Surface Islet Cell Antibodies and Insulin-Dependent Diabetes Mellitus After Autotransplantation of Human Pancreatic Islet Cells

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Endocrine tissue allografts have been assumed to be exempt of the immune rejection process, and immunosuppressive therapy is not routinely used after such procedures. We are reporting a patient (L.M.) who at age 28 yr underwent autotransplantation of pancreatic islet cells after a 90% pancreatectomy for otherwise intractable abdominal pain due to chronic recurrent pancreatitis. The excised pancreas was minced and dissociated by collagenase treatment, and the islet cell preparation was infused intraportally. Before surgery, an oral glucose tolerance test (OGTT) showed normal carbohydrate tolerance with an increased plasma insulin response, and a glucose clamp study showed a steady-state plasma glucose (SSPG) of 128 mg/dl, consistent with mild insulin resistance due to being overweight. Three weeks after islet cell autotransplantation, the OGTT showed a fasting plasma glucose of 101 mg/dl and a diabetic profile with normal insulin levels and persistent insulin resistance. Surface islet cell antibodies (ICAs) were assayed by indirect immunofluorescence with isolated rat islet cells; they were negative both before and 3 wk after surgery, but ICAs became positive 8 wk after islet cell autotransplantation. The patient required neither oral hypoglycemic agents nor insulin therapy for glycemic control. Six years after the pancreatic islet cell autograft, the patient developed diabetic ketoacidosis preceded by marked weight loss and symptoms of uncontrolled diabetes, and he has required 30 U lente insulin daily ever since. Plasma free C-peptide levels after glucagon stimulation indicated endogenous insulin deficiency. Two other recipients of islet cell autografts under similar clinical circumstances developed ICA and carbohydrate intolerance 3 wk postsurgery, associated with diet-controlled non-insulin-dependent (NIDDM; G.J.) and insulin-dependent (IDDM; W.G.) diabetes mellitus. G.J. was lost to follow-up 60 wk postsurgery. W.G. required insulin therapy immediately postsurgery, and therefore his diabetes represents technical failure of the islet cell autograft. Results are given in Table 1. In conclusion, the consistent observation of ICA after pancreatic islet cell autografts in three subjects indicates that islet cell immunogenicity can be elicited by either collagenase treatment and/or graft tissue modification at ectopic implantation sites. Islet cell autotransplantation in an obese subject was initially followed by diet-controlled NIDDM and normal insulin reserve and subsequent short-term development of ICA, resulting in long-term IDDM with severe insulin deficiency. Thus, ICA, autoimmune insulitis, and IDDM may follow pancreatic islet cell autografts. The long period between development of ICA and IDDM in our patient is consistent with current concepts about the pathogenesis of IDDM.

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TABLE 1
Results in recipients of islet cell autografts

	L.M.				G.J.			W.G.				Control
Time (wk)	0	3	8	312	0	3	60	0	3	14	18	(n = 26)
ΣPG (mg/dl)	494	662		1749	447	525	596	576	938			389 ± 61
ΣPI (μU/ml)	441	331		11	99	100	109	111	24			149 ± 77
SSPG (mg/dl)	128	166										72 ± 4
ICA	−	−	+		−	+	+	−	+	−	−	−

PG, plasma glucose; PI, plasma insulin.

Evaluation of Clinical and Metabolic Parameters in 14 Cases of Cultured Fetal Islet Transplantation

