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EDITORIAL

Liver Transplantation

DURING THE LAST FEW YEARS there has been mounting interest in the possibility that homotransplantation may be an effective technique for the treatment of various diseases that affect primarily a single organ system. There are sound reasons for this enthusiasm. Many patients have had considerable prolongation of life by virtue of chronically functioning renal homografts; in our experience more than 50% of the patients treated from 1½ to 3 years ago are still alive, having had continuous urine excretion by their new kidneys during these intervals.

In view of these encouraging results and those from several other centers (1), it has been natural to think of extending comparable replacement therapy to diseases that result in functional failure of other organs. At present, liver transplantation appears to offer the most immediate possibility of clinical utility. Because of the therapeutic implications involved for patients dying with hepatic failure or hepatic carcinoma, a sober look at the problem of homotransplantation of the liver is in order. The principal hope that homotransplantation of the liver may some day be a practical undertaking derives from studies with the dog.

The most incisive canine experiments have involved orthotopic transplantation in which the recipient liver is removed and replaced with a normally revascularized homograft (2, 3). Postoperatively, there can be no argument about the presence or absence of transplant viability since survival provides proof of continuous function. This procedure can be done with the rela-

tively low immediate mortality of 10% or less. If untreated, the homograft undergoes rejection that is not dissimilar to that observed with other tissues and organs; survival averages slightly more than 7 days.

The most effective agent for mitigation of rejection has been azathioprine.* Unfortunately, this drug is a hepatotoxic agent which, even in small doses, causes acute liver injury in the majority of animals within a few days after beginning administration (4). This high degree of toxicity is apparently specific for the dog; nevertheless, several cases of "hepatitis" have been observed in azathioprine-treated humans long after renal homotransplantation. The therapeutic dilemma is evident. At present, it is necessary to use a liver poison to prevent the effects of liver rejection.

In spite of this handicap, long-term survival has been obtained after orthotopic liver transplantation in the experimental animal. In a recently reported series of nearly 100 canine liver homotransplants (4), the potentiation of homograft function obtained was comparable to that reported after homotransplantation of the dog kidney. The four longest survivals from this study are now over 1 year, with a maximum of 20 months.

The great variability in response of the animals to the homograft is a matter of interest. About one fifth of the dogs being treated with azathioprine alone had clinical evidence of rejection, and their transplants in general had little histologic

* Imuran®, Burroughs Wellcome & Co., Tuckahoe, N. Y.

change when biopsied many months after operation. At the other end of the spectrum, approximately one third underwent overwhelmingly immunologic repudiation of their homografts in spite of comparable therapy, leading to liver failure and death in 1 to 6 weeks. Finally, in half of the animals evidence of rejection was present, sometimes to a severe degree, but with ultimate partial or even relatively complete reversal. In the last group, improvement in homograft function occurred without intensification of the pre-existing immunologic regimen, providing evidence for the important principle that homograft rejection has a tendency to spontaneous remission.

The great variability in these results is almost certainly explained by differences in the quality of chance histocompatibility matching between the donors and recipients. The same problem exists in the human population. The need for pre-operative identification of histocompatibility between donors and recipients is apparent in order to give some predictability to the results before, not after, either experimental or clinical operations of this type. Practical methods for such antigen analysis are not yet available, although many investigators are actively exploring this area (5).

One of the principal theoretical questions about the employment of whole organ liver homografts was whether the foreign tissue might be responsible for a graft reaction directed against the host. It has been noted (4) that the red cell survival time in canine recipients of orthotopic livers is usually shortened during the first several weeks after operation. Histologically, the homografts contain large amounts of hemosiderin. The prognostic significance or even the precise explanation of these findings has not yet been fully elucidated.

The greatly improved results after orthotopic transplantation in the laboratory

should not imply that clinical application will be comparably easy. The implication that patients can be benefited by such operations is still only a hope. To date, seven attempts at clinical orthotopic liver transplantation have been made (6-8). Two of the patients died of hemorrhage on the operating table or soon after. The other five survived for 6½, 7½, 12, 22, and 23 days. Experience with these cases has clearly delineated additional problems that are almost certain to be consistently encountered in future trials.

The element of chance histocompatibility matching has been alluded to above. In addition, the use of cadaveric organs introduces a further unpredictable element of ischemic injury. Almost all of the cadaveric livers thus far employed have had significant early malfunction consequent to anoxic injury during the moribund state of the donor and the subsequent interval of devascularization. In the two patients who died during or immediately after operation it is probable that the livers were functionless at the outset. Postmortem cooling and perfusion afford some protection from ischemic injury (3, 9, 10), but this is incomplete.

Moreover, the technical problems of clinical orthotopic transplantation are of an advanced nature. The indication for operation was hepatic malignancy in six of these seven patients, and in the seventh, there was biliary atresia. The livers were bulky, and in all but one of the cases there was coexistent portal hypertension, thus compounding the inherent risks of a complex procedure. Finally, abnormalities of the coagulation mechanism are almost inevitable. Such patients usually enter surgery with deficiencies of clotting that are exaggerated during the transplant by acute fibrinolysis (11). Ironically, the threat of a fatal hemorrhagic diathesis is succeeded by a phase of hypercoagulability in the successfully transplanted recipient. Three of the four patients in the Denver series

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who survived operation developed thrombosis in their peripheral veins or vena cava, with subsequent multiple pulmonary emboli. The postoperative rebound hypercoagulability seemed to have been exaggerated in these cases by the employment of the clot-promoting agents epsilon-amino caproic acid, fibrinogen, and fresh blood during operation. In the future, iatrogenic manipulation of the coagulation mechanism seems contraindicated unless absolutely necessary to prevent fatal operative hemorrhage.

