Multivisceral and Intestinal Transplantation

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In 1958, the year experimental liver replacement was first attempted in Chicago and Boston, intestinal transplantation was born in the same crib and involved many of the same problems and contributors. Eighteen years before Wall's and Benichou's contributions for prolonged liver preservation, Richard Lillehei gave a report at the 1959 American Surgical Association, describing the preservation of intestinal grafts by immersing them in iced saline.1 Owen Wangensteen, Lillehei's chairman at the University of Minnesota, dismissed the cool reception given this paper by citing Benjamin Franklin's report 3 centuries before to criticism about some matter of debatable merit. Franklin's rhetorical reply was: "What is the good of a newborn baby?" Well, who can say? The intestinal baby was premature and remained ICU-bound for 30 years.

At first, its fraternal twin, liver transplantation, fared only slightly better. The use of the two organs together (plus more) in an organ complex (Fig 1) was lampooned at the Surgical Forum of the American College of Surgeons of 1960 by a discussant who asked: "Why not just carry the anesthetized dog from one table to another?" The graft in question included all of the intra-abdominal viscera. After this very difficult operation, only five of 38 of the unmodified recipients survived perioperatively, thereafter living for 5½ to 9 days. The two questions which prompted these experiments were discussed in a more complete paper.2 They are still incompletely answered as we have heard throughout this meeting.

One nuclear issue was whether rejection of the complex of organs was less than that of the individual organs alone. This appeared to be the case: "Despite this limitation in the interpretation of data, there is evidence that the relation to the host of the multiple organ graft is quantitatively different than that of the single organ liver graft. The greater degree of structural and functional preservation ... in the multiple organ graft suggests mitigation of the rejection process."3

The matter was dropped until the classical publication of Calne et al4 in 1969 which described, in pigs, the protection with liver transplantation of kidney and skin grafts from the same donor. The concept was confirmed and elaborated in rats by the Japanese surgeon Naoshi Kamada,5 whose first work was in collaboration with Calne in England. Why the liver is protective of other organs (tolerogenic), sometimes at its own peril, is an even more pivotal issue today. The reason is not yet clear, but surely will be in the near future. For now, it is established at a practical level that it is easier to graft the intestine along with the liver from the same donor than it is to transplant it alone.

The second fundamental question in our original papers was about graft-versus-host disease (GVHD), which was known at that time, but associated almost exclusively with bone marrow (not solid organ) transplantation. Histopathologic evidence of GVHD was found in recipient tissues of the multivisceral recipients, all of whom eventually developed multiple organ failure. It was remarked: "Conversely, evidence for a graft-versus-host rejection response is stronger in the recipients of multiple organs than in those receiving the liver alone ... After multiple organ grafts, there was evidence of host organ failure.

Fig 1. Schematic view of the transplanted tissues and their anatomic relation to the host. The grafted tissues are not shaded (Starzl TE et al: Mass homotransplantation of abdominal organs in dogs, Surg Forum 28, 1960. Used with permission).
Examples included suppression of bone marrow activity and the invariable development of pulmonary edema. However, the precise rules of graft and host tissues in the production of these changes cannot be ascertained from our data. Evaluation of the extent of host-versus-graft and graft-versus-host reactions will depend on studies in which either the host or the graft is rendered immunologically incompetent by radiation or other means.

Such experiments were published 13 years later in “unbalanced” F1 hybrid rats in the classical studies by Monchik and Russell. Rejection and GVHD have dominated the intestinal field since then. Liver transplantation eventually grew robustly while intestinal transplantation suffered from Runt disease in spite of the demonstration in Toronto, London (Ontario), Pittsburgh, Keil, and Paris that the gut could be transplanted with long survival in large animals although with great difficulty. About a dozen human intestinal transplantsations were performed in the United States, South America, Europe, and Canada between 1967 and 1987. All failed. Other papers at this symposium have accounted for these historically important cases.

CLINICAL MULTIVISCERAL TRANSPLANTATION

In 1987, the liver and intestine were reunited clinically in the same controversial multivisceral transplant operation as originally described in dogs. Because the case provided in humans the first example of a long-functioning intestinal graft, it was an opening wedge to re-examine the intestine, which had come to be viewed as a forbidden organ. It also was the parent of numerous variations.

