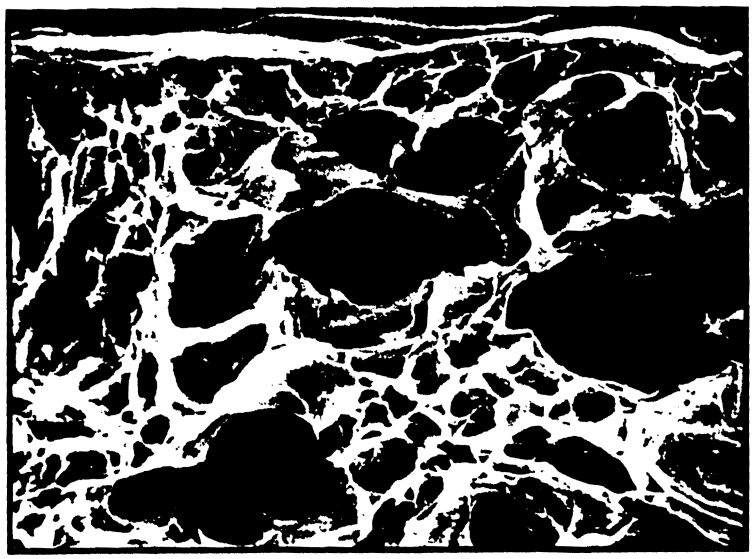
Lung Biology in Health and Disease Volume 88

Executive Editor: Claude Lenfant

1451

Alpha 1–Antitrypsin Deficiency

Biology • Pathogenesis • Clinical Manifestations • Therapy



edited by

Ronald G. Crystal

ALPHA 1–ANTITRYPSIN DEFICIENCY

BIOLOGY • PATHOGENESIS • CLINICAL MANIFESTATIONS • THERAPY

Edited by

Ronald G. Crystal
The New York Hospital–
Cornell Medical Center
New York, New York

Marcel Dekker, Inc. **New York • Basel • Hong Kong**

1451

24

α1AT Deficiency and Liver Transplantation

DAVID H. VAN THIEL

Baptist Medical Center of Oklahoma
Oklahoma City, Oklahoma

THOMAS E. STARZL

University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

I. Introduction

Alpha 1-antitrypsin (α_1AT) is a 52 kDa alpha 1-glycoprotein that is produced by hepatocytes and secreted into the blood, where it acts as a circulating serine protease inhibitor (1–4). It is a prototypical "suicide" protease inhibitor that combines with its complementary serine protease—be it polymorphonuclear leukocyte serine protease or pancreatic elastase—resulting in its own elimination from the plasma.

α1AT deficiency is a heritable autosomal recessive metabolic disease that results in the synthesis and secretion of a defective alpha 1-glycoprotein without enzymatic activity Z form that occurs as a consequence of a single amino acid substitution (Gly 342 to Lys 342) (1). It occurs as a result of a single nucleotide substitution in the DNA encoding for the normal M form of the serine protease inhibitor α1AT.

As noted in earlier chapters, many different alleles for the α_1AT gene exist. The frequency of various α_1AT protease inhibitor (PI) phenotypes in almost a thousand whites in Minnesota is shown in Table 1. The most common phenotype is M1, having a frequency of 0.724 (1). The mutant phenotype responsible for α_1AT deficiency, PiZ, has an estimated frequency of 0.014 (1–5). Thus, the

Table 1 Distribution of PI Phenotypes and Allele Frequencies in Whites Living in Minnesota

Phenotypes	No. observed	Allele frequencies
M1	478	PI*M1 = 0.724
M1M2	177	PI*M2 = 0.137
M1M3	121	PI*M3 = 0.095
M1S	28	PI*S = 0.023
M1Z	18	PI*Z = 0.014
M1F	4	PI*F = 0.003
M1I	5	PI*I = 0.003
M1P	2	PI*P = *0.001*
M2	19	Total = 1.000
M2M3	24	
M2S	4	
M2Z	4	
M3	9	
M3Z	3	
M3S	5	
S	2	
SF	1	
	Total = 904	

frequency of homozygous α_1AT PiZZ individuals can be calculated to be about 1/5000 individuals. The normal range for α_1AT levels in serum is 0.85 to 2.13 mg/ml. Individuals who are PiZZ have very low, but not zero, levels of the protein in their serum, with levels typically being below 0.3 mg/ml.

Individuals who are heterozygotes for the Z allele have reduced levels that range from levels half of those of the lower limit of normal to nearly normal levels (Fig. 1) (1,6–16). In contrast, heterozygotes with alleles other than Z often have increased levels of α_1AT in their serum, as shown in Figure 1 (6–16).

II. α1AT Deficiency and Liver Disease

Individuals with α_1AT deficiency are uniquely susceptible to the development of two disease processes (1–3): panacinar early-onset emphysema and hepatocellular liver disease that presents as either neonatal hepatitis (17–23) in infants or severe protein synthetic liver failure in adults (24–37). The latter presumably occurs as a result of an intrahepatic accumulation of abnormal α_1AT protein within hepatocytes (38,39).

