HEMORHEOLOGY IN CEREBROVASCULAR STROKE

THESIS

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BY

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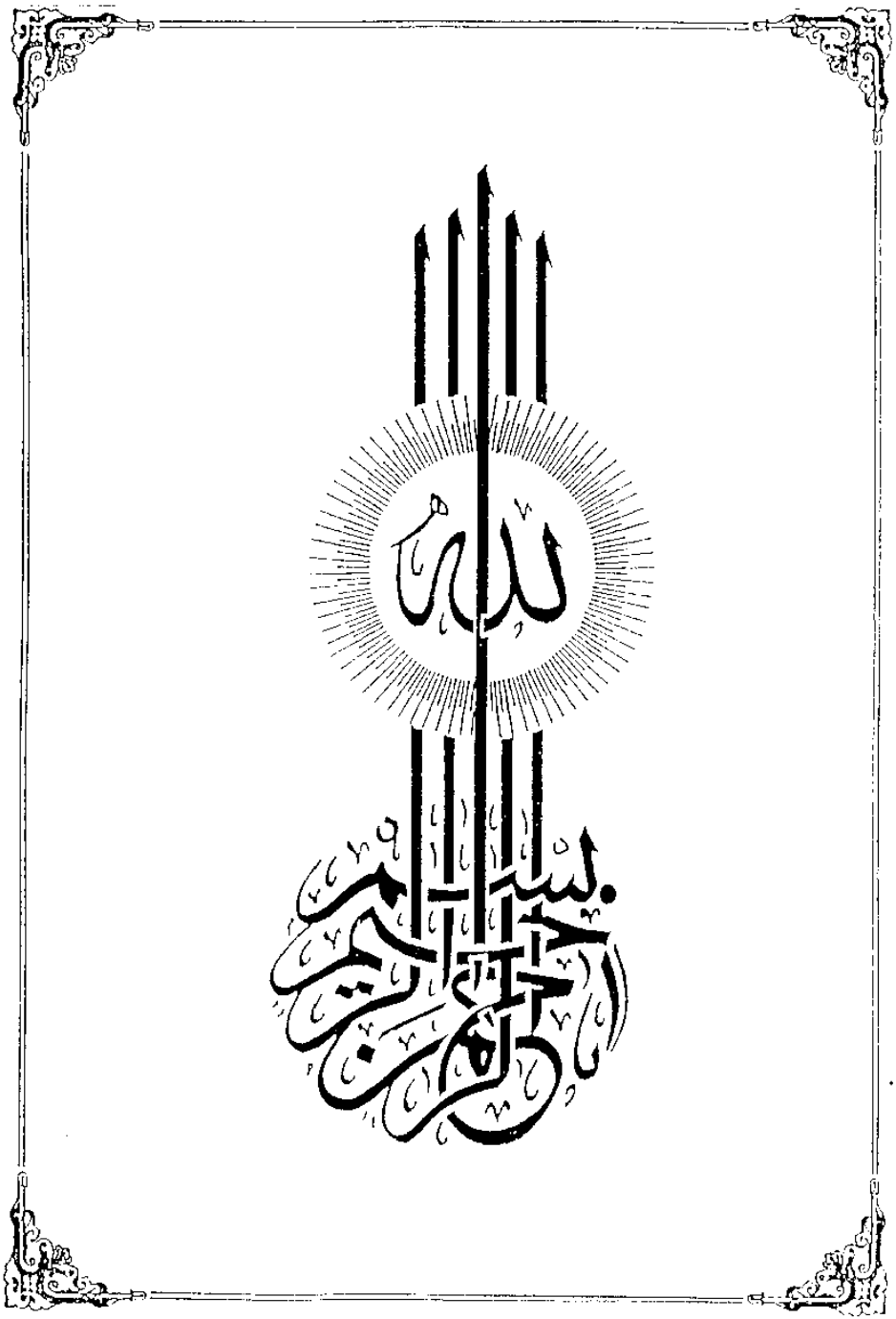
DEDICATION

This work is dedicated with love

to my wife Dr. SEHAM

and my children; KHALED and NOHA



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HEMORHEOLOGY,AN INTRODUCTION

The term "Rheology" was coined by Eugene C.Bingham in 1929, and modified by M.Reiner and G.W.Scott Blair in 1967 as "the study of the deformation of materials, including flow" (Reiner and Scott Blair,1967).

