TRANSPLANTATION IN DIABETIC PATIENTS

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- Diabetes is the pandemic of the new millennium
- 24 million diabetics (17.5 million diagnosed)
- Diabetes is the most common cause of ESRD in the U.S
  Diabetes 40%, Chronic GN 22%, HTN 20%
- Mortality of diabetics on dialysis
  Annual death rate 10.8% DM vs. 4.3% non-DM
  3 year survival 56% HTN, 69% GN, 78% PCKD, 39% DM
- DM is the leading cause of blindness in adults, number one cause of amputations and impotence and ranks among the leading chronic diseases of childhood.
- DM accounts for more than 170,000 deaths per year.
- Total cost= $ 174 billion.
- Average expenditure per person: $ 11.744 / year.

Pancreas Transplantation

- **Why do we need it?**
- **How do we do it?**
- **What are the current results?**
- **What is good, what is not so good about it?**
- **What are some of the unresolved issues for the future?**

Pancreas transplantation is the only treatment presently available for patients with Type I diabetes that establishes both insulin independence and sustained normoglycemia which in turn is associated with beneficial effects on the secondary complications of diabetes as well as improving the quality of life.

Pancreas Transplantation: Long-term mortality

Actual 10-yr pt survival, transplanted 1981-88

- **SPK** **65%**
- **SPK, pancreas failed < 2 yrs** **33%**
- **Diabetic KTA** **37%**
- **Nondiabetic, KTA** **72%**

Tyden, Clin Transpl, 2000.

Life Expectancy: SPK vs KTA

Group	Period	N	Pt survival	
Becker	1986-1995	335 SPK	85%	Annual Mort
		160 LDKTA	66%	1.5, 3.7, 6.3
		147 CADKTA	50%	**10 yr**
Reddy	1987-1996	4602 SPK	72%	
		3991 LDKTA	72%	**8 yr**
		9956 CADKTA	55%	
Ojo	1988-1997	4718 SPK	67%	Life Expect
		671 LDKTA	65%	23.4 yrs
		4127 CADKTA	46%	after SPK
				10 yr

Twelve-Month Pancreas Graft Function Significantly Influences Survival Following Simultaneous Pancreas-Kidney Transplantation

Andrew S. Weiss, Gerard Smits, and Alexander C. Wiseman
University of Colorado Health Sciences Center, Aurora, CO

Six year patient and kidney graft survival in patients with and without a functioning pancreas graft compared to living donor or deceased donor kidney transplantation

12 Month Survivors	84 Month Kidney Graft Survival %	P value	84 Month Patient Survival %	P value
SPK, P+ (6486)	72.0	---	88.6	---
SPK, P- (371)	59.8	< 0.001	73.9	< 0.001
DD KA (520)	49.7	< 0.001	64.8	< 0.001
LD KA (904)	63.6	0.015	80.0	< 0.001

Clin J Am Soc Nephrol 4: 988-995, 2009

Purpose of Pancreas Transplantation

- Restore endogenous insulin production and improve counter-regulation
- Normalize glucose homeostasis and metabolism at systemic and cellular levels (avoid hyper/hypoglycemia)
- Render patient insulin-free
- Improve quality of life and life expectancy
- Prevent, halt, slow, or reverse secondary diabetic (microvascular) complications

Pancreas Transplantation

- Simultaneous kidney-pancreas transplant (SPK)
- Pancreas after kidney transplant (PAK)
- Pancreas transplant alone (PTA)
- IDDM with CRF (CrCl <40 mg/dl
- IDDM with functioning kidney transplant, e.g. living donor
- IDDM, extremely brittle, poor metabolic control

Pancreas Transplantation

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Donor selection – Inclusion criteria

- Declaration of brain death, informed consent
- Age, 6 - 55 (ideal 10 - 45 years)
- Weight, 30 – 100 (ideal 30 – 80 kg)
- Hemodynamic stability with adequate perfusion
- Normal glycosylated hemoglobin levels (if there is hyperglycemia, obesity, family history of DM)
- Absence of infection or transmissible disease (tb, syphilis, hepatitis, HIV)
- Negative serology (HIV; Hepatitis A,B,C; VDRL/RPR)
- Absence of malignancy (unless skin or low grade brain Ca)
- Absence of pancreatic disease

Donor selection – Exclusion criteria

- h/o diabetes mellitus (type I or II)
- Previous pancreatic surgery, pancreatic trauma
- Pancreatitis (active, acute or chronic)
- Intraabdominal contamination
- Major (active) infection
- Chronic alcohol abuse, h / o I.V drug use
- Weight (> 150% ideal body weight)
- Severe atherosclerosis
- Prolonged hypotension or hypoxemia with evidence of significant end-organ (liver, kidney) damage
- Massive transfusions, prior splenectomy, extreme obesity, abnormal anatomy (relative contraindications)

Good Pancreas

Bad Pancreas

Recipient Inclusion Criteria

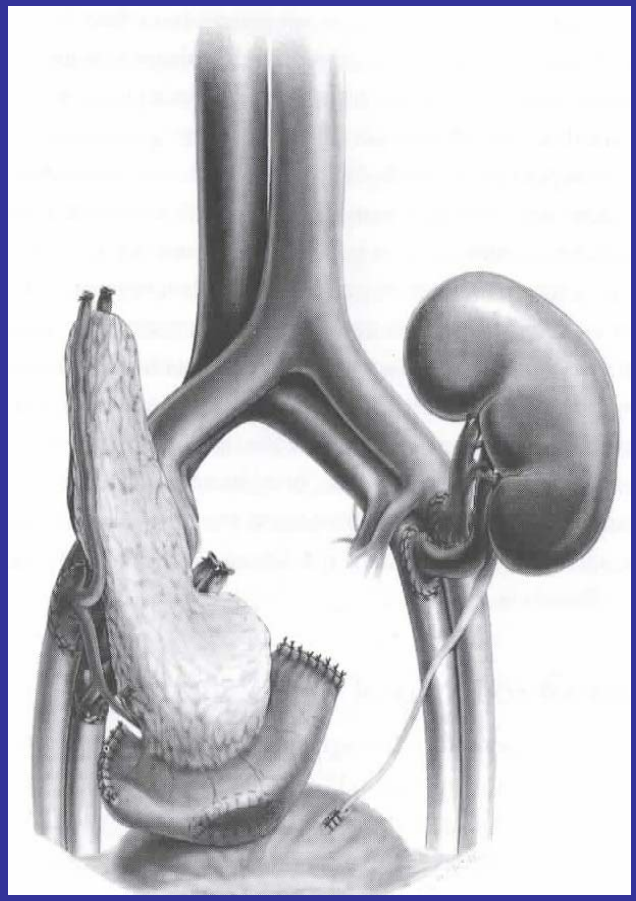
- IDDM documented by absence of circulating C-peptide.
- The predicted ability to tolerate surgery, immunosuppressives, and complications.
- Labile diabetes and failure of medical management, progressive secondary complications of diabetes (neuropathy, retinopathy)
- Age 18 – 60, Sufficient cardiac reserve
- Psychosocial and emotional suitability
- Thorough understanding of the risks and benefits
- Absence of exclusion criteria
- Microalbuminuria with a CrCl < 60 ml/min or proteinuria with projected requirement for dialysis or established ESRD (SKP)

Recipient Exclusion Criteria

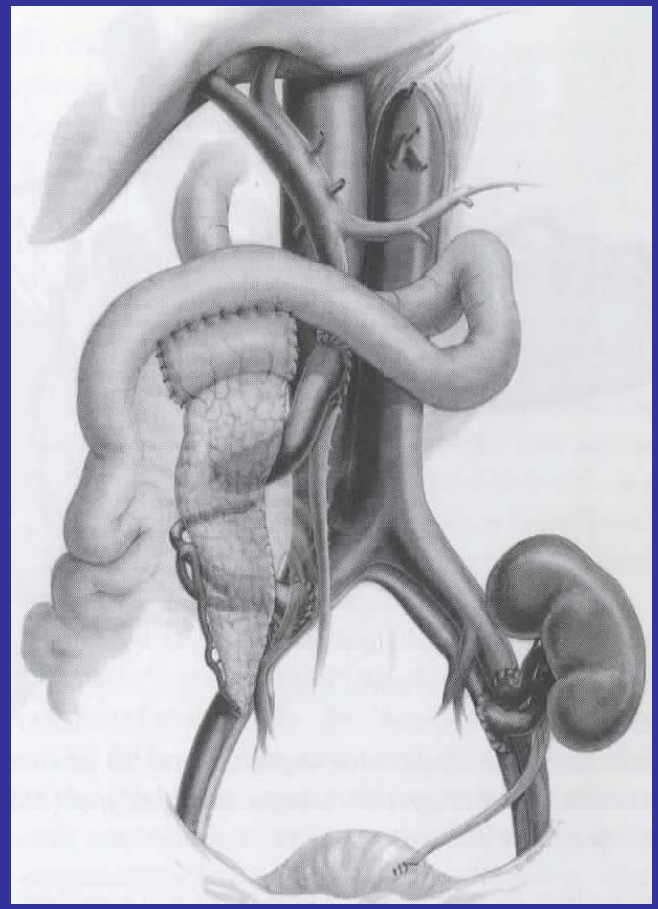
- Insufficient cardiovascular reserve
  - a) Angiographic evidence of noncorrectable CAD
  - b) Ejection fraction < 40%
  - C) Recent myocardial infarction
- Ongoing substance abuse (drug or alcohol)
- Ongoing psychiatric illness or recent history of noncompliance
- Active infection or malignancy
- Lack of well-defined diabetic complications (retinopathy, peripheral or autonomic neuropathy, microangiopathy)
- Extreme obesity (> 130% ideal body weight)
- Inability to understand the therapeutic nature of PTx.