In a review of the cause of death of adults with α_1AT, 69% were reported to

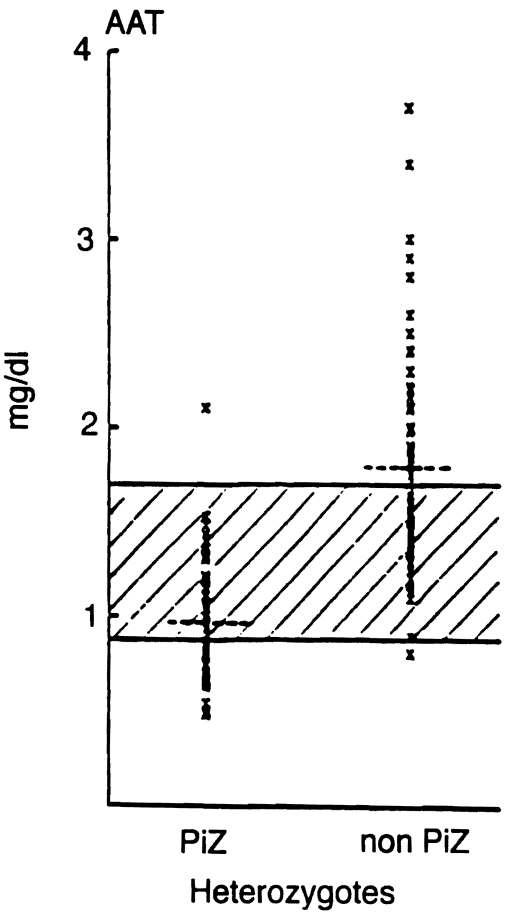


Figure 1 Serum α1AT levels in heterozygotes with and without a Z allele.

have died as a direct result of either respiratory failure associated with emphysema or a complication of their pulmonary disease (25). A much smaller fraction, 13%, died as result of either hepatic failure or bleeding esophageal varices (Fig. 2) (27,29–32,34,35). As impressive as these figures are, they underestimate the problem of liver disease as a cause of death in individuals with α_1AT deficiency, as the study from which these data were obtained examined the case of death of only adults with PiZZ α_1AT deficiency and, as a result, failed to include deaths as a result of α_1AT deficiency occurring in children (17–23). In the latter cases, essentially all the deaths are a result of liver disease or one of its complications, such as portal hypertension. In our own experience, the number of cases with

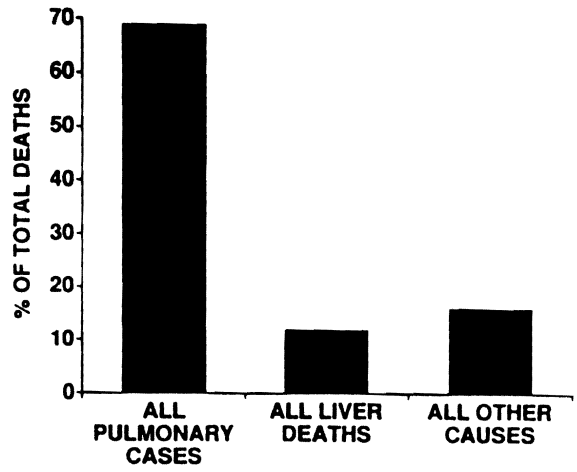


Figure 2 Cause of death in adults with α1AT deficiency.

α_1AT liver disease presenting for liver transplantation in infants or children exceeds the number of cases of adults who present with liver disease due to α_1AT deficiency. If the deaths that occur in both children and adults with α_1AT deficiency were determined, it would appear that liver disease accounts for 59% of the total deaths whereas pulmonary disease accounts for 23%. Even these figures underestimate the role of α_1AT as a cause of lethal liver disease because an increased prevalence of "cryptogenic" cirrhosis associated with α_1AT heterozygotes for the PiZ allele (particularly MZ) has been reported and the deaths of these individuals would not be included in these totals (7–15,40–42).

Neonatal hepatitis is a common clinical presentation of individuals with α_1AT deficiency during infancy (17–23,37). Almost 30% of infants with neonatal hepatitis ultimately can be shown to be homozygous for the Z allele. Nearly 6% of the cases of neonatal hepatitis will be heterozygotes (MZ) for the Z allele. Thus, the prevalence of neonatal hepatitis in α_1AT Z heterozygotes is twice that seen in individuals who have a "normal" MM phenotype. As noted above, adults with cryptogenic cirrhosis have a statistically increased incidence of heterozygosity for the Z allele ($p < 0.001$), which is almost ten-fold greater than the rate of cryptogenic cirrhosis in large, clinical liver-disease populations (Fig. 3) (7–16,40–42). Interestingly, the rates of autoimmune, viral, and alcoholic liver disease in α_1AT heterozygotes for the Z allele appear to be reduced by about 50%. Only the reduction in the prevalence of alcoholic liver disease, however, achieved a level of statistical significance ($p < 0.01$).

