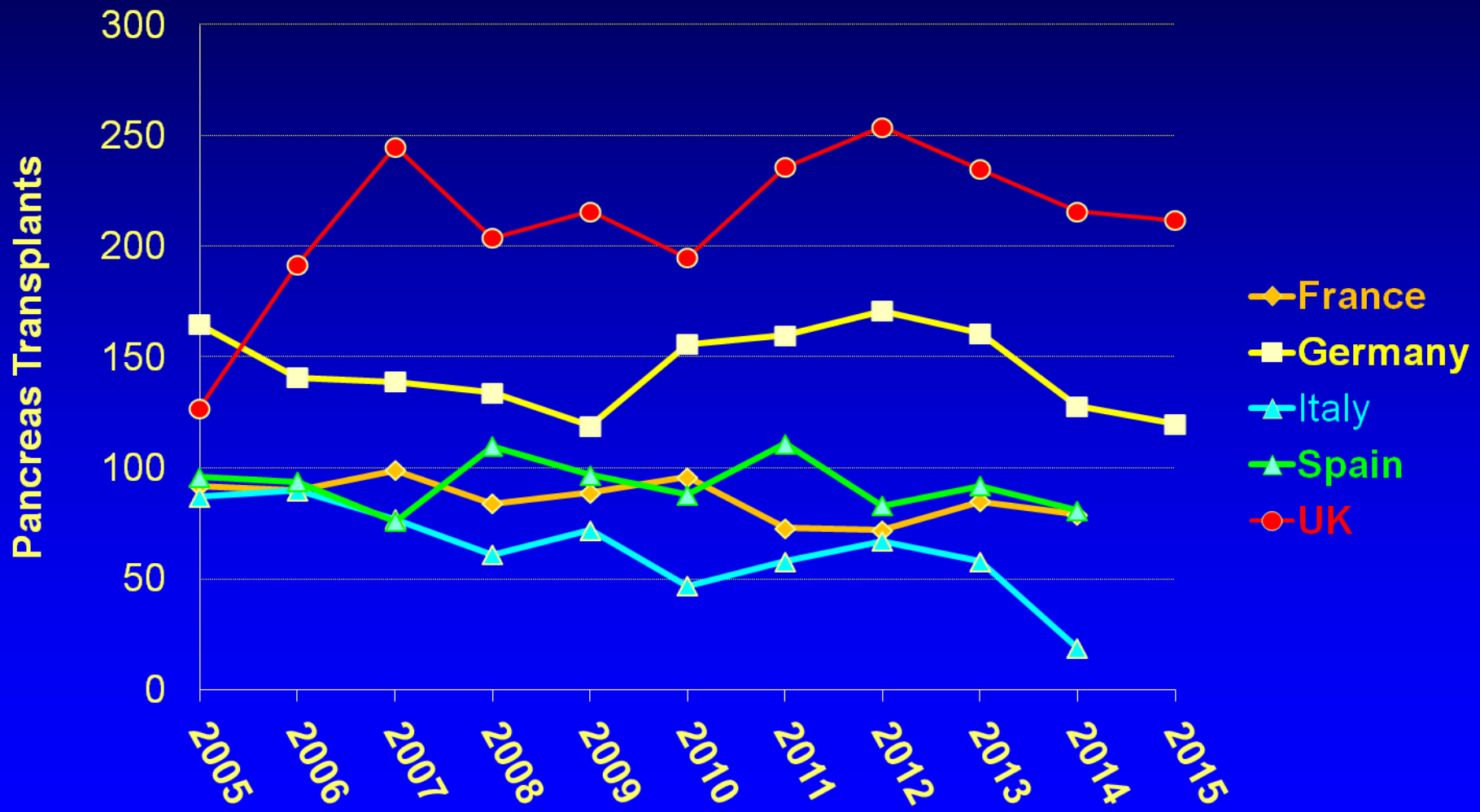
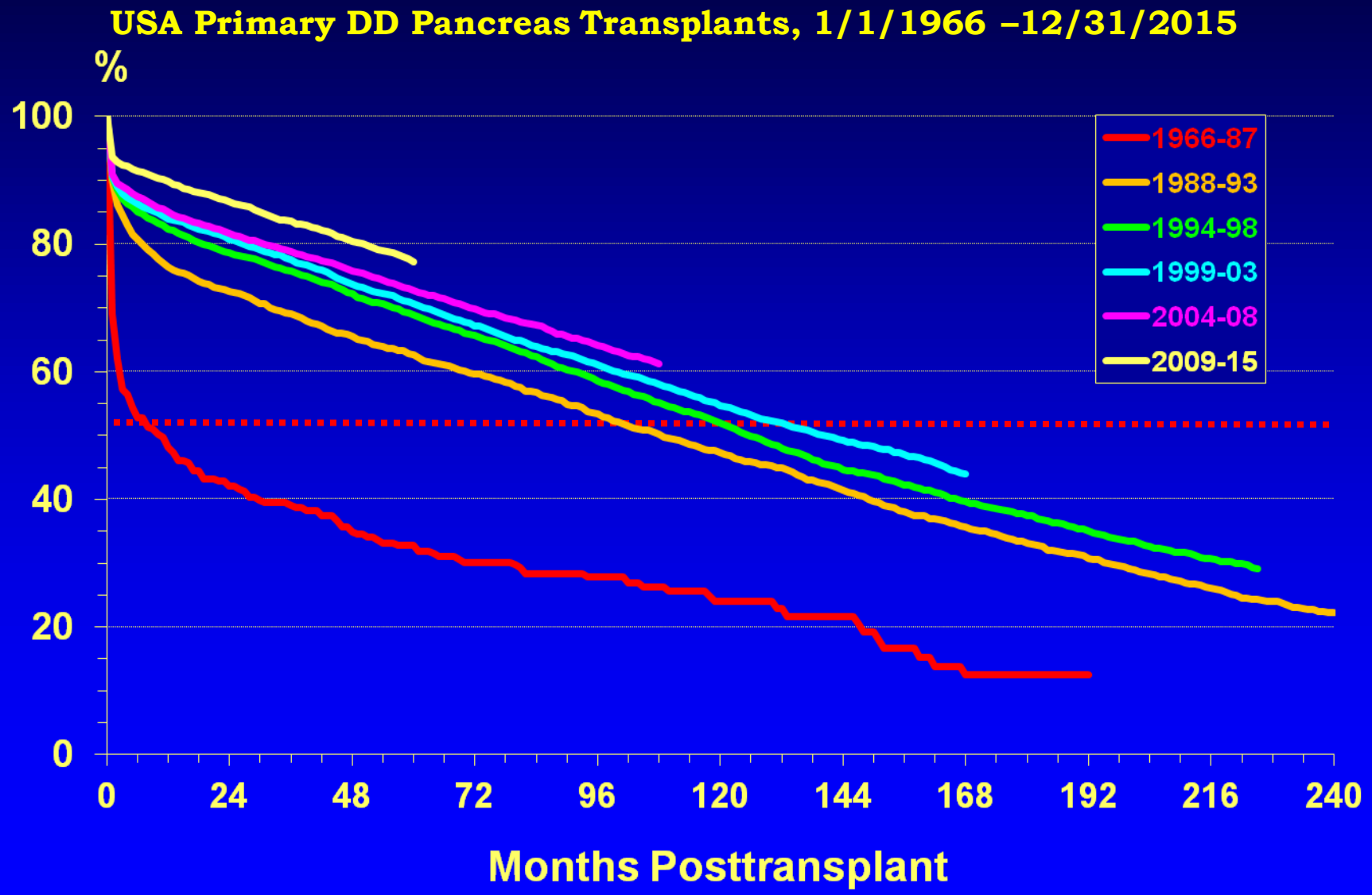
Vascular Remodelling in Pancreas Transplantation

