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Duckert F, Jung E & Shmerling D H. A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilizing factor deficiency.
Thromb. Diath. Haemorrhag. 5:179-86, 1960.
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The physiological role of the fibrin stabilizing factor (FSF) is demonstrated for the first time. An almost complete deficiency of FSF provokes recurrent, long-lasting haemorrhages after small traumas, such as small, clean cuts. In most patients, the hereditary deficiency of FSF is the cause of a delayed and abnormal wound healing. [The *SCI*® indicates that this paper has been cited in over 180 publications.]

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During a patient's first hospitalization at the Children's Hospital in Zürich, a complete analysis with the available methods gave absolutely no clues to the origin of a haemostatic defect. Capillary microscopy and electron microscopy of the thrombocytes were of no help.

During the second hospitalization, the patient bled from a small cut in the forehead. Again, all analytical efforts remained without success until after a brainstorming session, which I had organized. Among other more or less absurd investigation proposals, Jung mentioned a clot solubility test. Immediately, we looked around in the lab for urea or monochloroacetic acid. About two hours later, after incubation at 37° C, a clot made out of the patient's plasma was already dissolved in 5 molar urea, whereas a clot from a normal subject remained perfectly intact.

According to the biochemical literature, a plasma clot remains insoluble only when, besides fibrinogen and the enzyme thrombin, another factor[1]—the fibrin stabilizing factor (FSF)[2]—is present in the clotting mixture. Absence of FSF modified not only the solubility of the clot but also its resistance to mechanical stress. This FSF property explained the behaviour of the patient's clot in the thromboelastograph. The fibrin network was less rigid than normal. The thromboelastogram showed a rather rapid decrease of clot firmness.

Failure to correct the defect by administration *in vivo* or addition to plasma *in vitro* of ε-aminocaproic acid, an inhibitor of the fibrinolysis, excluded the participation of an enhanced fibrinolytic activity. Addition of 0.5 percent normal plasma was sufficient to restore the clot insolubility. Preliminary investigations after transfusion of normal plasma revealed a half-life of at least three days. The family history let us assume an autosomal recessive disease.[3]

The discovery of a patient with an FSF deficiency clearly demonstrated the importance not only of the quantity of fibrin formed and the formation rate, but also of the quality of the fibrin. Stabilization of the fibrin is required in order to produce a physiologically adequate haemostatic clot. In spite of these results, an English colleague pretended that FSF was no more than a biochemical curiosity.

However, biochemical research was greatly stimulated. FSF was numbered as factor XIII by the International Committee on Blood Clotting factors. It was soon established that it was an enzyme[4] and was later recognized as a ε-(γ-glutamyl) lysine transglutaminase introducing covalent bonds in the fibrin network between two γ-chains (γ-dimer) and between α-chains (α-polymers). Also α_2-antiplasmin was found to be covalently bound to fibrin by FSF, thus enhancing the resistance of the clot to fibrinolytic degradation.

After the publication of our results, several investigators reexamined their patients with haemorrhagic complications of unclear origin. Several patients were found to have a hereditary FSF deficiency characterized by early umbilical bleeding, recurrent bleeding after a small trauma, and, frequently, abnormal wound healing.[3]

Our team has continued to investigate the clinical possibilities of thrombolytic treatment and the correlation between thrombolytic agents and their dosages and therapeutic success. In addition to other basic research problems, we have discovered an abnormal antithrombin III,[5] and quite recently we were the first to describe a deficiency of heparin cofactor II.[6]

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3. **Duckert F.** Documentation of the plasma factor XIII deficiency in man. *Ann. NY Acad. Sci.* **202**:190-9, 1972. (Cited 70 times.)
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6. **Tran T H, Marbet G A & Duckert F.** Association of hereditary heparin co-factor II deficiency with thrombosis. *Lancet* **2**:413-14, 1985.

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