block the action of more cytotoxic antibodies. The ability to elicit these blocking antibodies would be of obvious importance in transplantation, and this technique holds much promise.

The second general way in which antibodies could act as immunosuppressants would be by feedback inhibition. One can inhibit the response to any antigen by passively immunizing the animal with antiserum. The most striking practical use of this phenomenon is seen in the prevention of erythroblastosis fetalis in children by the administration of anti-Rh antiserum to the pregnant mother. Here, the administration of the antibody inhibits the immune response to the fetal Rh antigen. This technique has been applied to experimental graft rejection with encouraging results.

More must be learned about blocking antibody and the mechanism of feedback inhibition of antibody synthesis. The distinction between these two methods of suppression is not always clear but they promise clinical applicability.

Immunosuppression by Specific Antigen

An animal injected with a specific antigen may either be stimulated to produce an immune response, or alternatively, develop an unresponsive state to subsequent exposure to the same antigen. This immunologically unresponsive state has been called "immunologic tolerance." It is specific for the antigen and differs from nonspecific immunosuppression in that it is antigen-directed. The best example of antigen-directed immunologic unresponsiveness is the unresponsive state enjoyed by animals to their own body constituents. During early life, before maturation of the immune mechanisms, animals apparently develop an immunologically unresponsive state to their own body constituents which is usually maintained throughout life. This unresponsive state appears to result from direct contact between the "self" components and the antigen-reactive cells. Following Burnet's prediction that specific unresponsiveness could be induced to antigenic material by injection during early life, Billingham, Brent, and Medawar demonstrated the induction of immunologic unresponsiveness in mice to histocompatibility antigens by the neonatal injection of replicating allogenic cells. Numerous investigators have since shown that immunologic unresponsiveness can be induced to a variety of nonliving substances, as well as living cells, by injecting these substances into neonatal animals, or, under selected conditions, into adult animals.

The conditions for producing immunologic unresponsiveness directed against foreign antigens are complex; the dose of antigen given must be carefully chosen. In appears that the maintenance of a critical concentration of antigen throughout all the tissue fluids is more important than the amount initially injected. The age of the recipient or the status of his immunologic competence is also important. Neonatal animals are more likely to develop immunologic unresponsiveness to an antigen than adult animals.

Certain antigens (like serum proteins) are endowed with properties that are particularly favorable for the induction of immunologic unresponsiveness, i.e., the ability to persist in the circulation and equilibrate within the extravascular spaces, thereby coming in contact with antigen-reactive cells in effective concentration. Viral and bacterial antigens and transplantation antigens do not have these properties and, in addition, may possess multiple antigenic specificities. The conditions for the induction of tolerance to one specificity may not be conducive to the induction of tolerance to others on the same macromolecule. As a result, only a hyporesponsive state of short duration can usually be induced to these antigens.

A diminished response to transplantation antigens can be induced in adult animals, however, but the antigen dose, physical state of the antigen, route of injection, and state of immunologic competence must be carefully chosen to avoid immunization rather than the induction of tolerance. Irradiation, chemical immunosuppression, and antilymphocyte globulins have been used to inhibit the immune response and permit a relative unresponsive state to develop to an antigen administered while immunocompetence is depressed.

It is likely that clinical transplantation depends, even for its present success, on the establishment of a degree of immunologic unresponsiveness to the antigens implanted in the form of the transplanted organ. It is far easier to establish immunologic unresponsiveness to a vascularized organ graft than it is to an implanted graft such as a skin graft. In experimental situations the route of an antigen injection is likewise very important, the intravenous route being the most tolerogenic.

The ultimate solution to the organ transplantation problem probably lies in immunologic investigation that will result in permitting the establishment of a permanent and specific immunologically unresponsive state to histocompatibility antigens. Histocompatibility typing must first be perfected so that the proper choice of histocompatibility antigen present in the donor, but absent in the recipient, can be made. The "weaker" the antigen, the easier it is to induce tolerance. The unresponsive state could then be induced by injecting pure soluble unaggregated histocompatibility antigens under conditions of generalized immunosuppression. The purity, proper physical state, dose, and timing have not been worked out, however.

It is possible that immunologic unresponsiveness (tolerance) truly represents a specific negative response to an antigen but the state of relative unresponsiveness is more likely due to the presence of an antibody that itself interferes with the further development of immunity. Immunosuppression by antibody and immunosuppression by antigen may, therefore, be essentially identical mechanisms of specific immunosuppression. The presence of such antibodies cannot always be detected in "tolerant" individuals, but antibodies can be detected in patients with excellent long-term functioning human renal allografts. Graft

function is thought to be prolonged by the presence of a specific antibody that inhibits the development of truly effective antigraft immunity. This would explain the common finding in clinical transplantation that reduction in doses of immunosuppressive agents leads to the rejection of the graft despite apparent immunologic unresponsiveness to the graft itself in the presence of very small amounts of chemical immunosuppressants.

Whatever the mechanism of adaptation an organ allograft makes within its immunosuppressed host, the success of clinical transplantation requires a degree of immunologic unresponsiveness to the grafted organ. Otherwise, the doses of immunosuppressants necessary would be so high that patients would fall prey to any passing organism.

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V

Liver Homotransplantation

Thomas E. Starzl, M.D., Ph.D., and Charles W. Putnam, M.D.

Treatment of terminal liver disease by transplantation was founded on the encouragement and knowledge provided by the steadily improving experience in renal transplantation.[21,23] However, the liver is a far more complicated organ, and its malfunction leads to vastly more complex physiologic derangements. Liver patients are further handicapped, as are heart patients, by the lack of a satisfactory means of artificial support comparable to renal dialysis that could take over the organ's compromised functions during the wait for a suitable donor, or over the critical immediate postoperative period. The transplanted liver must function efficiently practically from the moment of anastomosis or the patient is lost.

Despite these and other difficulties, there has been enough progress in the laboratory and clinic to state that liver transplantation is now a feasible and legitimate, although imperfect, form of therapy, and one that may in certain cases be considered the treatment of choice. Human survivals up to 2¾ years have been achieved. A great deal has been and is being learned at a pace that suggests that liver transplants will soon have at least as much chance to succeed as kidney grafts now have.

KINDS OF LIVER TRANSPLANTATION

There are two general approaches to transplantation of the liver. With the first method, the host liver is removed and replaced with a homograft (orthotopic homotransplantation). The alternative technique is the insertion of an extra liver (auxiliary homotransplantation) at an ectopic site. Both procedures were developed in dogs and later studied in other species including rats, pigs, monkeys, and humans. The most encouraging results have been with orthotopic transplantation, for which reason most of this chapter will be concerned primarily with this replacement operation. However, in a special section near the end of the chapter, auxiliary hepatic transplantation also will be briefly considered.

IMMUNOLOGIC CONSIDERATIONS

Is the Liver a Privileged Graft?

When research in liver transplantation was in its early stages, it was suggested by Cannon[7] that if the liver played a significant role in graft rejection, hepatic homografts might enjoy a better fate

than other transplants because presumably the grafted liver would not participate in its own repudiation. The case for this rather mystical view even seemed strengthened by certain experiences with laboratory animals. When immunosuppression in canine recipients was stopped after 4 months, a surprising number of animals continued to thrive either with no signs of rejection or with rejection episodes that waxed and waned remittently.[23, 24] One such dog is still alive in our laboratory with stable liver function 7 years after the transplant. This phenomenon of "graft acceptance" had been noted in dogs with renal transplants[21, 23] but less frequently.

If the liver thus seemed to be an immunologically favored organ for transplantation in dogs, its status in pigs as observed by Garnier,[11] Terblanche,[30] Calne,[6] and in our own laboratory[23] was even more noteworthy. In some experiments with pigs not treated with immunosuppressive agents, identifiable homograft rejection did not occur. In other experiments, rejection was indolent and spontaneously reversed. These suprising results occurred in only a minority of animals. Nevertheless, they had to be attributed to some special privilege of the liver since porcine skin[12] and kidney grafts[6] were regularly rejected in the usual way.

These observations in both dogs and pigs (and now in other animals) invited certain hypotheses in addition to the one stated above that the new liver helped create an internal milieu favorable to itself. Other possibilities[23] were that the liver was inherently less antigenic than other organs, that its relatively great antigenic mass was a beneficial factor, that its enormous regenerative capacity made it less susceptible than other tissues to the effects of chronic rejection, or, in the view of Calne,[5] that it possessed or released some special factor promoting the induction of specific immunologic tolerance.

Whatever the explanation, overstatement of the case for the liver's privileged status could lead to erroneous conclusions about the practical requirements for immunosuppressive therapy following hepatic transplantation in man. At a research level, another danger could stem from the notion that hepatic transplantation, especially in the pig, is somehow qualitatively unique. The fallacy of such a contention is obvious from the fact that even in the "easy" pig model, the majority of untreated liver recipients died from acute rejection.[23] In dogs and humans, control of hepatic rejection may be difficult or impossible in spite of very heavy immunosuppressive therapy.[23, 24]

Rejection Reversal

Instead of being unique, it is probable that liver homografts vary from other organs only by degree in the host immunologic response they evoke in all species including the pig. In this context, two key observations initially made with kidneys[21, 26] have been extended to the liver[23, 24] and there is little doubt that they apply to other tissues as well. The first is the reversibility of rejection. In patients, reversal usually requires intensification of treatment but it has sometimes been noted without any change in the pre-existing therapy, suggesting that such recoveries had an element of spontaneity. As mentioned earlier, "spontaneous remission" of rejection in the absence of all therapy has been seen both in dogs and in pigs, particularly the latter. The events with the liver in all three species are undoubtedly expressions of the same phenomenon, differing only quantitatively.

Graft Acceptance

The second observation of overriding practical and theoretical interest concerns what has already been referred to as "graft acceptance." In many of the human kidney recipients treated almost a decade ago,[21, 23, 26] it was shown that a melting away of host resistance to the homograft occurred surprisingly early after transplantation, often following an acute rejection crisis. This was manifested by eventual declines in the doses of immunosuppressive agents necessary to retain stable graft function. In many patients, the level of chronic immunosuppression has proved to be less than that which at the outset failed to prevent the onset of a severe rejection.

