Workshop on Pancreatic Islet Cell Transplantation in Diabetes

Sponsored by the National Institute of Arthritis, Metabolism, and Digestive Diseases and held at the National Institutes of Health in Bethesda, Maryland, on November 29 and 30, 1977

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The purpose of this workshop was to formulate recommendations for future research needs in islet cell transplantation based upon the present status of the various components of this field. The broad segments of this field that were reviewed included the following: transplantation of adult islet cells in diabetic animals and man; transplantation of fetal and neonatal pancreas into diabetic animals; effect of islet cell transplantation on microvascular complications in the kidney of diabetic rats; effect of the diabetic state on normal kidneys transplanted into diabetic patients and diabetic animals; transplantation of islets as allografts and xenografts; effect of in-vitro culture on prolongation of survival of allografts and xenografts of the thyroid; use of artificial membranes for in-vitro maintenance and tranplantation of islet cells.

The review of these broad topics provided new and exciting findings as well as indicating the future basic information and the future technical accomplishments that would be needed before a safe and successful means of islet transplantation could be accomplished in man.

As a general statement, it is now apparent that transplantation of islet cells is biologically feasible in experimental animals utilizing adult, neonatal, or fetal islet cells and employing many different sites for implantation of the islet cells. The development of these different models for islet transplantation provides an excellent opportunity and a most reasonable expectation of advancing our basic knowledge in the broad disciplines of immunology, endocrinology, metabolism, metabolic diseases, developmental biology, and diabetes in man. It is also reasonable to expect that with successful acquisition of new basic information, it should become feasible to explore the utilization of islet cell transplantation as a therapeutic approach to the possible prevention of the complications of diabetes in man. Based upon these general conclusions, it is recommended that the National Institutes of Health and other funding agencies continue to increase their support for research in this important area.

The following is a resume of more specific recommendations with respect to future research needs:

Islet cell isolation from the adult pancreas. Islets can be isolated in large numbers from the diffuse pancreas of rodents; however, the yields are very low from compact pancreases found in man, primates, and dogs. Partially digested fragments of pancreas have been used successfully for transplantation into the spleen and into the liver by portal vein injection.

New and improved methods need to be developed for the mass isolation of endocrine tissue from compact pancreases, and further studies are needed on the utilization of pancreatic fragments for transplantation into different sites.

Islet cell isolation from neonatal and fetal pancreas. Fetal rat pancreas and dispersed neonatal rat pancreas have been transplanted successfully into diabetic rats. A single fetal rat pancreas will induce normoglycemia in diabetic recipients if the fetal pancreas is transplanted first into a normal animal and subsequently into a diabetic recipient.

Some of the further studies needed are to determine

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the optimum period of gestation for fetal pancreas transplants in different species; determine the optimum sites for transplantation of the fetal pancreas; develop tissue culture techniques for optimum maintenance, growth, and development of the fetal tissue prior to transplantation; characterize and identify specific factors of the diabetic state that affect the growth and maturation of islet cells; determine the fate of human fetal pancreas transplants in immune-deficient animal models.

In-vitro maintenance and storage of islets. Adult islet cells and fetal rat pancreas can be transplanted successfully after maintenance in tissue culture for a few days.

Some of the future needs are improved culture methods for optimum maintenance of the islet cells; development of methods for obtaining, culturing, and transplanting only normal beta cells without other islet cell types present; studies on the effect of transplanting neoplastic islet cells and neoplastic beta cell lines in diabetic animals; development of methods for the long-term optimum maintenance of intact islets in culture prior to transplantation.

Fetal rat pancreas has been transplanted successfully after cryopreservation.

Further studies are needed to establish optimum means for cryopreservation of adult islets, pancreatic fragments, and fetal pancreas. Studies are also needed on the in-vitro responsiveness of the islet cells to secretagogues following cryopreservation and the effect of the preserved islet cells on the diabetic state following transplantation.

Metabolic effects of islet cell transplants. Transplantation of islet cells into diabetic animals will induce normoglycemia and aglycosuria; however, hyperinsulinemia is present in animals receiving either intraperitoneal or intrahepatic transplants.

Detailed metabolic and hormonal studies are needed for each of the models of islet cell transplants in order to determine whether normal carbohydrate, protein, lipid, and hormonal homeostasis have been established. Studies are needed on the fate, replicative activity, islet cell composition, morphology, and hormonal content of the transplanted islet cells for each of the transplant models.

Effect of islet cell transplants on diabetic complications. In diabetic rats, immunoglobulins are deposited in the glomeruli and the mesangium increases in thickness. Transplantation of islet cells into the diabetic rats results in a loss of the immunoglobulins from the glomeruli and a stabilization or decrease in thickness of the mesangium. Transplantation of normal kidneys into a diabetic patient results in the development of hyalinization of the afferent and efferent arterioles of the glomeruli and the production of a Kimmelstiel-Wilson lesion in one transplanted kidney. These findings indicate that the diabetic process plays a significant role in the production of microangiopathy in the diabetic and provides hope that islet cell transplantation could arrest or prevent the further progression of these diabetic complications.

