To the Editor:

Regarding the elegant discussion of liver transplantation recently published by Maddrey and Van Thiel (1), we would like to comment on patients with alpha-1-antitrypsin deficiency (2). The operations, on two girls and one boy, were performed on June 15, 1976; March 7, 1978 and November 1, 1979, when the children were 4%, 6% and 1½ yr old, respectively. At the time, the option of liver transplantation was neither satisfactory nor widely available. All three children had had neonatal hepatitis and a history of bleeding esophageal varices, ascites or both. Phenotypes were PiZZ (Pi = protease inhibitor). Liver function was abnormal but not gravely perturbed (Table 1).

The low serum alpha-1-antitrypsin levels were not appreciably different before and long after the portacaval shunt (Table 1). All three children had normal physical growth, and Patients 1 and 3 remain ostensibly healthy. Patient 2 was frequently ill, with a record of frequent school absenteeism. Diuretics were required intermittently for control of her ascites. Her liver function test results were abnormal at the time of portacaval shunt. Her test results worsened immediately afterward (2) but then became stable for more than 9½ yr (Table 1). In October 1987, she developed acute liver decompensation and on November 3, 1987, underwent successful orthotopic liver transplantation at the University of California at Los Angeles. It was previously reported (2) that the serum ammonia rose after portacaval shunt in all three patients and that the aminotransferase and alkaline phosphatase levels fell. The same pattern has persisted (Table 1) in Patients 1 and 3, neither of whom has practiced any dietary restriction.

All three patients had macronodular cirrhosis at the time of portacaval shunt, with biopsy findings typical of the liver disease associated with alpha-1-antitrypsin deficiency (2). The sample obtained from the excised liver in Patient 2 after 9½ yr and the repeat biopsy sample in Patient 3 after 3½ yr were fixed in buffered formalin. Patient 1 refused biopsy. Paraffin sections were prepared and stained with a variety of reagents, including periodic acid–Schiff stain, after the sections were treated with diastase. A peroxidase-antiperoxidase technique with specific antibody (Dako-patts) was used to identify alpha-1-antitrypsin. A standard morphometrical method revealed 10,000 hepatocytes in each liver sample (3). The proportion of hepatocytes with alpha-1-antitrypsin granules in the cytoplasm was recorded.

Both livers remained cirrhotic, and the cytoplasm of some of the hepatocytes contained granules of alpha-1-antitrypsin. Most of the granules were small and the number per cell varied greatly; they were more common at the periphery of the pseudolobules. When compared with the liver biopsy specimens obtained at the time of portacaval shunting, the severity of the cirrhosis appeared unaltered, but in Patient 2 severe intrahepatic cholestasis that had not been present before was found. In Patients 2 and 3 the hepatocytes were approximately 20% smaller than when the portacaval shunt was performed. The percentage of hepatocytes containing alpha-1-antitrypsin also was lower. In Patient 2, it was 19.3% (compared with 38.2% in the preshunt biopsy specimen and 28.5% in a biopsy sample taken 9 mo later). In Patient 3, the percentage was 19.05% (compared with 44.5% in the preshunt biopsy specimen, 48.2% 7 mo after portacaval shunting, 38.7% at 13 mo and 20.4% at 2 yr, 11 mo (2).

Portal diversion has been shown during the last 15 yr to palliate three congenital errors of metabolism: glycogen storage disease (3), familial hypercholesterolemia (4) and alpha-1-antitrypsin deficiency (2, 5). Because each of these errors can be corrected far more effectively by liver transplantation (6–8), portacaval shunts for metabolic purposes in these diseases have been almost completely and appropriately abandoned. The presence of a shunt introduces a technical risk factor at the time of transplantation. However, there may be occasional patients such as ours with alpha-1-antitrypsin deficiency, reasonable liver function and serious complications of portal hypertension, who submit to lifesaving portal diversion procedures when a liver cannot be found at the appropriate time. In our patients the process of liver injury thought to be caused by the intracellular accumulation of irritating alpha-1-antitrypsin particles that cannot be excreted at a normal rate (9) seems to have been slowed or stopped by portal diversion. It was previously speculated (2, 5) that
the portacaval shunt selectively damaged the rough endoplasmic reticulum where the synthetic processes of the liver are concentrated without a commensurate reduction in excretory function of the hepatocytes. The result would be a more favorable relation between deposition of the alpha globulin and its elimination from the hepatocytes. The histopathological findings in the livers of Patients 1 and 3 were consistent with this hypothesis in that the reduction in the size of the hepatocytes and in the percentage of hepatocytes containing alpha-1-antitrypsin granules noted in the earlier biopsies (2) has been maintained.

This letter is not intended to suggest that portacaval shunt for metabolic purposes is an alternative to liver transplantation. We have compiled no further cases in this group and the incidence and hepatic alpha-1-antitrypsin deposition after portacaval shunt.

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<tr>
<th>TABLE 1. Chemistries before end-to-side portacaval shunt and 8% to 12 yr later</th>
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<tr>
<td>Normal</td>
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<td>Age (yr) at testing:</td>
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<tr>
<td>Serum bilirubin (µmol/L)</td>
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<td>Serum ammonia (µmol/L)</td>
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<td>Prothrombin time (sec)</td>
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<td>Serum alpha-1-antitrypsin (gm/L)</td>
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<td>Serum protein (gm/L)</td>
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<td>Serum albumin (gm/L)</td>
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These tests were in early October 1987, 1 mo before liver transplantation on November 3, 1987. Liver function deteriorated rapidly during the next few weeks, necessitating transplantation.

The principal physiological function of alpha-1-antitrypsin is to inhibit neutrophil elastase (14). The destruction of alveolar walls by consequent emphysema in patients with alpha-1-antitrypsin deficiency (15) presumably results from the unchecked activity of neutrophil elastase. A favorable effect on lung disease is expected from liver transplantation, although with a maximal follow-up of only 13 yr (16), it is too soon to be sure that this will be achieved.

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REFERENCES