Prof Steve White
Consultant HPB/Transplant Surgeon
The Freeman Hospital Newcastle
President Elect EPITA

European Pancreas Transplants

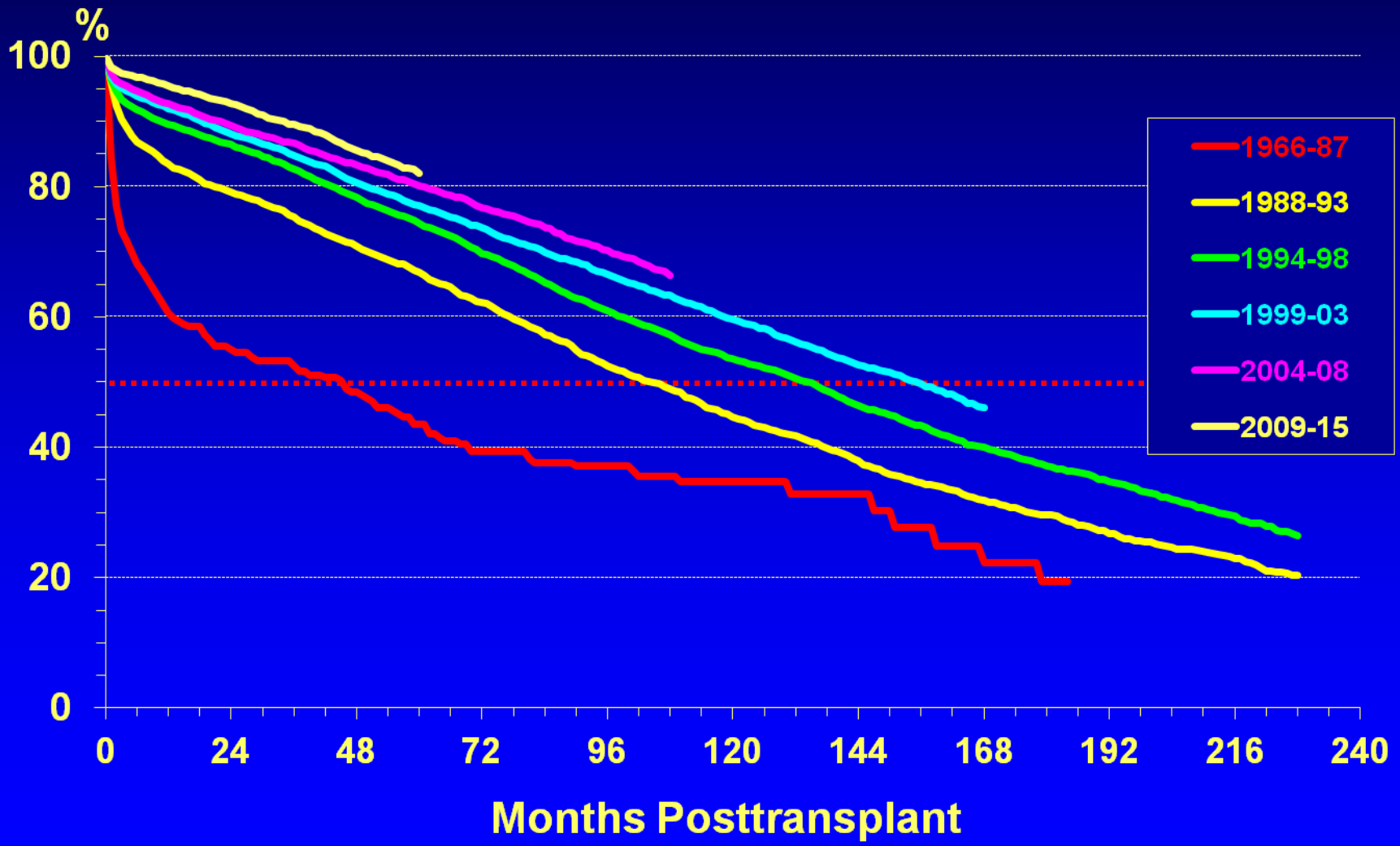


SPK Pancreas Graft Function

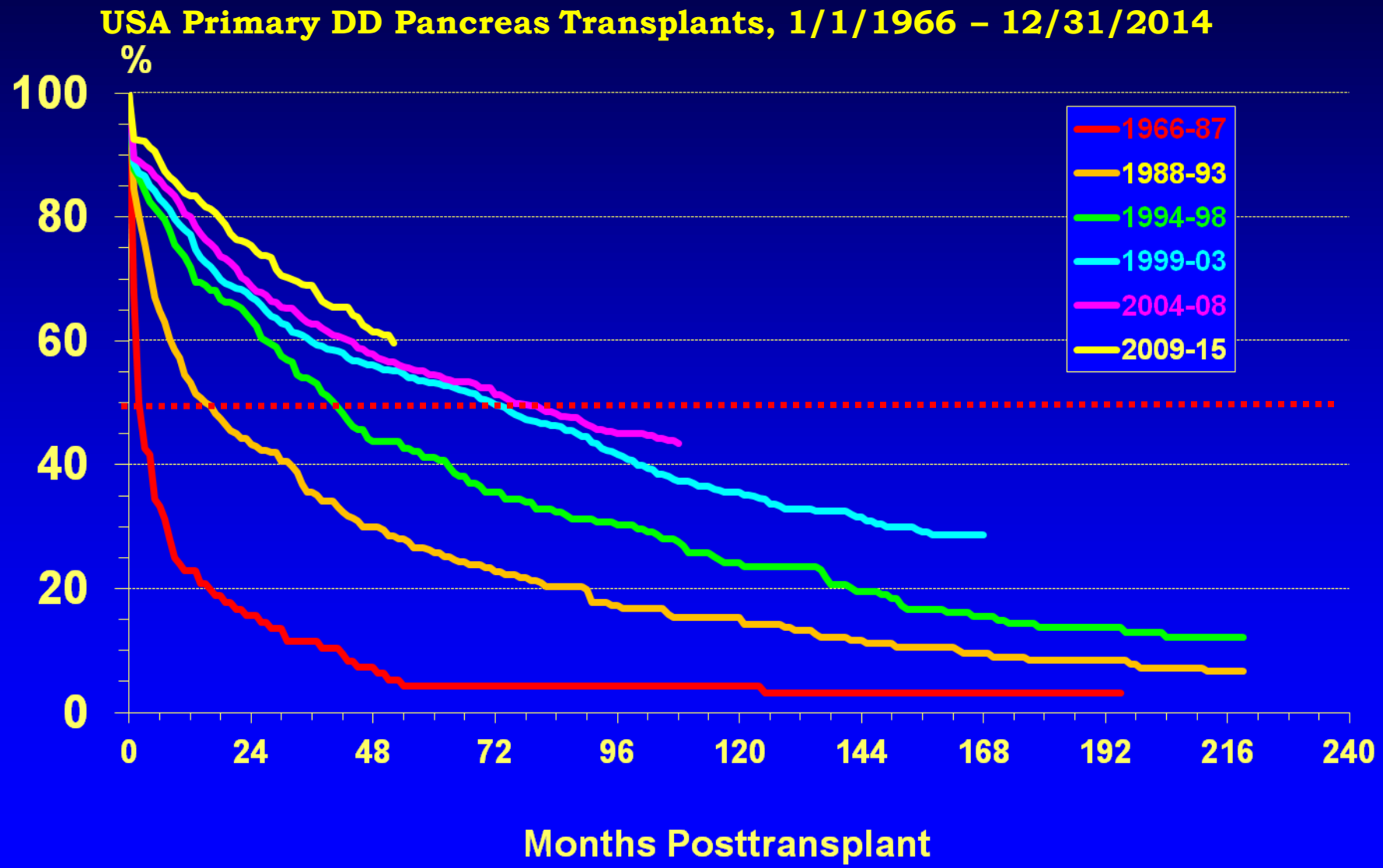


