Introduction

Juvenile vascular diseases, both arterial and venous, are presently arousing a growing interest in medical research, due to their human impact and social consequences in terms of early disability and mortality.

Considerable progress has recently been achieved in early-onset recurrent venous thrombosis [1]. Genetically transmitted deficiencies of the main coagulation inhibitors (anti-thrombin III, and protein C system) have been identified as pathogenic and ‘risk’ factors. Other inherited coagulation abnormalities contribute to familial juvenile recurrent venous thromboembolism although with lesser frequency and penetrance. However, it can be estimated that all the presently known inherited coagulation abnormalities, taken together, account for no more than 30% of all cases of early-onset recurrent and familial deep-vein thrombosis, thus suggesting the existence of a large domain for other still unknown or hitherto overlooked pathogenic factors. Among acquired factors responsible for recurrent thrombogenesis, immunologic abnormalities and especially the presence of anti-phospholipid antibodies, including the lupuslike anticoagulant [2], have a significant role. Acquired reduction of fibrinolysis, frequently induced by increased levels in PAI-I, is also often found in recurrent deep-vein thrombosis and is generally regarded as a secondary factor [3].

As regards the arterial side of thrombotic processes, it should first be noticed that the quoted congenital coagulation abnormalities are less frequently involved. This confirms the predominant role of the activation of blood coagulation in venous versus arterial thrombogenesis. A partial exception is offered by the abnormality of the protein C-protein S system, which acts upon the binding of thrombin to the endothelium; in this condition, arterial and microcirculatory thromboses can also be observed. Among acquired clotting abnormalities, the antiphospholipid antibody syndrome is also closely related to juvenile and recurrent arterial (as well as venous) thrombotic disease. As concerns fibrinolysis, it has been suggested that elevated plasminogen activator inhibitor I (PAI-I) levels may be a risk factor for recurrences of coronary thrombosis [4] in young survivors after a first episode of myocardial infarction. It is known that PAI-I behaves as an acute-phase protein and it could be speculated that its prognostic significance is not dissimilar to elevated fibrinogen levels. Moreover, our observation of elevated PAI-I levels in childhood obesity with no evidence of vascular disease [5] calls for greater attention to PAI-I assessment in conditions predisposing to early-onset thrombosis.

With regard to risk factors, not primarily related to clotting mechanisms, it is known that certain types of familial hypercholesterolemia are complicated by juvenile myocardial infarction or other vascular disease. The same can be said for juvenile diabetes and hypertension. Increased levels of a special lipoprotein-associated antigen, designated as apoLP(a), have been found in groups of patients with high incidence of atherothrombotic disease [6]. As this substance shows a striking molecular analogy with plasminogen, it can be specu-
ated that it may behave as an inactive plas-minogen variant, thus competing with normal plasminogen in fibrinolysis activation.

However, still too many cases of early atherothrombotic disease develop in the absence of any of the hitherto recognized risk factors and this again would seem to suggest that a number of important predisposing conditions are presently being ignored or overlooked.

Homocystinuria, a rare inherited metabolic disease [7], is generally due to deficiency of the transsulfuration mechanism responsible for conversion of homocysteine into cystathionine and cysteine, or, occasionally, to defective re-methylation of homocysteine into methionine (see paper by Skovby in this issue). Among its clinical features, severe venous and arterial thrombotic episodes and accelerated athero-thrombosis account for early mortality and disability (paper by Cacciari et al.).

Although the estimated frequency of overt homocystinuria varies between 1 in 200,000 and 1 in 24,000 [8], this condition has gained the attention of several investigators, as a natural model of accelerated thrombogenesis and atherogenesis. Elucidation of the pathogenic mechanism of vascular involvement in homocystinuria is still incomplete, and conflicting results have often been reported. However, it is generally agreed that homocysteine, a sulfated amino acid normally not detectable in blood, induces intimal injury both in endothelial cell culture experiments and in vivo [9, 10]. Altered endothelial function may result in disturbed platelet-vessel wall interaction, increased production of free oxygen radicals [9], and depression of prostacyclin synthesis [11], enhanced prothrombin activation on the endothelial surface [12]. None of these mechanisms, however, has been fully confirmed and accepted. A number of reports also suggest changes in blood coagulation factors, and the demonstration by our group of reduced antithrombin III levels reversed by effective metabolic therapy [13] may be of interest in this respect. Thus, homocystinuria provides useful patterns for experimental and clinical investigations aimed at the understanding of the general pathophysiology of thrombosis and arteriosclerosis.

In the early 70s, McCully [14] had formulated, on the basis of pathological observations, a ‘Homocysteine theory of atherosclerosis’, and in 1976 Wilcken and Wilcken [15] (see paper in this volume), in their pioneering clinical studies, suggested that mild homocysteinemia could be a risk factor for vascular disease. Up to now, a number of other contributions have been published confirming these views, but the impact of this knowledge on the lines of thought prevailing among thrombosis as well as arteriosclerosis experts has been rather limited. For these reasons, I felt that it was time to bring to the attention of hemostasis and thrombosis scholars, and of the general scientific public, some selected advances in homocystinuria and homocysteinemic states in relation to early-onset atherothrombosis.

Heterozygosity for homocystinuria has been studied, among others, by Boers et al. [16] (and in this issue). This condition has an estimated prevalence of 1:200 or more in the normal population, and is reportedly much more frequent (from 20 to 30%) in patients with early peripheral or cerebrovascular, rather than coronary, occlusive arterial disease. These data deserve attention and should be confirmed in prospective studies.

Abnormal homocysteine metabolism can be detected by slightly elevated baseline homocystinemia and/or by increased homocysteine levels after a standardized methionine load. The contributions by Brattstrom [8] (and in this issue), besides confirming the data of Boers, indicate that vitamin B12 and red cell folate levels are important modulating factors for borderline homocysteinemia, and that a pyridox-al-5-phosphate deficiency is a frequent finding in young patients with vascular disorders. The existence of acquired conditions predisposing
to mild homocysteinemia, such as renal failure, menopausal age, and the high protein (and consequently, methionine) dietary intake in affluent societies, open fascinating prospects for present and future research on early thrombosis and atherosclerosis. The Project on Homocystinuria of the Italian National Research Council (paper by Donati et al.) is proof that public research agencies can become interested in this problem if their attention is correctly stimulated.

I am grateful to the Council of the Mediterranean League on Thromboembolism for supporting my willingness to organize a Symposium on this topic, in the frame of the 10th International Congress on Thrombosis held in Athens, May 23-27, 1988, and to the President of that Congress, Prof. Titika Mandalaki, who accepted the idea and contributed to its realization. Most of the articles in this issue were in fact presented and discussed at that Symposium, the first, to my knowledge, devoted to this topic in an International Congress on Blood Coagulation.

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References