It is probable that all treatment could be stopped in some of these human renal recipients whom we have now followed for many years, but such a drastic final step has not been thought to be warranted. However, as described earlier, therapy has been successfully discontinued in dogs after kidney transplantation and even more consistently after liver replacement, indicating that graft acceptance may become very complete. In pigs, the barrier of natural host resistance is apparently low enough that the cycle of hepatic graft acceptance can be completed without any immunosuppression at all. Viewed in this way, the curious pig liver experiments become only a special example of, rather than an exception to, a general principle of transplantation. Recently, Perper and his associates[17] have provided evidence to support both this concept and the original idea that there is a slight but limited biologic advantage in transplanting the liver versus the kidney. Perper showed that a 3 day course of heterologous antilymphocyte globulin (ALG) treatment or other short-term therapeutic maneuvers in pigs permitted long-term acceptance of kidneys in precisely the same way as occurs with the liver in the absence of all iatrogenic intervention.

Explanations for Graft Acceptance

It is indisputable that some element of acceptance of various kinds of grafts occurs often in humans under the appropriate conditions of immunosuppression and that the degree to which this develops is a prime determinant of the long-term prognosis. Unfortunately, the reason for the change in the host-graft relationship is not known. More than one immunologic pathway may be involved.

Immunologic Tolerance. Schwartz and Dameshek[20] first suggested the possibility that the con-

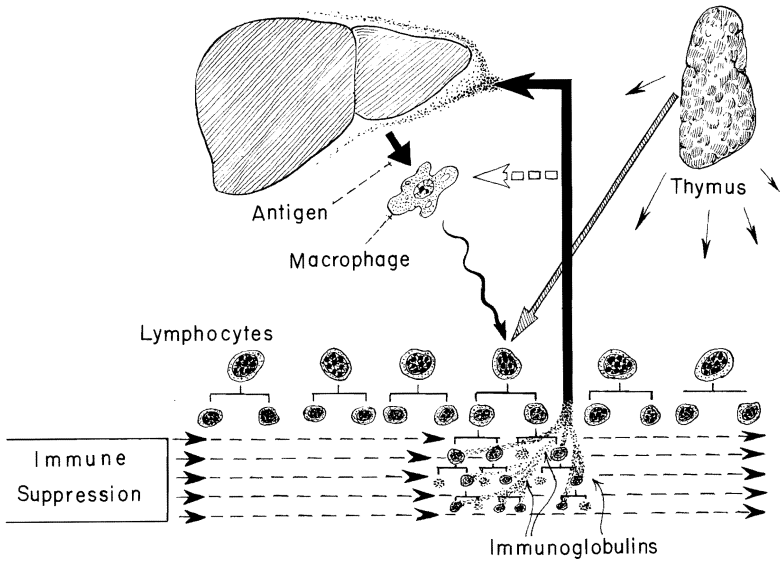

Figure 1 Hypothetical mechanisms by which nonspecific immunosuppression may lead to selective abrogation of the host immune response. Special susceptibility to these agents of a fraction of the lymphoid population could lead to exhaustion of a clone, and hence, tolerance. Since maintenance of such cell lines even in adult life is apparently thymic-dependent in experimental animals, thymectomy would be expected to aid the process; this appears to be true in rodents, but such an effect of thymus removal has not been proved in dogs or humans (see discussion in text). A possible protective role of immunoglobulins elaborated by the replicating cells is also shown.

tinuous presence of a transplanted organ in a host being treated with immunosuppressive therapy could lead to a selective loss of responsiveness to antigens. The suggestion is that specific lymphocyte clones, induced to replicate by the graft antigens, are thereby rendered more vulnerable to the killing effect of immunosuppressive agents than the rest of the lymphocyte population (Fig. 1). Inasmuch as the maintenance of such activated cell lines appears to be thymus-dependent even in adult life, at least in some experimental animals, it is reasonable to be curious about the effect of thymectomy as an adjuvant immunosuppressive measure. The results of thymectomy in a series of our human renal transplants were inconclusive.[27] While the patients with thymic excision did not have better survival or superior renal function, there were fewer and less severe histopathologic abnormalities when their grafts were examined long after transplantation.

The concept of specific, differential tolerance through "clone stripping" can partly explain the characteristic cycle of rejection and reversal occurring after whole-organ transplantation both in treated animals and man and in the weak and self-resolving crises in the untreated pig. Moreover, it is consistent with the fact that a wide variety of agents that are capable of general immunologic crippling can also provide specificity of action under the stipulated conditions of immunosuppressive treatment during presence of the antigen.

To date, few investigations have been performed in human recipients of chronically functioning renal homografts to establish the presence or absence of classic immunologic tolerance to their donor tissue. It would be interesting to know if skin from these donors would be accepted. One of the reasons why such a test has not been carried out in patients is the potential risk of precipitating an immune reaction that could damage the graft.[15] Of course, viable donor tissue is not available for such an experiment in liver recipients even if this were a desirable undertaking.

Amos and Bach[2] have provided evidence that at least some kidney recipients develop true tolerance to their donors. They performed mixed lymphocyte cultures with peripheral blood from a number of our renal recipients and their donors 2 to 4 years after transplantation. In some cases, the recipient lymphocytes no longer developed blast transformation when exposed to killed donor white cells, although they reacted vigorously to third-party cells. However, in other cases recipient lymphocytes retained their reactivity to donor cells. In experiments, dogs with tolerated kidneys may promptly reject skin or kidney grafts from the original donor.

Enhancement. These ambivalent findings do not disprove tolerance through "clone stripping" so much as they suggest that at least another mechanism of graft acceptance may be involved. One such mechanism, termed "enhancement," has been envisioned as a process in which immunoglobulins synthesized by the activated lymphoid tissues circulate to the target tissue and coat it or protect it in some way that is not yet understood (see Fig. 1). Antigraft antibodies, selectively capable of being absorbed by the nucleated cells of the original donor, have been detected in patients carrying well tolerated renal transplants. Extensive immunoglobulin deposition has been demonstrated by immunofluorescence techniques in long-functioning kidney homografts,[19] but this latter finding usually has an adverse connotation rather than a favorable one.

An understanding of the means by which grafts are accepted may hold the key to improvements in therapy. When we come to know more about these mechanisms, it may prove possible to arrange the conditions required for graft acceptance in advance of the arrival of the homograft rather than to rely on their development secondary to the events of rejection. The result might well be the prevention

of rejection with far less immunosuppressive crippling of the immune apparatus in the critical postoperative period. In this connection it is heartening to refer to the experiments of Stuart and his colleagues at the University of Chicago.[29] When enhancing antibodies were combined with tolerance induction by donor-specific antigen pretreatment, rat renal transplants functioned 18 months and longer even in the presence of strong histocompatibility barriers, the absence of immunosuppression, and the retention of immunologic reactivity to most antigens.

TISSUE TYPING

Another way by which clinical results might be improved would be effective donor-recipient matching of histocompatibility (HL-A) antigens as discussed elsewhere in this chapter. Unfortunately, the state of our knowledge about human histocompatibility systems is still primitive. While a good match between siblings appears to provide a more favorable prognosis after renal transplantation than a poor match, our experience with unrelated subjects provides no such correlation[27] and has led us for the moment to ignore the question of HL-A matching altogether in cadaveric cases. In liver transplantation, in which nonrelated cadaveric sources must be utilized exclusively, we have had some excellent results with poor histocompatibility matches and some discouraging results despite close matches.[23] Not only has a correlation with tissue typing been absent with regard to clinical outcome, but no connection at all has been found between the quality of the match and the appearance of the hepatic homograft at subsequent histologic examination.[23] Until the discrimination of the matching methods in nonrelated cases is improved, it is difficult to justify denying a patient an available organ solely on the basis of poor serologic histocompatibility. Nor do we even use most favorable matching as an instrument of selection among candidates for transplantation. At the present time, a more valid criterion may be who has the most pressing need.

THE PROCUREMENT OF ORGANS

In contrast to typing, the procurement of a fresh, functioning, nonischemic liver is of paramount advantage and provides the strongest correlation with success or failure.

The Source of Donors

In discussing homograft quality, the technical details of organ preservation become interwoven with, or even distinctly secondary to, ethical considerations about the conditions for the pronouncement of donor death and problems of cooperation by the medical and lay community. Unquestionably, one of the most important advances that have been made in transplantation has been social in nature, consisting of acceptance by the public of the concept of cadaveric organ removal. In turn, this was made possible by a willingness of many members of the medical profession to identify potential donors, to approach family members at a time of their bereavement, or to indicate in other ways their belief in the propriety of these efforts. By avoiding the glare of lay publicity, this can be and has been done impersonally and with restraint in many areas without exaggeration and without infringing on the personal right to privacy of the individuals involved.

Pronouncement of Death

After the donor has been identified and made available, an effort is made to maintain good liver perfusion up to the last possible moment in order to minimize the ischemic damage that even a short unperfused period may wreak under normothermic conditions. The extraordinary resuscitative efforts required in the donor to prevent circulatory depression in the face of a hopeless prognosis usually require explanation to relatives.

Ultimately, a final decision to discontinue supportive measures may be made after all is in readiness to proceed with the recipient. During the first years of liver transplantation at the University of Colorado, a considerable physiologic penalty was accepted because of criteria that required both brain death and cessation of heartbeat before commencing with organ removal. The price of this insistence was the loss of critical time, and variable ischemic damage both during the agonal stages of circulatory failure and in the minutes after cardiac arrest.[23]

The reason for accepting these conditions was the fear that the quality of terminal care for the donor might be compromised by the pronouncement of death in the presence of a heartbeat. In 1968 our criteria were liberalized in accordance with the concept of irreversible brain injury as it was first outlined and applied at the University of Louvain, Belgium, by Alexandre,[1] and later defended by the Harvard ad hoc committee.[8] Experience since then has convinced us that anxieties about terminal care were unfounded. Acceptance of the brain death concept alleviated one of the most serious problems in liver transplantation, for it virtually eliminated the interval of normothermic ischemic injury and often permitted the organ to be taken in the presence of an intact and effective circulation.