Reperfused pancreas

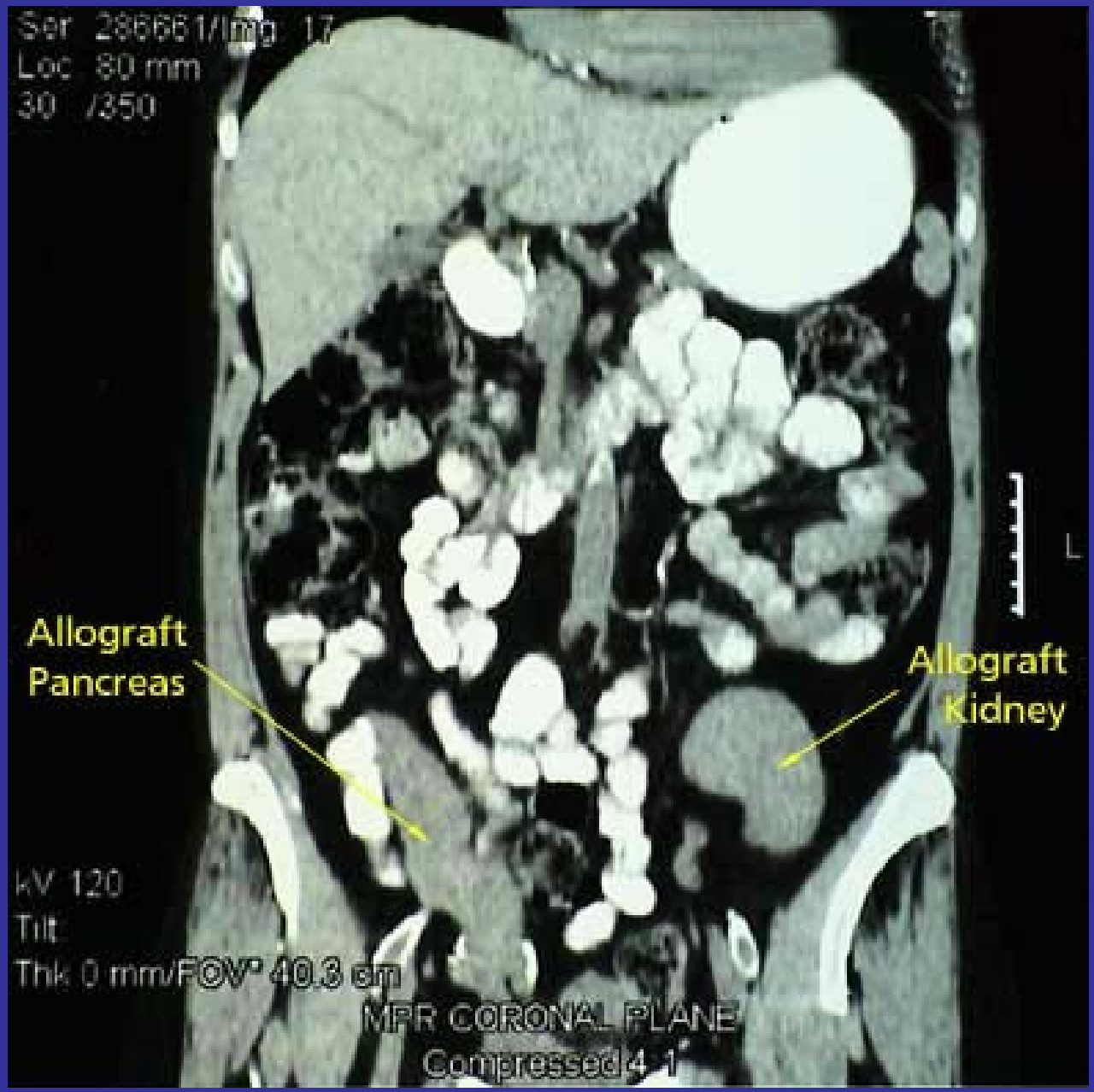
Modern Methods for Exocrine Drainage of a Pancreas Allograft



Duodenocystostomy
~20% SPK, ~50% Solitary



Duodenoenterostomy
~80% SPK, ~50% Solitary


Ser 286661/Img 17
Loc 80 mm
30 /350
Allograft
Pancreas
Allograft
Kidney
L
kV 120
Tilt
Thk 0 mm/FOV* 40.3 cm
MPR CORONAL PLANE
Compressed 4:1

Immunosuppression

- A quadruple drug regimen including antibodies (thymo, ATGAM, simulect, ALG, OKT3), Calcineurin inhibitors (cyclosporine, prograf), cell cept and steroids has been the back bone.

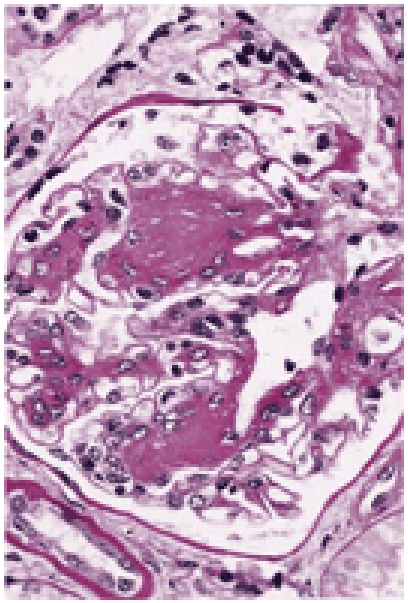
- Antibody therapy is started intraoperatively and continued 5-10 days postoperatively

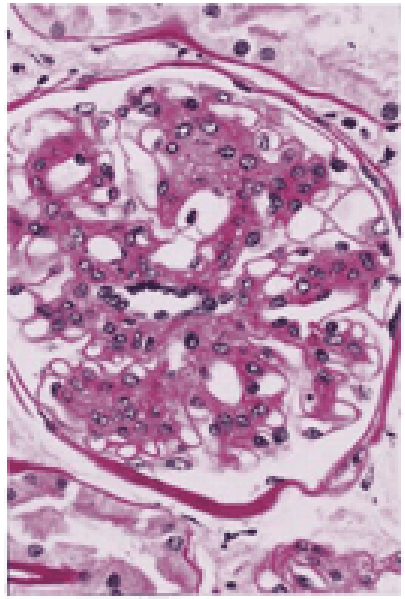
- Acute rejection is treated with high dose steroids and antibodies (thymo, OKT3)

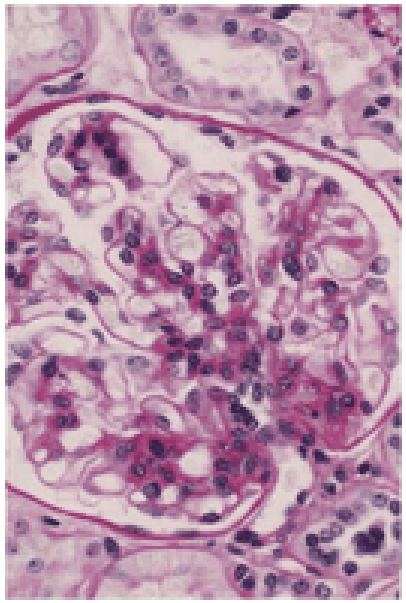
- Maintenance immunosuppression is with CI (CyA or prograf), prednisone and cell cept

