sented by both Oellerich (*7, 8*) and Gremse (*9*). Patients who died of complications of cirrhosis prior to transplantation in all 3 studies had MEG-X values below 10 ng/ml. Furthermore, MEG-X was a much better predictor of major complications than either standard tests of liver function (i.e., bilirubin, albumin, and prothrombin time) or Childs classification (Table 2 [*8*]). In the present study, 70% of patients who had not suffered any major complication of cirrhosis had MEG-X values below 30 ng/ml and 2/27 (7%) had values below 10 ng/ml. The data suggest that this latter group (MEG-X <10 ng/ml) is at the highest risk for developing future complications and mortality from cirrhosis.

The current criteria for identifying persons in need of hepatic transplantation vary considerably from center to center. While everyone would surely agree that patients with Childs class C, ascites, hypoalbuminemia, and coagulopathy should undergo transplantation as soon as possible, the criteria for patients with well-compensated Childs class A disease, no ascites, and normal albumin and prothrombin time are less clear-cut. MEG-X testing may prove to be extremely beneficial for this latter group by identifying those individuals at increased risk for developing major life-threatening complications of their liver disease. When all other tests of hepatic function are equal MEG-X could be utilized to stratify persons awaiting transplantation.

Of equal importance in the present study was the observation that no person with a MEG-X value greater than 30 ng/ml had suffered any major complication of chronic liver disease (Fig. 3). This suggests that such patients are at minimal risk for developing complications of cirrhosis and may not need to be on an active transplant waiting list unless other mitigating circumstances are present.

As long as the number of patients in need of hepatic transplantation exceeds donor supply, an appropriate method by which allocation of these scarce medical resources to those at greatest risk needs to be developed. The present studies may provide insight for the development of such a scoring system. This has the potential of improving organ allocation, reducing waiting list mortality, and improving outcome following hepatic transplantation.

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PAPER NO. V - 5 M.L. SHIFFMAN, M.D.,

RICHMOND, VIRGINIA

DISCUSSION

DR. RYCKMAN (Cincinnati, Ohio): I'd like to comment on our experience at the University of Cincinnati using MEGX to evaluate our potential recipient population. I will confine my comments to children, numbering approximately 125, who have been evaluated for transplantation.

We found this single test was the only thing that has allowed us to have a rapid and accurate way to stratify our patients. When we compared it to the previously used Malatack score, we found a very similar situation to what you found with the Childs score, that there was a direct linear relationship.

Our results confirmed your findings for MEGX of less than 10; we have not had a single potential recipient who survived over 120 days if they had a MEGX of less than 10. We think this is a very valuable, reproducible, and simple way to quantify hepatic functional reserve. As such it is a very accurate way to stratify the potential recipient population.

Are you presently stratifying your list according to their MEGX values? Do you plan such a strategy in the future? What is your recommendation for serial MEGX testing of patients who are in that indeterminate group on your list? Can MEGX be used to identify candidates early who are decompensating?

DR. SHIFFMAN: We currently perform MEGX testing in all candidates evaluated for liver transplantation. We repeat MEGX testing at bimonthly intervals thereafter as they await their procedure.

Individuals that have had initial MEGX tests above 30 ng/ml who then fall below this value have gone on to develop complications. We now routinely stratify patients on the waiting list based upon their MEGX values; we constantly rearrange the waiting list based upon our overall clinical assessment which includes the MEGX value. We feel MEGX is a very useful test for measuring hepatic reserve in individuals awaiting liver transplantation.

DR. POLLAK (Chicago, Illinois): Could you tell us what the positive predictive value is of a single test?

DR. SHIFFMAN: We occasionally see fluctuation. We're currently attempting to investigate the possibility of specific drug interactions as a cause for altered results. Although MEGX values are usually highly reproducible, we try to have more than a single value when possible. Once values fall below 30 ng/ml, they rarely rise in the future.

DR. SHEINER (Toronto, Canada): Have you looked at MEGX in fulminant hepatic failure, possibly as a predictor to recovery vs. who will need a transplant?

DR. SHIFFMAN: Yes, we don't feel it is a very good predictor at all. MEGX values in the setting of fulminant hepatic failure fall precipitously to very low levels; they then are late to recover. We have found Factor 7 values are much better predictors of recovery from fulminant hepatic failure. In fact, we've had people ready for discharge from the hospital after fulminant hepatic failure with MEGX values remaining around 15 ng/ml.

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TRANSPLANTATION

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IMPROVED RESULTS OF LIVING-RELATED LIVER TRANSPLANTATION WITH ROUTINE APPLICATION IN A PEDIATRIC PROGRAM[1]

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Living related liver transplantation (LRT) was introduced as a response to the shortage of donor organs that has existed for small children. Results were promising in the initial experience, with a one-year patient survival of 80% and a graft survival of 75%. Since the completion of the protocol, LRT has been considered routinely in the management of children in our center. We present here our experience with 45 consecutive transplants in which LRT accounts for 40% of grafts with an overall patient survival of 90%.

