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Number 77

Diabetes Mellitus

Achievements and Scepticism

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Hellenic Diabetologic Association
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Symposium Chairman
Professor **S. RAPTIS**
Director, 2nd Department
Internal Medicine—Propaedeutic
Athens University

Edited by
JANE CHURCH, BSc

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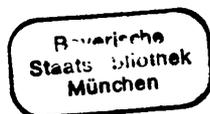
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Contributors

H. Arnqvist, MD

Associate Professor, Department of Internal Medicine, University of Linköping, Sweden

C. S. Bartsocas, MD, DMedSc

Associate Professor of Pediatrics, University of Athens; Director, First Pediatric Service, "P. & A. Kyriakou" Children's Hospital, Athens, Greece

E. J. Diamantopoulos, MD

Instructor, Department of Clinical Therapeutics, Athens University Medical School, Athens, Greece

F. H. Enzmann, PhD

Director, Division of Diabetes, Eli Lilly GmbH, Bad Homburg, West Germany

D. W. Erkelens, MD

Professor of Medicine, Department of Internal Medicine, University Hospital, Utrecht, The Netherlands

S. E. Fineberg, MD

Associate Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

J. A. Galloway, MD

Professor of Medicine, Lilly Laboratory for Clinical Research, Indianapolis, Indiana, USA

J. J. Hoet, MD

Professor of Medicine, Department of Internal Medicine, University of Louvain, Brussels, Belgium

L. P. Krall, MD

Director of Education, Joslin Diabetes Center, Boston, USA; President, International Diabetes Foundation

R. Landgraf, MD

Professor, Department of Internal Medicine "Innenstadt", University of Munich, West Germany

A. C. MacCuish, MD, FRCP

Consultant Physician (Medicine and Diabetes), Diabetic Clinic, Royal Infirmary, Glasgow, Scotland

M. Massi Benedetti, MD

Senior Registrar, Istituto di Patologia Speciale Medica, University of Perugia, Italy

Ž. Metelko, MD

Assistant Lecturer and Head of Out-Patient Department, Institute for Diabetes, Endocrinology and Metabolic Diseases, "Vuk Vrhovac", WHO Collaborating Centre, University of Zagreb, Yugoslavia

E. F. Pfeiffer, MD, Dres.h.c.

Professor and Chairman, Department of Internal Medicine I, Ulm University; Vice President, International Diabetes Federation, Ulm, West Germany

S. Raptis, MD

Director, Second Department of Internal Medicine-Propaedeutic, Athens University, Evangelismos Medical Centre, Athens, Greece

K. E. Schröder, MD

Professor of Internal Medicine and Director, Department of Internal Medicine, Bethesda Hospital, Duisburg, West Germany

N. C. Thalassinos, MD

Associate Professor of Medicine, Second Department of Internal Medicine-Propaedeutic, Athens University, Evangelismos Hospital, Athens, Greece

A. Tourkantonis, MD

Professor and Chairman, First Department of Medicine, University of Thessaloniki, AHEPA General Hospital, Thessaloniki, Greece

J. Traeger, MD

Professor and Chairman, Transplantation Unit, Department of Nephrology, INSERM U 80, Herriott Hospital, Lyon, France

H. G. Velcovsky, MD

Assistant Professor of Medicine, IIIrd Medical Clinic and Policlinic, Centre of Internal Medicine, University of Giessen, West Germany

W. K. Waldhäusl, MD

Associate Professor of Internal Medicine, Division of Clinical Endocrinology and Diabetes Mellitus, Vienna University, Vienna, Austria

G. Whincup, MB, ChB, MRCP

Clinical Research Assistant, Department of Paediatrics, Children's Hospital, Sheffield University, Sheffield, England

N. H. White, MD

Assistant Professor of Pediatrics, Division of Endocrinology and Metabolism, St Louis Children's Hospital, Washington University School of Medicine, St Louis, Missouri, USA

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Segmental pancreatic allotransplantation in type 1 diabetics

R. LANDGRAF, MD

Professor, Department of Internal Medicine 'Innenstadt'

M. M. C. LANDGRAF-LEURS, MD

Department of Internal Medicine 'Innenstadt'

H. WITZGALL, MD

Department of Internal Medicine 'Innenstadt'

D. BURG, MD

Department of Internal Medicine 'Innenstadt'