Renal biopsy specimens obtained before and after pancreas transplant from a 33 year old woman with Type I Diabetes of 17 years

A – Diffuse and nodular (Kimmelstiel-Wilson) diabetic glomerulopathy
B – 5 years after transplant. Persistence of diffuse and nodular lesions.
C – 10 years after transplant. Marked resolution of diffuse and nodular mesangial lesions and open glomerular capillary lumina

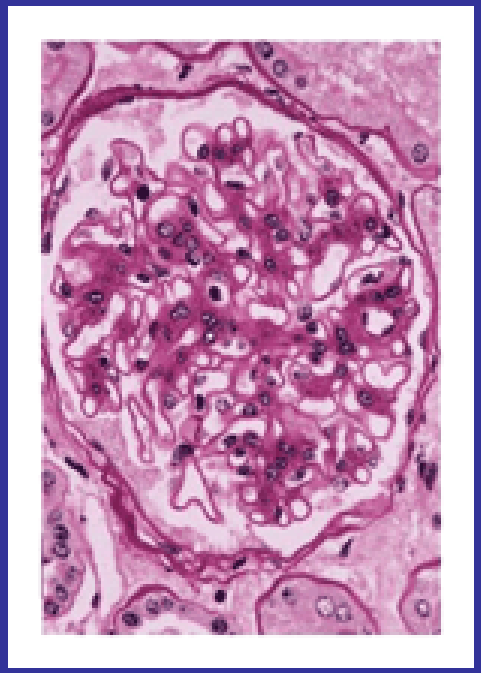


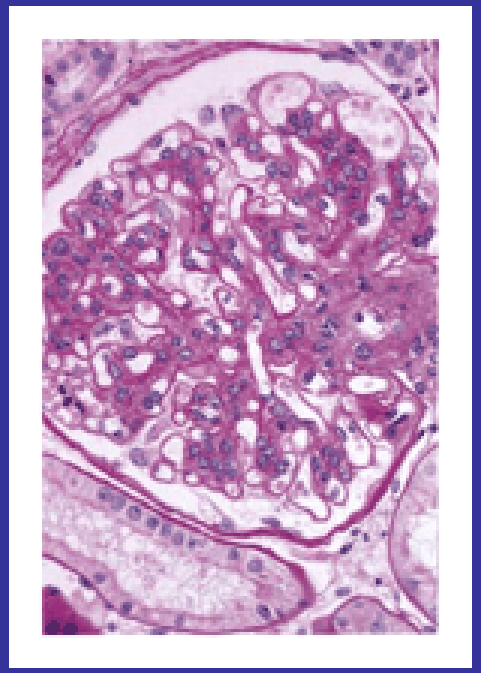


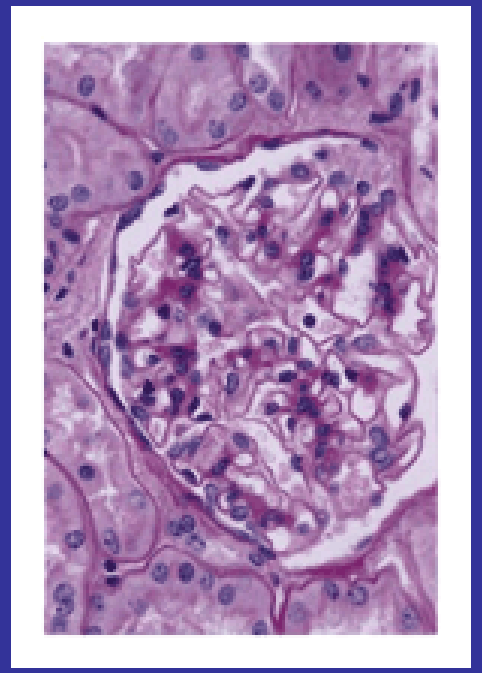


