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Mit 236 Abbildungen, davon 8 mehrfarbig, und 91 Tabellen



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Eppinger Prize Lecture: On Liver Transplantation*

TH. E. STARZL

Since receiving the news of the Eppinger Award, I have thought more than once about the ties that bind the United States to Europe, how immediate are the connections of most American citizens to a European culture and society, and the indebtedness which all of us have to our forebears. There is a minor literary classic by Thornton Wilder called "The Bridge of San Luis Rey". The central incident in this book is the collapse of a bridge in South America, with the death of several travelers. The number of lives lost was not great, but the influence of these people on their communities and therefore the world was far from trivial. By means of acts of love or compassion, their personalities had effected other lives and had become pervasive like the ripples in a tranquil pond into which a stone had been thrown.

I know the same thing could be said about Professor HANS EPPINGER. By the time the photograph in Fig. 1 was taken, his eyes reflected the sadness of a series of insupportable losses including those of his only son and his grandson during the Second World War. He did not have long to live in earthly terms and yet it is quite evident from the nature of today's meeting that he is still with us in spirit. I would like to acknowledge my own debt to Professor EPPINGER with a bit of *petite histoire* that illustrates well the thesis of Thornton Wilder.

More than 20 years ago as a medical student at Northwestern University in Chicago, I attended a series of pathology seminars conducted at the Cook County Hospital by Professor HANS POPPER, one of EPPINGER's pupils. I remember particularly well an autopsy performed for the class by Dr. POPPER on a patient who had died of post-necrotic cirrhosis. It excited in me an interest in liver disease which has persisted until now. The thousands of others who were eventually taught by EPPINGER's students now are part of the growing chain by which this man's influence will further spread. It is not hard to see why he is held in such honor.

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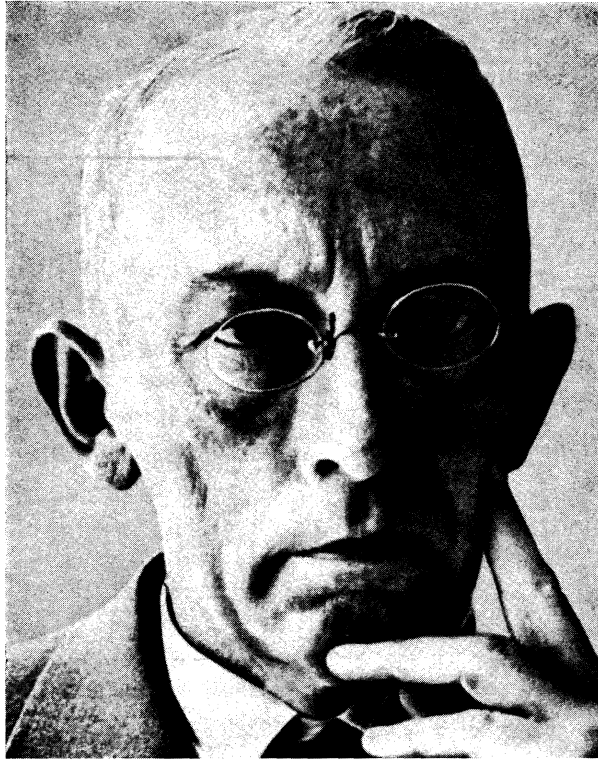


Fig. 1. Professor HANS EPPINGER, 1879–1946. [By reproduction from *Wien. klin. Wschr.* 78: 674 (1966).]

After these introductory remarks, it may be superfluous to say that the topic of my presentation concerns the liver and specifically, transplantation. In discussing the subject, I would like to convey some sense of the experimental background of such procedures, to comment about the immunosuppressive treatment that is required for success, and most importantly to review the evolving attitudes about the indications for clinical transplantation.

Auxiliary transplantation

It should be stressed that there are 2 fundamentally different kinds of hepatic transplantation procedures. In one, first described in dogs by C. Stuart Welch of Albany, New York, the host liver is not disturbed and the new organ is placed in some abnormal location. The heterotopic sites have included the paravertebral gutter (Fig. 2), the splenic fossa, and the pelvis. Providing an

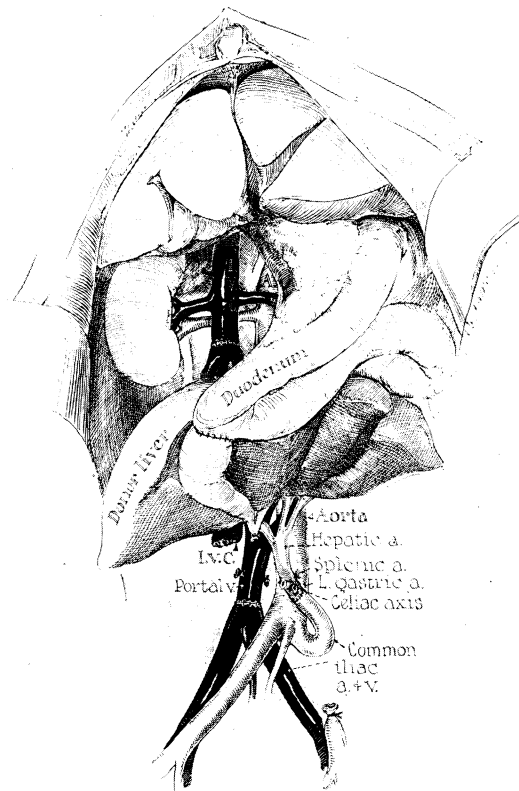


Fig. 2. Auxiliary liver transplantation in dogs by a modification of WELCH's original technique. Note that the reconstituted portal blood supply is from the distal inferior vena cava. Cholecystoduodenostomy is performed. [By permission of Ann. Surg. 160: 411 (1964).]

arterial supply under these circumstances is not difficult. However, establishment of an inflow to the portal vein has special metabolic implications.

Interliver competition

The significance of the source of portal blood supply was realized in 1963 and 1964 when auxiliary canine livers were transplanted by techniques similar to that shown in Fig. 2. The portal venous inflow was taken from the distal inferior vena cava or an iliac vein, establishing in essence a blood supply for these homografts like that after the experimental procedure of portacaval transposition. Somewhat to our surprise the transplanted livers quickly underwent major atrophy. The gross appearance and lobar proportions of the

now diminutive homografts remained relatively unaltered except for size (Fig. 3). Histopathologically, the major finding was a massive loss of hepatocytes. The duct system did not participate in the shrinkage and, if effective immunosuppression was provided, it often was more or less completely spared from rejection.

An explanation for these findings was subsequently provided by a series of papers from our laboratory which showed that two co-existing livers could engage in competition to their mutual disadvantage. Conditions favoring one organ over the other included the kind of portal venous blood; it was best for the source of this blood to be the effluent returning from the intestine rather than from some other capillary bed. Other factors included the *quantity* of portal venous flow, the presence or absence of biliary obstruction, and the magnitude of rejection to which the homograft was subjected. Depending on the circumstance, one of the livers usually could be shown to flourish whereas the other organ, which was laboring under a physiologic handicap of one kind or other, underwent atrophy.

