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Liver Transplantation and Portacaval Shunt in Genetic Diseases

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In this paper I will address two subjects: the use of portal diversion as a palliative treatment of some selected inborn errors of metabolism, and the actual provision of these patients with a missing enzyme by transplantation of a phenotypically normal new liver. Both are interesting new developments in surgery and pediatrics that, although controversial and not accepted initially, have been largely validated.

Portal Diversion

The basis for the use of portal diversion for metabolic as opposed to hemodynamic objectives was laid in the laboratory. I need not remind anyone here that the liver has a double blood supply. The hepatic artery usually provides 20–25% of the total hepatic blood flow, and the portal vein provides the remainder.

The portal blood flow is derived from blood returning from various splanchnic organs, including the pancreas, spleen, stomach, small intestine, and colon. Long before substances such as hormones were known, biologists of the 19th century concluded that this blood might contain specific and important components without which the liver could not survive. This was the accepted doctrine until an innocent little paper, one page long, upset the apple cart. In it, Nicholas Eck (*1*), a Russian military surgeon, described his experience with portacaval shunt in eight dogs. One of the animals died during the operation, six survived for a few days, dying of peritonitis or strangulation of the intestines and omentum, and one recovered completely and lived in the labora-

tory for two and one-half months. Dr. Eck blamed his associates for the fact that the dog then ran away. Revealing his thoughts about the clinical implications of this operation, he wrote, "I am conducting these experiments with the purpose of clarifying some physiologic problems, to determine whether it would be possible to treat some cases of mechanical ascites by performing such a fistula." Perhaps Dr. Eck overstated his case: he went on to say that, "the main reason to doubt that such an operation can be carried out in human beings has been removed because it was established that the blood . . . could be diverted without any danger to the body, and this by means of a perfectly safe operation." Despite the fact that he was confronted with an 88% mortality rate, he realized that the Eck fistula was technically feasible. This was more than 100 years ago.

The operation of portacaval shunt (Eck fistula), as it is usually done in the laboratory, consists of a side-to-side portacaval shunt above which the portal vein is tied off, converting the anastomosis to a completely diverting shunt (2). After such an operation, striking changes occur in the liver, the nature and rapidity of which have been completely understood in only the last 10-15 years. These changes affect the liver of all species so far studied, including humans.

The most striking morphologic change after portacaval shunt is acute atrophy of the hepatocytes to about half of their original size within less than a week. At the same time the livers accumulate fat and develop multiple and dramatic ultrastructural changes. The most specific change is depletion of the rough endoplasmic reticulum and its polyribosomes. Semiquantitative morphometric analysis shows that the rough endoplasmic reticulum is reduced to about one-fourth of its original volume. In addition, glycogen granules are depleted, and the mitochondria develop nonspecific abnormalities.

Until recently the explanation of the changes caused by Eck fistula was not known. Rather than detail the tortuous pathways we followed to determine the causes, I will skip to the final and crucial experiment (2, 3), in which we found that the changes caused by portacaval shunt in dogs could be prevented by the infusion of insulin into the tied-off central portal vein. The experiment was quite simple. We ligated the right and left portal veins in the hilum, but left the insulin-infusion catheter in one of the

main portal branches. One could compare the liver lobes that were directly infused with insulin with those that were not. Thus, we looked not only at the potential protective effect in the insulin-infused lobes, but also at whether there was a carryover effect on the side not receiving insulin. There was no carryover protection. On the treated liver side, this simple procedure of infusion of insulin completely prevented the involucional changes caused by portacaval shunt. We concluded that many or most of the changes caused by portacaval shunt were due to endogenous insulin bypassing the liver. This work in experimental pathology was the product of K. A. Porter of St. Mary's Hospital and Medical School in London, with whom we have collaborated for many years (3-7).

So far, I have discussed only the striking morphologic changes caused by portacaval shunt. In addition, portal diversion causes profound changes in metabolism, the following example of which is especially relevant to clinical applications. As we have demonstrated in dogs and humans, cholesterol synthesis is greatly decreased in livers deprived of a portal blood supply (8). Bilheimer and Brown of Southwestern University, Dallas, showed the same thing in a patient upon whom I had operated.

