

INTERNATIONAL ISLET TRANSPLANT REGISTRY



ITR access available on INTERNET

The Diabetes Research International Network (DRInet) was founded by Camillo Ricordi, MD, at the Diabetes Research Institute, University of Miami, on Feb 22, 1994. The goal of the DRInet is to facilitate and promote diabetes research via Internet, the world's largest computer network, providing access to international E-mail, online discussion groups, public domain software (e.g. Gopher), and files and databases in tens of thousands of distant computers.

For more information please contact the Diabetes Research Institute:

(Phone: +1-305-548-5300 E-Mail: drinet@mednet.med.miami.edu).

The ITR announces its participation in the DRInet. It is intended to place the ITR newsletter, other general information and the ITR Registration and Follow-up Forms on a Gopher Server.

The current E-Mail addresses for the ITR on the worldwide Internet are:

itr@med.uni-giessen.de or 100125.1452@compuserve.com

In addition, ITR access is provided via COMPUSERVE: 100125,1452.

Newsletter No. 5

*Vol. 4 (No. 1, March),
1994*

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Dear Islet Transplant Registry Participants,

The Islet Transplant Registry is now approaching its fifth anniversary and we are very grateful that you have faithfully supported our common efforts during these five years. Through your cooperation the status of clinical islet transplantation can be updated and circularized on a regular basis. In return, we are very pleased to provide you with the ITR Newsletter No. 5.

Between Dec 12, 1893, and Dec 31, 1993, 214 adult islet allografts and one adult islet xenograft have been performed at 30 different institutions, including 130 at 11 institutions in North America, 83 at 17 institutions in Europe, and 1 elsewhere. The total number of diabetic patients reported to be insulin independent for > 1 week at 1, at 3, at 6, at 12, at 24 and at 36 months after adult islet allotransplantation through Dec 31, 1993, is 21, 18, 16, 10, 6 and 2, respectively. Among these, one pancreatoc-tomized recipient of a simultaneous islet liver (SIL) allograft in Pittsburgh has sustained euglycemia in the absence of exogenous insulin for more than 4 years now. One type-I diabetic recipient of an islet after kidney (IAK) allograft in Milan and one type-I diabetic recipient of a simultaneous islet kidney (SIK) allograft in Edmonton have been insulin independent for 2.6 and for 2.3 years, respectively.

Thus, the principal feasibility of clinical islet transplantation has clearly been proven. However, only four type-I diabetic recipients of adult islet allografts are currently insulin independent. Since the number of transplants remains low - during the last four years approximately 30 transplants have been performed per year at 18 institutions - it is evident that the impact of different approaches can only be substantiated through a careful analysis of all data available.

From a detailed analysis of 55 well-documented adult islet allografts into pretransplant C-peptide negative type-I diabetic recipients performed from 1990 to 1992 (see page 8) the following lessons emerged:

- Results have improved compared to previous periods.
- One-year patient survival rate was 95%.
- One-year islet allograft survival rate assessed by basal C-peptide 1 ng/ml was 33%.
- Eleven percent of the recipients were insulin independent at one-year follow up.
- Insulin independence after single donor islet allotransplantation was demonstrated.
- Unequivocal examples of insulin independence were only obtained in association with other organ allografts.
- Only patients who received islets from pancreata with a mean preservation time < 8 hours became insulin independent.
- Only patients who received 6,000 IEQ (islet equivalents)/kg became insulin independent.
- Only intraportal islet allografts reversed insulin dependence.
- Only patients who received ALG/ATG/ALS or OKT3 became normoglycemic, however, only recipients who were treated with ALG/ATG/ALS, but not with OKT3 were insulin independent after one year.
- All pretransplant C-peptide negative type-I diabetic patients who ever became insulin independent following islet transplantation shared four

common characteristics: 1) mean pancreatic preservation time: < 8 h; 2) islet mass: 6,000 IEQ/kg; 3) implantation site: liver; 4) induction immunosuppression: ALG/ATG/ALS or OKT3. When all four criteria were met, 27% of all recipients were insulin independent at one-year follow up in contrast to 0% when at least one criterion was not fulfilled.

- Patients who became insulin independent had pretransplant insulin requirements and HbA1c levels varying from 0.6 to 1.2 U/kg/day and from 6.5 to 11.5 %, respectively.
- Thirty-six percent of all recipients lost their graft function within the first month posttransplant.
- Islet purity did not affect islet allograft survival. However, only one center continued to transplant unpurified pancreatic digest.
- No single patient who received only cryopreserved islets became insulin independent. However, one recipient of a 'cryo-only transplant' had basal C-peptide 1 ng/ml at one-year posttransplant.
- Primary non function after islet allotransplantation, as defined as negative C-peptide throughout the whole follow-up period, was observed in 5 out of 55 cases, all of which were characterized by lacking pretransplant islet quality control and by induction immunosuppressive protocols not including T-cell antibodies.

Comparing islet graft functional survival rates based on the presence of insulin independence in different recipient categories, important differences became apparent. The number (percentage) of patients who were insulin independent at one month and at one year in the four main recipient groups, namely, IAK-IDDM, SIK-IDDM, SIL-IDDM, and SIL-PanEx, were 5 (31%), 1 (4%), 0 (0%), 8 (57%), and 2 (13%), 3 (10%), 0 (0%) and 6 (43%), respectively. These data may suggest that a simultaneous liver graft is not an immunologically privileged situation per se, that not steroid-induced insulin resistance but underlying peripheral insulin resistance and potentially hyperglucagonemia in type-I diabetic recipients probably represent crucial obstacles preventing the reversal of insulin dependence in many recipients.

Besides the evaluation of transplant function by basal C-peptide levels and achieved insulin independence, HbA1c values represent an important parameter to evaluate metabolic control. For this reason, we showed on page 16 HbA1c levels before and one year after adult islet allotransplantation depending on basal C-peptide (< 1 ng/ml or 1 ng/ml). Values were available in only 32 of 55 cases pre- and one year posttransplant. Due to the limited number of data only a slight tendency can be assumed. During the last few weeks we had to accept on the basis of our inquiries that in several centers HbA1c values were not determined pretransplant.

A careful analysis also of failures, errors and complications will contribute to future improvements. Therefore, reporting islet transplantation-related complications represents an issue of crucial importance. The Edmonton group is to be respected for their frank report on bacteremia in two of their patients due to transplantation of contaminated cryopreserved pancreatic islets (Cell Transplantation 3: 103-106, 1994). Portal hypertension represents an actual potentially life-threatening risk if unpurified pancreatic digest is grafted intraportally. The recent analysis of the Registry revealed that islet purity did not affect islet allograft survival. However, there is increasing agreement that, for safety reasons, islet purification should be performed if intraportal islet transplantation is intended.

The Pittsburgh group reported on a higher frequency of kidney rejection episodes in recipients of simultaneous islet kidney grafts receiving FK 506 and steroids compared with diabetic patients and nondiabetic patients who had a kidney transplant alone (Transplantation 55: 761-765, 1993). In contrast, the Minneapolis group presented data suggesting that islet transplantation in ALG/cyclosporin-treated SIK recipients and in ALG/cyclosporin/ azathioprine-treated patients with established kidney grafts does not increase the incidence of kidney rejection episodes (Transplant Proc. in press). We have recently distributed questionnaires to all participating centers asking for information on kidney rejection episodes in SIK and IAK recipients. Regrettably, data on this relevant issue remains incomplete (see page 8). However, the available data seem to suggest that kidney rejection episodes are not more likely if an islet graft is added to the kidney graft.

In 1992 and 1993, a number of new approaches were initiated. One group implanted one portion of the total islet graft into the thymus. Another group transplanted simultaneously islets, bone marrow and a kidney or a liver from the same donor. Follow up data will be presented at the forthcoming 2nd Congress of the Cell Transplant Society to be held in Minneapolis on May 2-4, 1994.

Our group at Giessen University performed islet after kidney grafts using a protocol including new approaches such as peritransplant ATG and steroids, Biostatator-controlled normoglycemia and total parenteral nutrition (starting at day -3) and long-term application of nicotinamide and pentoxifylline. The first Giessen patient became insulin independent at day 400 posttransplant (see page 17).

Two groups started to evaluate the feasibility of immunoisolating islets. Empty capsules and capsules containing in total some hundred human islets were implanted subcutaneously in non-diabetic, type-I and type-II diabetic volunteers. Another group grafted a small number of islets into the muscle fascia of the forearm of a type-I diabetic patient to monitor histologically the fate of allogeneic human islets. A therapeutic effect was not intended in these trials, therefore these volunteers are not listed as islet graft recipients in this newsletter.

One group transplanted encapsulated allogeneic islets with a therapeutic intention into the peritoneal cavity of type-I diabetic recipients. So far, data have not been submitted to the Registry.

At present, one has to be cautious in attempting to draw any conclusions. This will only be possible when more patients are transplanted and the data reported are more complete and precise and when standardized criteria for islet assessment and patient monitoring are defined, generally accepted and applied. Key questions such as whether islet transplantation improves quality of life and whether islet transplantation prevents or slows progression of diabetic complications could then potentially be addressed in carefully designed multicenter trials.

The staff of the Islet Transplant Registry wishes to express its gratitude to all of you for your continuous support.

Giessen, March 1994

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The Islet Transplant Registry Newsletter is published regularly and distributed to all interested institutions. It is anticipated that the sixth newsletter will be issued towards the end of 1994.

