18. Present Status of Liver Transplantation*

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Historical Perspective

The concept of liver replacement was apparently first envisioned by Cannon [1] of Los Angeles, who performed liver replacements in animals without survival. His report was so brief that it did not have a title and did not even stipulate the animals used. The first detailed report of liver transplantation was by C. Stewart Welch [2] of Albany, New York, who transplanted auxiliary organs into the pelvis or right paravertebral gutter of dogs.

The technical requirements of *liver replacement* and the behavior of dogs submitted to this operation without immunosuppressive therapy were worked out by ourselves [3, 4] and by the team headed by Francis D. Moore at the Peter Bent Brigham Hospital in Boston [5]. The first chronic survivors after liver replacement in experimental animals were obtained in 1963 and reported in 1965 [6]. These animals were treated with azathioprine alone, which could often be stopped after only 3 or 4 months with prolonged subsequent good health of the recipients of mongrel nonrelated livers [7].

The first clinical liver transplantations were performed in early 1963 [8]. From this time until mid-1967 six attempts were made by us, all leading to the death of the recipients within a few days or weeks. The first extended survival after liver replacement in humans was achieved in the summer of 1967. Our experience with the first 25 cases of liver replacement was summarized in a book published in 1969 [7].

Including the first unsuccessful attempts, we had compiled 111 cases of orthotopic liver transplantation by the spring of 1976. Thirty-one of these 111 patients lived for at least one postoperative year and from that original group the longest current survivor is now more than 12 years. It became apparent during this time [9] that many general aspects of care could be improved including the technical details of the operation, diagnostic procedures during the postoperative period (which were designed to identify causes other than rejection for postoperative hepatic failure), and immunosuppression. The basis for liver transplantation was strengthened by the introduction of modifications to alleviate these sources of tragedy. The modifications included refined anatomical studies of the structures which had to be dealt with, increased application of

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modern diagnostic techniques (including postoperative biopsies, and cholangiographic studies), exploitation of microvascular techniques (particularly in pediatric recipients), and use of methods which had become available for detection and classification of hepatitis.

At the same time, another development occurred in preservation which could not be fully exploited because of other limitations, especially that of suboptimal immunosuppression. Benichou et al. [10] in our laboratories, and the group at Cambridge [11] described techniques for cold preservation of the liver after infusion of special solutions. These permitted the preservation in "slush" of animal livers for as long as 12 to 24 h. A bottleneck was thus broken, permitting harvesting of human livers in distant cities and their transportation to the site of the recipient operation. Previously it was necessary to have the donor and recipient in the same city, and preferably in the same hospital.

In the mid 1970s it appeared at first that a substantial improvement would be possible by refinements of surgical, medical, and immunosuppressive techniques that were already available. The 1-year survival rate in a series of 30 consecutive patients rose to 50% [12]. However, in a subsequent series of 30 patients the survival dipped again to a level only slightly better than in the first cases [13, 14]. Our conclusion was that some fundamental improvement would be necessary in immunosuppression before the full potential of liver transplantation could be realized.

This improvement was made possible by the introduction of cyclosporin A, an extract of two fungi, which was discovered and studied by Borel and his associates and Basel Switzerland [15, 16].

The first clinical trials of cyclosporin A were made in England by Calne and his associates [17, 18] at Cambridge and by Powles et al. [19] at the Royal Marsden Hospital, also in England. Calne's trials were for whole organ transplantation and Powles worked with bone marrow transplantation. In the United States, cyclosporin A became available in late 1979. Its combination with low dose steroids was advocated and standardized by our group [20, 21], working in renal transplantation. The optimal use of cyclosporin A required the coincident administration of steroids, but the amounts of prednisone and/or hydrocortisone were a fraction of those previously required. In March 1980, after having developed considerable experience with cadaveric renal transplantation, we undertook the first cyclosporin trials in liver transplantation. The results, as described below, have revolutionized the expectations after liver transplantation [14, 22].

Assessment of the Precyclosporin A Era

During the first years of our experience, detailed and finally repetitive analyses of the causes for failure were published, including delineation of the complex infectious patterns seen postoperatively. The high mortality was due principally to the lack of effectiveness of conventional immunosuppression by azathioprine, prednisone, and ALG. The vitality of efforts at liver transplantation was maintained mainly by the realization that many of the survivors enjoyed a high quality of life, especially beyond 1 year after transplantation.