The term hemorheology was introduced in 1951 by Copley as "the study of the deformation and flow (i.e.rheological) properties of cellular and plasmatic components of blood in macroscopic, microscopic, and submicroscopic dimensions and the rheological properties of vessel structure with which blood comes into direct contact " (Copley,1952). Additionally, it is also the study of the interaction of blood or its components and the vascular system with added foreign materials (e.g.drugs). Thus, hemorheology is the study of how the blood and the blood vessels can function and interact as parts of the living organism (Copley and Seaman,1981).

The real begining of hemorheologic studies has begun over two hundred years ago. Boerhaave (1750) observed intravascular cell aggregation in vessels of the conjunctiva. In 1840, Poiseuille developed a formula for the flow of fluids through cylindrical tubes as a consequence of his observations of blood flow through the mesentric vessels of laboratory animals. In 1921, Fahraeus described the clinical significance of cell aggregation in vivo. In 1929, Krogh made his classic studies of the capillary circulation. Knisely et al.(1947), studied the microcirculation by photomicrographic techniques, noting the major role the cell aggregation

(sludging) played in flow stoppage (Wells,1964).

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 ischemia, numerous instances of peripheral vascular disease, and most aneurysms of the lower abdominal Aorta (Ross and Glomset,1976; and Wissler, 1984).

In arteries of all sizes, the transected wall shows three major microscopic layers; the intima ,the media, and the adventia. The intima is formed of endothelium, basement membrane, an occasional smooth muscle myointimal cells, a few collagen and/or elastic fibers, 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 arterial endothelium probably both admits and discharges macromolecules of the size of low-density lipoproteins(LDL). Lipoproteins and fibrinogen are particularly likely to accumulate in the intima(Grimbrone, 1981). Large-pore transendothelial vesicle chains allow enterance into the arterial wall. Additional quantitative study is needed to determine the effect on this transverse channel of dilatation of arteries or increased tension on arterial wall(Gimbrone, 1981; and Wissler, 1984). Another factor suspected of being involved in controlling endothelial permeability is the glycocalyx-the thin fuzzy layer of complex carbohydrate on the luminal side of the endothelial cell. This layer is remarkably thin in those areas of the artery prone to the development of atherosclerotic plaques and at sites where plaques develop in some experimental animals (Gerrity et al.,1977).

The media is formed by multiple layers of smooth muscle cells (SMC). At present, both circumstantial evidence and careful in-vitro studies of the

arterial (SMC) indicate that it can 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.

The lesions of atherosclerosis

The intima is the cell layer principally involved in atherosclerosis, although secondary changes are occasionally found in the media. Three different types of lesions are classically recognized; the fatty streak, the fibrous plaque and the so called complicated lesion (Ross and Glomset, 1976).

The fatty streaks commonly found in young persons are characterized by a focal accumulation of relatively small numbers of intimal (SMC), containing and surrounded by deposits of lipid. The fibrous plaque, which is the most characteristic lesion of advancing atherosclerosis, consists of an accumulation of intimal, lipid-laden (SMC), the lipid being primarily cholesterol and cholesterol ester. the cells are also surrounded by collagen, elastic fibers and proteoglycans. Together, the cells and the extracellular matrix form a fibrous cap that covers a large, deeper deposit of free extracellular lipid and cell debris (Ross and glomset, 1976).

Although the fatty streaks has been suggested to be the precursors of the fibrous plaques, recent observations question this, both according to anatomical, biochemical and immunochemical studies (Wissler,1984).

THE PATHOGENESIS OF ATHEROSCLEROSIS

Historically, this subject has been approached from two points of view.

One holds that a principle factor in progression of the plaque is the increased passage and accumulation of plasma constituents into the arterial intima (insudation). The second, specifies that a small mural thrombi on areas of arterial intimal injury (hemodynamic and otherwise) occur early in atherogenesis (encrustation) and that the organization of these thrombi by (SMC) as well as their gradual growth play a definitive role in the progression of the plaque (Wissler, 1984). Other hypotheses include the monoclonal hypothesis and the clonal-senescence hypothesis (Ross and Glomset, 1976).