Preservation Techniques

The subsequent preservation of the liver is also of vital importance and has been accomplished by one or more preservation modalities, depending on circumstances, and always including organ hypothermia.[23] With the advantages conferred by the acceptance of brain death, it is often possible to maintain a naturally perfused liver in situ practically up to the moment of its excision. After removal, quick cooling may be accomplished by running a chilled electrolyte solution through the portal vein, thus lowering the donor organ temperature to about 10 or 15° C., which is sufficient

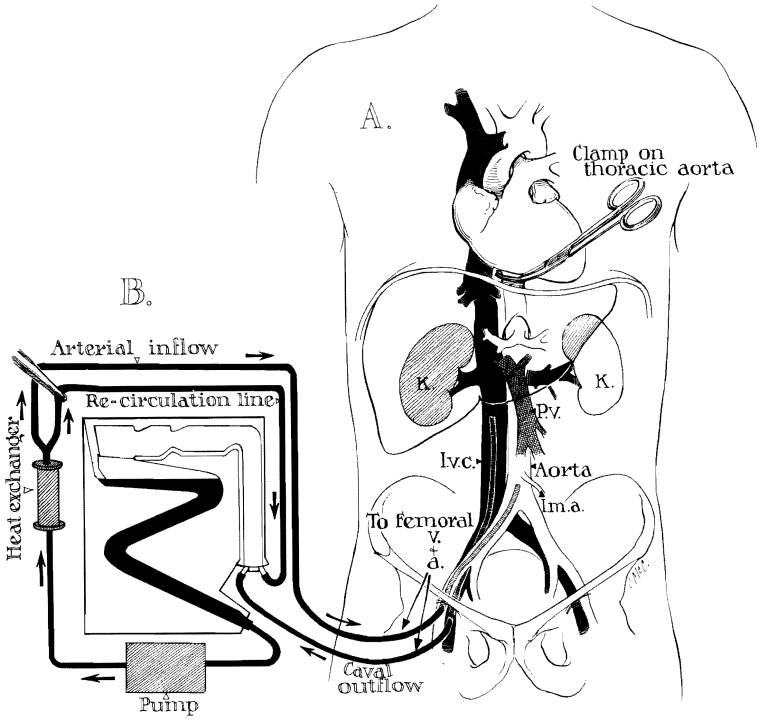

Figure 2 Technique of extracorporeal perfusion with a heart-lung machine. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with a glucose or electrolyte solution to which procaine and heparin are added. The cadaver is thus anticoagulated with the first surge of the pump. Temperature control is provided by the heat exchanger. Cross-clamping the thoracic aorta limits perfusion to the lower part of the body.

for adequate preservation during the hour or so required for the vascular anastomoses in the recipient. In the event of a heart standstill before the recipient is ready, it is possible to employ the procedure used before 1968, when cardiac arrest was required before proceeding; by means of a heart-lung machine, circulation in the cadaver is reinstituted in combination with cooling (Fig. 2). When longer periods of preservation and storage are needed (which has not been the case at our center since 1968) the liver may be removed and placed in a chamber such as that devised by Brettschneider,[4] which combines perfusion, refrigeration, and hyperbaric oxygenation. In one of our cases, the perfusion chamber permitted preservation of a liver without undue damage for a period of 9 hours, long enough for the recipient to make a transcontinental flight to Denver and to be prepared for surgery.

SURGICAL TECHNIQUES OF ORTHOTOPIC TRANSPLANTATION

Species Differences

The procedure of liver replacement was first accomplished in dogs. The transition from animal experimentation to clinical application required some major technical adjustments and in at least one important and unexpected way demonstrated the need to be alert to the special requirements of human physiology. With removal of the host liver it is necessary to cross-clamp temporarily the great veins draining the intestines (portal vein) and the lower half of the body (inferior vena cava). If provision is not made for decompression of the distal venous pools during the anhepatic phase, dogs either die of shock on the operating table or expire at a later time because of irreparable damage to the mesenteric capillary bed. It was assumed that the same precaution would be necessary in humans and this was accomplished in the first five human recipients by plastic bypasses from the splenic or femoral vein or both to the external jugular veins. There was a dismaying incidence of pulmonary emboli, which caused or contributed to the death of three of the first five recipients. It was suspected either that the clots originated within the bypasses and were actually carried to the lungs during the operation or that they formed a short time later at or near the site where the femoral catheter had been inserted.

The omission of the venous decompression procedure in later patients did not produce any serious or long-lasting circulatory effects, including hypotension. Although a slight duskiness of the intestine developed in some recipients, it immediately disappeared when blood flow was restored through the reconstructed venous channels. One can explain the ease with which portal and vena caval cross-clamping was tolerated by man's inherently richer network of potential collateral channels for the return of blood to the right heart, and by the presumed additional increase in their size and ramifications in consequence of the underlying liver disease.[23] Venous decompression with bypasses has not been used in any recent case. Omission of this step has been a major technical advance.

Vascular Anomalies

In planning a liver transplantation, the surgeon must be prepared for a high incidence of anatomic

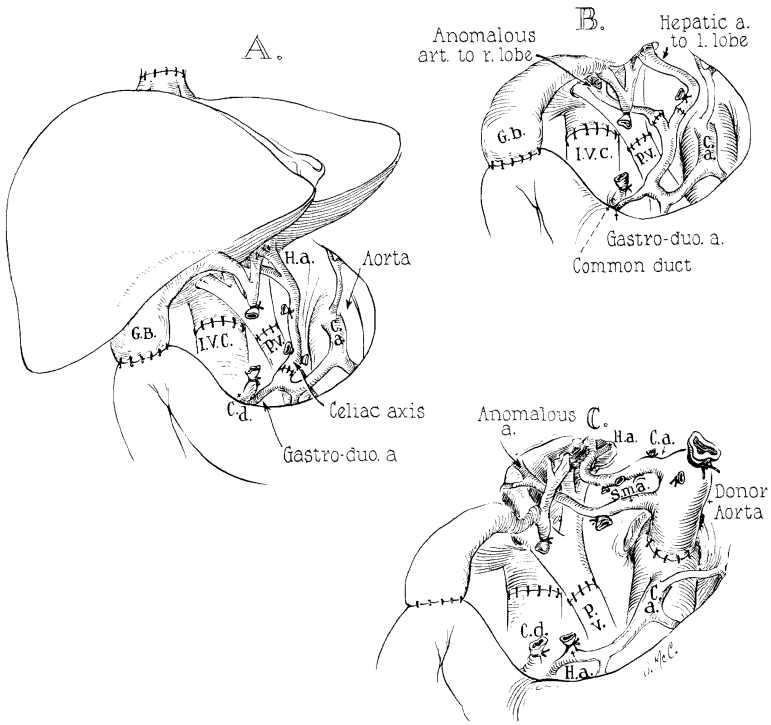

Figure 3 Recipient operations. In most recent cases cholecystoduodenostomy has been performed for biliary drainage as shown. C.a. = celiac axis; C.d. = common duct; G.B. = gallbladder; H.a. = hepatic artery; I.V.C. = inferior vena cava; P.V. = portal vein; S.m.a. = superior mesenteric artery. *A*, The kind of arterial anastomosis most commonly used. The homograft celiac axis or common hepatic artery is attached to the proper or common hepatic artery of the recipient. *B*, Arterial reconstruction of two homograft arteries. The vessels are individually anastomosed to the branches of the recipient proper hepatic artery. *C*, Anastomosis of the homograft aorta to the recipient aorta. The variation was used in a 16 month old recipient because of the double arterial supply to the transplanted liver.

variations in either the graft or host structures.[23] These have been encountered in almost 40 per cent of our cases. Multiple arteries have been the most frequent anomalies (Fig. 3). When these have been in the recipient, most commonly the graft celiac axis has been connected to the host aorta. When the multiplicity has been of the transplant vessels, multiple arterial anastomoses or other variant procedures have been used. There is no question that the need to improvise in these situations imposes an extra risk, particularly in very young recipients whose arteries are quite small and thin-walled even under the best of technical circumstances. In patients with biliary atresia, anomalies may be encountered of which the complexity may be so great as to make it virtually impossible to succeed. Two of our infants with biliary atresia had a curious type of malrotation in which the portal vein passed in front of the pancreas and duodenum, the arterial blood supply issuing from the superior mesenteric artery rather than from the celiac axis, which was absent.[23] In addition, the retrohepatic inferior vena cava was missing. In both cases, corrective maneuvers to overcome the structural deficits were unsuccessful and the patients died within a few days.

Bile Duct Problems

The problems of obtaining adequate bile drainage and avoiding technical errors that may lead to leakage or obstruction may also be complicated by the presence of biliary tract anomalies, and the surgeon must be prepared to tailor his procedure to the individual case.

Choice of Biliary Drainage. An end-to-end anastomosis of the common duct, if it were normal, would have the advantage of preserving the sphincter of Oddi, thus providing drainage through a normal distal channel and reducing the chances of reflux of food or bacteria. This method, which of course is not available in the case of biliary atresia, is considered the procedure of choice by some surgeons. Our own experience has led us to believe that this anastomosis involves too high a risk of leakage and infection. Moreover, it has been considered undesirable to leave a T tube prosthesis or a drain in an immunosuppressed patient after duct reconstruction in close proximity to the portal venous and hepatic arterial anastomoses. Finally, there may not always be an adequate blood supply to the distal portion of the homograft common duct, which normally receives its principal arterialization from retroduodenal sources but which now must depend on retrograde flow from arteries in the central hepatic hilum. Therefore, when feasible, the safer if somewhat less elegant technique is used – anastomosing the gallbladder directly to the duodenum and ligating the common duct (see Fig. 3).

Bile Duct Anomalies. Ligation of the transplant common duct in conjunction with cholecystoduodenostomy may be dangerous if anomalies are not recognized. Communication between the cystic and common ducts may not always be at the point of their juncture (Fig. 4). In one patient the ducts were externally fused but separated by an internal septum; in another the homograft cystic duct passed behind the common duct and descended for almost 2 inches as one compartment of a double-barreled lumen. In both cases, biliary drainage

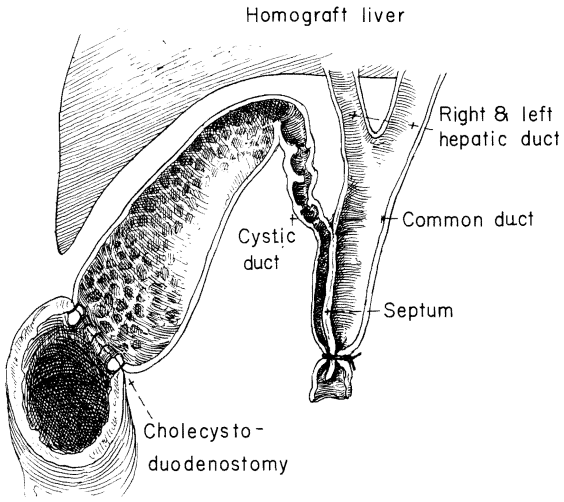

Figure 4 The anatomic basis for a technical error which cost the life of a patient. Distal ligation of the double-barreled extrahepatic duct system resulted in total biliary obstruction.

was inadvertently obstructed when the common duct ligature closed both parallel passages, a technical error that subsequent surgery failed to correct and that proved fatal.

