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THE PRESENT STATE OF LIVER TRANSPLANTATION AND THE FUTURE PROSPECTS FOR INTESTINAL TRANSPLANTATION

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INTRODUCTION

In this brief review, I will give an account of what has happened in the field of liver transplantation in the last 32 years and comment on the prospects for the transplantation of gastrointestinal organs, to be specific, of the intestines.

Case Report

Liver replacement always has been the most interesting of the transplant procedures. Let me start by illustrating with a case report what a powerful tool for scientific inquiry a liver transplantation can be.

A tiny child was seen shortly after birth at the Mount Sinai Hospital in New York City. The baby was lethargic, with convulsions and a blood ammonia of over 1000 μM/ml. The hyperammonemia immediately suggested the diagnosis of urea cycle enzyme deficiency. Although at least a half dozen hepatic mitochondrial and cytosolic enzymes are involved in the urea cycle, it seemed most likely that the child had a carbamyl synthetase deficiency. Since the liver is the sole, or almost the sole, site of the conversion of ammonia into urea, several years ago, Dr. Leon Rosenberg, Dean of the Yale University School of Medicine, had suggested to me the use of liver transplantation to treat patients with this inborn error of metabolism. Unfortunately, it was never possible to keep patients with this diagnosis alive for long enough after their birth to obtain an adequate donor liver. The baby in question was treated with

infusions that encourage alternative pathways of ammonia metabolism, allowing survival for 15 days. The transplantation was performed successfully with a newborn liver. Within a few hours the patient became metabolically normal.

Other Inborn Errors

This case report illustrates how expansive the indications have become for liver transplantation. Nearly a dozen inborn errors of metabolism have been somatically corrected with a new liver, including the clotting disorders of hemophilia (1) and protein C deficiency (2). The history of the inborn errors of metabolism is itself a fascinating one. The first such disease in which the pathogenesis was defined by a specific enzyme deficiency was Type I glycogen storage disease (glucose-6-phosphatase deficiency). This was only in 1956. The authors of this work were the Coris, husband and wife, and Illingworth of Saint Louis.

A Coincidence of Timing

In that same year, 1956, there was no journal dedicated to transplantation. Most of the few papers on transplantation were published either in the Bulletin of the New York Academy of Sciences or in the Transplantation Bulletin. The latter was an appendage to the journal, Plastic and Reconstructive Surgery. The first mention of liver transplantation was in an abstract in the Transplantation Bulletin. The article did not have a title and did not contain any indication of the animal species in which the transplantation was performed (3). Cannon suggested that transplantation might have clinical relevance in the future. He mentioned lung, liver, kidney, heart, and intestines as candidate organs for eventual transplantation. He also recognized that organ preservation would have to be developed before the clinical application of any of these organs could be considered.

Transplantation of tissues and organs was not a hot academic topic in the years 1955-60. During this period, the annual meetings of the Society of University Surgeons were almost void of this topic. Only seven articles on transplantation were presented throughout the

half-decade, and none with any lasting impact. One article by David Hume described the wrapping of transplanted kidneys in plastic bags to prevent contact with the recipient tissues. One discussed the effect of pyridoxine deficiency on rejection. In a deja vu article published in Science, 1988, Schreiner et al. have reevaluated the possibility of reducing macrophage activity by starvation of the recipient to ensure allograft acceptance. Dr. Robert Good and his colleagues from Minnesota focused on the possibility of inducing tolerance.

Transplantation was thought to be completely impractical until the early 1960's. In January 1961, roughly at the time of President John Kennedy's inauguration, the New England Journal of Medicine published an article by Sir Macfarlane Burnet (4) who wrote "much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success . . . ".

Burnet's words were hardly on paper before new insight was gained in several aspects of transplantation, which would make feasible the clinical grafting of kidneys and later of the liver and the heart. These advances in knowledge developed in three distinct areas; first, immunosuppression; second, organ preservation; and third, histocompatibility. These are the "struts" of the clinical discipline of transplantation.

STATE OF ART

Immunosuppression

In 1959 and 1960, the immunosuppressive qualities of 6-mercaptaopurine and azathioprine were described by Schwartz and Damashek (5). This was the beginning of the so-called era of immunosuppression. Although individual agents could not prevent rejection reliably or completely, combination therapy with azathioprine and prednizone opened the doors for widespread clinical application of renal transplantation (6). In 1966, antilymphocyte

serum (ALS) and its globulin derivitive (ALG) were introduced as immunosuppressive adjuncts (7). A giant leap forward was made possible by the discovery (8) and then clinical application of Cyclosporin A (9).

Even though Cyclosporin A has been proved to be highly nephrotoxic when used alone in large doses, combining it with other drugs brought impressive improvements in immunosuppressive therapy (10). After introduction of this drug for liver transplantation, the one-year survival doubled and, in succeeding years, the advantages became even greater. In 1981, Cosimi et al. (11) of Boston added another weapon to the therapeutic armamentarium, namely a modern-day ALG, which is a murine monoclonal antibody (OKT3) directed against mature lymphocytes.

