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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): These are really very impressive results, and I was happy to review the manuscript because it is excellent work.

I think that some people might be surprised to see this paper on the program of a surgical meeting, but it is worth remembering that diabetes is in a sense "a surgical disease." Not only as surgeons do we take care of its complications, but I think it is fair to say that many of the important contributions to the understanding and treatment of this disease have been made by surgeons.

It was only a hundred years ago that an experimental surgeon in Europe first made the association of the pancreas with diabetes. Even though this disease had been recognized since ancient times, it was not known until then that it had anything to do with the pancreas. Seventy years ago another young surgeon, a young Canadian surgeon, discovered how to isolate insulin, a story every medical student knows. Probably only our president and other Canadians would know that when Fred Banting went to Toronto to ask for 10 dogs to experiment on during a summer vacation, that he was told by the expert in diabetes, Professor Mcloud, that he was wasting his time and should instead, because he was a surgeon, try to transplant the pancreas. Fortunately, Banting did not take the expert's advice and within a couple of months, of course, he had isolated insulin and shown that he could keep pancreatectomized dogs alive.

Although our efforts in transplantation began a long time ago, they have not really been very successful so far. Back in the 1930s, Jonathan Rhoads, among other surgeons, tried to transplant isolated pieces of pancreas into diabetic patients. Our new vice president, Keith Reemtsma, was probably the first to do a bona fide isolated islet transplantation (in fish). Other members of our group such as Walt Ballinger and Rich Lillihei, John Najarian, and Dave Sutherland, have made major contributions in the transplant field.

I personally believe that pancreatic and islet transplantation will not be the ultimate treatment of this disease. I think that instead we will discover how to prevent it. I had the privilege of presenting a paper to this Society 11 years ago that was the first to show that diabetes in experimental animals could be influenced by manipulation of the immune system. Investigators who work with experimental models of diabetes, such as our president's wife Elenor, I think are going to find the clues to tell us how to prevent the autoimmune process that causes diabetes.

Meanwhile, transplantation and better methods of delivering insulin will be competing treatments. Particularly at European meetings, these modalities frequently share the same program. Transplantation has until recently had an edge, but I am not so sure after hearing Dr. Pitts' paper this morning that this dominance will continue.

I think it is hard to believe in this age of computers that we are not going to be smart enough to figure out how to normalize the blood sugar by improving methods of delivering insulin. Improvements in this technology such as Dr. Pitts uses are likely to allow normalization of the blood sugar. As far as we know, pancreatic transplantation offers nothing beyond that in terms of preventing the complications of diabetes, which in all probability are the result of the wide swings in hyperglycemia that conventional insulin therapy allows. The paper we have heard this morning is in my opinion the description of an excellent new and evolving technology.

I was particularly interested in the choice of the intraperitoneal route, because this is the first one that our group used in our islet transplantation experiments. It did not prove to be very good for transplantation because the dose of islets needed for reversal of diabetes was much larger in the peritoneal cavity than if transplanted to other sites such as the liver. But this may not be true for insulin therapy and, in fact, as Dr. Pitts and his colleagues have suggested, the intraperitoneal route may have the advantage of being more physiologic than subcutaneous or other routes because part of the insulin absorbed reaches the portal circulation. I wonder if he has data on the fraction of insulin that does directly reach the portal circulation and the liver.

The data on complications, as he indicated, are very early, and although they seem encouraging I predict it will be many years before we will see with this or any form of therapy convincing evidence that the complications actually can be prevented by tight control of the blood sugar. This is an important aspect of this evolving therapy, because tight control of the blood sugar, as Dr. Pitts has indicated, also has dangers. In the European experience, a number of patients, using more primitive insulin pumps than the one he's described, have suffered bad hypoglycemic episodes. It is very important to be able to prevent those.

In the European experience with insulin pumps, there were also some patients who had sudden unexplained loss of eyesight. It is encouraging that Dr. Pitts has not encountered this complication.