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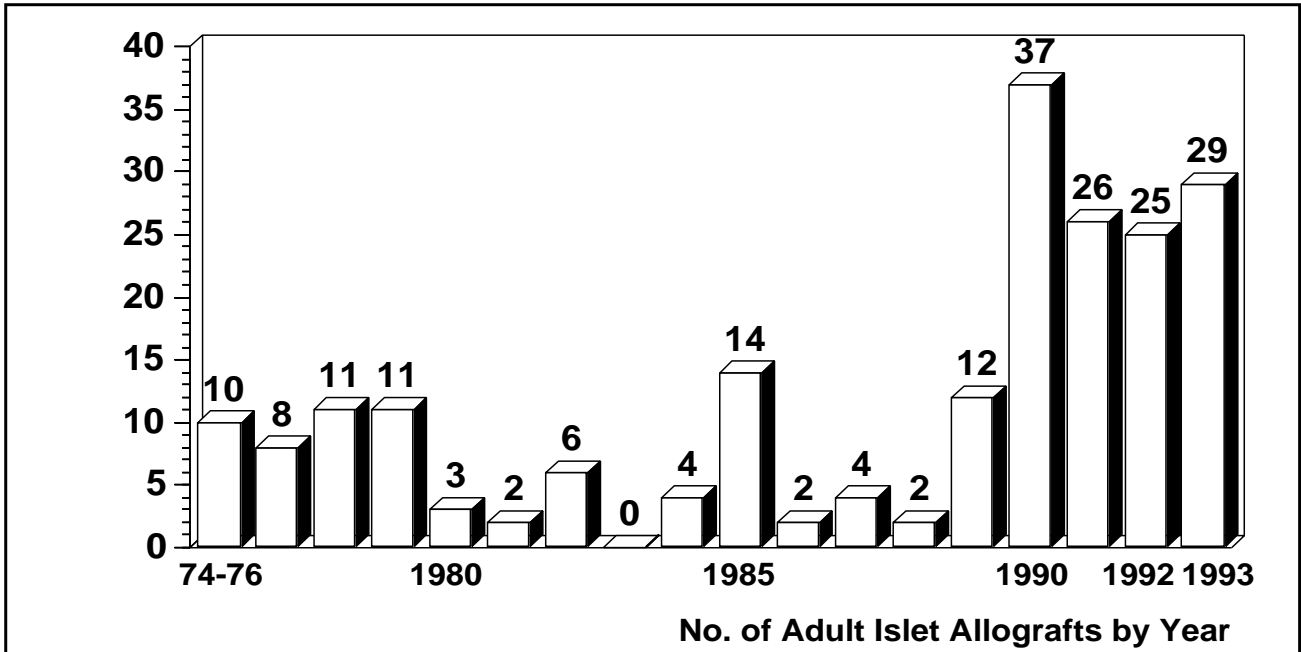
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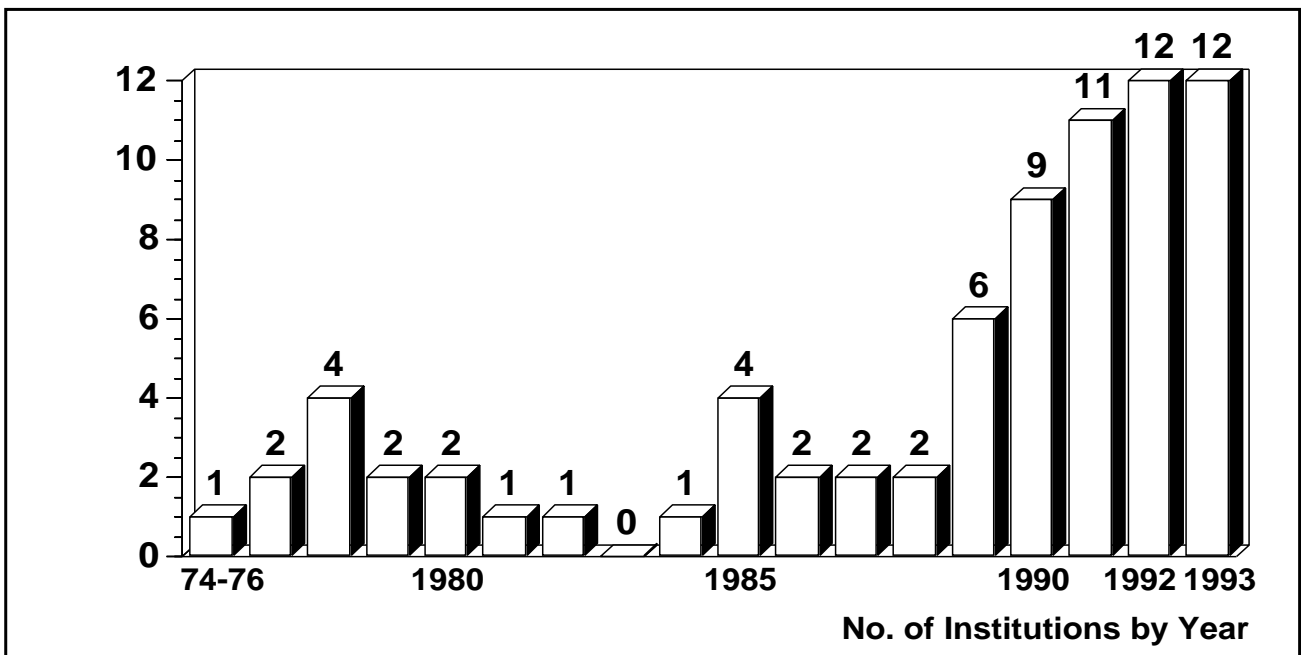
**Summary of Adult Islet Allografts (and one Xenograft*)
according to Institution and Year
through December 31, 1993**

INSTITUTION	YEAR OF TX	NO. OF CASES
• Bristol*	1893	1
• Newcastle-upon-Tyne	1916	2
• Padova	1927	2
• New York	1935	1
• Leiden	1944	1
• Petah Tikva	1968	1
• Minneapolis	1974-1993	38
• Zurich	1977-1988	8
• Genoa	1978-1979	13
• Hannover	1978	2
• Detroit	1980-1985	7
• Giessen	1980-1993	8
• East-Berlin	1982-1987	8
• St. Louis	1985-1993	25
• Miami	1985-1993	13
• Paris	1988-1991	7
• Perugia	1989-1991	5
• West-Berlin	1989	1
• Edmonton	1989-1993	5
• Milan	1989-1993	15
• St. Louis/London, Ontario	1990-1992	4
• Pittsburgh	1990-1993	30
• Leicester	1991-1992	3
• Oxford	1991-1993	3
• Charlestown	1991	2
• Los Angeles I	1992-1993	4
• Madrid	1992-1993	3
• Los Angeles II	1993	1
• Verona	1993	1
• Homburg/Saar	1993	1
TOTAL NO. OF CASES:		215
TOTAL NO. OF INSTITUTIONS:		30

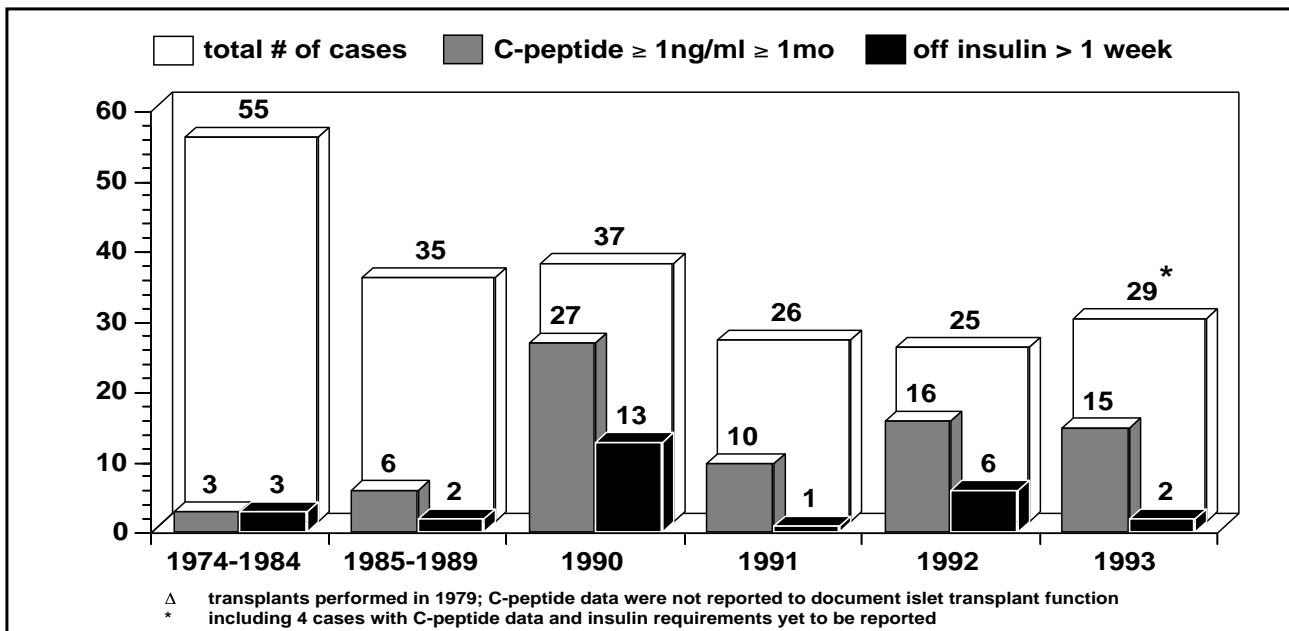
**No. of Adult Islet Allografts
by Year from 1974 through Dec 31, 1993**



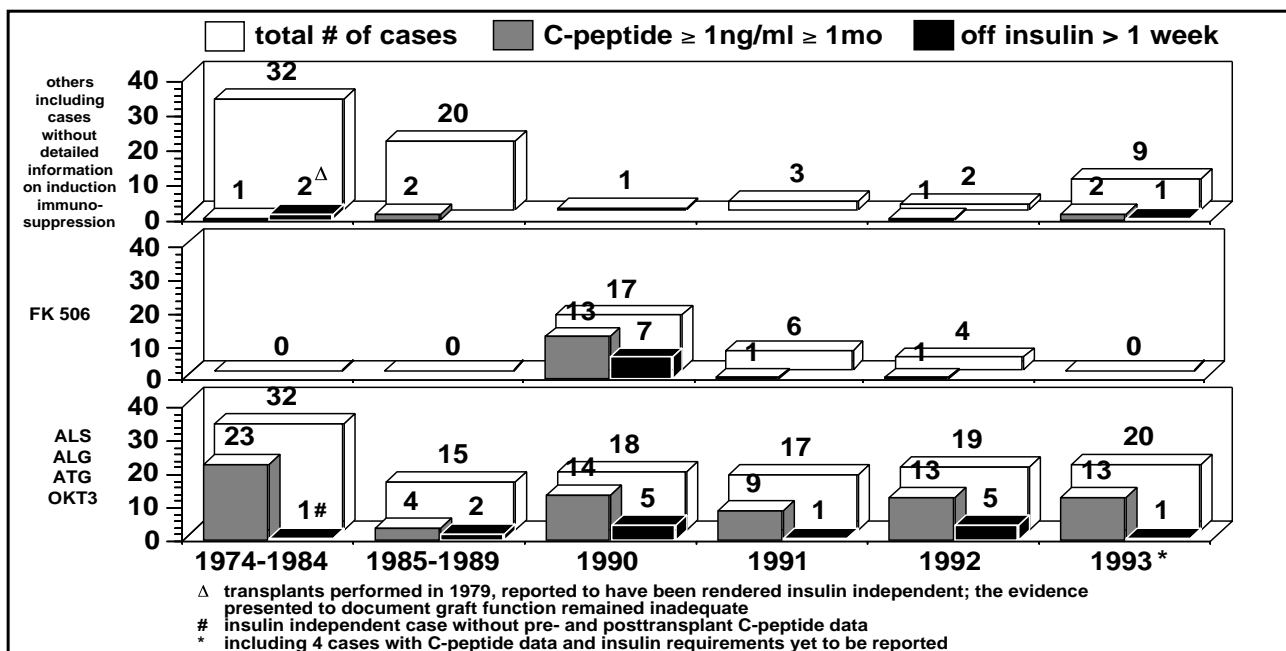
**No. of Institutions reporting Adult Islet Allografts
by Year from 1974 through Dec 31, 1993**



