vide evidence that such AGE products may contribute to the progression of diabetic nephropathy. Furthermore, their data indicate that normal renal function is an important component in clearing AGE from the circulation. However, as Steffes and Mauer (2) caution, whether such AGE products are responsible for the vascular complications of diabetes has not been proved. Thus, studies need to determine whether reducing the level of AGE can, without other changes, reduce or prevent the development of diabetic microvascular complications.

One such agent that has been used to prevent the formation of AGE is aminoguanidine, a hydrazine that has been shown to react with the early glycosylation products and form a substitute glycosylated product. Studies of diabetic rats suggest that pharmacological inhibition of the formation of AGE may prevent the late and early structural lesion of diabetes (1). Confirmation of these findings has come from the work of Ellis and Good (3) who demonstrated a decrease in glomerular basement membrane thickness in diabetic rats treated with aminoguanidine. Unfortunately, no functional data were presented in these two preliminary studies to indicate that the correction of structural abnormalities was accompanied by decreased proteinuria. Clearly, association does not prove causation, but the work of Makita provides another avenue of research worthy of further exploration to elucidate the pathogenesis of the microvascular complications of diabetes.

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References

1. Brownlee M, Cerami A, Vlassara H: Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Engl J Med* 381:1315–21, 1988
2. Steffes MW, Mauer SM: Toward a basic understanding of diabetic complications. *N Engl J Med* 325:883–84, 1991
3. Ellis EN, Good BH: Prevention of glomerular basement membrane thickening by aminoguanidine in experimental diabetes mellitus. *Metabolism* 40:1016–19, 1991

An Artificial Pancreas: 14 Yr of Progress

SULLIVAN SJ, MAKI T, BORLAND KM, MAHONEY MD, SOLOMON BA, MULLER TE, MONACO AP, CHICK WL: BIOHYBRID ARTIFICIAL PANCREAS: LONG-TERM IMPLANTATION STUDIES IN DIABETIC PANCREATECTOMIZED DOGS. *SCIENCE* 252:718–21, 1991

OBJECTIVE— To incorporate islet tissue onto a selectively permeable membrane that isolates this tissue from the immune system of the recipient.

RESEARCH DESIGN AND METHODS— Implantation of biohybrid pancreas devices containing canine islets and bovine islets into pancreatectomized dogs requiring exogenous insulin.

SETTING— Research laboratories of BioHybrid Technologies, Inc, Shrewsbury, MA, The New England Deaconess Hospital and Harvard Medical School, Brookline, MA, and W.R. Grace and Company, Lexington, MA.

ANIMALS— Pancreatectomized dogs were treated with insulin therapy to maintain the fasting glucose concentrations below 12.5 mM (250 mg/dl). Islets were prepared from either adult mongrel dogs or bovine calves.

INTERVENTION— The islets were seeded into the artificial pancreas device. This device uses a selectively permeable membrane with a nominal molecular mass cutoff of 50,000 M_r. The tubular membrane is coiled inside a protective housing that provides the compartment for the islet cells. The membrane is connected at each end to a standard terminal polytetrafluoroethylene graft that extends beyond the housing and is used to connect the device to the vascular system as an arteriovenous shunt. Blood flow through the graft and tubular membrane results in exchange of glucose and insulin across the membrane between the circulating blood and the cell compartment. Antibodies and lymphocytes responsible for immune rejection are excluded from the cell compartment. The output of insulin from one such device was 15–20 U/day; thus it was necessary to use two devices per dog.

PRIMARY OUTCOME MEASURES— Fasting blood glucoses, glycemic response to a meal, or intravenous glucose tolerance test.

RESULTS— Of the 10 original animals, 2 animals showed no response due to a high percentage of nonviable

islets and 1 animal died shortly after surgery due to a technical complication. In 6 of 7 remaining animals, the devices completely supplanted the need for exogenous insulin. Average fasting glucose concentrations ranged from 5.3 to 8.4 mM (107–168 mg/dl). However, the rate of glucose disappearance from the circulation was <1%/min, whereas the rate in normal dogs was 4.1%. One of these implants has continued to function for >5 mo.