A. KAMPIK, MD

Department of Ophthalmology

L. A. CASTRO, MD

Department of Internal Medicine Klinikum Grosshadern

W-D. ILLNER, MD

Transplantation Centre, Department of Surgery Klinikum Grosshadern

W. LAND, MD

Professor, Transplantation Centre,

Department of Surgery Klinikum Grosshadern

University of Munich, Munich, West Germany

Presented by R. LANDGRAF

Introduction

Clinical and (especially) experimental studies indicate that the late complications of insulin-dependent diabetes are mainly due to derangements of glucose metabolism (Engerman *et al.*, 1977; Pirart, 1978). It can therefore be assumed that early glucose normalization can prevent, arrest or even reverse vascular and neurological complications in diabetics (Cahill *et al.*, 1976; Tchobroutsky, 1978; Irsigler *et al.*, 1979; Viberti *et al.*, 1979; Little, 1981; White *et al.*, 1981, 1982; Abouna *et al.*, 1983; Lauritzen *et al.*,

1983). Normoglycaemia cannot generally be achieved by conventional insulin therapy, and it is obvious that new approaches to treatment, especially of type 1 diabetics, are required. One direction of development is concerned with artificial devices, such as implantable and non-implantable insulin delivery systems with or without glucose sensor function (Pfeiffer *et al.*, 1974; Blackshear *et al.*, 1979; Peterson, 1982; Shichiri *et al.*, 1982). Another possibility exists in the transplantation of insulin-producing tissue, i.e. isolated islets or pancreas segments (Sutherland, 1981a, 1981b).

The aims of pancreas transplantation in type 1 diabetes mellitus are to reduce the high morbidity and mortality (WHO, 1980), to improve psychosocial rehabilitation (Simmons *et al.*, 1980), and to normalize diabetic derangements of intermediary metabolism. End-stage renal failure is one of the major life-threatening complications for type 1 diabetics (McCrary *et al.*, 1981; Medical Service Study Group, 1981), and kidney transplantation has been performed quite often in these patients in recent years (Jervell *et al.*, 1979; Najarian *et al.*, 1979). Since there are still many problems associated with pancreas transplantation, pancreas grafting has mostly been carried out in selected type 1 diabetics with end-stage renal failure together with kidney transplantation (Sutherland, 1981b, 1983). In recent years particularly, an increasing number of pancreas transplants have been successful, and glucose metabolism can be improved dramatically (Traeger *et al.*, 1981; Sutherland *et al.*, 1982; Pozza *et al.*, 1983; Landgraf *et al.*, 1984).

In this study we will present clinical and functional data of 22 simultaneous kidney and pancreas transplants in 21 type 1 diabetics with end-stage renal failure.

Materials and methods

Patients

Twenty-one type 1 diabetic patients with end-stage renal failure were accepted for treatment. Combined pancreatic and renal allotransplantation was performed in all patients, pancreatic retransplantation alone in one patient. The important clinical data for the patients are listed in Table 1.

Indications for pancreas transplantation

The indications for simultaneous kidney and pancreas grafting so far accepted by our group are depicted in Table 2. Patients above the age of 50 years or those with severe vascular complications at a younger age were excluded. Blindness seems to increase the risk of pancreas transplantation because of difficulties in perioperative co-operation, and thus might be a relative contraindication. The usual preoperative check-up prior to transplantation was expanded by ultrasonography of the vascular system, radionuclide studies of the heart and, in most patients, coronary angiography.

Donor selection

Donor selection criteria and pancreatectomy have been described recently (Land *et al.*, 1984).

Duct obliteration

The duct obliteration procedure was started immediately prior to transplantation; the duct was cannulated under hypothermic in-vitro conditions. Ethibloc® (= prolamine) was injected into the ductal system under x-ray control. Duct obliteration was considered to be efficient when the first signs of overinjection were noticed by x-ray

Table 1

Clinical data of the type 1 diabetics with simultaneous kidney and pancreas transplantation

Patient number	Age/sex (years)	Duration of diabetes (years)	Late complications			
			Retinopathy grade	Neuropathy severity	Nephropathy ¹ (months)	Hypertension
1	39/♀	30	III	+	12 HD	+
2	21/♂	19	III	+++	5 HD	+
3	28/♂	26	II	++	24 HD	+
4	36/♀	30	II	+	36 HD	+
5	41/♂	20	II	++	24 HD	+
6	33/♀	20	II	+	12 HD	+
7	26/♂	26	III	+++	12 HD	+
8	49/♂	23	III ⁺	++	24 CAPD	+
9	25/♀	16	III ⁺	++	24 HD	+
10	42/♂	32	II	+	7 CAPD	+
11	40/♂	31	II	+	3 CAPD	+
12	33/♀	25	II	+++	4 CAPD	+
13	27/♀	18	II	++	9 HD	+
14	36/♂	29	III ⁺	++	6 HD	+
15	33/♂	25	III ⁺	++	26 HD	+
16	43/♀	15	II	+++	15 HD	+
17	32/♀	23	II	++	4 CAPD	+
18	31/♀	17	II	++	24 HD	+
19	38/♂	33	III ⁺	++	2 CAPD	+
20	40/♂	23	II	++	12 HD	+
21	35/♀	25	II	+	18 CAPD	+

HD = Haemodialysis; CAPD = Continuous ambulatory peritoneal dialysis; ⁺ Amaurosis.