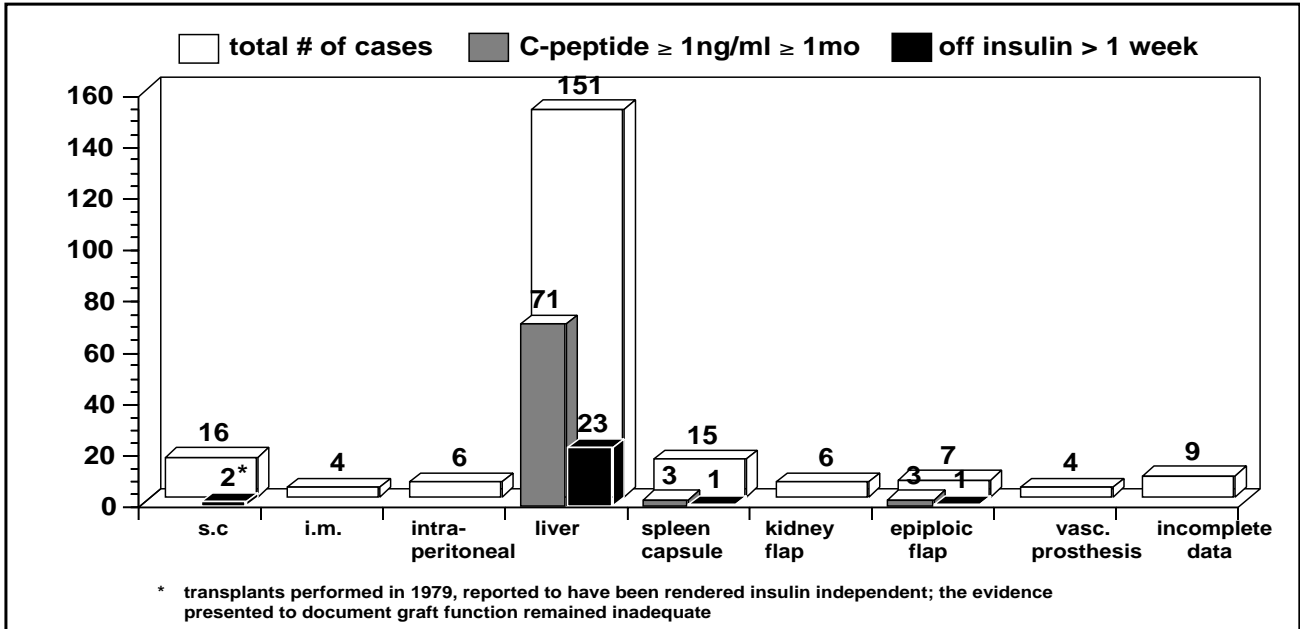
**Insulin Independence and Basal C-Peptide
after Adult Islet Allotransplantation through Dec 31, 1993, according to
Era**



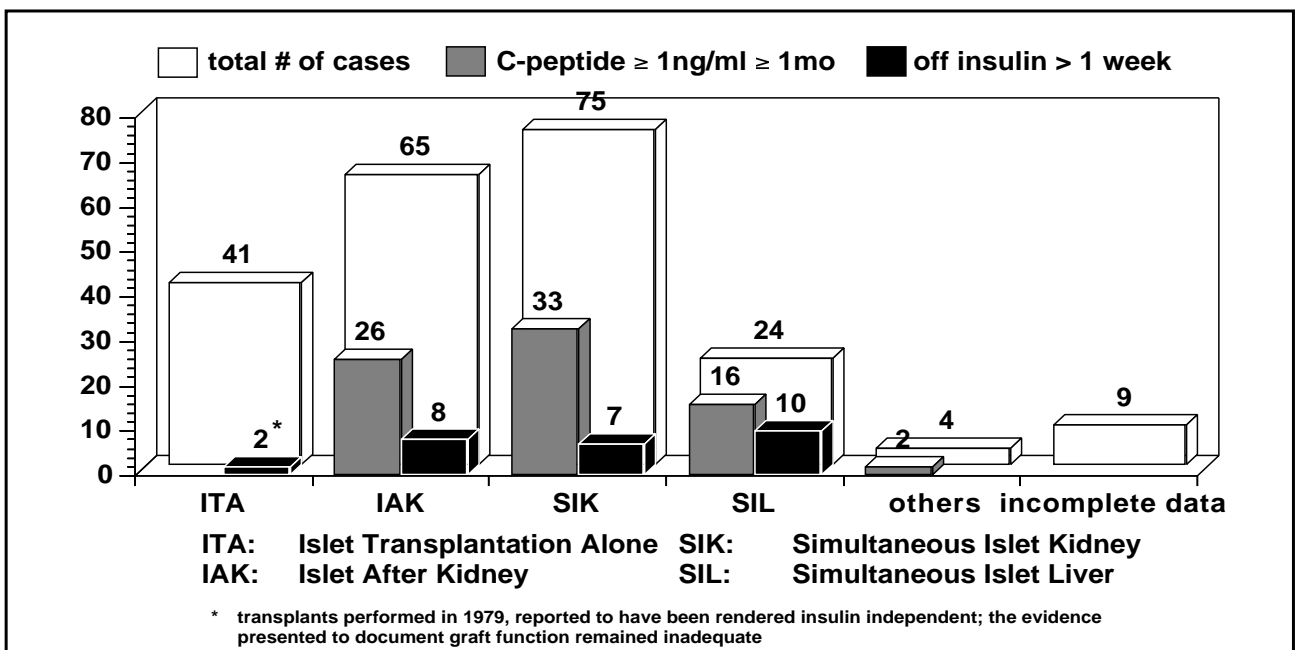
**Insulin Independence and Basal C-Peptide
after Adult Islet Allotransplantation through Dec 31, 1993, according to
Induction Immunosuppression**



**Insulin Independence and Basal C-Peptide after Adult Islet Allografts
(and one Xenograft) through Dec 31, 1993, according to
Site of Implantation**



**Insulin Independence and Basal C-Peptide after Adult Islet Allografts
(and one Xenograft) through Dec 31, 1993, according to
Recipient Category**



The 1990-92 Period

Tables and graphs on pages 8-15 and 16 (upper third) show the results of adult islet allografts performed from 1990 to 1992. Three additional cases were reported to the Registry since the completion of the ITR Newsletter No. 4. Thus, the total number of cases reported to have been performed from 1990 to 1992 is 88. It is assumed that more than 95% of all adult islet allografts performed worldwide have been reported to the Registry.

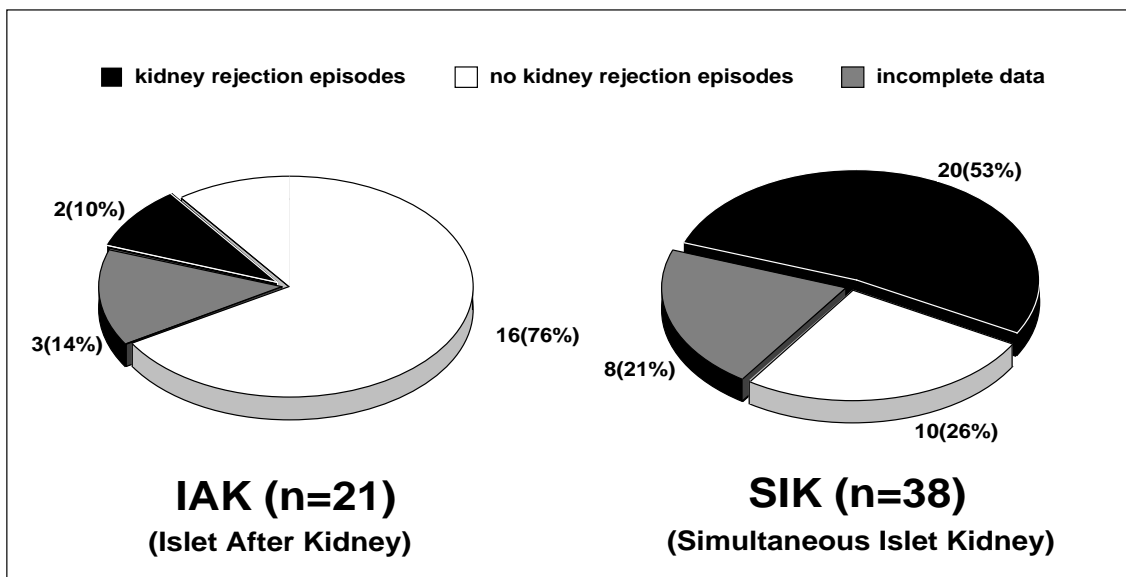
Page 8 (lower part) depicts the number of kidney rejection episodes in all IAK and SIK recipients, irrespective of their pre- and posttransplant C-peptide values.

Page 9 (upper part) shows all 88 adult islet allograft recipients subdivided according to type of diabetes. Among 71 type-I diabetic recipients, 14 had positive pretransplant plasma C-peptide levels and two died within the first week posttransplant. Only the remaining 55 pretransplant C-peptide negative type-I diabetic recipients were taken into the analysis and the results are depicted on pages 9 - 16.

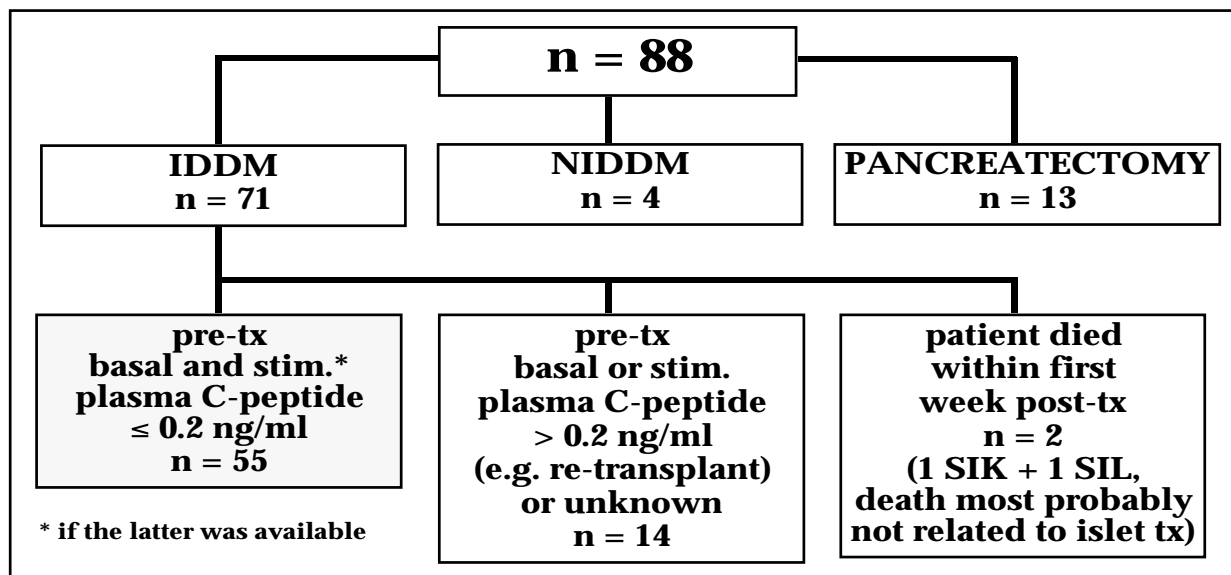
No. of Adult Islet Allografts according to Institution and Year