Table 1. Indications for transplantation in the precyclosporin A era, 1963–1979 (adults – 19 to 70 years)

Chronic aggressive hepatitis	33
Primary liver malignancy	16
Alcoholic cirrhosis	16
Primary biliary cirrhosis	7
Sclerosing cholangitis	6
Secondary biliary cirrhosis	3
Massive hepatic necrosis (B virus)	1
Budd-Chiari syndrome	1
Protoporphyria	1
	84

Table 2. Indications for transplantation in the precyclosporin A ery, 1963–1979 (≦18 years)

Biliary atresia	53
Inborn metabolic errors	13[a]
Chronic aggressive hepatitis	13
Hepatoma	3
Neonatal hepatitis	2
Congenital biliary cirrhosis	1
Congenital hepatic fibrosis	1
Secondary biliary cirrhosis	1
	87

[a] Inborn errors of metabolism

Alpha-$_1$-antitrypsin deficiency	9
Wilson's disease	2
Tyrosinemia	1
Type IV glycogen storage disease	1

In 1978 and 1979 it was hoped that the safety and efficacy of standard immunosuppression could be improved with the adjuvant use of thoracic duct drainage [23]. However, patients with end-stage liver disease almost always had ascites, and probably because of this the drainage collected through the thoracic duct was so voluminous that preoperative lymphoid depletion with this technique proved hazardous. Some patients prepared with thoracic duct drainage produced as much as 2 liters per hour in the preoperative period, making fluid and blood volume management a near impossibility. It became obvious that thoracic duct drainage could be applied sparingly if at all to prospective liver recipients [13].

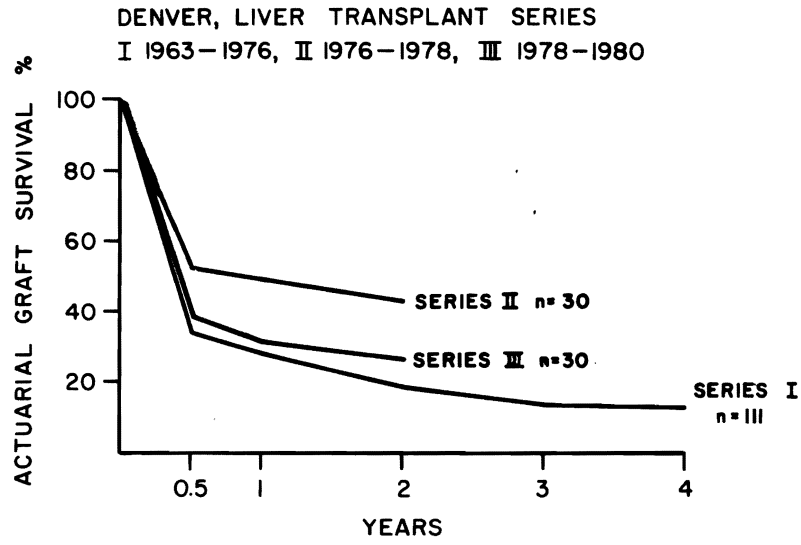
By the end of 1979, 171 patients had been treated with liver transplantation over a period of 16 years; of these, 84 were adults (Table 1).

During the same years 87 pediatric patients (18 years or younger) were also treated (Table 2).

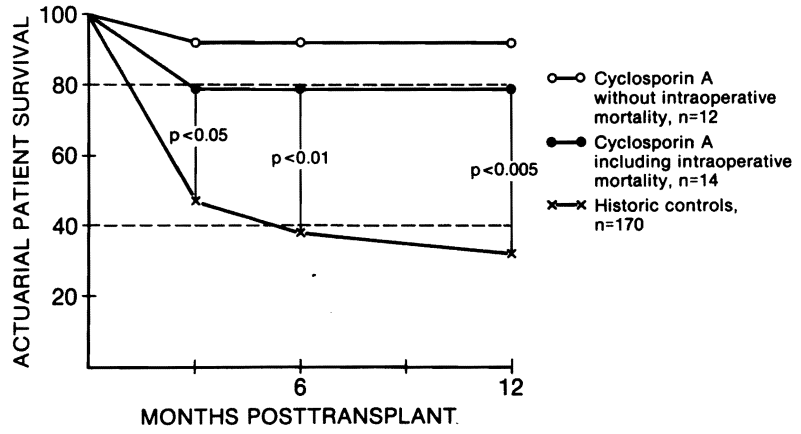
These 171 recipients were divided into three consecutive groups. The first 111 were treated between 1963 and 1976, and of these 31 (28%) lived for as long as 1 year. In a second wave of 30 patients, the 1-year survival increased to 50%, but in a subsequent further sample of 30 the 1-year survival declined again to a level almost as low as in the original series (Fig. 1).

