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Analysis of Liver Transplantation

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To be a service, a new surgical procedure must be within the capability of more than the occasional surgeon. In addition, the indications for its use should be clear, and the results should be good enough to justify the effort and expense. In this communication, we will indicate that orthotopic liver transplantation has met all three of these criteria.

MATERIALS AND METHODS

Two hundred and ninety-six patients were treated from March, 1963 through April, 1983. Until the end of 1979, “conventional” immunosuppression was used with azathioprine and prednisone to which antilymphocytic globulin was usually added (1,2). In 16 patients treated in 1971 and 1972, cyclophosphamide was substituted for azathioprine. From early 1980 onward, immunosuppression was with cyclosporine and steroids. The surgical and medical techniques have been described elsewhere (1,2).

The results were analyzed before and after the introduction of cyclosporine-steroid therapy. In the post-1980 era, we studied a greatly expanded volume of cases, the use of veno-venous bypasses with and without heparin, and the systematic training of younger surgeons whose objective could be to set up new centers. In all of the case material, the influence of original disease upon the results also was examined.

RESULTS

SURVIVAL WITH CONVENTIONAL IMMUNOSUPPRESSION (1963–1979)

From 1963 to the end of 1979, 170 consecutive patients were treated; which is an average case load of less than 12 per year. Fifty-six (32.9%) recipients lived for at least 1 year, and 32 (18.8%) are still alive with follow-up of 3½ to 13½ years. Six of the residual group are more than 10 years postoperative, and 26 are more than 5 years. Only one patient who lived for as long as 5 years subsequently died.

The patient survival during the first 18 months is summarized in Table 1. The predominant mortality was in the first three postoperative months and was due mainly to technical surgical accidents, acceptance of recipients with hopelessly advanced disease, use of damaged liver grafts, inability to control rejection, and a variety of infections (1,2). Most deaths in the first half of the second year (Table 1) were due to chronic rejection (2).

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SURVIVAL WITH CYCLOSPORINE-STEROID THERAPY (1980–1981)

Fourteen patients were treated in 1980 and 26 in 1982; follow-ups of 18 to 38 months are available for those still living. The 1-year survival was 28/40 (70%) (Table 1). Three 1-year survivors died in the 13th, 16th, and 20th months of recurrent cholangiocarcinoma, recurrent Budd-Chiari syndrome and chronic rejection (with an unsuccessful attempt at retransplantation), respectively. The actual 18-month survival (Table 1) was 65%, and the actuarial 2-year survival is projected at 60%.

THE BREAKOUT YEAR OF 1982

Until 1982, virtually all liver transplantations in our series over a span of almost 19 years were performed by a single surgeon (Table 2). The same surgeon also had performed all of the donor operations in the earliest years of these efforts and in all cases since 1979. The image created was of a procedure that was too difficult to be taught easily to other teams. Thus, policy changes were instituted upon which, it was thought, the practicality of liver transplantation would hinge.

The Donor Operations—Beginning on January 1, 1982, organ harvest teams which had been trained throughout the preceding year, assumed responsibility for 100% of the procurement procedures (Table 2). Any 1 of 5 faculty members (2 were urologists and 3 were general surgeons) headed the teams. In addition, training of other teams was begun in distant cities with the eventual objective of promoting graft hepatectomies by local surgeons instead of by mobile Pittsburgh teams.

Recipient Operations—The diffusion of recipient operative responsibility from one to several surgeons also began in 1982 during which 40% of the patients were treated by young faculty members or fellows (Table 2).

High Case Volume—The foregoing changes led to a considerable expansion of clinical efforts. In addition to the 62 primary transplantations, 18 retransplantations were performed, bringing the total number of liver replacements in 1982 to 80 (Table 2).

A Trial of Veno-Venous Bypasses—Bypasses were used 2 decades ago in the original trials of liver transplantation for decompression of the portal vein and inferior vena cava which must be obstructed during the hepatectomy and actual transplantation (1). The practice was abandoned for many years but tried again in 12 cases during the summer of 1982 using pump-driven bypasses under systemic heparinization. Cannulas were placed into the vena cava (via the femoral vein) and into the portal vein. The physiologic condition of the recipients during the anhepatic phase and the ease of vascular suturing of the grafts were enormously improved, but it was difficult or impossible to reverse the heparin effect which was responsible for three deaths in the operating room. Of 12 recipients who had 14 such bypasses (two were at retransplantation), only 3 became long-term survivors.