Females n = 10; males n = 11. Ranges: age 21–49 years (mean 34 years); duration of diabetes 15–33 years (mean 25 years); duration of nephropathy 2–36 months (mean 15 months).

Table 2

Patient selection for pancreas transplantation in type 1 diabetes mellitus

Indications	Rapidly progressive or end-stage renal failure Rapidly progressive proliferative retinopathy Brittle diabetes with unsuccessful insulin pump treatment
Contraindications	Age above 50 years Severe cerebral and/or cardiovascular complications Blindness (?)

control. Following occlusion, the ductal orifice and all the parenchyma near the cut surface were ligated.

Recipient operation

We have recently modified our technique of pancreatic transplantation (Land *et al.*, 1980). The segmental pancreas graft was situated in an upside-down position in the right iliac fossa by positioning the distal four-fifths intraperitoneally and one-fifth extraperitoneally. Circulation was established by end-to-side anastomosis of the portal vein to the right external iliac vein and of the coeliac axis (plus patch) to the right external iliac artery. Following closure of this wound, a renal graft from the same donor was placed in the left iliac fossa using the standard technique.

Postoperative management

Besides the common basic examinations of blood pressure, heart rate, body tem-

perature, pulmonary gas exchange, acid–base balance and bowel function, the transplantation of two grafts requires a special monitoring of kidney and pancreas function. The pancreas transplant function monitoring consists of blood glucose determinations every 2 h during the first 2 days. Thereafter the intervals depend on organ function. In addition, C-peptide measurements were performed. The blocking effect of somatostatin on the exocrine function of the pancreas is controlled by daily determination of alpha-amylase in serum and transplant pancreatic fluid. Kidney transplant function is assessed by measuring urinary output, urine osmolality, creatinine clearance, and creatinine and urea levels in the serum. In addition, fluid balance was monitored (Lenhart *et al.*, 1984).

Immunosuppression consists of the administration of Cyclosporin A (CyA) and methylprednisolone (for further details see Table 3). For the hormonal blockade of the exocrine and endocrine pancreas transplant function, somatostatin was used—240 µg/h i.v. (Landgraf *et al.*, 1983). The endocrine B-cell function was suppressed by insulin administered intravenously by perfusor. In spite of total parenteral nutrition with carbohydrates (up to 3000 kcal/day), amino acids (70 g/day) and fatty acids (500 kcal/day), we achieved normal blood glucose levels with this regimen. Oral nutrition was started as soon as possible depending on bowel function, which was significantly inhibited in some patients by somatostatin. To prevent venous thrombosis in the transplanted organs, intravenous heparin was administered by perfusor in a dosage of 600–1200 i.u. to achieve a partial thromboplastin time of 60–80 s. In most cases perioperative antibiotic prophylaxis with beta-lactams and aminoglycosides was extended for a period of about 6 days.

Table 3
Immunosuppressive protocol

Basic immunosuppression	
1. Cyclosporin i.v.	3–5 mg/kg daily over 10 days postoperatively
Cyclosporin orally	15 mg/kg→8–6 mg/kg over the next 5 months, then low-dose continuation
2. Glucocorticoids	
Methylprednisolone (MP)	500 mg i.v. intraoperatively 250 mg→30 mg daily over the first weeks postoperatively, then reduction to 8 mg daily within 2 months postoperatively. Discontinuation after 6 months postoperatively
Antirejection therapy	
First rejection episode	3 × MP: 500 mg i.v. daily
Second/third rejection episode	MP: 120 mg i.v. daily plus ATG (Fresenius) 4.5–7 mg/kg daily over a period of 7 days

Follow-up of the patients

The patients were trained in self-monitoring of blood pressure, body temperature, body weight, urine volume and blood glucose at least twice daily with a quantitative reflectometer system, and in recording of the data after discharge from the hospital. Intensive ambulatory check-ups at least every week for about 2 months and thereafter at 3- to 4-week intervals were performed. In addition, every 3–6 months neurological and ophthalmological investigations were carried out.