	90	91	92	Σ
• Charlestown	-	2	-	2
• Edmonton	2	-	1	3
• Giessen	-	-	1	1
• Leicester	-	2	1	3
• Los Angeles I	-	-	3	3
• Madrid	-	-	2	2
• Miami	4	2	1	7
• Milan	4	3	3	10
• Minneapolis	1	4	5	10
• Oxford	-	1	1	2
• Paris	3	1	-	4
• Perugia	1	1	-	2
• Pittsburgh	17	6	4	27
• St. Louis	3	3	2	8
• St. Louis/London, Ont.	2	1	1	4
Σ	37	26	25	88

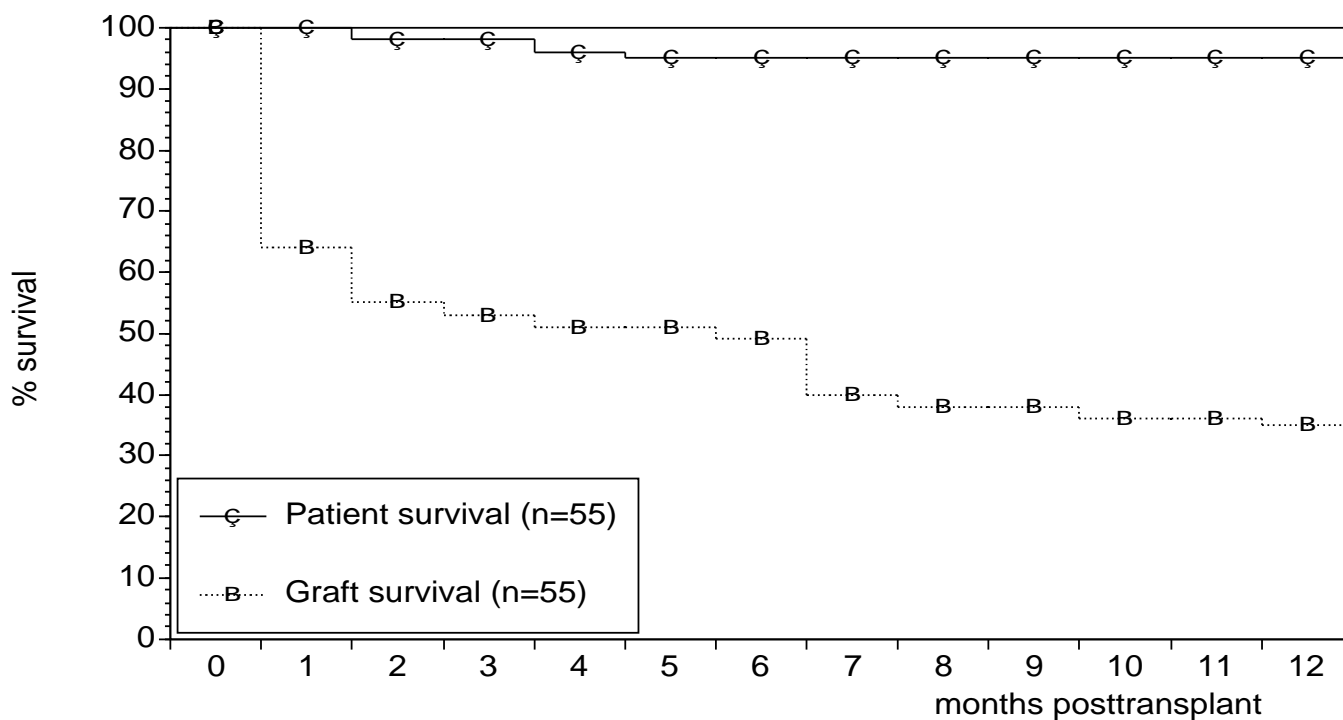
No. of Kidney Rejection Episodes in the First Year following Islet Transplantation according to Recipient Category (1990-1992 Cases)



Adult Islet Allografts 1990 - 1992



One-Year Patient and Islet Allograft Survival (Basal C-Peptide ≥ 1 ng/ml) in 55 Pre-Tx C-Peptide Negative IDDM-Recipients (1990 - 92)



Adult Islet Allograft Survival in 55 Pretransplant C-Peptide Negative IDDM-Recipients (1990 - 92 Cases)

No. (Percentage) of Cases Functioning							
Category	n	at ≥ 1 Month		at ≥ 1 Year			
		Basal C-Peptide 1ng/ml	Insulin Indep. (>1wk)	Basal C-Peptide 1ng/ml	P Values	Insulin Indep. (>1wk)	P Values
All cases	55	35 (64%)	10 (18%)	18 (33%)		6 (11%)	
A. Continent							
1. North Am.	35	24 (69%)	4 (11%)	12 (34%)	1 vs 2 p=1.000	2 (6%)	1 vs 2 p=0.176
2. Europe	20	11 (55%)	6 (30%)	6 (30%)		4 (20%)	
B. Rec. Sex							
1. male	34	22 (65%)	4 (12%)	9 (29%)	1 vs 2 p=0.246	2 (6%)	1 vs 2 p=0.188
2. female	21	13 (62%)	6 (29%)	9 (43%)		4 (19%)	
C. Rec. Age							
1. 21 - 40 y	33	23 (70%)	6 (18%)	11 (33%)	1 vs 2 p=1.000	3 (9%)	1 vs 2 p=0.652
2. > 40 y	18	10 (56%)	4 (22%)	6 (33%)		3 (17%)	
3. no data	4	2 (50%)	0 (0%)	1 (25%)		0 (0%)	
D. Duration of IDDM							
1. 20 y	17	12 (71%)	3 (18%)	6 (35%)	1 vs 2 p=1.000	1 (6%)	1 vs 2 p=0.650
2. > 20 y	32	19 (59%)	6 (18%)	10 (31%)		5 (16%)	
3. no data	6	4 (66%)	1 (16%)	2 (33%)		0 (0%)	
E. Average CIT							
1. < 480 min	39	27 (69%)	10 (26%)	14 (36%)	1 vs 2 p=0.326	6 (15%)	1 vs 2 p=0.113
2. 480 min	16	8 (50%)	0 (0%)	4 (25%)		0 (0%)	
F. No. of Donors							
1. 1	25	14 (56%)	3 (12%)	7 (28%)	p=0.612	2 (8%)	p=0.851
2. 2 - 3	19	15 (79%)	5 (26%)	8 (42%)		3 (16%)	
3. > 3	11	6 (55%)	2 (18%)	3 (27%)		1 (9%)	
G. IEQ / kg BW							
1. < 6,000	19	9 (47%)	0 (0%)	4 (21%)	1 vs 2 p=0.150	0 (0%)	1 vs 2 p=0.067
2. 6,000	36	26 (72%)	10 (28%)	14 (39%)		6 (17%)	
H. Pre Tx Viab. Tests							
1. yes	15	9 (60%)	4 (27%)	4 (27%)	1 vs 2 p=0.749	3 (20%)	1 vs 2 p=0.329
2. no	40	26 (65%)	6 (15%)	14 (35%)		3 (8%)	
I. Islet Purity (%)							
1. 90	49	30 (61%)	8 (16%)	16 (33%)	1 vs 2 p=1.000	5 (10%)	1 vs 2 p=0.518
2. > 90	6	5 (83%)	2 (33%)	2 (33%)		1 (17%)	
J. Islet Storage							
1. fresh/culture	36	25 (69%)	7 (19%)	12 (33%)	p=0.295	4 (11%)	p=0.770
2. fresh/culture and cryo	11	7 (64%)	3 (27%)	5 (45%)		2 (18%)	
3. cryo only	4	1 (25%)	0 (0%)	0 (0%)		0 (0%)	
4. not reported	4	2 (50%)	0 (0%)	1 (25%)		0 (0%)	
K. Rec. Category							
1. IAK	16	10 (62%)	6 (38%)	6 (38%)	p=0.978	3 (19%)	p=0.808
2. SIK	30	21 (70%)	4 (13%)	10 (33%)		3 (10%)	
3. SIL	4	3 (75%)	0 (0%)	1 (25%)		0 (0%)	
4. ITA	2	0 (0%)	0 (0%)	0 (0%)		0 (0%)	
5. others	3	1 (33%)	0 (0%)	1 (33%)		0 (0%)	
L. Induction Immunosupp.							
1. ALG/ATG/ALS	26	17 (65%)	8 (31%)	10 (38%)	1 vs 2 p=0.392	6 (23%)	1 vs 2 p=0.038
2. OKT3	17	12 (71%)	2 (12%)	5 (29%)	2 vs 3 p=0.567	0 (0%)	
3. no T-cell antibody	12	6 (50%)	0 (0%)	3 (25%)	1 vs 3 p=0.333	0 (0%)	1 vs 3 p=0.083
M. Site of Tx							
1. liver	46	32 (70%)	10 (22%)	17 (37%)	1 vs 2 p=0.244	6 (13%)	1 vs 2 p=0.574
2. others	9	3 (33%)	0 (0%)	1 (11%)		0 (0%)	
N. Common Charact. of Ins. Indep. Cases (see page 18)							
1. all four fulfilled	22	17 (77%)	10 (45%)	10 (45%)	1 vs 2 p=0.089	6 (27%)	1 vs 2 p=0.003
2. 1 not fulfilled	33	18 (55%)	0 (0%)	8 (24%)		0 (0%)	

P values comparing islet graft survival rates between groups at one year after transplantation were calculated by the one-sided (categories E, G, L, N) and by the two-sided (categories A-D, F, H-K, M) Fisher's exact test.

