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LOW MOLECULAR WEIGHT HEPARINS: ORAL ABSORPTION IN MONKEYS.
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An orally administered low molecular weight heparin-like derivative of the commercial polydisperse polysaccharide is desirable clinically. The dissociation of antithrombotic properties and the induction of bleeding as well as minimal effect on platelet function are characteristics of some low-molecular weight heparins; however the circulating level of the anti Xa activity associated with demonstrable theraputic efficacy is not yet defined.

The availability of a variety of low molecular weight heparins provided us with the opportunity to evaluate the gastrointestinal absorption characteristics of the preparations in the primate.

Average molecular weight is only one of a spectrum of variables associated with absorbability, while Xa/APTT ratio differences and non-equivalent structural alterations may be responsible for functional differences in a living test system. Nevertheless, because of the clinical potential it is instructive to evaluate the GI absorbability of several preparations for which we have precise molecular weight data.

Preparations: Low molecular weight heparins were prepared by a variety of methods including isolation by alcohol fractionation from broadly polydisperse commercial or crude heparins, depolymerization of commercial or crude heparin and franctionation of depolymerization products.

Methods: Molecular weights were established by equilibrium ultracentrifugation and anti Xa activity was assayed by the Yin-Wessler coagulation method. Fasted rhesus monkeys weighing 8-13 kg. were anesthestized and intubated with a radio opaque catheter. One cubic centimeter of a heparin preparation in saline was instilled directly into the duodenum. Blood samples assayed for anti Xa activity and thromboelasticity were drawn at periodic intervals from an indwelling femoral catheter.

Results: Standard unfractionated heparin was detectable in blood only after one-half hour. The maximum activity for low molecular weight preparations was achieved after one-half to one hour. One fraction demonstrated activity in the plasma after four hours. The dose response curve for one fraction at half-hour was curvilineal between 7 and 16 Mg/Kg.

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CONGENITAL AFIBRINOGENAEMIA: DIAGNOSIS,CLINICAL FEATURES,FOLLOW-UP STUDY.
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Authors followed 6 cases of congenital afibrinogenaemia (CA) by offsprings of two apparently unrelated families from the same village.The sex ratio was 4.m/3.f. CA is a rare autosomal recessive disease.Controlling 76 family members authors detected 11 cases of moderate and 2 cases of severe hypofibrinogenaemia.Among them-without any bleeding tendency-the mother of one case and both parents of two siblings with CA.The lack of fibrinogen was confirmed biochemically and immunologically too. The only symptom of the illness are the severe posttraumatic bleeding.They appear as epistaxis,bleeding of the gums,or any other bleeding after minor or severe injuries.Intraarticular bleeding,as in haemophilia rarely occurs in CA.One of our patients had profuse haematurias,caused by renal calculi. The only therapy is the substitution with transfusions of fresh blood,plasma,or fibrinogen concentrates.The risc of posttransfusional illnisses grows with the number of transfusions.Stomatological or surgical interventions could be performed only after correction of the clotting abnormality.So,one of our patients was submitted to splenectomy for spontaneous rupture at 12 years and to nephrectomy for severe pyelo-caliceal calculosis with 19.He recovered fully after both interventions but died at 21 years after a bicycle accident. The five other patients deceased at the age of 5,resp. 10 months and at 6-10-resp 12 years.In 3 cases there was a subdural hammorrhage,once an intracranial bleeding(non autopsiated)and once a severe intraabdominal haemorrhage after an accidental traumatism of the abdominal wall. The care of the CA cases is mostly a pediatric problem.The frequency of the pottraumatic bleeding decrease with the growth.The schoolchildren are paying more attention to avoid injuries.

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PLATELET AGGREGATE-ASSOCIATED FIBRIN FORMATION AS A FUNCTION OF AGGREGATE SIZE AND HEPARIN CONCENTRATION.
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The in vitro observation that fibrin forms within a few minutes in the crevices and niches inside and on the surface of platelet aggregates (PA), prepared from heparinized (5 U/ml) blood is consistent with the doubtful efficiency of heparin in the treatment of occlusive arterial disease (Thromb. Haemost. 46: 666,1981). Release of heparin-neutralizing proteins into limited and largely disclosed plasma compartments between aggregated platelets was held responsible for this remarkable phenomenon. However, the minimum number of aggregated platelets necessary to overcome the heparin inhibition remained undetermined then.
PRP prepared from whole blood anticoagulated with 0.5, 1 and 5 U/ml of mucosal heparin (Liquemin®), was aggregated with 10 or 100 µM ADP for 2 min at 37°C. Single PAs of various dimensions were withdrawn, washed, and incubated with a chromogenic substrate (S-2238, Kabi AB) to measure their thrombin content. Subsequently the number of platelets contained in the PA was evaluated by assaying the protein content of the aggregates. Microscopic PAs, their mass being too small to be determined precisely by a protein assay, were isolated with a filter technique, their extension was documented on photomicrographs for later calculation of aggregate volume and platelet content, before they were incubated with S-2238. Aggregates too small to develop detectable amidolytic activity, were checked microscopically for fibrin formed.
S 2238 amidolytic activity (thrombin) in heparinized PRP samples evolved as a linear function of the logarithm of PA mass. For a given heparin concentration (in whole blood) the following lower threshold platelet numbers of aggregates were found sufficient to allow the formation of detectable quantities of thrombin:

5 U/ml	1 U/ml	0.5 U/ml
500. - 1.000x10³	100 - 300x10³	20 - 50x10³

These results suggest a fatal role platelet aggregates of minute dimensions may well play as a nidus of coagulation in fully heparinized blood.

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PLATELET-DEPENDENT ACTIVATION AND AMPLIFICATION OF THE POLYMORPHONUCLEAR LEUKOCYTES LYSOSOMAL ENZYME RELEASE.
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The degranulation of human PMNs by opsonised zymosan (OpZ) was studied in the presence or in the absence of platelet alone or after stimulation by thrombin. Evidence is presented that the presence of platelets increased the extent of the liberation of lysozyme from PMNs stimulated by OpZ with a maximal intensity when they were stimulated by thrombin. The extent of the amplification was higher when the PMNs trigger was lower (i.e. 0.5 x 10^8 particles/ml as compared to 3.0 x 10^8 particles). This effect was dependent on the platelet concentration (from 10-80 platelets/PMN). Platelets stimulated by thrombin could also activate the resting PMNs with a maximum obtained at a thrombin concentration of 0.1 U/ml, corresponding to the maximal release by these cells of products stored in their granules. However, the substitution of platelet suspensions by the released products found in their supernatant after stimulation by thrombin, resulted in a comparable stimulation only at platelet concentrations above the ones for coincubation experiments. These findings suggest that the presence of platelets themselves or in combination with their released products are responsible for this amplification. The use of zymosan alone or coated with IgG, C3bi, C3b or OpZ did not reveal any specificity of the inducer for this amplification suggesting that platelets and/or platelet products acted by enhancing a common step of PMNs activation independent of the stimulus carried by the particles. Additionally, it could be noted that the maximal effect of the amplification by platelets occurred when the level of stimulation of the PMNs alone was the weakest.