Glycogen Storage Disease

In 1963, armed with some of the above information, we began a series of operations on patients with glycogen storage disease (6, 7) (Table 1). The patients had Types I, III, and VI disease, mostly Type I (glucose-6-phosphatase deficiency). After the operation there was a substantial amelioration of the metabolic perturbations of the patients. Those with Type I disease all had hyperlipidemia, which was alleviated immediately. Abnormalities of

Table 1. Inborn Errors Treated with Portacaval Shunt

<i>Disease</i>	<i>No. of cases</i>	<i>Length of followup, years</i>
Glycogen storage	11	2-20
Hyperlipidemia	7	2-6.5 ^a
α_1 -Antitrypsin deficiency	3	1.5-5

^a The xanthomas shrank or disappeared. The serum cholesterol decreased to 38-68% of the pre-portacaval shunt value. In five of the seven, the cardiovascular status stabilized.

coagulation and uric acid metabolism improved. The most striking occurrence was a growth spurt in these patients, who were all stunted. After portacaval shunt, the patients grew at the rate of 0.5–1 cm a month, during the first postoperative year. These growth spurts could be seen and documented by roentgenographic techniques of bone assessment. One child experienced such major growth that her bone age increased from 3.5 to seven years in the first 11 postoperative months. The bones lengthened and became mineralized, and new growth centers appeared in the wrists and elsewhere.

The full explanation of these striking effects is not yet clear. The blunted peripheral insulin response to a glucose meal, which is typical of Type I disease, was greatly increased after the shunt. Insulin being a powerful growth factor, perhaps the increased insulinemia was a factor in the growth. Not surprisingly, the one symptom that was not promptly relieved by portacaval shunt was the nocturnal hypoglycemia found in most patients.

One of my associates on this project, Dr. Harry Greene, later moved to Vanderbilt and introduced there the very interesting alternative form of therapy of continuous enteral alimentation (9). He provided continuous overnight feeding by nasogastric tube or by a gastrostomy and showed that many of the same benefits of portacaval shunt could be obtained thereby.¹ Consequently, I now recommend that continuous alimentation be carried out as the first option, with portacaval shunt reserved for a back-up treatment. The treatment of glycogen storage disease has been truly revolutionized in the last 20 years, first by portal diversion and then by continuous alimentation.

Familial Hypercholesterolemia

Familial hypercholesterolemia is a disease for which there is no such alternative (Table 1). Portacaval shunt often is the only effective form of treatment. The first patient treated was a nine-year-old girl with homozygous Type II hyperlipidemia, who had a massive myocardial infarction six weeks before portacaval shunt was performed (8, 10). She was taken to the operating room from

¹ Ed. note: Dr. Greene discussed this technique in the preceding volume in this series, *Human Nutrition: Clinical and Biochemical Aspects*, P. J. Garry, Ed., Am. Assoc. Clin. Chem., Washington, DC, 1981, pp 383–397.

the Intensive Care Unit at the University of Colorado, from which it was apparent that she would never emerge (8, 10, 11).

Homozygous familial hypercholesterolemia is characterized by deposits of xanthomatous material in the tendons, the skin, the coronary arteries, and the valves of the heart. The cardiovascular problems become so severe that these patients almost never live into or beyond the teen years. They often die of myocardial infarctions before puberty, and this, indeed, was the course this child was following (10). After portacaval shunt, her serum cholesterol, which had been about 8.00 g/L, decreased, and within six months it almost reached a normal concentration (8). We could easily see what happened to the xanthomatous lesions on her hands and other superficial areas, but comparable changes were taking place inside her body. The excrescences shrank and disappeared over a period of 16 months, leaving only faint skin stains. The child died about 18 months postoperatively, from a complication of her previous myocardial infarction. She developed a fatal arrhythmia when coming home from school.