Further studies are needed on the effect of islet cell transplantation on diabetic complications in experimental animals, including different animal models with spontaneous diabetes.

Immune rejection of islet cells. Islet cells are not immunologically privileged and are rapidly rejected when transplanted across major histocompatibility barriers. The islets may be even more susceptible to rejection than transplanted skin.

Further studies are needed on the mechanism of rejection, the role of immunocompetent cells and circulating antibodies in rejection, comparison of the rate of rejection of islet cells transplanted in different sites, and the effect of different degrees of histocompatibility on survival.

Studies of the thyroid gland have shown that marked prolongation of survival of the thyroid transplanted across major histocompatibility barriers can be achieved by in-vitro culture of the thyroid for three weeks prior to transplantation. This same procedure has been used to prolong survival of xenografts of rat thyroid in mice. It was suggested that the period of in-vitro culture removed passenger leukocytes, which may play a significant role in immune rejection of the transplanted tissue.

Further studies are needed with this interesting model to establish the mechanism of prolonged survival induced by in-vitro culture, to establish the precise identity and role of the passenger leukocytes in the rejection process, to devise in-vitro culture techniques and other procedures for the specific elimination of passenger leukocytes and preservation of the thyroid, and to utilize this model for allografts of the thyroid in studies on allografts and xenografts of islet cells.

Allotransplants of bone marrow, skin, and heart have been accomplished successfully in experimental animals by total lymphoid irradiation of the recipient animals. The recipients do not develop a graft-versus-host reaction, and they accept skin and heart transplants from the donor strain.

Studies are needed of this innovative approach for allotransplants of islet cells as well as utilization of other means of inducing immune tolerance in the recipients.

Mechanical barriers to immune rejection. An artificial capillary system has been devised that permits prolonged in-vitro survival and function of islet cells maintained on the outer surface of the artificial capillaries. This artificial system for maintenance of islet cells has been used as a vascular shunt in diabetic animals and has resulted in the production of normoglycemia in the recipients in acute experiments. Artificial membranes have also been used for the implantation of islet cells in the peritoneal cavity of diabetic animals.

Studies are needed to develop the appropriate artificial membranes that will permit prolonged survival of transplanted islet cells either as a vascular shunt or as an implantable device.

Human transplantation. No major break-throughs were reported that would permit extensive clinical trials of either islet cell transplants or whole pancreas transplantation in diabetic patients. Many basic problems remain to be resolved, and new innovative approaches are needed before these procedures could be utilized in the therapy of diabetic patients.

In 1974, the National Institutes of Health prepared a Position Paper on Pancreatic Islet and Beta Cell Transplantation in Humans. The basic tenets of this Position Paper are still applicable today.

Manpower. Additional manpower is needed from many disciplines in order to accomplish the research needs of this area. Increased support is urgently needed for postdoctoral training, young investigator awards, and research career development awards.

Future assessment. The informal interchange of information by the participants in this workshop provided not only the background needed for recommendations for the future but also new and provocative information from different disciplines that is of importance to future research in this area. Thus, it is recommended that similar meetings be held in the future for the exchange of information and for the reassessment of future research needs.

Future Meetings

1978

May 18-20	Hotel P.L.M., Paris	19th Journees de Diabetologie
May 21-24	Herzlia on Sea, Israel	4th International Beilinson Symposium: "Nutrition and the Diabetic Child"
May 31-June 4	San Francisco, Ca.	"Recent Advances in the Diagnosis and Treatment of Pituitary Tumors"
June 1, 2	Radisson South Hotel, Minneapolis, Minn.	19th Annual Meeting, American College of Nutrition
June 11-13	**Sheraton-Boston Hotel, Boston, Mass.**	**38th Annual Meeting**
June 15, 16	2nd Medical School, University of Naples, Italy	"Medical Complications of Obesity"
June 19-21	Marseille, France	5th International Meeting of Endocrinology at Marseille (Diabetes and Obesity)
June 26-28	University of Milan, Milan, Italy	International Symposium on Peripheral Neuropathies
July 2-8	Dresden, GDR	XII FEBS Meeting
July 5-7	Royal Infirmary of Edinburgh, Edinburgh, Scotland	International Symposium on the Immunology of Diabetes
August 31-September 1	Aarhus University, Denmark	Nervous System Abnormalities and Nervous Disease in Diabetes Mellitus
September 15, 16	London, England	Autumn Meeting, Medical and Scientific Section, British Diabetic Association
September 25-27	Zagreb, Yugoslavia	5th EASD Postgraduate Course
September 28, 29	**Rochester, New York**	**Combined Health Care Professionals Course—Region I**
September 28-30	Zagreb, Yugoslavia	14th Annual Meeting, EASD
October 5-7	Florence, Italy	4th International Symposium on Pediatric and Adolescent Gynecology
October	**Seattle, Wash.**	**16th Research Symposium**
November 9-11	**Phoenix, Az.**	**CHCPC—Region IV**
November 11, 12	**Birmingham, Ala.**	**CHCPC—Region II**