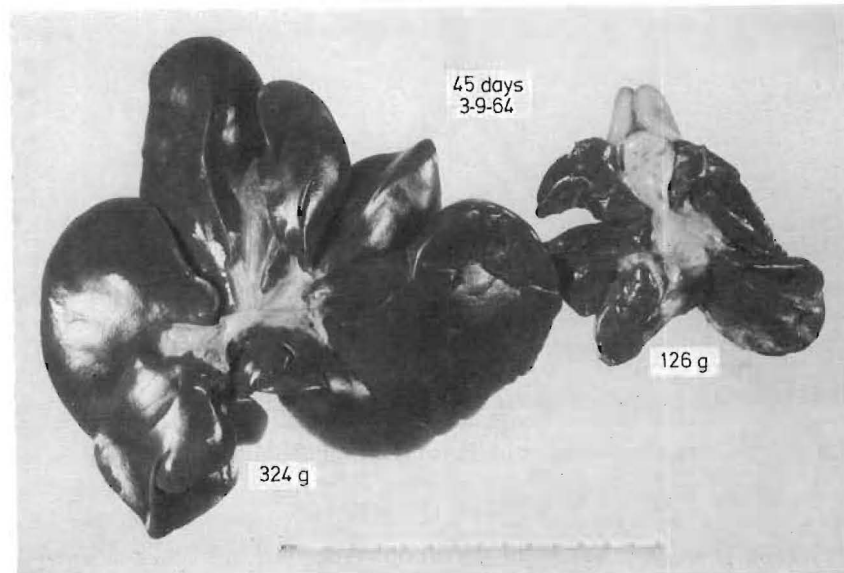


Fig. 3. The auxiliary homograft (right) and the recipient dog's own liver (left) in an experiment in which the host and transplanted organs had originally been about the same size. The method of revascularization was as illustrated in Fig. 2. Postoperative immunosuppression was with azathioprine. Note the well preserved but dimensionally reduced general structure of the homograft. The gallbladder did not shrink proportionately. The specimens were obtained 45 days after transplantation. [By permission of *Ann. Surg.* 160: 411 (1964).]

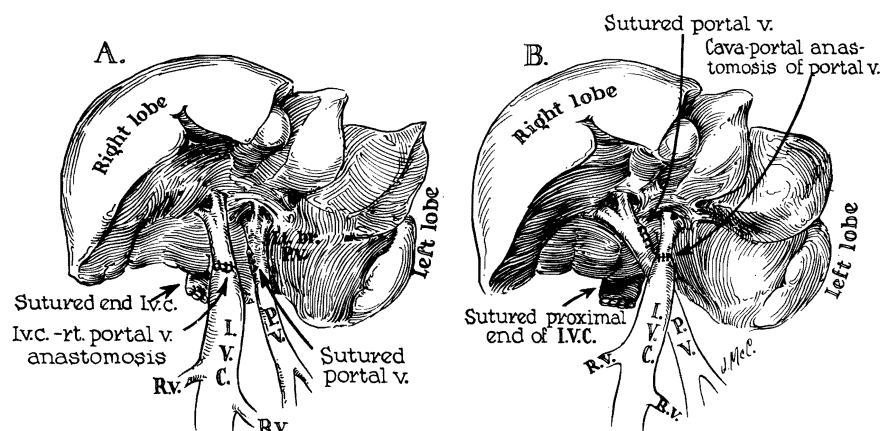


Fig. 4. An experiment designed to show the effect of splanchnic venous blood upon the liver (partial portacaval transposition). Note that one portion of the liver received venous blood from the intestinal effluent, but that the other part derived its portal inflow from the inferior vena cava. [By permission of *Surgery* 61: 723 (1967).]

Some of the best information about interliver competition has come from experiments in which dog livers have been divided into two portions using a preparation known as “split transposition” in which one of the portal radicles is fed with systemic venous blood and the other with splanchnic blood (Fig. 4). Immunologic effects in this model are eliminated making it possible to accurately study the influence of such things as splanchnic venous *versus* systemic blood. With the split transposition preparation, the concept of interliver competition which I have just described was confirmed beyond all reasonable doubt. I might say that these disclosures confirmed a general hypothesis that had been clearly stated by the Dutchman, L. SCHALM, and others a number of years earlier before its great significance for auxiliary liver transplantation was ever thought of.¹⁾

Clinical experience

In human candidates for hepatic transplantation, it may be assumed that the host liver will have been rendered relatively non-competitive by the disease for which treatment is indicated, the question being only one of degree. Consequently, the principle of interliver competition is probably less important in the clinical situation than in experimental animals. Nevertheless, the results with auxiliary transplantation in patients have been extremely discouraging. The longest survival in any patient treated for hepatic insufficiency has been only

¹⁾ The literature, concerning this point and other aspects of both auxiliary and orthotopic transplantations, is completely annotated in a recent book (1).

34 days (Fig. 5). In this case, the host disease was Laennec's cirrhosis. After auxiliary transplantation, there was immediate homograft function with clearing of the hyperbilirubinemia as well as obvious prothrombin synthesis (Fig. 5). Later, a rejection developed with secondary deepening of jaundice and finally death from infection. FORTNER of New York City has recently reported that a patient with carcinoma of the hepatic ducts lived for 240 days after auxiliary transplantation. The role, if any, that the second liver played in this 8 month survival is not clear since the patient at the time of operation was not dying of hepatic insufficiency, the main complaint being of jaundice. Eventually the cause of death was cholangitis of the obstructed host liver, a complication to which immunosuppression might actually be expected to contribute.

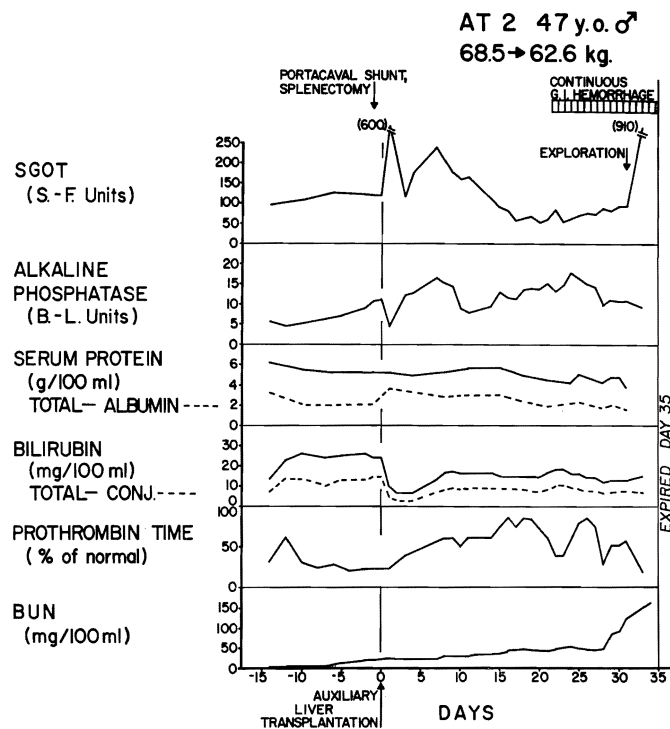


Fig. 5. The course of a patient who received an auxiliary hepatic homograft that was vascularized by a technique similar to that shown in Figure 2. There was apparently good initial function which later deteriorated when rejection was not controlled. Note the rapid development of azotemia late in the 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. Immunosuppressive therapy in this patient was with azathioprine and prednisone. Profound leukopenia developed in the fourth postoperative week. The patient died of infection. (By permission of W. B. Saunders Co.)