In our report of the 1987 case, there were 42 citations. Of these, the one published in early 1988 by Grant et al stood out in importance above all others. These workers showed that the entire pig small bowel could be transplanted successfully under cyclosporine (CyA), not as a rare achievement, but repeatedly, and with growth and maturation of the recipients. Having been through this experience myself with other organs, I understood the commitment that had been required, particularly because the intravenous route of CyA administration had been needed. Their experiments were models of sophistication, but the investigators were not diverted by the zealous pursuit of details. The core objective was recipient survival. It was the old-fashioned way of transplantation research, and I knew that we had not heard the last of Grant and his associates. In modern scientific papers, all passion is discouraged from articles like these, but here it could not be concealed.

Except for the spleen, the complete multivisceral graft consists of all of the intra-abdominal organs. The graft is envisioned as a grape cluster with a double central stem consisting of the celiac axis and superior mesenteric artery (Fig 2). The grapes, or individual organs, can be removed or retained but both arterial stem structures are preserved and revascularized. A Carrel patch with the origins of these arteries can be anastomosed directly to the recipient aorta above or below the level of the renal arteries or via an interposition graft of donor aorta.

The venous outflow from the grape cluster is hepatofugal and is kept intact up to or beyond the liver. Composite transplants which include the liver are drained into a short length of retrohepatic inferior vena cava which may be used to replace the recipient vena cava or anastomosed “piggyback” to the anterior wall of the retained recipient vena cava (Fig 3). If any of the residual splanchic viscera are retained, their venous drainage outflow can be into the vena cava, as Jim Williams of Chicago was the first to suggest, or into the portal or superior mesenteric vein of the graft (Fig 3).

For procurement, chilled solutions are infused into the arterial supply. We have used the University of Wisconsin (UW) solution although the experimental studies of Schweizer et al of Kiel, Germany, and of Hamamoto working with Todo in Pittsburgh suggest that for the intestine this may be inferior to the Euro-Collins solution. Fluid volume to the nonhepatic viscera should be minimal, something which Alan MacDonald of Halifax emphasized for the pancreas more than two decades ago. If necessary,
Fig 3. Liver-small intestinal transplantation in which a segment of donor retrohepatic vena cava is used to replace the excised recipient. Note that the venous outflow of the retained recipient visera is directed into the recipient inferior vena cava (IVC) by portacaval shunt. Inset: “Piggyback" method of transplant venous drainage with anastomosis of the graft inferior vena cava to the anterior wall of the retained recipient inferior vena cava. Note, the additional option of anastomosing the recipient portal vein (PV) to the graft portal vein, a maneuver designed to expose the hepatic allograft to hepatopancreatic constituents from the retained viscera. The techniques are essentially the same as for the full multivisceral procedure (Starzi TE, et al: The many faces of multivisceral transplantation. Surg Gynecol Obstet 172:335, 1991. By permission of Surgery, Gynecology & Obstetrics).

Fig 4. The recipient operation after removal of the host organs under venovenous bypass (inset), insertion of the cluster graft, completion of the vena caval anastomoses above and below the liver, and anastomosis of the Carrel patch to the aorta at the natural location of the celiac axis. CA = celiac axis. SMA(D) = superior mesenteric artery of the donor. SMA(R) = superior mesenteric artery of the recipient. SMV(D) = superior mesenteric vein of the donor. and SMV(R) = superior mesenteric vein of the recipient (Starzi TE, et al: Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:274, 1989. Used with permission).

Strasbourg who has passed the 4-month mark. Here, in London, in what is a landmark achievement, there is a well patient who will soon reach the 1-year mark. The indications for this operation will be rare, but the information learned from it can be prodigious.

**CLUSTER TRANSPLANTATION**

Cluster transplantation, which is derived from the multivisceral operation, is with the same basic organ complex from which the stomach above and the intestine below are removed. These replacement grafts have been used after upper abdominal exenteration for extensive tumors. The operation is shown schematically in Fig 4, including the use of a venovenous bypass to decompress the temporarily obstructed venous return from the recipient intestines and inferior vena cava. Because patients subjected to cluster operations develop serious nutritional problems, the stomach was retained in one patient who died 14 days postoperatively from a segmental venous infarction of the recip-
Fig 5. Gastrointestinal series, 6 days after operation, showing homograft duodenum and jejunum in continuity with the patient's own stomach and jejunum (left). Technique used (right). To preserve the recipient celiac axis and left gastric artery, it was necessary to place the donor CamII patch below the left renal vein and the recipient superior mesenteric artery (Starzl TE, et al: Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:374, 1989. Used with permission).

Patient (not donor) jejunum. The tragedy, as we heard in Jeejeebhoy's opening remarks at this meeting, was that the attempt to salvage the flawed segment of jejunum was not justified because this piece of intestine was not needed. The transplanted stomach was completely normal at autopsy. Margreter's patient and the London multivisceral recipient have demonstrated the feasibility of gastric transplantation.

