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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): This is an altogether remarkable paper describing one of the world's largest and most successful series of pancreas transplants. It is ironic that Dr. Sollinger's group, which was responsible for popularizing the bladder drainage technique, have experienced at least as great incidence of late complications from this procedure as others who followed their lead.

Although development of this method was a contribution in the evolution of pancreas transplantation, since it was safe and facilitated recognition of rejection, the Wisconsin group are now changing to the bowel drainage technique, as I think most other groups are doing. The overall results of graft survival in their series, which includes patients transplanted as long as 12 years ago are about 5% better than the current overall U.S. results and about 15% better than earlier results of others during the time comparable to this series.

One wonders what factors were responsible for the superiority of the Wisconsin experiences. The manuscript suggests several possible reasons about which I would like to ask Dr. Sollinger: Is his recipient selection unusually careful, excluding high-risk patients who might be accepted for transplantation by others leading to poorer outcome? Does their unusually low rate of acute tubular necrosis of the kidney (only 4%) favor the pancreas and the kidney?

Mentioned in their manuscript is an aggressive protocol employed in donors who they believe results in an observable decrease in donor pancreas edema. Is this a factor in the remarkably low incidence experienced by the Wisconsin group of pancreas allograft vascular thrombosis (less than 1%, no more than their incidence of thrombosis of the kidney transplant vessels). This is approximately 12 times lower than the incidence of complication reported by others over the time during which their series was compiled. Can Dr. Sollinger tell us how he avoids this catastrophic complication which is so commonly encountered by others?

Finally, it is of considerable interest that although they see acute rejection crisis in about 75% of their simultaneous kidney-pancreas patients, as compared with only 47% in the kidney alone patients, the eventual kidney allograft survival is actually better in the simultaneous kidney-pancreas recipients than in kidney alone, even those with related donors.

Is it conceivable that the greater antigen load of the double transplant or the large number of passenger leukocytes derived from lymphoid rich pancreaticoduodenal component of the double allograft actually provide an advantage over the kidney alone transplants? This would add further support to Dr. Starzl's contention that the lymphoid cell chimerism resulting from solid organ allografts is importance in their acceptance.

DR. HANS W. SOLLINGER (Madison, Wisconsin): Thank you, Dr. Barker. First of all, I do not know of any scientific evidence exploring why kidney-pancreas transplants, despite the high incidence of rejections, fare better than kidneys which have about half the incidence of rejection episodes. As far as antigen load is concerned, I hope that Dr. Starzl can shed some light on this issue.

As far as the preservation characteristics are concerned and why we do so well as compared with other series, obviously having been trained by Dr. Fred Belzer has helped us to understand how to preserve organs very well.

The low thrombosis rate has even surprised me. But we have trained a number of fellows over the years, and after they went out and started their own programs, they also had very low thrombosis rates. So there might be something about the technical aspects which we use in our procedure which leads to low thrombosis rates. Some of the critical points have been outlined in an editorial in *The Journal of the American College of Surgeons* a year ago. So I refer you to my editorial, which lists several points about how to address the low incidence of thrombotic complications.

DR. THOMAS E. STARZL (Pittsburgh, Pennsylvania): Dr. Robb Corry, a pioneer of pancreas transplantation at the University of Iowa, asked me to pay tribute to this landmark paper of Hans Sollinger, and also to the late Richard Lillehei, who was the first to perform whole pancreas transplantation 31 years ago. Under azathioprine-based immunosuppression, the procedure had such a high mortality that it was abandoned world-wide in 1971 for about a dozen years. After the advent of cyclosporine, we reintroduced the Lillehei procedure in Pittsburgh, with the modification of exocrine drainage through a duodenal bubble which was anastomosed to the host jejunum (Starzl et al., *Surg Gynecol Obstet* 1984;159:265–272. Sollinger at Wisconsin and Corry at Iowa further modified the operation by anastomosing the bubble to the bladder instead of bowel. This allowed monitoring of rejection with urinary amylase determinations, but with the urologic and metabolic complications that are well known.