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Since 1982, fourteen clinical transplantations of long-term–cultured fetal pancreatic islets have been performed at our institute. All recipients suffered from insulin-dependent diabetes mellitus with progressive retinopathy. Before transplantation, no detectable C-peptide level was observed. Fetal pancreatic islets were isolated from 15 embryos aged 20–32 wk with modified collagenase digestion technique. (All fetuses were premature infants with lethal congenital abnormalities.) The islets were cultured in vitro at 37°C in Eagle's medium in 5% CO_2 for 10 wk. Insulin production was continuous during this period. After tissue typing, grafting was performed to the liver through the umbilical vein. In all cases, immunosuppression was carried out (in 3 patients, prednisolone and azathioprine for 7–8 mo; in 11 cases, cyclosporin A permanently). Posttransplantation, serum C-peptide was detected in every patient, and in 10 of 14, specific insulin binding, anti-insulin antibody, and natural killer (NK) cell cytoxicity were recorded as well. Graft function was evident in every case for a long time (from 6 mo to 6 yr) as proved by increased serum C-peptide levels. The insulin dose was reduced in all patients in parallel with an increase in serum C-peptide level. Reduction of insulin dose was 50% in 5 cases. Retinopathy did not progress in 9 patients and improved in 5 patients. In seven of 10 cases, an increased anti-insulin antibody titer and a lower specific insulin binding were observed. The reduction of insulin dose was only moderate in these cases. NK cell cytoxicity was normal after administration of low-dose (2–3 mg/kg) cyclosporin therapy.

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Implantation of Human Pancreatic Islet Culture in Insulin-Dependent Diabetes Mellitus Patients: Long-Term Evaluation of Immunological Parameters

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The aim of this study was to examine the parameters of cellular immunity [phenotypes and phagocytosis of peripheral blood mononuclear cells (PBMC)] as well as autoantibodies (anti-insular antibodies-ICA and insulin antibodies) in 3 patients with insulin-dependent diabetes mellitus (IDDM) before and after implantation of human fetal pancreas cultured cells (FPCCs). Implantation was done under the fascia of right musculus rectus abdominis without immunosuppression. The first patient was a newly discovered IDDM patient [UPN-1 (unique patient number)]. The other two (UPN-2, UPN-3) were insulin dependent for >2 yr. Controls were patients with IDDM and healthy people. PBMC were marked either with monoclonal antibodies [CD3, CD4, CD8, IaDR, NK (BMA070)] or with heteroantibody for B-lymphocytes and examined under a fluorescence microscope or by flow cytometer. Phagocytosis was determined by ingestion of yeast in PBMC. Anti-insular antibodies were detected by indirect fluorescent technique, and insulin antibodies were evaluated by radioimmunoassay (RIA). In this study, we investigated the daily profile of C-peptide (RIA-Biodata, μM) and glucagon (RIA-Biodata, μM) on days −1, 7, 14, 30, 90, and 120 after implantation. Our investigation of parameters of cellular immunity showed that implantation of FPCCs in IDDM patients increased values of T-lymphocyte population CD3 and subpopulations CD4 and CD8, as well as the population of phagocytic cells, at first 40 days after implantation. We did not detect any changes in values of investigated autoantibodies (ICA, insulin antibodies) after implantation. Significant decrease of glucagon levels were detected in all patients in the postimplantation period (460 ± 46 vs. 40 ± 24 μM, comparing −1 vs. 90 days). C-peptide response to glucagon was detected between 30 and 90 days in two patients, whereas in the third, after 30 days there was no more C-peptide response. At the same time, we did not find correlation between investigated immunological and metabolic parameters (−1 vs. 90 day) except elevated levels of B-lymphocytes in UPN-2. Further investigation will predict whether the proportion and function of specific immunocompetent cells in PBMC of implanted IDDM patients can predict the function of FPCCs.

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Islet Transplantation in Shanghai