Between 4/91 and 4/92, 45 OLT were performed in 41 children. Median age was 2.7 years (3 months to 13 years) and weight was 10.4 kg (3.5–60 kg). Thirty-five were primary grafts, 10 were retransplants. One patient received 2 grafts in the orthotopic auxiliary position. Cholestatic disorders including biliary atresia accounted for 60%, metabolic diseases for 15%. Grafts were obtained from cadaver donors in 27/45 (60%) cases; reduction was required in 12/27 (44%). LRT was performed in 18 cases. Fifty-two percent of recipients of cadaver grafts were UNOS status 4, while 16% of LRT recipients met these criteria.

Actual patient survival for cadaver grafts is 21/24 (88%) and graft survival is 20/27 (74%). Patient survival in 18 LRT was 94%. Two grafts were lost to arterial thrombosis for a graft survival of 83%. All donors have been discharged and are well. One patient, a teenager with fulminant hepatitis, was successfully transplanted with a left lobe from his father.

This experience demonstrates the programmatic flexibility accorded by use of LRT. Since 40% of grafts were LRT, more livers were available for urgent use for patients who did not have a donor available, as reflected in the 73% incidence of cadaver recipients on status 3 or 4. Therefore, patients are more likely to receive a transplant at the optimal time. We are now prepared to offer LRT for fulminant hepatic failure since the benefit of graft availability appears to outweigh concerns about coerced donation. The successful treatment of a teenaged patient may herald extension of LRT to adults. We conclude that the use of LRT should be expanded.

Reduced-size liver transplantation (RLT)* was developed as a response to the shortage of pediatric donors (*1*). This technique, in which a cadaver liver is reduced by ex vivo hepatectomy has been used in many centers to transplant small children with livers from older donors. In the last five years, widespread use of RLT has lead to a marked diminution of waiting list mortality in children by overcoming the shortage of small donor organs (*2–6*). Despite RLT, which has addressed

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* Abbreviations: LRT, living-related transplantation; RLT, reduced-size liver transplantation.

the maldistribution of donors with respect to size, an absolute shortage of donor organs exists (7). Surgical measures to increase the number of donor organs include split liver transplantation, in which a single donor liver is divided to treat two patients (8) and partial hepatectomy for living-related liver transplantation (LRT) (9, 10).

Initially reported by Raia in Brazil (11), and Strong in Australia (12), LRT has been evaluated in two series, by Broelsch et al. from this center (9) and Tanaka from Kyoto University (10). Several other centers have performed individual LRT in Europe and Japan.

Despite these reports suggesting that LRT can be accomplished with results similar to those of cadaver grafting, the eventual impact of LRT is uncertain. Most liver transplant centers have delayed the initiation of programs in LRT because of concerns about donor risk. Continued increases in the number of candidates for liver transplantation are swelling the waiting lists of most programs (UNOS data) and resulting in increasing mortality prior to transplantation. If LRT is to increase access to liver transplantation, expansion of its use to other centers—and, eventually, for the treatment of adults—will be necessary. We suggest that LRT may possible in 20% of liver recipients, a proportion similar to that in renal transplantation.

Since our initial report of 20 cases of LRT performed in the context of an experimental protocol (9), we have offered LRT as an option routinely in the care of children needing OLT. The present report details our experience with 45 transplants in children performed over 12 months following the completion of the series cited above (9) with LRT accounting for 40% grafts. Overall patient survival in this series was 90%, with a survival of LRT patients of 94%. We propose that LRT enhances access and efficacy of OLT in children and recommend expansion of its use.

MATERIALS AND METHODS

Patient population. The patient population is described in Table 1. Forty-five consecutive OLT performed in 41 children 13 years and under, between April 1991 and April 1992, were included in this study. Six of 10 retransplants in this series were performed for chronic rejection in patients who received their initial grafts 6 months to five years earlier. These six patients were included in the denominator for survival calculations. The 4 other retransplants were done within six weeks for arterial thrombosis (n=3) or graft failure due to uncontrolled acute rejection (n=1). The overall distribution of diagnoses is typical of liver transplantation in children, with cholestatic disorders being the most common indications. Patients receiving LRT had the highest proportion of elective primary grafts and biliary atresia, and metabolic diseases were the predominant indications. The median age and weight of recipients were 2.7 years and 10.5 kg. Patients receiving LRT tended to be smaller and younger than those receiving full-size grafts.