Methods

After an overnight fast, oral glucose tolerance tests were performed with 100 g glucose as Dextro-OGT® (Boehringer Mannheim, F.R.G.) every 3–6 months. To test the glucagon secretory capacity, a combined test with 100 g glucose orally, followed 2 h later by 500 ml arginine solution (6 g/dl), infused over 30 min, was performed. Blood samples were collected at 0, 30, 60, 120 and 180 min during the oral glucose tolerance tests alone, and during the combined tests at 0, 30, 60, 120, 125, 130, 140, 150, and 180 min. The following parameters were measured: blood glucose (glucose oxidase method), C-peptide as radioimmunoassay (IRE Diagnostic GmbH, Frechen, F.R.G.), insulin (Hales and Randle, 1983) and glucagon (Heding, 1971) using antiserum K 5563 from Novo Copenhagen, Denmark. Cyclosporin A was monitored by measuring whole blood levels using a radioimmunoassay of Sandoz, Basel, Switzerland, with some modifications. The therapeutic range for blood concentrations was considered to be between 250 ng/ml and 750 ng/ml.

Results

Graft functions

Since patients 1 to 3 (see Table 1), treated with conventional immunosuppression (azathioprine and glucocorticoids), have already been discussed in detail elsewhere (Landgraf *et al.*, 1983), the results presented here are exclusively those for patients treated with CyA. Currently, from these 18 patients, 14 have functional renal grafts, resulting in a kidney transplant survival rate of 78%. Two of the kidneys were lost due to acute rejection and 2 patients died a few weeks after transplantation from acute liver insufficiency without functional grafts. This demonstrates that renal graft survival rate is not significantly different from that for kidney grafting alone (European Multicentre Trial Group, 1983), indicating that the simultaneous transplantation of a pancreas segment plus kidney did not increase the risk of renal graft loss.

Of the 19 pancreatic transplantations, 2 were lost due to venous thrombosis of the graft (patient 4), 2 grafts were acutely rejected, 2 were lost after graft infection and, as already mentioned, 2 patients died without functioning grafts. Eleven pancreatic transplants are currently functioning. The range of survival time of the pancreas grafts lies between 1 month and 31 months (Table 4). Of the 11 patients, 5 had an impaired glucose tolerance, 2 of them with elevated haemoglobin A_{1c} (HbA_{1c}) levels,

Table 4
Results of segmental pancreatic transplantation in CyA-treated patients

Total		19 (100)
Graft losses	Venous thrombosis	2 (10.5)
	Infection	2 (10.5)
	Rejection	2 (10.5)
	Patient death	2 (10.5)
Functioning grafts		11 (58)
	(31, 21, 12, 11, 10, 7, 5, 5, 2, 2, 1 months)	
	Impaired glucose tolerance	5 (45)
	Normal glucose tolerance	6 (55)

Figures in parentheses are percentages.

and 6 patients showed completely normal glucose tolerance by WHO criteria (WHO, 1980), and normal HbA_{1c} values.

The long-term individual follow-up of glucose tolerance tests should be able to answer the important question of whether duct occlusion-induced exocrine pancreas fibrosis also influences the endocrine part of the grafted gland. The functional data of the two diabetics with the longest pancreas graft survival are therefore depicted in Figs 1 and 2. Normal (Fig. 1) or impaired (Fig. 2) glucose utilization did not significantly alter during the observation time, of 19 and 32 months respectively. Nor did insulin release decrease. The glucagon values were comparable during these