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Until 30 June 1984, 50 type I (insulin-dependent) diabetic patients received fetal islet transplants, and 39 of them were followed up for >6 mo (6.5–32 mo). The grafts, with 1- to 2-wk–cultured human fetal pancreatic islet tissue, were transplanted intraperitioneally in 32 cases with 6–15 fetal pancreases and intramuscularly in 7 cases with 9–11 fetal pancreases. Posttransplantation, routine immunosuppressive treatment was not used. In 38 cases, there seemed to be an effect, whereas in 1, there was no effect. The mean daily insulin requirements pretransplant in the 38 effective cases were 46.97 ± 13.63 U, with mean fasting and postprandial plasma glucose concentrations of 207.03 ± 72, 92, and 221.71 ± 89.40 mg/dl. Posttransplantation, the mean daily insulin requirement was 18.16 ± 9.08 U, a reduction by 61.34% compared with those before the transplantation ($P < .001$); the mean fasting plasma glucose concentration was 161.07 ± 57.03 mg/dl ($P < .01$). Three patients became insulin independent, and two of them have remained insulin independent for >37 and 45 mo (till 30 June 1987). The mean serum C-peptide levels of most recipients were normal posttransplant. In the 36 patients with functioning islet grafts for >1 yr, the mean fasting and postprandial plasma glucose values posttransplant were reduced significantly compared with pretransplant ($P < .05–0.01$), and the 24-h urine glucose was also reduced ($P < .01$). The mean fasting serum C-peptide levels were normal or near normal, and the postprandial level was further enhanced. The long-term follow-up of the clinical status and the blood glucose as well as the serum C-peptide demonstrated that all the islet allografts functioned well and none were rejected. To address the long-term effect of islet transplants on diabetic complications, the development and progress of the diabetic retinopathy, nephropathy, and autonomic neuropathy in 36 type I diabetic subjects with functioning islet grafts for 14–43 mo pre- and posttransplant were studied. The results suggest that islet transplants may delay the development of diabetic retinopathy. Islet transplants with excellent or good function may also delay or even ameliorate the development of diabetic nephropathy, but those with fair function exert no such influence. Islet transplants might delay the development of autonomic neuropathy in recipients with excellent and good graft function but not exert any influence in the patients with fair graft function.

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Levels of Blood C-Peptide in Type I Diabetes Mellitus Patients After Pancreatic Islet Cell Transplantation

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The levels of C-peptide were investigated in blood samples from 20 patients with complicated insulin-dependent (type I) diabetes (patient age 19–45 yr) before and after allotransplantation of human fetal pancreas islet cells. The C-peptide concentration was determined by the radioimmune technique. The C-peptide concentration before transplantation was 0.3 ng/ml (mean). One or 2 wk later it had increased to 0.69 ng/ml, whereas after 1–2 mo, it had reached 2.85 ng/ml. Three to 4 mo later it was 1.98 ng/ml and remained at that level for the following months. By 7–8 mo the C-peptide level had decreased to 1.4 ng/ml, approaching the C-peptide level in healthy people, and by the end of the year, it had returned to the preoperative level. The increase of the C-peptide concentration in blood after allotransplantation of islet cells was accompanied by clinical improvement: the course of the disease appeared to become stable, painful diabetic polyneuropathy disappeared, the proteinuria decreased and the state of the eye vessels improved. Also, there was a decrease of the insulin dose.

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Effect of Clinical Transplantation of Fetal Islet Cell Cultures on Late Diabetic Complications

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By 10 November 1987, 244 transplantations of fetal islet cell cultures (FICCs) had been performed in patients with insulin-dependent diabetes mellitus: 140 allotransplantations (ATx) of human FICC, 71 xenotransplantations (XTx) of pig FICC, and 33 XTx of bovine FICC. No immunosuppression was used. After ATx of human FICC, a majority of the patients experienced an increase in plasma C-peptide and a concomitant reduction of the exogenous insulin dose. Data from three groups of patients are shown in Fig. 1. The patients in the groups differed in that they had high, normal, or low plasma C-peptide levels before transplantation. After ATx of FICC in patients with diabetic polyneuropathy, the pain in the extremities usually disappeared after 2–3 mo. In recipients with diabetic nephropathy, proteinuria disappeared or decreased, and arterial blood pressure became normal or near normal. In recipients with diabetic retinopathy of the second and third stage, the status of the fundus was improved, and visual acuity improved. Unexpected and therefore particularly interesting was the improvement of the ophthalmic status in the recipients with severe, preterminal stage of proliferative diabetic retinopathy. In such cases, a gradual resolution of preretinal hemorrhage, regression of proliferations, and partial attachment of the detached retina were observed. Such positive changes on the eyeground resulted in increase of the visual acuity of the recipients from 0.01–0.03 to 0.01–0.2. The positive effects of the FICC ATx existed for a significant period: from 6 mo to 2.3 yr. Repeated FICC ATx performed in 31 patients resulted in similar therapeutic effects as after the first ATx. The effects of FICC XTx on insulin requirement, the course of the diabetes, and diabetic polyneuropathy were similar to the effects of FICC ATx. The effects of XTx on diabetic retinopathy and nephropathy were, however, less prominent.