The serum cholesterol concentrations of the other six patients we treated, five children and one adult, also decreased. A summary of the results in the first seven hyperlipidemia cases after two to 6.5 years' survival is given in Table 1. The xanthomas all shrank or completely disappeared. The serum cholesterol invariably decreased in parallel with decreases in low-density lipoproteins. The cardiovascular disease, interestingly enough, improved or stabilized in most patients as the cutaneotendinous lesions disappeared. In some of the cases, we documented by serial catheterizations a reduction in the gradient of aortic stenosis or improvement in coronary artery disease.

α -Antitrypsin Deficiency

Perhaps this third inborn error of metabolism can also be palliated with portal diversion. α_1 -Antitrypsin deficiency is an inborn error that follows genetic rules, but the exact reason for the manifestations of this disorder is really not known. Although α_1 -antitrypsin is synthesized by the liver, its structure is sufficiently abnormal that it cannot be transported; thus, it accumulates in the liver and probably is responsible for hepatic injury. We have treated three patients with portacaval shunt and have followed them for 1.5 to more than five years.

These patients have been remarkably stable. In two of them, we biopsied the liver at the time of the shunt and one to two years later. In one case, the amount of α_1 -antitrypsin in the hepatocytes had actually decreased, as determined by morphometric analysis; and in the other, the amount remained the same. Perhaps with the depletion of rough endoplasmic reticulum the synthesis of the abnormal α_1 -antitrypsin was reduced without a commensurate decrease in the excretion of this alpha-globulin through the hepatocytes. If so, a favorable metabolic equilibrium would have been established that could, in a very subtle way, allow the disease to be more compatible with long life. However, these trials are still highly experimental, and we are not recommending portal diversion to treat this liver disease.

Liver Transplantation

Liver transplantation offers a more direct approach to enzyme-deficiency disease, or inborn errors of metabolism. For any of the liver-based inborn errors I will mention here, transplantation of a phenotypically normal liver supplies or probably supplies the missing enzyme. It is a simple concept. Phenylketonuria (PKU) for example, is known to be a liver-based inborn error, and so, by definition, is curable by liver replacement. Obviously, however, less drastic approaches are preferable.

Examples also can be found in laboratory animals. Several years ago a group at the Mayo Clinic reported experiments in which Dalmatian dogs, which suffered from gout, were given livers from mongrel donors and were cured of their gout (12). The defect in uric acid metabolism was eliminated.

Because the concept is so childishly simple, I do not think there is any need to dwell on it. The main prerequisite to exploiting the possibilities of liver transplantation has been the need to develop better ways of preventing liver rejection.

Recent developments in immunosuppression have made possible efforts considered unrealistic only a few years ago. The key factor in these new expectations is a new drug called cyclosporin A (cyclosporine) (13), first used in clinical trials in kidney transplantation (14, 15).

Before cyclosporin A was available, the most important development in immunosuppression occurred about 20 years ago with

the combined use of azathioprine (Imuran) and prednisone. With these drugs, kidney transplants became possible in other than twin recipients (16, 17). When, as often happened, transplanted kidneys began to be rejected after a few days or a few weeks, augmented steroid therapy allowed reversal of rejections. We also noticed that these patients subsequently developed what we called (perhaps incorrectly) partial tolerance. In many cases, the amount of immunosuppression could later be decreased. With that advantage, the patients were able to return home, have babies, go to the movies, and in general return to normal society.

This work (16) was done with Tom Marchioro (now at the University of Seattle in Washington) and Bill Waddell (at the University of Colorado). The technique of double-drug therapy has become the worldwide standard method of immunosuppression. Unfortunately, it was an achievement of which I personally became ashamed, because it was so limited, as illustrated by the results for nearly 5000 primary (first-time) cadaveric kidney transplantations in 105 centers from 1971 to 1976. The six-month graft survival was only 55% and the one-year survival 45% (18). Thus more than half of the patients given cadaveric kidneys were losing them within the first postoperative year. Moreover, the penalties, even with "success," were sometimes unacceptable and included cosmetic deformity from the steroids, infections, an increased incidence of de novo malignancies, bone disease, gastrointestinal disorders, and cataracts. Consistently good results could be obtained only with transplantation from living, related donors. Attempts to improve the outlook with antilymphocyte globulin, thoracic duct drainage, and tissue matching resulted in only small gains.