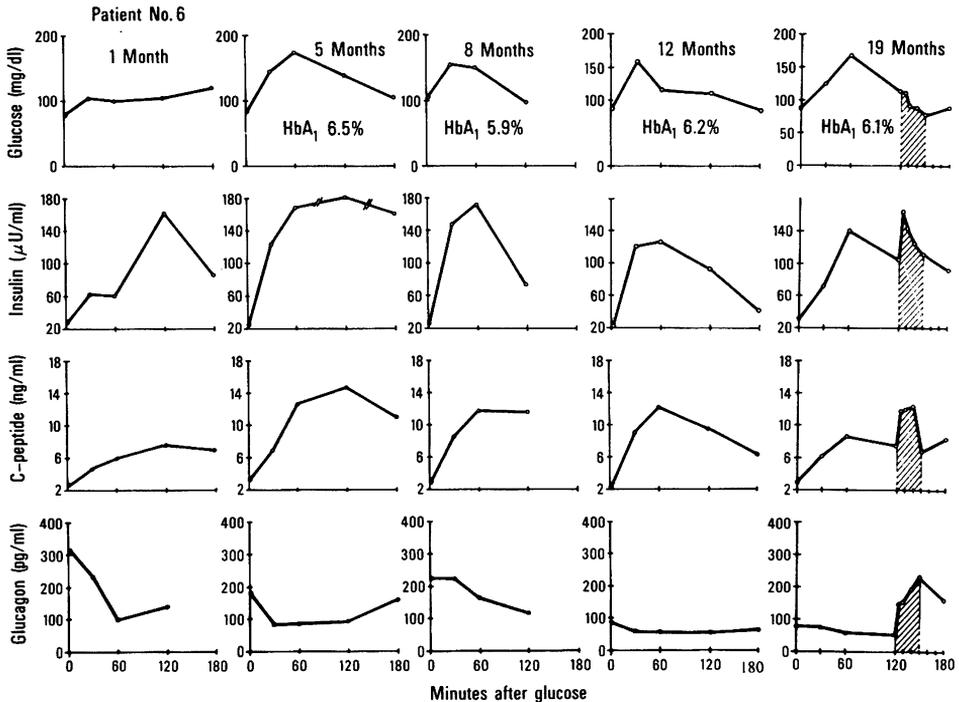


Fig. 1. Blood glucose, serum insulin, C-peptide and plasma glucagon during oral glucose tolerance tests or oral glucose (100 g) plus arginine i.v. (shaded area) 1–19 months after transplantation in patient number 6. HbA_{1c} levels were measured at the times of testing. (See also Table 1.)

observation times and reacted normally after glucose administration, i.e. partial suppression. Stimulation of insulin, C-peptide and glucagon after arginine infusion was documented (shaded areas in the figures). This demonstrates normal regulatory behaviour of the endocrine part of the grafted pancreas. The increasing levels of C-peptide of patient 5 (Fig. 2) are due to a slow progression of renal insufficiency with elevated creatinine values, leading to a decrease of C-peptide clearance.

After interruption of pancreas graft function with excessively high blood glucose values during an oral glucose load and very low values of insulin (Fig. 3) in patient 7, insulin dependency disappeared slowly after antirejection treatment, and only impaired glucose tolerance persisted 5 months later. HbA_{1c} levels were in the upper

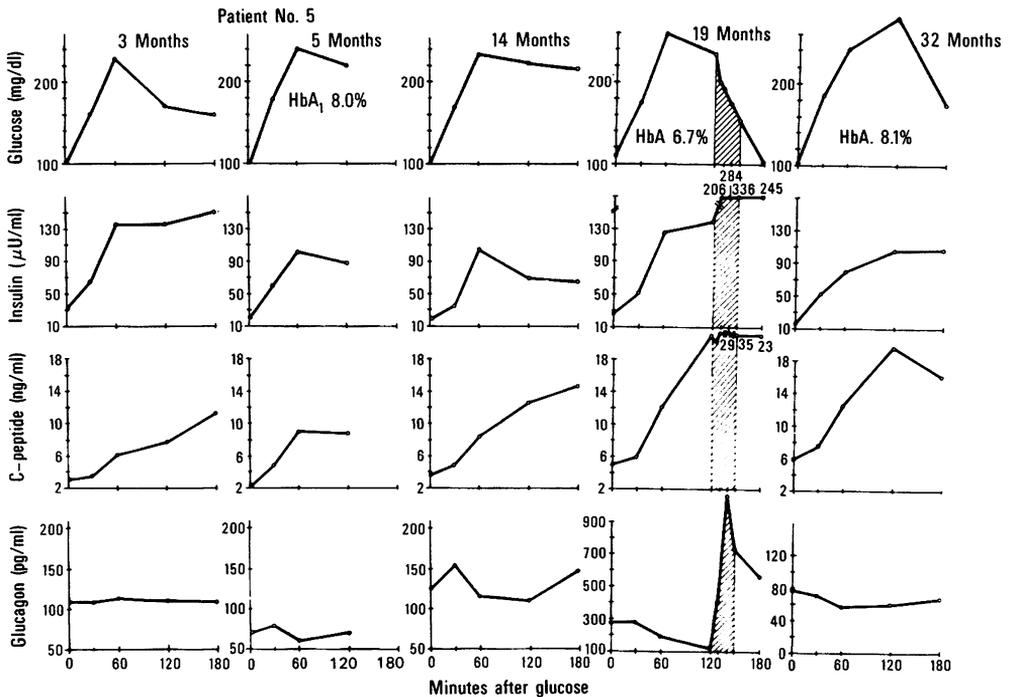


Fig. 2. Blood glucose, serum insulin, C-peptide and plasma glucagon during glucose tolerance tests or oral glucose (100 g) plus arginine i.v. (shaded area) 3–32 months after transplantation in patient number 5. HbA_{1c} levels were measured at the times of testing. (See also Table 1.)

normal limit (normal up to 8.0%). In this patient, glucose with or without arginine stimulated insulin and glucagon release markedly.