In the early years of clinical application, the kidney was the only whole organ transplanted. In 1963, the first attempts were made to transplant the liver (12). Four of the first five patients survived the operation, but the maximum survival was only 23 days. Nevertheless, the principles of orthotopic liver transplantation were nearly completely delineated. The first prolonged human survivals were achieved in 1967 under treatment with azathioprine, prednisone, and ALG (13). What has happened since has made liver transplantation a service that has changed the practice of hepatology (14).

FK 506

Despite its impressive advantages for immunosuppressive therapy in transplantation, cyclosporine still poses serious problems. Therapeutic doses of cyclosporine, even given in the framework of combination therapy with steroids and other drugs, can lead to kidney damage. On the other hand, lowering the doses excessively may allow allograft rejection. Therefore, a search for new drugs has powerful incentives.

At the transplantation congress in Helsinki in August 1986, a small but interested audience listened to the description, for the first time (15), of a new immunosuppressive agent termed "FK 506",

which was developed by the Fujisawa Corp., Osaka, Japan. This compound is not related chemically to Cyclosporin A. On a weight basis, its activity is 500 times greater than that of Cyclosporin A. FK 506 was purified from a culture of a species of Streptomyces isolated from soil collected 40 kilometers from Tokyo.

In an impressively short time, the physicochemical and immunologic properties of FK 506 were elucidated, and a monograph with a vast amount of clinically relevant experimental information was published as a supplement to Transplantation Proceedings (16). This illustrated how fast a discovery of basic biologic sciences now-a-days can be ready for clinical application. With FK 506, the latent period between discovery of FK 506 and its first clinical trials probably will be less than five years, far shorter than with any previous immunosuppressive agent. The physicochemical properties of FK 506 are similar in many aspects to those of Cyclosporin A. The effects of FK 506 on experimental kidney and liver transplantation compare favorably to those of Cyclosporin A (17).

Of exceptional interest is the synergism of FK 506 with Cyclosporin A. This synergism has been easy to study in a mixed lymphocyte culture assay system developed by Dr. Adrienna Zeevi in our laboratories (18) and called a minitransplantation system. The quantitative data obtained in Zeevi's well-controlled in vitro system are much more reliably and readily obtained than with any system in the past. Test results with this in vitro method can then be verified with classical in vivo heart, kidney, and liver transplant models in different animal species (16, 17).

Using Zeevi's assay system for lymphocytes from human homograft biopsies, it has been possible to identify distinct clones of cyclosporine-sensitive and resistant cells, and to show that very low doses of FK 506 and Cyclosporin A, which by themselves do not induce immunosuppression, have a convincing immunosuppressive effect when given together.

It is also highly promising that short courses of FK 506 may have long-lasting effects on graft rejection. Such long-lasting

immunosuppression in dogs after brief time treatment has been reported in the past only with antilymphocyte serum (ALS). In dogs treated on days 4, 5, and 6 after grafting of allogeneic kidneys - i.e. at a time when, without treatment, histological and biochemical signs of rejection can be seen - acceptance of grafts was observed in 50% of the animals for prolonged periods of time. Some of the dogs have had a functioning kidney graft for over six months (17). The same has been achieved with livers (17).

The results of toxicity studies on FK 506 can be summarized as follows. There is toxicity in dogs: intussusception of intestines and systemic arteritis have been described. However, even without FK 506 treatment, arteritis occurs in dogs after transplantation (17). In rats and baboons, FK 506 seems to have only minor toxic effects (17).

Concentration of FK 506 can be determined efficiently and reliably in plasma and in tissues. Monoclonal antibodies to FK 506 are being used in highly sensitive and specific assays.

Organ Preservation

Dr. Henry Swan of the University of Colorado was the first to minimize tissue injury during cessation of circulation for open heart surgery. In 1959, while in Chicago, I perfused livers with cold lactated Ringer's solution before their experimental transplantation in animals. In 1966, Christian Barnard and his colleagues developed the first ex vivo perfusion system for kidneys, using cold blood and a hyperbaric oxygen chamber. This was a major achievement on the road to clinically useful preservation of organs. Later, Dr. Fred Belzer removed the blood using an asanguinous perfusate which he had developed. In 1976, the introduction of a chilled high potassium electrolyte (Collin's) solution allowed preservation of human livers for 6 to 8 hours and opened the possibility of transporting cadaveric livers from city to city.

A quantum leap in liver preservation was achieved recently by Dr. Belzer, mentioned above, with a modified infusion solution. The effectiveness of this solution and its composition were reported last September (1987) in a Pittsburgh transplant conference (19).

