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The Transplantation of Gastrointestinal Organs

THOMAS E. STARZL, SATORU TODO, ANDREAS TZAKIS, and JOHN FUNG
Pittsburgh Transplant Institute, University of Pittsburgh Health Science Center, Pittsburgh, Pennsylvania

The history of whole-organ grafting through 1959 was largely confined to the kidney.[1] The vacuum began to fill during the mid and late 1950s with the development in several laboratories of canine transplant models with which to study all of the intra-abdominal and thoracic organs. Although it was not appreciated at the outset, the intimate anatomic, metabolic, and immunologic relationships of each of the intra-abdominal viscera (Figure 1) eventually influenced the conditions for transplantation of all of the others.

The Liver

In this revolution, the liver occupied a unique position, not only because it was the first vital organ beyond the kidney to be engrafted successfully in humans, but also because of the secrets yielded by research on its transplantation. Hepatic transplantation was introduced to the scientific literature in 1955 by C. Stuart Welch of Albany, New York, who described in dogs the insertion of an extra (auxiliary) liver into the pelvis or right paravertebral gutter of the recipient.[2] The allograft hepatic artery was revascularized from the aorta or iliac artery, and the portal flow was restored by rerouting the high-volume systemic venous return of the host inferior vena cava into the graft portal vein.

When the livers were destroyed within a few days in the nonimmunosuppressed animals, it was concluded that rejection was solely responsible. This was an understandable interpretation. After nearly 80 years of research on the experimental procedure of Eck's fistula (portacaval shunt), the dogma of 1955 was that the high concentration of hormones and nutrients in splanchnic venous blood had no relevance to liver structure or function or the capacity for regeneration.[3] The presumed nonspecificity of splanchnic venous blood was the central strut of the seemingly impregnable flow hypothesis of portal physiology which held that "all blood is equal."

In spite of his mistake in attributing auxiliary graft destruction to rejection alone, what Welch had done unwittingly was to create an experimental model of great power. The principle of the model was the coexistence of two livers in the same animal with identical conditions except for the constituency of the blood delivered to the graft and native portal veins. When Welch's experiments were repeated in 1963 under immunosuppression, auxiliary livers protected from rejection by azathioprine but deprived of splanchnic venous inflow shrank within a few days to a fraction of their original size.[4]

It soon became apparent that the liver with first access to the portal blood was able to remove substance(s) so completely that little was left for the competing organ. Insulin was the most easily identified of the portal blood factors, but it has long been known that the so-called hepatotrophic substances are multiple.[5] As new growth factors of pancreatic and enteric origin have become available in recent years, they have been discovered or screened with nontransplant models that in one way or other are direct descendents of the original auxiliary allograft (double-liver) preparations.[6]

The liver-replacement operation (orthotopic transplantation) in common clinical use today was first reported by Jack Cannon of the University of California, Los Angeles, who cited Welch's article as the stimulus for his own "several successful" replacement operations in dogs "without survival of the patient."[7] With the assumption that the liver played an important role in rejection, Cannon speculated that the graft would not contribute to its own repudiation. Details of his new operation were not given, and the procedure remained virtually unknown until major programs of canine "orthotopic" liver transplantation were begun at the Peter Bent Brigham Hospital (Harvard)[8] and independently at Northwestern University in Chicago.[9] At the time, there was no effective way to prevent rejection, nor would this objective be achievable for several more years.