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hC-PEPTIDE LEVELS AND INSULIN REQUIREMENTS AFTER ISLET CELL TRANSPLANTATION IN PATIENTS WITH DIABETES MELLITUS, TYPE I

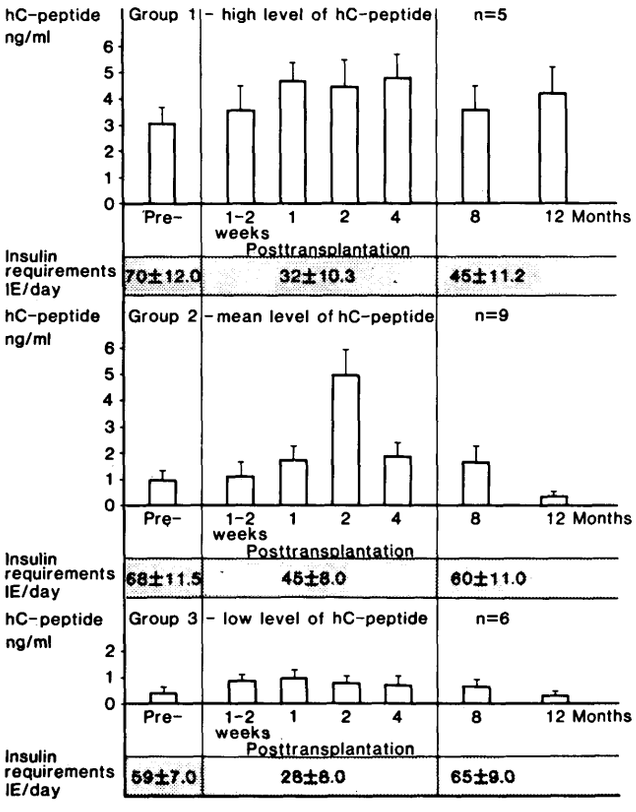

FIG. 1. Human C-peptide levels and insulin requirements after islet cell transplantation in patients with insulin-dependent diabetes mellitus.

Islet Cell Transplantation in Diabetic Patients With Purulent Septic Complications

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Islet cell transplantation was performed in 140 diabetic patients between April 1983 and October 1987. Cell cultures were not pretreated with collagenase. Cultivation period was 7–9 days. Transplantation was performed by an injection into the musculus rectus abdominis. Twelve patients who underwent transplantation had preexisting purulent septic complications. A control group consisted of 12 patients with similar complications who received routine insulin ther-

TABLE 1
Biochemical indices

	Glucose (mM)	Insulin requirement (U)	C-peptide (pg/ml)	HbA_{1c} (%)
Control subjects	18.0 ± 3.4	52 ± 17	0	10.3 ± 0.25
Cell transplantation	6.7 ± 2.4	25 ± 15	0.65 ± 0.27	8.5 ± 0.26

n = 12/group.

apy. By 10–14 days after islet transplantation, the infectious sites became cleaner and began to heal. The clinical course improved in all patients. In the control group, 2 patients died, whereas 3 patients had to undergo amputation of a lower extremity. Biochemical indices are presented in Table 1. Our data suggest that islet cell transplantation can be useful as part of the complex treatment of diabetic patients with purulent septic complications.