It was clear that the situation could not really change unless new drugs were developed. Such a new agent, cyclosporin A, surfaced in 1976 in a paper by Borel et al. (13). Cyclosporin A is an extract of two fungi. The most potent immunosuppressive agent yet described, it has no bone marrow toxicity. Until its development there had been no immunosuppressive drug, excluding steroids, that did not with chronic use depress the bone marrow.

In 1978, cyclosporin A was released for clinical trial to two groups in England—one at Cambridge, the other (for bone marrow transplantation) at the Royal Marsden Cancer Hospital near Lon-

don. The first reports on whole-organ transplantation, from Calne et al. (14, 15) of Cambridge in 1978 and 1979, were mixed. The good news was that many cadaveric kidney recipients treated with cyclosporin A never required steroid therapy. The bad news was that three of the first 33 patients developed lymphomas. In addition, the mortality from infection was high, and one in three of the patients died. Nonetheless, the Cambridge group recommended using cyclosporin A as the sole immunosuppressive agent.

Cyclosporin A was released in the United States in late 1979, to two centers—the Peter Bent Brigham in Boston, and to us at the University of Colorado. We quickly learned that for optimal use cyclosporin A needed to be used with steroids, and not as a sole immunosuppressive agent as the English had recommended. We recommended (19–21) that, in addition to cyclosporin A, adults be given a five-day course of rapidly decreasing daily doses of steroids, e.g., prednisone, starting at 200 mg/day and decreasing to 20 mg daily maintenance, as the subsequent course permitted. This was a revolutionary development, because decreasing steroids to such levels, when combined with azathioprine, had required months, not days.

The control of rejection with this combination of cyclosporin A and steroids has been really quite amazing. The actual one-year survival of cadaveric kidney grafts, even during a learning phase, was 80% (21). That is a stunning figure, almost twice as good as the graft survival after conventional immunosuppression. At the University of Pittsburgh, where I now work, graft survival has been even higher. The combination of cyclosporin A and steroids is almost a fail-safe method of immunosuppression.

Given the background that has been developed with the kidney, there has been a powerful movement to apply the same techniques for the transplantation of other organs. For the first time, the ability to perform hepatic transplants safely and relatively reliably is in sight. The procedure usually used for liver transplantation is organ replacement. The diseased liver is removed and a cadaveric organ is put in. The new liver can be preserved for 6 to 12 h if necessary, by infusing with cold solutions. All of the structures entering and leaving the graft are installed as anatomically normal as possible. For chemists, sewing in a liver must seem naive or anti-intellectual, which it probably is, but the results can be emotionally gratifying. The longest survival after liver transplantation

has been of a little girl whose operation was 12 years ago when she was four.

The problem with liver transplantation throughout the years has been that the undertaking was dangerous and unpredictable. Only 35 to 40% of the patients could be expected to survive through the first postoperative year, a situation that has changed with the use of cyclosporin A. The last year I was in Denver, we considered 14 patients for liver transplantation under the same cyclosporin-steroid therapy that we had developed for kidneys. Two patients died on the operating table. Of the other 12, 11 (92%) lived for at least a year. Even including the two operative deaths, the one-year survival rate in those liver recipients was almost 80% (20). Similar results have been obtained at the University of Pittsburgh.

Even in the early days of liver transplantation, the potential value of this technique for treating inborn errors was obvious. When liver replacement was first carried out in humans, there were changes in the recipient's alpha-protein phenotypes, haptoglobin, and group-specific components. These and subsequent observations of other phenotypes proved that the metabolic specificity of the new organ remained that of the donor for as long as the graft functioned (22).

For completely understood inborn errors, this expectation has been realized on a number of occasions (Table 2). The most experience (eight cases) has been with α_1 -antitrypsin deficiency (23). After orthotopic liver transplantation, the Pi type of the recipient has become that of the donor and the abnormally low values of serum α_1 -antitrypsin have increased to normal values. After liver transplantation, the accumulation of α_1 -antitrypsin in a homograft has never been seen.