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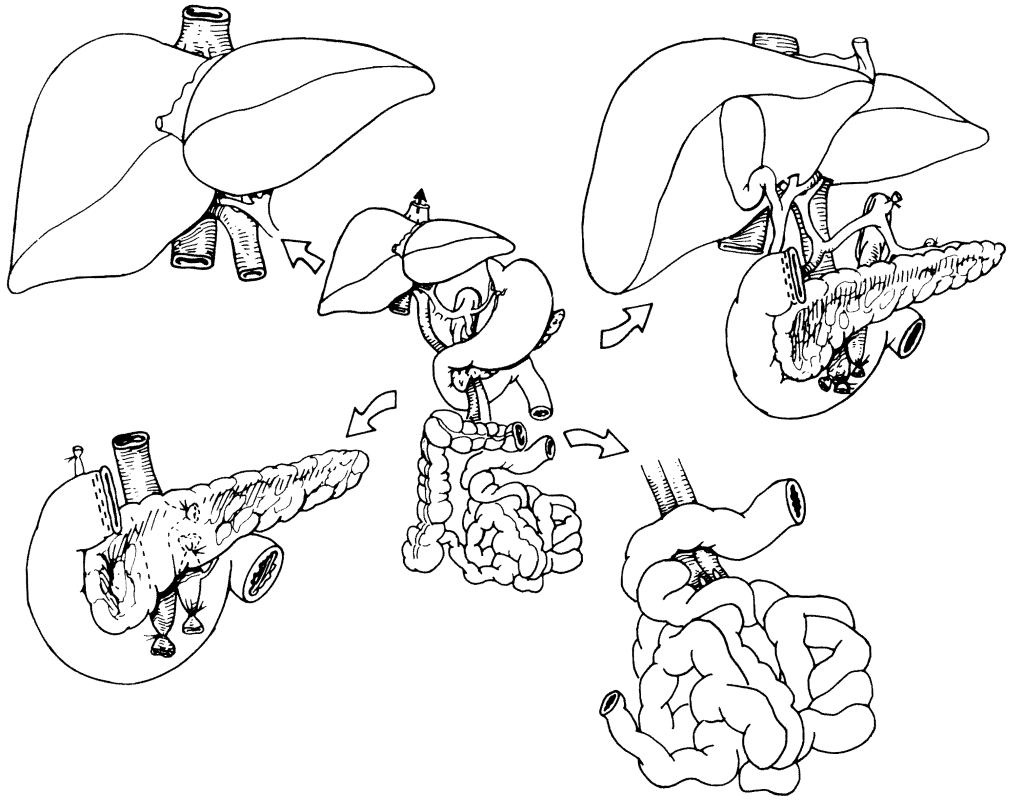

Figure 1. The complex of intra-abdominal viscera (center) from which come liver-pancreas, intestine, pancreas, or liver grafts (periphery).

The Boston effort under the direction of Francis D. Moore was part of an immunologically oriented institutional commitment to organ transplantation that extended back more than a decade previously with an initial emphasis on the kidney.[10] The Northwestern initiative stemmed from a hypothesis that the liver was a modulator of insulin activity or in turn was governed by this hormone.[11] In the course of the metabolic investigations, a new technique of total hepatectomy (the first half of a transplant operation),[12] and ultimately the insertion of an allograft into the vacated hepatic fossa,[9] were viewed at first as tools for metabolic investigations.

The superior liver-supporting qualities of portal venous blood were easily demonstrable by the results of the transplant experiments.[9] The other requirements for successful liver replacement also were straightforward. Intraportal infusion of the transplanted liver with chilled solutions during its removal allowed effective short-term storage in much the same way as in clinical operating rooms today.[9] Improved infusates in the succeeding years[13,14] eventually replaced the originally used lactated Ringer's and saline solutions. Since 1987, the University of Wisconsin solution developed by Belzer and Southard[15] has permitted the safe refrigeration of human livers for 18–24 hours.

Orthotopic liver transplantation could not be accomplished consistently in dogs without plastic external venous bypasses that passively redirected blood from the occluded splanchnic and systemic venous pools to the superior vena cava during the so-called anhepatic stage while recipient hepatectomy was performed and the new liver was sewn in.[8,9] Such venous decompression was later shown to be expendable in most clinical cases by experienced surgeons.[16] However, the introduction in 1983 of pump-driven bypasses without anticoagulation made the operation less stressful and placed it well within the grasp of most competent general and vascular surgeons.[17]

The sense of futility in the late 1950s at developing an operation that had no conceivable clinical use changed abruptly with the discovery by Schwartz and Dameshek of the immunosuppressive qualities of 6-mercaptopurine in nontransplant models. With the demonstration by Schwartz and Dameshek and workers in other laboratories that the drug mitigated the rejection of skin and kidney allografts in rats and dogs, respectively, the stage was set for the introduction by Murray et al. of the 6-mercaptopurine analogue azathioprine for clinical renal transplantation.[18] The combination of this drug with prednisone[19] permitted a treatment policy to be evolved that could be used with a succession of baseline drugs—azathioprine, cyclophosphamide, cyclosporine, and FK 506—over the

next 30 years. In these drug cocktails, the dose-maneuverable prednisone allowed quick changes in immune modulation on a day-to-day basis. In 1966, antilymphocyte globulin (ALG) was added as a short-term adjunct for induction treatment or as a prednisone substitute for secondary intervention[20]; eventually these polyclonal preparations were succeeded by monoclonal ALGs such as OKT3.