North Am.: North America; Rec.: Recipient; CIT: Cold Ischemia Time; IEQ: Islet Equivalents (no. of islets if all had a diameter of 150 μm)

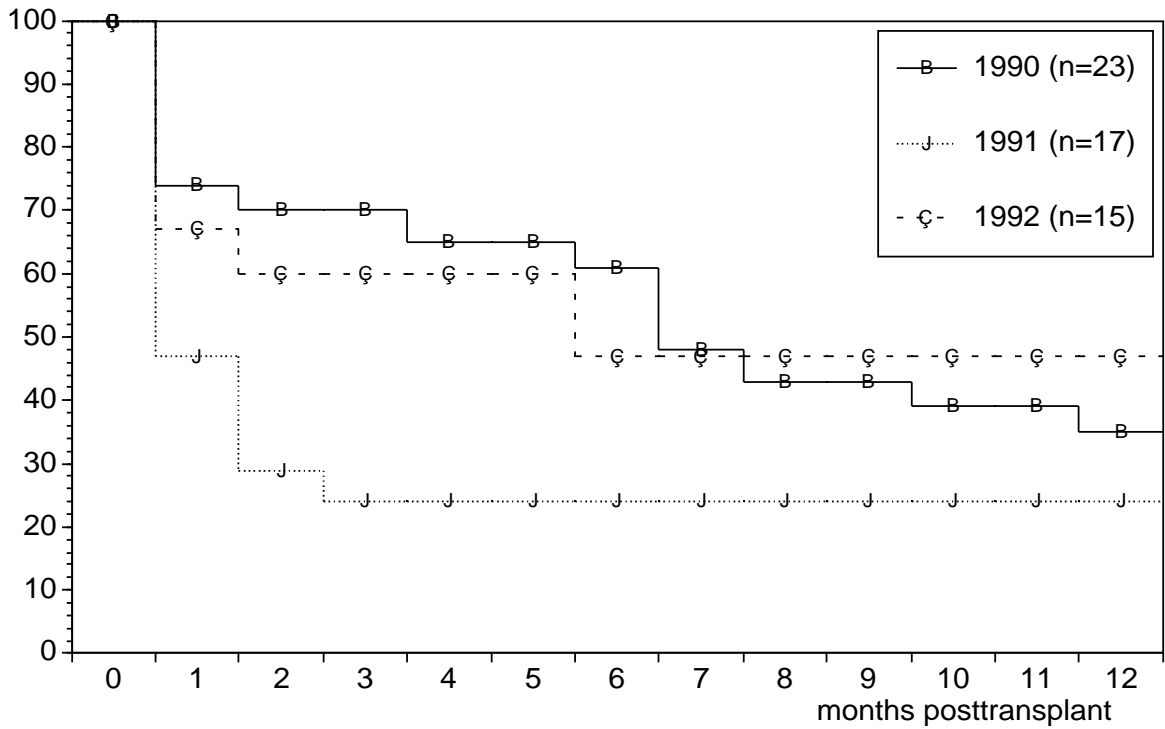
25 Single Donor Recipients in 1990-1992

Out of the selected 55 well-documented pre-tx C-peptide negative type-I diabetic patients transplanted from 1990 to 1992, 25 recipients received islets from a single donor, as given in F on page 10.

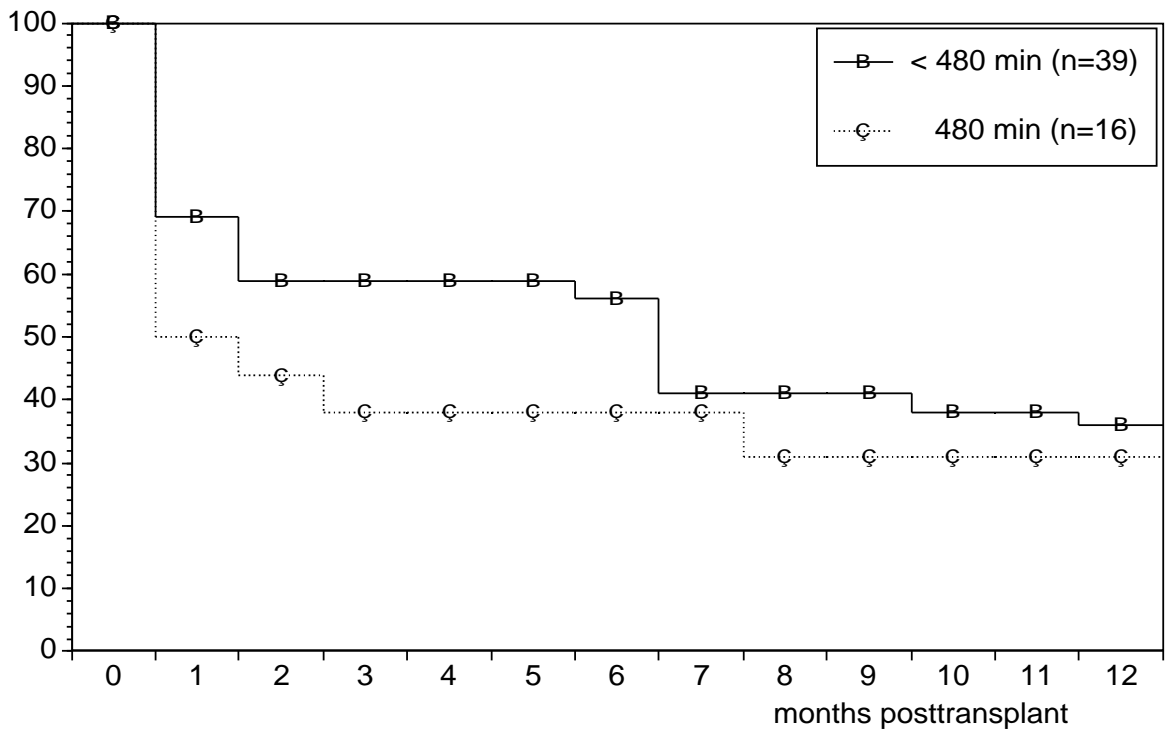
The impact of HLA MM (mismatches), sex compatibility and AB0 identity on islet allograft survival could - for obvious reasons - only be analyzed in these 25 single donor islet allograft recipients.

No. (Percentage) of Cases Functioning					
Category	n	at ≥ 1 Month		at ≥ 1 Year	
		Basal C-Peptide ≥ 1ng/ml	Insulin Indep. (>1wk)	Basal C-Peptide ≥ 1ng/ml	Insulin Indep. (>1wk)
All cases	25	14 (56%)	3 (12%)	7 (28%)	2 (8%)
A. ABDR MM					
0 - 2	5	3 (60%)	0 (0%)	1 (20%)	0 (0%)
3 - 4	6	5 (83%)	3 (50%)	4 (67%)	2 (17%)
5 - 6	7	3 (43%)	0 (0%)	1 (14%)	0 (0%)
no data	7	3 (43%)	0 (0%)	1 (14%)	0 (0%)
B. BDR MM					
0	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
1 - 2	7	4 (57%)	1 (14%)	1 (14%)	1 (14%)
3 - 4	10	6 (60%)	2 (20%)	4 (40%)	1 (10%)
no data	7	3 (43%)	0 (0%)	1 (14%)	0 (0%)
C. DR MM					
0	3	2 (67%)	0 (0%)	1 (33%)	0 (0%)
1	5	2 (40%)	2 (40%)	2 (40%)	2 (40%)
2	9	6 (67%)	1 (11%)	3 (33%)	0 (0%)
no data	8	4 (50%)	0 (0%)	1 (13%)	0 (0%)
D. Sex Compa- tibility					
1. yes	11	8 (73%)	2 (18%)	4 (36%)	1 (9%)
2. no	7	4 (57%)	1 (14%)	2 (29%)	1 (14%)
3. no data	7	2 (29%)	0 (0%)	1 (14%)	0 (0%)
E. AB0 Identity					
1. yes	18	11 (61%)	3 (17%)	5 (28%)	2 (11%)
2. no	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
3. no data	6	2 (33%)	0 (0%)	1 (17%)	0 (0%)

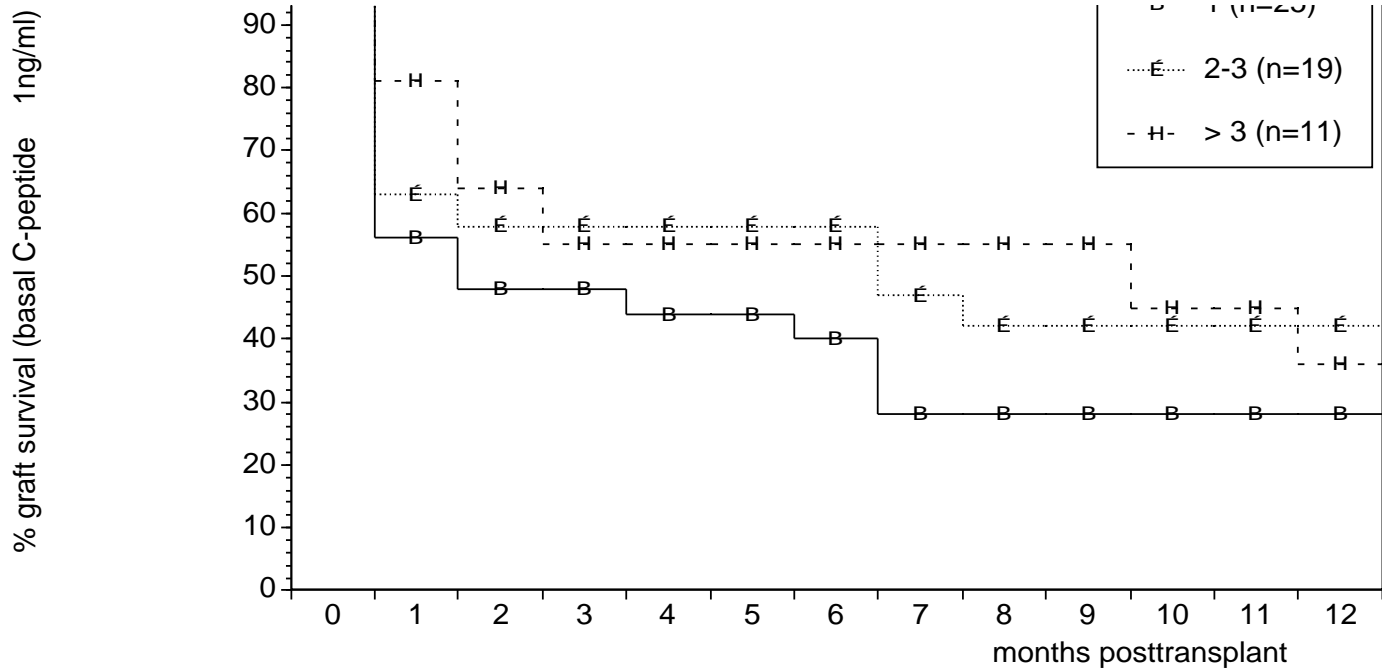
**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Year of Tx**