In spite of these difficulties pathologic studies of the homografts from the unsuccessfully treated patients have not diminished the hope that such operations may ultimately prove to be feasible. In the Denver series the four patients who survived operation and who received the same general immunosuppressive regimen employed after transplantation of the kidney all had relatively good preservation of liver architecture. The degree of mononuclear cell invasion, hepatocyte loss, and reticulin condensation seemed less than in animals at a comparable stage of convalescence. Death resulted from factors other than crushing rejection. Nevertheless, some of these complications, such as gastrointestinal hemorrhage and pulmonary sepsis, seemed much more difficult to control than after clinical renal transplantation.

Orthotopic transplantation has its clearest theoretical indication in the treatment of hepatic malignancy. With liver failure due to benign disease such as biliary atresia or Laennec's cirrhosis, heterotopic transplantation (12) may find a role. With the latter operation, the patient's own liver is not excised. The homograft is revascularized in an abnormal location in the pelvis, one of the paravertebral gutters, or the left subphrenic space. At first consideration such a procedure has considerable appeal. The exacting technical requirements of recipient hepatectomy are avoided. Moreover, the patient is not de-

prived of whatever function might remain in his own diseased liver.

Nevertheless, the use of an auxiliary liver introduces certain physiologic and mechanical problems that have not yet been completely defined. The most serious questions pertain to metabolic factors that may operate to the disadvantage of such ectopically placed organs. In the past, it has often been assumed that a prime determinant of normal hepatic metabolism was the volume of total hepatic flow irrespective of its source. More recent studies (13) have demonstrated that nonhepatic splanchnic venous blood may have a specific hepatotrophic effect and that the optimal method of hepatic vascularization probably requires perfusion by venous blood returning from the intestinal tract.

Such considerations become of the utmost importance with auxiliary liver transplantation. In the dog, an auxiliary homograft placed in the pelvis or paravertebral gutter, rearterialized from the aorta or one of its branches, and provided with a portal venous inflow from the terminal inferior vena cava, undergoes striking atrophy beginning within 2 weeks (8). When additional alterations are made that provide the homograft with portal venous inflow from the splanchnic venous blood (14) or that injure the recipient's own liver (15), the homograft atrophy is at least partially prevented. Such studies suggest that coexisting livers have an important reciprocal relationship and that each organ is capable, under the proper conditions, of injuring the other. Although these physiologic factors can be manipulated by choice of the appropriate operation, long-term function of auxiliary homografts has been less satisfactory than with the orthotopic preparation (14).

In addition to these physiologic considerations, the auxiliary operations may introduce unique mechanical problems by virtue of the space required in the abdomen for the additional organ. In one case

it is known that the incision could not be closed until the recipient's own greatly enlarged liver was removed, and in another the spleen and left kidney had to be excised for the same reason.

At least nine attempts at clinical auxiliary liver homotransplantation have been made in the human; in Denver (16), Minneapolis, New York, Richmond, and Cleveland. All the patients died in 34 days or less. Many of these auxiliary livers had unequivocal evidence of early function, but in the longest two survivors (23 and 34 days), good early function had deteriorated at the time of death, and the degree of histologic injury seemed more advanced than in the orthotopic cases.

In view of the uniform failure to date, the question of further clinical trials with either orthotopic or auxiliary transplantation must now be re-examined. That such efforts will be made seems inevitable. Inasmuch as homotransplantation of the liver can be effectively carried out in the laboratory, there should be no fundamental reason why it cannot succeed in the hospital. But what are the necessary circumstances? It seems clear that major changes in management will be necessary.

Presently, the most important deficiencies are in the immunosuppressive regimen. The combination of agents which has been used with some success after clinical renal transplantation also apparently provides comparable protection from immunologic injury to the liver homograft, but their use involves a greater risk both to the transplant and to the recipient. Both steroids and azathioprine may cause nonimmunologically mediated liver damage. The problems of pulmonary and generalized sepsis that have plagued efforts at renal transplantation have been almost uniformly observed after the more complicated and traumatic hepatic operations. The dose control of azathioprine is difficult since its hepatic pathway of detoxification is inconstant during the events of a rejection crisis.

The destructive peripheral catabolic effects of high dose steroid therapy are probably compounded in the presence of the poor homograft function that is usually present at some time during the postoperative period. The extracorporeal resuscitative measures developed by Eiseman (17) may prove to be of value in controlling the variability of hepatic function early after transplantation, but the short-term effect and the complicated nature of these techniques will probably limit their usefulness. Although the feasibility of reversing severe hepatic rejection has been proved, the risks imposed in achieving this effect are unacceptable.

Instead, the critical improvements will be to minimize rejection or to avoid it altogether. This may be done in one of two ways, singly or in combination. First, perfection of human histocompatibility analysis may allow selection of cadaveric donors on the basis of genetic similarity, thereby reducing the need for antirejection therapy. Equally important, more precise and presumably radically different techniques of immunosuppression will be required. These must have greater specificity so that protection of the graft is more complete, without the diffuse crippling of host immunologic potential which characterizes the present methods. The task is a large but necessary one which depends upon research in the animal laboratory and within the simpler experimental protocol of clinical renal homotransplantation. Without such improvements, further efforts at clinical hepatic homotransplantation will not connote progress, but only fruitless repetition.

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