More recently, the relationship between α_1AT deficiency and liver disease has been shown to be more complex than simply a deficiency of a normal

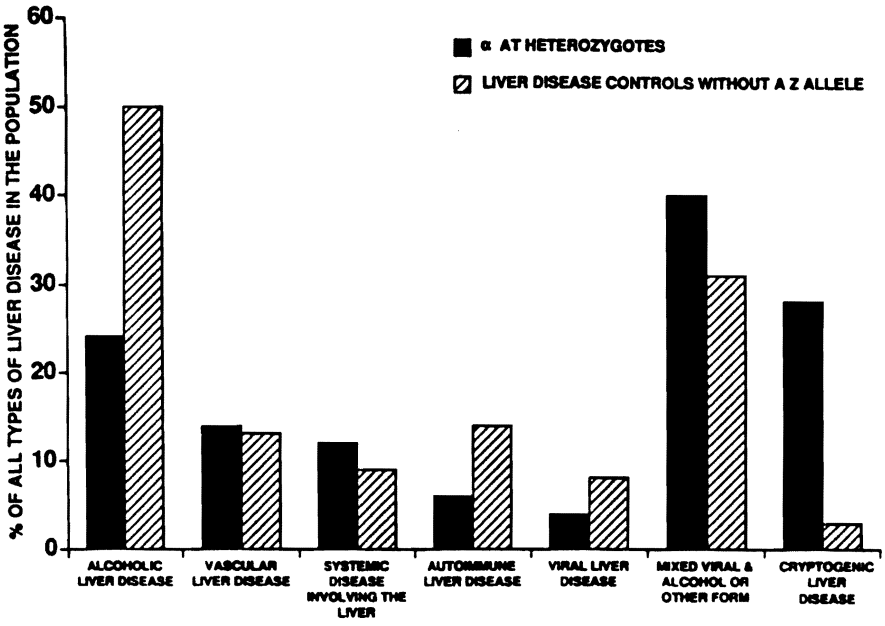


Figure 3 Frequency of Z allele in patients with cryptogenic cirrhosis seen as adults.

circulating secretory serine protease; it may also involve immunological or at least genetic factors, as the rate of α_1AT deficiency with liver disease is almost threefold higher ($\chi^2 = 7.124$; $p < 0.01$) in individuals who are HLA Dr3–positive (43,44). In contrast, HLA Dr4 appears to be protective, with a halving of the rate of liver disease in individuals who are homozygous for the Z allele ($\chi^2 = 4.010$; $p < 0.05$). The observation that HLA Dr3 occurs at an increased frequency in patients with α_1AT deficiency and liver disease, however, could not be confirmed in our own series of orthotopic liver-transplant (OLTx) patients (45). Nonetheless, RFIP studies have noted that the association with HLA Dr3 and α_1AT-deficiency liver disease is associated with the Dw24 and Dw25 subtypes (both $p < 0.05$) and that both Dr3 Dw24 and Dr3 Dw25 occur two and four times more frequently in individuals with α_1AT deficiency and liver disease than in controls (42,43).

The role of other genetic or environmental factors in the pathogenesis of the liver disease associated with α_1AT deficiency and the Z allele is either less clear or totally unknown (46). It should be noted, however, that a role for environmental factors may exist, as is the situation with smoking and the association of α_1AT deficiency and panacinar emphysema (1,2,24,46,47). Individuals who smoke and are homozygous for the Z allele develop clinically evident emphysema a full decade or more earlier than do homozygotes who do not smoke (1–3).

The clinical presentation of children with α_1AT deficiency is rather consistent, with greater than 75% presenting with neonatal hepatitis (jaundice) and smaller numbers presenting with either asymptomatic hepatosplenomegaly or hematemesis (Fig. 4) (17–23). In the vast majority of cases with neonatal hepatitis, the jaundice resolves within 8 months. A minority (<20%) die in the first year of life, usually in the seventh or eighth month of life. Most, however, do not die but live to develop liver disease that requires transplantation as either an older child or an adult. Table 2 shows the differential diagnosis of α_1AT disease in children segmented into those who present initially with evidence for liver disease as infants (<1 year of age) and those who are more than 1 year old at the time of initial presentation. In most cases, after the initial period of neonatal hepatitis characterized by cholestasis, the disease progresses as does any other hepatocellular disease, with the development of portal hypertension and protein synthetic defects that characterize the disease process. Six clinical findings are used to identify children with α_1AT deficiency who have a poor prognosis: the presence of hepatomegaly, a palpably hard liver, failure to thrive, clubbing of fingers, and two or more overt signs of portal hypertension (ascites and varices). Typically, the disease in children follows a characteristic histopathological progression from