In late 1961, the Northwestern University experimental transplant laboratory was moved to the University of Colorado, and a clinical kidney transplantation program was started there. After azathioprine-prednisone was shown to be effective antirejection therapy in a handful of kidney transplant recipients in 1962 and 1963, a decision was made to move on to the liver.[21] The first attempt at liver replacement on March 1, 1963, ended tragically when a child with biliary atresia and an intractable coagulopathy bled to death in the operating room of Colorado General Hospital. Through the rest of 1963 and January 1964, six more attempts were made—four in Denver and one each in Boston and Paris. When all of the patients died after 6½–23 days, pessimism settled in worldwide with a self-imposed moratorium that lasted 3 years. The principal concerns were that the methods of preservation did not allow time for the deliberate performance of such a complex operation, that the intraoperative medical management (including coagulation) was not well enough understood to be manageable, and that the available immunosuppression was inadequate to control rejection.

By the summer of 1967, these deficiencies had been at least partially rectified during an intensive period of laboratory research, and on July 23 the trial was resumed with a 1½-year-old girl whose liver contained a nonresectable hepatoma. Although she became the first long survivor after liver transplantation,[22] it was not a time of triumph. The child died of recurrent cancer after 400 days, and for the next dozen years the 1-year mortality rate never fell below 50% in cases that were accrued at the rate of about one per month. The terrible losses were concentrated in the first few postoperative months. After this, the life survival curve flattened, leaving a residual group of stable and remarkably well survivors. Thirty (18%) of the first 170 patients in the consecutive series that started March 1, 1963, and ended in December 1979 lived more than a decade, and 23 of these are still alive after 13–23 years. They were all treated with azathioprine (or cyclophosphamide), prednisone, and polyclonal ALG.

The continuing survival of these patients was a mute testimonial for liver transplantation, but it was asked increasingly if such a small dividend could justify the prodigious effort that had brought liver transplantation this far. The same questions were being directed to Roy Calne of Cambridge, England, who had opened a second liver program in February 1968. Other teams established subsequently in Hannover, Germany (Pichlmayr, 1972) and Paris (Bismuth, 1974) also reported the nearly miraculous benefits of this operation when it was successful, but always with the notation that the mortality rate resulting from the operation was too great to allow its practical use.

The frustration ended after Calne's clinical introduction of cyclosporine in 1979,[23] when this drug was combined with prednisone or lymphoid depletion in the first of the cyclosporine-based cocktails.[24] Of our first 12 liver recipients treated with cyclosporine and prednisone, 11 lived for more than 1 year,[25] and 7 are still alive more than a dozen years later. New programs proliferated worldwide as the news was confirmed that a 1-year patient survival rate of at least 70% was readily achievable. With the substitution of FK 506 for cyclosporine in 1989,[26] the 1-year patient and liver graft survival rate increased another 15% in the Pittsburgh experience, an improvement also recorded in a multicenter European trial. By now, liver transplantation had become the accepted court of last appeal for almost all nonneoplastic liver diseases, and even for selected patients with otherwise nonresectable hepatic malignancies. The principal limitation of the technology quickly became an inadequate supply of organs to meet the burgeoning needs.

Multivisceral and Intestinal Transplantation

At the same time in the summer of 1958 as orthotopic liver transplantation was under development in Boston and Chicago, Richard Lillehei of the University of Minnesota began studies of small intestinal transplantation in dogs[27] that led 8 years later to the first of numerous unsuccessful clinical trials.[28] Between 1967 and 1987, more than a dozen attempts failed during the operation or up to 76 days later, usually with the death of the patient.[29] Although improvements in immunosuppression were being made that allowed long survival after intestinal transplantation in dogs and pigs, none of these human grafts throughout the two-decade span provided significant nutritional function.

This barrier was broken in 1987 when graft function was recorded for more than a half year from a cadaveric intestine that was part of a multivisceral graft in a recipient treated with cyclosporine, predni-

sone, and OKT3.[30] The multivisceral operation had been developed in nonimmunosuppressed dogs in 1959 during early research on liver transplantation.[31] The allograft was envisioned as a grape cluster with a double central stem consisting of the celiac axis and superior mesenteric artery (Figure 2*A*). The grapes, or individual organs, could be removed or retained according to the surgical objectives, but both arterial stem structures were preserved. The venous outflow was kept intact up to or beyond the liver.