Subsequently, pump driven veno-venous bypasses *without heparin* were perfected in the laboratory and in 1983 bypasses have been used for most of the adult patients. This technique has been satisfactory in 14 recent transplantations and should place the operation of liver replacement within the grasp of a much greater number of surgeons.

The Results in 1982—Half of the recipients treated during this time of major change are alive with follow-ups of 5 to 16 months. The survival of the 1982 pediatric recipients (<18 years) in 16/28 (57.1%) which is higher than the 15/34 (44.1%) achieved during 1982 in adults.

THE PACE IN 1983

During the first 4 months, 24 primary and 10 retransplantation procedures were performed at a rate, what if sustained, will total 100 for the year. The new conditions developed in 1982 have continued with more than 70% of transplantations performed by young faculty members and fellows (Table 2) and with almost all adults having veno-venous bypasses. The present survival of new patients is 17/24 (70.8%), including 8/10 children and 9/14 adults.

THE INFLUENCE OF DISEASE UPON RESULTS

None of the diseases for which transplantation has been performed can be categorically excluded from future trials in spite of a high incidence of recurrence of the original disease which has been documented with primary hepatic malignancies (1,2) and with chronic active hepatitis in B virus carriers (2). Recurrence of Budd-Chiari syndrome (2,3) and primary biliary cirrhosis (3) have been less commonly seen.

The 1-year and current patient survival before and after the introduction of cyclosporine-steroid therapy is summarized in Table 3 for each main disease category; 237 consecutive patients were included whose transplantations were at least 1 year ago with the assumption that this follow-up period would permit detection of aggressively evolving recurrences. The only obvious conclusion is that the results have improved after the introduction of cyclosporine-steroid therapy no matter what the original diagnosis. It is noteworthy that no patients with alcoholic cirrhosis have been included in the cyclosporine series, a selection bias that will not be acceptable in the future. Alcoholic recipients from our earlier experience have been followed for as long as a decade.

THE INFLUENCE OF DISEASE STAGE UPON RESULTS

The stage of the original disease was of greater prognostic importance than its nature. The stage factor was examined in 114 consecutive patients treated in the cyclosporine-steroid era from 3 to 38 months ago. Patients who were not continuously hospitalized prior to operation were called Class I. Those who were hospitalized most of the time but not in Intensive Care Units were classed as Class II. Recipients who were taken from an Intensive Care Unit to the operating room were termed Class III. These last patients usually were mentally obtunded or unconscious. Many had the hepatorenal syndrome and most were ventilator-dependent. The majority had active gastrointestinal bleeding.

The perioperative mortality was almost 60% in the Class III patients (Table 4). In contrast, the mortality in the first 6 weeks was only 16% in Class II patients. The somewhat higher mortality (32%) in Class I patients was partly explained by the fact that many of these recipients had undergone operations in or around the hepatic hilum (such as portacaval shunt or biliary tract reconstruction) which greatly increase the technical risk (2). Such patients were accepted for candidacy only if they were in the kind of reasonable metabolic state that tended to place them in the Class I category.

DISCUSSION

With improved immunosuppression that became available almost 3½ years ago, came a revitalization of interest in hepatic transplantation. In spite of its use in most cases for pathologic conditions which will someday be viewed as unrealistically advanced, the number of successful-liver replacements has increased sharply.

Continuing observation of the first patients treated with cyclosporine-steroid therapy has dispelled skepticism about the ability to use cyclosporine chronically. Forty-two patients have now been followed for at least 1 year after liver transplantation under cyclosporine-steroid

therapy. Six deaths occurred after 1 year and all but two were caused by recurrence of the original disease (two examples of metastases from primary hepatic malignancies, one each of recurrent Budd-Chiari syndrome and chronic B virus hepatitis). One patient died of probable airway obstruction secondary to acute tonsillitis. Only one patient lost a graft to chronic rejection. The degree of rehabilitation of long-term survivors has been essentially complete.