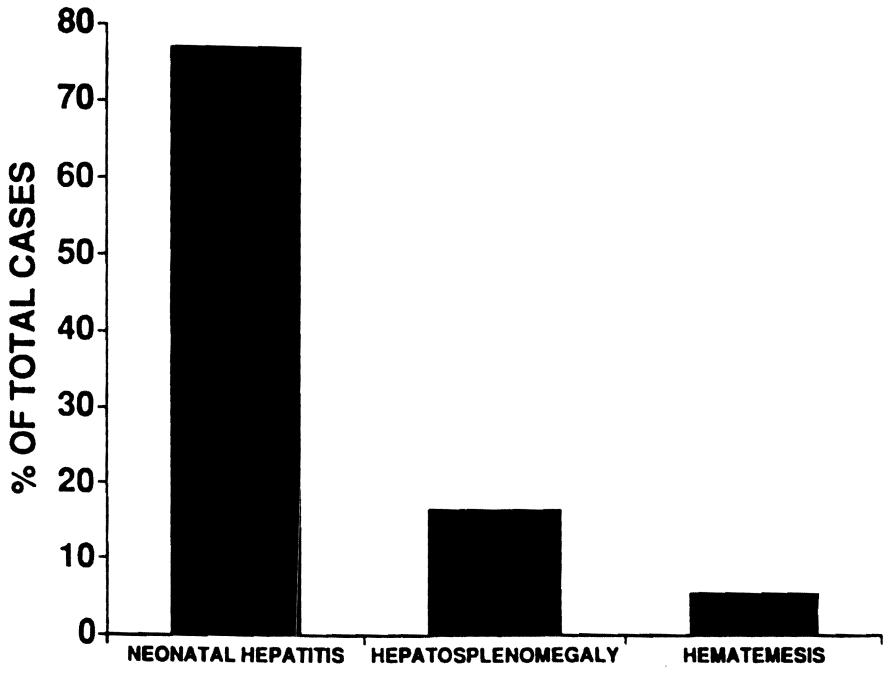


Figure 4 Frequency of various types of clincal presentations of children with α1AT deficiency.

Table 2 Differential Diagnosis of α1AT-Deficiency Liver Disease

Neonates to 1 year	>1 year
Neonatal hepatitis	Cystic fibrosis
TORCH[a]	Autoimmune chronic active hepatitis
Blood-group incompatibility	Wilson's disease
Cystic fibrosis	Microcytic liver disease
Galactosemia	Congenital hepatic fibrosis
Tyrosinemia	Chronic viral hepatitis

[a]TORCH = toxoplasmosis, rubella, cytomegalovirus hepatitis.

the newborn period through 2 years of age, when cirrhosis is usually present (Table 3). Signs and symptoms of portal hypertension typically occur after age 2 and lead to a need for transplantation or to death by age 8 ± 0.3 years (range 8 months to 13 years) (Fig. 4).

The situation is quite similar in adults, with most cases either giving a history of neonatal jaundice or silently developing cirrhosis that presents clinically when a complication of the cirrhosis becomes evident, typically, a problem related to portal hypertension such as ascites, variceal bleeding, or hepatic encephalopathy (24–37).

III. Liver Transplantation

Table 4 shows the frequency of the dominant clinical features of patients with α_1AT deficiency at a time point immediately prior to OLTx. Table 5 shows the age distribution of cases with α_1AT deficiency who have received a liver transplant in Pittsburgh. Table 6 shows the percentage of the total cases on an annual basis who were transplanted in Pittsburgh for α_1AT deficiency. As is evident from Table 5, two peaks in age at time of OLTx occur: the first at ages 2–11 years and the second between 18 and 59 years. Table 6 shows that the fraction of total transplant cases

Table 3 Hepatic Histology in Children with α1AT Deficiency Liver Disease: Effect of Age

Giant cell hepatitis	3 months or less
Hepatitis	3 months to 3 years
Portal fibrosis	4 months to 18 years
Cirrhosis	6 months to 18 months

Table 4 Dominant Clinical Features in Patients with α1AT Deficiency Immediately Before Liver Transplantation

Clinical features	%
Ascites	80
Variceal hemorrhage	59
Jaundice	38
Encephalopathy	10

with α_1AT deficiency has remained rather stable through the years, ranging from 4 to 9%, with minor variations above this figure.

The rate of graft and patient survival following liver transplantation for all cases with α_1AT deficiency is 68% and 76%, respectively, through 5 years (Figure 5A). The rate of graft and patient survival for children and adults with α_1AT deficiency through 5 years is shown in Figure 5B. Little difference in graft survival is evident, but patient survival through 5 years is clearly better for children (81%) than it is for adults (71%). The vast majority of cases (81.3%) require only one graft; 13.5% require a second graft and 5.2% require a third graft.

As for the technical details of the transplant operation, because most cases with α_1AT deficiency are neither very young (<1 year of age) nor very old (>65 years of age), little or no surgical difficulty is experienced as a result of the required vascular of biliary-tract reconstructions. The major problem during the operative procedure is a result of the portal hypertension and coagulopathy that characterize the disease. In adults, this problem is resolved in large measure as a result of the use of the portal systemic bypass developed by Denmark et al. (49) and used initially by Shaw et al. (50). In children, the bypass is frequently not used

Table 5 Age Distribution of α1AT-Deficient Patients at Time of Liver Transplantation

	n	%
Infant (under 2 years)	5	5.2
Child (2–11)	40	41.7
Adolescent (12–17)	4	4.2
Adult (18–59)	39	40.6
Senior (over 60)	8	8.3

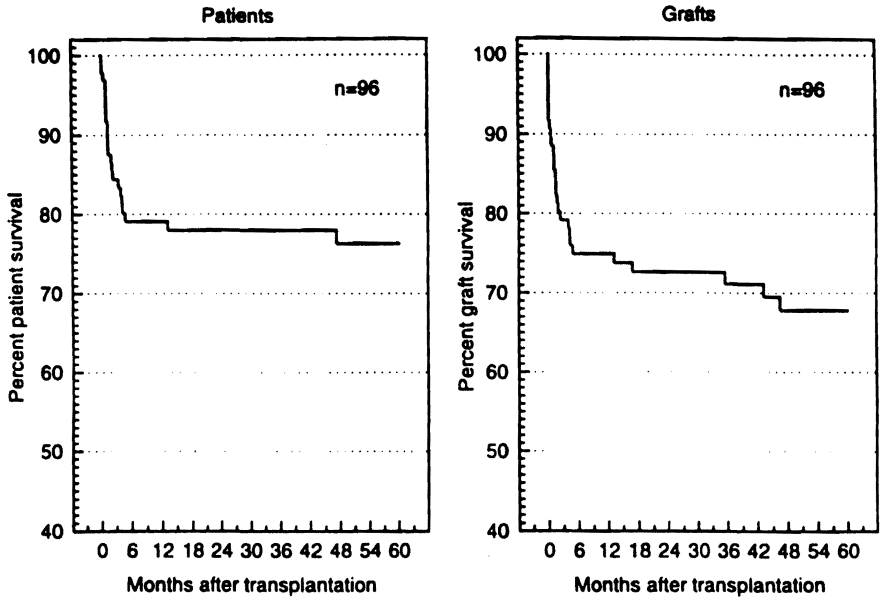
Table 6 Number of Cases Transplanted for α1AT Deficiency and the Years in Which the Transplant Procedure was Performed