The first patient who survived the multivisceral operation under cyclosporine-based immunosuppression died after 192 days of a B-cell lymphoma, but other patients have been treated successfully with the full multivisceral operation using FK 506 and are alive after as long as 15 months (Table 1). A variant procedure in which only the liver and small bowel are retained (Figure 2*B*) was described by Grant et al.[32] This operation has been particularly useful in patients with the short gut syndrome who developed liver failure after prolonged hyperalimentation.[33] Using FK 506, 13 (76.5%) of 17 patients in the Pittsburgh series are alive after 4½–30 months—all but 1 liberated from total parenteral nutrition (TPN) (Table 1).

The increasingly common use of such complex gastrointestinal grafts reactivated interest in an observation from the original multivisceral experiments in unmodified dogs that rejection of the organs making up the composite graft was less severe than that found when the organs were transplanted individually.[34] This impression was confirmed and greatly extended in 1969 by Calne et al.,[35] who described in pig liver recipients the protection of kidney and skin grafts from the same donor, and by the Japanese surgeon Naoski Kamada, whose experiments were performed in rats.

As recently as late 1991, some workers in the field believed that the protection to the intestine afforded by the concomitant transplantation of the liver from the same donor was sufficiently great to justify combined liver and intestinal transplantation, even when only a technically simpler intestinal transplant was needed. Enthusiasm for this draconian strategy began to fade with the successful transplantation in March 1989 of a cadaveric small intestine by Goulet et al.[36] of Paris and of an ileal segment from a living related donor by Deltz of Kiel, Germany.

These were isolated straws in the wind. The routine survival of cadaveric intestinal recipients then became possible under immunosuppression with FK 506 in Pittsburgh (Table 1), where the results have been better with isolated intestinal transplantation than with either the multivisceral operation or its liver-intestine variant.[33] Eight of 9 recipients survive, of whom all but one are TPN free. The expected release of FK 506 for general use in the near future is certain to stimulate rapid further development of the intestinal transplantation field.

When the intestine is transplanted alone, it is desirable and usually possible to drain its venous outflow into the host portal vein. However, the inability to do so for technical reasons and the consequent need to bypass the hepatotrophic contents of intestinal blood around the liver has not yet caused serious hepatic complications.

Another variation of the multivisceral operation is

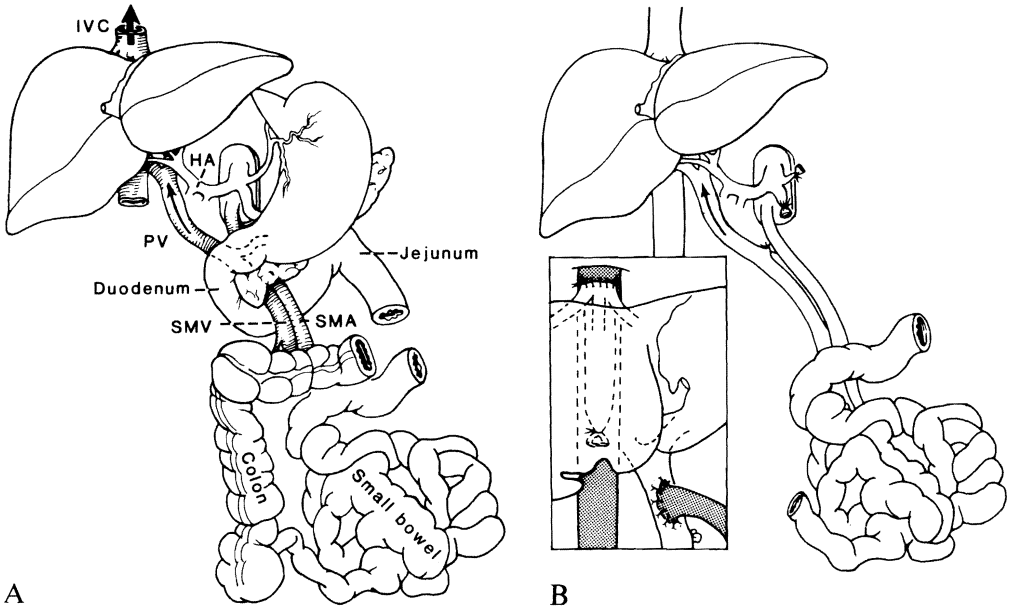

Figure 2. The multivisceral transplantation originally developed in dogs (*A*) and (*B*) a commonly used variant in which the central organs (pancreas and duodenum) are removed, leaving the liver and small bowel. These two procedures have been used successfully in humans and provided the first examples of functioning bowel allografts. *Inset:* Anastomosis of host portal vein into graft portal vein.