Some of the vascular and ductal anomalies could have been diagnosed preoperatively, resulting either in better planning for surgery or a decision not to operate at all. These earlier cases did not, however, have the benefits of the extensive arteriography and cholangiography that are now used routinely in the donor and sometimes in the recipient as well.

Hemorrhage

Other problems during and after operation may be caused by derangements in the coagulation mechanism that may result in either hemorrhage or thrombosis.[23] As one would expect, acute bleeding can be particularly troublesome during the actual liver transplantation. The very nature of the underlying hepatic pathologic process produces portal hypertension in nearly every patient and the nature of the operation tends to exaggerate it. The usual consequence is mechanical bleeding that can rapidly assume nightmare proportions during the procedure. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are therefore defective in the diseased recipient. These coagulation factors may be even more deficient during the anhepatic phase, or subsequently they may be of dubious quality, depending on the state of preservation of the homograft, on how much ischemia it has suffered, and on how much immediate functional capability it has retained.

When hemorrhage occurs, the surgeon's challenge is to use any and all available hemostatic tactics—ligating, suturing, cauterizing—until the revascularized homograft can participate in what is hoped will be appropriate coagulation function. With our earlier patients, whose homografts were generally of less than optimal quality for the reasons stated earlier, an attempt was made to treat bleeding problems by administering thrombogenic agents. However, hypercoagulability was caused in some instances. The unacceptable incidence of pulmonary embolism in these patients led us to abandon this approach.

In retrospect, it is possible that the coagulability induced by exogenous thrombogenic agents might be prohibitively additive to the clotting brought about by the homograft which, when it begins to function, may overreact. Indeed, the better the condition of the transplant, the greater the risk of unwanted coagulation. Almost every series of liver transplants, including our own, has at least one example of thrombosis of the hepatic arterial circulation to which a rebound phenomenon may have contributed. The use of anticoagulants to forestall this emergency is dangerous. Documented intravascular clotting during the operation would be an indication for heparin, but such proof is hard to obtain. Moreover, heparinization is a double-edged maneuver; depressed clotting can have devastating effects on patients submitted to such major trauma and with so many potential bleeding sites.

In general, it is now considered best to avoid iatrogenic manipulation of the clotting process with either thrombogenic or anticoagulant agents. Instead, our current approach is to leave correction of coagulation abnormalities to natural processes, intervening only under special circumstances and for very specific indications.

Anesthesia

During operation, there are other metabolic abnormalities than those concerned with coagulation. These contribute to the complexity of anesthetic management. Not only is the procedure long and difficult, but even more important, it is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. At any point during the operation, the liver is either inherently impaired, absent, or untried in its new setting. Hence, the task of the anesthesiologist is to administer correctly drugs that, first, are not hepatotoxic and, second, do not depend primarily on the liver for their degradation. In our cases, reliance has been placed mainly on combinations of volatile agents such as fluoroxene and nitrous oxide-oxygen in nonexplosive concentrations. Such management permits use of the electrocautery, gives flexibility in lightening or deepening anesthesia, and allows anesthesia to be abruptly stopped if required by changing physiologic circumstances.[23]

Other Operative Problems

The foregoing are some selected difficulties associated with liver transplantation. There is a long list of other technical pitfalls: adrenal venous infarction, air embolism, and crushing of the right phrenic nerve by too high a clamp on the upper

vena caval cuff, to mention but a few. The reader interested in a more detailed discussion of these and other surgical problems is referred to a recently published text.[23] These technical matters have played a major role in the mortality encountered in our first cases. However, deaths from such causes are avoidable. Consequently, surgical technique is of less critical significance to the future of transplantation than the immunologic problems. The most important factor in successful transplantation remains the prevention of graft rejection by the host.

IMMUNOSUPPRESSION

The immunosuppressive therapy in liver transplantation has borrowed heavily from the experience gained with human renal transplants. Two general treatment programs were evolved with the simpler kidney model and then applied to the liver recipients.

Double Drug Therapy

The first protocol, which was used from 1962 to 1966 for all organ recipients at the University of Colorado, consisted of "double drug" treatment with azathioprine and the synthetic adrenal cortical steroid, prednisone.[21] Evolution of the use of these two agents together, appreciation of their marked synergism, and demonstration that rejection could be readily reversed by increasing the steroid doses were among the advances that made clinical transplantation practical and that introduced what is known as the modern era of this field. But in spite of fair results with renal transplantation, the double drug therapy either did not prevent rejection of hepatic homografts or else it proved too toxic to permit host survival. Six patients treated with liver transplantation from 1963 to 1965 died in a month or less.

Triple Drug Therapy Including ALG

In 1966, heterologous antilymphocyte serum (ALG) was introduced clinically at our center as a third immunosuppressive agent, added to the drugs mentioned above.[23, 28] Since then, this triple drug therapy has been given to all our renal, hepatic, and cardiac recipients. In our experience, rejection has been more easily and regularly controlled, and the risks and morbidity imposed by the necessity for high-dose steroid therapy have been reduced.

Not all transplant surgeons concede the need for ALG. However, those most familiar with its use have enthusiastically confirmed the value of the triple drug regimen, including Traeger of France,[32] and Pichlmayr of Germany,[18] and most recently Najarian and Simmons of Minneapolis.[16] These last authors advocate producing the heterologous serum with cultured lymphoblasts as the antigen rather than mature lymphoid tissue and recommend administering the subsequently refined ALG by the intravenous rather than the originally employed intramuscular route.

All of our human liver recipients who achieved chronic survival were treated with the combination of azathioprine, prednisone, and intramuscular ALG. In the event of a rejection episode, it is the steroid component that has proved to be the agent most amenable to quick adjustment of dosage according to need.

Penalties of Immunosuppression

Some of the hypotheses of the actions of these immunosuppressive drugs have been discussed elsewhere[23] and reviewed earlier in this chapter. Suffice it to say, as was emphasized at the outset of this chapter, the method by which these agents are used in conjunction with the actual transplantation may conspire to permit selective abrogation of the host rejection response. If this were not true, there would be little hope of rehabilitating patients and returning them to life in an unrestricted environment since each of the individual agents

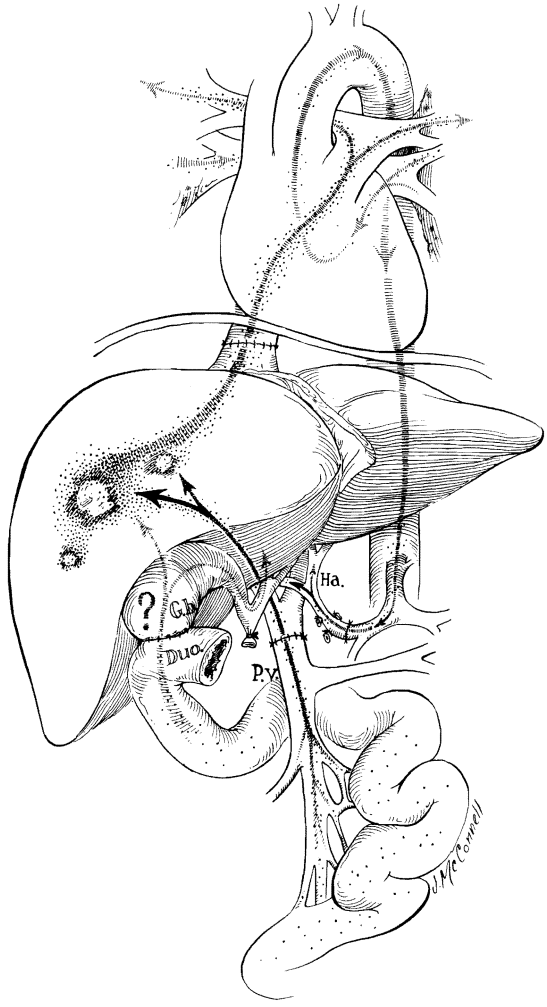

Figure 5 An explanation of the predisposition of the liver to bacterial sepsis. Presumably the invading microorganisms enter via the portal vein or through the reconstructed biliary tract. (From Starzl, T. E., et al.: Ann. Surg., *168*:392, 1968.)

can cause general immunologic crippling more or less in proportion to the dose used.

Risks with All Organs. The most obvious penalty of a depressed immune system is heightened susceptibility to infection.[21, 23] However, it has also become obvious that chronically immunosuppressed patients have an increased vulnerability to de novo malignancies.[23, 27] In our own series of chronic survivors after renal transplantation, more than 5 per cent have developed either mesenchymal or epithelial malignant tumors. Almost all other major transplantation centers have recorded this complication, which is presumably due to failure of the depressed immunologic surveillance mechanism to identify the tumor tissues as alien and to eliminate them or restrict their growth.

