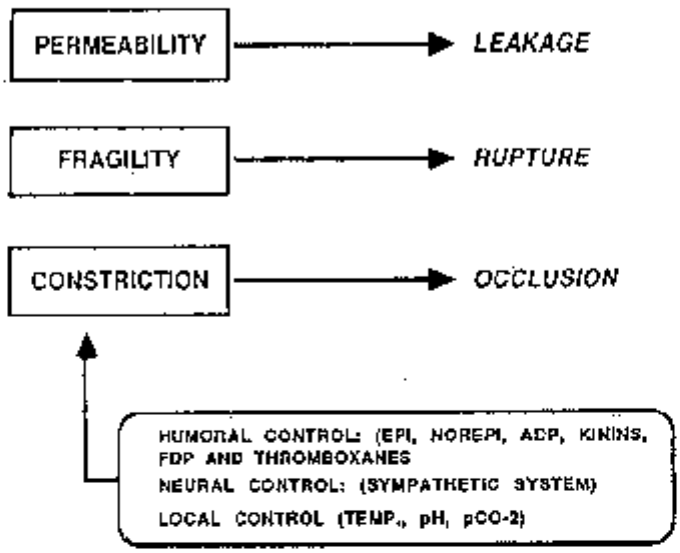

Fig (5): Vascular function.[5]

Vascular permeability, if increased, results in blood leaving the vessel and will manifest as petechiae and purpura, or in some instances, large echymoses. If increased vascular fragility occurs, there can be rupture of the vasculature with ensuing petechiae and purpura (especially in the integument and mucous membranes). Large ecchymoses and potentially serious deep-tissue haemorrhage. If vasoconstriction is inappropriately intense, there may be occlusion of the vessele via eventual thrombus formation. Vasoconstriction is under local, neural, and humoral control. The most important of these is humoral control; in Fig. 4 the compounds that mediate humoral control of vasoconstriction are primarily compounds released from platelets, including epinephrinc, norepinephrine, adenosine

diphosphate, kinins, and thromboxanes.[5,18,19] Fibrinogen degredation products (FDPs) librated when the fibrinolytic system acts on a fibrin clot will also modulate vasoconstriction.[5]

Properties of the endothelium are summarized in Table (1). Endothelial cells are contractile and contract when stimulated by histamine, serotonin. kinins, or thromboxanes. In addition, the endothelial cell is the major site of high-molecular-weight factor VIII biosynthesis (Von Willebrand factor/ restocetin cofactor).[20,21] Low-molecular-weight factor VIII or factor VIII coagulant (factor VIII:C) is synthesized by the hepatocyte and probably other cellular sites.[22] In addition, the endothelial cell provides on the two key activation pathways of the fibrinolytic system through the synthesis and release of plasminogen activator activity. [5,23,24]

Table (1): Properties of the endothelium and subendothelium :

Endothelium:

Contraction by histamine, kinins, 5- hydroxytryptamine, and thromboxanes.
Synthesis of plasminogin activator activity.
Synthesis of factor VIII: vW factor.
Synthesis of protein C inhibitor.

Subendothelium:

Platelet activation and atraction.
Factor XII activation.
Factor XI activation.

In addition, protein C activator activity and inhibitor activity appear to be synthesized and released by the endothelium.[25] Properties of the subendothelium are also depicted in Table (1). Platelet attraction and subsequent activation occurs when basement membrane or collagen is exposed. It should also be noted that subendothelial collagen can directly activate factor XII to become factor XIIa as well as factor XI to become factor XIa.[5,26,27] Evidently, any of these processes, if left unmodulated, could give rise to a generalized activation of the haemostatic system.[5,28]

Platelet function and Haemostasis :

Normal platelet morphology can be envisioned as being comprised of three primary zones: a peripheral zone, a sol-gel zone, and an organelle zone.[29] The peripheral zone is comprised of an extramembranous glycocalyx, inside of which is a plasma membrane, similar to any other trilamellar cellular plasma membrane. Under the plasma membrane is an open canalicular system. The sol-gel zone is comprised of microtubules and microfilaments, a dense tubular system that contains primarily adenine nucleotides and calcium. In addition, in the sol-gel zone is found the all-important contractile protein thrombosthenin. Thrombosthenin is similar to actomyosin. The organelle zone is comprised of dense bodies, alpha granules, mitochondria, and the usual array of organelles found in other cellular systems, including lysosomes and endoplasmic reticulum. Alpha granules contain and release fibrinogen and