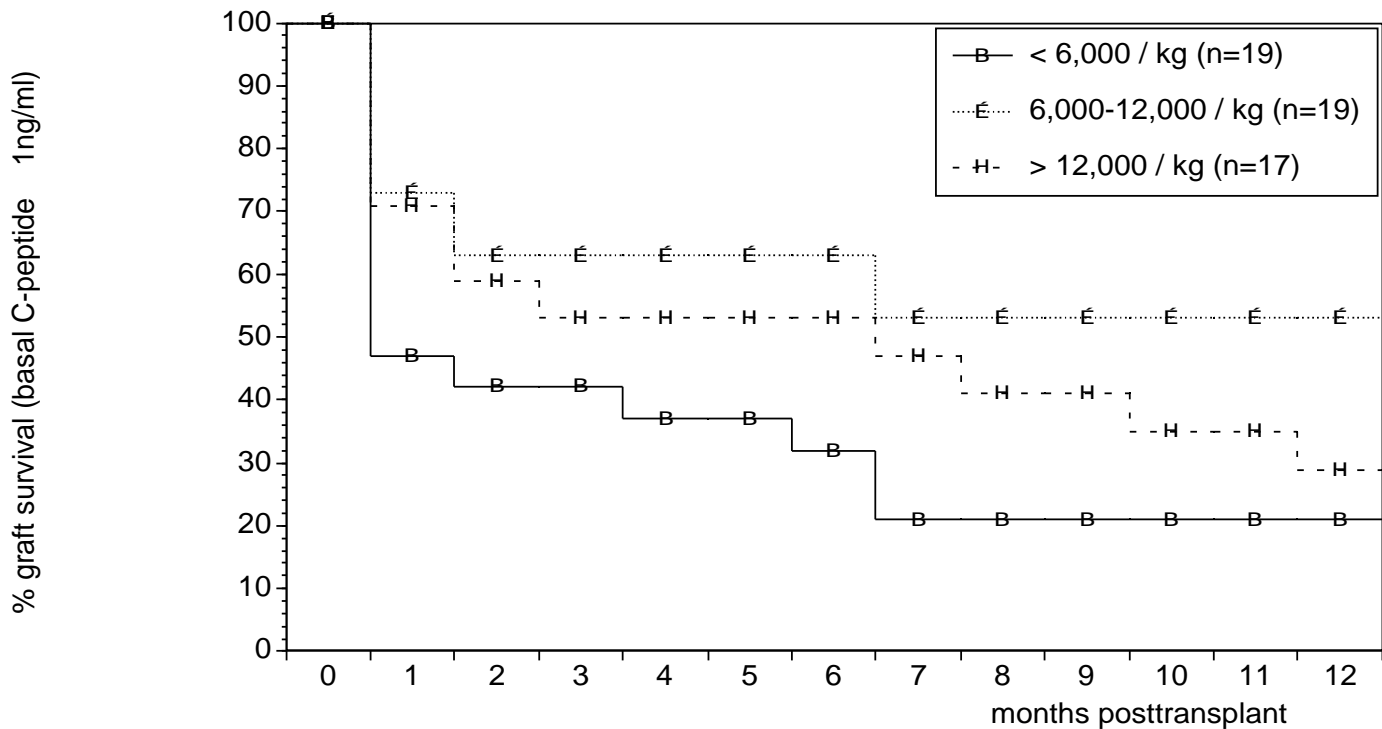
**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Mean Cold Ischemia Time**



**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
No. of Donors**

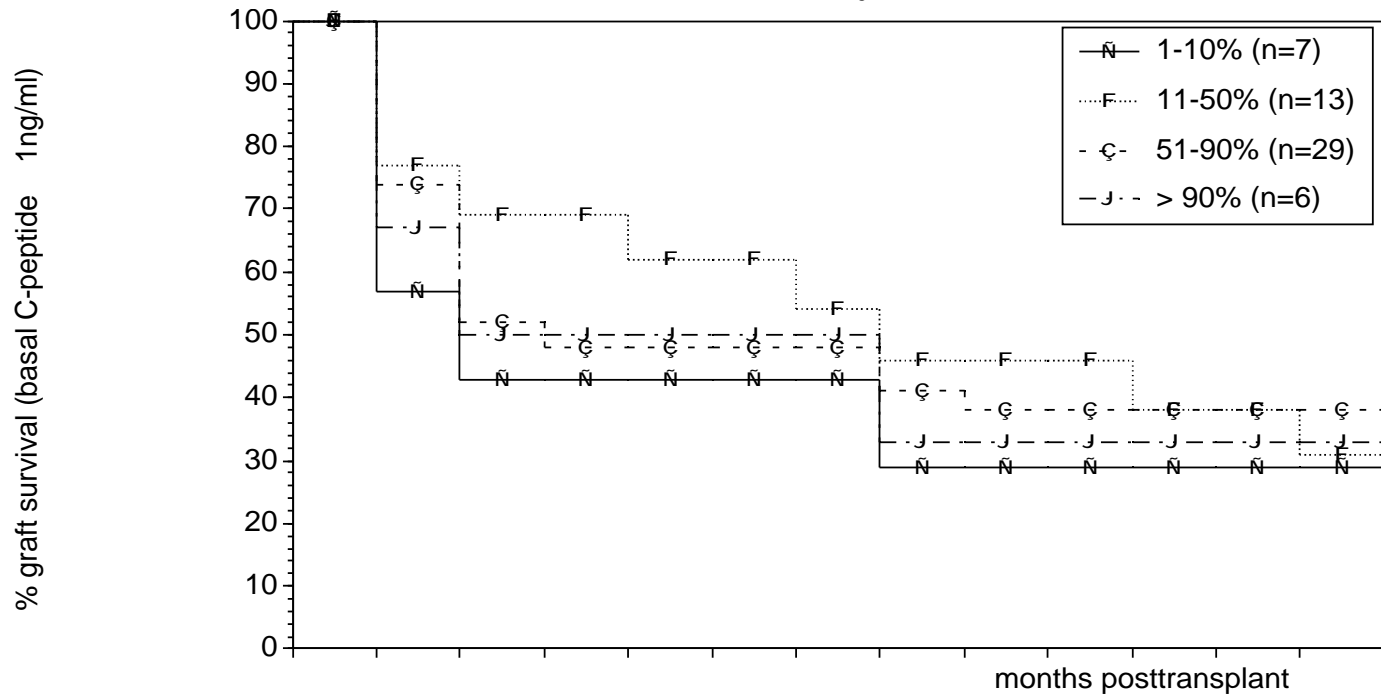


**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
IEQ* per kg Bodyweight**

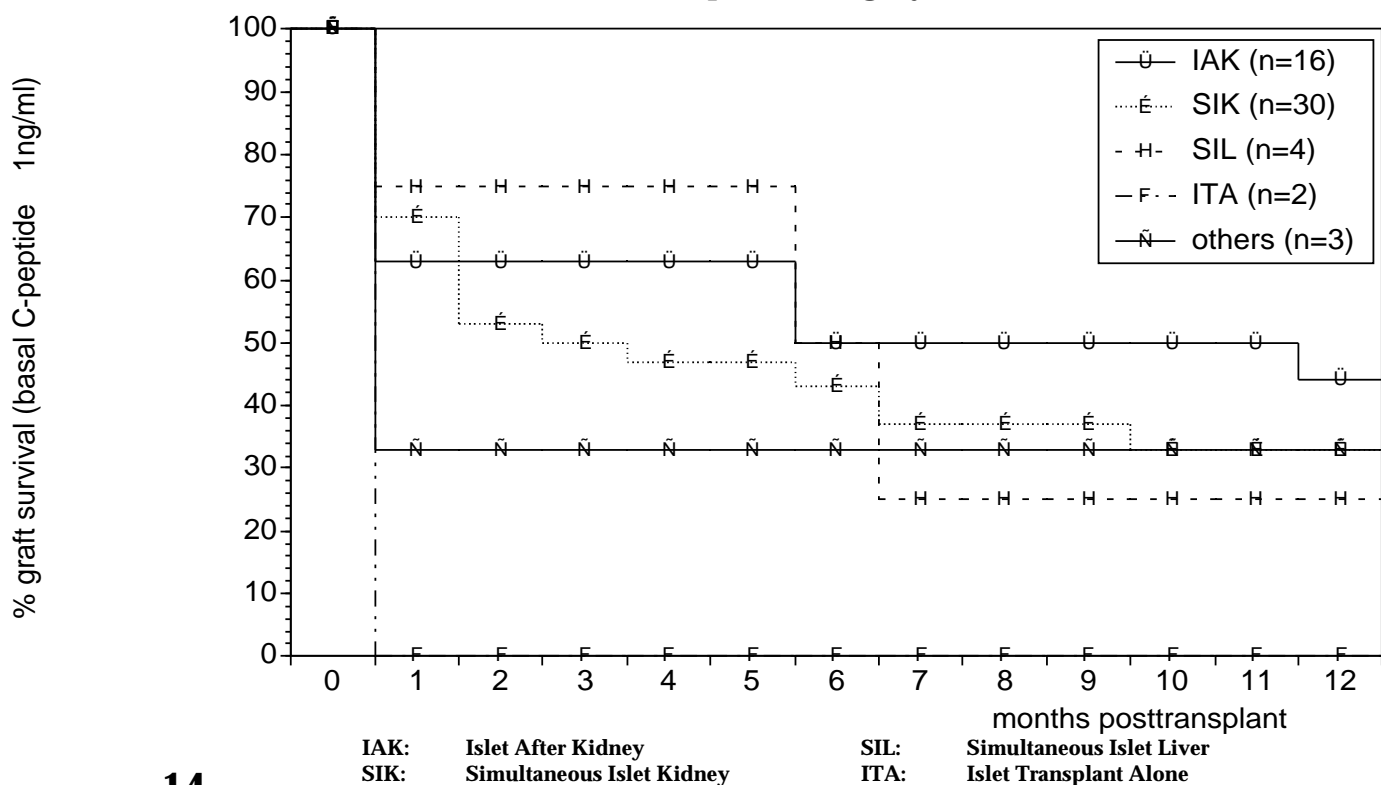


* IEQ: islet equivalents (no. of islets if all had a diameter of 150 μm)

