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Transplantation

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The modern era of whole organ transplantation began in 1962, when drugs were used in combination to treat patients after the technically easy operation of kidney transplantation. The simple kidney model continued for a long time to be the front-runner for advances in the four key elements of clinical transplantation, which could then be applied with minor adaptations for the extrarenal organs. The elements are (1) preservation, (2) tissue matching, (3) immunosuppression, and (4) surgical technique. This orderly progression changed within the last 10 years when the liver emerged as a focal organ of scientific inquiry.

For example, the liver has been central in testing better techniques of "slush" preservation. Such methods were introduced more than two decades ago, using a potassium-rich electrolyte solution or a plasmalike solution to cool kidneys by intra-arterial infusion, followed by refrigeration in an ice chest. Cadaveric kidneys could be cooled in this way for 24 to 48 hours, but the safety limit for livers treated in the same way was only 6 to 10 hours. Using a different electrolyte solution, hearts could be stored for a maximum of 6 hours.

A new preservative solution developed at the University of Wisconsin is in the process of expanding all of these outer limits. The University of Wisconsin solution was originally designed for preservation of the pancreas,[1] but after verifying its preservative powers in canine liver experiments,[2] full-scale clinical trials for hepatic transplantation followed, with revolutionary results.[3,4] The ability to store human livers for a day instead of a few hours allowed improvements at every level of what previously had been an exercise in urgency and administrative inconvenience. The University of Wisconsin solution protects the microvasculature of the transplanted whole organ, among other effects, and therefore should be beneficial for storing all organs, including the kidney and heart. Several experimental studies have already confirmed this expectation.

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With the kidney and perhaps the heart, good tissue matching of a recipient with a cadaveric donor can confer a small but significant advantage. A paradox has been reported from two large centers that found the outcome after liver transplantation to be actually degraded by good matching.[5,6] This has been explained by an "MHC (major histocompatibility complex) restriction" hypothesis, which holds that factors that destroyed the native liver are apt to damage the homograft in proportion to the quality of the HLA match.

Another curiosity in hepatic transplantation is the ability of the liver to resist destruction by the preformed cytotoxic antigraft antibodies that can immediately destroy kidney and heart grafts in a process called "hyperacute rejection." This has meant that the conventional cytotoxic crossmatch is irrelevant in pairing liver donors and their hepatic recipients.[7] Why the liver is excluded from a risk common to other organs has not been answered. One group[8] has shown that livers immediately produce soluble HLA antigens in quantities large enough to allow HLA typing in the plasma. Such antigens conceivably could neutralize antibodies or contribute to tolerance induction.

Nevertheless, there is mounting evidence that livers can be destroyed quickly by perioperative immune events that are not necessarily associated with cytotoxic antibodies.[9] When this occurs, a second liver transplant has a much higher than normal probability of prompt destruction (primary nonfunction). Such recipients have been referred to as "liver eaters."[9] Finding why some patients provide such a hostile environment for livers even when antigraft antibodies may be absent could explain why a significant number of kidneys and hearts are still being lost to hyperacute rejection, despite the most discriminating immunologic screening available today.

The revolution in clinical transplantation since

1979 would not have been possible without cyclosporine, an agent that allowed greater control of rejection with less toxicity than previously possible. Cyclosporine is used with other agents, of which prednisone is the most important, but also including azathioprine and the antilymphocyte globulin agents. Polyclonal antilymphocyte globulin has been replaced increasingly with monoclonal preparations that range in target specificity from all mature lymphocytes (OKT3) to interleukin 2 receptors.

The principal limitation of cyclosporine is its nephrotoxicity, which imposes dose ceilings and which may cause kidney lesions that are irreversible. This latter possibility has been particularly well studied in heart recipients.[10] The nephrotoxicity has not been completely eliminated by complex multiple-drug regimens in which low doses of the constituent drugs, including cyclosporine, are given. This impasse has stimulated a search for new agents.

The most promising new drug is FK 506, which is produced by a bacterium, *Streptomyces tsukubaensis*. FK 506 was discovered in 1984 and first described in the literature in 1987.[11] FK 506 has been studied exhaustively in rats, dogs, and baboons and is nearing clinical trials. It acts primarily by inhibiting interleukin 2 synthesis and binding in the same way as cyclosporine, with which it is synergistic.[12] It is relatively nontoxic in rats and subhuman primates, but has significant gastrointestinal toxicity in dogs. Nephrotoxicity has not been seen in animals, but neither was nephrotoxicity observed in animals treated with cyclosporine.

Various organ combinations have been transplanted, including the pancreas plus kidney or liver; heart and kidney; heart and liver; and heart-lung plus liver. Conventional operations were performed one after the other in each patient, under the same anesthesia and using the same donor. The use of multivisceral grafts (organ clusters) without first separating them has added a new dimension. In the most extensive such procedure, all of the intra-abdominal viscera were replaced, including the gastrointestinal tract from the stomach to the colon.[13] The maximum survival with this operation has been 6 months. Transplantation of smaller clusters has allowed removal of the stomach, liver, pancreas, duodenum, spleen, proximal jejunum, and most of the colon in treating malignancies involving the liver plus pancreas, duodenum, or colon.[14] The void in the upper abdomen has been filled with organ cluster grafts that contain at the minimum the liver, pancreas, and duodenum.

At least 16 inborn errors of metabolism are known to have been treated with liver transplantation.[15] In some of these diseases, the inborn error had been responsible for damage to the liver with resulting cirrhosis and/or malignant degeneration. Correction of the inborn error by transplantation in these patients was incidental. Recently, liver replacements have been carried out solely for the correction of inborn errors, removing and replacing a liver that was anatomically normal. Examples include familial hypercholesterolemia, primary oxalosis, Crigler-Najjar syndrome (glucuronyl transferase deficiency), and protein C deficiency. In some diseases in which the pathogenesis of the inborn error was imperfectly understood, study of these patients provided important clues or even definitive answers about the true nature of the disorder.

The cap for transplantation of any of the vital organs will be imposed by organ availability. Because of this, the criteria for donor candidacy are being reexamined. The number of available hearts and livers would be increased greatly by removing arbitrary upper age limits (usually 45 or 50 years) for donorship, as already has been done with kidney donors. Donors by the hundreds or perhaps thousands are undoubtedly being rejected because of rules or guidelines that are obsolete or inflexible. The cardiodynamic stability that was once a criterion of donor suitability may also be an unjustifiable requirement. It has been well documented in the United States and in a European study that so-called nonideal donors with unstable blood pressure, poor blood gas values, or even abnormal results on liver or kidney function tests can provide good organs.

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Liver replacements have been carried out solely for the correction of inborn errors