MEDICAL RESEARCH SOCIETY

A meeting of the Medical Research Society was held at St George’s Hospital Medical School, London, S.W.1, on Friday, 12 May 1972. The following Communications were presented.

COMMUNICATIONS

1. EFFECT OF HEPARIN ON RADIO FIBRINOGEN CATABOLISM IN RENAL DISEASE

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Radio-fibrinogen catabolism study is a sensitive way of assessing active participation of fibrin in the pathogenesis of renal disease. In general in oliguric patients accelerated fibrinogen catabolic rates are reflected by an increase of serum fibrin products. To evaluate further the role of intravascular coagulation and to assess the potential of heparinization in management, patients with oliguric glomerulonephritis, accelerated hypertension and transplant rejection underwent short-term administration of heparin during the course of a radio-fibrinogen study. Heparin produced an increase of glomerular filtration rate measured by Cr-EDTA clearances. Beneficial effects on fibrinogen catabolism were also found in some cases of accelerated hypertension and transplant rejection, but heparin alone did not influence rapidly progressive glomerulonephritis.

2. ACUTE RENAL FAILURE IN THE RAT: PROTECTION BY PASSIVE IMMUNIZATION AGAINST ANGIOTENSIN II

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Rats were dehydrated for 24 h and given a subcutaneous injection of 50% glycerol in normal saline (10 ml/kg). In group 1, eleven of these rats were also injected intravenously with a high titre angiotensin II antiserum. None increased the blood urea by more than 30 mg/100 ml at 48 h. In group 2, eleven control animals matched individually with group 1 animals, were given an identical volume of rabbit serum containing no angiotensin antibody. Five of eleven rats developed a rise of blood urea above 30 mg/100 ml at 48 h (P = 0.018 for the difference between groups I and II assessed by Fisher Exact Test).

The mean blood urea level after 48 h was 38.6 mg/100 ml in group 1 and 97.4 mg/100 ml in group 2 (P < 0.05).

To exclude the possibility that the inert serum was harmful, two further control groups were studied. Six of eight rats given glycerol alone (group 3) and none of the six rats given inert serum alone (group 4) developed a rise in blood urea above 30 mg/100 ml at 48 h.

All animals given glycerol in groups 1, 2 and 3 developed histological acute tubular necrosis. None did in group 4. There was no obvious difference in the severity of renal tubular necrosis when the kidneys of group 1 rats were compared with those of group 2.

Passive immunization against angiotensin II produced significant protection against acute renal failure but no apparent protection against tubular necrosis. The former observation favours the suggestion that angiotensin plays some part in the pathogenesis of acute ischaemic renal failure (see Brown et al., 1970, British Medical Journal, 1, 253). A potentially important possibility raised by these observations is that antagonists of the renin angiotensin system may be of use in the treatment or prophylaxis of acute renal failure in man.

3. INCREASED LYSOLECITHIN FORMATION IN HUMAN PLASMA AFTER INTRAVENOUS ADMINISTRATION OF HEPARIN

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(Introduced by E. M. M. BESTERMAN)

Administration of heparin or heparinoids has long been known to release and activate clearing factor or lipoprotein lipase and this enzyme has been extensively studied (Robinson, 1963, Advances in Lipid Research, 1, 133). Small doses of heparin administered either intravenously or subcutaneously have also been shown to increase the rate of formation of lyssolecithin from the plasma lipoprotein-bound lecithin (Berlin, Oldfelt & Vikrot, 1969, Acta Medica Scandinavica, 185, 433). Lyssolecithin has been shown to inhibit irreversible platelet aggregation initiated by adenosine diphosphate, adrenalin and collagen (Besterman & Gillett, 1971, Atherosclerosis, 14, 323) and increased enzymic formation of lyssolecithin in plasma may influence platelet behaviour in vivo.