Extra Risks for Liver Recipients. In addition to the foregoing general liabilities of immunosuppression, there are some special risks for the liver candidate. One is the fact that hepatic injury in all kinds of organ recipients has commonly been produced by the agents, individually or in combination, of the therapeutic regimen.[23] In some instances, virus hepatitis, apparently made chronic by the partial immunologic invalidism of the host, has been a plausible explanation. In others, hepatotoxicity of the drugs was probably responsible. With liver malfunction, dose control of some of the agents may become difficult since the liver participates in their pathways of action or degradation. These hepatic factors are obviously important in any situation requiring immunosuppression, but they have heightened significance for a trau-

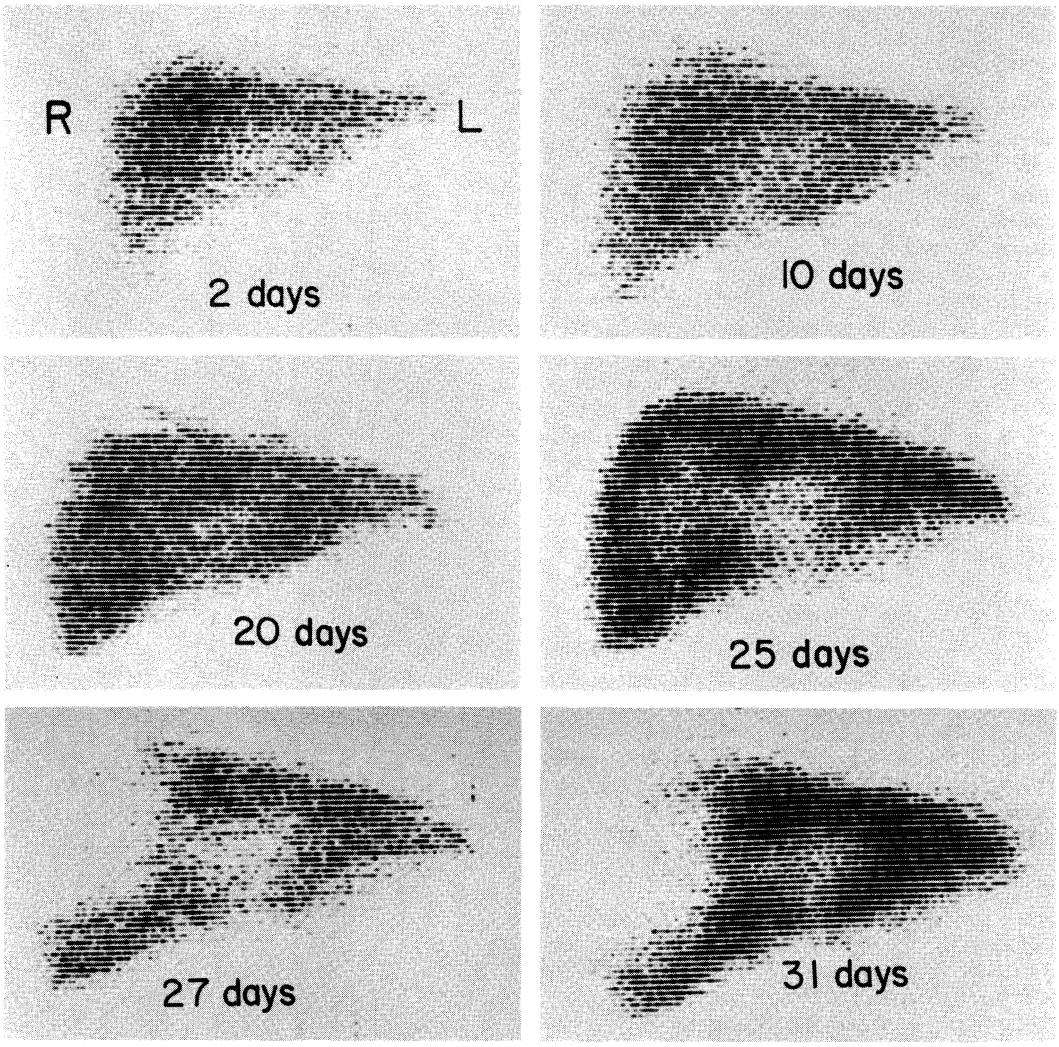

Figure 6 Postoperative technetium scans of the liver in a 13 month old infant whose indication for orthotopic transplantation was biliary atresia. *2 days:* The small homograft is normal. *10 days:* An increase in size is evident although the general configuration of the organ is still normal. *20 days:* No further change is noted. *25 days:* The examination was conducted as an emergency when gram-negative septicemia developed and very high increases in the transaminases appeared. Areas of decreased isotope uptake are obvious in the right lobe and the central part of the liver. *27 days:* A striking extension of the process can be seen less than 48 hours later. A debridement procedure was carried out the same evening. *31 days:* Four days after debridement the radiographic appearance was improved.

matized liver transplanted to a new and hostile environment.

It was mentioned in the preceding section that infection was a major risk to any immunosuppressed patient. In the liver recipient, postoperative sepsis of the graft itself has proved to be a special problem, without doubt partly because of the anatomic location of the orthotopically placed organ, interposed between the intestinal tract and the heart. Bacteria from the bowel, particularly of the gram-negative variety, can be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or, alternatively, by retrograde spread up the duct system after passage through the biliary anastomosis. (Fig. 5). In either event, the presence of nonviable hepatic tissue provides a perfect medium for bacterial growth. Eventually, partial gangrene of the transplant can result, with characteristic nonvisualizing areas on the liver scans (Fig. 6), gram-negative bacteremia, and all the findings of generalized sepsis.

Avoidance of Homograft Sepsis. Early in our clinical series, the above findings of graft and systemic infection led us to consider the essential problem to be one of bacterial invasion and thus prompted reductions of immunosuppression. Such decisions were tragically incorrect and were followed by necrosis and infection of large parenchymal areas. Experience soon taught that ischemia of portions of the liver was the initiating event, and that the basis for the ischemia was rejection.[23] Consequently, immunosuppression should ordinarily be increased rather than reduced if this complication is thought to be impending. When this was done by giving substantially higher doses of prednisone (as noted, the only highly dose-maneuverable component of the immunosuppressive triad), the incidence of regional hepatic gangrene fell to zero. It should be added that our prophylactic treatment protocol includes heavy antibiotic treatment for the first postoperative week, including agents effective against gram-negative bacteria, after which this therapy is stopped.

INDICATIONS FOR LIVER REPLACEMENT

The understanding of regional hepatic gangrene that evolved illustrates well the learning process of caring for patients receiving a new kind of treatment. With the acquisition of experience, other important issues have also been clarified, including that of the indications for liver replacement. A brief summary of our first 33 consecutive recipients, treated from March, 1963, to January, 1970, can be used to illustrate these indications in the light of the results after a minimal potential follow-up of 14 months (Table 1). The 33 patients were aged 11 months to 68 years.

Hepatic Malignancy

The indication for 12 of these transplants was hepatoma or cholangiocarcinoma, and an additional unsuspected hepatoma was found in a 4 year old child treated for extrahepatic biliary atresia. The latter is the only one of this group still alive, now 14 months after the operation; she has no evidence of recurrence of neoplasia. As for the other hepatoma patients, seven died within 39 days, badly damaged homografts being a major cause of failure in five who were among our early patients in the period before the criterion of brain death was applied. Technical accidents with subphrenic abscesses and bile peritonitis were the major causes of early death of the other two patients.

Of the five hepatoma patients who had more prolonged survival (76, 143, 339, 400, and 432 days), metastases developed in all, and in four instances the recurrences were directly responsible for death. Because of this high rate of recurrent carcinoma, it has become our policy to consider liver replacement for hepatoma only under the most exceptional circumstances even though our experience and that of Daloze of Montreal and Calne of Cambridge have demonstrated the possibility of an occasional tumor cure.

Biliary Atresia

Far more desirable candidates are those without neoplasms, in spite of the fact that the technical difficulties in benign hepatic disease are more severe because the patients tend to be sicker and to have more advanced portal hypertension. Moreover, if the diagnosis is biliary atresia, an increased incidence of vascular anomalies can be expected to compound the difficulties, together with the small size of the structures to be anastomosed in these young patients.[23] Nevertheless, the longest survivors of liver transplantation in the world are those who had this disorder (Fig. 7). Of our own series of 15 patients with biliary atresia, treated 14 months or longer ago, including the child with the incidental hepatoma already mentioned, five lived for longer than 1 year and two are still surviving with completely normal liver function, 1 1/6 years and 2 3/4 years, respectively, after operation. The three late deaths after 13, 13 1/2, and 30 months were from recurrent hepatic insufficiency caused in two instances by chronic rejection, but probably in the third by indolent virus hepatitis. Another four children survived 61 to 186 days, all expiring from regional hepatic gangrene for which the apparent cause was too little immunosuppression in the early post-transplantation period. The six other recipients with biliary atresia died within the first 40 days, two from hepatic necrosis probably attributable to ischemia of the donor organ, two from thrombosis of the hepatic artery, and the remaining patient from generalized infection and pneumonia.

TABLE 1 ORTHOTOPIC LIVER HOMOTRANSPLANTATIONS IN DENVER

Patient Number	Disease	Date of Operation	Survival (Days)	Age (Years)	Sex	Donor Age (Years)	Sex	Cause of Death
OT 1	Extrahepatic biliary atresia	3-1-63	0	3	M	3	M	Hemorrhage
OT 2	Hepatoma, cirrhosis	5-5-63	22	48	M	55	M	Pulmonary emboli, sepsis
OT 3	Cholangiocarcinoma	6-24-63	7½	68	M	69	M	Sepsis, pulmonary emboli, GI bleeding
OT 4	Hepatoma, cirrhosis	7-16-63	6½	52	M	73	M	Pulmonary emboli, ? hepatic failure, pulmonary edema
OT 5	Hepatoma, cirrhosis	10-4-63	23	29	F	64	M	Sepsis, bile peritonitis, hepatic failure
OT 6	Hepatoma	11-9-66	7	29	M	73	M	Hepatic failure, sepsis
OT 7	Extrahepatic biliary atresia	5-21-67	10	11/12	M	1	F	Hepatic failure, sepsis
OT 8	Hepatoma	7-23-67	400	1 7/12	F	1 6/12	M	Carcinomatosis
OT 9	Extrahepatic biliary atresia	7-31-67	133	1 9/12	F	4	F	Septic hepatic infarction, hepatic failure
OT 10	Extrahepatic biliary atresia	9-5-67	186	1 1/12	F	1 6/12	F	Septic hepatic infarction, hepatic failure
OT 11	Extrahepatic biliary atresia	10-8-67	61	1 2/12	F	1 8/12	F	Septic hepatic infarction
OT 12	Extrahepatic biliary atresia	11-24-67	105	1 4/12	F	1 2/12	M	Septic hepatic infarction
OT 13	Extrahepatic biliary atresia	2-9-68	901*	2	M	3	M	Died of peritonitis 3 weeks after late retransplantation
OT 14	Hepatoma	3-17-68	432†	16	F	27 17	M M	Peritonitis, subhepatic abscess, carcinomatosis
OT 15	Hepatoma, cirrhosis	4-14-68	339	44	M	20	F	Carcinomatosis
OT 16	Extrahepatic biliary atresia	5-26-68	405‡	1 11/12	M	3 7	M F	Hepatic failure