Table 1. FK 506: Transplantation of Intestine Alone or As Part of Composite Graft

	Dates	n	Alive (1/29/93)	TPN free	
				Total	Partial[a]
Intestine	5/2/90 to 6/7/92	9	8	7	—[b]
Liver-intestine	7/24/90 to 9/7/92	17	13	12	1
Multivisceral	10/14/91 to 8/12/92	3	3	2	1

[a]Night TPN only.
[b]Graft removed after 239 days because of encephalitis and need to stop immunosuppression therapy.

shown in the upper right portion of Figure 1, in which the stomach above and intestine below is discarded.[37] The remaining pancreaticohepatic graft has been used as partial replacement for the organs removed at upper abdominal exenteration (spleen, liver, stomach, pancreas, duodenum, proximal jejunum, and ascending colon). In some of these so-called cluster recipients, the duodenum and a segment of the jejunum have been placed in continuity with the residual gastrointestinal tract from the outset. These short segmental bowel grafts along with the liver and pancreas have functioned as long as 4½ years.

Graft Acceptance

Throughout the modern history of transplantation, it has not been possible to comprehend, nor even to have a plausible theory about, how grafts were able with the aid of immunosuppression to weather the initial attack by the recipient immune system and later to merge half forgotten into the host. Study of the gastrointestinal organs and their recipients have provided unique insights into these processes.[38] In 1969, the liver became the first transplanted organ to be recognized as having a composite (chimeric) structure. It was noted that the Kupffer cells and other tissue leukocytes became predominantly recipient phenotype within 100 days of transplantation, whereas the hepatocytes permanently retained their donor specificity (Figure 3). At the time and long afterward, this transformation was assumed to be unique to the hepatic allograft.

However, 22 years later, first in rat models and then in humans, it was realized that the same process occurred in all successfully transplanted intestines. The epithelium of the bowel remained that of the donor, whereas the lymphoid, dendritic, and other leukocytes of recipient origin quickly invaded and became the dominant cells in the lamina propria, Peyer's patches, and mesenteric nodes. Subsequent studies of the kidney and thoracic organs made it obvious that all whole-organ grafts underwent similar changes, differing only quantitatively in the number of substituted tissue leukocytes, which ranged from large in the case of the liver to small in such organs as the kidney and heart.

What remained to be determined was the fate of the leukocytes vacating the grafts. The answers were provided by the longest survivors in the world after kidney (30 years) or liver (23 years) transplantation, who came to Pittsburgh in the spring and early summer of 1992 to be restudied.[38,39] Biopsy specimens were obtained from each of these patients bearing someone else's liver or kidney, and also from more recently treated recipients of hearts, lungs, and intestines. The samples were taken from the transplanted organ as well as from the patient's own skin, lymph nodes, and other tissues. Then, after special staining procedures (immunostaining or sex identification after fluorescence in situ hybridization), the tissues were examined under the microscope to see if the individual cells that made them up had come from the organ donor, the recipient's own body, or both. Alternatively, the donor and recipient contributions to any specimen could be separated by polymerase chain reaction ("DNA fingerprinting") techniques.

As the answers came from these analyses and from new laboratory experiments in animals, a grand design emerged (Figure 3) that was always the same no matter what the engrafted organ. Within minutes after restoring the blood supply of any transplant, myriad sessile but potentially migratory leukocytes that are part of the normal structure of all organs left the graft and migrated all over the recipient, while similar recipient cells took their place in the transplant without disturbing the highly specialized donor parenchymal cells. The relocated donor and recipient leukocytes learned to live in harmony, provided they were given sufficient protection during their nesting, by immunosuppressive drugs. In this new context, the drugs could be viewed as traffic directors, allowing movement of the white cells in both directions (to and from the graft) but preventing the immune destruction that is the normal purpose of this traffic.

