METABOLISM OF PLASMA PROTEIN FRACTIONS AFTER ORTHOTOPIC HOMOGRAFTS AND AUTOGRAFTS OF THE DOG LIVER

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PLASMA PROTEIN ABNORMALITIES are observed following transplantation of various tissues (1–5). The exact nature and significance of these changes remains unclear. The present study was designed to distinguish between protein changes related to the surgical stress of transplantation and those which are related to the unmodified homograft rejection mechanism.

METHODS

Plasma protein concentrations, synthesis, and turnover indices were determined for 7 plasma protein fractions before and after hepatic transplantation in 14 dogs. All dogs received 250 μc. S^{35} methionine intravenously; and blood samples were drawn at intervals of 3, 6, 9, 12, 24, and 72 hr., and thereafter at 5, 7, 10, 14, 21, and 35 days. Repeat studies were done on all dogs on the fourth day after: a) orthotopic homografts of liver from unlabeled animals, recipient Group I—4 dogs; b) orthotopic homografts of liver from labeled animals, Group II—5 dogs; c) orthotopic autografts, control Group III—5 dogs. All anastomoses were anatomical except for biliary continuity which was via a cholecystojejunostomy in Groups I and II. In all groups the liver was cooled prior to transplantation with iced Ringer's lactate by portal vein perfusion for 10 to 15 min. No immunosuppressive drugs were used. All blood samples were separated into serum and plasma and analyzed for concentration (milligrams per cent) and specific radioactivity (counts/min./mg. protein). Paper block electrophoreses were used to separate the albumin and globulin fractions and fibrinogen and seromucoid were determined by thrombin precipitation, and by phosphotungstic acid precipitation respectively.

RESULTS

A 20% to 110% rise in the concentration of all plasma protein fractions was noted after all transplantations except the albumin

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Reprint from Vol. XVII, *Surgical Forum,* American College of Surgeons, 1966

fraction which showed a 20% to 80% decrease. Greatest increases were noted in the glycoprotein rich fractions of α globulins, fibrinogen, and seromucoid. Increases in circulating levels were correlated with 50% to 200% increases of S^{35} uptake (synthesis) and increased S^{35} disappearance with shorter half-lives (turnover). The albumin fraction showed a 40% to 80% increase in uptake (synthesis). Only the γ globulin fraction of serum showed a significantly greater increase in concentration, synthesis, and turnover rate after liver homografts than after autografts. The 9 dogs in Groups I and II had a mean survival of 12 days. This unusually long survival in untreated animals was largely the result of 2 unique dogs which lived 18 and 31 days. The animals in Group III were killed after 1 year.

DISCUSSION

Previous studies have shown a lowered albumin concentration and an increased globulin concentration after experimental renal and hepatic transplantation (3, 4). The reason for lowered albumin remains obscure but increases in globulins especially the α globulins were related to a nonspecific inflamatory response (4). The present study supports this view since changes in albumin and α and β globulins with homografts parallel those seen after autotransplantation. The additional finding of increased uptake of S^{35} methionine into albumin (synthesis) in the face of a decreased concentration probably indicates an actual increase in synthesis and turnover in a sequestered albumin pool. The increase in γ globulin concentration and uptake appeared most prominently in the homotransplanted group and most likely represents increased antibody production and turnover. However, whether γG or γM is primarily involved cannot be stated from our data. It is known that γM antibodies appear earlier than γG, although this sequence can be altered by immunosuppressive drugs (6).

CONCLUSION

Increases in metabolic turnover of all plasma proteins after liver transplant are due to a nonspecific response to the surgical trauma of transplantation except for the increased synthesis and turnover of the γ globulins (circulating antibody) which is specifically related to the homograft rejection mechanism. Increases in synthesis and turnover of albumin with a decrease in concentration suggest increased utilization in a sequestered extravascular space.

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