OT 17	Hepatoma	6-18-68	35	24	F	22	M	Pneumonitis
OT 18	Extrahepatic biliary atresia	6-29-68	4	1	F	1 9/12	M	Hepatic artery thrombosis
OT 19	Intrahepatic biliary atresia	7-20-68	985§	4	M	10	M	Alive, normal liver function
OT 20	Posthepatitic cirrhosis and cholangiectasis	8-13-68	1/2	8	F	10	M	Nonthrombotic occlusion of hepatic artery
OT 21	Extrahepatic biliary atresia	8-20-68	1/2	2	F	5	M	Portal vein thrombosis
OT 22	Laennec's cirrhosis	10-24-68	10	33	M	25	M	Biliary duct obstruction, hepatic and renal failure
OT 23	Hepatoma	10-26-68	143	15	M	6	M	Carcinomatosis
OT 24	Extrahepatic biliary atresia	11-10-68	11	3	F	2	M	? Hepatic arterial insufficiency, hepatic failure
OT 25	Hepatoma	2-11-69	39	45	M	20	M	Bile peritonitis, sepsis, hepatic failure
OT 26	Intrahepatic biliary atresia; hepatoma	5-11-69	76	11	F	17	F	GI hemorrhage, intra-abdominal sepsis, metastases, left lung
OT 27	Wilson's disease	7-15-69	620§	11	M	11	M	Alive, normal liver function
OT 28	Laennec's cirrhosis	7-26-69	13	39	M	22	M	Bile peritonitis, disrupted choledochocholedochostomy
OT 29	Intrahepatic biliary atresia	9-20-69	378	5 6/12	M	10	M	Hepatic insufficiency and chronic aggressive hepatitis
OT 30	Extrahepatic biliary atresia	9-24-69	37	11/12	M	2	M	Partial biliary obstruction, cholangitis, and pneumonitis
OT 31	Juvenile cirrhosis	1-8-70	9	15	F	19	M	Massive homograft necrosis
OT 32	Laennec's cirrhosis	1-16-70	3	46	M	17	M	Unexplained coma
OT 33	Extrahepatic biliary atresia; hepatoma	1-22-70	430§	3 10/12	F	7 11/12	M	Alive, normal liver function

*Retransplantation 19 days before death. Survival is from date of first transplantation.
†The patient received two homografts. The first was removed after 380 days and replaced. The survival noted is from the time of the initial operation.
‡The child received two homografts. The first was removed after 68 days and replaced. The survival noted is from the date of the initial operation.
§Alive April 1, 1971.

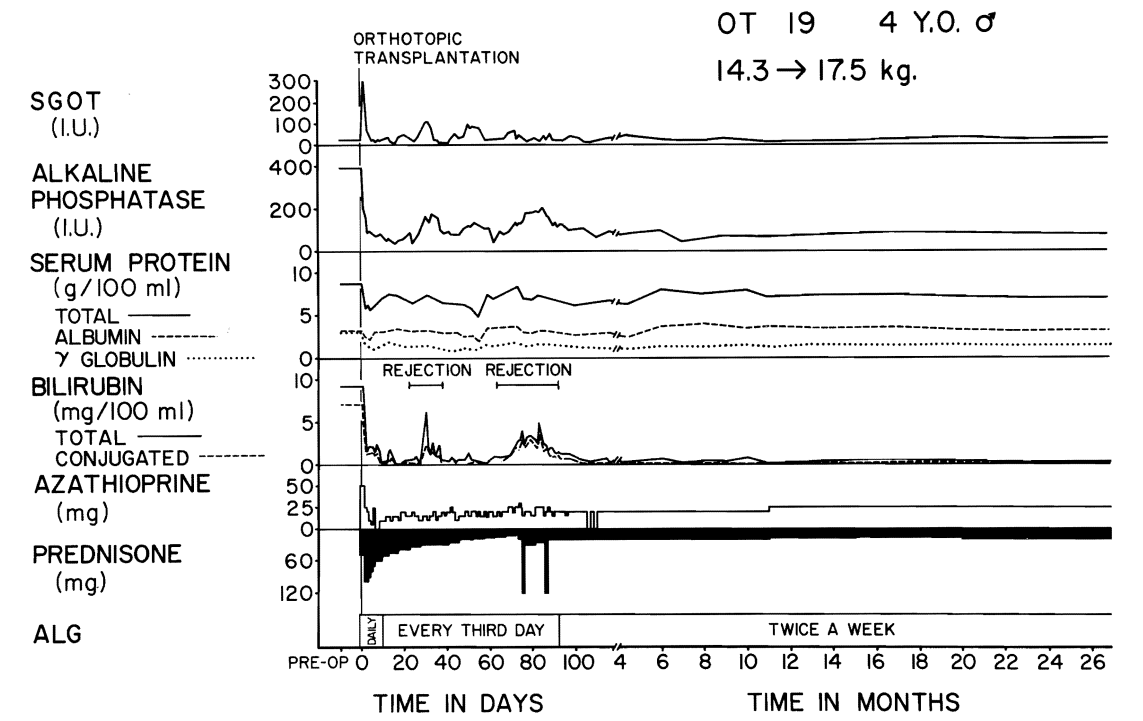

Figure 7 The course of a 4 year old child after orthotopic liver transplantation for the indication of biliary atresia. Note the rejection episodes at 1 month and 2½ months, which were easily controlled. The patient continues to be in satisfactory health now, 2¾ years after operation.

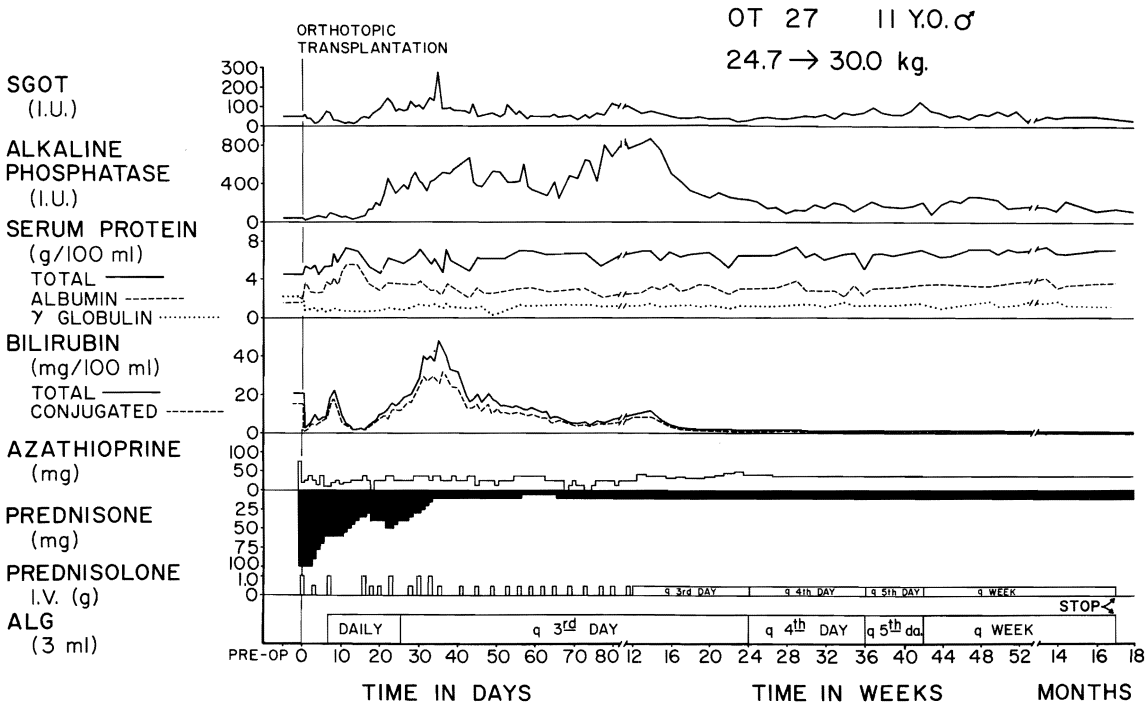

Figure 8 Course of a child with Wilson's disease and hepatic cirrhosis who was treated with liver replacement in July, 1969. He remains well and has no stigmata of recurrent Wilson's disease. (From DuBois, R. S., et al.: Lancet, *1*:505, 1971.)

Cirrhosis

Six patients were treated for cirrhosis a year or longer ago, with the disappointing record of five early deaths. Reasons for the heavy acute mortality included the extremely poor physical condition of the recipients, major hemorrhage due to portal hypertension and depressed coagulation, and technical or metabolic mishaps. The survivor is an 11 year old child whose cirrhosis was secondary to Wilson's disease. After liver replacement, the child suffered an extremely severe rejection crisis, but the process was eventually reversed, with normal liver function continuing now more than a year and a half after the operation (Fig. 8). Moreover, the new liver, which was biopsied at 6 and 17 months, has not reaccumulated copper and it appears to have corrected the genetic error in copper metabolism, a finding that may be important in the search for the etiology of this disease.[9]

Undoubtedly, one reason for the bad experience with cirrhotic patients has been a reluctance to recommend such therapy except in the agonal stages of the disease. Now that the feasibility of long-term survival and rehabilitation has been demonstrated, transplantation at an earlier time probably should be considered, particularly in cases of postnecrotic cirrhosis in which the maximal value of medical management and of abstinence from alcohol has already been realized.