	n	%
1981	6	6.3
1982	4	4.2
1983	7	7.3
1984	9	9.4
1985	9	9.4
1986	15	15.6
1987	8	8.3
1988	12	12.5
1989	8	8.3
1990	13	13.5
1991	5	5.2
Total	96	100.0%

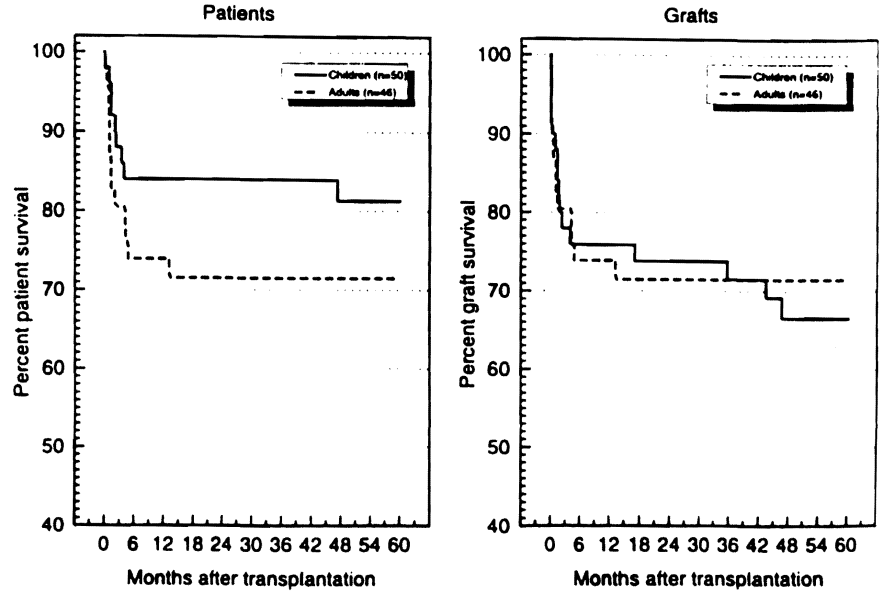
and bleeding can at times be a difficult management problem during the initial parts of the transplant operation.

Following transplantation, the α_1AT phenotype of the serine protease present in blood becomes that of the organ donor and the serum level returns to the normal range (51–53). As a result, not only is liver function returned to normal with OLTx but also the hepatic disease is cured (51–53). Moreover, because of the normal serum levels, most likely either the pulmonary disease is stabilized or its rate of progression is markedly slowed. This does not occur with portal caval shunting, the only other surgical procedure shown to have benefit in children with this disease (54,55). A major question that remains to be resolved is whether the act of liver replacement also cures or at least halts the progression of the pulmonary disease that occurs as a consequence of α_1AT deficiency. Studies to examine the serine antiprotease activity, α_1AT levels, and phenotype in alveolar lavage specimens in long-term survivors of OLTx for α_1AT deficiency are currently in progress in Pittsburgh. Similarly, studies characterizing the presence or absence—and, if present, the severity—of the pulmonary disease in liver recipients following successful OLTx for α_1AT are currently in progress.

With the recent demonstration that donor lymphodendritic cell seeding from liver allografts occurs following successful OLTx (56,57), it has become understandable why liver allograft recipients transplanted for metabolic diseases (both



(a)



(b)

Figure 5 Graft and patient survival of (a) all individuals transplanted for α1AT deficiency at the University of Pittsburgh and (b) for the same cases divided into children and adults.

hepatically based and nonhepatically based) such as type 4 glycogen storage disease (57), type II hyperlipoproteinemia (58), Wilson's disease (59), Wolman's disease (60), Nieman-Pick disease (61), Gaucher's disease (unpublished observations), and seablue histiocyte syndrome (unpublished observations) have experienced benefits well beyond what was anticipated from liver transplantation. Because the lungs are natural repositories of dendritic cells, it is to be expected that donor-specific α1AT-positive dendritic cells would be found in the bronchi and alveolar walls of liver allograft recipients who were α1AT-deficient prior to OLTx. The presence of these cells locally in the lungs following OLTx as well as the fact that normal levels of α_1AT are achieved in the serum of patients transplanted for α_1AT deficiency would be expected to either slow or, more likely, halt the progression of any α_1AT deficiency-dependent pulmonary disease following successful OLTx.