Diabetic complications

Retinopathy. Preproliferative and proliferative retinopathy was documented in all patients. Five patients were blind prior to transplantation. During strict anticoagulation immediately postoperatively and up to 6 weeks after transplantation, no significant deterioration of vision occurred in those patients who were not already blind. The follow-up of the 4 patients with the longest pancreatic survival time is summarized in Table 5. In all patients, the visual acuity did not decrease during the time of observation. In patient 5, the visual acuity of the right eye was very low (light perception) prior to transplantation; about 18 months after successful transplantation, vitrectomy of this eye was performed, but without success. During these 18 months the visual acuity of the left eye improved significantly and fundoscopy demonstrated stabilization of retinopathy and disappearance of cotton-wool exudates. However, about 20 months after transplantation, the first signs of preproliferative retinopathy (PPDR) existed and peripapillary proliferative retinal changes could be documented which stabilized after the initiation of laser coagulation therapy. Patient 6 had PPDR prior to transplantation. After complete normalization of renal

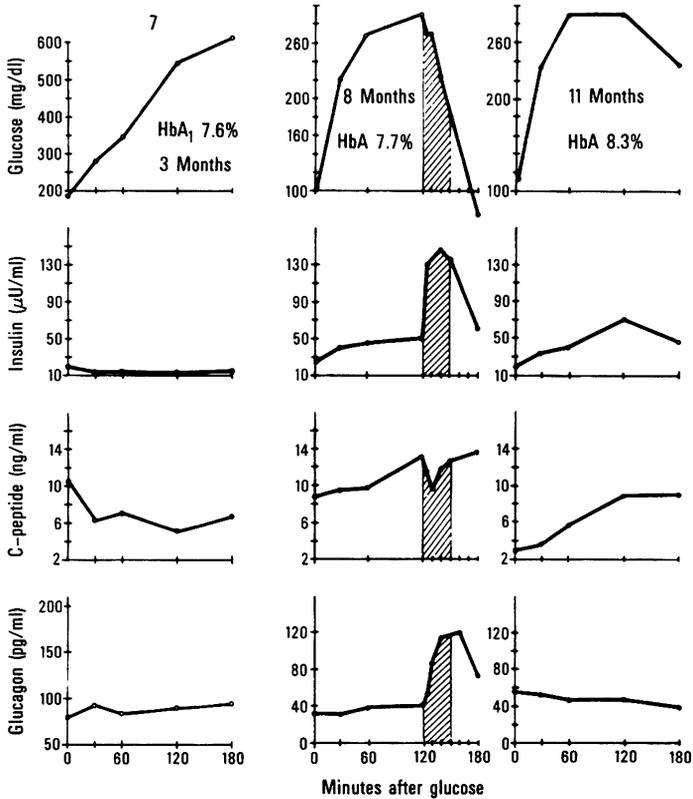


Fig. 3. Blood glucose, serum insulin, C-peptide and plasma glucagon during glucose tolerance tests or oral glucose (100 g) plus arginine *i.v.* (shaded area) 3, 8 and 11 months after transplantation and after antirejection treatment immediately after the first test at 3 months in patient number 7. (See also Table 1.)

function, glucose metabolism and disappearance of hypertension, PPDR improved and a mild and stable background retinopathy could be seen. In patient 7, who had proliferative retinopathy (PDR) with an almost complete loss of visual function prior to transplantation, not only did visual acuity improve but, more importantly, macula oedema decreased significantly. The PPDR of patient 10 stabilized and the number of cotton-wool exudates decreased markedly after successful transplantation of both pancreas and kidney.

Peripheral neuropathy. In most patients the time after successful transplantation is too short to enable objective verification of change in diabetic neuropathy. However, in 6 patients who had severe subjective peripheral neuropathy, symptoms such as burning sensations, hyperaesthesia and paraesthesia disappeared within 3 months after successful pancreatic grafting. So far, it has been possible to follow-up 4 patients in more detail (Fig. 4). Patient 10 had no subjective or objective signs of peripheral neuropathy immediately after transplantation, and did not show any change during the subsequent year. Patient 6 suffered from moderate neuropathy with decreased ankle jerks and loss of vibration sense in both feet. While motor nerve conduction velocity remained normal, the sensory nerve conduction velocity increased within 21 months after grafting (Fig. 4). Two of the patients (5 and 12) had

Table 5
Ophthalmological follow-up after successful pancreatic transplantation

Patient number	Prior transplantation	After transplantation (months)						Comments		
		1981			3	8	20	26	31	
5	OD	0			0	0	0	0	0	PPDR to mild
	OS	0.2			0.3	0.5	0.5	0.5	0.5	PDR under
	PPDR				PPDR	PPDR	PDR	PDR	PDR	control
	Cotton wool						peri-	slow		progression
	Cotton wool						papillary			
6		1974	1976	1981	6	14	21			
	OD	0.8	1.0	1.0	1.0	0.8	0.8			Mild and stable
	OS	0.1	0.8	0.4	0.5	0.5	0.5			BDR
	PPDR				BDR	BDR	BDR			
7		1981			11					
	OD	0.05			0.1					No progression
	OS	0.03			bleeding					of PDR
	PDR				macula					
	cotton wool				oedema ↓					
					PDR					
10		1981			4	10				
	OD	0.8			0.8	0.8				Stable PPDR
	OS	0.6			0.6	0.6				
	PPDR				PPDR	PPDR				
	cotton wool					cotton wool ↓				

BDR = background diabetic retinopathy, PPDR = preproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, OD = right eye, OS = left eye.

