It has been proposed that FXII zincogen can cleave pre-kallikrein without prior conversion into one of its proteolytically cleaved forms FXIIa or FXIIf with pro-Arg-Val-CH2ketone (PAKMK) to remove all measurable amidolytic activity due to traces of FXIIa or FXIIf. Prekallikrein (PK) and kallikrein similarly treated were unable to remove all traces of kallikrein. FXII was diluted to 0.016 µg/ml, using 3.8 µg/ml IgG as the diluent, and mixed 1:1 with 25 lg/ml PK. The rate of generation of kallikrein activity was negligible in the absence of FXII, and increased with time. The approach to the rate of activation obtained with FXIIa or FXIIf at equivalent concentrations. When 10 µg/ml dextran sulphate was present the rate of PK activation was maximal from the beginning. This experiment was repeated in the presence of a specific inhibitor of activated FXII or derived from corn; 1 mg/ml inhibitor prevented the activation of PK. This indicates that the PK activator is the same species that reacts with the inhibitor, namely FXIIa or FXIIf. In another experiment, 1.67 µg/ml of PAPMK-treated FXII and 2.6 µg/ml PAPMK-treated PK were mixed in glass cuvettes containing 5000 nM chromogenic substrates specific for either FXIIa or kallikrein. The resulting curves of absorbance vs time showed that both FXII and PK became activated in accelerating reactions after short lag phases; corn inhibitor blocked this reaction too. Thus the rapid activation and the lack of a lag phase seen in the experiment with dextran sulphate was the result of an induced formation of an active site in FXII zincogen but was a result of the very rapid activation of surface bound FXII by traces of kallikrein. The kallikrein may have been generated by traces of FXIIa which are present treatment of FXIIa with inhibitors. This amount of FXIIa may also be present in vivo and provides a potential mechanism for the initiation of contact activation.

Certain activators of the contact system of coagulation have been reported to induce full activity in the single-chain form (80,000 MW) of factor XI (XIa). The effects of soluble ellagic acid (EA) and dextran sulphate (DSX) (-500,000 MW) on purified components of the contact system were studied. Soluble EA (40 µM) was found to exert a dose-dependent procoagulant effect on purified FXII added to FXII-deficient plasma whereas the maximal activity observed was much less than that elicited by kaolin in the same mixtures. 5 µM soluble EA increased the amidolytic activity of FXII against H-D-Pro-Phe-Arg-pNA from 2.5 to 5.0 mol substrate/mol enzyme/min. Purified A-FXIIa (28,000 MW) or FXIIa that had been preincubated with trypsin hydrolyzed 900 mol substrate/mol enzyme/min in the presence or absence of soluble EA. Thus soluble EA induces minimal (30%) amidolytic activity in FXII. We also examined the generation of FXII in the presence of 5 µM soluble EA, FXI, high MW kininogen, and FXII or A-FXIIa (two-chain form, 80,000 MW). The rate of cleavage of 125I-FXI in the presence of 10 ng/ml DXS, FXI, high MW kininogen, and FXII or A-FXIIa was also measured. In the presence of either DXS or soluble EA under the concentrations and conditions employed, A-FXIIa exhibited an initial rate of FXI activation that was 20 times higher than that achieved by single-chain FXII. In addition, the presence of both high MW kininogen and either DXS or EA enhanced the activity of A-FXIIa 20 fold for FXI activation. The results show that single chain FXII in the presence of either DXS or soluble EA expresses less than 5% of the enzymatic activities of its proteolytically derived forms whereas either "activator" growth enhances the action of A-FXIIa on FXI in the presence of high MW kininogen.

A parallel decrease of factor XII and an inhibitor of plasminogen activator (PA inhibitor) earlier described by Hedner (1973, 1980) was observed in a small series of patients postoperatively. Factor XII and PA inhibitor levels were studied in 80 patients postoperatively in order to further investigate this, 52 patients (29 males and 23 females) were studied in connection with vascular surgery. The following parameters were analyzed: factor XII (clotting and imm.chem.assay), PA inhibitor, α2-antiplasmin (α2P), α2-macroglobulin (α2M) and CI-inactivator (CI-INA)(rocket technique) and factor IX (clotting assay). A significant parallel decrease to about 50% of factor XII measured with both methods reaching its minimum on day 4-5 postop as well as of the PA inhib was seen. This decrease was found in all patient groups except those operated upon because of varicose veins. These latter patients all left the hospital already on the 2nd or 3rd postop day. No concomitant decrease of α2P, α2M, CI-INA was seen. The observed lowering of f XII and PA inh. on day 4-5 did not depend on changes in hematocrit associated with the operation.

The findings of a parallel decrease of f XII and the PA inhib shown to inhibit f XIIa (Hedner and Martinsson 1978) may indicate that an activation of f XII followed by consumption of this factor as well as of the inhibitor to f XII occurs during or after surgery. Whether the f XII dependent fibrinolysis is of importance in the development of deep venous thrombosis is still debatable. It is, however, striking that low levels of f XII occurs postop at a time when most proteins show an increased synthesis rate because of stimulation by the surgical trauma. Furthermore inhibitors against the activation phase is known to be associated with thrombotic disease (Hedner and Nilsson 1976).