It is not known yet how the two sets of white cells—a small population of predominantly dendritic cells from the donated organ and a large one that is in essence the entire recipient immune system of the patient—reach a "truce." This is so complete in some cases that immunosuppression can be stopped, particu-

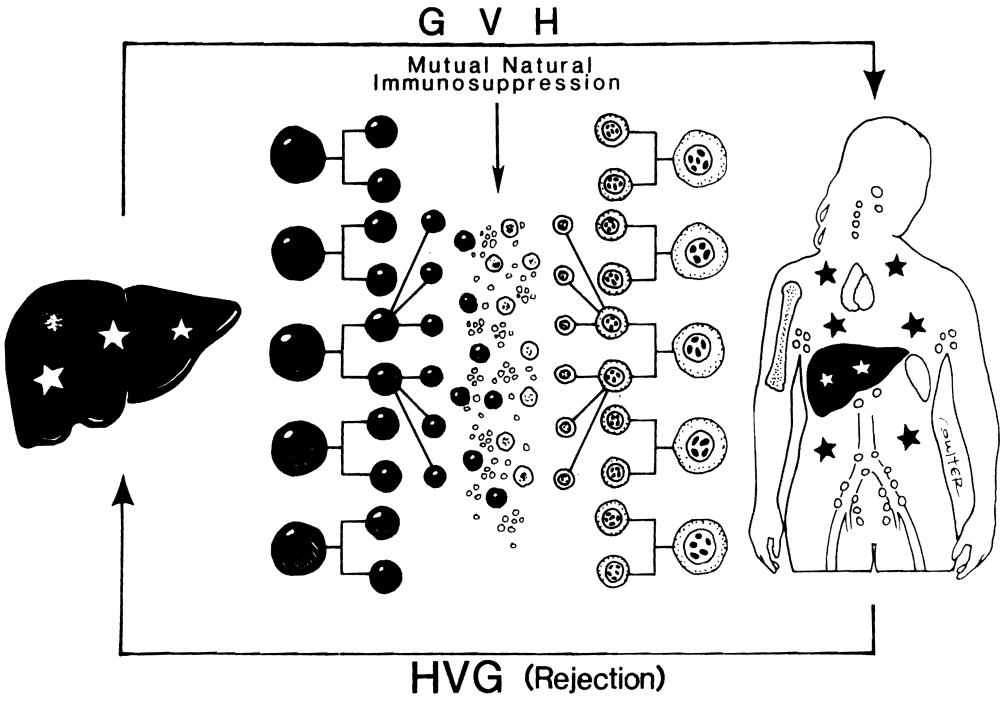

Figure 3. The phenomenon of cell migration (with repopulation and chimerism), which is postulated to be the basis of graft acceptance. Note the interaction at the site of donor-recipient mutual cell engagement. This is thought to be the first step toward donor-specific nonreactivity (tolerance) by a mechanism of peripheral clonal "silencing."

larly after liver transplantation but less constantly with other organs. Such a stable biological state can be induced more easily by the liver than by other transplanted organs because of the liver's higher content of the critical missionary leukocytes that apparently include pluripotent stem cells. This was thought to be the explanation for the protection afforded the intestine by a concomitantly transplanted liver.

While still incomplete, this much information already provides a tool with which to shape future strategies. The migratory cells can be purified from the bone marrow or spleen of a donor and then infused to improve the "acceptability" of various organs from that specific donor, including those taken from an animal for use in humans as xenografts. The cell-migration and mixed chimerism phenomena make comprehensible the unexpected inability of donor-recipient HLA matching to accurately predict the outcome of whole organ transplantation; neither the new organ nor its new host remains the same as at the time of the matching tests.

Summary

Over a period of 33 years, it has become possible to successfully transplant individual intra-abdominal viscera or combinations of these organs. The consequences have been, first, new information about the metabolic interrelations that the visceral organs have in disease or health; second, the addition of several procedures to the treatment armamentarium of gastrointestinal diseases; and third, a more profound understanding of the means by which all whole organ grafts are accepted.

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Address requests for reprints to: Thomas E. Starzl, M.D., Ph.D., Department of Surgery, 3601 Fifth Avenue, 5C Falk Clinic, University of Pittsburgh, Pittsburgh, Pennsylvania 15213.

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