Another disorder that has been cured metabolically by liver replacement in spite of its unknown pathogenesis is Wilson's disease (Table 2) (24), characterized by widespread accumulation of copper in tissues. We have treated two patients with orthotopic liver transplantation. One died six years after the operation because of biliary tract complications that could not be rectified. The other is still well after more than 10 years. Both recipients underwent a protracted decoppering process, as documented by urine copper excretion. Progress could be monitored as the Kayser-Fleischer rings of the cornea receded and disappeared. Serum ceru-

Table 2. Inborn Errors of Metabolism Corrected by Liver Transplantation

<i>Disease</i>	<i>No. of cases</i>	<i>Enzyme defect</i>	<i>Longest survival</i>
α_1 -Antitrypsin deficiency	8	Unknown	5 yr.
Wilson's disease	2	Unknown	10.5 yr.
Type IV glycogen storage disease	1	Amylo-1,4-transglucosidase (branching enzyme)	3 mo.
Tyrosinemia	2	<i>p</i> -Hydroxyphenylpyruvic acid oxidase	6 mo.
Niemann-Pick disease ^a	1	Sphingomyelinase	1.5 yr.
Crigler-Najjar syndrome ^b	1	Glucuronyl-transferase	1 mo.

^a Patient treated by Dr. Pierre Daloze, Notre Dame Hospital, Montreal.

^b Treated by auxiliary liver transplantation (see text); all other transplants were liver replacements.

lplasmin, which is almost always very low in patients with Wilson's disease, was restored to normal within a few days after transplantation and has remained so for more than 10 years in our second patient.

At least four other inborn errors with known and specific enzyme deficiencies have been treated by liver transplantation (Table 2). In a child with Niemann-Pick disease (25), a metabolic cure was obtained after orthotopic transplantation, but the pre-existing neurologic injury was not ameliorated and eventually was indirectly responsible for death. Children treated by us for Type IV glycogen storage disease and congenital tyrosinemia (26) died soon after transplantation (Table 2), but complete studies in the latter patient showed that essentially normal tyrosine metabolism had been achieved (26).

The foregoing experience was with liver replacement. Seven years ago, we attempted to treat a two-year-old child with Crigler-Najjar syndrome by transplanting an auxiliary liver. With this disease, a nearly complete absence of hepatic glucuronyl transferase makes impossible the conjugation of bilirubin by the liver. Yet, all other measures of liver function are normal, making removal of the original liver not entirely desirable. We transplanted an auxiliary liver to the right paravertebral gutter, taking its hepatic arterial supply from the aorta, and anastomosing the portal vein end-to-end to the transected recipient portal vein. Outflow

was established by anastomosing the end of the graft intrahepatic inferior vena cava to the side of the recipient vena cava. The graft and recipient gallbladders were also anastomosed. The auxiliary graft produced bile immediately and by the following morning the deeply jaundiced sclera (serum bilirubin 500 mg/L) had become white and the bilirubin was normal. Unfortunately, the portal vein and hepatic artery thrombosed several days later, and the auxiliary liver was removed. The child was returned to the previous treatment with plasmapheresis and died several months later of kernicterus.

The results shown in Table 2 were obtained in an era when conventional immunosuppression was used (27). "Metabolic engineering" in the new era of better immunosuppression with cyclosporin A and steroids will become increasingly common and successful. At the University of Pittsburgh, we have already used liver transplantation to treat patients with α_1 -antitrypsin deficiency, subacute Wilson's disease, tyrosinemia, Type I glycogen storage disease, and the sea blue histiocyte syndrome. With the improved new immunosuppressive therapy, these kinds of diseases will be effectively treated with increasing frequency.

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Discussion

Q: What is the mechanism of cyclosporin A?

DR. STARZL: Jean Borel thought that the drug was a relatively specific inhibitor of activated T lymphocytes. That idea seems to be holding up in various in vitro experiments. Also in experimental animals and perhaps in humans, part of the population of specific suppressor cells seems to be at least passively preserved. If these two suggestions hold up, and they can be put together, they would explain the great safety with which cyclosporin A can be used. George Santos of Johns Hopkins is convinced the

suppressor cell preservation is important, and several others agree with him.

