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LIVER TRANSPLANTATION ACROSS ABO BLOOD GROUPS

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Liver transplantation across ABO blood groups

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Six hundred seventy-one first, second, and third orthotopic liver allografts in 520 patients were reviewed to determine the effect of donor-recipient mismatches or incompatibilities for the ABO blood groups on graft survival. A significant advantage for ABO donor-recipient identity was found, especially in adults and for first grafts. However, a surprisingly large number of ABO incompatible grafts were successful. We recommend that nonidentical or incompatible grafts be limited to patients such as small children for whom the supply of available donors is severely limited or for patients in urgent need of transplantation or retransplantation.

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MORE THAN 20 years ago the importance was demonstrated in renal transplantation of avoiding placement of kidney grafts into recipients possessing preformed antidonor antibodies. The first preformed antibody system to be studied thoroughly was that of the ABO isoagglutinins,[1] and not long after the threat posed by cytotoxic antibodies was appreciated.[2,3] With either type of recipient antibody, hyperacute rejection occurred at a high rate. Observance of ABO blood group compatibility rules and avoidance of positive lymphocytotoxic cross-matches have been the most universally used immunologic criteria for selection of recipients of renal allografts.

The extent to which these guidelines apply to other organs has not been completely delineated. In past publications,[4-6] we have pointed out that the liver is resistant to hyperacute rejection from either type of antibody. However, no extensive study has been reported in recent years of high survival after liver transplantation about the effect, if any, of ABO compatibility on outcome. In addition, recent attention has been focused on a special kind of graft versus host reaction caused by antihost isoagglutinin production by liver grafts that are compatible with liver recipients but of a different ABO type.[7]

In this article we have reviewed 672 transplants in 520 patients performed between March 1, 1980, and Dec. 31, 1985, in an effort to determine if the outcome of liver transplantation is influenced by ABO conformity, compatibility, and incompatibility between donor and recipient.

MATERIAL AND METHODS

Case material. Five hundred twenty patients received 672 orthotopic liver allografts between March 1, 1980, and Dec. 31, 1985. All patients have been followed through Jan. 31, 1986 (Table I). Actuarial patient the and graft survivals were calculated by life table method.[8,9] The age range of the patients was 4 months to 67 years (mean, 25.3 ± 18.1, SD years), including 310 adults given 387 grafts and 210 children given 285 grafts. There were 520 primary grafts, 124 second grafts, and 27 third grafts.

One pediatric patient received a fourth transplant during this period. The graft was from an ABO matched donor, and to date the patient has survived with this graft. This is the only graft not included in the statistics here reported.

All patients were treated with cyclosporine and prednisone as described elsewhere.[10] Since December 1983, OKT3 monoclonal antibody (Ortho Pharmaceuticals, Raritan, N.J.) has been given for brief periods

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Table I. Adult and pediatric transplants classified by ABO match

ABO Class	*Failed (%)*	*Functioning (%)*	*Total*
Adult grafts	181 (46.8)	206 (53.2)	387
ABO Identical	142 (43.2)	187 (56.8)	329
ABO Compatible	33 (66.0)	17 (34.0)	50
ABO Incompatible	6 (75.0)	2 (25.0)	8
Pediatric grafts	139 (48.9)	145 (51.1)	284
ABO Identical	102 (46.4)	118 (53.6)	220
ABO Compatible	23 (56.1)	18 (43.9)	41
ABO Incompatible	14 (60.9)	9 (39.1)	23
Totals	320 (47.7)	351 (52.3)	671
ABO Identical	244 (44.4)	305 (55.6)	549
ABO Compatible	56 (61.5)	35 (38.5)	91
ABO Incompatible	20 (64.5)	11 (35.5)	31

