

STUDIES ON THE EXCRETION OF  $^3\text{H}$ -HEPARIN. R. Losito, E. Lemieux and B. Longpré. Centre Hospitalier Universitaire, Sherbrooke, P.Q., CANADA.

Disappearance of heparin is still not well understood; because of this, we studied the excretion of  $^3\text{H}$ -heparin in (a) rats with biliary fistula and cystotomy, (b) rats with cystotomy, (c) hepatectomized rats and (d) in the isolated perfused rat liver. During 5 hours of perfusion, there was never more than 8% of the  $^3\text{H}$  excreted into the bile; most of the radioactivity (80%) remained in the blood. In bile, one radioactive component, which possessed slight anticoagulant and metachromatic activity was found and appears to be similar to heparin on chromatography and microelectrophoresis. In the intact animal, utilizing similar doses, the biliary excretion was similar to that of the isolated system; in contrast to the isolated system, radioactivity was quickly removed from the blood (over 90% in 5 h) and excreted into the urine (30% and 60% after 5 h and 10 h respectively). In hepatectomized animals, it was observed that only 15% of heparin radioactivity could be excreted in 24 hours. Hence it is postulated that the liver appears to have an important role to play in the metabolism and biological actions of heparin since (1) it removes  $^3\text{H}$ -heparin from blood and excretes it into the bile and (2) the results of the hepatectomized experiments showing that only one-fifth the heparin was excreted compared to the control rats without hepatectomy.

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THE KINETICS OF CLEARANCE FROM THE CIRCULATION OF MAN OF HEPARIN AND A SEMI-SYNTHETIC HEPARIN ANALOGUE. D.A. Lane, R. Michalski and V.V. Kakkar. Thrombosis Research Unit, King's College Hospital Medical School, London.

A study has been made of a low molecular weight semi-synthetic heparin analogue, (SSHA) that may be clinically useful as an antithrombotic agent because of its reported high specificity for potentiating antithrombin III activity. The clearance from the circulation of both heparin and the analogue has been studied in man following intravenous injection. Heparin obeyed almost zero order kinetics when assayed using a specific anti-Xa assay and first order kinetics when measured with KCCT. At high concentrations the heparin analogue was cleared with first order kinetics when assayed both with the anti-Xa assay and with KCCT. At low concentrations the analogue produced between one half and two-thirds of the anti-Xa activity of an equal dose of heparin, producing only a small prolongation of KCCT. With increasing dose, the more specific anti-Xa potentiating effect of SSHA decreased in part because of the difference in kinetic behaviour between heparin and SSHA but largely because of a flattening of its anti-Xa dose response curve. Because of the initial more rapid clearance of higher doses of heparin from plasma when it is measured by the KCCT, these results suggest that the use of KCCT can cause a small underestimate of circulating heparin anti-thrombotic activity.

#### HEPARIN ELIMINATION IN PATIENTS WITH VARIOUS DISEASES.

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Heparin (100 U/kg bodyweight) has been administered as i.v. single injections and heparin concentration in plasma determined by polybrene titration (PT), previously shown to be an accurate assay for heparin concentration in plasma. Mean concentration half-life was 74.7 min. in normals (n=6), 118.6 min. in anephric patients (n=5), 97.8 min. in uraemic patients with kidneys (n=6), 115.5 min. in patients with liver cirrhosis (n=6), 79.6 min. in patients with disseminated cancer (n=5) and 59.3 min. in patients with hyper-lipaeimia (n=6). The differences between mean values for the normals and the anephric patients or the patients with liver cirrhosis were highly significant (p<0.01). One patient with very high content of triglycerides in plasma (25.6 mmol/l) had an extremely short heparin half-life (33 min.). The plasma of this patient had a heparin neutralizing effect of 0.75 U/ml (measured by PT). Short half-lives were also found in patients with thrombocytaemia or acute thrombo-embolic disorders.

In normals and uraemic patients there was a significant fall in heparin co-factor activity from before heparin injection to 4 hours after injection (10 per cent and 20 per cent, p<0.05 and p<0.005, respectively), in contrast to no significant fall in patients with liver cirrhosis. A possible explanation may be that the normal liver removes heparin bound to At-III, and that this function is impaired in liver cirrhosis.