DR. GREENBLATT: When you compare cyclosporin A with some of the other immunosuppressives, do you notice any difference in the virus infections?

DR. STARZL: Infections have been less, about one-fifth of what they were with conventional therapy. In Minnesota they found less fungal and almost no bacterial infection with cyclosporin A. At a Cambridge conference in September, A. G. Bird of Birmingham, England, reported six lymphomas. The lymphomas had occurred in patients who had an Epstein-Barr virus infection. The evidence that this virus caused lymphoma is circumstantial in some cases, but direct and incontrovertible in others.

Q: Does the report of an 8-14 translocation in these cases suggest that there is another event besides the cytogenetic event?

DR. STARZL: Yes. The present hypothesis is that the Epstein-Barr infection plays a background role in the sense of creating a proliferating population, and that the cytogenetic transformation is the second necessary condition. Incidentally, this kind of pathogenesis is not unique to immunosuppression under cyclosporin A. It is probable that the same events explain many of the lymphomas under conventional therapy with azathioprine and prednisone.

Q: Are there any hematopoietic ramifications following liver transplantation? Do you see any new blood types or blood products that are related to the liver?

DR. STARZL: Yes, two of the early protein phenotypes that were demonstrated to change were haptoglobin and group-specific component. Once these alpha-globins had changed phenotypes, the change persisted for the life of the patient. Since then several other phenotypes have been studied and documented in a paper by Alper et al. (22). Basically they are not too important.

Q: With liver transplantation for Niemann-Pick disease, is it realistic to hope that the extrahepatic tissues will receive a supply of the missing enzyme? I ask because I wonder if the macromolecules can be cleared from the central nervous system?

DR. STARZL: The patient I mentioned did not recover from his pre-existing neurologic status, and that was the reason for death a year and a half later. The Montreal physicians who studied

the patient with Niemann-Pick disease reported the development of demonstrable sphingomyelinase in the peripheral blood.

We do know that the neurologic disorder of Wilson's disease can be strikingly reversed with provision of a new liver, but of course that is a completely different disease.

Q: The question of whether the products of the new liver can cross the blood-brain barrier and be able to mobilize the lipid material is extremely important. The possibility that this may occur is a very exciting one, but unproven.

DR. STARZL: I hope that this occurs. The degree of reversal that can occur in a disorder such as Wilson's disease is really quite striking.

Q: Could you comment on the susceptibility to infectious disease of patients under cyclosporin A?

DR. STARZL: The incidence of all kinds of infections is distinctly less under cyclosporin A than with conventional immunosuppression. Our preliminary impression is that bacterial and fungal infections have become extremely uncommon, occurring at about one-fifth the rate of our past experience. Patients under cyclosporin A do have a significant incidence of virus infections, but the incidence is still only half of that observed with azathioprine-prednisone therapy. Incidentally, the same kind of data is being generated by investigators of the University of Minnesota.

Q: What are the side effects of cyclosporin A?

DR. STARZL: The incidence of lymphoma has been no greater per month of graft survival and function than with conventional immunosuppression. The most specific side effect of cyclosporin A is nephrotoxicity. However, the guidelines for management of this have been well worked out in Colorado and in Pittsburgh (20, 21). In essence, one must determine what the dose ranges are in which cyclosporin A toxicity can be expected and reduce the dose when there is a suspicion of drug injury to the kidney. The renal impairment is quickly responsive to dose reductions. So far, there have been no specific and diagnostic lesions that can be identified by conventional pathologic studies. Probably the nephrotoxicity causes proximal tubular damage. At one time, some of the European workers thought that they were seeing abnormal giant mitochondria in the renal tubules, but this has not been confirmed.

One of the unusual opportunities which we have had in the combined Colorado-Pittsburgh experience is to be able to study renal function in liver recipients and to study hepatic function in kidney recipients. By so doing, we have been able to eliminate the confusion that is inevitable when one is looking for organ toxicity with the organ that has just been transplanted. To put it more simply, it has been exceptionally difficult in renal graft recipients to study renal toxicity, but it has been simple to study renal toxicity in patients with liver transplants. The essence of management is dose manipulation.