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Side effects of antihemophilic concentrates

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Liver disease and thromboembolism are the most frequent and severe side effects associated with the use of clotting-factor concentrates in haemophiliacs. Knowledge and careful evaluation of the risk factors related to their development appear to be the most reasonable policy for prevention. Hemolysis due to significant isoantibody infusion and bleeding associated to abnormal platelet function occur more rarely during intensive replacement therapy with clotting factor concentrates. Finally, abnormalities of renal function have been observed in a number of patients, though they seem to be of minor clinical importance.
These complications do not justify withdrawal or limitation of the very effective and life-changing use of concentrates. However, awareness of their occurrence and of their danger requires that specialized hemophilia centres carry out, at frequent intervals, clinical and laboratory testing of the target organs to allow an early detection.

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In the last ten years there have been spectacular developments in haemophilia: we now have the knowledge of how to stop bleeding; how to avoid new deformities and how to improve or correct those which are already established. Such crucial advances have been based essentially on the greatly increased availability of clotting factor concentrates, accompanied by an improved knowledge of how to use them and improved social and medical organization in applying this knowledge to the effective treatment of the patients. It has been known for some time that replacement therapy with plasma and antihemophilic concentrates may be associated with complications and side-effects; and that some of them may be so severe as to overcome the benefit of such therapy. The recent advent of home self-treatment, a revolutionary approach to the problem of the management of hemophilia, emphasizes the possibility that complications may develop far from the control of the specialized centre. Therefore, it seemed timely and necessary to review the problems related to side ef-

fects of antihemophilic concentrates. This issue contains the papers presented at the Symposium organized by the World Federation of Hemophilia together with the International Society of Blood Transfusion during their joint Congress (Helsinki, July 27th- August 1st, 1975).

Liver disease. Haemophiliacs are a group among multitransfused patients who are exposed most frequently and for the longest period of time to the agent(s) implicated in *post-transfusion hepatitis.* The rate of exposure has probably increased since the widespread adoption of the freeze-dried concentrates of Factor VIII and Factor IX; these carry a higher risk of contamination, having been manufactured by pools of plasma from a large number of donors. Despite this, the incidence of clinical illness associated with jaundice is surprisingly low in hemophiliacs, ranging from 0.6 to 1.8 cases per 100 patients per year (Kasper & Kipnis, 1972; Biggs, 1974; Lewis et al, 1974; Mannucci et al, 1975). This figure, however, does not exclude the occurrence of anicteric hepatitis, which is particularly frequent in children, as well as the possibility that repeated and prolonged contact with the infective agent(s) may cause chronic liver damage not associated with overt illness. Such assumption is supported by results reported in this issue by Hasiba et al and Yannitsiotis et al. Studying large series of multitransfused hemophiliacs, both groups of investigators found a high incidence of abnormal liver function tests. The very high prevalence rate of the markers of the hepatitis B virus (hepatitis B surface antigen, HB_sAg, and antibody, anti-HB_s) found in these patients suggests that the observed abnormalities are likely to be related to the frequent and repeated exposure to the agent contaminating the blood derivatives. The observation of Hasiba et al that abnormal liver function was more frequent in patients treated with commercial concentrates than in those treated with blood-bank cryoprecipitate is rewarding, because it clearly shows a way in which prevention can be attempted.

The clinical and prognostic significance of the observed abnormalities is presently unknown, and the great majority of the patients were asymptomatic and free of physical signs of liver involvement. Hence, until an answer to this problem can be given by a long-term prospective evaluation, it appears unjustified to withdraw or reduce the very effective and life-changing use of concentrates. This concept is supported by the findings of Hilgartner and Giardina, who have related the incidence of abnormal liver function tests to the amount of concentrates received by hemophiliacs on home care. Elevations of serum enzymes and the occurence of HB_sAg and/or Ab were not remarkably different in patients on prophylactic and episodic therapy, although the amount of concentrates transfused in the latter group was significantly lower. The papers on liver dysfunction in hemophiliacs are concluded by an inte-

resting investigation carried out by Sultan et al. They found that the factor VIII-related antigen increases in hemophiliacs during the course of acute hepatitis, and that some of its physiochemical properties become abnormal; high values have also been found in the plasma of symptomfree hemophiliacs with abnormal liver function test. Such observation suggests a word of caution in the interpretation of the results obtained when the measurement is used in the diagnosis of hemophilia and of different types of von Willebrand's disease, unless abnormal liver function can be ruled out.