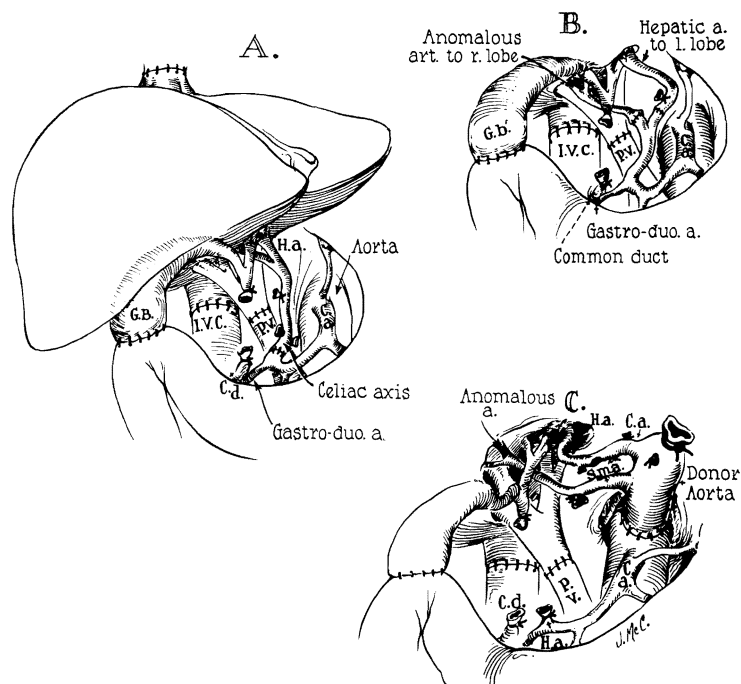


Fig. 6. Techniques of orthotopic liver transplantation. A, The kind of arterial anastomosis most commonly used. The homograft celiac axis or common hepatic artery is attached to the proper or common hepatic artery of the recipient. B, Arterial reconstruction of two homograft arteries. The vessels are individually anastomosed to the branches of the recipient proper hepatic artery. C, Anastomoses of the homograft aorta to the recipient aorta. The variation has been used in the presence of a double arterial supply to the transplanted liver. [By permission of *Ann. Surg.* 168: 392 (1968).]

Our own animal research into the matter of auxiliary liver transplantation dates back almost eight years. In addition, we have tried to treat 4 patients with auxiliary homografts, the first time almost 6 years ago. If only for these reasons, I would hate to be considered a nihilist about the possibility of using this "conservative" approach to treatment. Yet, I must concede that auxiliary transplantation has yielded inferior results in laboratory animals in comparison to liver replacement, that it has not been an effective procedure in man, and that there has been no proven instance in which the life of a patient has been meaningfully prolonged. Moreover, I will be telling you about some additional observations in patients whose diseased livers were removed and replaced that further weaken the case for the concept of an auxiliary organ. These discouraging statements should serve as my summary comment about auxiliary transplantation as well as an introduction to a discussion of orthotopic transplantation.

Orthotopic transplantation

With orthotopic transplantation, the diseased host liver is removed and replaced. In principle, the operation could hardly be more straight forward since the anatomic structures entering and leaving the hepatic homograft are reconstructed in as anatomically a normal arrangement as possible. There are usually four vascular anastomoses, the vena cavae above and below the liver, the portal vein and the hepatic artery (Fig. 6). Because of its ease of performance and freedom from a need for drains or tubes, we usually use cholecystoduodenostomy to provide for biliary drainage (Fig. 6).

I do not wish to convey the impression that liver replacement should be attempted by people of minor surgical experience or by those who have not recapitulated the important technical lessons that can be easily learned in the experimental laboratory. In patients, the presence of intrinsic hepatic disease, the resulting portal hypertension, and the defective clotting which is often present may make liver replacement one of surgery's most formidable technical undertakings.

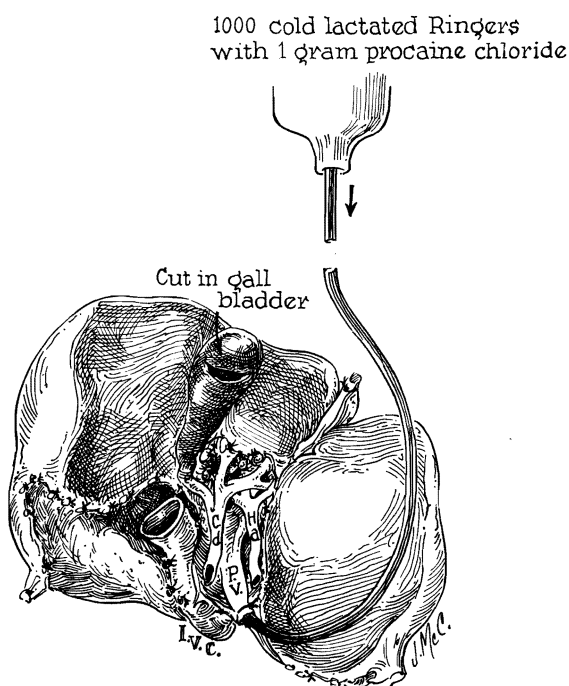


Fig. 7. Infusion of the portal vein of an excised hepatic homograft with a chilled electrolyte solution. In recent years dextran has been added for oncotic control. [By permission of Surg. Gynec. Obstet. 117: 659 (1963).]

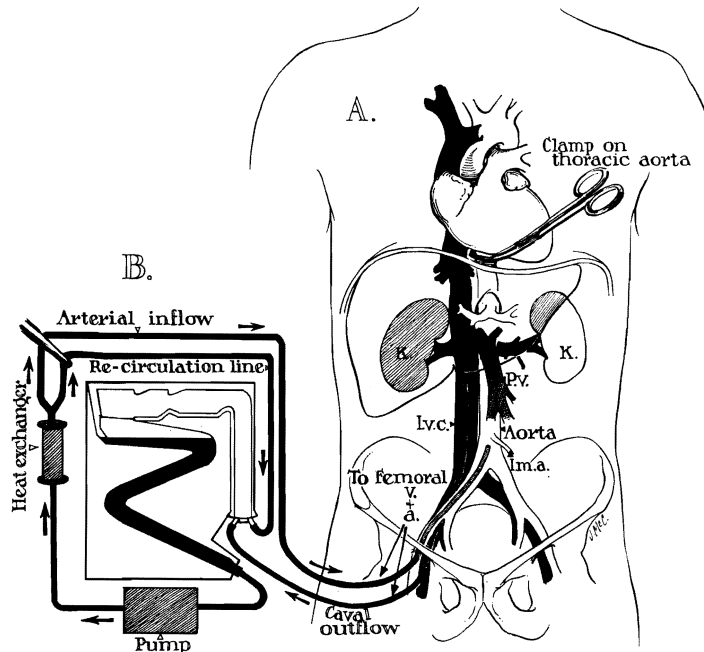


Fig. 8. Technique of extracorporeal perfusion with a heart-lung machine. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. The extracorporeal circuit is primed with a glucose or electrolyte solution to which procaine and heparin are added. The 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. (By permission of W. B. Saunders Co.)

