Discussion

Dr. John R. Brooks (Boston): I have been following Dick Lillehei's work in pancreatic transplantation for a long time. He has certainly gone ahead and has continued with the human work.

Our experience goes back to the early 1950's. At that time we were interested in trying to get a fragment of the pancreas to be accepted. In the late 1950's and then in the early 1960's, we attempted to allograft human pancreatic tissue in fragment form to eight patients with total diabetes.

We first used neonatal tissue and then later chamber protected insulin on a tissue. This experience proved fairly conclusively that fragmented pancreatic tissue would not succeed as functioning grafts.

Then along with Dr. Lillehei and Dr. John Howard and several others, we then also obtained long-term successful grafts of pancreatico-duodenal tissue in dogs such as seen in Dr. Lillehei's slides.

So far yet, at the Brigham, we have not gone on to use this technic in humans. But there are many questions that must be answered by those of us in this field before pancreatic grafting can have a firm foothold in the treatment of complications of the disease which, after all, is the important aspect of the whole problem.

First, to have any effect upon the vascular complications of diabetes the graft must survive for at least many months, if not years, and time alone will answer this particular question.

Second, will the constant flow of insulin actually decrease the vascular complications to which a diabetic is subject, or is it conceivable that the microvascular basement membrane disease of diabetes is in part also genetically derived, like insulin lack, and therefore perhaps unaffected by the constancy at which insulin is supplied to the individual?

Third, is it conceivable that with the passage of time recipient antibody will build up to the insulin molecule from the graft and destroy it?

Parenthetically, we do know at the moment that the single component type of homologous insulin is not antigenic.

Fourth, what if any evidence is there that diabetes or its complications may in part also be a disease of overproduction of the alpha cell?; or, some other islet containing substance or a lack of some other substance as well as insulin?

And, then, finally, an interesting concept has been suggested by Soeldner at the Joslin Foundation in Boston who feels that constancy of insulin flow is the *sine qua non* of preventing vascular complications. He suggests that a small machine combining both a glucose monitoring system and insulin delivery system might be devised which a patient could carry with him, as a pacemaker or a chemotherapy infusion machine, to control accurately his blood sugar level from moment to moment during the day and particularly at night.

Dr. John Connolly (Irvine): We have also been interested in pancreatic transplantation and six months ago we placed a donor pancreas and kidney into a 32-year-old woman with juvenile diabetes, who was in terminal renal failure.

In the six months since operation there has been no evidence of rejection of the pancreas, while we have detected and treated successfully three episodes of rejection of the concomitantly transplanted kidney.

Blood sugar, blood amylase and glucose tolerance tests have been repeatedly normal since the transplantation. No insulin has been given since operation and the patient has consumed unlimited amounts of sugar.

One major complication did occur—the early occurrence of a massive pancreatic fistula which was successfully treated by continuous suction and hyperalimentation via a central venous catheter. During that hyperalimentation we administered large amounts of 50% dextrose, and in spite of this the blood sugar remained normal.

Two technical details that helped us to successfully treat the pancreatic fistula I believe were (1) the retroperitoneal placement of the transplanted pancreas, and (2) a drain down to the closed duodenal stump.

The hookup employed was the same as that suggested by Dr. Lillehei. As you see, here is the closed duodenum and the Roux-en-Y jejunal connection to the third portion of the transplanted duodenum.

In future patients we plan to avoid this method of restoring the alimentary tract. In our patient it appeared that some of the food went down this blind end and caused increased pressure on the closed duodenum. Thus we plan in the future to trim this donor portion of duodenum down to just a tuft of bowel wall containing the ampulla of Vater and then placing a loop of jejunum alongside and using this tuft of donor duodenum as a side patch.

We believe this will possibly decrease the likelihood of (1) fistula formation from either bowel ischemia of the large amount of duodenum that has been used to date, and (2) that it will also eliminate the possibility of a blind end subject to hydrostatic or trapped food pressure.

Of course, our optimism about pancreatic transplantation must be guarded, but we do believe that a small number of such transplants will be necessary to evaluate the ultimate potential of this modality.

We are most interested in the effects of transplantation of the pancreas alone without a concomitant kidney. We have selected as recipients several juvenile diabetics who are losing their eyesight.

One such patient has been in our medical center for the past 10 days awaiting a suitably matched donor pancreas. We hope to find out if a successful transplant in such a patient will stop

the progression of the disastrous complications of blindness, renal failure and peripheral vascular disease that occur in juvenile diabetics even though ideal insulin control is maintained.

In closing, I would like to commend Dr. Lillehei and his associates for their ingenuity, courage and possible foresight in initiating pancreatic transplantation.

DR. RICHARD C. LILLEHEI (Closing): It was John Brooks' summary of endocrine organ transplantation in 1959 which first aroused our interest in pancreatic transplantation.

I do not know about recipient antibody against insulin formed by the new pancreas. Dr. Fred Goetz our diabetologist is studying these patients to see whether a separate antibody will form against the new insulin in the absence of rejection of the pancreas. So far he has not detected anything of this nature yet.

The artificial pancreas is an interesting idea and one that we are working on because it seems with our ability to go to the moon, we ought to be able also to manufacture an artificial pancreas. It is possible that such an implanted device might be all that is needed and the risks of pancreatic transplantation could then be avoided.

I thank John Connolly for his comments. I am pleased to hear that his patient with the combined renal and pancreaticoduodenal grafts is now doing so well.

Dr. Connolly referred to a pancreatic fistula in his patient. More properly he should have called it a duodenal fistula since the pancreatic juice was leaking from the duodenum rather than the pancreas.

I noticed that John said he used a drain down near the duodenum of the graft in his patient. This may have been the cause of the fistula. We have not had any such fistulas in the immediate postoperative period so far.

Rejection of the pancreas is a very difficult problem to assess. We have radiated the pancreas with cobalt when we have seen elevations of serum or urinary amylase but we really don't know what these elevations mean because the blood sugar has remained normal and other signs of pancreatitis have not occurred.

One thing is clear, the pancreas is a hardy organ. One woman in our series was doing well in the early postoperative period and then apparently received a contaminated dose of antileukocyte globulin. She developed a very high fever and function of her renal graft which had been good, abruptly ceased. She then developed an acute abdomen. We explored her and found her transplanted kidney to be completely infarcted. The graft duodenum was also infarcted but the pancreatic graft looked good and was continuing to secrete insulin until removed.

Whether this was a Shwartzman type reaction from pyrogens or endotoxins in the antileukocyte globulin we do not know, but the pancreas was not damaged to the extent of the kidney or duodenum.

So far we have not seen any clear-cut rejection of the pancreas so we are looking for ways to eliminate the duodenum while still preserving exocrine drainage of the pancreas.

The problem in carving off duodenum is to prevent leaks and pancreatitis but I agree with John Connolly that we hope to eliminate as much of the duodenum as we can because this is apparently the Achilles heel of this procedure.

Finally, I wish to thank John Connolly also for his commendation to us for boldness or courage. Much as I would like to accept this accolade, I cannot because I am reminded of a statement of Will Mayo's made many years ago. You may recall he said that "a bold surgeon is one who knows that the patient takes all the risks."