This approach is quite promising, possibly more so than encapsulation of islet tissue to prevent rejection; perhaps better than any form of transplantation. But it is not as good as prevention.

DR. DAVID E. R. SUTHERLAND (Minneapolis, Minnesota): Dr. Pitt is making a concerted effort to improve the management of diabetic patients and to improve their quality of life, a goal similar to that of pancreas transplantation.

I look on diabetic patients as hovering between purgatory and hell, and the physician's role is to figure out which of the alternative treatments tips the balance more toward purgatory than toward hell for an individual patient. Dr. Pitt needs to inform us as to how the patients are selected for his alternative modality.

None of the current options available will get diabetic patients to heaven, and we continue to search for the Holy Grail. A pump coupled to a glucose sensor might be that grail. Dr. Pitt, please comment on the current status of closed-loop pumps with a servo-type feedback system *versus* the open-loop pump that you used.

As alluded to by Dr. Barker, the pancreas transplant provides a servo system, but has the drawbacks of requiring immunosuppression. For that reason, most pancreas transplants are performed in kidney transplant recipients who are already obligated to immunosuppression.

There is, however, an incentive to provide better control of diabetes at the onset of the disease, because we know that nearly 50% of those afflicted will get serious complications over a lifetime on conventional therapy. Whether 20 years of immunosuppression would give less, the same, or more morbidity than 20 years of diabetes in the patient population as as whole is not known, but the complications of immunosuppression, as currently administered, are sufficient to limit the application of pancreas transplants alone to diabetic patients with ongoing problems.

To return to patient selection, I note that Dr. Pitt said none of his patients had hypoglycemic unawareness before placement of the pump. In contrast, hypoglycemic unawareness is one of the main indications for pancreas transplants alone in nonuremic individuals. Thus, I would look at pancreas transplants and open-loop pumps as being complementary modalities, one being applicable to one group and one to another group of diabetic patients.

Dr. Pitt appears to be treating patients who are highly motivated to control their disease very well, whether they do or do not have difficulty with conventional insulin administration. In contrast, the patients that receive pancreas transplants alone are those that have defective counterregulatory mechanisms. Pancreas transplants are usually performed with systemic venous drainage. As Dr. Pitt mentioned, one of the advantages of his system is the ability to deliver at least part of the insulin into the portal system by intraperitoneal absorption. Nevertheless, pancreas transplant recipients are absolutely euglycemic with normal glycohemoglobin levels in spite of systemic venous insulin delivery. Furthermore, both hypoglycemic and hyperglycemic episodes are abolished.

Dr. Pitt alluded to quality of life issues, but he did not show any data. Quality of life studies need to be done formally to assess the impact of new modalities. Standard scales to measure quality of life have been developed by social researchers, and the American Diabetes Association has a standard quality of life assessment form for diabetic patients. Such an assessment should ideally be made before and after a new therapy is applied. Dr. Pitt, have you and your colleagues initiated any such studies?

Finally, Dr. Henry Buchwald, who could not be here, asked me to make a few comments. As you know, Dr. Buchwald has presented his work on implantable pumps to the American Surgical Association, first as a delivery device for heparin, chemotherapeutic agents, and other drugs, and then in the early 1980s, for the delivery of insulin. The Minnesota group prefers to use an intravenous catheter, and actually believes that the severity of complications is less by this than by other routes. Dr. Buchwald would like to know if Dr. Pitt has made any comparisons between intravenous and intraperitoneal delivery, and whether one route truly gives better control of diabetes than another. The advantage of portal insulin delivery is hypothetical; can you show that it makes a difference?

Dr. Pitt's device has the potential for treatment of a large number of diabetic patients, and is certainly one method that may improve the quality of life of such patients.

DR. HENRY A. PITT (Closing discussion): With respect to Dr. Barker's comments, I agree that the surgeon is an indispensable member of the team evaluating this new technology. The endocrinologist is clearly a key player, but the surgeon, the nurse and the patient are also important members of the team.

