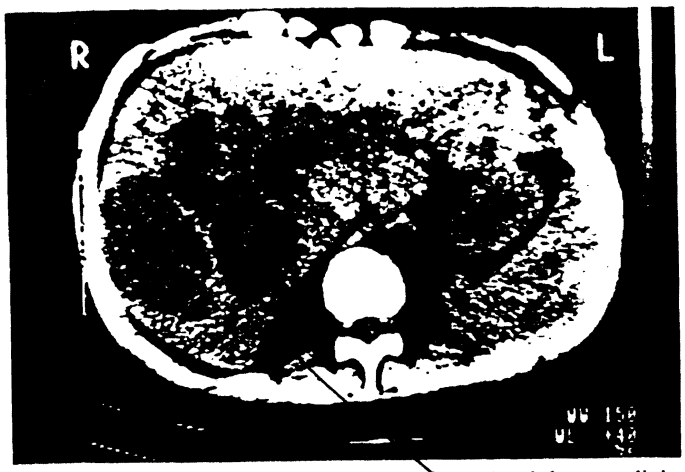

FIGURE 1. Computerized tomography of the patient's hepatocellular carcinoma with nearly complete occupation of the right lobe and infiltration of the left lobe.

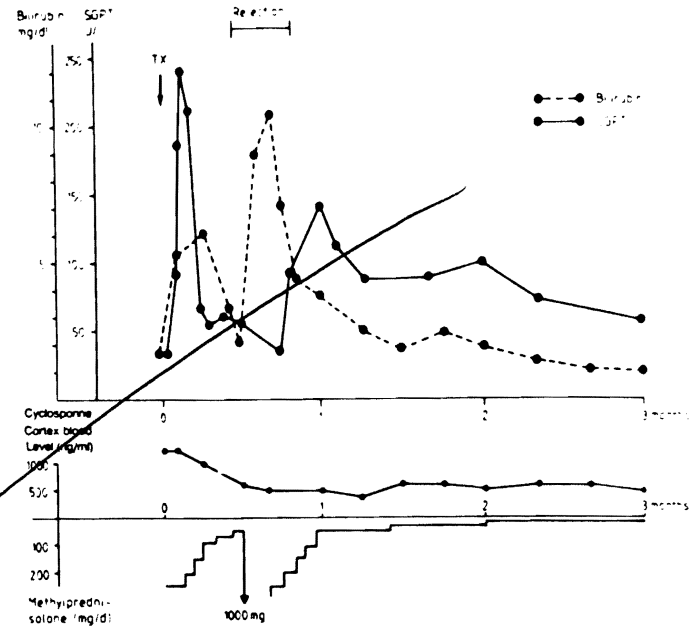

FIGURE 2. Bilirubin, serum glutamate dehydrogenase, and immunosuppression during course after liver grafting.

On the whole, the patient feels well 6 months after transplantation. He is treated with 12 mg methylprednisolone and cyclosporine. The cyclosporine serum level is kept between 300 and 500 ng/ml. The patient is able to work in his father's business several hours a day.

Even though in our patient hepatocellular carcinoma and not galactosemia was the indication for liver transplantation, the complete compensation of this systemic metabolic defect by the transplanted liver is noteworthy.

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PRIMARY NONFUNCTION OF HEPATIC ALLOGRAFTS WITH PREEXISTING FATTY INFILTRATION[1]

One of the unresolved problems in liver transplantation is how to determine accurately the cause of the primary nonfunction that is seen in about 10% of hepatic grafts (*1*, *2*). It is often assumed that ischemic injury has occurred when the new liver does not function. Acute immunologic injury comparable to the humorally mediated hyperacute rejection of kidneys probably occurs rarely, if at all (*3*), but an indolent version of hyperacute hepatic rejection that is not clearly associated with demonstrable preformed antibodies can cause hemorrhagic necrosis within 1 or 2 days (*4*). The other most common etiology of primary nonfunction probably is intraoperative injury of the transplant when a flawed operation is performed by the recipient team (*1*).

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Preexisting acute or chronic hepatic disease in the recipient will undoubtedly aggravate any of the foregoing factors, or may itself preclude success. Although hepatic injury may occur as part of the trauma that has led to brain death or may be an iatrogenic complication of the care that is provided, this may be difficult to prove even with biopsies of the homograft. Makowka et al. (*5*) have reported a surprising lack of correlation between so-called good- and bad-risk donor parameters and the clinical outcome of the recipient.

We report here 2 examples of acute fatty infiltration of livers that had been procured from seemingly good donors who had been in good health until 1 and 2 ½ days previously. The grafts that were full of fat never functioned and were replaced immediately in 1 case and 3 days later in the other. This report suggests how to identify and avoid this lethal situation.