IV. Conclusion

Based on these recent observations (56,57), the role that whole-organ transplantation plays in the management of metabolic disease in general may need to be reevaluated. It may well be that all such procedures, regardless of the organ being transplanted, result in a gain of metabolic function determined by the content of lymphodendritic cells that migrate from the donor organ throughout the body of the recipient (56,57). The concept that a kidney, spleen, liver, or other organ could bring a systemic supply of a missing lyzozomal enzyme has been suggested before (62–64) but was abandoned because of the lack of a rationale and the inability to demonstrate benefit.

Even if the abnormality of α_1AT deficiency in the lungs were not cured as a result of liver transplantation, patient survival and quality of life would be greatly enhanced. It appears more likely, however, that because the level of α_1AT is either normal or greatly enhanced as a result of OLTx, the lung disease is likely to be stabilized or at least its rate of progression markedly reduced following successful OLTx. One might anticipate further that, since the liver disease is cured, the risk for the development of a hepatocellular carcinoma would decline dramatically (8,65–71). Because individuals with α_1AT deficiency are not at increased risk for a biliary cancer prior to liver transplantation, following transplantation the risk for this condition should not be altered (28).

References

1. Perlmutter DH. The cellular basis for liver injury in α_1-antitrypsin deficiency. Hepatology 1991; 13:172–185.
2. Banda MJ, Rice AG, Griffin GL, Senior RM. The inhibitory complex of human

α_1-proteinase inhibitor and human leukocyte elastase is a neutrophil chemoattractant. J Exp Med 1988; 167:1608–1615.

3. Janoff A. Elastases and emphysema: Current assessment of the protease-antiprotease hypothesis. Am Rev Respir Dis 1985; 132:417–433.
4. Banda MJ, Rice AG, Griffin GL, Senior RM. The inhibitory complex of human α_1-proteinase inhibitor and human leukocyte elastase is a neutrophil chemoattractant. J Exp Med 1988; 167:1608–1615.
5. Cook PJL. The genetics of α_1-antitrypsin: A family study in England and Scotland. Ann Hum Genet Lond 1975; 38:275–287.
6. Hodges JR, Millward-Sadler GH, Barbatis C, Wright R. Heterozygous MZ alpha$_1$-antitrypsin deficiency in adults with chronic active hepatitis and cryptogenic cirrhosis. N Engl J Med 1981; 304:557–560.
7. Eriksson S, Moestrup T, Hägerstrand I. Liver, lung and malignant disease in heterozygous (Pi MZ) α_1-antitrypsin deficiency. Acta Med Scand 1975; 198:243–247.
8. Lieberman J, Silton RM, Agliozzo CM, McMahon J. Hepatocellular carcinoma and intermediate α_1-antitrypsin deficiency (MZ phenotype). Am J Clin Pathol 1975; 64: 304–310.
9. Sparos L, Tountas Y, Chapuis-Cellier C, Theodoropoulos G, Trichopoulos D. Alpha$_1$-antitrypsin levels and pheotypes and hepatitis B serology in liver cancer. Br J Cancer 1984; 49:567–570.
10. Eriksson S, Lindmark B, Olsson S. Lack of association between hemochromatosis and α_1-antitrypsin deficiency. Acta Med Scand 1986; 219:291–294.
11. Eriksson S, Carlson J, Velez R. Risk of cirrhosis and primary liver cancer in alpha$_1$-antitrypsin deficiency. N Engl J Med 1986; 314:736–739.
12. Fargion S, Klasen EC, Lalatta F, Sangalli G, Tommasini M, Fiorelli G. α_1-antitrypsin in patients with hepatocellular carcinoma and chronic active hepatitis. Clin Genet 1981; 19:134–139.
13. Crowley JJ, Sharp HL, Freier E, Ishak KG, Schow P. Fatal liver dissease associated with α_1-antitrypsin deficiency PiM$_1$/PiM$_{duarte}$. Gastroenterology 1987; 93:242–244.
14. Kueppers F, Dickson ER, Summerskill WH. Alpha$_1$-antitrypsin phenotypes in chronic active liver disease and primary biliary cirrhosis. Mayo Clin Proc 1976; 51:286–288.
15. Vecchio FM, Fabiano A, Orsini G, Ragusa D, Massi G. Alpha-1-antitrypsin MZ phenotype and cryptogenic chronic liver disease in adults. Digestion 1983; 27: 100–104.
16. Sharp HL, Bridges RA, Krivit W, Freier EF. Cirrhosis associated with alpha-1-antitrypsin deficiency: A previously unrecognized inherited disorder. J Lab Clin Med 1969; 6:934–939.
17. Sveger T. Liver disease in alpha$_1$-antitrypsin deficiency detected by screening of 200,000 infants. N Engl J Med 1976; 294:1316–1321.
18. Moroz SP, Cutz E, Cox DW, Sass-Kortsak A. Liver disease associated with alpha$_1$-antitrypsin deficiency in childhood. J Pediatr 1976; 88:19–25.
19. Sveger T. The natural history of liver disease in α_1- antitrypsin deficient children. Acta Pediatr Scand 1988; 77:847–851.
20. Psacharopoulos HT, Mowat AP, Cook PJL, Carlile PA, Portmann B, Rodeck CH. Outcome of liver disease associated with α_1 antitrypsin deficiency (PiZ). Arch Dis Childhood 1983; 58:882–887.