Renal biopsy specimens obtained before and after Pancreas Transplantation from a 31 year old woman with Type I diabetes of 27 year duration at the time of transplant.

A – A typical glomerulus with mild, diffuse mesangial expansion.
B – 5 years after transplant. Persistence of diffuse mesangial expansion.
C – 10 years after transplant. Reversion to nearly normal glomerular architecture.







Pancreas Transplantation.

- Why do we need it?
- How do we do it?
- What are the current results?
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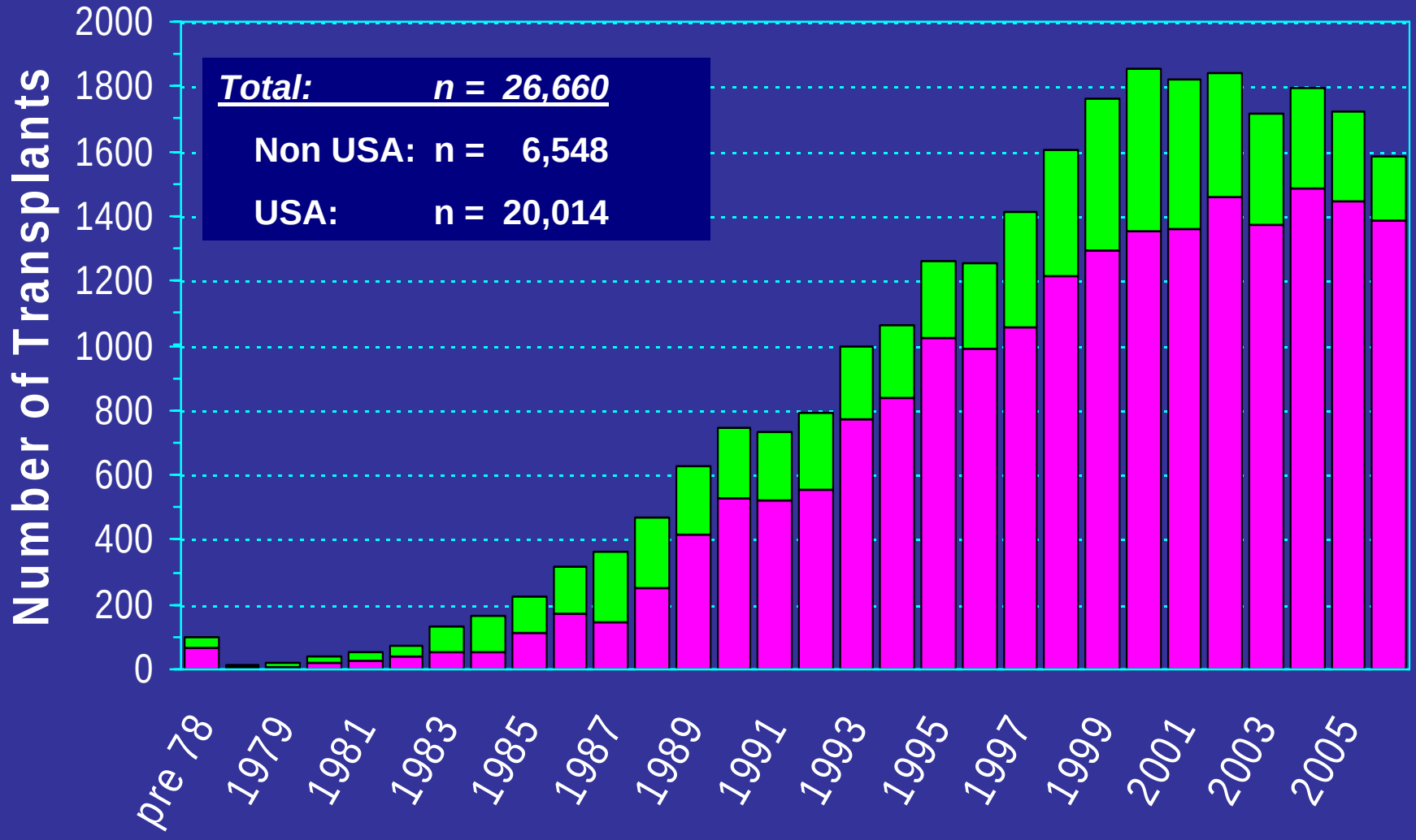
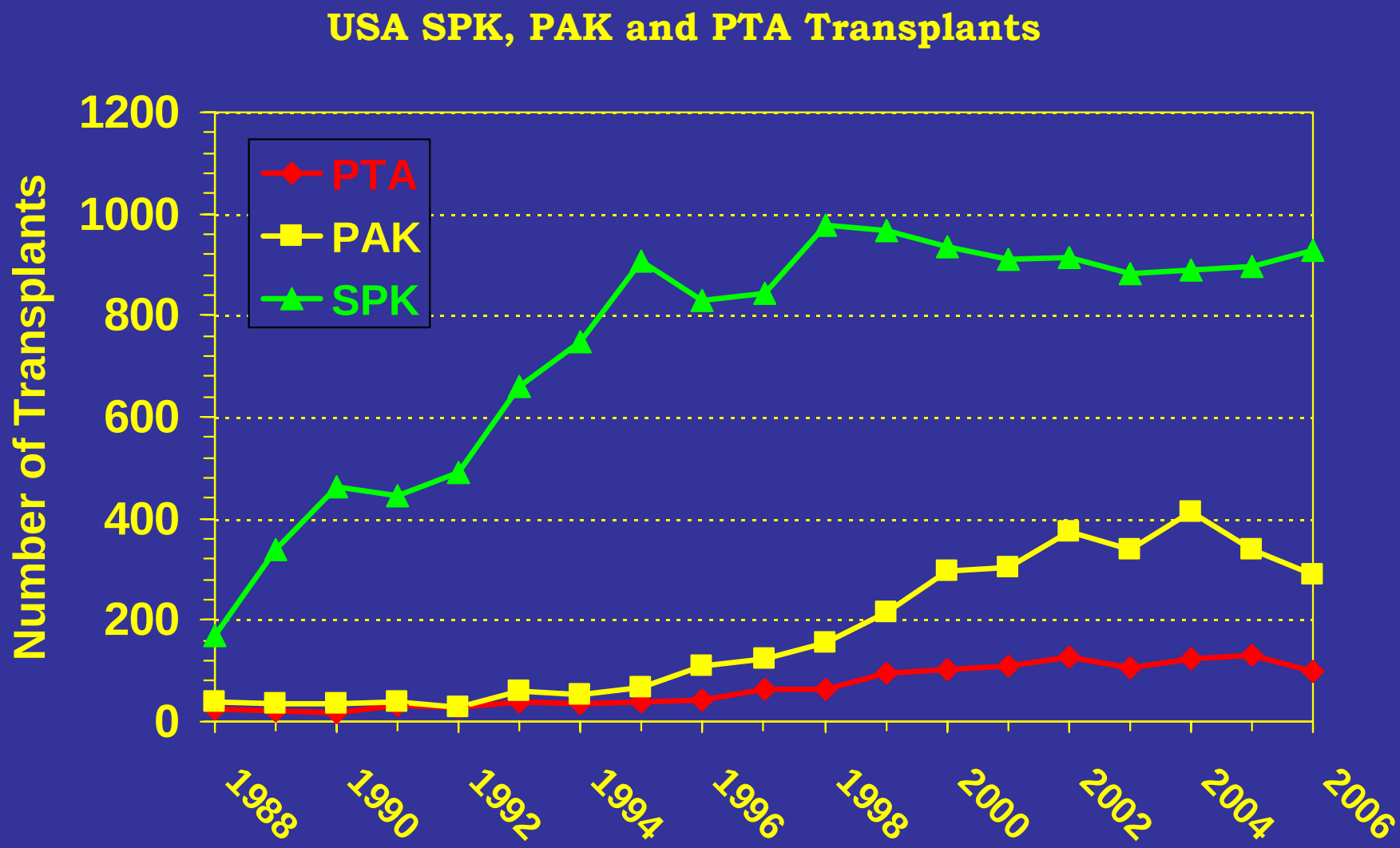
Pancreas Transplants Worldwide

