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# The Succession From Kidney to Liver Transplantation

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THE temptation to indulge in reminiscences would be greater if the story of transplantation had gone to the glorious climax and denouement that seemed so imminent a decade and a half ago. Sixteen years ago (September 6, 1963) many of the people here today met in Washington, D.C. at the National Research Council to consider what seemed to be electrifying recent events in transplantation. It seemed certain that a new clinical specialty was at hand in which there would be widespread replacement not only of kidneys but of other organs. Within the preceding few months, the first efforts had been made in Denver and in Boston to transplant an extrarenal vital organ, namely, the liver. Although the recipients had died, it was predicted (and correctly as it turned out) that success would not be far off.

However, the expectations of 1963 have not been fully met. As we all know, nostalgia has the power and magic to blur reality and to make gray things bright. Yet, I doubt if many here would claim that transplantation today offers a safe and predictable service to a much greater extent than it did in the 1960s. To the degree that this is recognized, perhaps it is justifiable to glance back over our shoulders and describe some of the problems of human organ transplantation as they were perceived at the time of our first clinical trials 18 years ago and subsequently. I was not involved in transplantation until 1958, 4 years before the first consistent successes began to be obtained with kidney transplantation. I have reviewed the importance of these years preceding 1962.[1] The central role of the workers at the Peter Bent Brigham Hospital can be appreciated from the catalogue of landmarks in renal transplantation provided by Groth of Stockholm after his study of the written record and after discussions with most of the workers actually involved in the work done from 1950 onward.[2]

It became my personal opportunity to participate in the great advances in kidney transplantation starting in 1962 and to apply what was being learned with the kidney to transplantation of the liver. The interorgan transfer of such information was natural since the liver was the means of my first involvement in transplantation. In the summer of 1958, while at Northwestern University in Chicago, I developed a new method for one-stage hepatectomy in dogs. I appreciated how easy it would be to replace the liver with a graft using a temporary portacaval shunt with or without an external bypass to decompress the blocked splanchnic and systemic circulations. At about this time, I had decided to remain in university work in preference to entering private practice and had spent several weeks in the medical library trying to decide on some broad area of research in which to make an investment.

Transplantation seemed a worthwhile challenge, partly because of the deeply pessimistic attitudes that prevailed about the prospects of clinical organ transplantation in any except the most unusual cases, such as those involving fraternal twins. Transplantation of the liver was especially appealing at that time because of its technical challenge.

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Another factor that gave the liver special interest was speculation by Dr. Jack Cannon of Los Angeles that the liver played an important role in rejection. Because of this, Cannon, who was the first to attempt liver replacement,[3] apparently hoped that a hepatic homograft might suffer a different fate from that of other transplanted tissues, since it presumably would not contribute to its own repudiation. Although the liver was rejected, it has seemed to be less susceptible to rejection than any other major organ but for reasons that are still not understood.[4] By mid-1958, work on orthotopic liver transplantation in dogs had also begun in the Harvard laboratories of Francis D. Moore. The studies from the Boston[5] and Chicago[6,7] laboratories showed the technical feasibility of orthotopic liver transplantation, but they held no clue to the prevention of rejection. As reviewed elsewhere,[1] such clues depended on different kinds of laboratory investigation that showed that steroids, 6-mercaptopurine, and azathioprine were immunosuppressive.

## THE PROTOTYPE KIDNEY MODEL

The kind of laboratory research with steroids, 6-mercaptopurine and azathioprine mentioned above was applicable in one way or another to organ replacement in man, but the connection was not straightforward. In occasional dogs a protracted life proved possible after renal transplantation with the use of steroids,[8] 6-mercaptopurine,[9] or azathioprine[10–12] as the sole immunosuppressive treatment. In man occasional similar successes were also achieved solely with 6-mercaptopurine or azathioprine, as summarized by Groth.[2] Nevertheless, the consistency with which really long-term survival was obtained was poor. The obvious reason was that complete control of rejection was rarely achieved.