21. Ghishan FK, Greene HL. Liver disease in children with PiZZ α_1-antitrypsin deficiency. Hepatology 1988; 8:307–310.
22. Alper CA, Johnson AM. Alpha$_1$-antitrypsin deficiency and disease. Pediatrics 1970; 46:837–840.
23. Cottrall K, Cook PJL, Mowat AP. Neonatal hepatitis syndrome and alpha-1-antitrypsin deficiency: An epidemiological study in south-east England. Postgrad Med J 1974; 50:376–380.
24. Berg NO, Eriksson S. Liver disease in adults with alpha$_1$-antitrypsin deficiency. N Engl J Med 1972; 287:1264–1267.
25. Larsson C. Natural history and life expectancy in severe alpha$_1$-antitrypsin deficiency, PiZ. Acta Med Scand 1978; 204:345–351.
26. Cox DW, Smyth S. Risk for liver disease in adults with alpha$_1$-antitrypsin deficiency. Amer J Med 1983; 74:221–227.
27. Triger DR, Millward-Sakler GH, Czaykowski AA, Trowell J, Wright R. Alpha-1-antitrypsin deficiency and liver disease in adults. Quart J Med, New Series 1976; 178: 351–372.
28. Rabinovitz M, Gavaler JS, Kelly RH, Prieto M, Van Thiel DH. Lack of increase in heterozygous α_1-antitrypsin deficiency phenotypes among patients with hepatocellular and bile duct carcinoma. Hepatology 1992; 15:407–410.
29. Carlson J, Eriksson S. Chronic cryptogenic liver disease and malignant hepatoma in intermediate alpha$_1$-antitrypsin deficiency identified by a PiZ-specific monoclonal antibody. Scand J Gastroenterol 1985; 20:835–842.
30. Eriksson S, Hägerstrand I. Cirrhosis and malignant hepatoma in α_1-antitrypsin deficiency. Acta Med Scand 1974; 195:451–458.
31. Eriksson S. α_1-antitrypsin deficiency and liver cirrhosis in adults. Acta Med Scand 1987; 221:461–467.
32. Eriksson SG. Liver disease in α_1-antitrypsin deficiency. Scand J Gastroenterol 1985; 20:907–911.
33. Rawlings W, Moss J, Cooper HS, Hamilton SR. Hepatocellular carcinoma and partial deficiency of alpha-1 antitrypsin (MZ). Ann Intern Med 1974; 81:771–773.
34. Rakela J, Goldschmiedt M, Ludwig J. Late manifestation of chronic liver disease in adults with alpha-1-antitrypsin deficiency. Dig Dis Sci 1987; 32:1358–1362.
35. Gherardi GJ. Alpha-1-antitrypsin deficiency and its effect on the liver. Hum Pathol 1971; 2:173–175.
36. Larsson C, Eriksson S. Liver function in asymptomatic adult individuals with severe α_1-antitrypsin deficiency (Pi Z). Scand J Gastroenterol 1977; 12:543–546.
37. Sharp HL. The current status of alpha-1-antitrypsin, a protease inhibitor in gastrointestinal disease. Gastroenterology 1976; 70:611–621.
38. Carlson JA, Rogers BB, Sifers RN, Finegold MJ, Clift SM, DeMayo FJ, Bullock DW, Woo SLC. Accumulation of PiZα_1-antitrypsin causes liver damage in transgenic mice. J Clin Invest 1989; 83:1183–1189.
39. Dycaico MJ, Grant SGN, Felts K, Nichols WS, Geller SA, Hager JH, Pollard AJ, Kohler SW, Short HP, Jirik FR, Hanahan D, Sorge JA. Neonatal hepatitis induced by α_1-antitrypsin: A transgenic mouse model. Science 1988; 24:1409–1412.
40. Craig JR, Dunn AE, Peters RL. Cirrhosis associated with partial deficiency of alpha-1-antitrypsin: A clinical and autopsy study. Hum Pathol 1975; 6:113–120.