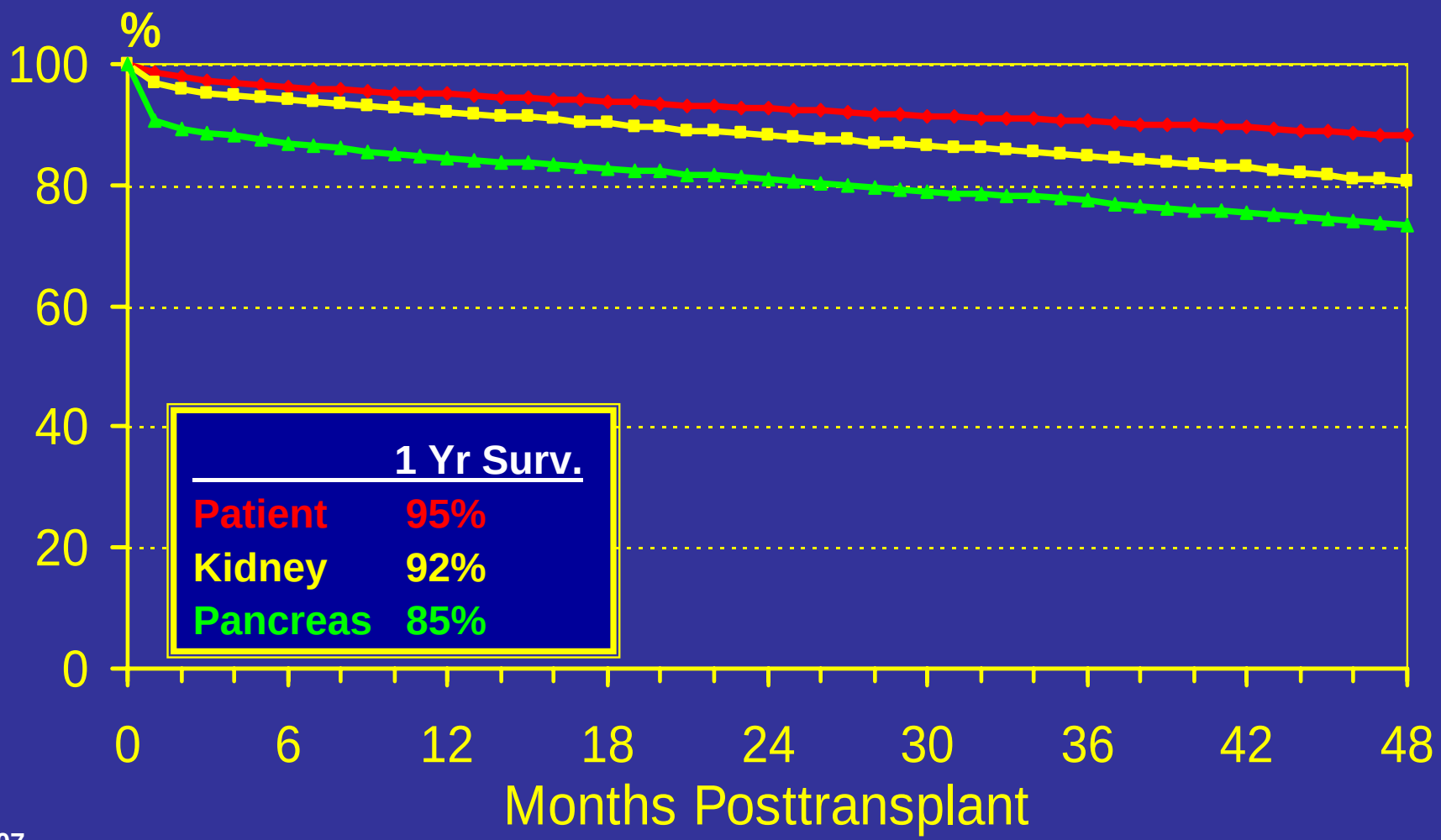


Pancreas Transplant Categories



SPK Patient and Graft Survival

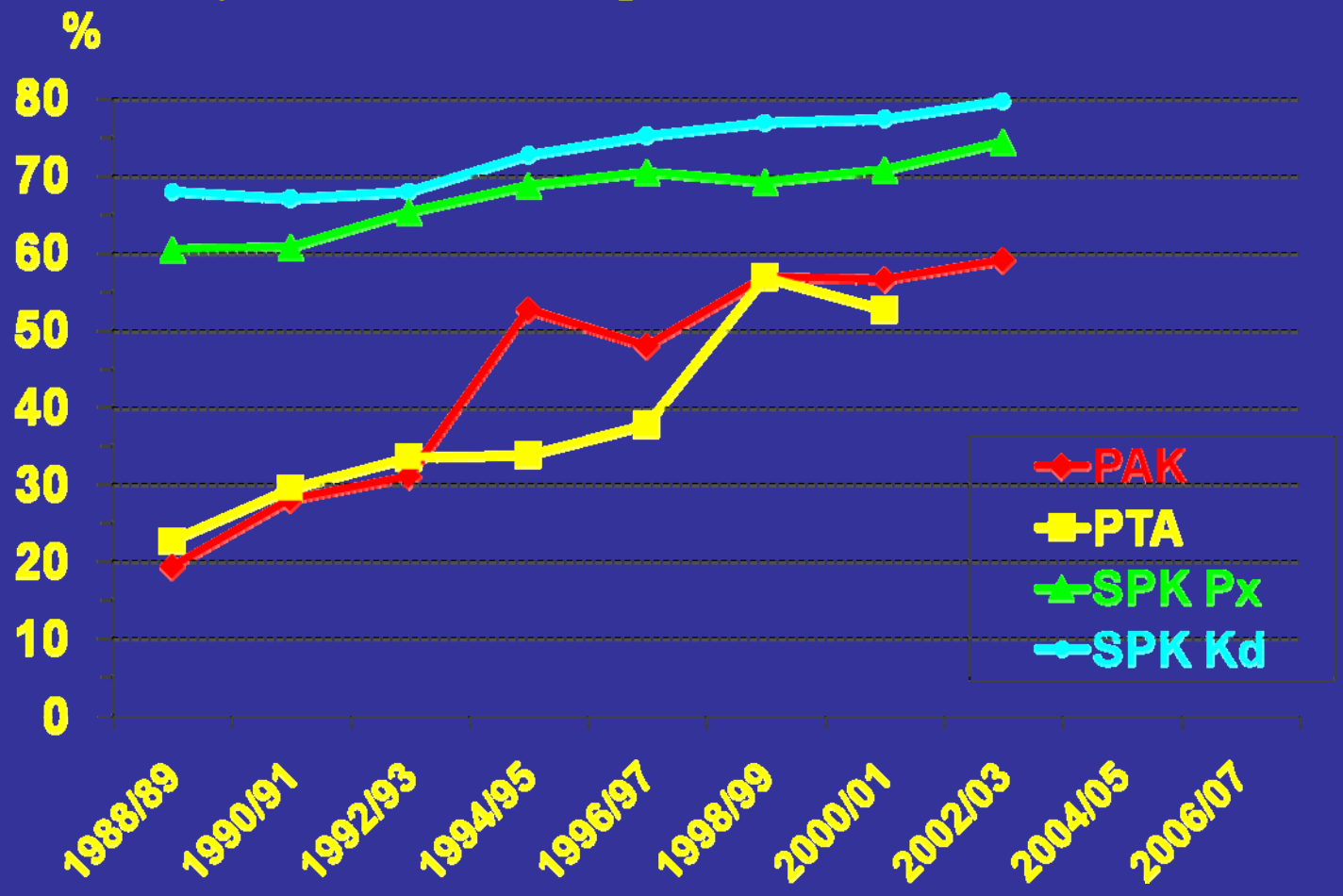
6,102 US DD Primary Pancreas Transplants 1/1/2000 – 3/ 1/2007



