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ABSTRACTS

Dickerman, Richard M.; Twiest, Melvin W.; Crudup, James W.; and Turcotte, Jeremiah G. (Dept. of Surg. Section of General Surg., Univ. of Michigan Med. Cntr., Ann Arbor, Michigan): TRANSPLANTATION OF THE PANCREAS INTO A RETROPERITONEAL JEJUNAL LOOP. Am. J. Surg. *129*:48, 1975.

A new technic of pancreatic transplantation was developed and assessed in 69 dog experiments. The body and tail of the pancreas were transplanted into the side of a Roux-en-Y retroperitoneal limb of jejunum. A dual venous anastamosis of the splenic vein to the vena cava was utilized to avoid venous congestion. Mean survival of immunosuppressed animals with normal glycemia was 32.4 days in 30 dogs with autografts and 24.6 days in 27 dogs with allografts. Two dogs with autotransplants remain alive at 106 and 128 days, and the longest normoglycemic survival achieved with an allograft was 85 days. With experience the incidence of pancreatitis and abscess formation decreased. The problem of venous thrombosis was eliminated and the patency of the pancreatic duct was maintained.

Mirkovitch, V.; and Campiche, M. (Dept. of Experimental Surg., Univ. of Surg. Services, Centre Hosp. Univ. Vaudois and Lab. of Electron Microscopy, Inst. of Path. Anatomy, CH-1011, Lausanne, Switzerland): SUCCESSFUL INTRASPLENIC AUTOTRANSPLANTATION OF PANCREATIC TISSUE IN TOTALLY PANCREATECTOMIZED DOGS. Transplantation *21*:265, 1976.

The canine pancreas was infiltrated with a solution of collagenase, removed, cut into small pieces, and incubated with collagenase. After incubation and centrifugation, the segment was implanted into the spleen of the same animal. Seven animals were operated on, and all were long-term survivors. After a 10-day period of postoperative hyperglycemia, all animals were normoglycemic for over two months. Their responses to oral glucose loading were prompt and almost normal. In the third postoperative month, six of the dogs who were still normoglycemic underwent laparotomies and splenectomies. At operation it was found that in all animals the splenic vein contained blood with higher amounts of insulin than that of the inferior vena cava. Morphologic examination of the spleen showed the presence of both exocrine and endocrine pancreatic tissue. Following the splenectomies, the animals developed severe hyperglycemia and died. The results obtained suggest that this simplified procedure for pancreatic tissue preparation may have eventual clinical applications.

Matas, Arthur J.; Sutherland, David E. R.; Steffes, Michael W.; and Najarian, John S. (Dept. of Surg. Univ. of Minnesota Health Sciences Center, Minneapolis, Minn.): ISLET TRANSPLANTATION USING NEONATAL RAT PANCREATA: QUANTITATIVE STUDIES. J. Surg. Res. *20*:143, 1976.

This investigation analyzes the insulin and amylase content of neonatal and adult rat pancreata on the assumption that tissue insulin is proportioned to the pancreatic islet beta-cell mass and that tissue amylase is proportional to the digestive enzyme content. The insulin/amylase ratio of the tissue would thus provide an index of the islet mass in relation to the exocrine tissue mass. The neonatal pancreas had a relatively high insulin content per gram of tissue (575 mg.) when compared with that of adults (162 mg.). More important, neonatal pancreata have a very low exocrine enzyme content (0.04 mg.) compared with that of adults (14.2 mg.). Using the insulin/amylase ratio as an index of the quantity of islet tissue in relation to acinar tissue, we have demonstrated that the neonatal whole-rat pancreata have a ratio 37 times greater than that of the adult. Mincing and collagenase digestion decreases the insulin content of the neonatal pancreas to 27 per cent. Even after processing, however, the insulin/amylase ratio of neonates is still ninefold greater than that of the whole adult pancreas. Infusion of islet tissue via the portal vein from as few as two neonatal isogeneic donors ameliorated diabetes in adult animals. This response occurred when transplanted tissue contained less that 7 per cent of the insulin content of a normal adult pancreas, and successful transplants required a tissue insulin content of less than the insulin content of a single neonatal pancreas. The authors conclude that the pancreas of the neonate may be the ideal islet donor and that it may be possible to cure diabetes with the islet tissue of only one neonatal pancreas for each recipient provided technics for isolating islets of Langerhans can be improved.