Numbers are the visual acuities.

severe neuropathy with distal sensory loss of all modalities, complete or incomplete loss of tendon reflexes, and severe motor dysfunctions. These signs were accompanied by autonomic nerve involvement such as severe postural hypotension. After transplantation, subjective and objective signs of peripheral and autonomic neuropathy decreased and motor nerve conduction velocity (nervus peroneus) improved (Fig. 4).

Discussion

Technique

Our technique of combined segmental pancreatic and renal grafting using CyA as an immunosuppressant is a relatively safe procedure. However, the mortality rate, of around 10%, has to be taken into account when patients are counselled for transplantation, but all the patients in our study were already extremely ill as a result of their severe diabetic syndrome. Therefore, mortality could be reduced by earlier transplantation before the onset of the uraemic state of the disease. In addition, a strict selection of donors and recipients and improvement in the management of the patients, together with the opportunity for the transplant team to gain experience,

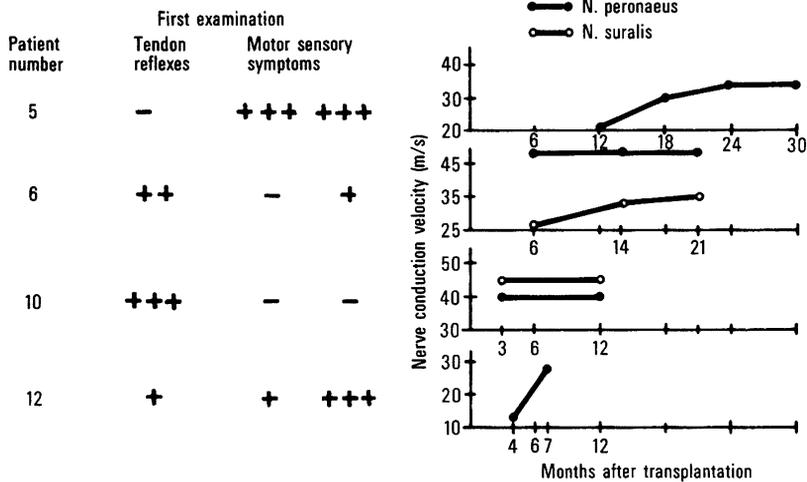


Fig. 4. Neurological follow-up in patients number 5, 6, 10 and 12. Neurological examination revealed normal tendon reflexes (+++) in patient 10 and no motor or sensory nerve symptoms (-). Conversely, patient 5 showed a complete areflexia (-) and severe symptoms of peripheral neuropathy (+++). Motor nerve (nervus peroneus) and sensory nerve (nervus suralis) conduction velocities were measured at time intervals depicted in the figure. (See also Table 1.)

play an important role in increasing the positive outcome of transplantation in diabetics. We assume that the relatively high rate of functioning pancreatic grafts is primarily due to the strong immunosuppressive potency of the new agent, cyclosporin A, which reduces the occurrence of irreversible allograft rejection. This is in accordance with the results in cadaveric renal transplantations, using CyA as immunosuppressive therapy (European Multicentre Trial Group, 1983).

The morbidity observed in our patients following combined transplantation is certainly higher than that following kidney transplants. This morbidity mainly concerns the incidence of early local complications, such as peripancreatic fluid collection, transient pancreatic fistula at the site of the pancreatic graft with and without secondary infection, and severe wound haematomas at the site of the renal graft. The incidence of complications due to the residual function of the exocrine system of the duct-occluded pancreatic graft is particularly worrying. These local complications probably arise from a too early reabsorption of the occlusive substance (Ethibloc®) before the acini are completely atrophied (for a comparison of the effects of Ethibloc® and Neoprene, as used by the Lyon group, see Dubernard *et al.*, 1983). It is worth mentioning that the administration of somatostatin intra- and postoperatively did not prevent these complications arising from residual exocrine secretion. On the other hand, the property of early reabsorption of Ethibloc® may be the reason for the good long-term function of the pancreatic grafts because of its milder fibrosis-inducing effect (Gebhardt and Stolte, 1978).

