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Some Aspects of the Protein Metabolism in Human Liver Transplant Recipients

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In early experimental and clinical studies, the not unexpected finding was reported that most of the electrophoretically measurable protein fractions declined rapidly after the implantation of a poorly functioning hepatic homograft. In contrast, these fractions were well maintained after provision of a well functioning graft. A similar relationship between quality of graft function and protein levels was found also for the liver-based clotting factors. The changes in these latter factors were very rapid and reflected changes in consumption as well as synthesis [2].

Studies of Complement

Recently, the plasma proteins of the complement system were assayed in five recipients of hepatic homografts [3]. All the patients were in terminal liver failure due to cirrhosis, chronic hepatitis or Wilson's disease.

Following replacement of the patients' diseased livers with well functioning homografts, total complement activity as well as the C4 and C3 component activities, rose from distinctly low to normal levels. At the same time, the C5 component increased from low to high normal (Figure 1). In contrast, the C2 and C9 components remained normal throughout, while C1 showed variable changes. Good subsequent

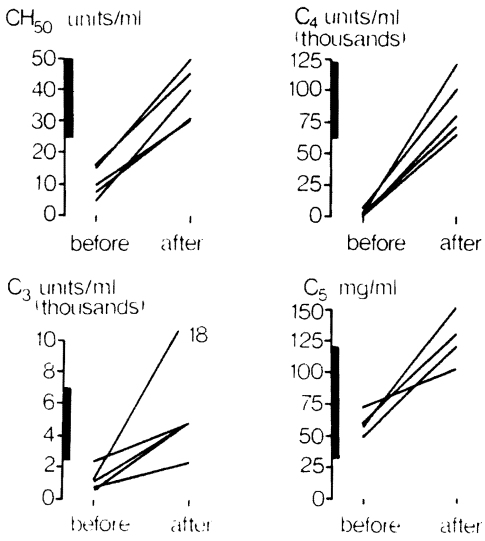

Fig. 1 Levels of total complement activity (CH 50) and of the components C4, C3 and C5, before and 7—10 days after orthotopic hepatic transplantation. Each line represents an individual patient. Normal range is indicated by a heavy line along the ordinate.

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graft function was accompanied by normal complement levels except in one patient who exhibited supernormal values for several months.

Some of the recipients developed postoperative liver function abnormalities that were thought to be due to homograft rejection. Concomitantly, there were marked decreases in total complement activity and in the C4 and C3 components (Figure 2). One of these patients later developed biliary obstruction which required surgical correction. At this time there were no changes in the complement system.

Two other patients had temporary liver dysfunction at a time when steep rises in Australia antigen titers indicated the occurrence of serum hepatitis. In one of these patients, a transient decrease in complement activities was recorded, but in the other, the complement remained unaffected.

Based on the above data, it has been concluded that complement assays might aid in the otherwise equivocal diagnosis of rejection. In addition, as has been completely discussed elsewhere [3], the data are consistent with the hypothesis that the liver is a main or possibly even the sole source of the C4, C3 and C5 components of the complement system.

Inborn Errors of Protein Metabolism

In several liver transplant recipients, the genetically determined phenotypes of the α-globulins haptoglobin and group specific component have converted to those of the donors. This indicated that the hepatic homograft retained its metabolic specificity in a new host and that liverbased inborn errors of metabolism should be correctable by the provision of a new, normal liver.

There have not yet been any successful liver transplantations for proven inborn errors of hepatic metabolism. However, two teenage boys have undergone liver replacement for *Wilson's* disease, a disorder that has been speculated to be due to some fundamental hepatic defect. The course of the first patient has been reported earlier [1]. Following transplantation, there was a marked cupriuresis and biopsy specimens have shown no accumulation of copper in the graft as had occurred in the native liver. The patient is presently alive and well three years after transplantation.