41. Bell H, Schrumpf E, Fagerhol MK. Heterozygous MZ alpha-1-antitrypsin deficiency in adults with chronic liver disease. Scan J Gastroenterol 1990; 25:788–792.
42. Reid CL, Wiener GJ, Cox DW, Richter JE, Geisinger KR. Diffuse hepatocellular dysplasia and carcinoma associated with the Mmalton variant of α_1-antitrypsin. Gastroenterology 1987; 93:181–187.
43. Doherty DG, Donaldson PT, Whitehouse DB, Mieli-Vergani G, Duthie A, Hopkinson DA, Mowat AP. HLA phenotypes and gene polymorphisms in juvenile liver disease associated with α-1-antitrypsin deficiency. Hepatology 1990; 12:218–223.
44. Nemeth A, Möller E. HLA in juvenile liver disease with alpha-one-antitrypsin deficiency. Acta Pediatr Scand 1987; 76:603–607.
45. Casavilla A, Gordon R, Van Thiel DH, Starzl TE. Lack of an association between HLA antigens DR3 and alpha-1-antitrypsin deficiency in liver transplant recipients. Submitted.
46. Rabinovitz M, Gavaler JS, Kelly RH, Van Thiel DH. The association between heterozygous α_1-antitrypsin deficiency and genetic hemochromatosis. Hepatology 1993; 18:703–708.
47. Wewers MD, Gadek JE, Keogh BA, Fells GA, Crystal RG. Evaluation of danazol therapy for patients with PiZZ alpha-1-antitrypsin deficiency. Am Rev Respir Dis 1986; 134:476–480.
48. Eriksson S. The effect of tamoxifen in intermediate alpha$_1$-antitrypsin deficiency associated with the phenotype PiSZ. Ann Clin Res 1983; 15:95–98.
49. Denmark SW, Shaw BW Jr, Starzl TE, et al. Veno-venous bypass without systemic anticoagulation in canine and human liver transplantation. Surg Forum 1983; 34:380–382.
50. Shaw BW Jr, Martin DJ, Marquez JM, et al. Advantages of venous bypass during orthotopic transplantation of the liver. Semin Liver Dis 1985; 5:344–348.
51. Hood JM, Koep LJ, Peters RL, Schröter, Weil R, Redeker AG, Starzl TE. Liver transplantation for advanced liver disease with alpha-1-antitrypsin deficiency. N Engl J Med 1990; 302:272–275.
52. Esquivel CO, Marino IR, Fioravanti V, Van Thiel DH. Liver transplantation for metabolic disease of the liver. Gastroenterology 1988; 17:167–175.
53. Gartner JC, Zitelli BJ, Malatack JJ, Shaw BW, Iwatsuki S, Starzl TE. Orthotopic liver transplantation in children: Two-year experience with 47 patients. Pediatrics 1984; 74:140–145.
54. Starzl TE. Portacaval shunt in three children with alpha-1-antitrypsin deficiency and cirrhosis: 9 to 12⅓ years later. Hepatology 1990; 11:152–154.
55. Starzl TE, Porter KA, Francavilla A, Iwatsuki S. Reversal of hepatic alpha-1-antitrypsin deposition after portal caval shunt. Lancet 1983; ii:424–426.
56. Starzl TE, Demetris AJ, Murase N, Ildstad S, Ricordi C. Cell migration, chimerism, and graft acceptance. Lancet 1992; 390:617–618.
57. Starzl TE, Demetris AJ, Trucco M, Ricordi C, Isdstad S, Murase N, Kendall RS. Chimerism after liver transplantation in patients with type IV glycogen storage disease. N Engl J Med 1993; 328:745–749.
58. Starzl TE, Bilheimer DW, Bahnson HT, Shaw BW Jr, Hardesty RL, Griffith BP, Iwatsuki S, Zitelli BJ, Gartner JC Jr, Malatack JJ, Urbach AH. Heart-liver transplantation in a patient with familial hypercholesterolaemia. Lancet 1984; i:1382–1383.

59. Bellary SV, Van Thiel DH. Wilson's disease: A diagnosis made in two individuals greater than 40 years of age. J Hepatol. In press.
60. Ferry GD, Whisennand HH, Finegold MJ, Alpert E, Globmicki A. Liver transplantation for cholesteryl ester storage disease. J Ped Gastroenterol Nutr 1991; 12:376–378.
61. Daloze P, Delvin EE, GLorieux JH, et al. Replacement therapy for inherited enzyme deficiency: Liver replacement in Niemann-Pick disease Type A. Am J Med Genet 1977; 1:229–239.
62. Parkman R. The application of bone marrow transplantation to the treatment of genetic diseases. Science 1986; 232:1373–1378.
63. Groth C, Collste H, Dreborg S, Hakansson G, Lundgren G, Svennerholm L. Attempts at enzyme replacement in Gaucher disease by renal transplantation. Acta Paediatr Scand 1979; 68:475–479.
64. Desnick RJ, Simjmons RL, Allen KY, Woods JE, Anderson CF, Najarian JS, Krivit W. Correction of enzymatic deficiencies by renal transplantation: Fabry's disease. Surgery 1972; 72:203–211.
65. Piggott M, Wagaine-Twabwe D, Ramcharan JE, Taylor D. Alpha$_1$-antitrypsin deficiency and liver disease. Br Med J 1981; 283:1262–1263.
66. Chio L, Oon C. Changes in serum alpha$_1$-antitrypsin, alpha$_1$ACII glycoprotein and beta$_2$ glycoprotein I in patients with malignant hepatocellular carcinoma. Cancer 1979; 43:596–604.
67. Vergalla J, Jones EA, Kew MC. Alpha-1-antitrypsin deficiency and hepatocellualr carcinoma. S Afr Med J 1983; 64:950–951.
68. Zwi S, Hurwitz SS, Cohen C, Prinsloo I, Kagan E. Alpha$_1$-antitrypsin deficiency—An association with hepatic malignancy. S Afr Med J 1975; 59:1887–1890.
69. Rubel LR, Ishak KG, Benjamin SB, Knuff TE. α_1-antitrypsin deficiency and hepatocellular carcinoma. Arch Pathol Lab Med 1982; 106:678–681.
70. Lindmark B, Millward-Sadler H, Callea F, Eriksson S. Hepatocyte inlcusions of α_1-antichymotrypsin in a patient with partial deficiency of α_1-antichymotrypsin and chronic liver disease. Histopathology 1990; 16:221–225.
71. Schleissner LA, Cohen AH. Alpha$_1$-antitrypsin deficiency and hepatic carcinoma. Am Rev Resp Disease 1975; 3:863–868.