3/07

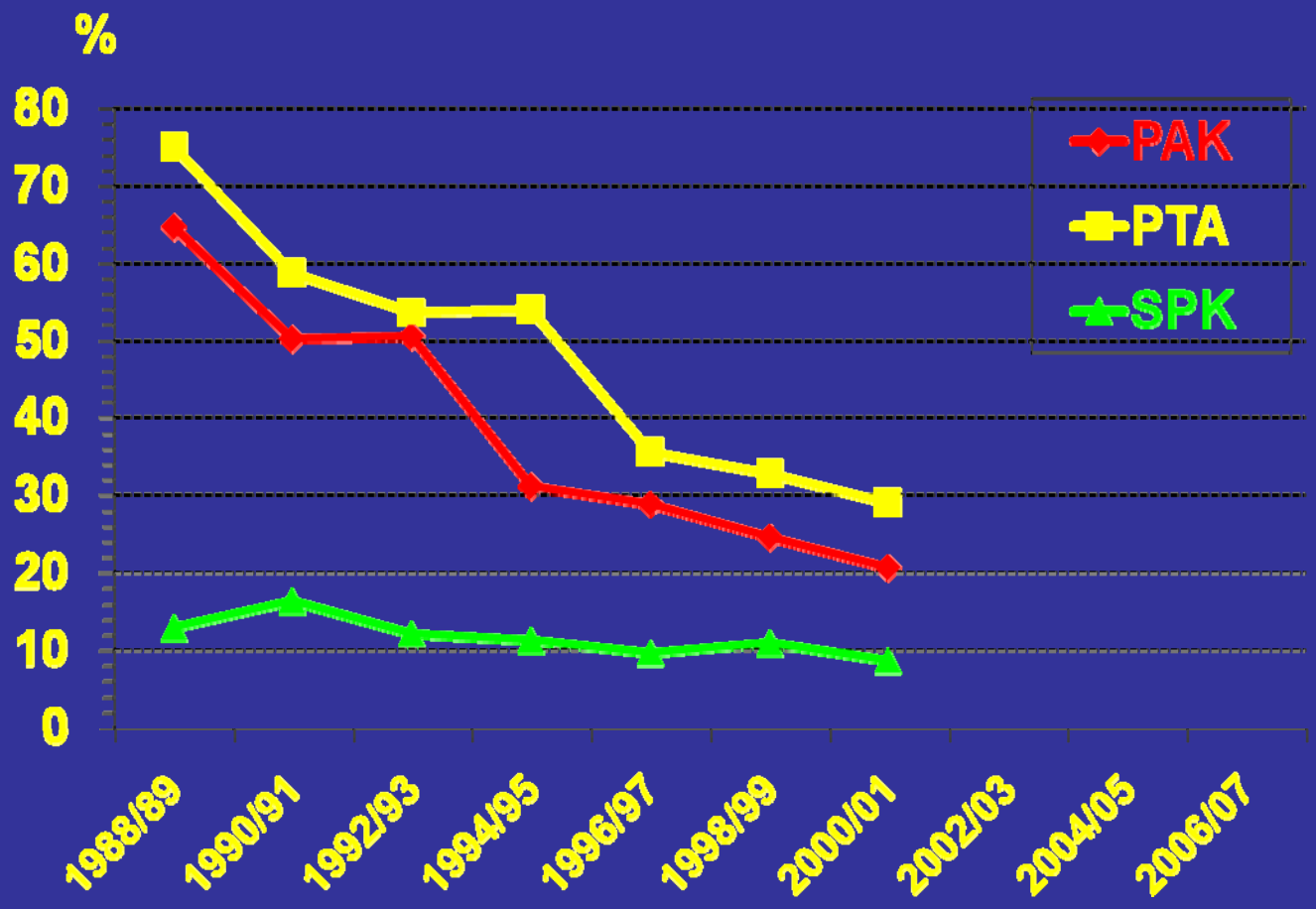
5-Year Pancreas/Kidney Graft Function

USA DD Primary Pancreas Transplants, 1/1/1988 – 12/31/2006

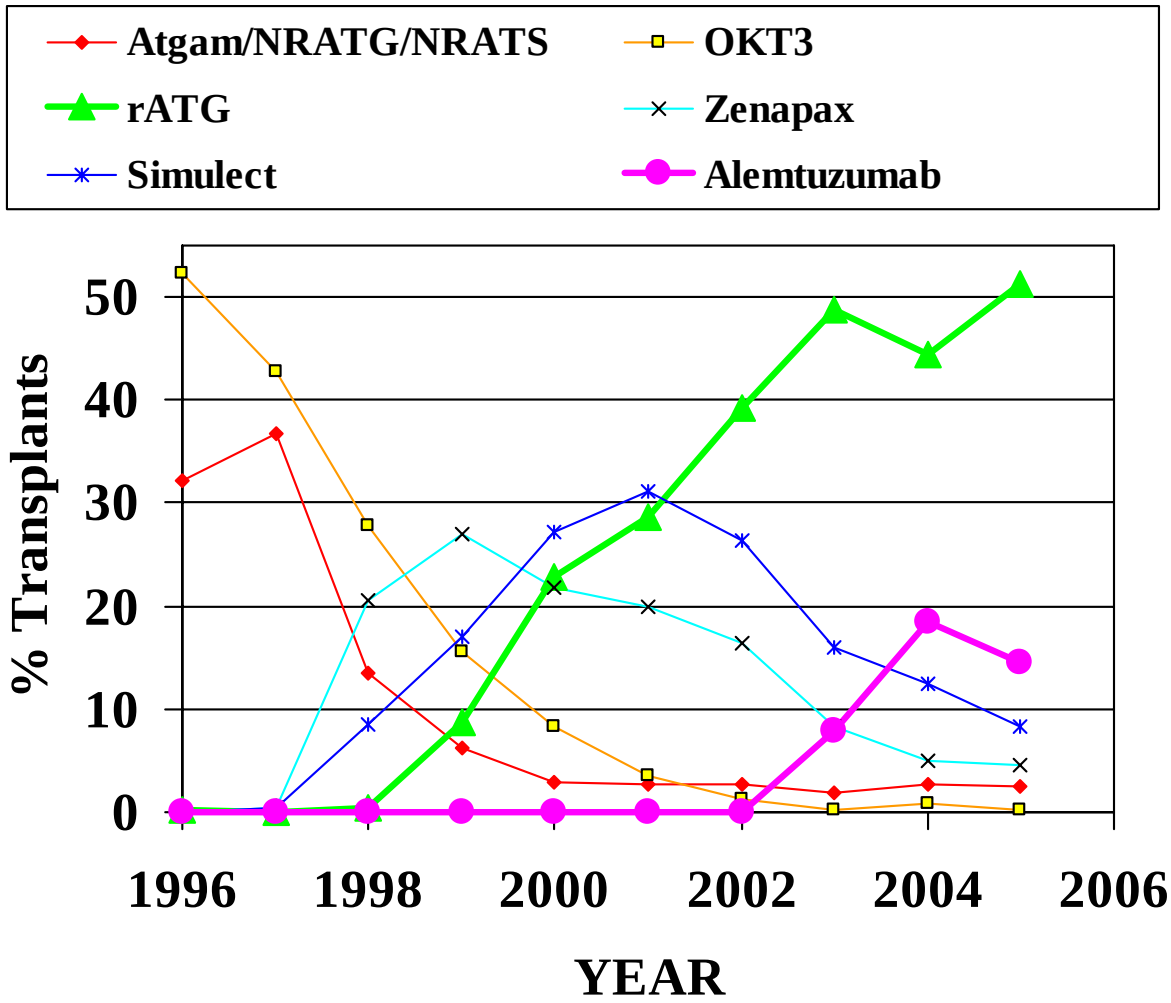


5-Year Immunological Graft Loss

USA DD Primary Pancreas Transplants, 1/1/1988 – 12/31/2006



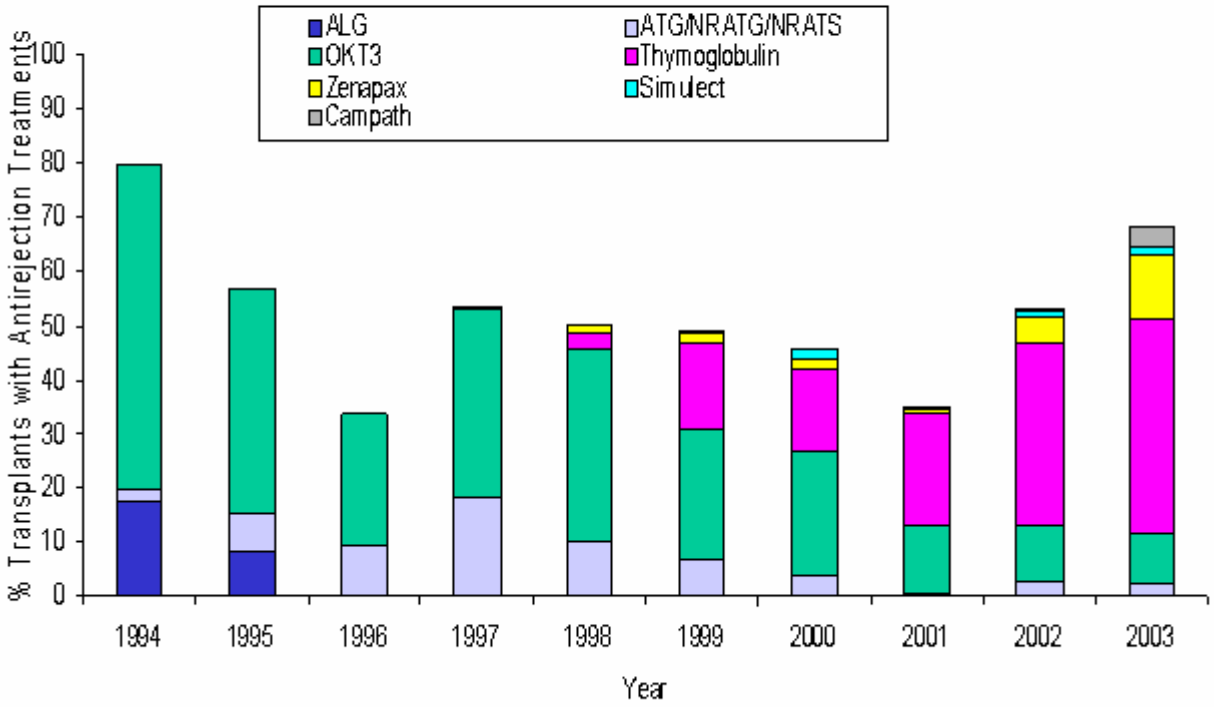
Induction in Kidney-Pancreas Transplantation 1996-2005



- 88% (in 2005) received induction
- Thymoglobulin (rATG; 51%)
- Alemtuzumab (15%)

2006 OPTN/SRTR Annual Report, Table 8.6a

Figure III-15. Trends in Antibody Therapy for Rejection Episodes in First Year Following Simultaneous Kidney-Pancreas Transplantation, 1994-2003



Source: *2005 OPTN/SRTR Annual Report*, Table 8.6i.

