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Surgery:

## **Transplantation of Extrarenal Organs**

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## Transplantation of Extrarenal Organs

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During the past decade great progress has been made in the field of organ replacement. This has established renal transplantation as an accepted method of treatment of chronic renal failure and to date more than 9,000 kidney transplants have been performed throughout the world. Experience with replacement of other major organs is limited and the procedures are being carried out in only a few transplantation centers.

### LIVER TRANSPLANTATION

Since the first liver transplantation in man was performed in Denver in March 1963, 162 such operations have been performed throughout the world.<sup>3</sup> Approximately one-third of the patients have been treated at the University of Colorado Medical Center and the Denver Veterans Administration Hospital.

Liver transplantation may consist of an orthotopic operation, in which the patient's diseased liver is removed and replaced with a healthy one, or an auxiliary transplant in which the host liver is left undisturbed and an extra liver is placed in an ectopic position within the abdomen. Theoretically, the latter procedure is attractive as it retains whatever function still remains in the host organ. In practice, however, the operation has great

drawbacks. There is little room in the abdomen for a second liver; it may be technically difficult in man to provide blood flow from the intestines into the ectopic liver's portal system; and from animal studies it appears that there may be competition between the two livers with the result that the liver which fails to receive splanchnic blood (usually the auxiliary liver) undergoes atrophy. The clinical results with this operation have been very disappointing and the procedure will not be considered any further.

*Indications and Contraindications.* Orthotopic replacement of the liver is indicated in patients with serious liver disease whose life expectancy is a matter of days or weeks or perhaps a few months. The reasons for operation in our center are listed in Table 1. We have not transplanted the liver for metastatic malignancy, as has been attempted in other centers, because of the strong likelihood of other, extrahepatic, metastases. With the exception of one case where the tumor was adherent to the pylorus which also required resection, we have not performed transplants for primary hepatic cancers which have extended beyond the confines of the liver.

The current status of liver transplantation can be illustrated by some examples from our own clinical material.<sup>25-28</sup> In our early experience it was hoped that hepatic replacement might be useful therapy for primary cancers of the liver. However, as long-term survival was achieved, it became obvious that tumor recurrence was a major problem. In 6 of 7 patients treated for cancer and followed from 2 to 14 months after transplantation, metastases appeared in the lungs, the brain and even in the homografts (Figs. 1 and 2).

The sole exception was a child aged almost 4 years who was operated upon for severe congenital biliary atresia. An incidental finding in the liver specimen was a hepatoma about 2 cm in diameter. The pa-

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TABLE 1  
Indications for Orthotopic Liver  
Transplantation

Disease	Number of Transplantations
Biliary Atresia	26*
Primary Hepatic Tumors	13
Cirrhosis	9
Chronic Aggressive Hepatitis	6
Wilson's Disease	2
Lupoid Hepatitis	1
Retransplantation for severe rejection	4
Total	61

\* One patient had an incidental hepatoma.

tient has now been followed for more than 2 $\frac{3}{4}$  years with no clinical, radiologic or serologic ( $\alpha$ -fetoprotein estimations) evidence of recurrent tumor. Isolated long-term successes have also been achieved by Prof. Roy Calne<sup>5</sup> of Cambridge and Dr. Pierre Daloze<sup>8</sup> of Montreal.

These disappointing results have made us adopt a policy of restricting liver transplantation almost exclusively to patients with benign hepatic disease.

Encouraging results have been obtained in patients with congenital biliary atresia. Six recipients have lived at least one year

after transplantation. Three of these survived more than two years and one lived for 3 $\frac{1}{2}$  years. The last recipient had a very poor tissue match. Despite this he had two minor rejection episodes in the early postoperative period. Thereafter, he enjoyed good health and excellent liver function until shortly before his death. A biopsy of the homograft 914 days after transplantation showed almost normal liver architecture. A few months later, the patient developed a hemophilus type B septicemia which led to circulatory collapse, renal failure and massive hepatic necrosis that contributed to death a few weeks later.