Table II. First, second, and third transplants classified by ABO match

ABO Class	*Failed (%)*	*Functioning (%)*	*Total*
First grafts	222 (42.7)	298 (57.3)	520
ABO Identical	179 (40.0)	268 (60.0)	447
ABO Compatible	35 (58.3)	25 (41.7)	60
ABO Incompatible	8 (61.5)	5 (38.5)	13
Second grafts	83 (66.9)	41 (33.1)	124
ABO Identical	57 (67.9)	27 (32.1)	84
ABO Compatible	15 (62.5)	9 (37.5)	24
ABO Incompatible	11 (68.8)	5 (31.2)	16
Third grafts	15 (55.6)	12 (44.4)	27
ABO Identical	8 (44.4)	10 (55.6)	18
ABO Compatible	6 (85.7)	1 (14.3)	7
ABO Incompatible	1 (50.0)	1 (50.0)	2
Total	320 (47.7)	351 (52.3)	671

(10 to 21 days) to about 75 patients for treatment of acute cellular rejection or during periods of reduced cyclosporine coverage.[11]

Cirrhosis was the indication for liver replacement in 133 (25.6%) of the patients. This group consisted mainly of patients with chronic aggressive hepatitis or cryptogenic cirrhosis and included a small number of patients with alcoholic cirrhosis. Biliary atresia was the reason for transplantation in 107 (20.6%) patients and accounted for more than half of the transplantations performed in children. Other indications for transplantation were primary biliary cirrhosis in 89 patients (17.1%), inborn errors of metabolism in 68 (13.1%) patients, sclerosing cholangitis in 42 (8.1%) patients, and primary liver tumors in 20 (3.9%) patients. Sixty-one (11.7%) primary grafts were done for other indications, including acute hepatic necrosis, familial cholestasis, neonatal hepatitis, secondary biliary cirrhosis, and trauma.

Donor-recipient matching. Recipients were selected on the basis of medical need, estimated liver size and body weight, and ABO blood group. Histocompatibility antigen typing and lymphocytotoxic cross-matching were done retrospectively and played no role in recipient selection. We have continued to transplant preferentially between ABO identical donors and recipients except for very small children, for whom the supply of available organs is severely limited and for patients in perilous condition.

RESULTS

Patient survival. Actuarial survival for the 520 patients is presented in Fig. 1, *A* and is 69.3% at 1 year and 60.8% at 5 years. Survival for children (under 19 years old) is 70.2% at 1 year and 67.6% at 5 years compared with 68.6% at 1 year and 55.1% at 5 years for adults. There is no significant difference in the actuarial curves for children and adults (Fig. 1, *B*).

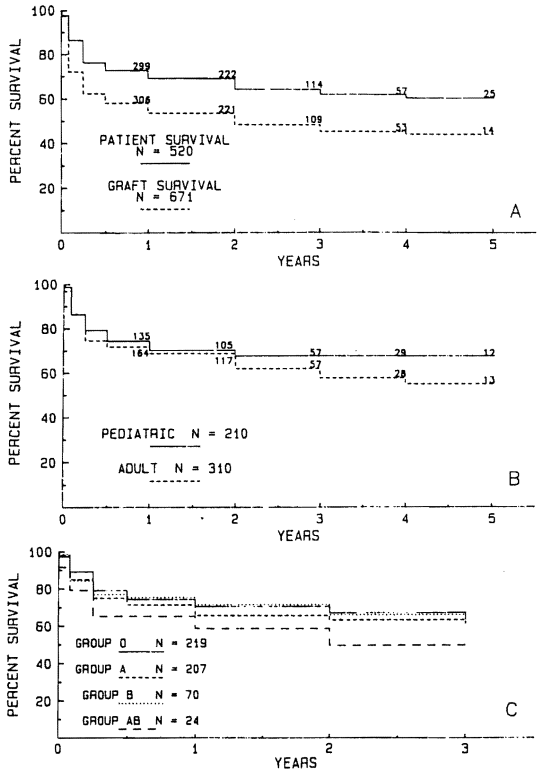

Fig. 1. A, Actuarial survival for 520 patients and 671 first, second, and third grafts. **B,** Actuarial survival of 210 pediatric and 310 adult graft recipients. Pediatric recipients were 18 years of age or under at the time of transplantation. **C,** Actuarial survival of 520 graft recipients according to recipient ABO blood type. There is no significant difference in survival among the four groups.