Table 2 presents the waiting times for cadaver grafts and transplant status of children in this series. Of patients receiving LRT, 60% were elective (UNOS status 1 or 2) while only 16% were critically ill. In contrast, for patients receiving cadaver grafts, the majority were hospitalized (18%) or critically ill (55%). Mean waiting times varied from 172 days for patients initially listed as status 1 to 9 days for those initially listed at status 4. Moreover, most patients experienced medical deterioration while on the waiting list, with all status 1 patients, 33% of status 2 patients, and 66% of status 3 patients needing to be upgraded to a more urgent category before receiving a graft. During the period of this study, no child died without receiving a graft.

Medical and surgical procedures. Patient selection, medical management and surgical techniques have been described in previous reports (9, 13, 14). Postoperative care of patients receiving LRT was according to standard protocols in our institution. Baseline immunosuppression with cyclosporine, azathioprine and steroids was used in all primary grafts. Rejection episodes were treated with bolus therapy of methylprednisolone; OKT3 was used in cases of steroid resistance or bacterial infection. FK506 was used as rescue therapy for patients not responding to the above regimen.

The donor operation involved excision of segments 2 and 3 in all cases but one teenaged recipient, in which the entire left lobe of the donor was used. All grafts were implanted orthotopically following recipient hepatectomy, except in one patient who received orthotopic auxiliary replacement of the left lobe of her liver for correction of a metabolic defect. For arterialization of grafts, extension of the hepatic artery with the saphenous vein (in LRT) or iliac artery was used with implantation on the infrarenal aorta in all cases.

Patient selection. All families were informed of the possibility of LRT in the initial interview at the time of evaluation of the recipient for transplantation. Most who chose LRT were aware of this option, and chose our center because of a desire to participate. Donors underwent stepwise evaluation as described elsewhere (9, 14) prior to enrollment in the program. While patients with fulminant hepatic failure (FHF) were not considered for LRT initially, we accepted this indication after June 1992. Families who did not participate in LRT did so for the following reasons: medically unsuitable or unmatched by blood type n=10 (37%), inadequate social or cultural support n=8 (29%), no interest n=8 (29%), FHF n=1 (4%).

Live donors were used in 18 of 45 transplants (Table 3). All donors were parents, except in two cases in which an uncle and an aunt desired to be donors. The medical workup included a careful evaluation by a physician unrelated to the team caring for the recipient. Donors without a history of medical or surgical illness were chosen, with normal serum hematologic and chemistry tests and negative serology for viral hepatitis. Volumetric CT scanning was used to ascertain liver size and arteriography was used to evaluate the adequacy of the left hepatic artery for grafting.

TABLE 1. Characteristics of recipients of liver grafts (n=15)

	Graft type		
	Full (n=15)	RLT (n=12)	LRT (n=18)
Diagnosis			
Cholestatic	7	5	11
Retransplant	4	4	2
Cirrhosis	2	1	
FHF	1	1	1
Metabolic	1	1	4
Age (years) $\bar{x}$ (Range)	3.8 (0.2–12.8)	4.7 (0.3–12)	2.7 (0.2–13.3)
Weight (kg) $\bar{x}$ (Range)	15.1 (4.4–40)	15.5 (3.5–40)	10.4 (4–45)

TABLE 2. Analysis of the cadaver waiting list for children in our center (April 1991–April 1992); A. Waiting time as a function of initial listing status; B. Clinical status at the time of transplantation

UNOS status[a]	Waiting time (days)	% Changed
1	172 (93–201)	100%
2	94 (16–193)	33%
3	18 (2–66)	66%
4	9 (1–14)	

Status	Cadaver	LRT
1		16%
2	27%	44%
3	18%	22%
4	55%	16%

[a] UNOS listing categories: status 1 = stable, at home; status 2 = requiring continuous outpatient care; status 3 = in hospital; status 4 = in ICU.

RESULTS

Status of donors of LRT (Table 3). All donors survived the operation and were discharged from the hospital with a median hospital stay of six days. All donors are clinically well and all but one were back to normal activities between 2 and 8 weeks after surgery. Three surgical complications were observed. One patient experienced sensory loss in the median nerve distribution due to positioning during surgery, resulting in the longest disability. This injury has resolved with return to work 5 months following surgery. In another patient an injury to the anterior wall of the bile duct was repeated intraoperatively without sequel. A third patient experienced a wound infection that prolonged her hospital stay to 11 days. None of the donors required blood transfusions.