Fasted subjects undergoing routine right heart catheterization have been given intravenous heparin
at doses of 1000–5000 units. Lysolecithin formation in pre- and post-heparin samples of plasma, incubated at 37°C without added substrates, has been determined by a thin layer chromatography method. The characteristics of post-heparin lysolecithin release have been compared with those of lecithin:cholesterol acyl transferase (LCAT) in pre-heparin plasma. Mean lysolecithin formation was increased by about 80% within 5–10 min of administering heparin. The effect was independent of the heparin dose (above 1000 units) and was inhibited, in vitro, by protamine sulphate (1 mg/ml) which had no inhibitory effect on LCAT. Parahydroxymercuribenzoate (2 μmol/ml) inhibited LCAT activity, but lysolecithin formation was still observed in post-heparin plasma. These results indicate that increased lysolecithin release after heparin administration is due to an enzyme which is distinct from LCAT. This differentiation is supported by the observation that esterification of triitated cholesterol in plasma is not significantly altered as a result of intravenous heparin. Post-heparin lysolecithin releasing enzyme may be similar to lipoprotein lipase, and probably contains heparin as an essential co-factor, which would explain the inhibitory effect of protamine sulphate, in vitro.

The possible effects of increased lysolecithin formation in post-heparin plasma on platelet function and aggregation will be discussed.

4. ORAL CONTRACEPTIVES AND ANTI-THROMBIN-III ACTIVITY: A NEW METHOD OF ANTIITHROMBIN ESTIMATION

P. W. Howie, C. R. M. Prentice and G. P. McNicol
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Antithrombin-III activity in serum is reduced during oral contraceptive therapy, a change due to the oestrogen component (Howie, Mallinson, Prentice, Horne & McNicol, 1970, Lancet, ii, 1329). This could be due either to a true reduction of antithrombin in vitro or to an increased consumption of antithrombin in vitro due to increased thrombin generation during clotting, since prothrombin concentration is augmented by oral contraceptives. To resolve this dilemma we have developed a method of antithrombin estimation in plasma. The plasma requires to be defibrinated prior to antithrombin estimation and we have found that defibrination by ancored (Arvin, Twyfords), the venom of the Malayn pit viper, has advantages over other methods as it does not neutralize or destroy antithrombin. Defibrination of plasma by the currently available methods of heating to 56°C or addition of thrombin causes neutralization of variable amounts of the antithrombin prior to its estimation. By use of ancored defibrination a significant fall in plasma antithrombin during oral contraceptive therapy was still present, but this was less than the fall in serum antithrombin. This indicates that the fall in serum antithrombin during oral contraception reflects both a decrease in circulating antithrombin and an increased generation of thrombin during in vitro clotting. These findings may have a bearing on the increased risk of thrombosis during oral contraceptive therapy.

5. THE OSMOTIC CHARACTERISTICS OF THE LEUCOCYTE

J. Patrick and P. J. Hilton
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(Introduced by N. F. Jones)

Measurement of cell swelling and shrinkage produced by alterations in extracellular fluid osmolality and the degree to which such changes are dependent upon active transport processes are of great importance in understanding the patho-physiology of disease.

The degree of volume change induced by a series of alterations in extracellular fluid osmolality in canine leucocytes has been measured. A quantitatively unexpected relationship between osmolality and cell water was demonstrated in that cells swelled more and shrank more than would be predicted from the Van Hoff Mariotte law. The relationship between cell water and osmolality was paralleled by the relationship between total intracellular sodium content and cell water. Potassium content decreased in hypotonic media. However, total intracellular (Na+K) content was positively correlated with cell water.

These effects indicate important changes in leucocyte membrane and sodium pump characteristics consequent upon alterations in extracellular fluid osmolality.

6. THE RESPONSE OF THE RENAL AND FEMORAL VASCULAR BEDS TO CORONARY EMBOLIZATION IN THE CLOSED-CHEST DOG

R. E. Falicov, C. J. Mills and I. T. Gabe
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Left coronary artery embolization with mercury (0.12–0.30 ml) in the closed-chest, anaesthetized dog produces acute severe left ventricular failure characterized by a decreased cardiac output, increased left ventricular end-diastolic pressure and raised systemic vascular resistance (Falicov, Resnekov & King, 1971, American Heart Journal, 82, 521). In the present study, the responses of the renal and femoral vascular beds to coronary embolization were studied in eleven dogs. Hind limb flow was measured by an electromagnetic cuff probe, and renal arterial blood velocity by an intravascular electromagnetic probe (nine dogs) or by an external cuff probe after laparotomy (two dogs). By 30 min after coronary embolization, cardiac output (measured by the indicator-dilution technique) had decreased 33 ± 5% (SEM), while mean aortic pressure had fallen by 13 ± 4%; the systemic