The second patient when first seen by us at age 11, had cirrhosis of the liver, a very low level of the coppercontaining serum protein ceruloplasmin, a high liver copper, *Kayser-Fleischer* rings, and the characteristic histopathologic findings in a liver biopsy of *Wilson's* disease. In spite of treatment with chelating agents, the patient became severely crippled by neurological symptoms. At the age of 14, he underwent orthotopic hepatic transplantation. Except for an early period of graft dysfunction, probably caused by serum hepatitis, liver function has been normal during a follow-up of 15 months (Figure 3). After transplantation, serum ceruloplasmin and total serum copper rose to normal levels and have remained so. An initially elevated urinary excretion of copper has declined toward normal (Figure 3). Biopsy specimens of the homograft have shown no accumulation of copper. The findings are consistent with the hypothesis that the

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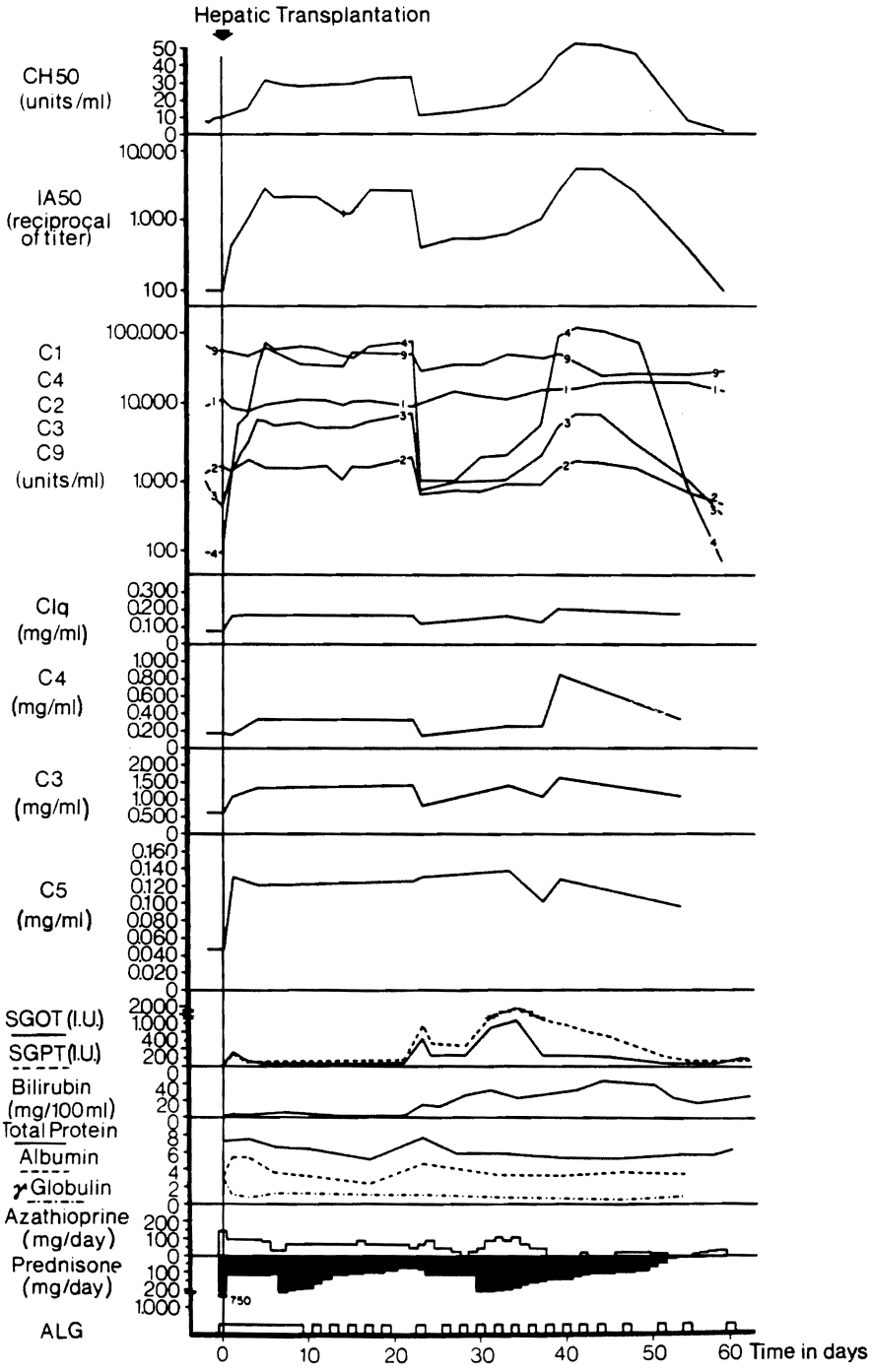
Fig. 2 Changes in the complement system in a patient who developed liver dysfunction 3 weeks after operation presumably due to rejection. Note the concomitant marked drop in total complement and several of the components. Subsequently, biliary tract obstruction was diagnosed without the occurrence of changes in complement. The patient succumbed 16 days later; shortly before death complement levels again decreased (By permission of Clin. Exp. Immunol.).