Graft type and outcomes. Overall, 45 OLT were performed in 41 children during this period. Eighteen were LRT, 12 RLT (7 grafts were full left lobes (segments 2, 3, 4), while 5 were left lateral segments (segments 2, 3), and 15 full-sized grafts. Overall, 37 of 41 patients are alive between 3 and 15 months after OLT (90%). Overall graft survival is 35/45 (78%). Table 4 demonstrates comparative results for patient and graft survival broken down by graft type. Patient and graft survival was highest for LRT (94%), with two patients surviving with retransplants. Causes of patient death and graft failure broken down by graft type are presented in Table 5. A single graft in the series was lost to uncontrolled rejection leading to graft failure in an infant who received a transplant from his mother. Four cases of arterial thrombosis occurred in the series (9%), 2 in full-sized grafts and 2 in LRT. Three of 4 were retransplanted successfully; the fourth who was neurologically damaged after the initial transplant died of sepsis without regrafting. Fatal infections occurred in 3 patients (7%). One case of lymphoproliferative disease resulted in the patient's death. Postoperative cerebral death occurred in one patient with FHF who waited 8 days on status 4 prior to obtaining a liver.

Two complex cases representing technical variants mentioned above will be described in brief. In the first case, in a 12-year-old girl with Crigler-Najjar syndrome and otherwise normal liver function, left hepatectomy was performed with implantation of a graft comprising segments 2 and 3 of her father's liver. Despite successful grafting and resolution of her cholestasis, arterial thrombosis resulted in biliary necrosis and graft infection. The graft was removed, and after resolution of the infection a segment 2 and 3 graft from a cadaver liver was transplanted in the left hepatic fossa 3 weeks later. She remains well 9 months after retransplantation. This case demonstrates successful use of the auxiliary position for grafts originating from LRT or cadaver donors.

A second patient, a 13-year-old boy, weighing 48 kg had fulminant hepatic failure. As a donor was not immediately available, and the family was agreeable to living-related transplantation, an urgent LRT was performed using the entire left lobe of his father's liver. Postoperative surgical recovery was entirely uneventful, with the exception of a period of cholestasis with discharge on day 16. Selection of the graft size was based on an estimate that a graft volume of approximately 50% of expected liver mass would be adequate. The left lobe of the father's liver measured 650 g by volumetric CT scanning and was the basis for proceeding with the operation despite the large size of the recipient.

A comparison of postoperative complications by graft type is presented in Table 6. As discussed above, arterial thrombosis occurred in 4 cases. Portal vein thrombosis was diagnosed in one patient eight months following LRT and has been managed expectantly with diuretic therapy. Portal vein thrombosis occurred in two RLT, both of which were successfully revised early after surgery. One of these was in the auxiliary retransplant described above in which the portal vein of the native

TABLE 3. Demographic description and operative complications of live donors (n=18)

	Number
Demographic data:	
Relationship	
Fathers	7
Mothers	9
Uncle	1
Aunt	1
Age (years), $\bar{X}$ (range)	34 (21–45)
Weight (kg), $\bar{X}$ (range)	65 (49–18)
Operative data:	
Complications (n=3):	
Brachial plexus injury from positioning	
Intra-operative bile duct injury	
Wound infection	
Median blood replacement[a]	200 ml (0–600)
Median hospital stay	6 days (4–16)

TABLE 4. Outcomes of 45 pediatric transplants

	Graft type		
	Full (n=15)	RLT (n=12)	LRT (n=18)
Survival:			
Patient	12/14 (86%)	9/10 (90%)	16/17 (94%)
Graft	11/15 (73%)	9/12 (75)	15/18 (84%)
Retransplantation	1/15 (7%)	0	3/18 (16%)
Mean follow-up (months)	10.7	9.3	8.9

TABLE 5. Causes of graft loss/patient death in 45 pediatric transplants

	Graft type		
	Full (n=15)	RLT (n=12)	LRT (n=18)
Rejection	0	0	1 (5%)
Arterial thrombosis	2 (13%)	0	2 (11%)
Fatal infection	1 (5%)	2 (9%)	0
Lymphoproliferative disease	0	1 (9%)	0
Cerebral death	1 (5%)	0	0

TABLE 6. Postoperative complications in pediatric transplants (n=45)

	Graft type			
	Full (n=15)	LRT (n=12)	CADAVER (n=27)	LRT (n=18)
Vascular:				
Arterial	2 (13%)	0	2 (7%)	2 (11%)
Portal	0	2 (16%)	2 (7%)	1 (6%)
Biliary	0	0	0	3 (16%)
Intestinal	0	0	0	3 (16%)
Infectious	3 (20%)	6 (50%)	9 (33%)	2 (11%)
Neurologic	1 (7%)	0	1 (4%)	1 (6%)