The contribution of the various components of the solution to its effectiveness still is poorly understood, but it seems that raffinose and lactobionate (two sugars) are the most important ingredients. The use of this infusion solution allows livers to be preserved for 24 to 30 hours, a capability that has revolutionized liver transplantation (20). In Todo's studies, SGOT-level and prothrombin-time increases after transplantation showed no correlation with the time of tissue preservation (20). It should now be possible to exchange donor livers between Europe, Canada, the United States and South America and even with countries as far away as Australia, New Zealand and most of Southeast Asia.

We hope that in the near future, preservation of livers for a week or more will become feasible.

Tissue Matching

The role of histocompatibility antigens, encoded by genes of the MHC on chromosome 6, had been predicted by Jean Dausset and Paul Terasaki to be a crucial determinant of success in transplantation. However, the relevance of these antigens for "classical" allograft rejection has become small because of the availability of potent immunosuppressive drugs. On the other hand, crossmatching has become increasingly important in kidney transplantation in view of hyperacute rejection of renal homografts to recipients possessing antigraft cytotoxic antibodies. Cyclosporin A and other immunosuppressive drugs do not influence the hyperacute rejection.

The first examples of hyperacute rejection caused by isoagglutinins were reported by us 25 years ago. The first patient with blood group O received a kidney from a blood group A donor. Within a few minutes, the kidney was destroyed. Other such experiences dictated the blood group schemes in use today for donor recipient matching. These are designed to avoid placing organs into a recipient whose plasma contains antigraft antibodies (21).

Terasaki reported in 1965 on a hyperacute kidney rejection in a patient whose serum contained cytotoxic antibodies directed against the recipient (22). W. J. Dempster had shown hyperacute

rejection of kidneys in presensitized dogs as early as 1955 (23). The term hyperacute rejection was coined by Kissmeyer-Nielsen much later (24). With hyperacute rejection, the microvasculature is ruined. Small vessels are plugged with blood cells, neutrophils, and fibrin. These changes result in acute cortical necrosis of the kidney. Felix Milgrom emphasized the pivotal role of antibodies in hyperacute rejection. Ito et al. in 1985, also working in Buffalo, analyzed the involvement of various humoral mediators of inflammation in hyperacute rejections (25). Ito's preoccupation was with platelet activating factor (PAF).

Whereas kidneys usually are destroyed in 2-3 minutes after grafting to a highly sensitized recipient, the liver seems to be much more resistant to this type of rejection. There is little correlation of outcome of liver transplantation with or without cytotoxic crossmatches with the donor. Even the presence of immunoglobulins picked up in the liver is poorly correlated with rejection of the organ. If hyperacute rejection occurs, it may present as a hemorrhagic necrosis developing at a much slower pace (over 2-3 days) than the hyperacute rejection of the kidney.

Transplantation of Intestines

Until recently, clinical intestinal transplants have not been performed successfully, i.e., with a functional intestine after grafting. Twenty-five years ago, I developed a surgical procedure by which all of the abdominal viscera were transplanted (liver, stomach, pancreas, spleen, small intestine, and most of the colon) (26).

Last November 1, an infant was treated at our clinic who had lost all of her midgut but who had survived with the shortgut syndrome for 2.5 years on parenteral hyperalimentation. She then developed irreversible liver disease. We decided to attempt the same transplantation of multiple viscera which had been worked out in animals in 1960. A donor was available 407 miles from Pittsburgh. We treated the donor with OKT3. Later, Shaffer et al. (27) reported that donor pretreatment with ALS in rats completely abolished the

undirectional graft versus host reaction (GVH) of their experimental model.

Our patient never had evidence of GVH disease. The intake of nutrients through the intestinal graft improved over time, so that hyperalimentation could be reduced and ultimately almost completely stopped (28). Gastrointestinal x-ray series showed a normal transit time. Biopsies of intestines were normal. Three months after treatment, however, the liver became the site of lymphomas associated with an Epstein Barr virus (EBV) infection (29). These lymphoproliferative tumors of the liver had both monoclonal and polyclonal components and were of recipient origin. Cyclosporin A was discontinued. The cyclosporine levels in circulation decreased, and the liver lesions resolved with calcification of the lesional margins.

Cyclosporin A was then reinstituted, and the lesions started to grow again, compressing the biliary ducts. We could decompress partially the duct system, but just as we considered retransplantation of the liver, the child died of bacterial sepsis. Even though the transplantation eventually was thwarted by the destructive liver lesions, and the patient was lost, the parents of the child may find some consolation in the memory that everything possible was attempted. The surgical and pediatric teams were encouraged by the fact that the transplanted intestines functioned impressively in the child for many months.

Of this child, and other patients who have been the pioneers of transplantation technology in the last 30 years, it can be said that: "Diseases desperate grown by desperate appliance are reliev'd or not at all" (Claudius, in "Hamlet").

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