Both Drs. Barker and Sutherland discussed the relative roles of transplantation *versus* implantable insulin pumps. At this point, we believe that these two techniques are more complimentary than competitive. In fact, they have been applied to different subsets of diabetic patients. For the most part, transplantation has been reserved for patients with severe life-threatening complications, which is appropriate because the treatment is more involved and dangerous. We have tended to implant insulin pumps in patients with very few complications and believe that the balance between a treatment with relatively minor risks for patients with minimal disease is appropriate.

With respect to patient selection, the system is very patient-friendly, even though the pump and transmitters are very sophisticated. As a result, patients do not need to be overly intelligent to be eligible for this treatment. They do need to have an understanding of their diabetes and what factors affect their blood sugar, but the daily use of the system is really quite simple.

The relative merit of intraperitoneal *versus* peripheral insulin delivery was mentioned. At this point, the question of whether peripheral hyperinsulinism is bad for the patient is not really answered. With respect to intraperitoneal insulin, animal studies have shown that absorption is better from the upper abdomen than from the lower abdomen and that the majority of the insulin enters the circulation via portal rather than systemic absorption. We believe that intraperitoneal insulin delivery may explain the low incidence of severe hypoglycemia that has been observed in our patients. Other techniques employing peripheral insulin delivery that have tried to achieve tight glucose have had more problems with severe hypoglycemia. By putting insulin in the peritoneum, systemic delivery may be regulated by other hormones and processes within the liver.

With respect to the diabetic complications, I agree with Dr. Barker that we have not proven that intraperitoneal insulin prevents diabetic complications. The number of patients is too small, and the length of follow-up is too short. A multi-institutional, long-term trial of the effect of tight insulin control on diabetic complications is ongoing and should help to answer this question. However, this trial is studying peripheral and not peritoneal insulin delivery. With respect to retinopathy, our two patients with severe eye problems when they began on intraperitoneal insulin have progressed and have required vitrectomy, but their eyesight has subsequently been stable. Our other 19 patients have had no sudden loss of eyesight and no progression or new retinopathy.

I have already addressed Dr. Sutherland's questions about patient selection and balancing the treatment with the degree of disease. With respect to quality of life, he is correct that we have not done formal studies. Quality of life studies have been done with pancreas transplantation and have shown improvement. When we began this clinical trial in 1986, we did not formally address this issue. However, the multi-institutional trial with the new pump system at our and other institutions is studying quality of life, but these data are not yet available.

With respect to a glucose sensor and a closed-loop system, I am told that we are still 5 to 10 years away. However, this answer was given 5 years ago and may still be appropriate 5 years from now. Nevertheless, a lot of work is being done with glucose sensors, and my guess is that we will see this technology applied clinically within our lifetimes, but not necessarily in 5 years.

Dr. Buchwald needs to be credited with much of the initial work done with insulin pumps. His work differed from ours, however, in that he used a fixed-rate infusion system with intravenous delivery, and he treated type 2 diabetics. We have used a variable-rate infusion system with intraperitoneal delivery in type 1 diabetics. We have not specifically compared our technique with the intravenous route. However, recent reports from the University of California at Irvine as well as a multi-institutional evaluation suggest that catheter blockage may actually be greater with intravenous than with intraperitoneal insulin delivery.

Finally, with respect to ongoing trials, our patients are part of a multi-institutional, multinational implantable pump study. To date, more than 250 of the new pumps with intraperitoneal delivery have been implanted worldwide. The follow-up is currently too short, however, to know the long-term results. The Department of Veterans Affairs is also conducting a randomized trial in type 2 diabetics of the pump *versus* tight insulin control. Thus, in a few years, we will have more data available to evaluate this new technology. My expectations are that these studies will be an important step toward a closed-loop system and will confirm the theoretical advantage of intraperitoneal insulin delivery.