Our experience with liver transplantation has given us a better understanding of Wilson's disease. The condition is believed to result from an enzyme deficiency which causes disturbed copper metabolism and leads to extensive copper deposition in the liver, basal ganglia, the corneas (Kayser-Fleischer rings) and other tissues. The main clinical manifestations are severe cirrhosis, or neurologic disturbances or both. Experience with liver transplantation suggests that the enzyme deficiency may be corrected by replacement of the diseased liver with a healthy one and that copper metabolism may be restored to normal. One such patient, aged 11 years, was seriously ill with advanced cirrhosis. Three weeks after transplantation the homograft underwent one of

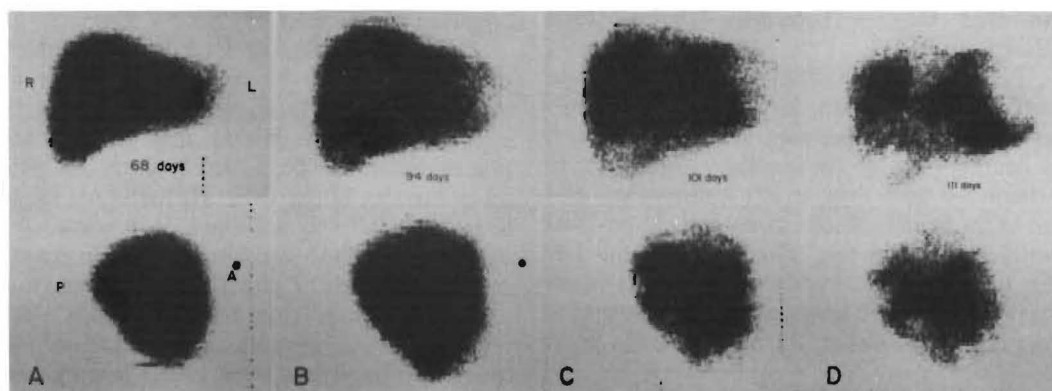


FIG. 1. Destruction of an hepatic homograft by tumor recurrence, as demonstrated by serial technetium liver scans. A. 68 days—The scan appears normal. B. 94 days—The patient had become jaundiced. Hepatomegaly is evident. C. 101 days—Multiple areas of poor isotope concentration are now visible. D. 111 days—The process has continued its rapid progression. By the time of death—143 days after transplantation—the homograft was almost completely replaced by tumor. (By permission of W.B. Saunders Co., 1969)

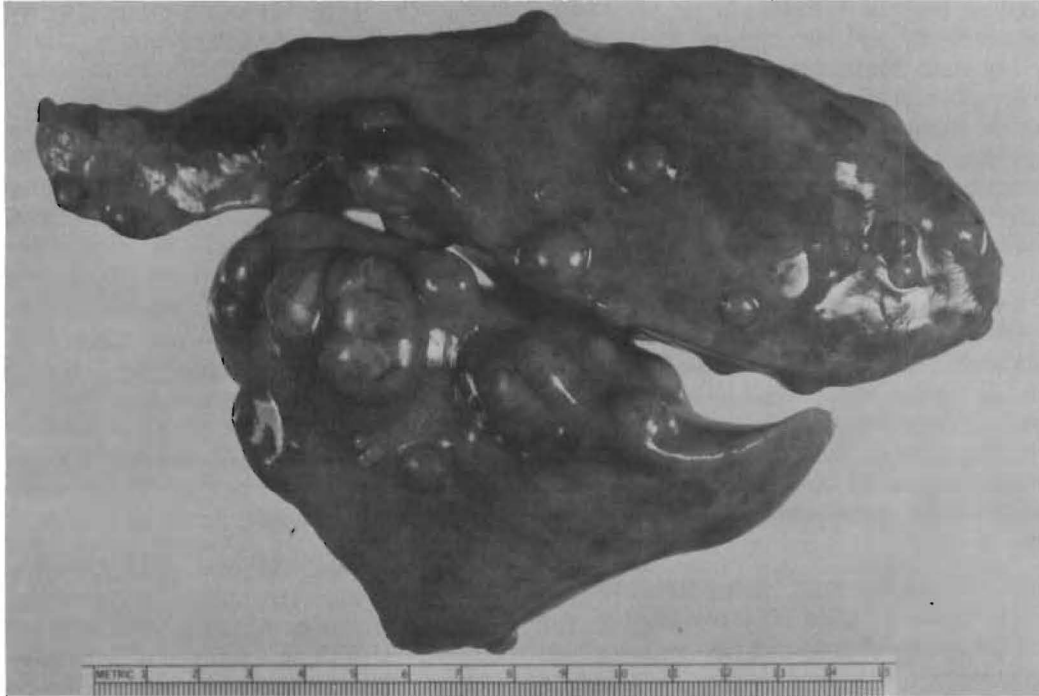


FIG. 2. Same patient as in Figure 1. Autopsy specimen showing multiple large pulmonary metastases. (By permission of W. B. Saunders Co., 1969)