Glucose metabolism

Half of the patients with functioning pancreatic grafts (i.e. insulin-independency) showed normal glucose disposal. This observation is supported by others (Ostmann *et al.*, 1980; Sutherland *et al.*, 1982; Pozza *et al.*, 1983; Landgraf *et al.*, 1984). The reasons for abnormal glucose disposal in the other half of the patients are certainly

complex and include denervation of the pancreas, and drainage of the islet hormones into the main circulation and not into the portal vein. Furthermore, only a part of the organ is transplanted, which might in addition be disturbed by circulatory and immunological mechanisms induced by duct-occlusion and allogenic transplantation. Most of the patients received glucocorticoids in addition to CyA, which will certainly contribute to impaired glucose tolerance. The possibility that CyA itself also leads to further deterioration of glucose utilization cannot be ruled out (Gunnarsson *et al.*, 1983b).

The monitoring of pancreatic graft survival must be based primarily on blood glucose monitoring. However, hypoglycaemia might be a sign of irreversible damage of most of the endocrine tissue in the graft. Therefore measurements of direct parameters of the transplanted islet tissue are urgently needed; determination of C-peptide might provide this information (Gunnarsson *et al.*, 1983a). But as the C-peptide assay is time consuming, it cannot be considered as very useful. Other candidates for use in the determination of early islet cell damage might be pancreatic polypeptide or gamma enolase (Lindsey *et al.*, 1983), but again these assays, if available, are time consuming. Radiolabelled platelets seem to accumulate in the graft soon after initiation of rejection and have been used for the early detection of this process (Jurewicz *et al.*, 1984; Sollinger *et al.*, 1984), but wide-ranging experience has not yet been gained. In combined transplantation of kidney and pancreas from the same donor, a rise in serum creatinine and a decrease in creatinine clearance seem to be the earliest signs of allograft rejection.

Analysing glucose-induced insulin release in patients with functioning pancreatic grafts revealed patients with a normal secretory pattern, with excessively high or with subnormal values. In most patients, insulin release was delayed and maximal values were reached approximately 120 min after glucose load. In the transplanted patients receiving CyA, renal function was generally not completely normal, which may lead to changes in peripheral insulin sensitivity and in insulin clearance. In addition, most of our patients received glucocorticoids, which are known to reduce peripheral insulin responsiveness. Due to this complexity, glucose- and arginine-induced insulin and C-peptide secretion are not markers solely for pancreatic graft function, but in addition reflect peripheral insulin sensitivity and insulin and C-peptide clearance. The data for glucagon release are even more difficult to interpret since, in addition to what has been discussed for insulin and C-peptide, glucagon in the peripheral blood is derived from the grafted pancreas as well as from the endogenous pancreas. However, since A-cell function is often impaired in type 1 diabetics (Unger and Orci, 1981a, 1981b), and since glucagon is an important glucoregulatory hormone, normal glucagon secretory behaviour, for example glucose-induced suppression and arginine-induced stimulation, is an indicator for normalization of intermediary metabolism.

Late diabetic complications

One of the important aims of pancreas transplantation is to prevent, arrest or even reverse late diabetic complications by normalization of the diabetic derangements of intermediary metabolism. The close follow-up of diabetic retinopathy and neuropathy in pancreas-transplanted patients should answer some of the questions concerned with late complications and diabetic metabolism. The worldwide experience with pancreas transplantation and the number of patients with long-term survival of their pancreatic grafts are currently insufficient to enable definite conclusions to be drawn (Sutherland, 1984). However, diabetic neuropathy seems to be very sensitive to the degree of hyperglycaemia. Normalization of blood glucose with insulin pumps has led to improvements of diabetic neuropathy (Pietri *et al.*, 1980). The neurological follow-up of our patients with long-term functioning grafts

also revealed significant improvements of the severe neuropathy which had disabled most of them. Since combined pancreas and kidney grafting was performed in our patients, the positive changes in neuropathy are certainly a combined effect of the improvement or normalization of glucose metabolism and the disappearance of end-stage renal failure. The documentation of changes in diabetic retinopathy after glucose normalization is even more difficult. This is due to the problems of defining qualitatively and quantitatively the exact degree of ocular changes in diabetics and the complexity of the causes inducing functional and morphological changes of the vascular system of the eyes. End-stage renal failure and high blood pressure add to the diabetic retinopathy, and eliminating one of these factors might improve the ocular function. The study of Pirart (1978) and the prospective study of the Steno Memorial Hospital (Lauritzen *et al.*, 1983) have demonstrated that good blood glucose control might positively influence the degree and progression of diabetic retinopathy. In our patients with longer functioning pancreatic grafts, improvement or at least stabilization of diabetic retinopathy could be documented, although in one patient a further progression was observed.

Although comprehensive data are not yet available, studies to date indicate that it is not possible to define a point of 'no return' for patients suffering from the severe late complications of diabetes, and therefore the use of intensive therapeutic approaches, even when the disease has reached an advanced stage, is justified.

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