liver was not adequately ligated, resulting in a steal from the graft. This was corrected operatively. Biliary leaks occurred in all 4 patients with arterial thrombosis and were not tabulated as separated complications. Three other grafts sustained biliary complications; two leaks occurred in LRT that were revised successfully over stents, and one additional stricture was repaired eight months after transplantation. Intestinal complications occurred in 2 patients with LRT who required suturing of small perforations that resolved without further incident. A third, with extensive adhesions following a Kasai operation, developed extensive interloop abscesses that required surgical drainage. No intestinal complications occurred in patients receiving RLT or full-size grafts in the present series. Infections were seen in all groups and were most frequent in the reduced-size liver transplants, but they were most severe as the consequence of a failed primary graft. Severe neurologic complications occurred in 3 patients who waited at least 5 days on status 4 in hepatic coma. The first sustained severe neurologic damage, as described above, and was not regrafted, despite arterial thrombosis. The second, a four-year-old child with fulminant hepatic failure who waited eight days prior to identification of a cadaver graft was neurologically dead following the procedure. A third patient who received LRT was grafted urgently after waiting 5 days on status 4 in coma and had transient neurologic deficits due to brain edema, which resolved completely over a period of three weeks.

Table 7 presents a comparison between cadaver grafts and LRT with respect to immunologic complications. Of patients receiving LRT, 61% required at least one course of steroid therapy, in contrast to 52% of those receiving cadaver grafts. Resistant rejection requiring rescue therapy was more common in patients receiving LRT, with three patients going on to FK506 maintenance therapy. A single case of graft loss due to rejection occurred in the LRT group, and none in the cadaver transplant group. Two cases of lymphoproliferative disease occurred three and seven months after transplantation. The first patient required retransplantation due to unresolved hepatitis 6 weeks after the initial transplant. After retransplantation she developed rapidly progressive fatal, EBV-associated lymphoproliferative disease. The second, a child with LRT who had never been treated for rejection had extensive cervical and mediastinal adenopathy due to EBV-associated lymphoproliferative disease. She has responded promptly to alpha interferon with complete resolution of clinical disease and is currently well, although follow-up is only of 3 months duration.

TABLE 7. Immunologic complications in 45 pediatric transplants

Observation	Graft type	
Rejection (steroid therapy)	14 (52%)	11 (61%)
Resistant rejection	4 (15%)	5 (27%)
OKT3	4 (15%)	4 (22%)
FK506	1 (4%)	3 (17%)
Graft loss	0	1 (6%)
Lymphoproliferative disease	1 (4%)	1 (6%)

DISCUSSION

The results presented in this series demonstrate that LRT can be used successfully as an alternative graft source in pediatric liver transplantation with high patient and graft survival. In this series, patient survival was 94% and graft survival 83%. The most important impact of LRT is on donor availability, which was strikingly documented by the contrast with the waiting times and listing status for children awaiting cadaver grafts during this period. In this series, only 27% of cadaver liver transplants were performed on patients who were outpatients at the time of transplantation, and over 50% of recipients required intensive care at the time of grafting (Table 2). The majority of these urgent indications were due to deterioration of patients previously listed. There was a marked contrast between the initial medical condition of the patients at the time of inscription on the waiting list and their status at transplantation. All patients who were medically well at the time of initial listing (status 1) and 33% of those requiring outpatient care required listing to add a higher status prior to obtaining a liver. Two-thirds of patients requiring hospital care prior to transplantation (status 3) experienced complications and required transfer to intensive care prior to obtaining a graft. In contrast, the majority of LRT were performed on medically stable patients. Nonetheless, LRT can be made available urgently and was performed successfully in 3 cases.

In contrast to our initial report (*9*) and expectations that LRT would confer immunologic advantages, rejection was more common in LRT than cadaver grafts. Furthermore, resistant rejection requiring rescue therapy, with either OKT3 or FK506, occurred nearly twice as frequently after LRT (27% vs. 15% [Table 7]). One of 18 LRT (6%) and none of the cadaver grafts were lost due to rejection. All LRT in this series were blood group–compatible with negative T cell crossmatch. While it is premature to draw strong conclusions from this small series, these observations suggest that immunologic advantage is probably not an adequate basis for arguing the need for LRT, but rather the availability of grafting and the high quality of transplants. It is clear from these results that more detailed studies will be needed to clarify the immunologic risk of LRT—and, eventually, for the design of pretreatment strategies.

While survival was highest in patients receiving LRT, it is likely that this advantage is due to the generally good condition of patients in that group. When the overall complication rates are compared between LRT and cadaver grafts (Table 6), overall complications are seen to be more frequent and retransplants more common in LRT. Because the patients were grafted electively, however, surgical complications and graft failure were more readily overcome, resulting in a higher patient survival rate. In particular, infectious complications and fatal infections were less common in LRT.