the worst rejection crises we have ever observed in any of our liver transplant recipients. The bilirubin rose to almost 50 mgm/ml with an associated elevation of the alkaline phosphatase. Fortunately, it was possible to reverse the immunologic reaction and the patient has enjoyed virtually normal liver function for the ensuing three years. After operation large amounts of copper were passed in the urine for six months. Biopsies of the homograft at 6, 18 and 30 months showed a normal copper concentration within the organ. The patient is now  $3\frac{1}{2}$  years post-transplantation and is attending school. Similar good results were obtained in another boy aged 15 years who is now 18 months post-transplantation.

Is there any hope of treating lethal serum hepatitis with liver transplantation? In the present state of our knowledge it is not possible to give a definite answer to this question. We have no experience with hepatic replacement in the treatment of acute fulminating hepatitis, although it has been unsuccessfully attempted elsewhere. However, we have performed liver replacement in

cases of hepatic failure caused by chronic aggressive hepatitis, Australia antigen positive. The serum of one such patient, a 28 year old woman, has been persistently positive for the Australia antigen for two years. At the time of admission to the hospital she was gravely ill with severe ascites, large pleural effusions, a serum albumin of less than 2 gm/100 ml and a prothrombin time of less than 20%. Following transplantation her serum promptly became negative for the Australia antigen and remained so for approximately two months when it again became positive. Soon afterwards her liver chemistries became abnormal and it was apparent that she again had hepatitis. Despite slowly deteriorating liver function she was restored to a useful life among her family and friends for 20 months, when she died of disseminated *Nocardia* infection. At autopsy, there was recurrence of chronic aggressive hepatitis.

*Complications.* The most frequent problems after liver transplantation have been with rejection or infection. The former may

manifest itself as a cholestatic jaundice with hepatomegaly and elevation of the alkaline phosphatase. More severe rejection may lead to hepatic necrosis with increases in transaminases. Frequently it is possible to reverse rejection with increased immunosuppressive therapy. However, in some cases this has proved impossible and caused the patient's death unless another homograft could be obtained and retransplantation performed.

Infection is common in any patient whose immunologic system is impaired by immunosuppressive therapy. It is particularly common in hepatic transplantation as a rejecting liver is unable to handle micro-organisms reaching it from the bowel. Septic hepatic infarcts may occur or even frank septicemia, usually with gram negative enteric organisms.

*Long-Term Survival.* Long-term survival can be achieved after liver transplantation. In experiments in dogs and pigs we have had many survive more than a year. One dog is still alive more than eight years after transplantation. In our first 46 patients, in whom a minimum potential follow-up of 12 months was or is available, 12 survived at least one year (26%). Five of these recipients lived more than two years, one of whom died 3½ years after transplantation. At present nine of our patients are alive at 1½, 4, 5, 5, 7, 14, 18, 32 and 38 months posttransplantation, respectively. Other current long-term survivors include a patient of Dr. Daloz<sup>8</sup> (30 months) and of Prof. Calne<sup>5</sup> (43 months).

### HEART TRANSPLANTATION

The first cardiac transplant was performed in Jackson, Mississippi in 1964, when a chimpanzee heart was transplanted to man. Three years later the first human to human transplantation was attempted. To date 189 heart transplantations have been performed throughout the world.<sup>3</sup>

*Indications and contraindications.* In the selection of cardiac transplant recipients the patients must have terminal heart disease not amenable to any other surgical procedure or medical treatment. Since most heart disease is caused by coronary arteriosclerosis, this has been the most common reason for cardiac transplantation.<sup>7, 22</sup> Myo-

cardiopathy is another indication despite the theoretical danger that the immune factors responsible for the original disease could damage the homograft.<sup>17</sup> Rheumatic multivalvular disease, although often correctable by valve replacement, may have caused such severe damage as to require cardiac transplantation. Severe uncorrectable congenital anomalies also may warrant heart replacement.

Definite contraindications are severe pulmonary hypertension and, as with other kinds of transplants, severe systemic disorders such as diabetes, infection or cancer. Most patients with multiple organ disease should not undergo cardiac transplantation, and patients of advanced age or questionable emotional status are usually not suitable.