There is also no significant difference in patient survival based on recipient ABO blood group (Fig. 1, *C*).

Graft survival. Actuarial survival for all 671 grafts is shown in Fig. 1, *A*. One-year survival is 53.7% and 5-year survival is 44.4%.

Each transplantation was classified as an ABO identical graft (ABO identity between donor and recipient), an ABO compatible but nonidentical graft (O to any non-O, A, or B to AB), or an ABO incompatible graft (A to B, B to A, B or A to O, or AB to any non-AB). The results to date are summarized in Table I, and actuarial graft survival out to 3 years on the basis of ABO donor-recipient match is shown in Fig. 2, *A*. Beyond 3 years for compatible grafts and 2 years for incompatible grafts, the sample sizes are usually too small for valid comparisons. Survival of grafts with ABO identity is significantly better than that of compatible but nonidentical grafts ($p < 0.01$) and incompatible grafts ($p < 0.03$).

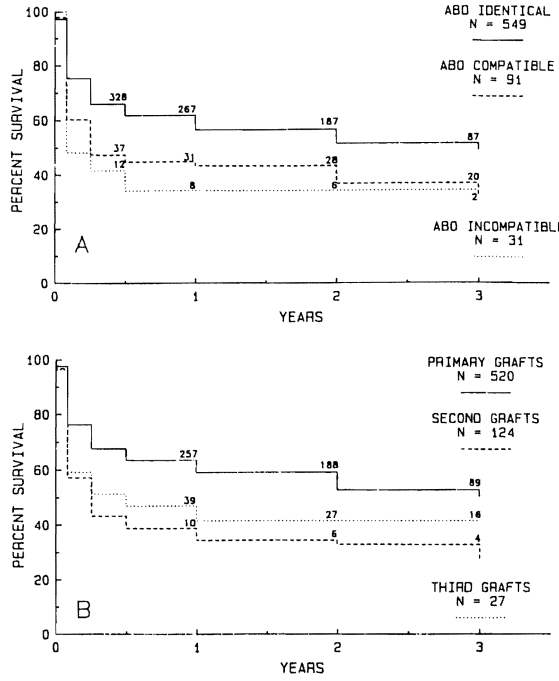

Fig. 2. A, Actuarial graft survival based on donor-recipient ABO matching. **B,** Actuarial graft survival for first, second, and third transplants. Primary graft survival is significantly better than survival for retransplanted grafts.

Graft survival is stratified for pediatric and adult patients with transplants in Table I. Three hundred fifty-one (52.3%) grafts are functioning, including 145 (51.1%) in children and 206 (53.2%) in adults. Actuarial survival for pediatric and adult patients with grafts is shown in Fig. 3. Survival for ABO identical pediatric patients with grafts (Fig. 3, *A*) is not different from that for patients with compatible but nonidentical grafts (Fig. 3, *B*). Survival of pediatric patients with ABO identical grafts (Fig. 3, *A*) is better ($p < 0.02$) than that for pediatric patients with incompatible grafts (Fig. 3, *C*) out to 2 years, but this finding should be interpreted cautiously since the sample size of incompatible grafts is small.

Actuarial survival of ABO identical grafts in adults (Fig. 3, *A*) is significantly better than for either adults with compatible but nonidentical ($p < 0.01$, Fig. 3, *B*) or incompatible grafts ($p < 0.05$, Fig. 3, *C*).

Survival of first, second, and third grafts is summarized in Table II. Fifty-seven percent of first grafts, 33% of second grafts, and 44% of third grafts have survived. Actuarial survival of primary grafts versus retransplants is shown in Fig. 2, *B*. Primary graft survival is significantly better than survival of second grafts ($p < 0.001$) and is significantly better out to 2 years ($p < 0.04$) compared with third grafts.