Of particular interest for this conference were three patients whose grafted duodenums and short segments of jejunum joined the mainstream gastrointestinal continuity as segmental grafts which were expected to function from the time of operation (Fig 5). In one of these patients, endoscopic biopsies of the duodenal homograft showed rejection at 3 weeks, widespread replacement of the duodenal mucosa with granulation at 2 months, but normal histopathologic structure at 1 and 2 years. This patient is clinically well after nearly 3 years, having demonstrated the enormous capacity for intestinal regeneration.

Another of these three patients, whose original diagnosis was carcinoma of the cecum with hepatic metastases, developed ampullary dysfunction of the graft common duct necessitating secondary duct anastomosis to a Roux-limb of recipient jejunum at a very difficult second operation. She died of recurrent carcinoma after 9 months.

What role denervation plays in the function of the visceral grafts and whether this was responsible for the ampullary dysfunction, needs further examination. Fresh from an earlier life in neurophysiology, I attempted an analysis 30 years ago of the interrupted neural pathways in my original article on multivisceral transplantation (Fig 6). This neglected area of research relating specifically to the intestine was discussed earlier this week, particularly in the report from Nebraska.

Cluster operations were performed 21 times in Pittsburgh 1½ to more than 3 years ago and, on a number of unreported occasions, elsewhere. Our 3-month mortality was 24%, usually related to graft pancreatitis. Seven (33%) of these patients still are alive, six are tumor free after 21 to 38 months (Table 1).

LIVER-INTESTINAL GRAFTS

The liver and intestine were transplanted together by Muncy Kalayoglu of Wisconsin in December 1988, but not...
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Table 1. Original Cluster

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Date—July 22, 1988 to September 20, 1991</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>7 of 21 (33.3%)*</td>
</tr>
</tbody>
</table>

* No evidence of disease: 6; alive with disease: 1.

Reported until now. His patient rejected transplantation and died after 52 days. We all know the magnificent achievement of Grant et al. who began with their first case in November 1988—and fanned the embers into flames.

The index patients of the Ontario team are now nearing the end of their third and second postoperative years. I have become a pen pal of the second patient, and finally met her yesterday. Seeing the lovely and functional woman was more informative and encouraging than any 10 scientific articles.

With this multivisceral variation, the small bowel and liver are retained in continuity, removing the other grapes from the stem vascular structures (Fig 3). Removal of the discarded organs can be done piecemeal at the donor operation or on the back table. The most inaccessible vessel, the superior mesenteric vein, is approached by inserting a finger along its avascular anterior surface, and transsecting the neck of the pancreas. This allows the numerous medial and lateral splanchnic tributaries to be ligated under direct vision. The uncinate process and duodenum are thrown away.

We have treated two adults and six children with this operation (cases 2 through 9) with follow-up times noted for each case listed in Table 2. The recipient operations and aftercare were by Satoru Todo and Andreas Tzakis. Seven of the eight patients are alive after 6 weeks to 14 months, some with spectacular rehabilitation. However, it will be emphasized in detail by Tzakis how difficult it has been to care for these patients. Only three of the patients are completely well. A stampede to do these cases is an invitation to disaster.

ISOLATED INTESTINE

There was one further case of isolated intestinal transplantation with present survival of more than 1½ years (Table 2, patient 1). This operation involves the same principles, but with removal of all the other grapes from the cluster. Dr Tzakis could relate his experience with the troubled course of this patient who is half success—half failure.

INTESTINAL SEPSIS

The restoration of gastrointestinal continuity is dependent on the nature of the allograft. We have used exteriorizing ostomies because prolonged enteric decompression usually is required postoperatively. Full continuity is restored later, after the intestine has settled in and is free of rejection or other complications. Before doing this, the patient must be free of infection.

The intestine is the Achilles heel in all the abdominal multiorgan variations. It has appeared to be more vulnerable to rejection than the liver and other organs. When rejection occurs, bacterial leakage through the disrupted barrier follows, even with minimal mucosal lesions. With the next stage of cryptitis, the intestine becomes a leaky sieve. The problem and solution are based on the same principles in more extreme form that were identified with the liver in the 1960s. A description of liver sepsis written in 1969 could be transposed unchanged to 1991.