*Complications.* As with transplantation of other organs, the major postoperative problems have been rejection and infection. Decrease in exercise tolerance is a warning of impending acute rejection.<sup>7, 22</sup> Clinical findings in the early stages are the appearance or accentuation of a previously present pericardial friction rub, and the development of an abnormal diastolic heart sound, usually an early diastolic gallop, although a presystolic gallop may occur.

The electrocardiogram provides many of the primary indices of acute rejection. Characteristic and reversible changes include decreased electrocardiographic voltage, atrial arrhythmias, rightward deviation of the mean electrical axis, and ischemic type ST segment changes. Ultrasound cardiography shows increased total heart and right ventricular chamber size, thickening of the left ventricular wall, and variable decreases in the transverse diameter of the left ventricular cavity.<sup>30</sup> Elevations of the enzymes LDH, CPK and SGOT do not provide an early warning but merely reflect the severity of the rejection process. Decreased uptake of Caesium 131 chloride by the myocardium may also be useful in the diagnosis.<sup>17</sup>

Chronic rejection results from intimal thickening in the coronary arteries and their branches and has been responsible for many of the late deaths following cardiac transplantation.<sup>7</sup> It manifests itself by a progressive reduction in exercise tolerance and the

development of cardiac failure. In some centers attempts have been made to prevent this complication with long-term anticoagulant therapy and the use of the platelet deaggregator, dipyridamole.<sup>18</sup> Experience with this form of treatment is still too small to draw any definite conclusions.

*Long-term Survival.* As heart failure develops medical treatment for this condition will have to be instituted. Attempts have been made to replace chronically rejecting hearts with secondary cardiac homografts, but no long-term survivals have yet been obtained.<sup>7, 17</sup>

The results of cardiac transplantation have been steadily improving. Shumway and his colleagues, with the largest experience, have performed 45 transplants in 43 patients. Currently they have a 43% one-year and 37% two-year survival.<sup>11</sup>

Of the 189 patients treated throughout the world 29 are still alive.<sup>3</sup> The longest survivor is now more than four years post-transplantation.

### LUNG TRANSPLANTATION

The first attempted lung transplantation in man took place in Jackson, Mississippi in 1963. Since then, 29 such procedures involving either a lobe, a whole lung or the heart and both lungs have been performed.<sup>3</sup>

*Indications and contraindications.* Lung transplantation is not indicated in unilateral pulmonary disease where a lobectomy or pneumonectomy should suffice. The prime candidates for this procedure are patients who are gravely ill with chronic restrictive lung disease or conceivably with primary pulmonary hypertension.<sup>10, 35</sup> Unilateral transplantation in patients with chronic obstructive pulmonary disease has failed, largely owing to a serious ventilation/perfusion imbalance between the homograft and the host's residual lung. Attempts have been made to overcome this problem with bilateral lung replacement. Occasional transplants have also been performed for acute respiratory insufficiency caused by toxic pneumonitis or trauma.<sup>35</sup>

*Complications.* Postoperatively, acute rejection is heralded by general malaise,

cough, dyspnea and a fall of arterial pO<sub>2</sub> values. The risk of pulmonary infection is particularly great, and a disconcerting feature is that it is well-nigh impossible to distinguish between this and rejection of the homograft.

*Long-Term Survival.* Thus far the results of lung transplantation have been very disappointing as most patients have succumbed within a few weeks. The longest survivor, Derom's<sup>10</sup> patient in Belgium, died of bronchopneumonia and chronic rejection of the transplant 10 months after the operation.

### PANCREATICODUODENAL TRANSPLANTS

The first pancreaticoduodenal transplant was performed in Minneapolis in 1966. To date, 25 such operations have been performed.<sup>3</sup>

*Indications and Contraindications.* Transplantation of the pancreas and duodenum (to provide drainage of the exocrine secretions of the former organ), or of the body and tail of the pancreas alone, is indicated in cases of severe juvenile-onset diabetes complicated by marked retinopathy and nephropathy.<sup>20, 21</sup> In most cases so far treated, the kidney damage has been so marked as to necessitate renal replacement at the same time as the pancreatic transplantation. As more experience is gained, a trend may develop towards replacing the pancreas before the stage of terminal nephropathy, thus eliminating the need for concomitant renal transplantation. In addition, new techniques will be required which will eliminate the need for concomitant transplantation of the duodenum.