The response-to-injury hypothesis dates back to the pioneering work of Virchow (1856). Factors such as hyperlipidemia, hormone dysfunction, and the increased shear stress in hypertension may injure the endothelium and alter the nature of the endothelial barrier to the passage of blood constituents into the artery wall. This action alters endothelial cell-cell or endothelial-cell-connective tissue relations, or both, permitting hemodynamic forces to elevate and possibly to detach endothelial cells from the arterial wall. Focal desquamation of the endothelium exposes the underlying subendothelial connective tissue to platelets. The platelets adhere, aggregate, and release platelet factors; the infiltration of which, along with lipoproteins and other plasma factors, at these sites of injury leads to focal proliferation of arterial (SMC), to formation of large amounts of connective tissue matrix, and to deposition of lipids both within the cells and around them. Later restoration of the endothelial barrier is expected only when the injury is neither continuous nor repeated. Risk factors possibly affect the balance between cell proliferation and endothelialization. Thus, increased plasma (LDL) may lead not only to endothelial injury but also could convert a limited tissue response to injury into atherosclerosis (Ross and Glamset, 1976, and Stemerman ,1981). The above described hypothesis accomodates nicely both the idea of

insudation and the idea of encrustation. In addition,it is compatible with the known relationship between elevated serum cholesterol and atherosclerosis. In fact, no population has been identified in which progressive atherosclerosis develops if the serum cholesterol level is low. these relationships are also supported by clinicopathological studies, experimental animal studies, and investigations in cell biology and molecular pathology (Brown et al.,1981;and Wissler, 1984).

ARTERIAL CELLS and LIPOPROTEINS

The key advance of the 1960's which has helped to foster the modern era of atherosclerosis research was the demonstration by numerous methods that most of the cholesterol and cholesterol esters in human plaques were probably derived from (LDL) or (VLDL) that gained enterance to the intima and the inner media from the blood-stream. Then, it has become increasingly evident that in addition to the (LDL) from hyperlipidemic serum, several other lipoprotein fractions may be important in deposing cholesterol and cholesterol esters in the artery. It has now become clear that the (LDL) particles are not a homogenous family. The large, cholesterol-rich (LDL) from hyperlipidemic serum has a number of important features which distinguish it from (LDL) derived from subjects with normal basal levels of (LDL). Furthermore, recent work, has yielded important new evidence of heterogeneity of (LDL), which has been classified into LDL I, II, III, IV (Fless et al.,1982; and Wissler, 1984).

As the interactions between various cells and lipoproteins are studied further,it has become evident that (LDL) which is altered in the test tube or by platelet or endothelial cell action also has distinguishing features which decrease its avidity for apo B receptors on the smooth muscle cells and increase its binding for macrophages (Henriksen et al.,1981 ; and

wissler, 1984). Furthermore, apo B appears to be the only apoprotein which increases as the plaque develops in size and severity (Wissler, 1984).

ROLE OF PLATELETS AND ENDOTHELIAL DAMAGE

Using balloon catheter injury as an experimental method to produce denudation of the arterial intima and modern pathobiological methods to study cell, it was discovered that platelets stick to the damaged arterial intimal surfaces and disintegrate, liberating a potent peptide (or peptides), that promotes proliferation of arterial SMCs in vitro (Ross,1981). These observations were combined with important in_vivo studies which demonstrated that factors which inhibit platelet sticking, spreading, and disintegration also inhibit SMCs proliferation in areas of damaged endothelium (Wissler,1984).

Recent advances in the understanding of the platelet factor have included its purification, and that it binds specifically with a receptor on the surface of cells it stimulates (Bowen-Pope and Russel, 1982).

ROLE OF HEMODYNAMIC STRESS

hemodynamics may well be the local factor responsible for the topographic distribution of atherosclerosis. The importance of these local factors is substantiated by the following observations; (1) Caliber- the larger the artery, the more severe is the atherosclerosis.

(2)Blood pressure - the disease is more severe in the systemic arteries than in the pulmonary arteries.

(3)Atherosclerosis is more severe in the abdominal aorta and iliac ateries than in the thoracic aorta, this may be attributed to the heightened pulse pressures distally, and to the origin of the segmental vessels from

the posterior surface of the abdominal aorta.