By the time Dr. Corry joined the Pittsburgh faculty, the more potent drug, tacrolimus, was available. In agreement with what Dr. Sollinger has said, secondary reforms were possible with the more reliable control of rejection. First, the perioperative induction therapy with ALG and OKT3 that had become standard with cyclosporine-based therapy was no longer necessary. In addition, the more physiologic enteric drainage procedure could be performed safely. We have almost exclusively used the original enteric drainage procedure described in 1984, which also has become Sollinger's preferred technique.

This slide shows Dr. Corry's results with 110 cases after he joined our Pittsburgh faculty in 1994. You can see the very high 2-year survival of patients, 98%; kidneys, 94%, and pancreas grafts, 81%. In connection with Dr. Barker's comments, these patients were not highly selected. There were many who had had previous amputations, were blind, and had other complications. Thus, it is a procedure that is applicable across the board. Incidentally, as Dr. Barker implied, the better survival of kidneys in the Wisconsin double organ recipients *versus* that of kidneys alone probably is due to the greater dose of donor leukocytes and consequent augmented chimerism under the former circumstances.

I think what we have heard today is an announcement, and a far-reaching one, from Dr. Sollinger, who is a very important figure in the field, that the day of pancreas transplantation as a legitimate, cost-effective, and efficient service has arrived. All we can say is thank you for what you have done.

DR. CARL G. GROTH (Huddinge, Sweden): Dr. Sollinger, just like the previous discussants, I would really like to congratulate you on this remarkable series of transplantations. In Stockholm 18 years ago, we accumulated a series of patients that had successful pancreatic transplantations using enteric drainage, and reported in the Lancet. The number of patients in that series was three. So pancreatic transplantation has really come a long way since then with your 500 cases.

Finally, I have a question to you, Dr. Sollinger. What is going on now in the other places in the U.S.? Maybe you should tell this audience: What is the evolution at the other centers? Are they also becoming more and more interested in the enteric drainage technique?

DR. HANS W. SOLLINGER (Madison, Wisconsin): Thank you very much. I would also like to thank Dr. Starzl for his kind comments. As Dr. Sutherland has shown in Milan at the IPITA meeting in October 1997, there is an increasing number of centers in the United States switching over to primary enteric drainage. It is somewhat ironic, as it has been said before, that we have been the leader of the trend in the United States, after having first described the bladder drainage technique.

DR. DAVID E. SUTHERLAND (Minneapolis, Minnesota): As alluded by Dr. Sollinger, the evolution of pancreas transplantation into a highly successful procedure was hastened by the collaborative efforts between institutions, such as developing the techniques for procuring liver and pancreas from the same donors in the early 1980s. (Marsh CL, Perkins JD, Sutherland DER, Corry RJ, Sterioff S: Combined hepatic and pancreaticoduodenal procurement for transplantation. *Surg Gynecol Obstet* 1989;168:254–258). Dr. Sollinger and his colleagues at the University of Wisconsin made some unique contributions, including the bladder anastomosis technique making the urinary drainage easy and safe; inventing a preservation solution (Belzer's) that was as effective as a plasma based solution but without the risk of disease transmission; and introducing of Mycophenolate Mofetil which, along with tacrolimus, has had a dramatic effect on decreasing pancreas allograft rejection episodes, and definitely has allowed the enteric drainage technique to become routine for simultaneous kidney pancreas transplants.

Simultaneous pancreas kidney transplants have advantage over the solitary pancreas transplants in that kidney function can be used to monitor for rejection. In the cyclosporine era at Minnesota we found that for bladder-drained, simultaneous pancreas-kidney transplants about 10% of rejection episodes presented with a decrease in urine amylase preceding an elevation in serum creatinine. In the mycophenolate mofetil/tacrolimus era, this is very rare.