The most serious area of concern regarding LRT is the safety of the donor operation. In the current series, in all but one case the donor operation was limited to resection of segments 2 and 3. Furthermore, the dissection of the vascular pedicles has been moved far to the left so that the left bile duct is divided at the base of the round ligament. The occurrence of a bile duct injury in this current series emphasized the need to move the biliary dissection as far to the left as possible and the need for operative cholangiography to ascertain the position of the biliary confluence. The current technique preserves the gall bladder and avoids any dissection in the hilum, with liberation of the left portal vein very far to the left, just anterior to the caudate lobe. Ideally, the point of transection of the left hepatic duct can be distal to the insertion of the segment 4 duct, thereby preserving the biliary drainage of segment 4 and still leaving a common channel draining the ducts of segments 2 and 3, permitting a single anastomosis in most cases. The creation of two separate anastomoses for the ducts to segments 2 and 3 was only needed

in 3 cases (16%). Bleeding complications have not occurred in this current series, and none of the donors have required transfusions with banked blood.

In recipients, the extremely high rate of arterial thrombosis (30%) reported in the initial series of LRT (*9*) has been diminished by several modifications in technique. The first is the systematic use of magnification, which was not utilized previously. Additionally, strict adherence to the use of the aorta as the arterial source has been associated with a lower thrombosis rate in our experience (*15*). The arterial thrombosis rate was 9% overall and 11% for LRT. While this is substantially improved, it remains the most important cause of graft loss in LRT in our hands. Using microsurgical techniques for anastomosis at high magnification, the Kyoto University group has reported eliminations of arterial thrombosis in a series of LRT (*10*), so this may eventually be adopted as the ideal method of arterial reconstruction.

Results observed in this present series provide the opportunity to evaluate the impact of LRT on a transplant program. The ability to transplant patients electively at the time that is appropriate for the patient, and not that mandated by deterioration of the clinical condition, completely changes our approach to liver transplantation. The marked contrast between the status at transplantation in the cadaver group and LRT group attests to these differences. While optimal timing of liver transplantation was possible using cadaver grafts prior to 1989, the increase in the demand for liver transplantation that has occurred in the past three years has forced us to list patients earlier and has increased the proportion of livers being transplanted into decompensated recipients.

Most of the families who participated in LRT arrived at our transplant center fully aware of this procedure and, indeed, many had chosen the transplant center because of the availability of this technique. In our initial interviews with families, we informed them of the existence of LRT but took care to avoid pressing families to choose this modality. Based on our data and that of others (*2–6*), it is clear that, despite the increasing difficulty of identifying cadaver organs for children, waiting list mortality is still less than 5% for programs that use reduced-size transplants for children. In this series, 40% of grafts were obtained from live donors. LRT was not used in the majority of cases for a variety of reasons, including a lack of interest in the program, absence of adequate social support within the family, medical contraindications, or other family constraints upon this option. In one case, a cadaver liver became available electively during the period of initial evaluation of a new patient for LRT, and cadaver grafting was chosen.

During the first part of the study period we were comfortable with the use of LRT in elective liver transplantation, but were reluctant to use LRT in urgent indications. This hesitation was due to the coercive nature of the emergency transplant and its impact on the ability of the potential donor to give informed consent (*14*). In May of 1991, we were faced with a 4-year-old child in stage 4 coma due to fulminant hepatitis. Initially, we chose not to make LRT available to that family. The child was maintained for six days in the ICU without identification of a donor when we finally decided to initiate donor evaluation. Immediately prior to beginning the donor operation, a cadaver liver became available that was transplanted into that child. Despite successful grafting, the patient was brain-dead postoperatively. That experience, coupled with the good results of LRT, caused us to change our policy and we now make LRT available within 48 hr of admission in cases of acute hepatic failure. The present series includes three patients transplanted who met criteria for status 4, two of whom had hepatic coma at the time of grafting.

The use of LRT as an orthotopic auxiliary transplant was performed in a single case.The goal was the treatment of a metabolic disease in which the liver was otherwise normal, Crigler Najjar syndrome. Although graft failure occurred due to arterial thrombosis, the technique was validated in that the graft was removed without further complications and, subsequently, replaced with a reduced-size cadaver graft in the orthotopic auxiliary position. While this experience is anecdotal, it suggests that it may be possible to use LRT as an auxiliary graft in several indications. In addition to the correction of an inborn error of metabolism, auxiliary transplantation can be contemplated for the treatment of fulminant hepatic failure in which part of the native liver is left in place, with the anticipated opportunity for regeneration and eventual independence from the transplant.