Thus, both the animal data and the initial clinical experience discouraged further trials, even with kidney transplantation. The most important development that made immunosuppression practical was the discovery of the way in which azathioprine and prednisone could be advantageously used together. There were essentially no preceding laboratory data to indicate that the benefit with this now universally accepted combination of agents would be as great as proved to be the case. Indeed, the first publication on experience in animals[13] was a belated confirmation of the far more convincing observations already made in humans.[14–17]

Standardization of combined azathioprine–steroid therapy cannot be ascribed to any single authority or transplantation group. What is clear is that by early 1963 the two drugs were being used together in one way or another and with varying degrees of conviction about their synergism for the prevention or reversal of renal homograft rejection in at least one British[14] and three American centers.[15–17] Since then, variations of these regimens have been adopted throughout the world.

The reversibility of rejection in these patients was only one of the features that established the clinical feasibility of organ transplantation. The quantities of adrenal corticosteroids necessary to achieve reversal were often too large to be compatible with long survival of the recipient if continued indefinitely. Fortunately, another event of equal practical importance transpired coincidentally with the reversal of rejection or shortly afterward. With the passage of time, the need for intensive therapy usually diminished both in patients who did and especially in those who did not pass through a clinically evident rejection.

There was little reason to doubt that a homograft became more or less privileged if it could be kept alive through the initial onslaught of rejection. This fact strongly influenced the way in which newer therapeutic agents such as heterologous antilymphocyte globulin (ALG) were used clinically,[18] and it was a prime stimulus for the extension of transplantation techniques to organs other than the kidney in which both reversal of rejection and "adaptation" proved

not to be very different from what they were with the kidney.

## THE LIVER TRIALS

Looking back at the Colorado scene of the early 1960s, it was inevitable that transplantation of the liver would be performed. Optimism was high because of the success of multiple drug immunosuppression in controlling renal homograft rejection. The assumption was made that the same therapy would be applicable for other organs, a view that was proved correct both in animals and man.[4] Finally, the ability to carry out liver transplantation had been assiduously developed in research involving hundreds of dogs during the preceding 5 years and was known to be within our technical capability. Thus, a policy decision was made in early 1963 to proceed with orthotopic liver transplantation, an operation that requires removal of the diseased native organ and its replacement with a cadaveric graft.

The first four attempts were made in 1963 on March 1, May 5, June 24, and July 16. A fifth patient was treated by Francis Moore in Boston on September 16, 1963, followed by another in Denver on October 4, 1963 (all early cases in Denver and elsewhere are catalogued in Starzl,[4] pp 503–532).

Our first recipient bled to death during the operation; the other four first Denver patients survived operation but died from 6.5 to 23 days later. Success was nearly achieved in some of these cases.[19] For example, our second patient, a 48-year-old male with cirrhosis and a hepatoma, was in remarkably good condition postoperatively. He died 22 days later of systemic and pulmonary infection. At autopsy there were no serious complications in the abdominal cavity. The liver had no unequivocal findings of rejection. Biliary duct reconstruction with choledochocholedochostomy over a T-tube was satisfactory. Portions of both lungs were necrotic. The pulmonary arteries contained multiple old clots. Apparently, these were deposited at the time of operation from a plastic bypass tubing that had been used to return blood from the vena caval and splanchnic venous pools while these systems were obstructed during the intraoperative anhepatic phase. Ironically, it was later proved that such temporary bypasses are unnecessary because of the well-developed venous collaterals in end-stage liver disease.

The series of consecutive early failures caused a moratorium of 3 years to be declared on further cases. Only one more patient was treated at our center until the summer of 1967. The justification to then start another series came from experience with the triple drug immunosuppressive program (including ALG) which by then seemed to be helping the kidney recipients.[4,18] On July 23, 1967, the chance presented to treat a 1.5-year-old girl who had a hepatoma. She lived through the operation of liver replacement and for 13 months afterward before finally dying of widespread tumor metastases. Each of the next 8 recipients lived for at least 2 months postoperatively, and 3 of these 8 lived for more than 1 year with the longest survival of 29 months and 16 days.