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Report of Islet Transplantation in 36 Cases of Insulin-Dependent Diabetes Mellitus

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The 36 patients (22 males, 14 females, aged 10–40 yr) suffered from diabetes with a duration of 3–17 yr and had repeated attacks of severe ketoacidosis before this study. Before transplantation, their average fasting blood glucose was 284 ± 80.1 mg/dl, 24-h urine glucose was 50.8 ± 29.2 g/dl, the C-peptide was 0.099 pmol/ml, and the insulin requirement was 66.6 ± 17.9 U/day. Islets were isolated from 4- to 7-mo-old fetuses obtained through waterbag induction. Under strict aseptic conditions, the whole pancreas was taken out and placed into cold culture medium for washing. The tissues surrounding the blood vessels were removed, and the gland was cut into 1- to 1.5-mm fragments, which were placed into RPMI-1640, pH 7.2, culture medium containing 10% bovine serum and antibiotics. The culture medium was changed every 3 days. Meanwhile, appearance of insulin in the medium and electron-microscopic studies provided proof of the viability of the islet cells. The islets were implanted intraperitoneally in 31 cases and in the triangle muscle in 5 cases. Each recipient received 2–23 fetal pancreases, the islets having been cultured for 2–16 days. After transplantation, 14 of the patients received azathioprine, and 3 patients were treated with horse antilymphocyte globulin (AHTG). AHTG induced severe urticaria, and in one case, serum sickness was observed. There was an apparent improvement of the clinical symptoms during 9–90 mo of follow-up posttransplantation. The average fasting blood glucose fell from 290 to 144.6 ± 71.2 mg/dl. The 24-h urine glucose diminished to 9.6 ± 7.8 g/dl. C-peptide increased to 0.31 ± 0.29 pmol/dl. Insulin dose decreased by 25–75% in most patients. Three patients could suspend the insulin treatment, and 2 patients did not have any change in insulin dosage. One patient was given 23 fetal pancreases, but his insulin dose decreased only by 50%, whereas a 10-yr-old girl who received 2 fetal pancreases could discontinue insulin treatment 3 mo later. Thus, transplantation results depend not only on the number of fetal pancreases but also on the culture conditions, the site of transplantation, and the prevention of islet rejection.

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Control of Glucose Metabolism and Effect on Diabetic Complications in 15 Cases of Implantation of Pancreatic Islets in Diabetic Patients

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The 15 patients had type I (insulin-dependent) diabetes mellitus (12 males, 3 females, aged 26–58 yr, avg 39). Duration of illness was 1–26 yr (avg 9.5 yr). Eleven had recurrent attacks of acetone acidosis, 6 suffered from varied degrees of retinal disease, and 1 suffered from general superficial dermatitis. The fasting blood glucose levels were

TABLE 1
Comparison of blood glucose levels and insulin doses

	Preimplantation			Postimplantation				
	n	Range	Mean ± SE	*n*	Range	Mean ± SE	*t*	*P*
Blood glucose (mg/dl)	15	175–350	217.2 ± 57.3	15	124–240	165.2 ± 32.4	3.11	<.005
Dosage of insulin (U/day)	15	24–78	45.46 ± 15.61	15	0–46	23.46 ± 11.01	7.77	<.001

between 175 and 350 mg/dl (avg 217), and the doses of insulin required before implantation were between 24 and 78 U/day (avg 46). The pancreatic islets were obtained from fetal cadavers of 16–32 wk gestation after induced abortion. Six to 10 fetal pancreases were used for each recipient. The tissue of each fetal pancreas was divided into 1-mm^3 pieces and incubated for ~10 days in a CO_2 incubator. Implantation was into the greater omentum in 2 cases and into the peritoneal cavity in 13 cases. No immunosuppressive drugs were used. There were no postoperative complications. After implantation an effect was seen in 14 of 15 cases. Hypoglycemic episodes occurred in 12 cases, and blood glucose dropped to 17 mg/dl in 1 case. The average fasting blood glucose and dosage of insulin administered were reduced. In 1 case, no insulin was needed 1.5 yr after implantation. Another recipient needed only 8 U/day. During a follow-up of 1–2.5 yr, acetone acidosis did not occur, and some patients were able to return to work. The retinal condition did not worsen and dermatitis resolved in the 1 case. The details of the clinical data are summarized in Tables 1 and 2. In conclusion, implantation of fetal pancreatic islets in type I diabetic patients is a simple and safe method that provides aid in the control of glucose metabolism and reduces diabetic complications.