SPK Kidney Graft Function

USA Primary DD Pancreas Transplants, 1/1/1966 –12/31/2015



PTA Pancreas Graft Function



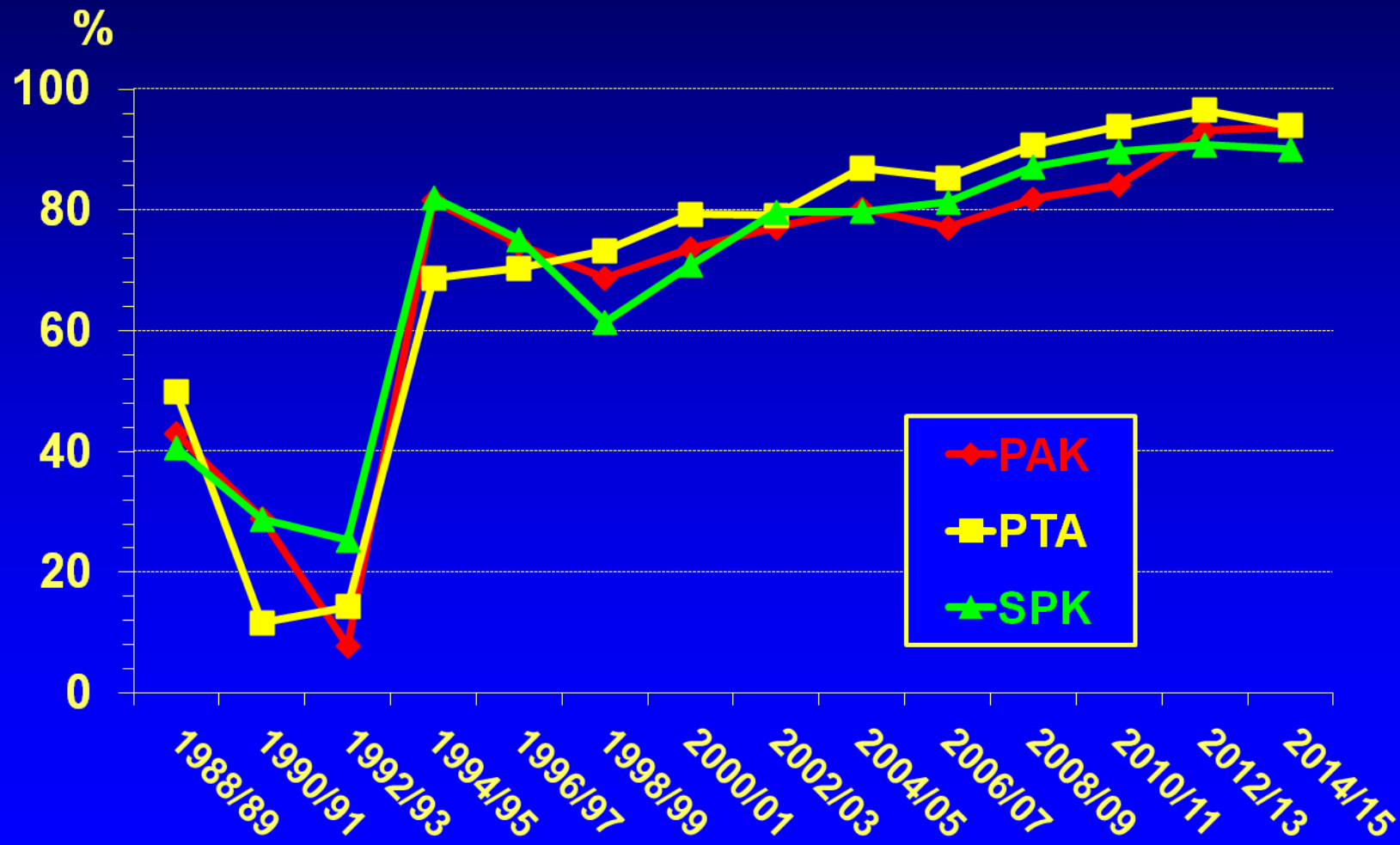
Pancreas *Graft Function*

USA DD Pancreas Transplants, 1/1/2003 – 12/31/2012

	SPK (8,345)		PAK (1,869)		PTA (884)	
	Primary only	All Txs	Primary only	All Txs	Primary only	All Txs
1- Year	86.2%	88.0%	78.6%	84.0%	78.0%	83.2%
3-Year	79.7%	81.4%	66.8%	72.0%	61.6%	68.0%
5-Year	73.0%	77.5%	58.1%	62.3%	53.9%	58.9%