The use of LRT in a pediatric program allows great flexibility in the management of transplant candidates. LRT permits the rediscovery of elective liver transplantation and provides a graft of uniformly high quality. The benefits of LRT will not be fully realized, however, unless this therapy can be made applicable in adults. While the number of pediatric liver transplant candidates is relatively fixed, more and more adults are being recognized as candidates for transplantation. A recent analysis suggested that it will not be possible to increase the cadaver donor supply to meet the growing demand for liver transplantation (*7*). The successful grafting of a 13-year-old child with a liver from his father, as well as reports of successful teenage and small adult recipients in the series from Kyoto (*10*), provide evidence that it will be possible to graft adults using LRT. The minimum graft volume required for successful liver transplantation is not known. It is clear that hepatic resections of up to 80% of parenchyma result in successful regeneration. However, these usually involve the removal of large tumors and do not necessarily represent the removal of 80% of functional parenchyma. We arbitrarily chose 50% of predicted hepatic mass as a minimum graft volume to provide adequate functional reserve in case of graft dysfunction. To achieve a graft of this size, it is necessary to have a large donor and a small recipient, or else to increase the extent of resection in the donor, which we are reluctant to do. The third alternative, which may be the ideal solution, would be auxiliary grafting, taking advantage of the regenerative capacity of the liver in order to minimize the donor operation and yet safely transplanting the recipient with a small liver.

For LRT to have a meaningful impact in the treatment of patients with liver disease, its use must be expanded. Development of the techniques to perform this operation in adults and expansion of this capability to other liver transplant centers will be the prerequisites for this to occur.

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PAPER NO. D-5 BY JEAN C. EMOND, M.D.
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DISCUSSION

DR. MAKOWKA (Los Angeles, California): When retransplantation is required, do you use a cut-down liver or a whole liver?

DR. EMOND: Two of the living-related grafts were retransplants, one for chronic rejection and one for arterial thrombosis of a primary graft. We have not made a point of choosing the graft type based on the need for retransplantation. One exception is that we have been reluctant to use a reduced-size graft in an infected abdomen, for example, in arterial thrombosis complicated with infection. We have been concerned that the cut section may be more vulnerable to bacterial colonization.

DR. MAKOWKA: Have you approached a second parent yet for a retransplant; have they approached you?

DR. EMOND: As a matter of fact, that was done in two cases from Dr. Broelsch's initial series. I believe this poses some very troubling ethical issues. The parents frequently come forward when the primary graft is failing. We must take care to maintain a mechanism to protect the potential donor. An outside physician should serve as the donor's advocate. We must not place the recipient's needs ahead of the donor's safety.

DR. OTTE (Brussels, Belgium): I would like to ask you three questions. First, do you always reconstruct from the aorta? Do you use venous or arterial grafts?

Second, what was the fate of the auxiliary graft; do you believe there is a requirement regarding the venous sharing between the two grafts?

Third, if you apply the concept to an adult recipient, what would be the minimal weight ratio between donor and recipient? Do you believe we should apply the same policy in settings of fulminant liver failure?..... in elective patients?

DR. EMOND: Donor saphenous vein has been used for arterial grafting. The competition between the auxiliary graft and the native liver has been discussed by Dr. Starzl and others since the 1960's. I don't know a proper way to quantitate it, but some effort should be made to favor the blood going into the graft since it will always be disadvantaged immunologically with increased portal resistance. The groups that have more experience with auxiliary grafts in Europe have pointed out the need to compromise the portal vein of the native liver. We have done so with a subtotal ligature of the native right portal vein.

The issue of graft in the adult recipient is extremely difficult to evaluate. We know that right trisegmentectomy can be performed safely, but most people with large tumors have had some degree of hypertrophy of the healthy liver on the left. My estimate is that 50 percent of expected liver mass in the recipient would be a safe minimum in planning the donor-recipient combination. Finally, it may be possible to avoid the problem of donor-recipient sizing by the use of the living donor grafts as auxiliary grafts.

In fulminant hepatic failure, it remains unclear, except for a few anecdotal case reports, whether the diseased liver must be excised. But, I suspect that a relatively small amount of liver mass would be adequate to get the patient through the acute period of fulminant liver failure.

DR. ILDSTAD (Pittsburgh, Pennsylvania): Did you observe any growth of the transplanted liver in your teenage recipients?

DR. EMOND: Yes. We had the occasion to evaluate one patient because of fever after 14 days. CT scan demonstrated that the liver had doubled in size. Although, I suspect some of the increased size was because of edema, the complete regenerative process should require 8 to 12 weeks. Regardless, the liver seems to grow very fast. The Pittsburgh group has reported a number of cases both with experimental animals and clinically demonstrating rapid growth of small livers after transplantation.