Amamoo, David G.; Woods, John E.; and Holley, Keith E. (Mayo Graduate Sch. of Med., Univ. of Minnesota, Rochester, Minn.): EFFECT OF INTRAHEPATICALLY IMPLANTED ISLETS OF LANGERHANS ON HEPATIC FUNCTION IN THE RAT. Mayo Clin. Proc. *50*:416, 1975.

Diabetes mellitus is satisfactorily controlled in the rat by hepatic implantation of isolated isologous pancreatic islets. The transplanted islets remain viable for at least six months after implantation. The intrahepatic presence of the islets did not disturb the microscopic architecture of the liver, and the hepatic environment did not adversely affect the morphology of the implanted islets. Despite the presence of the islets in the terminal branches of the portal vein (600 to 800 islets per liver) no signs of portal hypertension, hepatic congestion, or embolism were found. These studies indicate that hepatic implantation of isolated pancreatic islets not only controls diabetes in the rat but also causes no adverse hepatic reactions.

Andersson, Arne; Borg, Hakan; Groth, Carl-Gustav; Gunnarsson, Rolf; Hellerstrom, Claes; Lundgren, Goran; Westman, Jan; and Ostman, Jan (Dept. of Histology and Human Anatomy, Univ. of Uppsala and Dept. of Surg. and Intern. Med., Hunddinge Hosp., Stockholm, Sweden): SURVIVAL OF ISOLATED ISLETS OF LANGERHANS MAINTAINED IN TISSUE CULTURE. J. Clin. Invest. 57:1295, May 1976.

Verbatim summary: Transplantation of human pancreatic islets to diabetic patients may require that donor islets be kept viable in vitro for extended time periods before transfer to the recipient. We have maintained isolated pancreatic islets obtained from the human cadaveric pancreas in tissue culture for 1-3 wk., after which we studied the structure and function of the islets. Electron micrographs of the cultured islets showed a satisfactory preservation of both β-cells and α_2-cells. After culture for 1 wk., the islet oxygen uptake proceeded at a constant rate at a low glucose concentration (3.3 mM) and was significantly enhanced by raising the glucose concentration to 16.7 mM. Likewise, after culture for 1 wk., the islets responded with an increased insulin release when exposed to 16.7 mM glucose with or without added theophylline (10 mM). Islets cultured for 1-3 wk. were able to incorporate $[^3H]$leucine into proinsulin, as judged by gel filtration of acid-alcohol extracts. Glucagon release from the cultured islets was reduced significantly by 16.7 mM glucose alone, but stimulated by glucose (16.7 mM) plus theophylline (10 mM).

It is concluded that viable pancreatic islets can be isolated from the pancreas of adult human donors and maintained in tissue culture for at least 1 wk. without loss of the specific functions of the α_2- and β-cells. It remains to be established whether such islets will survive and remain functionally competent after transplantation to human recipients.

Scharp, David W.; Murphy, James J.; Newton, William T.; Ballinger, Walter F.; and Lacy, Paul E. (Dept. of Surgery and Pathology, Washington Univ. Med. Sch., St. Louis, Mo.): TRANSPLANTATION OF ISLETS OF LANGERHANS IN DIABETIC RHESUS MONKEYS. Surgery 77:100, January 1975.

Verbatim summary: Islets of Langerhans from unrelated donor rhesus monkeys were transplanted into the portal vein of five rhesus monkeys which had been made diabetic by partial pancreatectomy and streptozotocin. There was definite improvement of the diabetic state with an increase in the mean KT½ from 0.71 to 1.52 per cent per minute. The islets were isolated by a more efficient digestion-filtration process than previously had been described. This process has allowed, for the first time, successful isolation of large masses of islets permitting islet transplants in subhuman primates.