*Complications.* A successful pancreatic transplantation is followed by a normal fasting blood sugar and glucose tolerance test. Postoperatively, the major problems have been with sepsis, often due to duodenal necrosis, and rejection of the kidneys even though in each case the renal grafts were obtained from the same donors as the pancreata.<sup>20, 21</sup> Pancreatic rejection is heralded by recurrence of diabetes or elevation of the serum amylase or lipase levels.<sup>20, 32</sup>

Partial pancreatic transplants have not functioned for periods longer than four months. Failure was caused by pancreatitis, infection, autolysis and/or other technical problems associated with the procedure.<sup>20, 21</sup>

*Survival.* The longest survivor following pancreatic transplantation succumbed after 12 months. Currently two patients are alive following the procedure.<sup>3</sup>

### **BONE MARROW TRANSPLANTATION**

Several hundred bone marrow transplants have been performed to date. Since January 1, 1968 the A.C.S.-N.I.H. Organ Transplant Registry has recorded 146 such procedures in 130 recipients.

*Indications and Contraindications.* Bone marrow transplants are usually performed in patients who are seriously ill with one of the following disorders<sup>4, 34</sup> which have failed to respond to other forms of treatment: 1) Accidental whole-body irradiation; 2) Aplastic anemia; 3) Immune deficiency diseases, including agammaglobulinemia, hypogammaglobulinemia, the Wiscott-Aldrich syndrome and the DiGeorge syndrome (the aim in these conditions is to either reconstitute all the hemopoietic cells or only those belonging to the lymphoid series). 4) Leukemia; 5) A variety of advanced cancers. In the last two conditions the aim is not only to restore depleted blood elements, but to provide immunocompetent cells which, it is hoped, will destroy residual malignant cells which have persisted despite other forms of therapy.

Preoperative donor workup should exclude the possibility of transmissible infections or malignant disease. For successful bone marrow transplantation, the ideal donor is an identical twin, as there is no need for immunosuppressive therapy in these cases. Otherwise, a relative who is closely matched for the ABO, Rh and HL-A antigens should be used. The one-way mixed lymphocyte culture test seems to be particularly useful in selecting well matched combinations. In the absence of a familial volunteer, an unrelated donor, either living or cadaveric, may be used. However, at present most of the worthwhile long-term results have been

obtained in transplants between HL-A identical siblings.

Recipients with leukemia and other types of cancer usually require treatment with one or more cancer chemotherapeutic agents. Before transplantation immunosuppressive pretreatment is given using total body irradiation, steroids, azathioprine, cyclophosphamide or anti-lymphocyte globulin. In some centers pretreatment of the donor with ALG is being investigated.<sup>24</sup>

Except in transplants between identical twins, the recipients often require continuation of immunosuppressive therapy post-transplantation to prevent rejection of the homograft or a graft versus host reaction.

Frequent hematologic studies are necessary to establish that the grafted bone marrow is functioning and that a state of partial or complete chimerism has been established. Survival of the transfused cells is determined by means of erythrocyte or leukocyte antigenic markers, or both.

*Complications.* After transplantation the most frequent problems are persistence of the original malignant disease, or the development of infection or rejection. In cases of leukemia the disease may persist or it may involve the transplanted *donor* cells as occurred in two cases reported by Thomas.<sup>33</sup> Infectious problems are prone to occur because many patients already have impaired immune responses which may be further reduced by immunosuppressive agents.

Rejection may be of two types:<sup>4</sup> 1) Failure of engraftment is heralded by a disappearance of the initial symptomatic and hematologic improvement. Hemorrhage or infection may occur and further bone marrow transplants may be necessary; 2) Graft versus host disease (G.V.H.D.) is a disorder in which immunologically competent donor cells become established and react to the host's tissues as if they were foreign. The resulting immunologic reaction results in an illness characterized by generalized wasting and malaise, gastrointestinal dysfunction (with anorexia, diarrhea, malabsorption and weight loss), exfoliative dermatitis, destruction of hepatic tissue with abnormal liver function tests and jaundice, fever and an increased susceptibility to fun-

gal and viral infections.<sup>13</sup> The disorder may occur despite HL-A identity,<sup>13</sup> suggesting that antigenic differences must reside in as yet undetected non-HL-A sites. G.V.H.D. occurs in two forms: an acute type which begins within a few days of transplantation and either results in early death of the host or regresses, with recovery within 4 to 6 weeks; and a chronic syndrome which occurs more than 30 days after transfusion.<sup>31</sup>