The paradox was the use of strong immunosuppression with its known adverse effect on infection control to prevent rejection, but for the opposite objective: “It is almost ironical to state that one of the most important ways to prevent this peculiar form of liver infection is to provide very heavy immunosuppression, especially during the early postoperative period. Adherence to the converse policy of minimum immunosuppression...was a key factor in at least some, and probably all, of the consecutive tragedies of that era...[A steroid increase] was the only real adjustment that could be made since there was little maneuverability in the use of azathioprine and ALG.”

IMMUNOSUPPRESSION

We owe much to the brave patients and their doctors in Europe (Deltz, Ricour, Goulet, Margreiter to mention only four); the Canadian groups in Toronto (led by Zane Cohen, whose name should not be omitted in such discussions) and in this special place of London; and in the United States (Richard Lillehei and others) who have brought us

Table 2. Clinical Small Bowel Transplantation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Transplantation</th>
<th>Date of Tx</th>
<th>Graft Intestinal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31.1</td>
<td>M</td>
<td>Small bowel</td>
<td>May 2, 1990</td>
<td>Partial*</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>F</td>
<td>Liver-intestine</td>
<td>July 24, 1990</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>26.7</td>
<td>F</td>
<td>Liver-intestine</td>
<td>August 3, 1990</td>
<td>Good</td>
</tr>
<tr>
<td>4</td>
<td>4.3</td>
<td>M</td>
<td>Liver-intestine</td>
<td>November 24, 1990</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>M</td>
<td>Liver-intestine</td>
<td>March 24, 1991</td>
<td>Partial**</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>F</td>
<td>Liver-intestine</td>
<td>August 9, 1991</td>
<td>Died, GVHD</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>F</td>
<td>Liver-intestine</td>
<td>August 10, 1991</td>
<td>Partial**</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>F</td>
<td>Liver-intestine</td>
<td>August 12, 1991</td>
<td>Partial**</td>
</tr>
<tr>
<td>9</td>
<td>21.0</td>
<td>M</td>
<td>Liver-intestine</td>
<td>August 21, 1991</td>
<td>Partial**</td>
</tr>
</tbody>
</table>

* Nighttime only for parenteral supplementation.
** Still ICU-bound for ventilator support.
this far. Perhaps, we can go further with the new immunosuppressive drug, FK 506, which was used to treat all nine of our last patients.17

Our most promising experimental work with FK 506 by Murase et al19 has been in rats who survive routinely after transplantation of either the intestine alone or of a complete multivisceral graft. Murase showed the weights of a series of near normally growing rats. In the Brown-Norway to Lewis strain combination, FK 506 can prevent rejection as well as the development of OVHD.

In these rats, a critical observation was made by Murase with monoclonal antibody phenotype detection techniques developed by Iwaki and Demetris and their associates in Pittsburgh. Within 2 weeks, a massive replacement occurred of the lymphoreticular cells of the intestine by mesenteric and lymphoid cells of the recipient. The original donor epithelium remained, but it rested on a recipient lymphoreticular bed in the lamina propria. The changes were in the Peyers patches as well, and in the graft mesenteric lymph nodes.19

A local graft chimera was systematically created under FK 506. In reporting this, we neglected to cite a brilliant previous study published by Arnaud-Battandier of Ricour and Goulet’s group who showed the same finding in swine.20 The French team had not cited their own investigations in subsequent articles, and we failed to find this work which was published in 1985.

These observations changed our therapeutic strategy for GVHD control in the recent human cases. In our earlier multivisceral recipients treated with CyA, the graft lymphoid population was depleted by donor pretreatment with OKT3 and by irradiation of the intestine after it had been implanted. These steps, which were supported by rat studies of Shaffer and Monaco in Boston,21 were omitted in all of the FK 506 cases.10,17

In these patients, circulating donor lymphoid cells were found during the first postoperative month,22 an observation also recorded in the first patient of Grant and Wall18 without clinical evidence of GVHD. GVHD was not seen in our series except in a patient whose immunosuppression was lightened because of a technical complication. The circulating donor cells disappeared after a few days or weeks. Where these cells go was the subject of other papers at this meeting, particularly one by Murase et al, which has been published elsewhere.23 The distribution is diffuse, even including the thymus—especially when GVHD develops.

In the human intestine graft itself, it was shown as in the rat that lymphoreticular repopulation of the intestinal lamina propria occurred with replacement by cells of the recipient but with maintenance of donor epithelium.22 Both class I and class II cells participated. The time for this to be complete has been 45 to 90 days. Amongst the recipient cells now in the graft are those which produce IgA and, on the endothelial surface, secretory IgA can be seen with monoclonal staining as Nakamura et al14 showed.