Organ preservation

A critical issue in transplantation of the liver is the quality of the organ to be used. In the first human trials in 1963 and 1964, the liver homografts were quite badly damaged by ischemia incurred both pre- and postmortem. Today, with acceptance in most centers of the concept of brain death, this is less apt to happen. If a liver is excised under the conditions of brain death in which an effective hepatic circulation may be present during the actual organ removal, the liver can simply be cooled by infusing a chilled solution through the portal vein (Fig. 7); the resulting safe preservation time is more than 2 hours. Should circulation fail, either before or during hepatectomy, an artificial circulation can be provided with a stand-by heart-lung machine. If a heart exchanger is built into the apparatus, the corpse can be cooled as the organ removal is proceeding (Fig. 8). Finally, it is worth mentioning in passing that livers have been success-

fully preserved in our laboratory for as long as one day after their excision with a combination of low flow intravascular perfusion, hyperbaric oxygenation, and hypothermia.

Immunosuppression and rejection

With liver transplantation, as with the transplantation of all other organs, the central issue after a technically satisfactory operation is the prevention of homograft rejection. In dogs, it was first demonstrated on March 23, 1964 that long term survival could be obtained with one of the same agents that has been used for renal transplantation. On that date, the dog shown in Fig.9 had his



Fig.9. Recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The animal is still in perfect health more than $6\frac{1}{2}$ years posttransplantation. (By permission of W. B. Saunders Co.)

own liver removed and replaced with the organ of a nonrelated mongrel donor. Immunosuppressive therapy was with azathioprine. After 4 months, this drug was discontinued (Fig. 10). The dog is still alive, two-thirds of a canine lifetime later. The same kind of success has been achieved in dogs with the globulin derivative (called ALG) of horse antilymphocyte serum (ALS). In fact, there has been very strong evidence from the beginning of the animal experimentations that rejection is easier to control and that long-standing tolerance is somewhat easier to achieve with the liver than other organs. This has been particularly well demonstrated in pigs by GARNIER in Paris and confirmed by TERBLANCHE of Leeds, CALNE of Cambridge, and in our own laboratories. In pigs, hepatic transplantation can sometimes be successfully done between nonrelated donors and recipients without any immunosuppressive treatment at all.

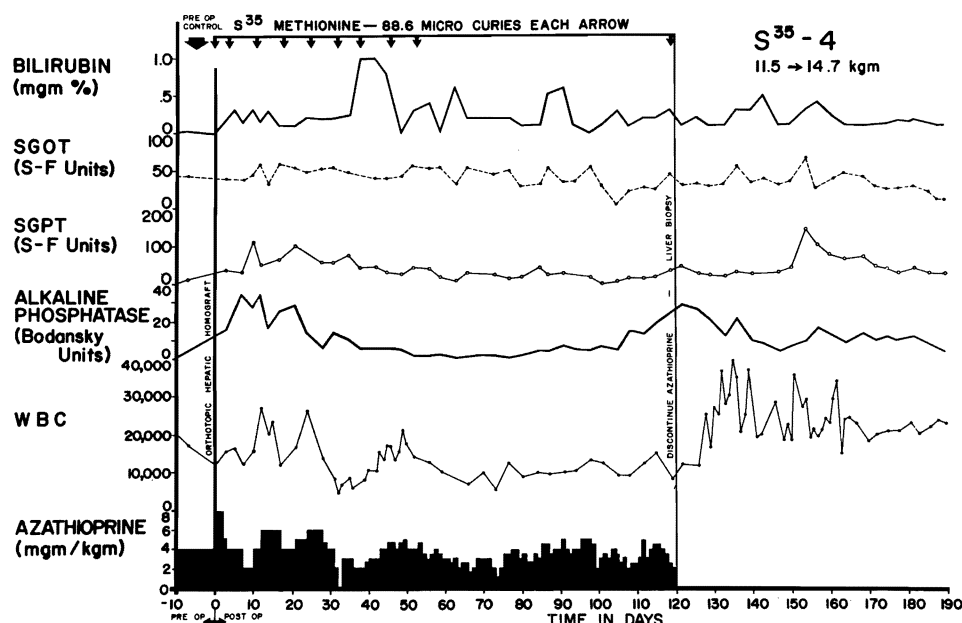


Fig. 10. Course of a dog after orthotopic homotransplantation of the liver. Overt clinical rejection has never been observed. Liver biopsies after three, six and a half and 10 months were normal. The operation was performed on March 23, 1964. The animal is in good health more than 6½ years later (see Fig. 9). Note that immunosuppression was discontinued after four postoperative months without subsequent deterioration of liver function. Resumption of treatment has never been required. [By permission of Surgery 58: 131 (1965).]

Although it is my belief for the foregoing reasons that the liver is biologically somewhat favored in transplantation, it would be easy to overstate this point since, in patients, very severe rejection has quite often been seen, necessitating extremely aggressive treatment. I would like to illustrate two ways in which the process of immunologic repudiation may manifest itself. Shown in Fig. 11 is the course of a man treated with orthotopic liver transplantation for the indication of hepatoma. Liver function in the first several days was quite satisfactory. Then, despite combined immunosuppression with azathioprine, prednisone, and ALG, there ensued a savage rejection crisis. Within a day, the bilirubin rose to 15 mg% with associated increases in the serum transaminases. At the same time, the patient was prostrated with fever and was demonstrated to have a gram negative septicemia. Fortunately, all the adverse findings reversed. The patient recovered completely and was discharged from the hospital two months later.

During the critically important first two weeks of convalescence, liver scans are usually ordered every few days. Several such examinations were obtained

(indicated by the letters A-F) in the patient whose clinical course is summarized in Fig. 11. At the peak of rejection, large areas of the homograft ceased to pick up the technetium isotope (Fig. 12), particularly at the time of the gram negative bacteremia (Fig. 12D). The “disappearing” hepatic tissue was apparently still viable since later scans returned to or toward normal.