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TABLE 2
Blood glucose level and insulin dose pre- and postimplantation in relation to time of follow-up

Years followed	*n*	Preimplantation	Postimplantation	Average reduction	*t*	*P*
Blood glucose (mg/dl)						
>2	4	218.25 ± 33.93	160.00 ± 28.07	52.25	1.87	>.05
1–2	5	211.60 ± 27.35	172.80 ± 17.83	38.8	2.65	<.05
0.5–1	5	238.8 ± 75.20	158.60 ± 37.43	80.2	4.67	<.01
Insulin dose (U/day)						
>2	4	38.0 ± 11.48	18.0 ± 10.39	20	2.58	<.05
1–2	5	54.8 ± 16.47	27.2 ± 8.54	27.6	3.36	<.01
0.5–1	5	46.4 ± 8.97	23.6 ± 10.76	22.8	3.64	<.01

Islet Transplantation in Patients With Type I Diabetes in China

Y.-F. HU ET AL.

At our institution, we have performed experimental studies of islet transplantation since 1978 and clinical islet transplantation in patients with type I (insulin-dependent) diabetes since 1981. By the end of 1986, 73 cases of type I diabetes had received islet grafts. To further study islet transplantation, the Ministry of Health of the Chinese government sponsored four special courses on islet transplantation in 1984 and 1986. There were 168 participants from 64 hospitals all over China. The Chinese National Cooperating Group for the Study of Islet Transportation was established in 1984. The First National Symposium on Islet Transplantation was held in 1985. Up to 30 November 1985, 242 diabetic subjects received islet transplants in >20 hospitals of China, and 12 of the patients became insulin independent. In the majority of the remainder, the mean insulin dose was reduced compared with pretransplant.

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Fetal Pancreatic Grafting

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Fragments of the pancreas taken from fetuses during the third trimester in animals and the second or third trimester in humans (unviable fetuses) were procured. After implantation of syngeneic islets in animals, full correction of streptozocin-induced diabetes was achieved. Implantation of allogeneic islets in animals did not completely correct diabetes but prolonged the life of the animals. Implantation of human fetal pancreas was carried out in 30 patients with type I (insulin-dependent) diabetes. Three types of responses were seen. The patients in group 1 were characterized by clinical stabilization without alterations in the dosage of injected insulin; the patients in group 2 experienced an improvement in the clinical condition, and there was a decrease in the dosage of exogenous insulin given. In group 3, a further positive effect was a regression of diabetic complications for a period up to 3–4 yr.

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Xenotransplantation of Human and Animal Fetal Pancreas in Diabetic Rats

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Cultured xenogeneic fetal islet cells (ICCs) were transplanted to diabetic rats. ICCs were prepared from human, porcine, and bovine pancreases by a simple method based on enzyme digestion, microdissection, and incubation in a culture medium at 37°C for 5–10 days. Adult male rats with stable alloxan-induced diabetes mellitus (hyperglycemia >20 mM) were used as recipients and control rats. ICCs obtained from one human or porcine fetal pancreas were transplanted to one diabetic rat. ICCs obtained from one bovine fetal pancreas were transplanted to 3–4 recipients. In all cases, ICC were injected into the splenic pulp. Immunosuppressive treatment was not used. In the majority of the recipients, there was a significant reduction of blood glucose concentration after ICC xenotransplantation (XTx). Three or 4 wk after ICC XTx, blood glucose reached normal or near-normal levels. Simultaneously, insulin appeared in the serum. Clinical signs of diabetes such as polydipsia, polyuria, loss of body weight, and hypodynamia disappeared. Improvement of the diabetic state (nonfasting blood glucose <11 mM) was maintained for the entire observation period (total 20 wk after ICC XTx). In a control group consisting of nontreated diabetic rats, high blood glucose levels were present throughout the period of observation. Some of the normoglycemic recipients of intrasplenic XTx were subjected to splenectomy 10 wk posttransplantation. Soon after removal of the spleen, high blood glucose levels and clinical signs of diabetes occurred. Histologic examination of the removed spleen revealed groups of implanted islet cells without signs of destruction in the splenic pulp.

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