Orloff, Marshall J.; Lee, Sun; Charters III, A. Crane; Grambert, David E.; Storck, L. Gunnar; and Knox, Dale (Dept of Surgery, Sch. of Med., Univ. of California, San Diego, La Jolla, Calif.): LONG TERM STUDIES OF PANCREAS TRANSPLANTATION IN EXPERIMENTAL DIABETES MELLITUS. Ann. Surg. *182*:198, 1975.

Verbatim summary: Alloxan diabetes was induced in inbred rats that then were divided into four groups consisting of unoperated diabetic controls, sham-operated diabetic controls, rats given pancreaticoduodenal isografts, and rats given duct-ligated pancreas isografts. The animals were studied for from 18 months (controls) to two years (transplants) and the following important results were obtained: 1) In striking contrast to the diabetic controls, pancreas transplants of both types produced immediate and permanent relief of hyperglycemia, immediate and lasting elevation of serum insulin levels, a normal weight and growth curve, and good health for two years. Removal of the graft was followed by recurrence of severe diabetes. 2) Pancreas transplants of both types prevented the widespread and severe renal, ophthalmic and neural lesions of diabetes that were found in the diabetic controls. 3) The duct-ligated pancreas graft and pancreaticoduodenal transplant were equally effective in controlling diabetes. Ligation of the pancreatic duct was not followed by significant morphologic or clinical evidence of pancreatitis or by loss of endocrine function. 4) Portal venous drainage of the pancreas transplant was unnecessary for good endocrine function.

Weber, Collin; Weil III, Richard; McIntosh, Rawle; Hogle, Hugh; Warden, Glen; and Reemtsma, Keith (Dept of Surg. and Pediatrics, Columbia Univ. Coll. of Physicians and Surgeons, N. Y., N. Y., and Dept. of Surg., Univ. of Utah, Col. of Med., Salt Lake City, Utah): XENOTRANSPLANTATION OF PISCINE ISLETS INTO HYPERGLYCEMIC RATS. Surgery 77:208, February, 1975.

Verbatim summary: In some fish, insulin-producing pancreatic tissue is anatomically separate from exocrine tissue. Finely minced fragments of this tissue were placed into rats made diabetic by streptozotocin treatment under a variety of circumstances. Untreated rats usually had a period of normoglycemia lasting less than 24 hr. This was slightly prolonged by 300 to 400 rad total-body radiation to the recipient 24 to 48 hr. prior to the transplant. Enclosing the tissue in Millipore chambers prolonged the effect for a day or two in some animals, but tissue enclosed in Cupraphan dialysis tubing had prolonged normoglycemia for up to 5 days. The authors suggested that the fish may be an acceptable source of relatively pure insulin-producing pancreatic tissue.

Koncz, Lajos; Davidoff, Frank; DeLellis, Ronald A.; Selby, Mark; and Zimmerman, Clarence E. (Dept. of Med. and Surg., Beth Israel Hosp. and Harvard Med. Sch. and Dept. of Pathology, Tufts Univ. Med. Sch., Boston, Mass.): QUANTITATIVE ASPECTS OF THE METABOLIC RESPONSE TO PANCREATIC ISLET TRANSPLANTATION IN RATS WITH SEVERE KETOTIC DIABETES. Metabolism *25*:147, February 1976.

Verbatim summary: Injection of 100-140 mg./Kg of streptozotocin produced severe, ketotic diabetes in 12 pairs of adult rats. Transplantation of intact islets of Langerhans from syngeneic adult donors into a muscle pocket or a pouch created from pancreatic tissue of one animal from each pair eliminated ketonemia in the immediate postoperative period, while ketonemia persisted in the sham-operated controls. Mean survival of transplanted animals

was 145 days, versus 70 days for controls. Mean body weight increased and blood sugar decreased in transplanted animals compared with controls; the differences were greatest in those animals which received the largest number of islets per unit body weight. In one animal, all metabolic indices returned to normal for a period of 8 wk. following transplantation of 650 islets. After gaining to 300% of initial body weight, diabetes reappeared in this transplanted animal and was again reversed by a second transplantation.