Thromboembolism - In the last few years, reports from the United States have warned us of the hazards of *thromboembolism* associated with commercial prothrombin-complex concentrates employed in the management of patients with hemophilia B, factor II, VII and X deficiencies. Although such complications have not been reported with the products used in Europe, the problem is a serious one.

Reviewing the available data, Aledort reports in this issue the findings of a recent survey carried out in the United States under the auspices of the National Heart and Lung Institute and Food and Drugs Administration. Twenty out of 188 patients with hemophilia B and/or liver disease had thrombotic complications. The content of activated clotting factors in the concentrates, the presence of liver failure in some patients (with decreased removal of the injected procoagulants from the circulation) and the hypercoagulable state associated to surgery are likely to be the most relevant risk factors in the occurrence of complications.

Aledort suggests that a careful evaluation of these prognostic indices is one of the main points in prevention; and that satisfactory *in vivo* and *in vitro* tests are clearly warranted to predict the risk of the products.

Anemia - Anemia has been rarely observed in hemophiliacs treated with large volumes of plasma concentrates. Destruction of patient's red blood cells by anti-A or anti-B *agglutinins* contained in the preparations is likely to be the most frequent cause of such a complication, as suggested by Schimpf in his excellent review. Although severe clinical symptoms are rare, this possibility must be considered when progressive anemia develops in patients intensively treated, unless type-specific concentrates are used. Louizou et al also show that in Greek polytransfused hemophiliacs there is a high incidence of *blood group antibodies* and suggest that the immunization is likely to be related to the transfusion of incompatible red cell antigens contained in pooled plasma. Careful cross-matching is thus mandatory to avoid transfusion reactions in these patients.

Another cause of anemia and bleeding which may follow intensive replacement therapy has been identified by Sutor et al. They describe 8 patients with classical hemophilia A, in whom

defective platelet function developed during treatment with conventional doses of commercial factor VIII concentrates. The observed abnormalities of platelet function tests (bleeding time, hemorrhagometry and platelet adhesiveness) returned to normal when concentrates were discontinued and freshly-prepared cryoprecipitate was administered. Such alterations of primary hemostasis are unusual and resemble those observed in von Willebrand's disease. Since they also occur in patients treated with small doses of commercial concentrates, hyperfibrinogenemia is unlikely to be the most frequent cause as previously suggested by Hathaway et al. (1973); on the other hand, the levels of fibrinogen degradation products shown in two patients are too low to justify the abnormal platelet function, as shown by Solum et al (1973).

Renal abnormalities - The last paper of this issue (Forbes and Prentice) deals with the *renal complications* associated with hemophilia. In a detailed survey of renal function carried out in 35 patients with hemophilia A, they found a high incidence of abnormalities, such as microhematuria, filling defects following intravenous pyelography and abnormal renography. Although the observed findings were of minor clinical significance and there is no evidence of deterioration in the follow-up, the problem is important and puzzling. Six of these patients had been previously treated with synthetic antifibrinolytic drugs: since the incidence is not different from the overall incidence of abnormalities in the series, the use of these drugs is unlikely to be an important pathogenetic factor. Prentice et al (1971) have also reported on a case with renal amiloidocis apparently secondary to repeated isoimmunizations with incompatible Gm antigens (see also Kernoff & Bowell, 1973). Thus, the possibility that the observed renal abnormalities are the expression of an immuno-complex pathology cannot be ruled out and deserves further investigations.

In conclusion, the reports of this Symposium clearly show that antihemophilic concentrates are frequently associated with side effects which may be of clinical relevance. However, they do not justify withdrawal or limitation of replacement therapy, which would be accompanied by a consistent deterioration of the present pattern of life of hemophiliacs. A more detailed knowledge and assessment of risk factors is likely to reduce, if not to abolish, the most frequent and severe side effects such as liver disease and thromboembolism. Since the growing adoption of home therapy has considerably reduced the burden of routine work in the specialized hemophilia centres, the free time now available should be directed towards research, and more frequent clinical and laboratory controls for an early detection of these complications.

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