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TRANSPLANTATION

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REDUCTION BY COMBINATION PROPHYLACTIC THERAPY WITH CMV HYPERIMMUNE GLOBULIN AND ACYCLOVIR OF THE RISK OF PRIMARY CMV DISEASE IN RENAL TRANSPLANT RECIPIENTS[1]

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CMV-seronegative recipients of kidneys from CMV-seropositive donors (D^+/R^+) are at highest risk for developing clinical CMV disease. Even with routine prophylactic use of low-dose acyclovir we had a CMV disease incidence of 26% (5/19) in these patients. Published studies using either acyclovir or CMV hyperimmune globulin (HIG) alone as prophylaxis have also shown clinical disease in 20–30% of D^+/R^+ patients—less than controls but still significantly greater than in comparable CMV^+ recipients (R^+). The purpose of this study was to determine whether the risk of primary CMV disease in D^+/R^- patients was reduced by prophylaxis with combined CMV-HIG and low-dose acyclovir as follows: CMV-HIG (Immuno) 1 ml/kg i.v. immediately prior to transplantation and at 3-week intervals for 6 months; acyclovir 600 mg/day p.o. for 3 months. A total of 361 consecutive renal transplants were studied prospectively. All D^+/R^- pts (n=73) received CMV-HIG and acyclovir, the others (91 D^+/R^+, 74 D^-/R^+, 123 D^-/R^-) received only low-dose acyclovir. The incidence of clinical CMV disease, CMV-related graft loss, graft and patient survival, and the influence of ALG and OKT-3 were analyzed and compared between groups. Of the 361 patients only 18 (5%) developed CMV disease, with 5 CMV-related graft losses. CMV disease occurred in only 10% of the D^+/R^- patients, lower than in previously reported studies. Significantly the incidence was as low as in CMV^+ recipients of kidneys from both CMV^+ (6%) and CMV^- (7%) donors. Use of OKT-3 for steroid-resistant rejection increased the risk of developing CMV disease: 11/50 (22%) receiving OKT-3 developed CMV disease vs. only 7/311 (2%) who did not ($P<0.001$); 11/18 (61%) with CMV disease had received OKT-3. ALG induction immunosuppression did not increase the risk of CMV in patients who subsequently received OKT-3. No patient developed CMV disease after discontinuing prophylaxis. There were no complications related to either CMV-HIG or acyclovir use. Compared with all other patients, the D^+/R^- group had superior graft survival at 1 and 3 years (94% vs. 87% and 86% vs. 74%, $P<0.05$) but similar patient survival.

Combined CMV-HIG and low-dose acyclovir appear to be better than either agent alone in preventing primary CMV disease in CMV^- patients who receive CMV^+ kidneys. Low-dose oral acyclovir (600 mg/day) may be as effective in preventing CMV disease as higher-dose prophylactic regimens, at least when accompanied by CMV-HIG. Treatment of steroid-resistant rejection with OKT-3 is a major risk factor for CMV disease in D^+/R^- and all CMV^+ renal transplant recipients.

Cytomegalovirus is the most common virus causing clinically important infections after renal transplantation. While most CMV infections in the general population are asymptomatic, immunosuppression predisposes to the development of frank clinical disease that can be associated with significant morbidity, increased risk of graft loss, and mortality. After transplantation CMV infection may be occasionally acquired de novo through environmental exposure, as occurs in the normal host, or it may result from exposure through transfusion of infected blood products. Most commonly, however, the virus is either transmitted directly in the donor organ, or dormant virus is reactivated in a previously infected recipient (*1, 2*).

The intensity of immunosuppression influences the incidence and severity of CMV infection and clinical disease. Infections therefore usually occur during the first 3 months following transplantation and are exceedingly rare after 4 months (*3*).

CMV seronegative recipients of transplants from CMV seropositive donors are at greatest risk of developing primary CMV infection and are most prone to severe CMV disease (*3–5*). Because of the risks of primary CMV infection and clinical disease, prior to 1986 we avoided transplanting CMV^- recipients with kidneys from CMV^+ donors (D^+/R^-). Unfortunately, because approximately half our population is CMV^+ and half CMV^-, this policy restricted both cadaver and live-related donor transplant opportunities for potential recipients who were CMV^-.

Alternative solutions to this problem were therefore sought. Using low-dose acyclovir for the first 3 posttransplant months in a herpesvirus prophylaxis study (*6*), 5 of 19 (26%) D^+/R^+ patients developed CMV disease, similar to the experience of others (*7*). Following the initial report of the efficacy of CMV hyperimmune globulin in reducing the incidence of CMV disease in renal transplant recipients (*8*), we initiated a prospective trial in which high-titer CMV specific hyperimmune globulin (HIG)* was added to the low dose oral acyclovir regimen in all D^+/R^- transplant combinations. This report extends our earlier preliminary experience with the combined CMV-HIG/acyclovir protocol (*9*) and compares the associated incidence of CMV disease, morbidity and graft survival in D^+/R^- com-

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* Abbreviations: CF, complement fixation; HIG, hyperimmune globulin.