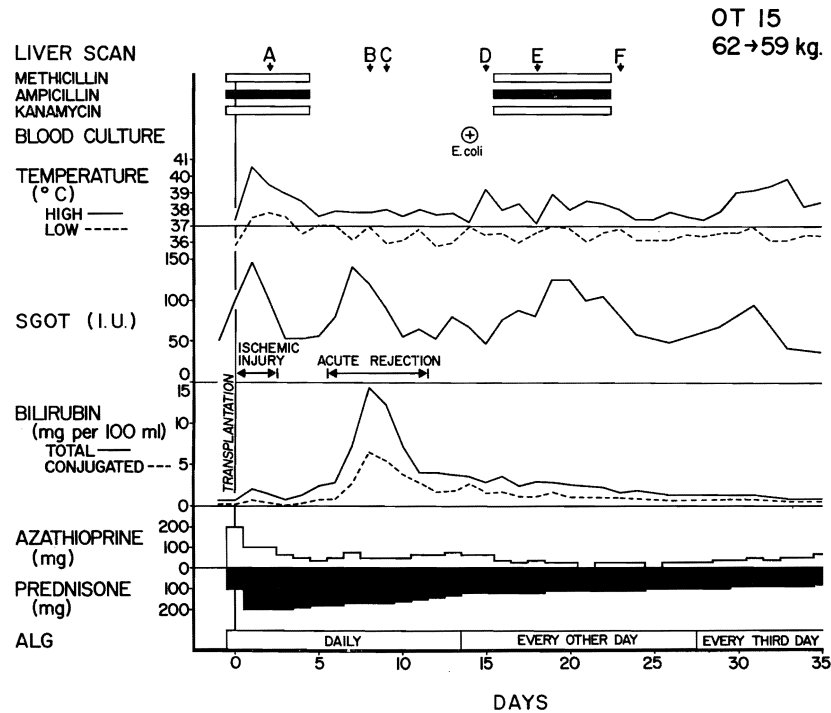


Fig. 11. The postoperative events in patient OT 15. An explosive rejection began on the sixth day, reached a peak within two days and receded promptly. Gram negative bacteremia was diagnosed from a blood specimen obtained on post-transplantation day 14. The liver scans indicated by the letters A to F are shown in Figure 12. Note that the immuno-suppressive therapy was actually lightened with the development and evolution of the rejection episode. (By permission of W. B. Saunders Co.)

Using the xenon washout technique, it was demonstrated several years ago by Dr. CARL GROTH in our laboratories that one of the features of acute rejection of livers was a reduction in hepatic blood flow which if unreversed could proceed to focal or even massive necrosis. The changes in liver scans that may occur during an acute rejection episode in patients are undoubtedly a reflection of such flow changes. Moreover, the pathogenesis of the bacteremia alluded to above was probably by the mechanism shown in Fig. 13. The illustration suggests that there has been injury to the hepatic parenchyma, that the bacterial

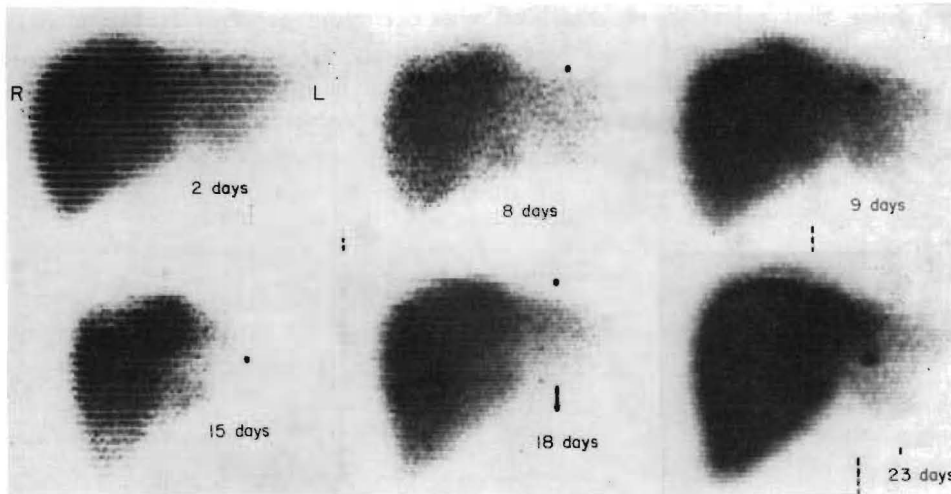


Fig. 12. Anteroposterior liver scans obtained with ^{99m}Tc -technetium in patient OT 15. Note the temporary disappearance of portions of the homograft on the eighth and fifteenth postoperative days; the first of these occasions was at the beginning of an explosive rejection crisis. At the time of the 15-day scan, the patient had developed gram negative septicemia, presumably from a hepatic focus. The remittent changes in the liver scans were thought to be due to variations in hepatic blood flow during the rejection crisis. The patient recovered completely from these episodes and was discharged from the hospital 65 days postoperatively. Correlate the scans with the clinical events shown in Fig. 11. (By permission of W. B. Saunders Co.)

filter action has been lost as a consequence, and that microorganisms indigenous to the gastrointestinal tract then find their way into the blood stream. If rejection is permitted to proceed to the point where major hepatic necrosis occurs, the lethal complication of bacterial gangrene of part of the homograft is the inevitable consequence.

Not all rejections are as violent as that shown in Fig. 11 and 12. A more indolent kind may be indistinguishable from biliary obstruction as I will mention later in connection with a case of Wilson's disease. Finally, there may be significant rejection without much derangement at all in the liver functions as exemplified by the course shown in Fig. 14. The patient was a child with biliary atresia. After transplantation, the bilirubin fell to nearly normal levels. Beginning late in the first postoperative month, there were low grade increases in the transaminases and alkaline phosphatase but without a recurrence of jaundice and with no alterations in the serum protein.

In this form of rejection, which we have called the "anicteric" variety, serial liver scans may reveal a very substantial swelling of the liver homograft which then recedes with the waning of the immunologic attack (Fig. 15). Failure to

recognize that rejection of this kind was occurring in several of our early patients led to errors of undertreatment with the tragic results that some of them developed regional gangrene of their hepatic homografts. The best way to avoid this kind of infectious complication in the post-transplantation period is to use very heavy early immunosuppression.

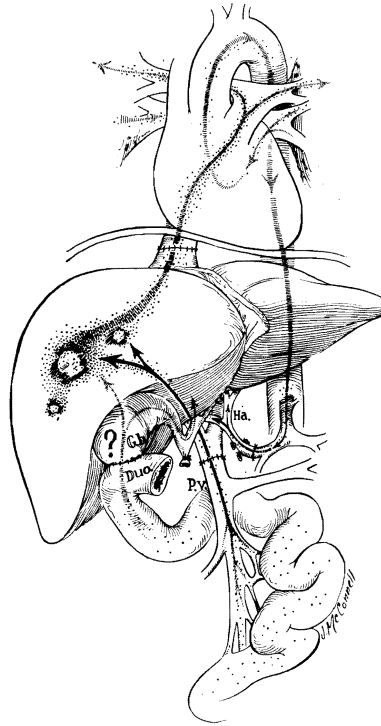


Fig. 13. An explanation of the predisposition of the liver to bacterial sepsis. Presumably the invading microorganisms enter via the portal vein or through the reconstructed biliary tract. [By permission of *Ann. Surg.* 168: 392 (1968).]

Indications for orthotopic transplantation

I would now like to develop some thoughts about the results with and the indications for orthotopic liver transplantation, based primarily on our own experience with this procedure which dates back to March 1963.