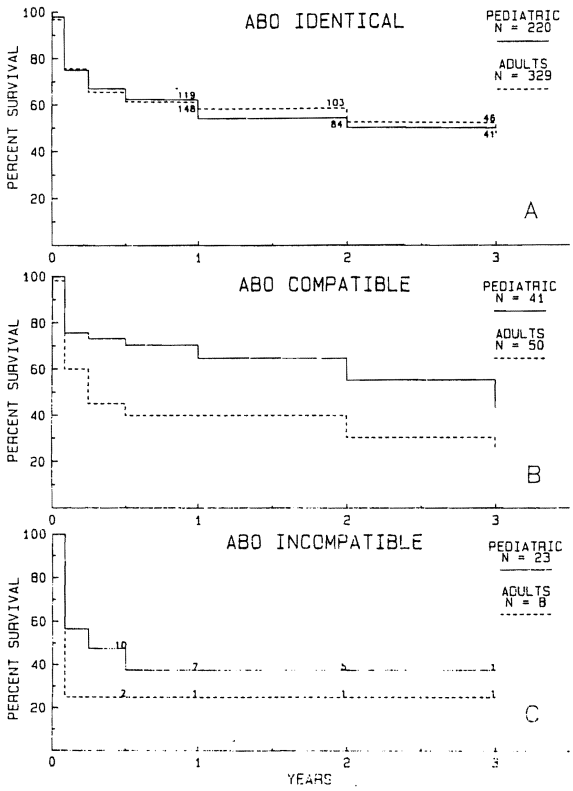

Fig. 3. Actuarial survival for pediatric and adult ABO identical *(A)*, compatible but nonidentical *(B)*, and incompatible *(C)* grafts. ABO identical grafts in adults *(A)* are significantly better than compatible *(B)* or incompatible *(C)* adult grafts.

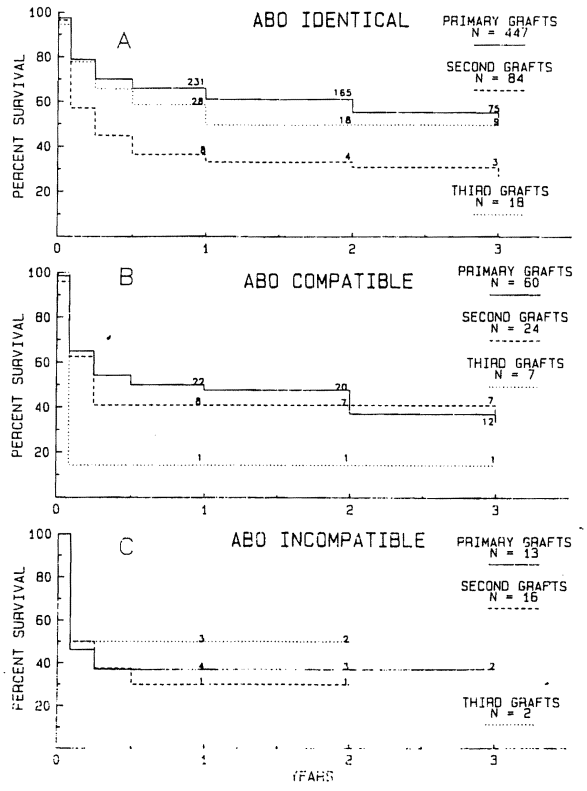

Fig. 4. Actuarial survival for first, second, and third ABO identical *(A)*, compatible *(B)*, and incompatible grafts *(C)*. Graft survival for identical primary grafts *(A)* is significantly better than survival for compatible primary grafts *(B)*.

Actuarial survival for first grafts and retransplants according to ABO matching is presented in Fig. 4. Primary ABO identical grafts (Fig. 4, *A*) have survived significantly better than ABO compatible but nonidentical grafts ($p < 0.01$, Fig. 4, *B*). The better results with primary ABO identical grafts versus ABO incompatible grafts (Fig. 4, *C*) approaches statistical significance ($p < 0.10$) but is limited by small sample size.