CONCLUSIONS — Although insulin output from these islets is not sufficient to decrease acute rises in blood glucose concentrations, the data provide evidence for the potential of the artificial pancreas as a therapy for insulin-dependent diabetes. They also indicate that xenografts can be used, which are more abundant than allografts.

COMMENTARY — This work is a continuation of previous studies that used a similar device reported in 1977 (1). These previous studies demonstrated the effectiveness of such a device in producing insulin and decreasing blood glucose. However, these were short-term studies demonstrating the feasibility of such an approach. The current work demonstrates that such an approach can maintain fasting normoglycemia for as long as 5 mo. These studies are important for several reasons. They demonstrate that xenografts can be used and remain functional for a long time, thus obviating the need for procurement of allograft material to be transplanted. Thus, the approach of Sullivan et al. would provide more transplantable material. This approach also obviates the need for immunosuppressive therapy and the risk of rejection, which remains the major reason for transplant failure. Furthermore, it is impressive that the devices could remain in place without more clotting than was seen. Thus, the potential exists for long-term maintenance of such devices.

It is clear that normalization of glucose metabolism is the best way to prevent and reverse the microvascular complications of insulin-dependent diabetes mellitus. Intensified exogenous insulin therapy is fraught with the difficulties of increased hypoglycemic reactions. Replacement of islet tissue through the use of pancreas transplantation is becoming a more routine procedure but the selection of patients for this procedure is limited to those with complications and the supply of organs for such transplantation is limited, although living-related pancreas transplantation is being performed. However, the cure of diabetes is achieved at the expense of the immunosuppressive therapy used. The need to provide such therapy limits the recipients of such transplantation to patients whose disease is worse than the immunosuppressive therapy. Criteria for patient selection for pancreas transplantation have been set forth by the Minnesota group (2) and the Michigan transplant group (3).

Islet transplantation has also been used in the past but again limited availability of tissue and the risk of rejection limit the usefulness of this technique. Scharp et al. (4) reported their experience with islet transplantation in a patient with diabetes. For the first time, using only islet cells, the patient was able to achieve complete independence from exogenous insulin for ~25 days. Two donor sources were needed. As noted by the authors, many questions are raised by their experience: what is the correct islet dosage, what should be the duration of insulin therapy after transplantation, the duration of islet culture before transplantation and the form of immunosuppression and potential sites of administering the islets, and the importance of HLA-DR matching. Much more experience with islet transplantation is needed before this is used as a cure for diabetes.

Thus, innovative methods are needed that provide normalization of blood glucose concentrations, that can be used for patients before microvascular complications become evident, and that are widely available and can remain in place for a long time without the use of potentially toxic immunosuppressive agents. The biohybrid device may be one such method; the current article demonstrates a major advance over the previous one (1). We look forward to the next series of studies.

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References

1. Chick WL, Perna JJ, Lauris V, Low D, Galletti PM, Panol G, Whittemore AD, Like AA, Colton CK, Lysaght MJ: Artificial pancreas using living beta cells: effects on glucose homeostasis in diabetic rats. *Science* 197:780–82, 1977
2. Sutherland DER: Who should get a pancreas transplant? *Diabetes Care* 11:681–85, 1988
3. The University of Michigan Pancreas Transplant Evaluation Committee: Pancreatic transplantation as treatment of IDDM: proposed candidate criteria before end-stage diabetic nephropathy. *Diabetes Care* 11:669–75, 1988
4. Scharp DW, Lacy PE, Santiago JV, McCullough CS, Weide LG, Falqui L, Marchetti P, Ginerich RL, Jaffe AS, Cryer PE, Anderson CB, Flye MW: Insulin independence after islet transplantation into type I diabetic patient. *Diabetes* 39:515–18, 1990