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Letter to the Editor

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The Last Contribution of Hemophiliacs to Blood Coagulation: Atherosclerosis Is Not Prevented by Hypocoagulability

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To the Editor

"In principio omnes errant hemophiliacs". In the past, all bleeding patients were considered as hemophiliacs. Quick demonstrated in the mid thirties that hemophiliacs had a normal prothrombin time (P.T.). This allowed the first distinction of "bleeding patients" in two groups, some with a normal P.T. and some with a prolonged P.T. [1].

Only in 1947, "hemophilia" could be suspected to comprise two different diseases, when Pawlowski in Argentina showed the correction of the defect after mixing the plasmas of two patients known to have hemophilia, thereby suggesting the existence of two types of defect [2]. This was independently confirmed later on by Aggeler et al in the U.S.A. and in England by the Oxford Group in 1952 [3, 4].

Since that time the contribution of hemophilic patients to the understanding of blood coagulation was astonishing and could be summarized along the following lines, without the presumption to be complete: 1). Cryoprecipitates corrected Hemophilia A but not, or very little the hemophilia B defect [5]. 2). Immunological studies on hemophilia A and B have opened new horizons on VWD and demonstrated the existence of hemophilia variants with cross reacting material (CRM) [6, 7]. These studies were then instrumental in the classification of other clotting defects, especially, FX and F VII defects [8]. 3). A hemophilia B variant, hemophilia BM, showed a prolonged prothrombin time when a reagent containing ox-brain thomboplastin was used in the assay system [9]. This opened new horizons in prothrombin complex diseases with regard to their reactivity towards tissue thromploplastins of different origin [10]. 4). Another peculiar contribution was the observation that, in a special type of hemophilia B (Hemophilia B Leyden) there was a variable correction of the defect as the patients aged [11]. This cast light on the androgen-dependent maturation of FIX at the hepatocyte level. 5). Hemophilia patients payed heavily for our delays and faults in the developing of safe concentrates. The pain, sacrifice and the size of the cemetery of hemophiliacs has still to be properly acknowledged and described. 6). Synoviectomy carried out in hemophiliacs in an attempt to impede or delay the occurrence of the arthropathy has considerably spurred the use of this procedure in several orthopedic diseases [12]. 7). The development in some patients of antibodies after replacement therapy has opened important lines of investigation in the genetic control of immunological mechanisms. 8). The widespread treatment of HIV and hepatitis B and C in hemophilia patients has supplied valuable information for the management of these infections even in non-bleeding subjects. 9). The role of liver transplantation in the management of hemophilia is still disputed. However some success has been obtained even by the live donor transplant [13-15]. 10). The status of genetic therapy of hemophilia is still open and very controversial but hemophiliacs have given a contribution even to this field [16, 17]. They represent, at least on theoretical grounds, ideal subjects for gene therapy [16].

Now, hemophiliacs supply us with a new important information. They have shown that atherosclerosis' may occur in them as in normal persons [18, 19]. Old studies had suggested that the clotting defect could exercise a protection against atherosclerosis.

They were wrong. Now it is known that this is not the case. A new medical field has been opened. How to treat hemophilia patients with atherosclerosis and its complications, notably acute coronary syndromes. So, after so many contributions, another major contribution has emerged.

Thanks to the improved overall care and to the safety of replacement therapy, the hemophilia population has aged and with age , age related problems have appeared [19, 20].

The demonstration that atherosclerosis may occur in patients with hemophilia and with other congenital coagulation disorders is an event of great importance in blood coagulation. It indicates that hypocoagulability does not prevent the aging of the arteries, namely the formation of fatty streaks or plaques in the intima of the arteries.

The focus on the pathogenesis of atherosclerosis must rest therefore on lipids (mainly cholesterol) and inflammation.

Congenital hypocoagulability may still protect from atherothrombosis which refers to the formation of a thrombus on fissured on ulcerated plaques. However an arterial occlusion may occur without the formation of a thrombus.

This may explain at least part of the myocardial infarctions (M.I.) seen in patients with Hemophilia and other clotting disorders. Autopsy and coronographic data indicate that atherosclerotic streaks and plaques are always present, sometimes complicated by the formation of a thrombus [21, 22].

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There are now in the literature about 100 cases of hemophilia patients with proven M.I. or other acute coronary syndromes as demonstrated by enzyme elevation. EKG changes, coronary angiography [23, 24]. Furthermore the number of hemophilia patients undergoing invasive coronary interventions (I.C.I.) even before a myocardial infarction has occurred is increasing at a sharp rate. It is clear that aging hemophiliacs have the same incidence of atherosclerosis as that of subjects with no hemorrhagic disorders [19].

These accomplishments, seen as a whole, have probably no rivals in any other set of diseases. They have contributed immensely to our understanding of blood coagulation. The gratitude towards the different generations of hemophiliacs should be shared by all coagulation experts even by those who, working in the laboratory, are confronted only with plasma and blood samples present in syringes and or in tubes. Nobody should forget the personal suffering that lies beyond these plasma or blood samples.

The title of this note reads "The last contribution of hemophiliacs to blood coagulation: etc." May be it should have read "The latest contribution etc". Hemophiliacs may reserve us a few more surprises.

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