The factor of clinical need. An urgent factor existed in the vast majority of recipients given other than ABO identical grafts. Of the 31 incompatible livers, 18 were used for retransplantation (Table III). Most of the other three livers were transplanted to patients whose needs were also great. Only two of the adults and 11 of the children received an ABO incompatible transplant under elective conditions. The scarcity of small donors was the reason for the more frequent acceptance of mismatched pediatric organs.

The urgency factor and the use of incompatible organs in tiny recipients made discriminating assessment difficult of the role of ABO matching, particularly since the difficulties in controlling rejection were so variable. Fig. 5 presents the postoperative course after a primary B to A liver transplant in a 9 kg, 2-year old boy with α_1-antitrypsin deficiency. The liver functioned well starting on the day of surgery, and the patient was discharged from the hospital 23 days later after an uneventful recovery. He continues to do well 17 months after transplantation.

The other end of the spectrum is shown in Fig. 6. A desperately ill 5-year-old girl with blood type B with biliary atresia was given the liver of a blood type A donor. After surgery moderate rise increases in transaminase levels were typical of moderate but reversible ischemic injury. However, the bilirubin level rose quickly during the first week and remained elevated. An arteriogram obtained 5 days after transplantation showed patent vessels. High-dose prednisone resulted only in transient improvement. Repeat angiography on day 15 showed severe "pruning" of arteries in the liver characteristic of severe rejection. Transaminase levels rose sharply between days 18 and 21. A biopsy specimen obtained at this point showed only massive hepatic necrosis. Death occurred on day 27.

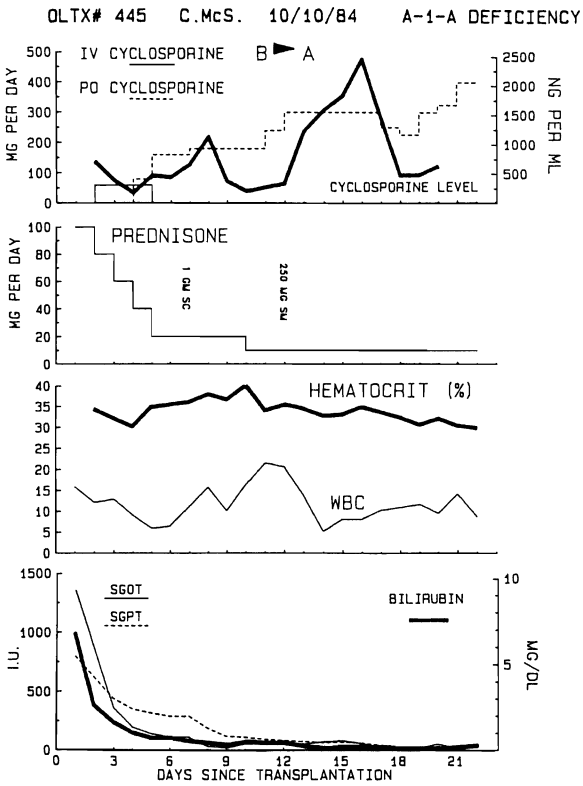

Fig. 5. Clinical course after transplantation of a primary type-B liver graft to a type-A 2-year-old child with α_1-antitrypsin deficiency, which demonstrates uneventful recovery after ABO incompatible transplantation. (*IV,* intravenous; *PO,* by mouth; *WBC,* white blood count; *SGOT,* serum glutamic-oxaloacetic transaminase; *SGPT,* serum glutamic-pyruvic transaminase.)