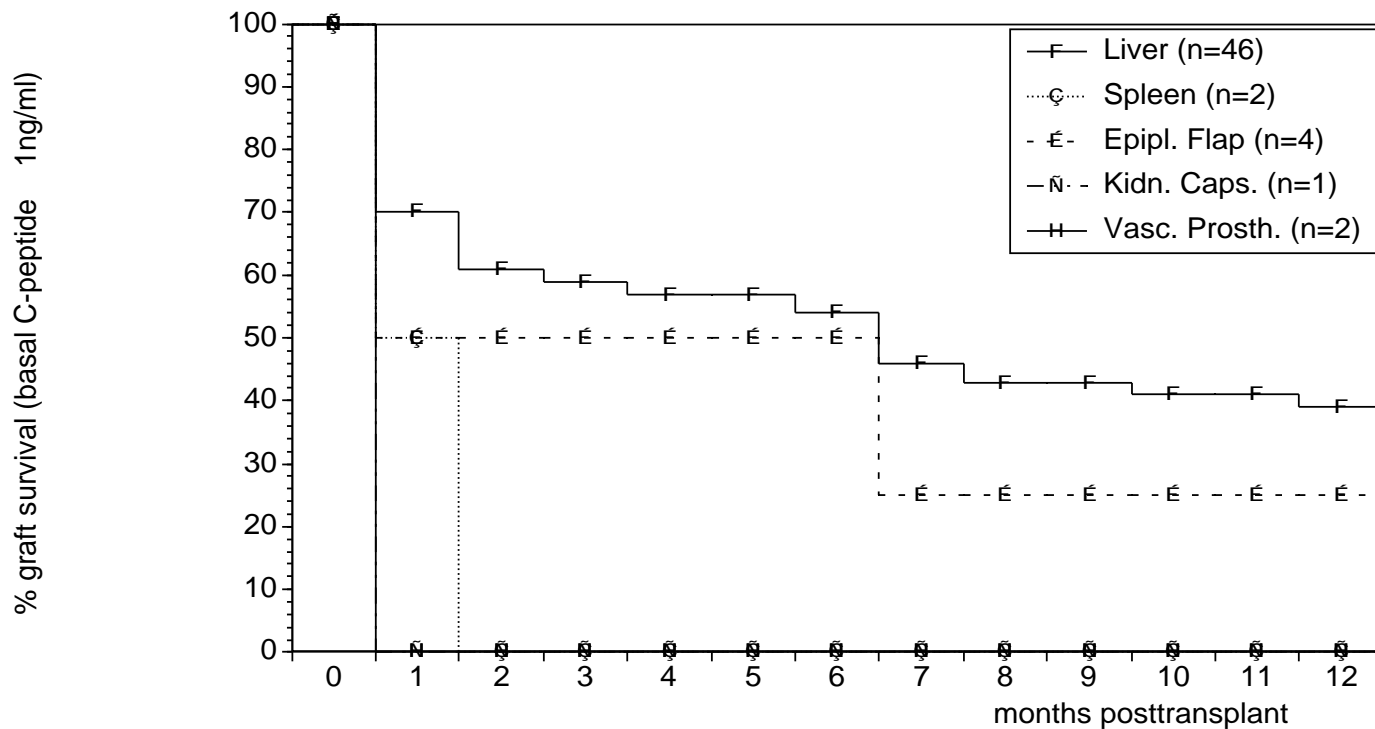
**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Islet Purity**



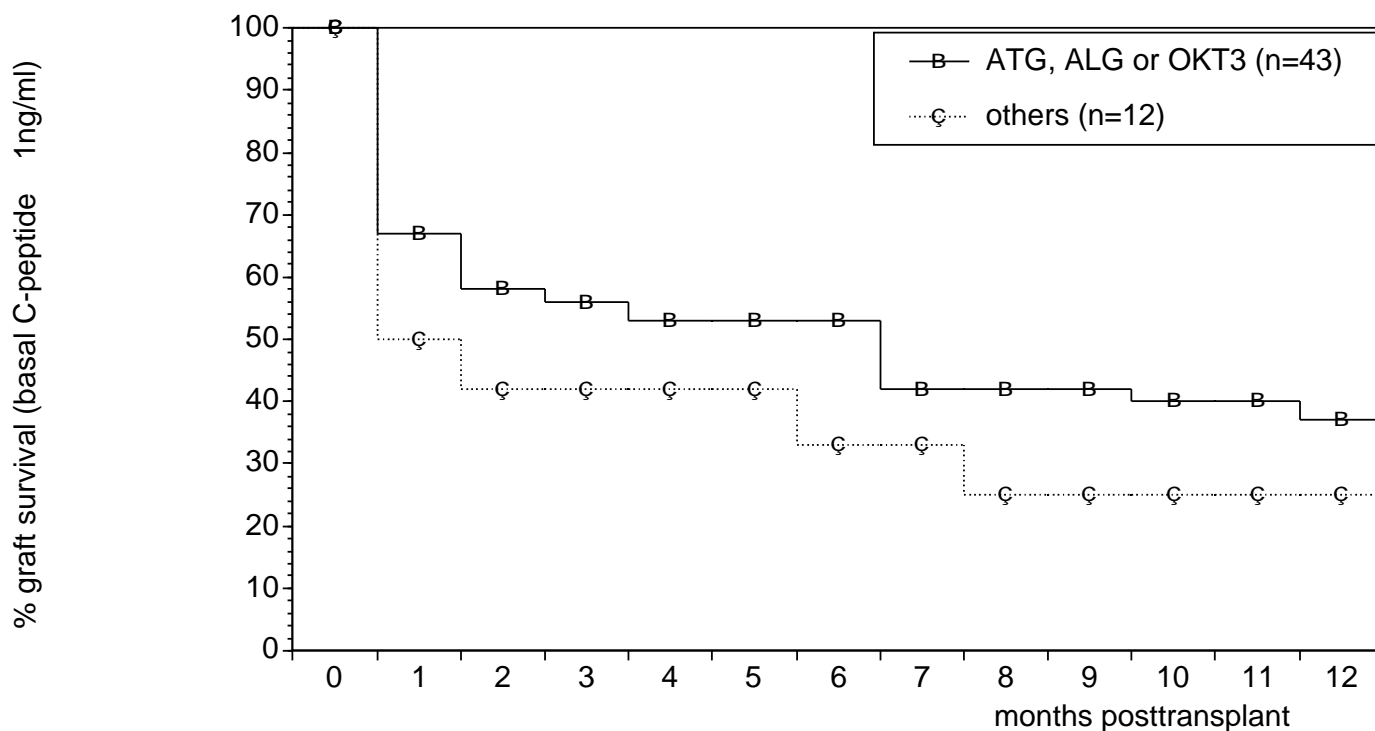
**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Recipient Category**



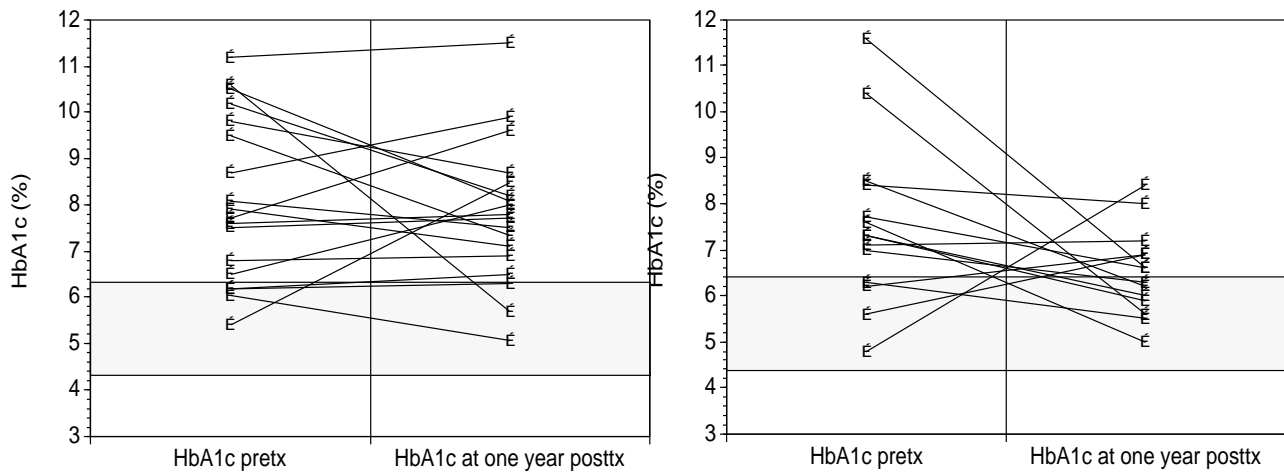
**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Site of Tx**



**One-Year Islet Allograft Survival
in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to
Induction Immunosuppression**



HbA1c before and One Year After Adult Islet Allotransplantation according to Basal C-Peptide Levels*



* HbA1c levels both before and one year after islet transplantation were available only in 32 out of 55 pretransplant C-peptide negative type-I diabetic patients transplanted from 1990-92 (see page 9)

The Insulin-Independent Cases

The Zurich Case (Transplantation 29: 76-77, 1980)

A 32-yr-old uremic patient, who had insulin-dependent diabetes for 22 years, received simultaneously with a kidney transplant an intrasplenic injection of pancreatic microfragments from a 2.5-yr-old totally histoincompatible donor. Immunosuppression was induced with antilymphocyte globulin, cyclophosphamide, azathioprine, and prednisone. Exogenous insulin therapy was stopped at 9 months posttransplant, and the patient remained insulin independent until shortly before her sudden death 20 months after transplantation. Unfortunately, pre- and postoperative C-peptide data were not reported in this remarkable case to clearly document the preoperative insulin-dependent status and the posttransplant islet function. Nevertheless, the Zurich patient, transplanted in 1979, displayed special aspects such as the simultaneously transplanted kidney, the use of T-cell antibodies for induction immunosuppression, and the potentially long interval between the time of transplant and the begin of the insulin-independent state. These aspects should prove to be important characteristics of islet allograft recipients who became insulin independent in 1989 or later.

Insulin Independence After Simultaneous Liver and Adult Islet Transplantation Summary of Cases through Dec 31, 1993

Institution	Year of Tx	No. of Donors	IEQ ¹ x 1000	Site of Tx	Period of Insulin Independence Post Tx	Comments
Paris	1988	1	150 ²	epiploic flap	month 7 - 49	hemochromatosis
Paris	1990	1	250 ²	epiploic flap	day 1 - 8	type-I diabetes
Pittsburgh	1990	1	474	liver	month 2 - > 42 ³	simult. islet, liver and kidney tx; CMV inf.
Pittsburgh	1990	1	289	liver	month 2 - 4	cluster tx/FK 506 ⁵
Pittsburgh	1990	2	578	liver	month 2 - 15	cluster tx/FK 506
Pittsburgh	1990	2	258	liver	month 5 - 15	cluster tx/FK 506
Pittsburgh	1990	1	285	liver	month 3 - 10	cluster tx/FK 506 ⁵
Pittsburgh	1990	2	726	liver	month 2 - 20	cluster tx/FK 506 ⁵
Pittsburgh	1990	2	332	liver	month 1 - 15	cluster tx/FK 506 ⁵
Milan	1992	2	830	liver	month 2 - 14	residual C-peptide secretion pre tx
Verona	1993	1	325	liver	month 2 - > 8 ⁴	type-I diabetes, marked pre-tx basal C-peptide

1) IEQ = islet equivalents 2) number of islets 3) as of June 10, 1993 4) as of March 14, 1994 5) died off insulin

Insulin Independence After Adult Islet Transplantation into Type I Diabetic Patients Summary of Cases through Dec 31, 1993