Attempts have been made to prevent or minimize G.V.H.D. by using grafts of hemopoietic stem cells with as few lymphoid cells as possible.<sup>1</sup> Pretreatment of the recipient with ALG has also been successfully used to prevent G.V.H.D.<sup>24</sup>

*Survival.* At the present time, 43 patients are alive with functioning bone marrow grafts. The longest survivor is 43 months post-transplantation.<sup>3</sup>

#### **SPLEEN TRANSPLANTS**

At least eight patients have received splenic homografts. The chief indication has been in patients with terminal carcinoma in whom it was hoped to induce a graft (donor spleen) versus host (recipient's carcinoma) reaction by providing a continuous source of immunocompetent cells which were foreign to the host lymphatic system.<sup>23</sup> The spleen donors had been sensitized with non-viable tumor cells obtained from biopsy of the recipient's cancer. Other splenic transplants have aimed to replace the suspected enzyme deficiency in Gaucher's disease;<sup>14</sup> to correct the immunologic deficiency in a child with agammaglobulinemia;<sup>23</sup> and to provide Factor VIII in a severe case of hemophilia.<sup>15</sup> The results thus far have been disappointing, with survival of the transplant for only a few weeks.<sup>9</sup>

#### **THYMUS TRANSPLANTS**

Transplants of fetal thymic tissue have been used in an attempt to restore immunologic competence in various syndromes of congenital immunologic deficiency. Many of these transplants have failed and some patients have developed graft-versus-host disease. However, in two cases of the DiGeorge syndrome (congenital thymic aplasia) immunologic competence has persisted for 16

and 18 months respectively, with gratifying clinical improvement;<sup>2, 6</sup> while a child with Swiss-type agammaglobulinemia was making good progress almost six months after receiving a cadaver fetal thymus plus a bone marrow transplant from his sister.<sup>9</sup>

#### **LARYNX TRANSPLANTS**

Transplantation of the larynx has been performed in one patient who underwent a total laryngectomy for carcinoma. He died of recurrent cancer 10 months later.<sup>19</sup>

#### **SMALL BOWEL TRANSPLANTS**

The first small bowel transplant was done in Minneapolis in 1967. Less than 10 cases have been performed since then.

Small bowel transplantation may be indicated in patients with severe malnutrition resulting from "the short bowel syndrome" caused by removal of most of the small bowel for Crohn's disease, mesenteric vascular occlusion, trauma or congenital atresia. After transplantation the patient is initially maintained mainly by parenteral nutrition until the lymphatics of the homograft have had an opportunity to link up with those of the host—after which full oral feeding may be commenced. It is useful to bring out a small isolated loop of the homograft to the skin surface to provide serial biopsies which may provide an indication of impending rejection.<sup>16</sup> The longest survival to date has been for only 2½ months.<sup>12</sup>

#### **TRANSPLANTATION OF ENDOCRINE AND OTHER ORGANS**

Replacement of organs such as the thyroid or the adrenal gland is not necessary, as the missing hormones can be readily supplied by mouth with no risk to the patient. In our own center a parathyroid gland transplant has been successfully performed in a patient who was already receiving immunosuppression to prevent rejection of a renal homograft.

At the present time transplantation of organs such as the testis, ovary, uterus or urinary bladder are not justified, because the risks of immunosuppressive therapy far outweigh any benefits to be gained from replacement of these organs.



### FUTURE PROSPECTS

Most of the techniques of transplantation of the extrarenal organs have been fully worked out. Much more experience needs to be gained with pre- and post-operative management of the recipients before these procedures can be practiced as extensively as kidney transplantation is today. But there are grounds for optimism. As mentioned previously, the results of cardiac transplantation are steadily improving. Furthermore, we should be able to improve on our 26% one-year survival figures with liver transplantation. We have learned to avoid many of the pitfalls encountered in our early experience. Another reason for hope hinges on new developments in immunosuppression. Studies in renal homograft recipients during the past 18 months have shown that azathioprine can be effectively replaced as an immunosuppressive agent by small doses of cyclophosphamide, which does not appear to be as hepatotoxic.<sup>29</sup> In addition, a poorly functioning liver may fail to metabolize azathioprine properly. Cyclophosphamide, on the other hand, is given in its metabolically active form and should be effective no matter what the state of hepatic function. In our most recent experience using cyclophosphamide in combination with prednisone and antilymphocyte globulin, 5 of 6 liver recipients have done well from 1½ to 7 months after operation. If these preliminary encouraging findings are confirmed by further experience, new advances in liver transplantation may become feasible.

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