

CLINICAL USE OF FACTOR IX CONCENTRATES. D. Ménaché, Hôpital Beaujon, Clichy, France.

The clinical efficacy of Factor IX concentrates in the treatment of patients with Factor IX deficiency is well recognized. The availability of such concentrates has brought a radical change in the management of these patients. The basis for treatment is to obtain an effective Factor IX hemostatic level *in vivo*. In these conditions, concentrates have been used to reduce the incidence of hemorrhagic episodes in patients particularly exposed and more often to control hemorrhagic episodes or to prevent hemorrhage in the post operative period.

Although thromboembolic complications have occurred in some instances the major indication of Factor IX concentrates still remains replacement therapy in patients with Factor IX deficiency.

More recently Factor IX concentrates have been used for the treatment of patients with antibody to Factor VIII. Although the therapeutic principle(s) responsible for the Factor VIII inhibitor bypassing activity has not yet been characterized several beneficial effect of both "activated" and non activated Factor IX concentrates have been observed in such patients experiencing minor or severe bleeding episodes. On the other hand we are aware of some cases without beneficial effect of Factor IX concentrates in patients with Factor VIII inhibitor. The major complication would seem to be an anamnestic response in some patients resulting in either a moderate or a considerable increase of the Factor VIII inhibitor titer when compared to the initial level before Factor IX concentrates therapy. If Factor IX concentrates prove to be efficacious in the treatment of patients with Factor VIII antibody special attention would be required in the manufacturing processing in order to avoid an anamnestic response.

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INVITED SYMPOSIUM VII

Contact Phase Coagulation Factors.

MOLECULAR MECHANISMS OF CONTACT ACTIVATION. John H. Griffin. Scripps Clinic and Research Foundation, La Jolla, CA 92037 U.S.A.

Exposure of human plasma to various negatively charged surfaces (glass, kaolin, connective tissue components, urate crystals, endotoxin, etc.) leads to "contact activation" of plasma and thereby initiates the activation of the intrinsic coagulation, the kinin-forming, and the plasma fibrinolytic systems. Studies of plasmas which are functionally defective in contact activation reactions implicate the following proteins in contact activation reactions: (1) Hageman Factor (HF) (Factor XII); (2) prekallikrein (Fletcher Factor); (3) high MW kininogen (Fitzgerald, Flaujeac, or Williams Factor) (Contact Activation Cofactor); and (4) Factor XI. Recent studies suggest that a previously postulated HF-dependent plasminogen proactivator is identical to prekallikrein.

A mixture of purified HF, high MW kininogen, prekallikrein, and kaolin gives the same rapid rate of activation of purified Factor XI as does an equivalent aliquot of plasma plus kaolin, thus suggesting that contact activation of Factor XI is fully explicable in terms of the interactions between these proteins. Using these purified proteins, the molecular mechanisms of contact activation have been studied extensively, and the results which will be presented support the following new hypothesis. Surface-binding of HF does not convert a detectable fraction (<1%) of HF molecules to active enzymes as previously supposed, but instead it renders HF much more susceptible (100 to 400-fold) to proteolytic activation by plasmin or kallikrein in the presence of high MW kininogen. High MW kininogen is a surface-bound HF cofactor for each step in the reciprocal activation of prekallikrein and HF, and for the limited cleavage of Factor XI by activated HF.