127 PLASMA INHIBITOR OF GLOMERULAR FIBRINOLYSIS (GF) IN HUMAN RENAL DISEASE.

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To detect a circulating inhibitor of GF, serial dilutions of human plasma were incubated with 2 frozen sections from a single normal human kidney. The slides were washed and studied by the fibrin slide technique. The Lysis Inhibitory Titer (LIT) was defined as the highest dilution completely inhibiting GF. Of 146 controls with normal urinalyses and renal function, none had a LIT greater than 1:2. Defining an elevated LIT as 1:8 or greater, we found an elevated LIT in plasma from 42 of 119 patients with various forms of renal disease including 14 of 14 patients with the Hemolytic-uremic Syndrome (HUS) and 15 of 57 with glomerulonephritis. In patients with renal disease, no difference was found in the frequency of anemia, leukopenia, or prolonged PT when comparing patients with normal against those with elevated LIT. Diminished renal function (64% vs. 36%), thrombocytopenia (42% vs. 5%), and prolonged PTT (30% vs. 0%) were more common in patients with elevated LIT. No correlation was detected between the LIT and plasma concentrations of the antiplasmins α_1-antitrypsin, α_2-macroglobulin, and C_1-esterase inhibitor. Daily analysis of plasma from 3 patients with HUS showed a close correlation between the LIT and clinical course. In each case, removal of the inhibitor from the plasma by peritoneal dialysis was associated with recovery of renal function. Results suggest that the inhibitor may play an important role in the pathogenesis of glomerular fibrin deposition.

128 PLATELET-AGGREGATING IMMUNE COMPLEXES (IC) IN CHILDREN WITH IDIOPATHIC AND HENOCH-SCHÖNLEIN PURPURA (HSP) NEPHRITIS.

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Unlike most assays for detecting IC, the platelet aggregation test (PAT) detects both complement and non-complement fixing IC. The platelet aggregating material (PAM) is not monomeric antiplatelet antibody, thrombin or platelet aggregating factor, and has a molecular weight consistent with IC. We compared PAT with Clq binding and Raji cell assays in sera from patients with different forms of nephritis including minimal change glomerulonephritis. In minimal change glomerulonephritis, 64% of sera showed the aggregating titre 1/4 or greater (most of the normal subjects showed the titre 1/2 or less). Raised levels of PAM ($\geq$ 1/4=10ug/ml IgG) were found in membranous nephropathy (MN)(81%), HSP nephritis (83%),postinfectious nephritis (100%),SLE (65%) and MCGN (89%); the other two assays were only occasionally positive in MN and HSP nephritis. In HSP, IgG IC, presumably non-complement fixing IC,rather than IgA IC are associated with more severe nephritis (Lancet ii,1100,1979). The simpler,quicker and cheaper PAT, which reacts with a wide range of IgG IC may be useful in monitoring treatment and assessing prognosis in these diseases.

129 KIDNEY FUNCTION IN HABU VENOM NEPHROPATHY IN RATS.

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The injection of Habu snake venom into rats has been discussed as a useful model for studying focal mesangioproliferative glomerulonephritis(GN)(Cattell et al. Am.J.Pathol.87:511[1977]).Morphological,immune fluorescence and clearance studies were performed for further characterisation of this model.50 inbred Lewis rats received 3.3mg/kg Habu venom i.v.Three different phases of response could be observed:I.One to 12hrs after injection shock,coagulopathy,hemolysis and thrombocytopenia occurred suggesting DIC.Mortality rate was high (40%),many organs showed hemostasis and diffuse bleeding.Mesangiolyis was not observed.II.One to 3d after injection blood pressure,coagulation and thrombocytes returned to normal levels.Kidney function remained normal.Mortality was low.Mesangiolysis was rare.III.Four to 30d after injection kidney function did not differ from controls although there was focal mesangial hypercellularity.Glomerular immune fluorescence was negative for IgM,IgG and C3 during all three stages of Habu nephropathy.

Habu venom induced a variety of alterations in rats including shock,DIC,vasculopathy and mesangioproliferative glomerulonephritis,however,kidney function did not show acute or chronic deterioration.