The metabolic data indicate that: (1) islet tissue from adult donors survives and functions in severely diabetic, ketotic hosts; and (2) metabolic response to transplantation is a function of the ratio of islet tissue to body mass, a minimum ratio of about 2-3 islets/gm. body weight being required to maintain normal homeostasis.

Hegre, O. D.; Leonard, R. J.; Schmitt, R. V.; and Lazarow, A. (Dept. of Anatomy, Univ. of Minnesota, Minneapolis, Minn.): ISOTRANSPLANTATION OF ORGAN-CULTURED NEONATAL PANCREAS: REVERSAL OF ALLOXAN DIABETES IN RAT. Diabetes *25*:180, March 1976.

Verbatim summary: Pancreases from neonatal rats four to 16 days postpartum were grown in organ culture for from two to nine days. Approximately 10-20 explants, each measuring 1 $mm.^3$ (1 mg.), were grown on a single Millipore filter placed at the gas-liquid interface of a medium consisting of 50 per cent horse serum and 50 per cent chick embryo extract. Following organ culture, an estimated 9-20 mg. of cultured islet tissue were dissociated with collagenase and isotransplanted into the peritoneal cavity of alloxan-diabetic recipients.

In seven of eight recipients the diabetes was reversed between 11 and 53 days posttransplantation. Animals receiving 12-16 mg. of cultured islet attained normoglycemia in 11-20 days; animals receiving 9-10 mg. of cultured islet tissue recovered between 45 and 53 days. These animals have remained sympton-free for over six months.

Biopsies of grafts taken from the peritoneal cavity following reversal of diabetes contained well-vascularized islets comprised primarily of heavily granulated beta cells. Quantitative analysis of host pancreases by the linear scanning method (biopsied at one to two weeks and four to five months following reversal of the diabetes) demonstrated that the total beta-cell mass was 3 per cent and the total insulin content was 6 per cent of the normal values. Little or no evidence of regeneration of host beta cells was observed.

These studies show that a period of organ culture prior to isotransplantation does not impair the ability of islet tissue to reverse alloxan diabetes in the rat.

Brown, Josiah; Clark, William R.; Molnar, I. G.; and Mullen, Yoko S. (Dept. of Med. and Microbiology and Immunology, Sch. of Med. Dental Rsch. Inst. and Dept. of Biology, U.C.L.A., Los Angeles, Calif.): FETAL PANCREAS TRANSPLANTATION FOR REVERSAL OF STREPTOZOTOCIN-INDUCED DIABETES IN RATS. Diabetes *25*:56, January, 1976.

Verbatim summary: Streptozotocin-induced diabetes in rats was completely reversed by transplantation of syngeneic fetal pancreases placed beneath the kidney capsule. To accomplish complete reversal of diabetes, four or more pancreases were necessary; three resulted in partial reversal, and two produced a slight but significant effect in some recipients. Removal of the transplants resulted in the prompt return of diabetes. The islets of Langerhans in the transplants functioned homeostatically; this was indicated by regular normal blood glucose values, in addition to normal findings in blood IRI response and glucose disappearance rate after glucose injection. Disappearance of exocrine elements, with only ducts and fibrous tissue remaining, resulted in a pure endocrine organ. The advantages of this technic, such as ease of accessibility for placement, observation, and removal, are of great importance for possible application to humans.