The Cyclosporin A Era

By the end of 1979 our first and profoundly encouraging experience was being obtained with cadaveric *renal* transplantation under cyclosporin A and steroids. It was natural and justifiable to extend this new form of therapy almost immediately to liver recipients in view of the poor survival obtained with livers in the past. After 22 cadaveric kidney transplantations had been performed, the first liver recipients were treated in early 1980. The results have already shown a profound influence upon survival in liver transplantation. In the first group of 14 patients entered for consideration for cyclosporin A therapy in Denver,



0082 **Fig. 1.** Survival in three consecutive series of orthotopic liver recipients treated over a 16-year period.
0083 Note that a second group of 30 patients enjoyed a higher survival rate than patients in the first
0084 series, but that these gains could not be maintained in a third series



0086 **Fig. 2.** Denver liver transplant series, cyclosporin A vs. conventional treatment. (New England Journal
0087 of Medicine 305:266–269, 1981)

two died on the operating table and could not be treated with any kind of immunosuppression. Of the 12 who survived operation, 11 (92%) lived out the first postoperative year [22]. These recipients enjoyed a greater freedom from irreversible rejection than had ever been seen before, and the steroid requirements to meet this objective were a fraction of those in our historical experience. The combined historical life survival curves with conventional immunosuppression compared to those achieved with cyclosporin A and low dose steroids are shown in Fig. 2.

Table 3. The Pittsburgh experience with liver replacement

Number	Dead		Alive
26	1981	8	18 (69.2%)
17	1982	2[a]	15 (88.2%)

[a] These deaths were in patients with hypoplastic or absent portal veins

Table 4. Diagnoses in 57 patients[a] treated in the cyclosporin A era (1980–1982); five patients had two diagnoses

Chronic aggressive hepatitis	14
Hepatic neoplasm	10
Alpha-$_1$-antitrypsin disease	8[b]
Biliary atresia	7
Sclerosing cholangitis	4
Primary biliary cirrhosis	4
Budd-Chiari syndrome	3
Choledochal cyst and biliary cirrhosis	2
Hepatic fibrosis (Byler's)	2
Secondary biliary cirrhosis (trauma)	2
Caroli's disease	1
Neonatal hepatitis	1
Sea blue histiocyte syndrome	1[b]
Subacute Wilson's disease	1[b]
Type I glycogen storage disease	1[b]
Tyrosinemia	1[b]
	62

[a] Two thirds of the recipients were adults, one third were children
[b] Inborn errors of metabolism

The liver transplantation team moved to the University Health Center of Pittsburgh on 1 January 1981. The first four patients treated in this new environment died, all as a direct consequence of transplanting poorly preserved organs. Analysis of these tragic events showed that the procurement techniques which were slightly different in the Eastern center had not fit perfectly with those used in the Colorado program. The problems were rectified. Of the next 22 recipients 18 are still living after 4 months to a year. The only four deaths amongst the last 22 patients were caused by: a biliary tract leak leading to a subhepatic abscess and rupture of the portal vein, systemic infection with aspergillus, failure in a patient with preexisting massive right to left V-A shunts to have these shunts close postoperatively, and development of a hepatic artery fistula into the reconstructed common duct. The Pittsburgh results are summarized in Table 3.

The diagnoses in all patients treated in the cyclosporin A era are summarized in Table 4.

In pediatric recipients, the great advantage of treatment with cyclosporin A and low doses of steroids has been apparent in the rapid and seemingly normal growth of infants and children in this series [24].

Auxiliary Liver Transplantation

The alternative to orthotopic liver transplantation (liver replacement) is the transplantation of an extra liver (auxiliary transplantation) without removal of the diseased native organ. Clinical trials with this approach have been profoundly discouraging, as summarized to the autumn of 1978 by Fortner et al. [25] from the compiled world experience. Of nearly 50 well-documented auxiliary transplantations, only one could be pronounced an unequivocal success. Subsequently a report from Paris has described a second success [26].

Our opinion has been that auxiliary liver transplantation should be restricted to patients with potentially reversible liver disease. In such a situation, the extra liver could be construed as a temporary support organ that could be later removed. However, we have encountered increasing numbers of patients whose portal vein has clotted in the hepatic hilum, making it technically impossible to consider liver replacement. Such patients could theoretically be helped by an auxiliary liver transplantation, particularly when the superior mesenteric vein or other distal tributories to the main portal circulation are still open. In earlier work in our laboratories, it was shown that the optimal conditions for vascularization of an auxiliary liver graft required input from the portal circulation [27], largely because of the high concentrations of endogenous hormones that are to be found in this venous blood. These experiments, which eventually resulted in an interesting new field of hepatology (termed hepatatrophic physiology), have been summarized elsewhere [28].

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