Overall results: Our first 7 trials all resulted in the death of the patients in 3 weeks or less. The first chronic survival was not obtained until the eighth attempt which was on July 20, 1967. Since then, we have had 9 patients who have lived for a year or longer after orthotopic liver transplantation. That is the

numerator shown in Table 1. The denominator shows the 33 consecutive cases that were complied from 1963 until late last year. Thus the uncorrected one year survival was 27%. Obviously, the success rate in more recent times has increased. It should be emphasized that the majority of deaths occurring early (within the first month) have been caused by technical surgical accidents of one kind or other. Such complications should be avoidable in future cases with a greater background of experience.

Table 1. 33 Orthotopic transplantations.

One year survival:
9/33 (27%)

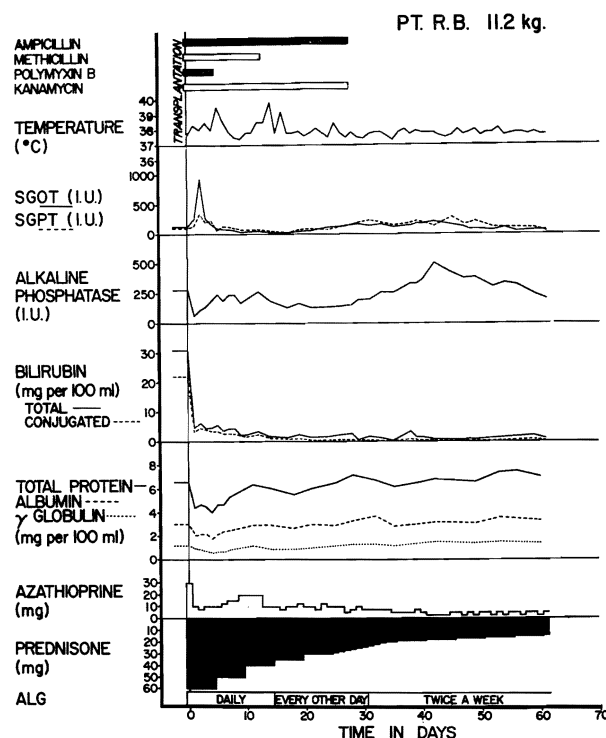


Fig.14. Example of subclinical rejection (OT 13). The indication for operation was extrahepatic biliary atresia. The bilirubin fell almost immediately from more than 30 mg per cent to less than 5 mg per cent. There was no recurrence of the jaundice in the interval shown. However, there were rises in the alkaline phosphatase, SGOT, and SGPT from the third to the seventh postoperative weeks. Antibiotic therapy was stopped after four weeks. The temperatures shown are the maximums for each day. [By permission of Ann. Surg.

168: 392 (1968).]

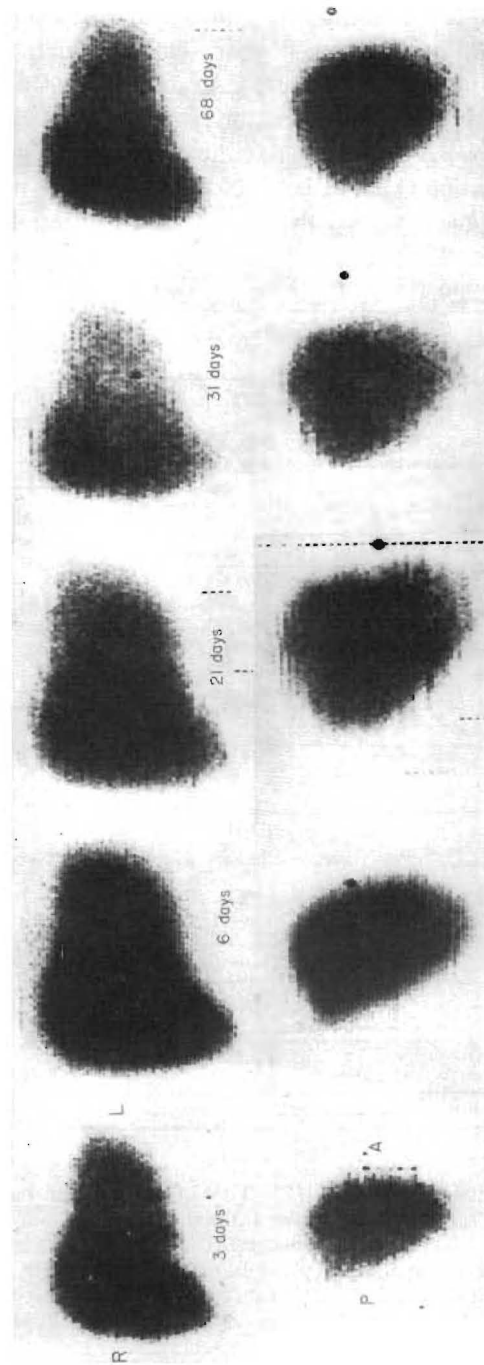


Fig. 15. Anteroposterior and lateral liver scans in patient OT 23, using ^{99m}Tc -technetium. The patient, whose diagnosis was hepatoma, was 15 years old. He received the liver of a six year old cadaver. The chemical evidence for the rejection began about one week after operation but did not include jaundice. Note the remarkable liver swelling which occurred at this time and which lasted for more than two subsequent weeks. By 68 days the anteroposterior view appeared to have returned to about the same dimensions as had been present shortly after operation. However, the lateral view showed that the liver mass was increased; liver function was then completely normal. Note that the pickup of the isotope remained homogeneous throughout the period of observation, except possibly at 31 days. (By permission of W. B. Saunders Co.)

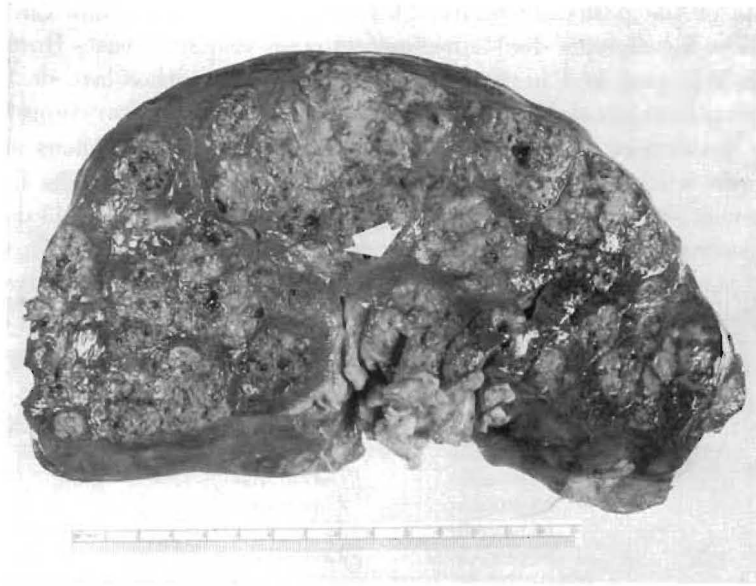


Fig.16. Metastases in a liver homograft, 143 days after its orthotopic transplantation. Except for a very small residual area of hepatic parenchyma (arrow), the organ has been replaced by recurrent tumor. (By permission of W. B. Saunders Co.)