However, for solitary pancreas transplants, we believe that bladder drainage still has an advantage over enteric drainage because rejection episodes will still present with only a decrease in urine amylase without a preceding rise in serum amylase. Serum amylase may increase as a marker of solitary pancreas rejection, but in many cases there is not a rise, or it is at least preceded by decreasing urine amylase. Therefore, if one does not use bladder drainage for solitary transplants, the recipient will be at a disadvantage.

At the University of Minnesota we primarily perform solitary pancreas transplants (of over 900 done between 1968 and 1998, more than 60% were solitary). On the slide shown here, you can see that for 1997, out of 87 pancreas transplants, 51 were solitary. In this series of solitary pancreas transplants, the success rate has been high only with bladder drainage. In our organ procurement organization (OPO), it is very difficult to allocate kidneys for simultaneous pancreas kidney transplants because we are a multicenter OPO and not all centers have pancreas programs. Thus, for the uremic diabetic we must primarily do pancreas after kidney, something eminently possible by using living donors for the kidneys. Dr. Sollinger, in your current series of pancreas after kidney transplants, are you using bladder drainage or enteric drainage? If you went to pancreas transplants alone, what technique would you use? Would you persist with enteric drainage or would you use bladder drainage?

Finally, I would like to comment on the impact of pancreas transplantation on secondary complications of diabetes. In a collaborative study between our institutions we have shown that we can actually prevent recurrence of diabetic nephropathy in kidney transplants by the addition of a pancreas. You have also shown an effect on retinopathy in your SPK recipients, and we have shown an effect on neuropathy, not only in SPK, but also in pancreas transplant alone recipients.

I do not believe that uremic diabetic patients will continue to be the main recipients of pancreas transplants. Dr. Sollinger, how do you see the evolution of immunosuppression in regard to pancreas transplantation alone? In the early series of Dr. Richard Lillehei done between 1966 and 1973, three of 14 patients received a pancreas alone, and it was his vision that pancreas alone transplants would become the norm. Are we now ready to fulfill this vision? Most pancreas transplants alone have been done to treat patients who have extremely labile diabetes, with hypoglycemic unawareness or lose day-to-day quality of life because of their immediate problems with diabetes. My colleague in nephrology, Dr. Michael Maurer, has shown that regression of diabetic nephropathy can occur in native kidneys following a pancreas transplant alone. The potential for using pancreas transplantation to ameliorate or prevent diabetic complications is apparent. Dr. Sollinger, do you see pancreas transplants alone as something that we can now apply to a wider array of diabetic patients than in the past?

DR. HANS W. SOLLINGER (Madison, Wisconsin): Concerning the drainage procedure for isolated pancreas, we are using primary enteric drainage. But we will follow your work very closely and we might have to reverse our decision in a year or 2. But you are the leader in this field, and we will compare our results with yours.

As far as pancreas transplantation prior to end-stage renal failure, I think once immunosuppression has been optimized—and as you know, we are working in our laboratory on the induction of tolerance now—I think this will become a very exciting field.

DR. DIXON KAUFMAN (Chicago, Illinois): A couple of very brief questions: When your patients ask you how long will a pancreas transplant last, what do you tell them? Finally, in your striking slides showing the poor outcome in the diabetic uremic on dialysis, clearly more people should be able to benefit from this procedure. What can be done so that more patients can benefit?

DR. HANS W. SOLLINGER (Madison, Wisconsin): I believe we have to have more organ donors and we have to have more

nephrologists who refer their patients early to us before those patients reach a stage where long-term survival is unlikely. That would be my recommendation at this point. And, of course, we shall never stop looking for a better cure for diabetes.

What do we tell our patients? We give them pretty much the same information as reported in this manuscript, including some of the data showing an impact of pancreas transplantation on secondary diabetic complications and quality of life.

DR. R. SCOTT JONES (Charlottesville, Virginia): Mr. President? Could I ask one question from the floor, please? Dr. Sollinger, in your patients that had the duodenal lesions, did you find any evidence for infections with helicobacter pylori?

DR. HANS W. SOLLINGER (Madison, Wisconsin): No. But about 50% C and B.