The first 25 liver recipients in the Colorado series eventually provided the experience for a text of liver transplantation.[4] Five of these 25 patients lived a year or more. The feasibility stage of human liver transplantation had been passed, but with 1-year mortality of 80%, widespread exploitation of the procedure was a long way off.

Nor was there a quantum improvement in the succeeding 7 years. The patients surviving for 1 year in the second, third, and fourth groups of 25 patients each were only 6, 8, and 9, respectively. However, one of these recipients is now 10 years postoperative and a total of 14 have lived more than 5 years; 13 of these 14 are still alive.

During a sabbatical leave in 1975 and 1976, I had an opportunity to live in London and work with Professor K. A. Porter, the great English pathologist who had earlier worked in Boston with Gustave Dammin and with whom I had collaborated continuously since 1963. Together, we reviewed the first 93 cases of orthotopic liver transplantation and

tried to recatalogue the main reasons for failure. Our conclusions were (1) uncontrolled rejection was a relatively uncommon cause of mortality; (2) technical mistakes and mechanical problems with the homografts accounted for the greatest numbers of deaths; and (3) if the complications were of duct reconstruction, they frequently caused untreatable infections.

Better management guidelines were developed based on more accurate postoperative diagnosis with emphasis on frequent needle biopsies and transhepatic cholangiography, avoidance of overimmunosuppression while using the triple drug therapy, and better technical performance at the original operation. The most fundamental technical adjustment was to perform biliary duct reconstruction with choledochocholedochostomy over a T-tube stent, or by anastomosis of a Roux-en-Y jejunal limb to the graft gallbladder or common duct. The various changes were completed and standardized by late spring 1976.

In the ensuing 2 years, the 1-year survival in 30 consecutive patients rose to 50%,[20] and 13 of these 15 1-year survivors are still alive now after 2–3.5 years. The same improvement in recent results has been noted also by Calne and Williams working in England.[21] Unfortunately, it does not now seem that a further increase in survival will be possible without some fundamental improvement in immunosuppression.

## PHYSIOLOGIC FALL-OUT

One of the major by-products of liver transplantation has been new insight about the effect of portal blood and its so-called hepatotrophic constituents on liver structure, function, and the capacity for regeneration. This new area of research[22] was opened during inquiries into the optimum means of revascularizing auxiliary liver homografts while leaving the native organ in place.[23] The essence of the portal hepatotrophic concept is that the liver is controlled or influenced profoundly by hormones coming from the venous effluent of splanchnic viscera into the portal vein. Insulin is the most influential of these hormonal factors, although not the only one. From a practical point of view and as it relates to transplantation, the implication is that the portal vein of an auxiliary liver should be supplied with splanchnic venous blood if it is to have an optimal chance of survival.

Auxiliary liver transplantation was first attempted in humans by Absolon et al.[24] and was also given a brief trial at our center.[4] The only person to definitely benefit from this procedure so far has been a child cared for by Dr. Joseph Fortner of New York who is now 6 years after auxiliary transplantation for biliary atresia.[25] We have not performed this operation for several years.

## OUR DEBT TO THE BRIGHAM

It is fitting today to reflect on the remarkable influence that came from Harvard University and the Peter Bent Brigham Hospital in the beginning of clinical organ transplantation. In any scholarly summary of the publications from that era can be found the names of Dave Hume, Joe Murray, John Merrill, Roy Calne, Gus Dammin, and numerous others of the Brigham alma mater who are gathered here today. Even vineyard workers like myself who did not visit Harvard until years later were directly affected by the intellectual emanations from the Mecca.

What may not be so evident from the written record was the omnipresence of Francis D. Moore. I am sure that I was not the only one who saw Franny as a spiritual leader to whom we could turn in difficult times. In addition to his sponsorship of the Brigham kidney program, Dr. Moore involved himself in laborious and often heartbreaking laboratory research that made liver replacement a respectable clinical possibility. Furthermore, Franny's generosity to and support of younger colleagues played an indispensable role in making the clinical trial of liver transplantation in Denver and in Cambridge, England, acceptable to our peers.

I have often wondered how many of us would have been destroyed by our own efforts had it not been for Franny Moore.

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