Hepatitis

In addition to the 33 consecutive liver recipients recorded above, another patient with a shorter follow-up will now be mentioned because of the exceptionally interesting circumstances of transplantation.[31] This is a 28 year old woman with chronic active hepatitis who was operated on in August, 1970. For a year before the operation, as well as on the day of the transplantation, immunodiffusion tests for the hepatitis-associated (Australia) antigen[3] were positive. She provided an opportunity to examine the thesis that this antigen has an essentially hepatic source. The argument for this proposition was supported by the

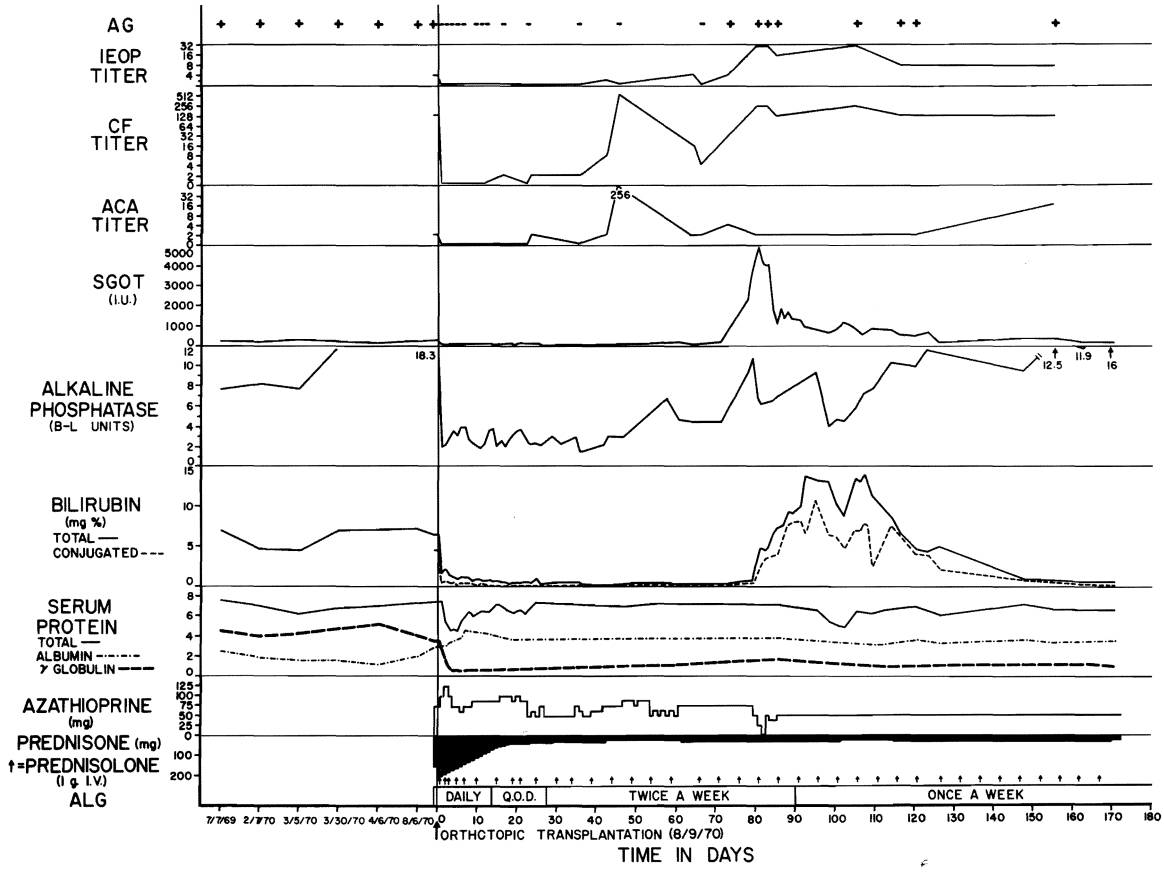

Figure 9 The course of a patient who was terminally ill with chronic aggressive hepatitis, Australia (Au) antigen-positive. She was treated by liver replacement. Note that all serologic evidence of serum hepatitis disappeared immediately after operation only to return some weeks later. AG, agarose gel micro-Ouchterlony test for Au antigen. IEOP, quantitative immunoelectro-osmophoresis test for Au antigen. CF, complement fixation test for Au antigen. ACA, anticomplementary activity, which is thought to reflect the presence of circulating antigen-antibody complexes; the test is not immunologically specific for Au antigen. Normal Bessey-Lowry (B-L) units for alkaline phosphatase are less than 3. (From Torisu, M., et al.: Ann. Surg., *174*:620, 1971.)

immediate disappearance of the Australia antigen from the bloodstream after the operation (Fig. 9). About 6 weeks later, it reappeared and within a few days there followed an attack of acute serum hepatitis with joint pain, anorexia, jaundice, and evidence of hepatic necrosis by transaminase determinations. Fortunately, her liver function abnormalities have regressed nearly completely (Fig. 9), but she remains Australia antigen-positive, now 8 months post-transplantation. It remains to be seen if the virus will condemn the new liver to the same fate as the old one, if the long-term pace of the infection will be affected by the chronic immunosuppression, and if the patient will continue to be a virus carrier.

The case has other interesting implications. It is customary to think of the incubation period of infectious diseases in terms of the host immune defenses. In this patient, the immune apparatus was retained but systematically weakened. Yet the latent period of the disease was about that to be expected with a fresh infection, indicating that the incubation period in this patient was primarily concerned with the target organ.[31]

AUXILIARY LIVER TRANSPLANTATION

Both in experimental animals and in patients, survival after auxiliary transplantation has been inferior to that with the orthotopic procedure. The reasons for these disappointing results have not been entirely clear, but plausible explanations have been advanced indicting both metabolic and mechanical factors.

Metabolic Considerations

When auxiliary liver transplantation was first attempted in immunosuppressed canine recipients, a curious and disquieting observation was soon made.[25] The extra organs underwent rapid shrinkage which was usually evident within 2 weeks and which was very advanced at all times after 1 month. Many subsequent studies, especially those of Marchioro,[13,14] have been designed to explain the atrophy and to define the conditions for its avoidance.

The results of these investigations, which have been reviewed in detail elsewhere,[23] have shown that two coexisting livers may engage in a physiologic competition that can result in serious injury to one or the other organ. The competitive potential of the individual livers can be unbalanced by a variety of factors. Advantageous conditions include perfusion of adequate quantities of blood, particularly if the portal component is derived from the intestinal venous (splanchnic) effluent. Handicaps may be imposed by obstructing the biliary drainage, by reducing the total blood flow, by depriving the organ of flow from splanchnic sources, or by hindering it in a variety of other ways. The favored liver in such a situation will flourish while the disadvantaged one shrinks.

The first step in minimizing or preventing auxiliary homograft atrophy in animal experiments is to avoid situations in which the transplanted liver is placed at a physiologic disadvantage. The second step is to fully appreciate that the homograft requires a better than equal environmental opportunity to counteract the immunologic duress which it alone must suffer, if there is not a perfect histocompatibility match or else totally effective immunosuppression. In dogs, auxiliary homograft atrophy can largely be prevented if it is rearterialized and also given a portal inflow from the splanchnic venous system, and if the host liver is damaged with an Eck fistula. Additional privileges can be extended to the homograft by injuring the host liver in other ways, such as by ligation of the common duct.

Clinical Experience

It is virtually certain that the principle of inter-liver competition applies in a general way to auxiliary hepatic transplantation in humans. However, what is not known is how important this factor will be. In adult patients with cirrhosis who might be candidates for hepatic transplantation, the competitive capacity of their own livers would be expected to be largely lost. On the other hand, it is conceivable that the host liver in pediatric victims of biliary atresia could be capable of promptly and seriously compromising the welfare of the new organ, since the hepatic parenchymal function in such patients is often surprisingly well maintained until just before death.

These comments remain speculative since the longest survival to date after auxiliary liver transplantation in man for the indication of hepatic failure has only been 34 days. In this case, the diagnosis was alcoholic cirrhosis. One day before transplantation a portacaval anastomosis was performed. The extra liver was obtained from a 12 year old boy and placed in the right paravertebral gutter (Fig. 10). It functioned promptly for several days until the onset of a rejection that was never reversed (Fig. 11). The patient eventually died of multiple infections.

During life several liver scans were obtained with rose bengal iodine-131 and with gold-198 isotopes. The rose bengal scans showed an approximately equal division of the specific radioactivity between the two livers. The gold isotope was concentrated almost exclusively in the homograft. With both kinds of studies there appeared to be a diminution in the size of the transplanted organ. The impression of atrophy could not be supported with certainty from the histopathologic studies of the homograft.[23] Both hepatocyte loss and collapse of the supporting reticulin were features of the autopsy specimen, but these findings have been seen in orthotopic homografts.

Recently, Fortner[10] reported survival of 8 months after auxiliary liver transplantation for the indication of cholangiocarcinoma. The recipient was not dying of hepatic failure but had jaundice and intractable itching as the primary complaints. The auxiliary liver relieved these symptoms for several weeks or months before the hyperbilirubinemia returned. Eventually, the cause of death was

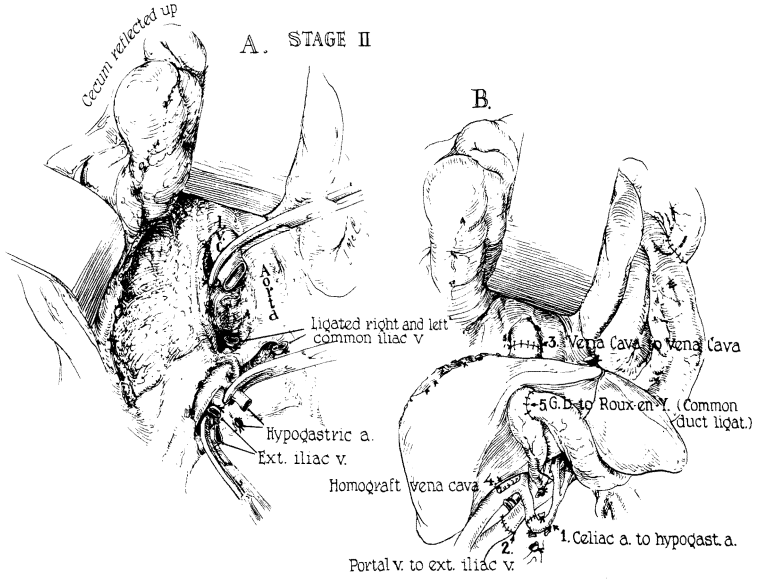

Figure 10 The method of auxiliary liver transplantation used in a 47 year old patient; both donor and recipient had O blood type. The donor, a 12 year old boy, died from head trauma a few minutes after arrival at the hospital. Circulation was maintained for 45 minutes by external cardiac massage until the liver could be cooled by intraportal infusion of a chilled electrolyte solution. The subsequent hypothermic period required to remove the liver and revascularize it in the recipient was 120 minutes. The outflow of the new organ was directed into the transected inferior vena cava. The portal blood supply was obtained from the common iliac vein. The hypogastric artery easily reached the celiac axis for end-to-end anastomosis. The liver was small enough to readily fit behind the reflected cecum. The operation was done in 5 hours with a blood loss of 2500 ml. *A*, Recipient operative field. *B*, Completed operation. Note the Roux-en-Y cholecystojejunostomy. (From Halgrimson, C. G., et al.: Arch. Surg., *93*:107, 1966.)

suppurative cholangitis of the native liver. The extent, if any, to which life was prolonged by insertion of the homograft must be speculative.