Mauer, S. Michael; Steffes, Michael W.; Sutherland, David E. R.; Najarian, J. S.; Michael, Alfred F.; and Brown, David M. (Dept. of Pediatrics, Lab. of Med. and Pathology, Surg. and Univ. of Minnesota Sch. of Med., Minneapolis, Minn.): STUDIES OF THE RATE OF REGRESSION OF THE GLOMERULAR LESIONS IN DIABETIC RATS TREATED WITH PANCREATIC ISLET TRANSPLANTATION. Diabetes *24*:280, March, 1975

Verbatim summary: Diabetes was induced in Lewis rats with streptozotocin. Six to eight months later glomeruli showed mesangial thickening: IgG, IgM and C3 were seen in large quantities in the mesangium by immunofluorescent microscopy. Ten animals then had successful pancreatic transplantation resulting in normal glucose and insulin levels within one to three weeks.

Biopsies obtained within the first two weeks following transplantation demonstrated a significant reduction in mesangial thickening and in mesangial staining for IgG, IgM and C3. Three to four weeks after transplantation C3 staining was no longer detected. A gradual reduction in mesangial IgG and IgM localization continued so that by nine weeks following islet transplantation only minimal staining for immunoglobulins was present. Although mesangial thickening was reduced, this abnormality could still be detected in most animals six to nine weeks after transplantation. Three rats showed improvement in glomerular morphology within two weeks despite persistent hyperglycemia. These rats had normal insulin levels at this time. Islet transplantation in inbred diabetic rats effectively returns glucose and insulin levels to normal and results in rapid regression of the light microscopic and immunopathologic glomerular lesions. These studies support the concept of reversible mesangial dysfunction in diabetic rats.

Frankel, Barbara J.; Gylfe, Erik; Hellman, Bo; and Idahl, Lars-Åke (Dept. of Histology, Univ. of Umeå, S-901 Umeå, Sweden): MAINTENANCE OF INSULIN RELEASE FROM PANCREATIC ISLETS STORED IN THE COLD UP TO 5 WEEKS. J. Clin. Invest. *57*:47, January, 1976.

Verbatim summary: Insulin content and release were measured from hand-dissected pancreatic islets from non-inbred *ob/ob* mice after 1-5 wk. storage in tissue culture medium 199 at various temperatures and glucose concentrations.

After storage of islets for 1 wk. at 37°, 22°, or 8° C in 18 mM glucose medium and preincubation with 1 mM glucose, glucose-stimulated insulin release during the subsequent incubation was only 20-35% of that of fresh islets. The addition of a 4-h period at 37° C with 18 mM glucose between the cold storage and preincubation restored glucose-stimulated insulin release from 8° C-stored islets to fresh-islet levels. Release throughout the 1-18

mM glucose range was strikingly parallel to that of fresh islets. Exposure of fresh islets to the same 4-h period increased basal release but did not affect maximal release.

When islets were stored at 8° C with 18 mM glucose for more than 1 wk., a short period at 37° C every week was necessary for maintenance of release. After 5 wk. of this procedure, glucose-stimulated insulin release was one-third that of fresh islets, or similar to that of islets stored for only 1 wk. at 37° C. Storage at 8° C for 1 wk. with 3 mM glucose, or continuously for 3 or 5 wk. with 18 mM glucose, maintained islet insulin content, whereas release was lost.

Thus, glucose-stimulated insulin release is best maintained by storage of pancreatic islets in tissue culture medium with a high concentration of glucose at 8° C with short weekly periods at 37° C.

Erratum

In the July 1976 Journal figures 2 and 3 were transposed in "Diabetes Mellitus: Incidence, Prevalence, Survivorship, and Causes of Death in Rochester, Minnesota, 1945-1970," by P. J. Palumbo, M.D., and associates.

ORGANIZATION SECTION

FOURTEENTH RESEARCH SYMPOSIUM

Current Topics in Diabetes Research

Thursday and Friday, October 14-15, 1976

Chase Park Plaza Hotel
St. Louis, Missouri

Thursday, October 14

Morning: Immunological and Genetic Aspects of Diabetes
Chairman: Arthur H. Rubenstein

9:00-9:30	Twin Studies and the Etiology of Diabetes. D. A. Pyke.
9:30-10:00	Discussion.
10:00-10:15	Intermission.
10:15-10:45	HLA Factors and Autiommunity in Juvenile Diabetes Mellitus. Jørn Nerup.