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5.15 0181 DEFECTIVE THROMBIN BINDING BY ABNORMAL FIBRIN ASSOCIATED WITH RECURRENT THROMBOSIS

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Studies of clotting activity and radioactivity (with ^{125}I-thrombin) indicated that binding of human thrombin to fibrin depends upon the initial concentrations of the reactants. Scatchard analysis suggests two classes of binding site: a high affinity site with a Ka 5.8±0.9 x $10^5 M^{-1}$ and a maximum molar binding ratio of thrombin to fibrin 0.4±0.2, and a low affinity site with a Ka 6.8±0.6 x $10^4 M^{-1}$ and a maximum molar binding ratio of 1.6±0.5. The active site of thrombin is not required for binding since neutralization with phenylmethyl sulfonyl fluoride does not affect the binding. Thrombin also binds to fibrin formed in whole blood and can be recovered with full clotting activity when the clot is dissolved by plasmin, suggesting that binding of thrombin to fibrin is a potential mechanism for limiting thrombosis. Fibrinogen New York I, in a patient with recurrent venous and arterial thrombosis, was characterized by abnormalities in fibrinopeptide release by thrombin and fibrin polymerization. The patient's plasma contained equal amounts of normal and abnormal fibrinogen. Thrombin was bound normally by fibrin derived from the normal fibrinogen but was not bound at all by fibrin from the abnormal fibrinogen. Fibrinogen New York II, in an asymptomatic patient, was characterized by delayed fibrinopeptide release and fibrin polymerization. Thrombin was bound normally by this fibrin. Thus defective binding of thrombin by fibrin is suggested as a new mechanism predisposing to recurrent thrombosis.

5.30 0182 MOLECULAR CHARACTERIZATION OF HUMAN FOETAL FIBRINOGEN

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Until eight days after birth, the human newborn synthesizes a molecular variant of fibrinogen. This foetal fibrinogen is characterized by several biochemical and functional properties.
Previous results led to the assumption that the peculiarities of the foetal protein are caused by a special sequence of amino acids.
Comparison of the tryptic peptide maps showed the identity of foetal and adult Bβ- and γ-chains, whereas the Aα-chain tryptic peptides and cyanogen bromide fragments are different. By thin layer chromatographic and sequence analyses the special amino acid sequence of the foetal Aα-chain can be localized in the amino acid sections 50 - 250 and/or 500 - 620. Because it could be ruled out that posttranslational constituents of the molecule are the cause of the "foetal" features it is quite probable that the foetal fibrinogen is genetically determined.

5.45 0183 CORRECTION OF THE DELAYED FIBRIN AGGREGATION OF FETAL FIBRINOGEN BY PARTIAL REMOVAL OF SIALIC ACID

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Human umbilical cord fibrinogen characteristically displays delayed fibrin aggregation under conditions of relatively high ionic strength. This delay is greater in fibrinogen obtained from premature (P) (24-35 weeks gestation) infants, as compared with that from full term (FT) infants. We compared the sialic acid content of (fraction I-2) fetal (P and FT) with adult (A) fibrinogen, obtained from pooled plasma. The mean sialic acid µg/100mg protein) values were: P, 818 (±135 SD, range 621-1030); FT, 720 (±212, range 505-1280); A, 626 (±110, range 487-806). One P fibrinogen preparation (thrombin time 22.6 seconds) was partially desialated (resulting sialic acid value 490) by incubation with Vibrio cholera neuraminidase, dialyzed, and precipitated with ethanol to remove free sialic acid. The thrombin time of the resulting preparation was 15.4 (range 15.2-15.8), compared to 16.1 (range 15.5-16.4) for untreated A fibrinogen. The results suggest that the delayed fibrin aggregation of fetal fibrinogen is attributable to its relatively high sialic acid content. Moreover, the intermediate sialic acid (and thrombin time) values of FT (as compared to those of P) fibrinogen intimate the presence of a mixture of adult and fetal fibrinogen in full term cord blood.