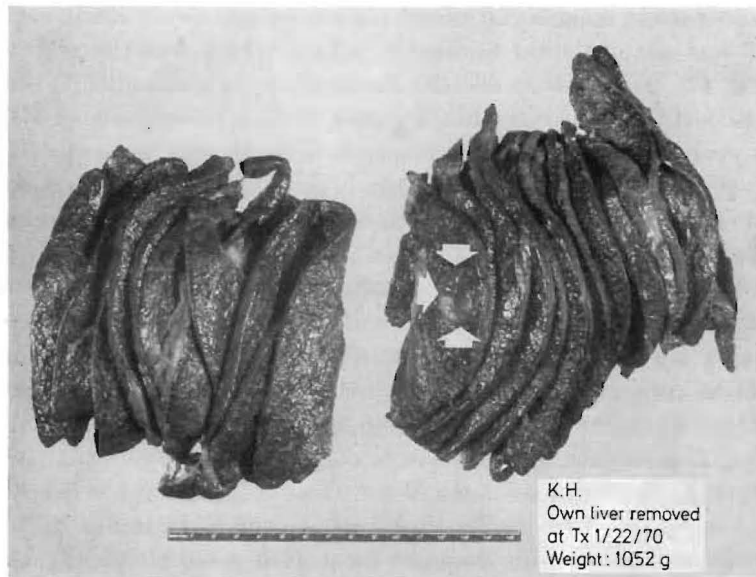


Fig.17. The liver removed from a four year old child who was dying of biliary atresia. A small hepatoma was found in the specimen (arrows).

The fate of the patients who lived for at least one year is shown in Table 2. Five of these 9 recipients died subsequent to one year, in 2 cases from chronic homograft rejection and hepatic insufficiency. The 3 other late deaths were caused by carcinomatosis from the hepatomas for which the operations had been originally performed. Actually 2 additional deaths beyond those shown in Table 2 were also caused by hepatoma but before the end of the first post-operative year. The liver homograft of one of the latter patients 143 days post-transplantation is shown in Fig. 16. The hepatic homograft had been virtually replaced by metastases of the same hepatoma which originally destroyed the native liver.

Table 2. 9 one year survivors.

Alive $\frac{4}{9}$	1-2 $\frac{1}{4}$ years
Died $\frac{5}{9}$	1-2 $\frac{1}{2}$ years
12 months	Carcinoma
14 months	Carcinoma
15 months	Carcinoma
15 months	Liver failure
30 months	Liver failure

The curability of hepatoma: Our cure rate of hepatoma by the operation of transplantation is actually limited to only 1 case out of 7 in which chronic survival was obtained and in which long enough followups were therefore available to permit meaningful observations. In the exceptional patient, the hepatoma was an incidental finding in a liver which was the site of biliary atresia (Fig. 17). Obviously, a decision for auxiliary transplantation in this case would have cost the patient her life. Instead, there is no evidence of metastases, almost a year after orthotopic transplantation. In this patient serum fetoprotein, a primitive α_1 globulin that is produced by hepatoma tissue was present in significant quantities prior to operation. After the liver replacement the abnormal protein slowly disappeared from the circulation over a period of some months (Fig. 18). In a number of other patients with hepatoma who were not cured, fetoprotein in the serum invariably persisted and in 2 cases, this finding was a tip-off that recurrence was present, many months before metastases became apparent by any other criterion. These analyses were performed by Dr. ELLIOT ALPERT of the Robert Bent Brigham Hospital, Boston.

In leaving this subject, I would like to summarize by saying that because of the high rate of recurrent carcinoma in our own experience, it has become policy in cases of hepatoma to consider liver replacement only under the most exceptional circumstances. This does not mean that some recipients with hepatoma cannot be cured nor does it imply criticism of other transplantation groups who persist in similar therapeutic efforts. In fact, besides one of our reci-

patients, one of CALNE's Cambridge patients has no evidence at all of tumor recurrence and has probably been cured; DALOZE of Montreal has made a similar observation.

Biliary atresia: Whatever the virtues and faults of liver replacement for hepatoma, far more desirable candidates for the procedures are those without neoplasms. On the average, the performance of orthotopic transplantation for benign disease is more difficult since the patients tend to be sicker, have more advanced portal hypertension, and, if the diagnosis is biliary atresia, as it has been in 15 of our patients, an increased incidence of vascular anomalies can be anticipated. Nevertheless, the most lengthy followups in the world after liver transplantation have been in patients who had biliary atresia. The longest survivor died about 2 months ago in Denver after $2\frac{1}{2}$ years. The course of the next one is shown in Fig. 19. The child has perfectly normal hepatic function after 2 years and 3 months. I call your attention to the fact that ALG is still being administered.

Cirrhosis: So far there have been few patients with cirrhosis who have benefited from liver transplantation. However, in Fig. 20 is an example of a successful outcome in a special kind of cirrhosis, namely that of Wilson's disease. The 11 year old child was admitted in hepatic precoma. After liver replacement, he had a grave rejection crises, the most severe one we have ever seen with

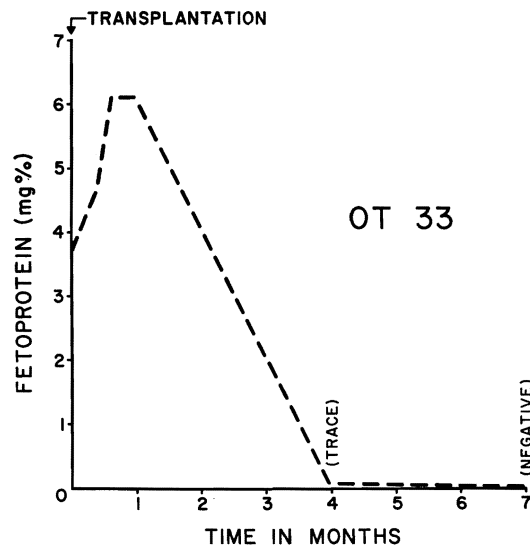


Fig. 18. Serial fetoprotein determinations in the patient whose liver contained an unexpected hepatoma (Fig. 17). Note the gradual disappearance of the primitive α_1 globulin. The analyses were performed by Dr. ELLIOT ALPERT of the Robert Bent Brigham Hospital, Boston.