Many other attempts have been made at auxiliary hepatic homotransplantation of which only a few have been formally reported. Groth of Stockholm recently made an international survey and found 34 cases. Among the 34 reported and unreported recipients, there were only five, including the two patients just described, who lived for as long as 3 weeks. Within the total group there was an extraordinary incidence of technical difficulties. Moreover, almost all the patients who lived for more than a few days after operation developed

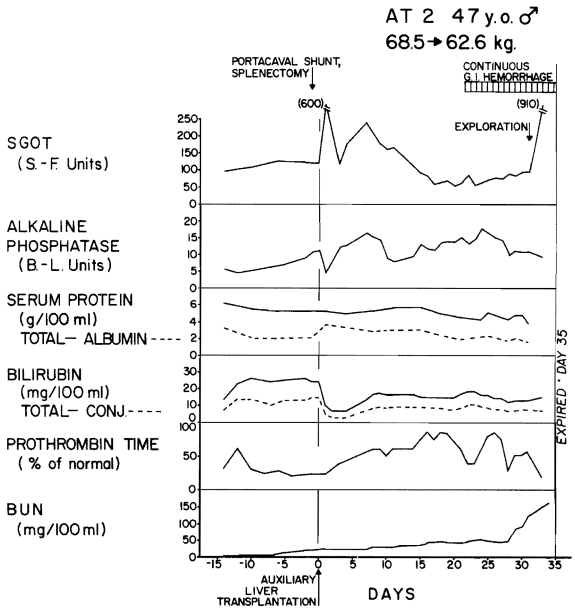

Figure 11 The course of the patient whose operation is depicted in Figure 10. There was apparently good initial function which later deteriorated when rejection was not controlled. Note the rapid development of azotemia late in the course. The gastrointestinal bleeding which was the immediate cause of death was due to widespread intestinal moniliasis; the exploratory laparotomy was made in an effort to control the bleeding. The immunosuppression in this case was the azathioprine and prednisone. Profound leukopenia developed during the fourth postoperative week.

lethal pulmonary complications; abdominal overcrowding by the extra organs appeared to have been a contributory factor in several instances.

In view of this experience, it would seem prudent to give special thought to the relative size of the homograft that is available. Our present belief is that the organ would ideally come from a smaller donor and would be placed in a recipient whose abdomen had been prepared by stretching with long-standing ascites. Such a perfect anatomic situation was present in the recipient who lived for 34 days.

In the human it may be exceptionally difficult to provide an auxiliary liver with a portal flow from splanchnic venous sources. For this reason it is our present opinion that the best and simplest operations are compromise procedures such as that depicted in Figure 10. With such a technique, the homograft is revascularized in the right side of the abdomen as with portacaval transposition. Portal blood flow is diverted away from the host liver with a portacaval anastomosis. If the portal decompression can be done in advance of the transplantation, insertion of the homograft is made immeasurably easier by obviating the need to work in a retroperitoneal space filled with high-pressure venous collaterals.

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VI

Lung Transplantation

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HISTORICAL ASPECTS

Among the various organs, the lung was one of the last to be used in experimental transplantation. Demikhov[9] first investigated experimental pulmonary transplantation extensively. He developed techniques for transplantation of lobes and the intact lung in dogs. Metras[22] was the first to utilize the atrial cuff technique for the venous anastomosis. Juvenelle in 1951 performed the first successful orthotopic autograft, and function of this lung was demonstrable 35 months later.[27] In 1963 Hardy reported the first human pulmonary allograft.[20]

EXPERIMENTAL PULMONARY TRANSPLANTATION

A reported mortality rate of 35 to 80 per cent attests to the complexity of experimental lung transplantation.[12] As these figures refer to autogenous reimplantation in dogs, which consistently survive pneumonectomy only, the anatomic and physiologic alterations produced by the reimplanted lungs are appreciated. The autogenous reimplanted canine lung has been the most frequently employed preparation for evaluation of pulmonary function and technical factors. Results of these studies will be summarized in discussions of technical aspects and functional evaluation. Canine allografts and experiments in other animals will be discussed and compared separately.

Technical Aspects of Autogenous Reimplantation

The high early mortality has been due primarily to technical failures. Venous obstruction and the resultant pulmonary edema has been the most common cause of failure and decreased function.[1] A high incidence of thrombosis occurs with anastomosis of individual pulmonary veins. For this reason, individual lobes are less frequently reimplanted, and the atrial cuff technique is utilized in most lung reimplantations. This method does not prevent venous obstruction entirely, however. Decreased function and pulmonary hypertension were found in lungs in which excision and reanastomosis of a cuff of atrium containing the pulmonary veins were the only procedures.[5] Acute thrombosis, chronic fibrotic narrowing of the suture line, and fibrous plugs originating proximal to the anastomosis have been described.[31]

Thrombosis at the pulmonary artery anastomosis has not been observed frequently except in the presence of vascular stasis in the lung secondary to narrowing of the venous anastomosis. A pressure gradient across the arterial anastomosis is often demonstrable and is more severe when the contralateral pulmonary artery is occluded.[29] Veith has shown that this is due to the inability of the anastomosis to dilate, and he has advocated the creation of a distensible anastomosis by spatulating the ends of the pulmonary artery or by use of a vein patch in the anastomosis.[34]

Bronchial complications have been observed in as many as 50 per cent of animals undergoing reimplantation.[11] Ischemia of the bronchial anastomosis is the major cause. Stone,[32] after division and reanastomosis of only the bronchus, found necrotic changes at most of the anastomoses. By 6 weeks, however, the majority of these changes had regressed and healing was occurring. Subsequent scar tissue formation may narrow the bronchus, but this must be severe to be functionally significant. Most investigators have found that if the bronchus is divided as close to the hilum as possible, the incidence of bronchial complications is

markedly reduced.[1,19] Ellis[14] has demonstrated that collateral blood flow via the pulmonary artery to the bronchus is present at the hilum but not more centrally. This would explain the lack of necrosis of the short bronchial stump. Others feel that reconstruction of the bronchial arterial supply is indispensable if bronchial complications are to be avoided.[23]

Division of hilar lymphatics has been found to have no effect, and regeneration of lymphatics is demonstrable within 2 to 3 weeks.[19]

Functional Evaluation and Pathophysiology of the Reimplanted Lung

Several methods have been employed to evaluate function of the reimplanted lung. Differential bronchospirometry with measurement of ventilation and oxygen uptake has been used most frequently. Reliable separation of function of the reimplanted lung from that of the normal lung is difficult. Angiography has been used to evaluate circulation in the graft but gives little quantitative information. Right heart catheterization is employed to measure cardiac output and pulmonary vascular resistance. Balloon tamponade of the contralateral normal pulmonary artery and its effect on pulmonary resistance and cardiac dynamics also may be accomplished by this method. Arterial blood gas determinations are used routinely to evaluate the status of the graft. The xenon-133 scintiscan is one of the most promising methods for evaluation of lung transplants. It is noninvasive, and sedation of the animal may not be required. Both ventilation and perfusion are evaluated in a quantitative fashion.[21] Oxygen uptake and intrapulmonary shunts are not measured by this technique. The most stringent test of function has been simultaneous or delayed contralateral pneumonectomy or pulmonary artery ligation.

Function of the lung decreases immediately after reimplantation. Within 2 to 3 weeks the ventilation and oxygen uptake increase but do not return to normal in most instances.[11,28] Perfusion of the graft is decreased also, especially to the upper lobe. However, in many instances abnormal vascular anastomoses are found in conjunction with the decreased perfusion.[21] In those lungs without structural abnormalities, perfusion also will return toward normal.

Pulmonary arterial hypertension is present to a variable degree in all reimplanted lungs, and is a major cause of death.[2,25] Although hypertension decreases with time, the recovery phase is more prolonged, and pressure does not return to normal. Elevated pulmonary artery pressures may be secondary to arterial or venous stenosis, or vasoconstriction of the pulmonary vascular bed. Depending on whether pressures are measured proximal or distal to the anastomosis, the true source of the pulmonary hypertension may be difficult to determine. Nigro[25] demonstrated increased pulmonary artery pressures in the absence of angiographically demonstrable defects in the arterial or venous anastomoses.

Pulmonary vascular resistance may be normal or increased. If the contralateral pulmonary artery is occluded or if contralateral reimplantation is done, resistance is usually elevated.[24] Although resistance is elevated, it is not fixed and will respond to infusions of acetylcholine with an improvement in oxygen uptake. Veith has demonstrated that the vascular bed will dilate in response to oxygen following the vasoconstriction produced by hypoxia.[33]

When simultaneous reimplantation and contralateral pulmonary artery ligation are carried out, most animals die within 48 hours. The mechanism is acute pulmonary edema with right ventricular failure.[8,24] Pulmonary artery pressures may increase to three times the normal level. In normal dogs Daicoff has shown that occlusion of the right pulmonary artery causes a substantial increase in the left pulmonary artery pressure, suggesting that the capacity for pulmonary vasodilation is slight in the dog.[8] Factors other than increased capillary hydrostatic pressure may be involved in the production of pulmonary edema. Increased capillary permeability, decreased blood osmotic pressure, and obstructed lymphatic drainage have been implicated.

The denervation of the lung that occurs as a consequence of reimplantation has been of serious concern to many investigators, as it was feared that respiratory paralysis would occur. It is generally recognized that the Hering-Breuer reflex is absent in reimplanted lungs, and regression of the intrinsic pulmonary nerves and afferent autonomic stretch receptors has been demonstrated. Denervation also has been postulated as an explanation for the increased vascular resistance.

The fact that animals survive after bilateral reimplantation or unilateral reimplantation with simultaneous contralateral pneumonectomy lessens the functional significance of denervation.[15] The rate and rhythm of respiration in the resting state after these procedures usually are altered. More important, however, is the fact that these animals will respond normally to hypoxia and hypercarbia.[30] In a dog studied 22 months after bilateral reimplantation, it was found that pulmonary function had continued to improve. Vagal block effected no change, indicating that regeneration had not occurred. Pulmonary hypertension also had shown progressive improvement, although a small gradient was present across the arterial anastomosis.[29]

Immediate functional adequacy of the reimplanted lung may be ascertained by occluding the contralateral pulmonary artery. It has been shown that arterial blood gas levels remain satisfactory and, although it is decreased, ventilatory function is adequate immediately after reimplantation.[35]

Lung compliance either decreases or remains unchanged. Mucous transport has been studied, by means of tantalum particles, and found to be subnormal up to 120 days following reimplantation, but subsequently it became normal. This was ascribed to the effects of denervation.[13]

Ischemia of the lung while reimplantation is