Patients. The first donor, a muscular man in his late twenties, was inured in a motor vehicle accident 1 day before the liver

procurement on 17 August 1985. Although the donor's cardiovascular parameters were stable, and the liver functions were completely normal, the procurement surgeon warned that the liver was "greasy." The liver was preserved in Euro-Collins' solution for 5 ½ hr. After its revascularization in a recipient who had a large hepatic tumor, a bleeding diathesis ensued, which required 8 hr for control. The graft functioned poorly if at all, and the recipient was rescued with a second graft 3 days later.

The second donor was a previously healthy 42-year-old woman, 5-feet, 1-inch tall and weighing 191 lbs. She was admitted to a West Coast hospital with a seizure 2 ½ days before organ donation. CAT scan showed an intracranial hemorrhage. her cardiovascular state was stable throughout. Laboratory studies at the time of organ donation included: total bilirubin 0.6 mg%, SGOT 54 IU, alkaline phosphatase 68 IU, BUN 37 mg%, creatinine 3.2 mg%. Blood glucose was 191 mg. Echocardiography and cardiac catheterization showed normal anatomy and function of the heart. The heart and kidneys were transplanted in the local region. Although the heart beat, the cardiac recipient had a stormy recovery with low ejection fractions necessitating pressor support. Myocardial biopsies demonstrated only severe edema without any cellular evidence of rejection. One of the kidney recipients had prompt and good graft function with a creatinine that leveled off at 2.2 mg%. The other kidney suffered from a prolonged bout of acute tubular necrosis and subsequent rejection. The creatinine is now 6.0 mg%.

The liver was brought to Pittsburgh. Initially, it looked normal when the donor was opened, but it had a greasy feel that prompted comment. After aortic crossclamping and perfusion with cold lactated Ringer's solution, the now bloodless liver looked yellow. It was preserved using UW solution (6, 7) and was revascularized after 17 hr of cold ischemia time. The recipient had previously undergone liver transplantation that failed because of CMV hepatitis. Upon reperfusion, the new liver had a mottled appearance, the blood pressure dropped, there was a profound coagulopathy, and bile was not produced.

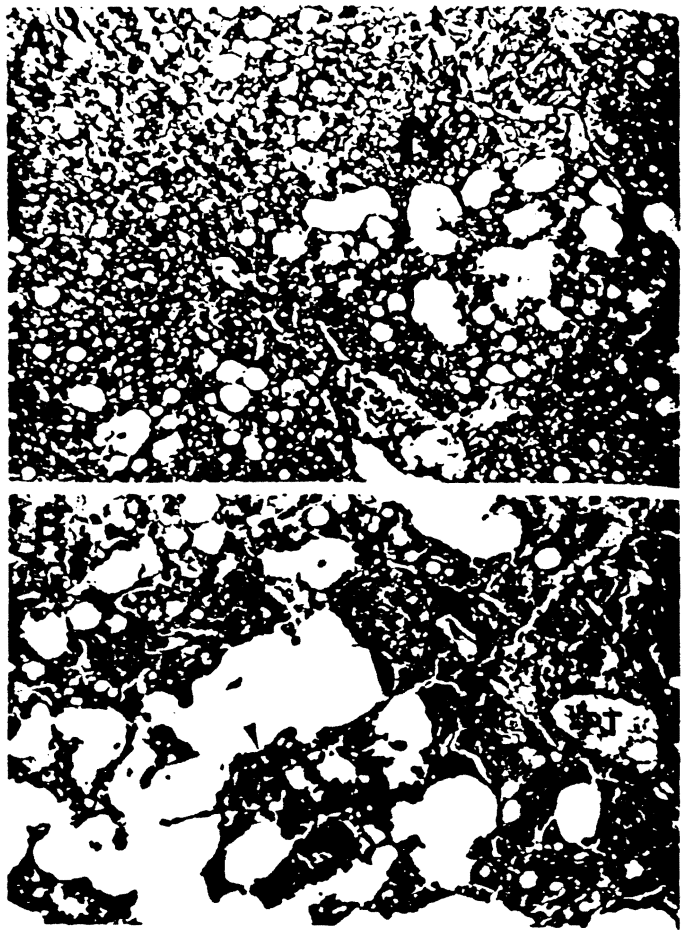

FIGURE 2. Pathologic findings in the failed allograft (case 2). A. Note the large extracellular fat globules (arrow), and distortion of the hepatic sinusoidal architecture (reticulin stain, original magnification: ×100). CV:central vein; PT:portal tract. B. Closer examination demonstrates the extracellular nature of the fat globules (large arrowhead), focal hepatocellular necrosis, congestion, and mild inflammation (small arrowhead) (H&E; original magnification: ×300) (PT:portal tract).