Hepatic Transplantation
CH50 (units/ml)
50
40
30
20
10
0
IA50 (reciprocal of titer)
10.000
1.000
100
C1
C4
C2
C3
C9 (units/ml)
100.000
10.000
1.000
100
Clq (mg/ml)
0.300
0.200
0.100
0
C4 (mg/ml)
1.000
0.800
0.600
0.400
0.200
0
C3 (mg/ml)
2.000
1.500
1.000
0.500
0
C5 (mg/ml)
0.160
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0
SGOT (I.U.)
SGPT (I.U.)
2000
1.000
400
200
0
Bilirubin (mg/100ml)
40
20
0
Total Protein
Albumin
γ Globulin
8
6
4
2
0
Azathioprine (mg/day)
200
100
0
Prednisone (mg/day)
100
200
1.000
750
ALG
0
10
20
30
40
50
60 Time in days

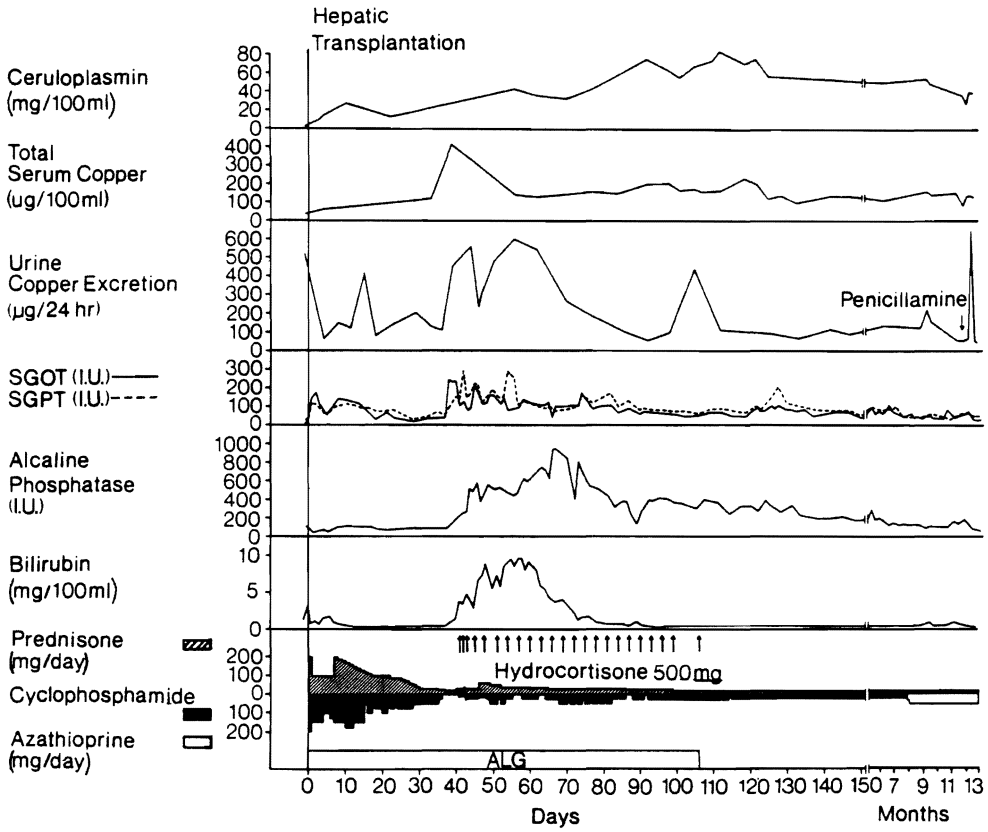


Fig. 3 The course of the second patient treated with orthotopic hepatic transplantation for *Wilson's* disease at the University of Colorado. Note the prompt recovery of serum ceruloplasmin after transplantation.

metabolic defect in *Wilson's* disease is liver-based, although they do not prove it.

Summary

The important relationship between hepatic homograft quality and the maintenance of plasma proteins is reemphasized. The results of serum complement assays in liver transplant recipients are presented. The recovery of the copper-containing protein ceruloplasmin after hepatic transplantation for *Wilson's* disease along with a cessation of hepatic copper accumulation is described.

References:

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