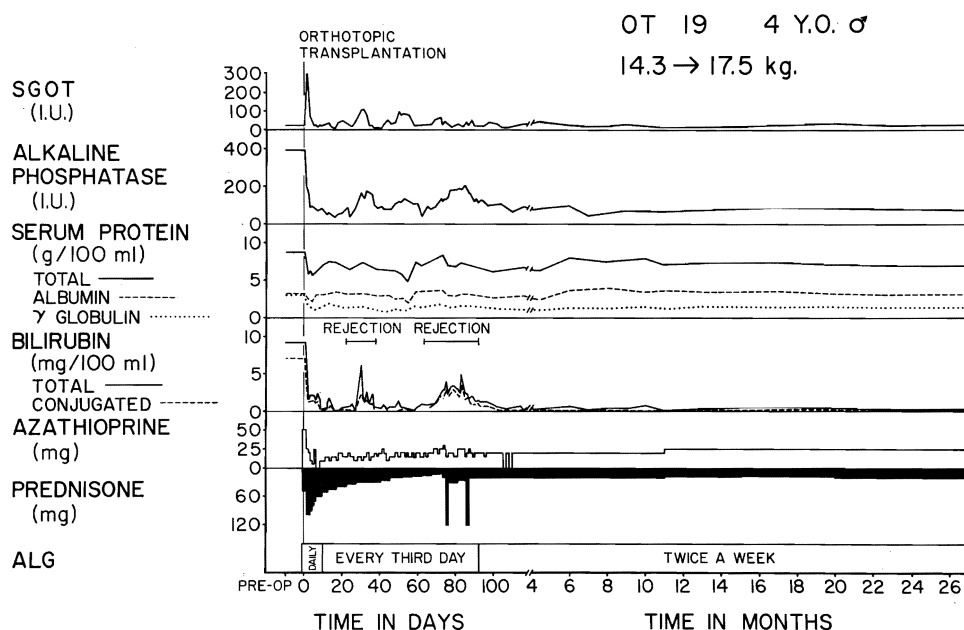


Fig. 19. The course of a four year old child after orthotopic liver transplantation for the indication of biliary atresia. Note the rejection episodes at one and two months which were easily controlled. The patient has perfect liver function 2 $\frac{1}{4}$ years after operation.

recovery. His bilirubin rose to 48.6 mg% (Fig. 20) but eventually the process was reversed so that now he has completely normal liver function 14 months later. As mentioned earlier, most of the chemical features of the rejection episode were those of biliary obstruction rather than hepatic parenchymal necrosis.

A number of special studies were done including measurement of the copper content of the excised liver as well as the biopsied homograft after 6 months. Plasma ceruloplasmins and urine copper excretion were also quantitated. After transplantation the results of all these analyses became normal. Thus, insofar as can be determined in this recipient, an inborn error of copper metabolism was cured by provision of a new liver. It is possible that further study of this and similar cases will permit identification of the basic cellular defect in Wilson's disease and resolution of the controversies about its real etiology.

There are rewards as well as responsibilities of being a celebrity. Shown in Fig. 21 is the celebrated patient talking in Houston recently to 2 other young men, NEIL ARMSTRONG and BUZZ ALDRON, who took a well publicized stroll on the moon 14 months ago, a few weeks after the boy's liver replacement. I would not like to have to decide whose courage was of the higher order.

Hepatitis: Before closing I would like to record another case in addition to the 33 consecutive ones with potential long term followup. Two months ago, a 28 year old woman with chronic active hepatitis was treated with orthotopic liver transplantation. For at least 2 years before operation and even on the day of liver replacement, immunodiffusion tests for the Australia (Au) antigen had been positive. After operation, the Au antigen disappeared and it has not since been found in any of the subsequent blood specimens. Two months after operation, the patient has not had a rejection and is in excellent condition. Frankly, we were quite astonished by the disappearance of the Australia antigen which has been widely assumed to represent the actual serum hepatitis virus. The findings in Table 3 provide striking evidence for an essentially exclusive hepatic source of the antigenic factor, at least in the patient under discussion. They do not shed light on whether this was the actual virus or something manufactured by the liver after induction by the virus. If it was virus and the native liver was a "carrier" organ, the use of an auxiliary hepatic graft might be subjected to an extra risk that was avoided by the orthotopic procedure.

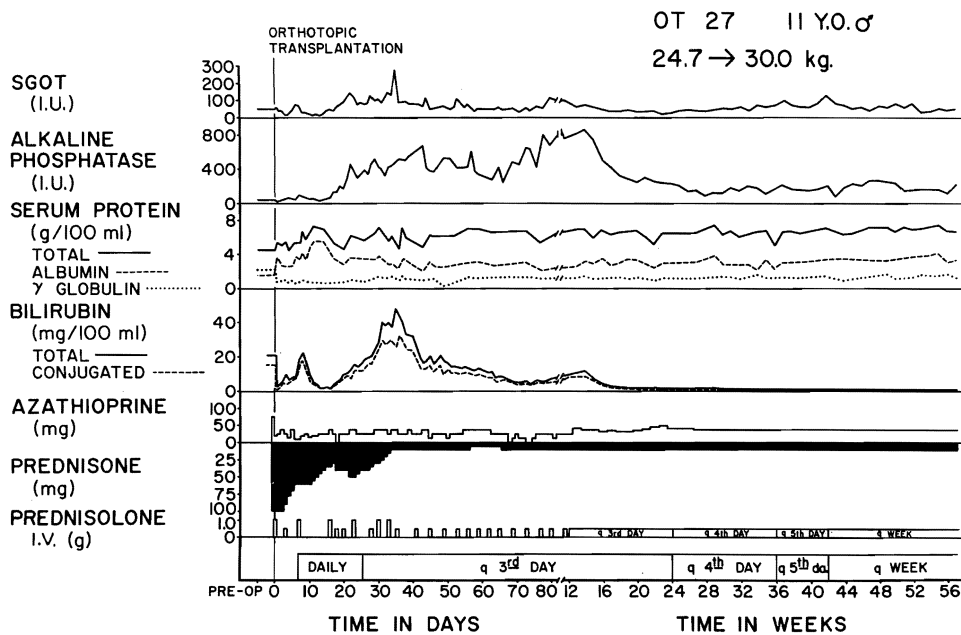


Fig. 20. The course of a child with Wilson's disease whose diseased liver was replaced with a cadaveric homograft. Note the tremendous rejection episode which reached its peak after 5 weeks but which was completely reversed. The child has perfect hepatic function after 15 months. In addition, his defective copper metabolism probably has been cured.



Fig. 21. Liver (boy) and kidney (girl) homograft recipients with moon walking friends.
(See text for details.)

Table 3. Australia antigen and antibody tests.

Date	August									September				
	9	10	11	12	15	18	21	25	28	1	8	15	22	29
Days post-op.	Pre	1	2	3	6	9	12	16	19	23	30	37	44	51
Au antigen	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-Au antibody	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Summary

Perhaps it is foolish to attempt to summarize a subject which I have had time to review only superficially in the first place. However, I do believe that the following concluding remarks would be in order. First, hepatic transplantation has passed through the feasibility stage of development since survival of humans for as long as $2\frac{1}{2}$ years has been achieved following removal of the liver and its replacement with a cadaveric homograft. Consequently, the position can now be taken that liver transplantation is a legitimate albeit imperfect form of treatment. I now believe that with the demonstration of chronic survival, liver transplantation should be considered before the prospective recipient has reached an agonal condition, a circumstance that was more or less insisted upon in our early trials. If patients come to treatment at a somewhat earlier time, the results will of course improve. Personally, I am certain that the patient who receives a technically satisfactory liver replacement has at least as good a prognosis and possibly a better one than the renal recipient since the problems of immunologic control are probably inherently less difficult. The prime indication for liver transplantation is benign hepatic disease. If the procedure is used to treat hepatoma, there is a high recurrence rate of tumor, 86% in our hands.

Reference

- (1) STARZL, T. E. (with the assistance of C. W. PUTNAM): Experience in hepatic transplantation. Saunders, Philadelphia 1969.