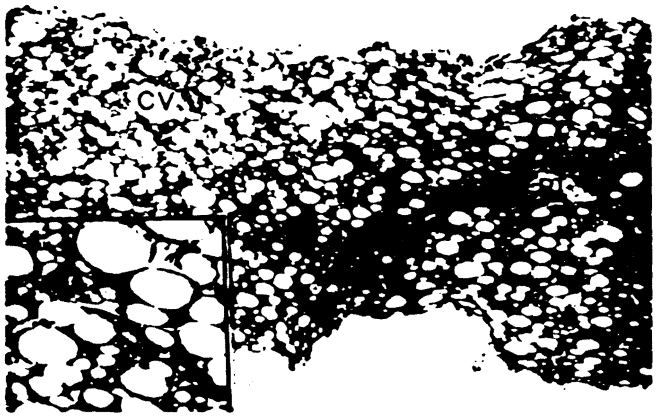

FIGURE 1. Pretransplant needle biopsy in Case 2 demonstrating severe macrovesicular steatosis (H&E; original magnification: ×40). Note the large but intracytoplasmic fat vacuoles (inset, H&E; original magnification: ×200). C:central vein; PT:portal tract.

Severe lactic acidosis developed. Fortunately, another liver was in the operating room. It was immediately substituted for the defective organ, and it perfused normally.

Pathology. The observations in both cases were essentially identical, the only difference between the two being the lack of a pretransplant biopsy in case 1. In case 2, the pretransplant biopsy had an intact lobular architecture, no portal inflammation, and severe diffuse macrovesicular steatosis. The fatty metamorphosis was characterized by large intracytoplasmic globules, which pushed the nucleus toward the periphery of the cells (Fig. 1). No necrosis, lobular inflammation, hepatic vein sclerosis, or Mallory's hyaline were detected.

After their removal, both failed allografts were enlarged (3300 and 2200 g), yellow, and congested. The vascular and biliary systems were intact and patent. With sectioning, the diffusely congested livers had focal areas of hemorrhage and small subcapsular hemorrhagic infarcts. The cut surface was extremely greasy to the touch.

On histologic examination, neither of the failed allografts contained appreciable portal tract inflammation, ruling out the

possibility of acute cellular rejection. No arterial necrosis, intrahepatic thrombi, or fibrin deposition in arteries or veins were present. Stains for immunoglobulins and complement were negative. These findings made antibody-mediated rejection unlikely. Most striking was the presence of large extracellular globules (Fig. 2), which were identified as fat with the oil red stain. The globules were conspicuous in midzonal and centrilobular regions. Associated disruption of the normal sinusoidal reticulin architecture, congestion and hemorrhage, focal hepatocellular necrosis, fibrin deposition, and a mild neutrophilic exudate were seen (Fig. 2). A mild but diffuse microvesicular steatosis was also detected, especially in the relatively preserved periportal regions.

Macrovesicular steatosis, which was the diagnosis on these livers, is a rather common finding in liver biopsies. Increased uptake of fatty precursors, increased fat production by the hepatocytes, or a defect in secretory mechanisms could be responsible. Obesity, diabetes, alcohol intake, nutritional disorders, or drug therapy may be associated with the steatosis that in most cases causes little if any functional impairment (*8*) as was exemplified by the lack of any criteria to disqualify these donor livers. The question is why their transplantation was followed by such marked functional impairment.

Mechanical disruption of the hepatic sinusoidal microvasculature was the most likely cause of the acute allograft failure. A certain degree of hepatocellular death with cell turnover is an inevitable consequence of hepatic preservation, with any known technique. Random rupture of hepatocytes in a liver with severe steatosis probably resulted in the release of large fat globules into the hepatic microcirculation. Presumably, coalescence of the extracellular globules caused plugging, distortion, and disruption of the sinusoidal architecture with congestion, focal hemorrhage, hepatocellular necrosis, local fibrin deposition, and neutrophilic exudation. The Cambridge group has reported a similar experience but did not speculate on the reason for graft malfunction (*9*).

In our own cases, a fatty appearance, or feel, of the liver was noticed by the procurement surgeon, although in case 2 these qualities were evident only after infusion with the preserving solution. A pretransplantation biopsy was not taken in case 1, and in case 2 the biopsy was taken but not processed until later.

The consequences in both cases were so grave that special precautions are in order to avoid using such organs in future cases. Descriptions of a fatty liver or expressions of concern by the donor surgeons should be checked out by biopsy. This could be done in the donor hospital so that an answer could be available by telephone by the time the donor team has returned home. Even if such pathologic services are not available in the donor city, the greater leisure that has been made possible by better liver preservation (*6, 7*) should make possible the more-discriminating study of these organs.

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DISPARATE ACTIVITIES OF HUMAN NATURAL KILLER CELL CLONES AGAINST ALLOGENEIC BONE MARROW AND TUMOR CELL TARGETS[1]

As well as being cytotoxic toward certain tumor cells, natural killer cells have been implicated in the process of allogeneic bone marrow rejection in vivo (*1-3*). Although it has been reported that this is an antibody-dependent process (*4*), mice with SCID are capable of eliminating allogeneic marrow in the absence of detectable antibody (*5*). The phenomenon of allogeneic lymphocyte elimination (*6, 7*) may be another in vivo manifestation of this process and is also thought to be mediated by NK cells in an antibody-independent fashion (*8*). Mice of certain strains are also capable of eliminating parental bone

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