Thus, intestinal graft chimerism is a central event in human as well as rodent and pig intestinal recipients. Achievement of this state obviously is dependent upon powerful immunosuppression. It is of historic interest that K.A. Porter showed this special kind of chimerism in our liver transplants 22 years ago,23 and that John Fung reported the same thing in heart-lung grafts in 1986.24 I now believe that it is a general phenomenon with all solid organs, differing only in the extent of the cell traffic.

NONIMMUNOLOGIC RELATIONSHIPS

Finally, I should note the importance of nonimmunologic factors in the success or failure of abdominal organ grafts. Normally, the venous effluent from all of the nonhepatic splanchnic organs contributes to the portal blood supply, assuring first-pass delivery to the liver of intestinal nutrients, and of the so-called portal hepatotrophic substances which are important for normal hepatocyte structure, function, and the capacity for regeneration.27 The hepatotrophic factors, of which endogenous insulin is the single most important, are multiple and apparently cumulative.

Thus, when partial multivisceral grafts are used, such as the liver-intestine, it is preferable to direct the gastroduodenal-pancreatic effluent from the retained recipient organs as well as from the intestinal graft into the portal circulation of the new liver (Fig 3). Otherwise, subtle injury of the liver can be expected as occurred in one of our liver-intestine recipients whose native pancreaticoduodenal-gastric effluent was bypassed around her liver graft. The hepatic graft developed histopathologic findings typical of, although less than, those after Eck fistula. These eventually stabilized with a satisfactory result.

Another consideration of portal versus systemic drainage of the intestine is worthy of mention. In a classic study published in 1945, the distinguished physician, Paul Beeson, showed that the liver is the most effective of all human organs in filtering out bacteria in the blood stream.28 Thus, the liver stands as a barrier between the transplanted intestine and systemic bacterial translocation. A decision not to use it, which is implicit with drainage into the vena cava, should not be taken lightly.

Nowhere can the linkage between the past and present be seen more clearly than in Beeson’s writings. The bacterial gradients across central vital organs were determined in some of the first patients in the world submitted to the then new cardiac catheterization techniques. These also were amongst the last patients with bacterial endocarditis, who were doomed, because penicillin and other antibiotics were not yet available. The painful dichotomy of pure investigation versus treatment was fresh in Beeson’s mind 40 years later when he concluded that he probably would not permit such studies if he sat today on a modern Institutional Review Board.29 Yet, the results were immortal and can help us today, providing we know of their existence.

Now in his 80s, Beeson lives in Redmond, Washington.
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I met him and other ancient warriors at a reunion in Pittsburgh in June 1991 of those left from this earlier generation. With him was George Thorn, one of the founders of the Peter Bent Brigham kidney transplant program. There is much to learn from wise men like these.

Aside from its infectious significance, the liver has long been thought to be a screen for toxic substances and antigens absorbed from the intestine. If, as suspected, the liver can diminish the immunologic response by modifying allograft antigens or the action of immunoreactive cells in the recipient, directing the venous output of intestinal grafts into the portal vein (and through the liver) could provide a therapeutic advantage. Many articles (summarized to 1977 in ref. 30) have been published claiming such an effect. However, in our own earlier studies, carried out with Giuseppe Mazzoni, we were unable to detect a difference in rejection of pig or dog allografts which were drained into the portal versus the systemic circulation.20 Similarly, the results reported at this meeting by Li et al11 of London and Murase et al12 of Pittsburgh did not show a difference in rejection with portal versus vena caval drainage.

CONCLUSION

I came here today mainly to pay homage to the intrepid pioneers, many here today and others now dead, who had the conviction to persist with what must have seemed like vain and hopeless efforts stretching back a third of a century. Now, there is evidence that the intestine will be joining the family of organ transplants.

As Tzakis will emphasize in a few minutes, we must not spoil the victory by overplaying our hand and beginning a mad race to the gold fields. We must remember that we have consistently succeeded so far only in transplanting the cadaver intestine with the advantage of a companion liver. The only long survivors so far with intestinal transplantation alone are the child reported at this meeting by Goulet et al of Paris (2½ years) and the adult in Pittsburgh (1½ years). This is the operation which will have the greatest use if it can be perfected.

A real team is needed for these trials. Remember that not every place can have a Cal Stiller, a Bill Wall, and a David Grant together. People like this cannot be bought like high-priced baseball players and quickly assembled into a unit. They can only be thanked and admired. So my Canadian friends, thank you.

REFERENCES