Major Immunosuppressive Protocols

USA Primary DD Pancreas Transplants 1/1/2000 – 12/31/2006

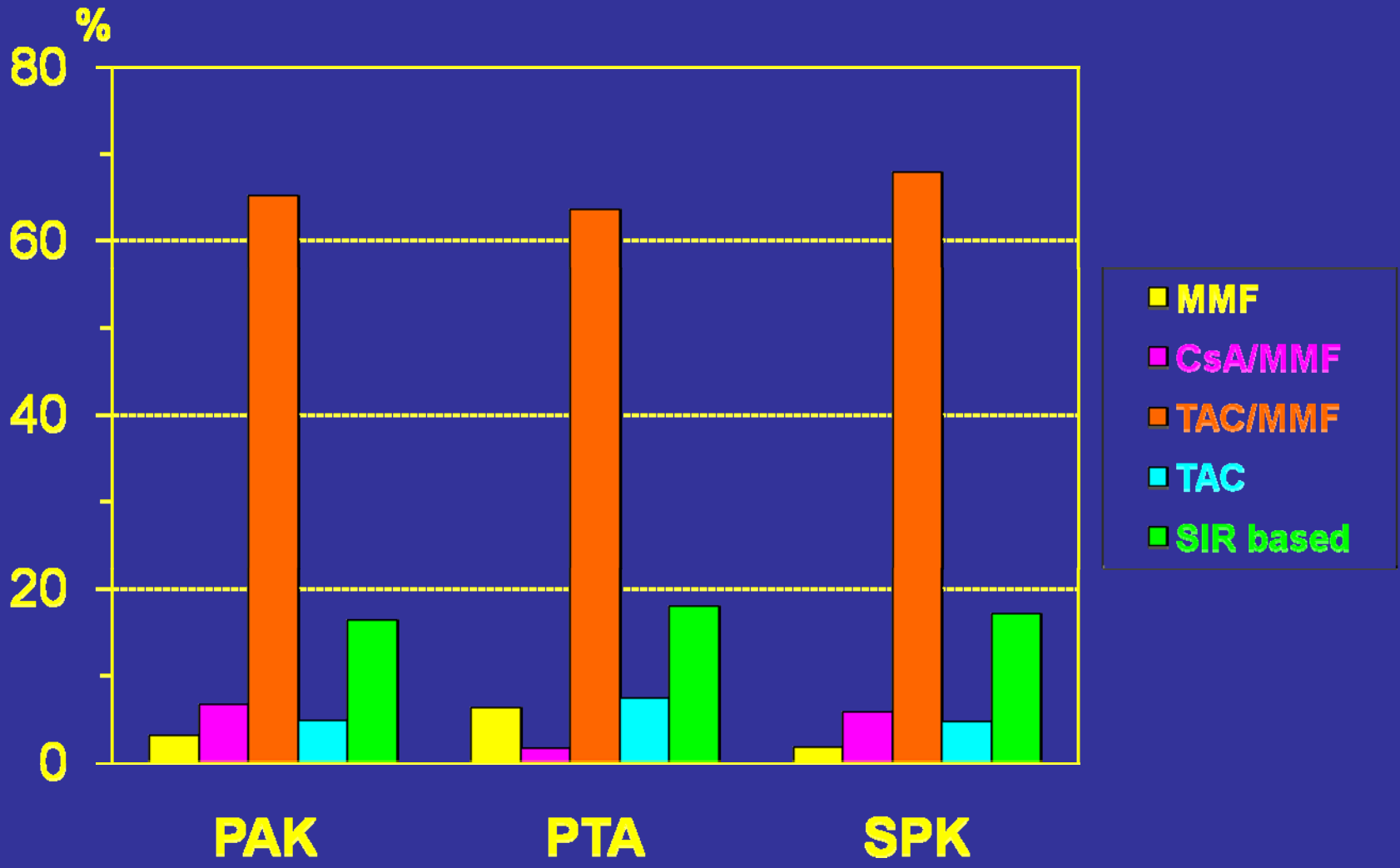
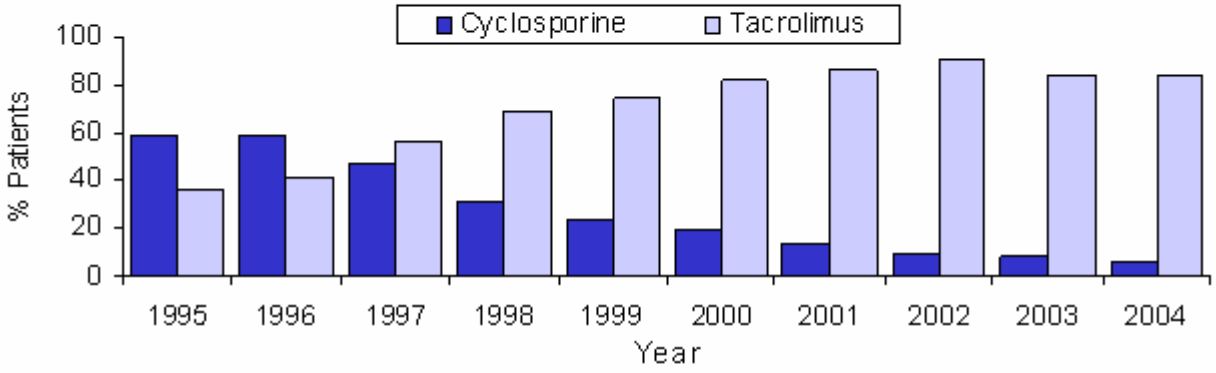
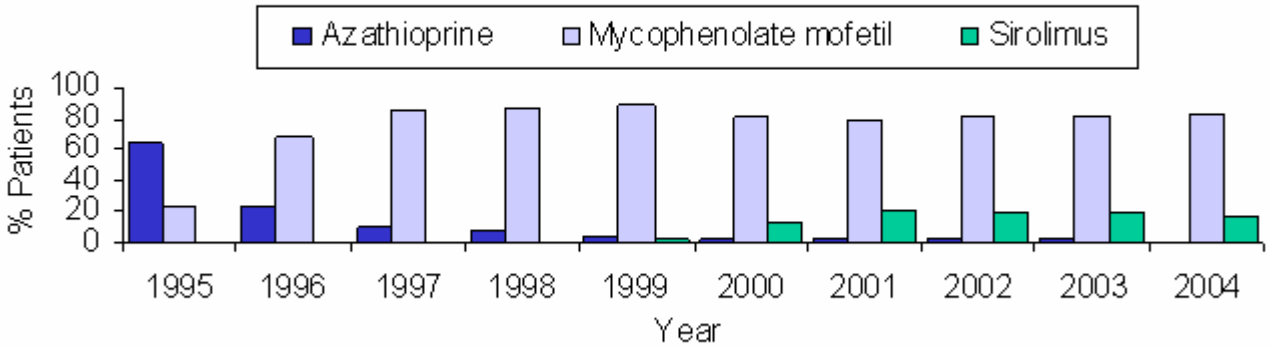


Figure III-10. Trends in Maintenance Immunosuppression Prior to Discharge for Simultaneous Kidney-Pancreas Transplantation, 1995-2004

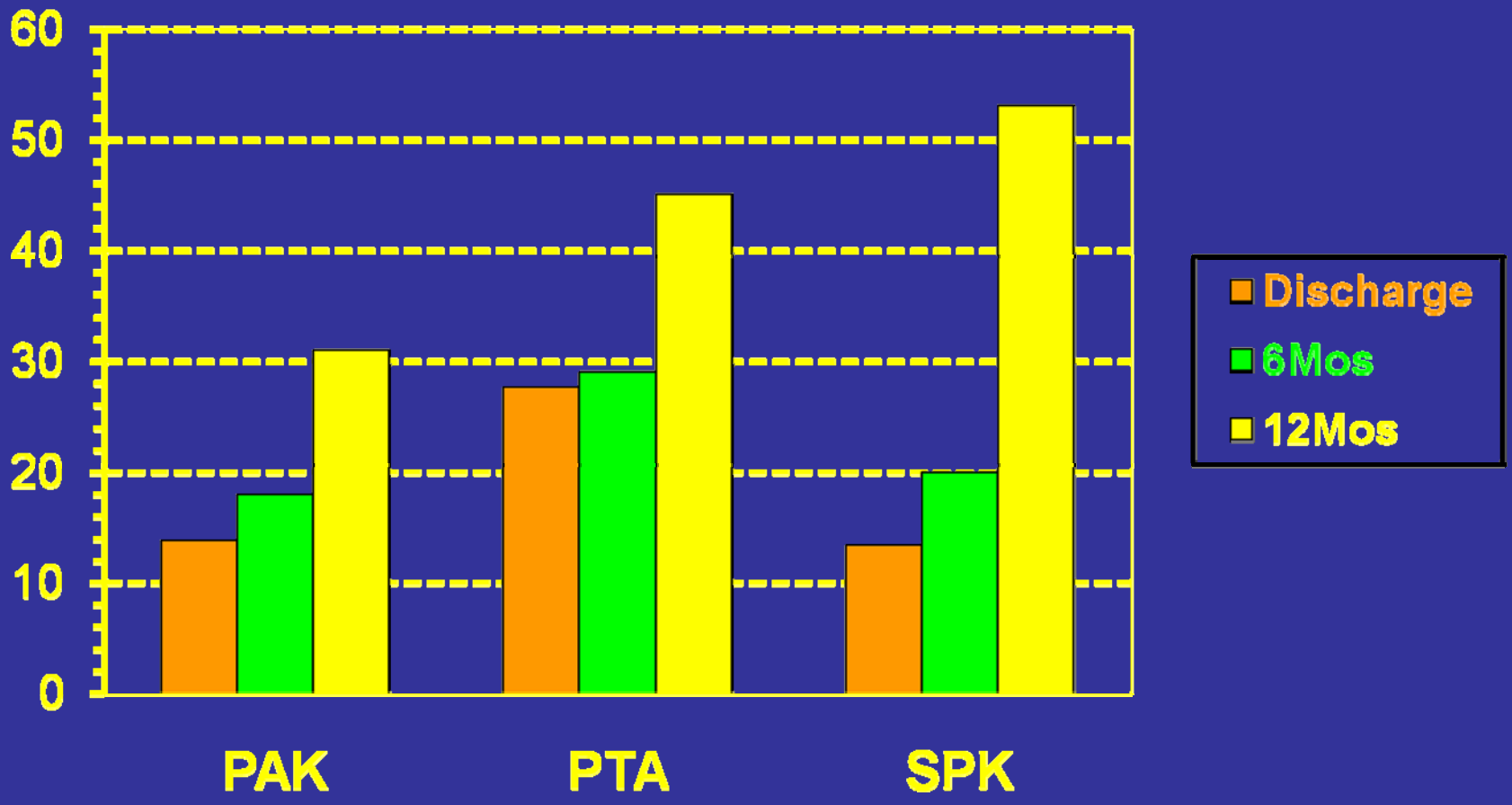




Source: *2005 OPTN/SRTR Annual Report*, Table 8.6e.