Institution	Year of Tx	No. of Donors		IEQ* x 1000	Islet Purity	Site of Tx	Type of Tx	HLA Match		Induction- Immunosuppression	Period of Insulin Independence Post Tx	Glucose Control †
		Fresh	Cryo					AB	DR			
St. Louis	1989	1.4	-	785		p.v. ^Δ	IAK*	1/3	2/1	ALG (+M-Pred)	day 10 - 25	i.v. Insulin
St. Louis	1990	1	+ 2	550+555	98%	p.v. ^Δ	IAK*	1/2/2	1/1/0	ALG (+M-Pred)	day 33 - 341	i.v. Insulin
St. Louis	1993	1	+ 7	1,354	90%	p.v. ^Δ	SIK*	2 (fresh)	1 (fresh)	OKT3 (CsA+AZA+Pred)	day 92 - > 210 #	i.v. Insulin
Edmonton	1990	1	+ 4	243+368	70%	p.v. ^Δ	SIK*	3 (fresh) 1/0/2/0	0 (fresh) 0 (cryo)	ALG (+M-Pred, AZA, CsA at day 10)	day 69 - 821	i.v. Insulin
Edmonton	1992	1	+ 5	284+308	55%	p.v. ^Δ	SIK*	3 1/0/0/1/0	1 (fresh) 1/1/0/0/1 (cryo)	ALG (+M-Pred, AZA, CsA at day 8)	day 155 - 166	i.v. Insulin
Milano	1990	1	-	592	95%	p.v. ^Δ	IAK*	1	0	ALG (+M-Pred, CsA, AZA)	day 120 - 330	i.v. Insulin
Milano	1990	2	-	482	75%	p.v. ^Δ	IAK*	1/2	1/0	ALG (+M-Pred, CsA, AZA)	day 60 - 1,178	i.v. Insulin
Milano	1991	1	+ 2	453+370	80%	p.v. ^Δ	SIK*	ND	ND	ALG (+M-Pred, CsA, AZA)	day 210 - 360 + day 480 - 635	i.v. Insulin
Milano	1992	2	-	613	80%	p.v. ^Δ	IAK*	ND	ND	ALG (+Pred, CsA, AZA)	day 150 - > 545 #	i.v. Insulin
Miami	1990	3	-	1,122	55%	p.v. ^Δ	IAK*	0/2/0	1/1/0	OKT3 (+M-Pred, CsA, AZA)	day 42 - 78	i.v. Insulin
Miami	1990	3	-	1,209	50%	p.v. ^Δ	IAK*	0/0/0	0/1/0	OKT3 (+M-Pred, CsA, AZA)	day 87 - 125	i.v. Insulin
Mnpls	1992	1	-	536	1%	p.v. ^Δ	SIK*	1	1	ALG (+Pred+CsA+DSG)	day 326 - > 753 #	i.v. Insulin
Mnpls	1992	1	-	626	1%	p.v. ^Δ	SIK*	2	0	ALG (+Pred+CsA+DSG)	day 123 - 231	i.v. Insulin
Giessen	1992	1	-	351	92%	p.v. ^Δ	IAK*	2	1	ATG (+M-Pred+CsA)	day 400 - > 473 #	i.v. Insulin

* IEQ: Islet Equivalents (no. of islets if all had a diameter of 150 μm)
 IAK: Islet After Kidney
 SIK: Simultaneous Islet and Kidney

Δ portal vein
 † in the early posttransplant period
 # as of March 14, 1994

Common Characteristics of Insulin-Independent Cases

It is evident that many unknown factors might have operated in the type-I diabetic recipients listed on page 17 who became C-peptide positive and insulin independent following adult islet allotransplantation.

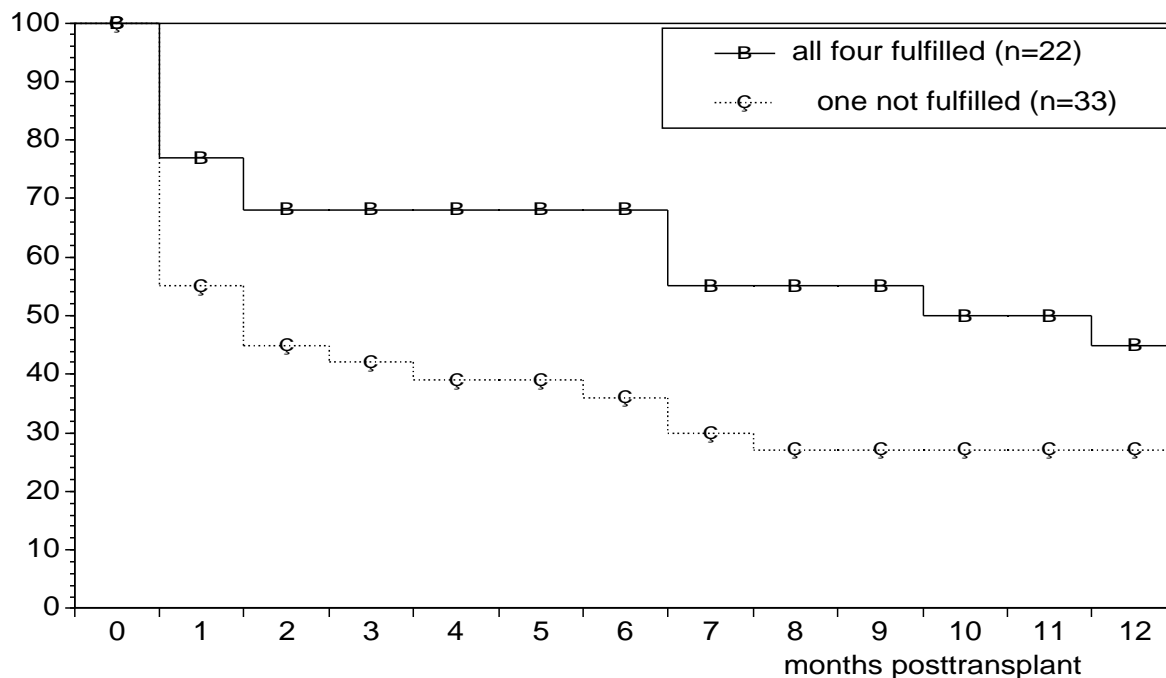
However, four common characteristics can be identified when the individual protocols that have been applied in these successful cases are being compared.

These four common characteristics are as follows:

1. Mean preservation time of the donor pancreas (pancreata): < 8 h
2. Islet mass: 6,000 IEQ / kg
3. Implantation site: liver via portal vein
4. Induction immunosuppression: ALG/ALS/ATG or OKT3.

When all four criteria were met, the number (percentage) of patients who had basal C-peptide 1 ng/ml and who were insulin independent at one year posttransplant was 10 (45%) and 6 (27%) in contrast to 8 (24%) and 0 (0%, $p=0.003$), respectively, when at least one criterion was not fulfilled (see page 10 and this page).

One Year Islet Allograft Survival in 55 Pre-Tx C-Peptide Negative IDDM Recipients (1990-92 Cases) according to Common Characteristics



No. of Adult Islet Allografts according to Institution in 1993

	93
• Giessen	6
• Homburg	1
• Los Angeles I	1
• Los Angeles II	1
• Madrid	1
• Miami	1
• Milan	4
• Minneapolis	5
• Oxford	1
• Pittsburgh	3
• St. Louis	4
• Verona	1
Σ	29

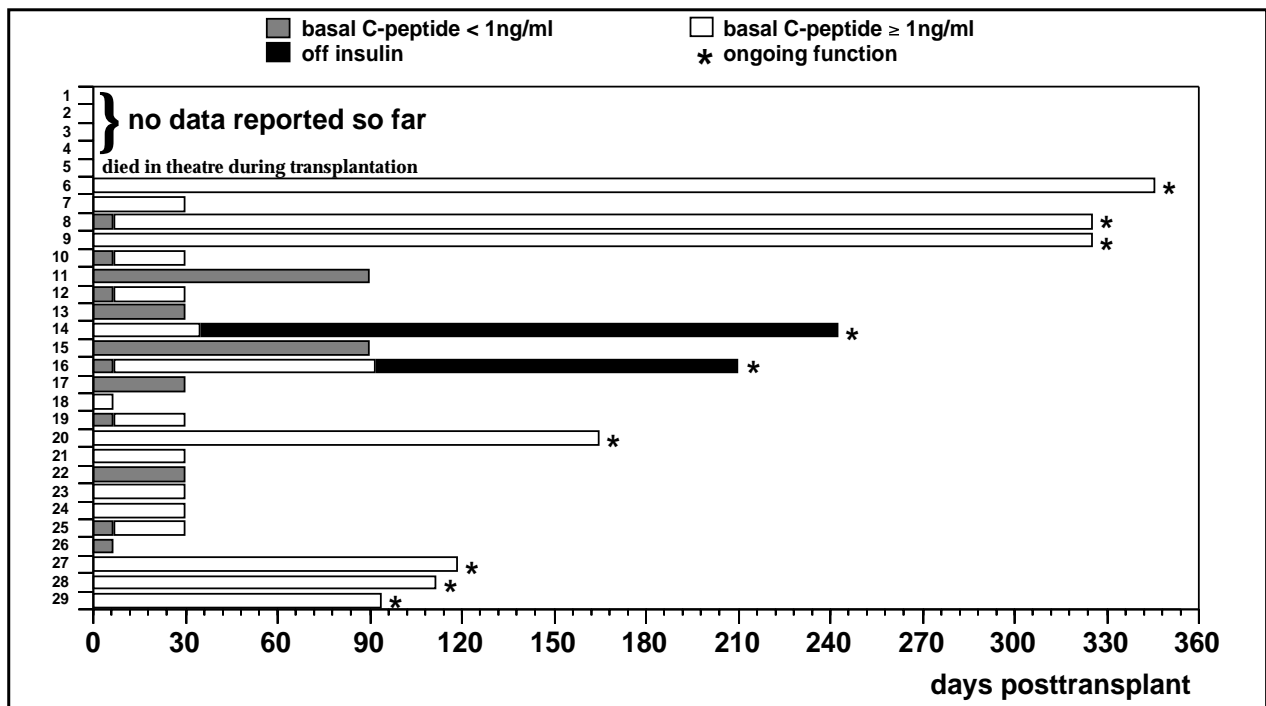
The Year 1993 (and 1994)

The number of adult islet allografts performed in 1993 did not increase compared with previous years (see pages 5, 8 and this page).

The outcome as assessed by basal C-peptide and insulin independence is demonstrated below. We hope that the missing forms on four patients as well as updated follow-up forms on the other patients will be provided soon in order to be able to provide you with current trends in the field of clinical islet transplantation.

In 1994, adult islet allografts have so far been reported from Edmonton, Giessen, Milan, and Omaha.

Course of 29 Patients Being Transplanted in 1993



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When the responsibility for the islet component was transferred to Giessen in 1989 the reports to the International Pancreas Transplant Registry (IPTR) were graciously passed on to the ITR by Dr. David E.R. Sutherland and Kay C. Moudry-Munns.

¹ Centers that had reported to the IPTR before 1989 only

² Centers that had reported to both the IPTR and the ITR until 1989

³ Centers reporting to the International Islet Transplant Registry since 1989



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