130 COAGULATION AND FIBRINOLYSIS PROTEINS IN CHILDREN WITH NEPHROTIC SYNDROME.

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The main coagulation and fibrinolysis proteins have been studied in nephrotic children (Plasma albumin (Alb) $<$ 30g/l), to precise which patients run a high risk of thrombosis. Besides routine hemostasis study, the plasma (P) (31 cases) and 24 h urine (U) (20 cases) concentrations of plasminogen (Plg), α_2 macroglobulin (α_2M), antithrombin III (AT III) and α_1 antitrypsine (α_1AT) were determined by radial immunodiffusion and $P\alpha_2$ plasmin inhibitor (α_2PI) biological activity by the method of Teger-Nilsson (25 cases). Fibrinogen (F.I.) was over 2 SD of normal in 23 children and α_2M in 29. Plg and α_1 AT were each below 2 SD of normal in 12 children, AT III in 17 and α_2 PI in 4. Significant negative correlations were observed between P and U concentrations of AT III ($p<0.01$), α_1 AT ($p<0.05$) and Plg ($p<0.05$). Significant correlations were found between the P concentrations of Alb and of FI ($r=-0.57$, $p<0.001$), AT III ($r=0.64$, $p<0.001$), α_1AT ($r=0.48$, $p<0.01$) and α_2M ($r=-0.47$, $p<0.01$), as well as between the P concentrations of AT III and of F I ($r=-0.59$, $p<0.001$), Plg ($r=0.57$, $p<0.001$) and α_1AT ($r=0.48$, $p<0.01$). All children with Alb$<$15-17g/l except 1, and 1 child with Alb$>$20 g/l, had AT III levels$<$70% of normal which has been shown to represent a high risk of thrombosis, possibly enhanced by the associated low Plg and α_1AT, and high F I and α_2M levels. Low AT III levels may induce resistance to heparin, and heparin has been shown to lower the antithrombic activity of α_2M. Oral anticoagulants therefore appear more appropriate for prevention of thrombosis. The low Plg levels must be taken into account in case of thrombolytic treatment.

131 RENOGRAM ABNORMALITIES IN THE HEMOLYTIC UREMIC SYNDROME (HUS)

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Twenty-five patients with HUS had radionucleotide studies performed while oliguric or anuric in order to determine functional parameters and assess prognosis. 99m-Tc-DTPA (5-15 mCi) and 131-I orthoiodohippurate (50-150 muCi) were sequentially injected according to established techniques. Initially the renograms were obtained using dual scintillation probes. More recently a scintillation camera with computer was used to image sequentially the passage of these radionuclides through the kidneys. After appropriate background subtractions were made, 11 of 25 renograms were flat (same as background), with the remainder showing varying degrees of uptake. Renogram abnormalities did not correlate with symptoms, initial blood pressure levels or initial biochemical parameters (BUN, creatinine). Of the patients with a flat renogram, 8 presently have normal renal function (1-8 year follow-up) and 7 are normotensive. Thus, the presence of a flat renogram does not indicate irreversible renal damage. The observed absence of renal blood flow in HUS may be secondary to severe vasospasm caused by aggregation of platelets at sites of endothelial injury with subsequent release of vasoactive substances. The detection of platelet membrane antigen(s) and fibrin by immunohistochemical techniques supports this contention.

132 OCCURENCE OF INTRAVASCULAR COAGULATION IN THE HEMOLYTIC-UREMIC SYNDROME.

No evidence of active intravascular coagulation is found in the hemolytic-uremic syndrome (H.U.S.) by conventional coagulationtests. The development of a radioimmunoassay of fibrinopeptide A, (F.P.A.) providing a sensitive and direct quantitation of thrombin activity, opened new possibilities for the study of the presence of intravascular coagulation.

In 9 children with H.U.S. plasma F.P.A. was measured in blood collected immediately after admission before any treatment. The in vitro generation of F.P.A. was studied and the level of plasma F.P.A. determined 20 minutes after an intravenous injection of heparin (100 U/kg body weight).

In 2 out of 9 children the plasma F.P.A. was distinctly increased. In these two children the F.P.A. generation was high and the F.P.A. level normalised after heparin injection.

This study provides evidence for the occurence of intravascular coagulation even after admission in 2 out of 9 children with H.U.S.

On the basis of these results heparin anticoagulant therapy might be indicated in some children with H.U.S.