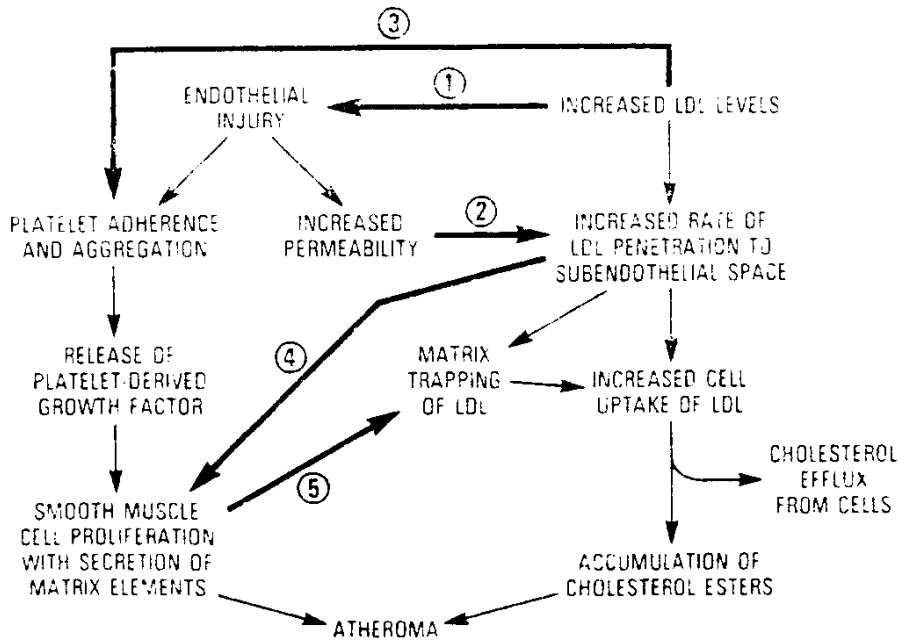
(4)It is known to show a predilection for sites of branching, curvatures, and unions.

(5)It is more severe in the right radial artery than the left in right-handed and vice versa.

It has also been demonstrated that in cholesterol-fed rabbits lipid accumulates at the site of arteriotomy wound but not at the site of phelebotomy in the same animal (i.e. localization of lipids is not due to trauma alone; arterial hemodynamics act synergistically). On the other hand,it is known that arteriovenous fistulae produced for the purpose of renal hemodialysis in human patients, do not only produce atherosclerosis in the venous segment of such fistulae, but also, thrombosis, aneurysms, and stenosis(Stehbens, 1979).

In conclusion,as the concepts of lipoprotein insudation and arterial endothelial injury advances, it becomes increasingly evident that we are dealing with strongly interacting pathogenetic mechanisms.

These interactions have been recently summarized in the following diagram (Steinberg,1981).



This diagram indicates the probable interactions between the two major pathogenetic mechanisms proposed for atherogenesis. The steps involved according to the endothelial injury formulation are on the left, and those for the lipid-cholesterol formulation are on the right. The interactions are numbered as follows: (1) LDL in high concentrations induces endothelial injury; (2) endothelial injury increases influx of LDL; (3) hyperlipoproteinemia stimulates platelet aggregation; (4) high LDL levels stimulate proliferation of arterial SMC which are in the stationary phase; and (5) SMC-produced extracellular matrix binds and traps LDL molecules, which in turn may permit increased cellular uptake of LDL. (From Steinberg, D.: Metabolism of lipoproteins at the cellular level in relation to atherogenesis. *In* Miller, N. E., and Lewis, B. (eds.): Lipoproteins, Atherosclerosis and Coronary Heart Disease. Amsterdam, Elsevier, 1981, p. 31.)

HEMORHEOLOGY and HEMODYNAMICS OF ISCHEMIA

Occlusive arterial disease is complex and our understanding of its pathogenesis is rather limited. Neverthless, we can draw some points which may direct our studies of blood rheology: (1) We can define certain clinical syndromes of organ ischemia, and relate hemorheology to these clinical events, (2) Extensive atherosclerosis appears to be a common pathological basis for most of these clinical events, with or without additional lumen occlusion by platelets and/or fibrin. The localization of lesions suggests that fluid-dynamic forces may play a role in their formation, (3) certain well-recognized risk factors are associated in epidemiological studies with the development of clinical events, (4) In morphological studies, arterial occlusion by wall disease or by intraluminal mass derived from blood is commonly incomplete. A further reduction in blood flow which precipitates ischemia may exist. Impaired blood fluidity is a possible factor, (5) As there is evidence that aggregates of platelets and fibrin are associated with some clinical events, the relationship of blood rheology to these processes may also be of interest (Lowe et al., 1981b).

MECHANISMS BY WHICH ABNORMAL RHEOLOGY MAY PROMOTE ISCHEMIA

1-Blood flow reduction:

A rise in hematocrit of 7% and of blood viscosity of 17% was recorded in healthy young men after 5 minutes strenuous exercise. Similar acute impairment arises following acute illness or injury, and after heavy