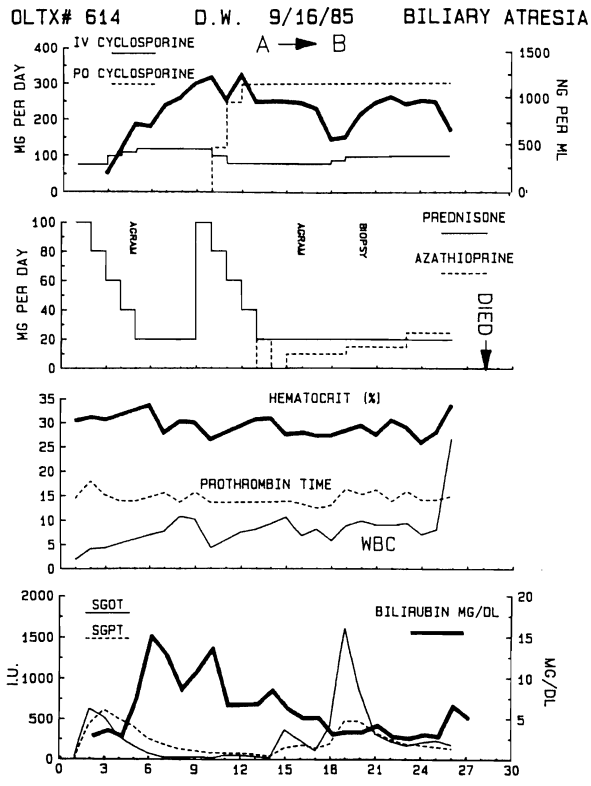

Fig. 6. Clinical course after transplantation of a primary type-A liver to a type-B 5-year-old child with biliary atresia, which demonstrates progressive graft failure and death 27 days after transplantation of an ABO incompatible graft. (*IV,* intravenous; *PO,* by mouth; *WBC,* white blood count; *SGOT,* serum glutamic-oxaloacetic transaminase; *SGPT,* serum glutamic-pyruvic transaminase.)

Table III. Outcome according to urgency of transplantation of ABO incompatible grafts

	Failed graft	*Functioning graft*	*Patient alive*	*Patient dead*
Adults	6	2	2	6
Elective	0	1	1	0
Urgent	6	1	1	6
Children	13	10	12	11
Elective	6	5	6	5
Urgent	7	5	6	6

Double immunologic jeopardy. In both of the foregoing cases there was double jeopardy from immunologic factors. The grafts, which were confronted with preformed antigraft isoagglutinins, were capable in turn of producing isoagglutinins that could lyse recipient red blood cells.[7] Such bidirectional immunologic risk can occur with A to B or B to A transplants. These risks were accepted in 14 patients, including six of the retransplantations. In eight patients, the results were good, and in the other six the grafts failed or the patients died soon after transplantation. Obvious hemolysis was not diagnosed in any of the patients.

DISCUSSION

The hyperacute rejection of renal allografts in patients who receive kidneys from incompatible donors

with ABO blood group has been well described.[1,12] Such grafts do not sustain an effective renal blood flow, and angiography reveals that the small vessels of the excised kidneys are closed. Histopathologically the arterioles and capillaries are plugged with formed blood elements, particularly erythrocytes and platelets.

The blood group substances that allow red cells to be typed are found in other tissues, including the kidney and liver,[13,14] and these tissues will bind naturally occurring anti-A or anti-B isoagglutinins if transplanted into an ABO incompatible recipient.[1] However, hyperacute rejection of kidneys does not automatically follow, and some of the longest surviving kidney grafts in the world have been across ABO blood groups, including one of our A-type patients treated more than 23 years ago who still has perfect function of his B-type kidney. The expected incidence of hyperacute rejection of incompatible kidneys is not known. Recently Alexandre et al.[15] have shown that removal of ABO isoagglutinins by plasmapheresis and drug pretreatment can permit the reliable transplantation of kidneys across ABO barriers. The studies of Rapaport et al.[16] showing that the ABO system is a histocompatibility determinant have suggested possible increased late hazard even for grafts that survive early, but this conjecture has not been proved.