Patients off Steroids

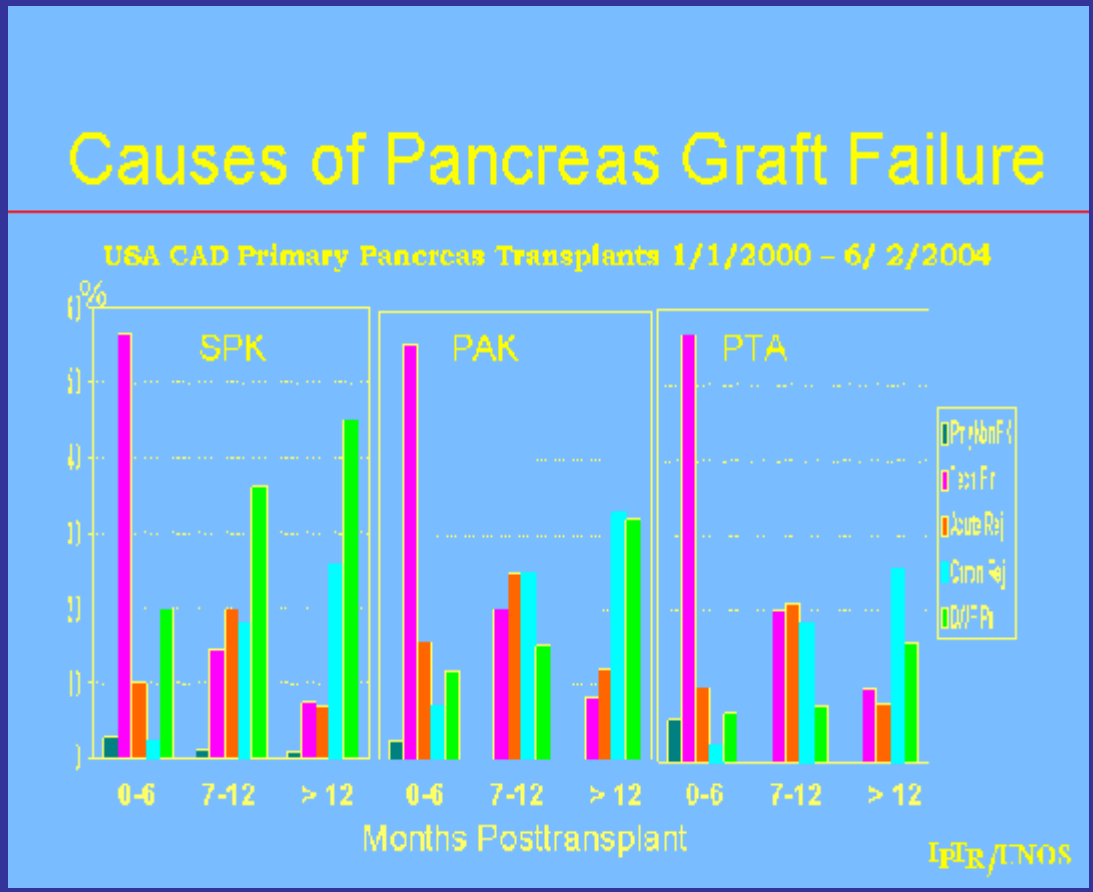
USA DD Primary Pancreas Transplants 1/1/2000 – 12/31/2005



0 – 6 Months: Technical failure

6 -12 Months: Immunological graft loss

> 12 Months: Death With a Functioning Graft (DWFG)



Pancreas Transplantation: 1980s

- Cyclosporine, OKT3, quadruple therapy
- Multiple organ retrieval / UW preservation solution
- Evolution from segmental to whole organ PTx.
- Bladder drainage of the exocrine secretions
- Simultaneous Kidney-Pancreas (SKP) transplantation

Pancreas Transplantation: 1990s

- FK, MMF, new monoclonals, biopsy directed therapy
- Improved viral (CMV) monitoring, detection, prophylaxis
- Evolution from bladder to enteric exocrine drainage
- Revolution from systemic to portal venous delivery of insulin.
- Solitary pancreas transplantation (PAK-PTA)

Pancreas Transplantation in 2000s

- Improving results due to advances in immunosuppression and refinements in surgical techniques
- One year PS >95%, PGS >85%
- Rates of rejection decreased to <10%
- Rates of reoperation decreased to <10%
- LOS decreased to 6-8 days; readmission rates decreased to <25%
- Rates of infection decreased to <25%

Summary

- As of January 2009 > 30,000 PTx reported
- Progressive improvement in outcome from 1999 to 2009
  - SKPTx graft survival rate 75% -> 85%
  - PAKTx graft survival rate 50% -> 78%
  - PTA graft survival rate 50% -> 78%

These improvements are due to:

1- Decrease in technical failure rates 20% -> 5%

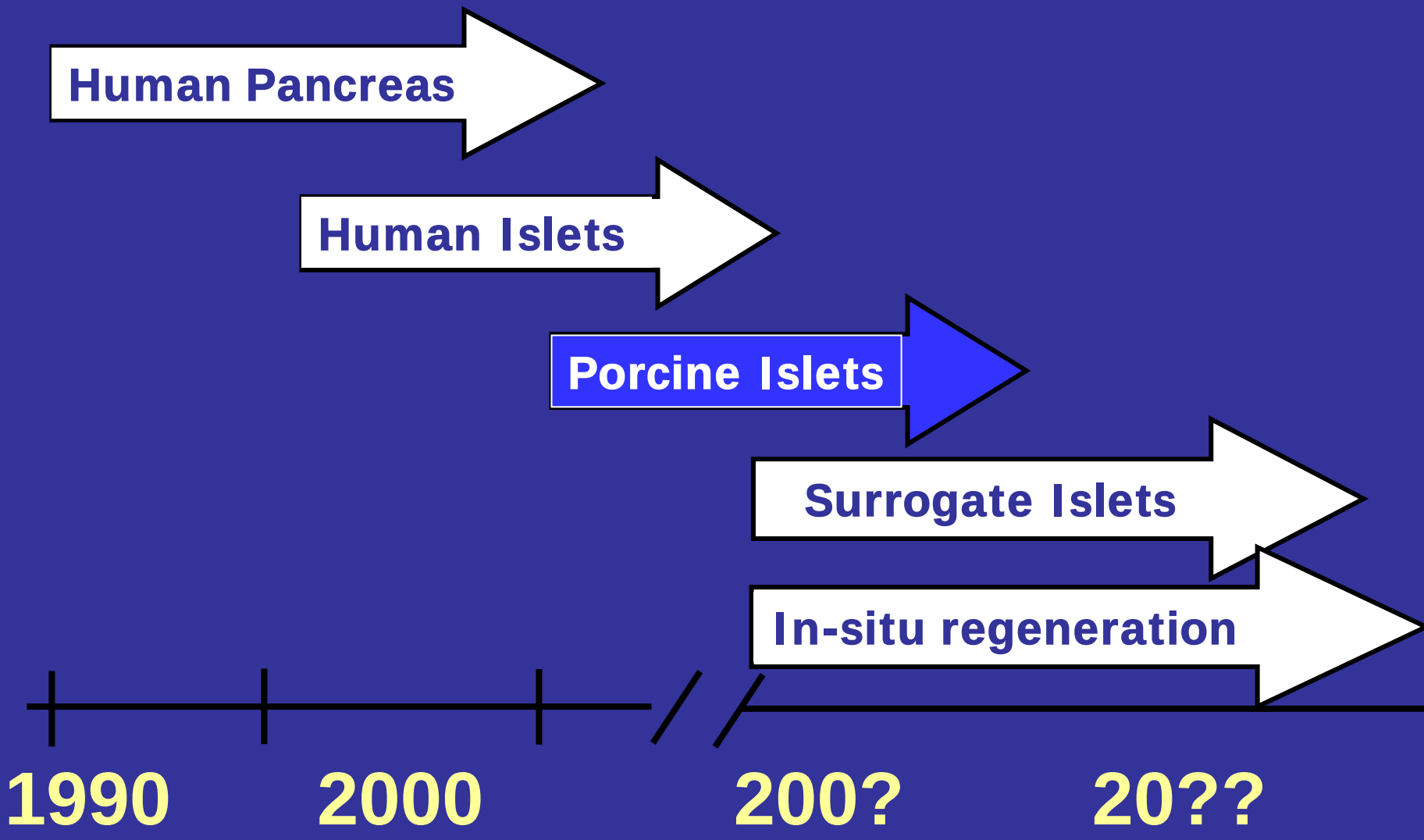
2- Decrease in immunological failure rate 25-30% -> 2%

Excellent long term outcomes with 1-year patient survival of 95-97%, an improved life span with quality of life and stabilization of diabetic complications.

Future Prospects

- New immunosuppressive regimens that are less nephrotoxic and islet toxic: steroid avoidance, CNI minimization or withdrawal
- More liberal use of antibody agents as tolerizing, long-term immunosuppressants
- Improved physiology of procedure (enteric ± portal venous drainage)
- Expanded donor and recipient selection (age, BMI, type 2 diabetes, HCV, ethnicity)
- Shift in focus from short-term immunologic and surgical outcomes to long-term aspects
- Islets are the future (and always will be)

Beta cell replacement therapy



Thank you