The mystique surrounding liver transplantation largely has been dispelled by events of the last 2 years at our institution and elsewhere. Other units in the United States and in other countries have been able to mount effective programs. In Pittsburgh, more than two thirds of the liver transplantation operations are now being done by young faculty members and by surgeons in training. The ease with which the admittedly difficult operation can be performed is being reduced with the pump-driven nonheparin bypasses that are being used this year for the first time.

SUMMARY

Liver transplantation has been developed to the point of a service operation, the exploitation of which depends upon the estblishment of multiple regional centers. The increased use of this procedure will permit the delivery of optimum health care to victims of endstage liver disease.

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Table 1

Actual 18-month survival of 210 consecutive recipients

Treatment	No.	Time in months				
		1	2	6	12	18
Triple drug conventional (1963–1979)	170	120 (58%)	95 (55.9%)	65 (33.2%)	56 (32.9%)	47 (27.6%)
Cyclosporine-steroids (1980–1981)	40	32 (80%)	31 (77.5%)	29 (72.5%)	28 (70%)	26 (65%)

Table 2

The sharing of primary operative responsibility by multiple surgeons

	1963–1979	1980–1981	1982	1983 (4 months)
New patients	170	40	62	24
Total transplantations	191	45	80	34
Transplantations by single surgeon (TES)	187	45	48	10
	(97.9%)	(100%)	(60%)	(29.4%)
Donor operations by single surgeon (TES)	Minority[a]	100%	0%	0%

[a] The majority of these donor operations at the University of Colorado were by Dr. Charles Halgrimson.

Table 3

Influence of disease upon 1 year and subsequent survival in 237 patients[a]

	Conventional therapy			Cyclosporine-steroids		
	No.	1 year	Now[b]	No.	1 Year	Now[c]
Biliary atresia	51	14 (27%)	7 (14%)	11	6 (54.5%)	6 (54.5%)
Nonalcoholic cirrhosis	46	16 (34.8%)	10 (21.7%)	16	9 (56.3%)	8 (50%)
Primary liver malignancy	18	5 (27.8%)	1 (5.6%)	9	6 (66.7%)	4 (44.4%)
α-1-antitrypsin deficiency	11	6 (54.5%)	5 (45.5%)	6	3 (50%)	3 (50%)
Other inborn errors[d]	4	2 (50%)	1 (25%)	4	4 (100%)	4 (100%)
Alcoholic cirrhosis	15	4 (26.7%)	3 (20%)	0	—	—
Primary biliary cirrhosis	6	1 (16.7%)	1 (16.7%)	6	5 (83.3%)	5 (83.3%)
Sclerosing cholangitis	7	2 (28.6%)	0 (0%)	3	2 (66.7%)	1 (33.3%)
Secondary biliary cirrhosis	4	3 (75%)	2 (50%)	5	1 (20%)	1 (20%)
Budd-Chiari syndrome	1	1 (100%)	1 (100%)	3	3 (100%)	1 (33.3%)
Miscellaneous[e]	7	2 (28.6%)	1 (14.3%)	4	3 (75%)	3 (75%)

[a] The same case material was analyzed in detail elsewhere (2) but with shorter follow-ups.

[b] Follow-ups 3½ to 13½ years.

[c] Follow-ups 1 to 3¼ years.

[d] Wilson's disease (3 examples), tyrosinemia (2 examples), glycogen storage disease (2 examples), and sea blue histiocyte syndrome (1 sample).

[e] Neonatal hepatitis (3 examples), congenital hepatic fibrosis (2 examples), Byler's disease (2 examples), adenomatosis, hemachromatosis, protoporphyria, and acute hepatitis B (1 example each).

Table 4

Effect of disease stage on 6-week survival (114 consecutive patients)

Class	Definition	No.	Survival (%)
I	Outpatient care-dependent	63	68
II	Hospital care-dependent	25	84
III	Intensive Care Unit-dependent	26	42