The liver has been regarded as a privileged organ able to be transplanted across ABO barriers without suffering hyperacute rejection[4-6] from antigraft antibodies. With livers a different kind of complication has occurred in patients after transplantation from compatible donors of different ABO types. Examples are O to A, B, or AB; A to AB; or B to AB. In such cases the production by the graft of anti-A or anti-B antibodies directed against the host has caused hemolytic anemia 12 to 21 days after transplantation.[7] The hemolytic anemia is usually self-limited and mild. However, no serious examination has been reported of the influence on the results of the transplanting of ABO compatible but nonidentical livers.

In this article the possible disadvantages of ABO nonconformity have been examined in a large series of consecutive orthotopic liver transplantations under cyclosporine and prednisone immunosuppression. The data have shown a significant advantage for ABO identical grafts, especially for primary grafts and grafts used in adults. Thus our policy will continue to be to search for ABO identity in our donor-recipient pairing.

However, the success rate with transplantation from ABO nonidentical or even incompatible donors has been substantial. Patients needing retransplantation are more likely to receive a graft under urgent circumstances in which whatever the penalties may be of an ABO mismatch or ABO incompatibility, these may be less than the alternatives of graft sepsis, coagulopathy, depression of the central nervous system, and metabolic derangements.

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DISCUSSION

Dr. Rupins (Irvine, Calif.). This is fascinating work. I was a little concerned in terms of how you viewed your data on your graphs. It seemed to me that most of the losses you have in your transplant group occurred within the first 6 months, about 90% I would say. It also seems that the ABO groups demonstrate a clear advantage in the matching, as you pointed out. Thus it would seem that ABO is very important in 6-month survival of the graft, and I wondered if you analyzed your data at 6 months and is that significant?

Dr. Nancy Ascher (Minneapolis, Minn.). It is incredible the amount of data that you have analyzed. However, I have several questions. Have you been measuring antibody levels in the patients who are going to receive ABO incompatible or mismatched grafts? The group from Belgium who have used ABO incompatible kidney grafts suggest plasmaphoresis or the use of ALG. They advocate the measurement of the antibody level so that you can monitor the titers and determine when plasmaphoresis is necessary. We have performed four grafts across ABO incompatibilities, all As to Os, without any untoward event. We have also followed their advice of performing splenectomy at the time of transplant. A second question is whether you analyzed the A to O groups or the A subtypes? As you know, individuals with A-type blood can now be divided into two groups; 80% of the individuals are A-1 and 20% are A-2. Individuals who are A-2 will not elicit any antibody response in O recipients; thus that is another factor that has to be evaluated. Finally, do you have a matched group of individuals who received ABO mismatched livers and individuals who received matched livers, according to severity of disease? I am troubled by the poor results in the individuals in whom you are hard pressed to find a liver, forcing you to cross blood group barriers.

Dr. Gordon (closing). Dr. Rupins, the life table survival curves were analyzed with the log rank χ^2 method. We also calculated z scores for each interval of observation. As you might expect, the sample sizes available at 6 months are large for most populations studied and therefore the differences observed are highly significant at the 6-month interval.

Dr. Ascher, the use of plasmapheresis to remove preformed anti-ABO blood group antibody has special relevance for kidney transplantation, since it might permit transplantation across ABO barriers in a situation that is otherwise usually prohibitive. However, we know that the ABO blood groups are not prohibitive in most circumstances for liver transplantation. We have not measured levels of preformed antibody before transplantation, but I agree that it would be worthwhile to correlate such measurements with outcome.

The poorer results we see with patients for whom ABO blood groups are crossed because of urgent need probably reflect medical circumstances and patient selection rather than a pronounced effect of ABO immunity. Nonetheless, we cannot be certain of this in every case and further study is needed. The difficulty, of course, is that liver transplantation occurs in such a complex setting that analysis is often difficult.

The A-2 subtype is a small percentage of patients, and even in a series of liver transplantations as large as this one, when we begin to subdivide at the level of ABO subtypes, the sample sizes get too small for meaningful analysis. We will require a larger study to address this interesting question.