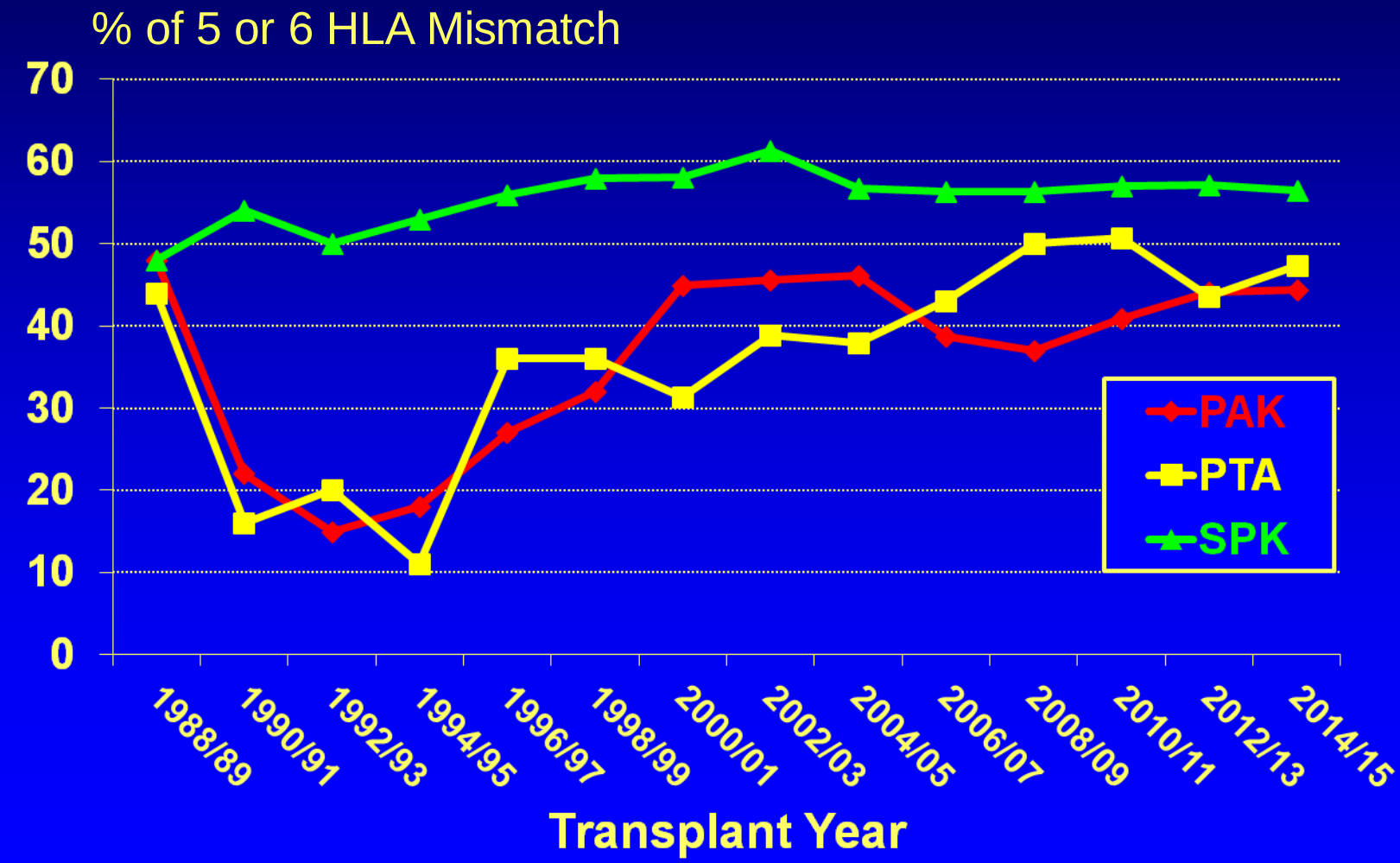
Anti-T-Cell Induction

USA DD Primary Pancreas Transplants 1/1/1988 – 12/31/2015



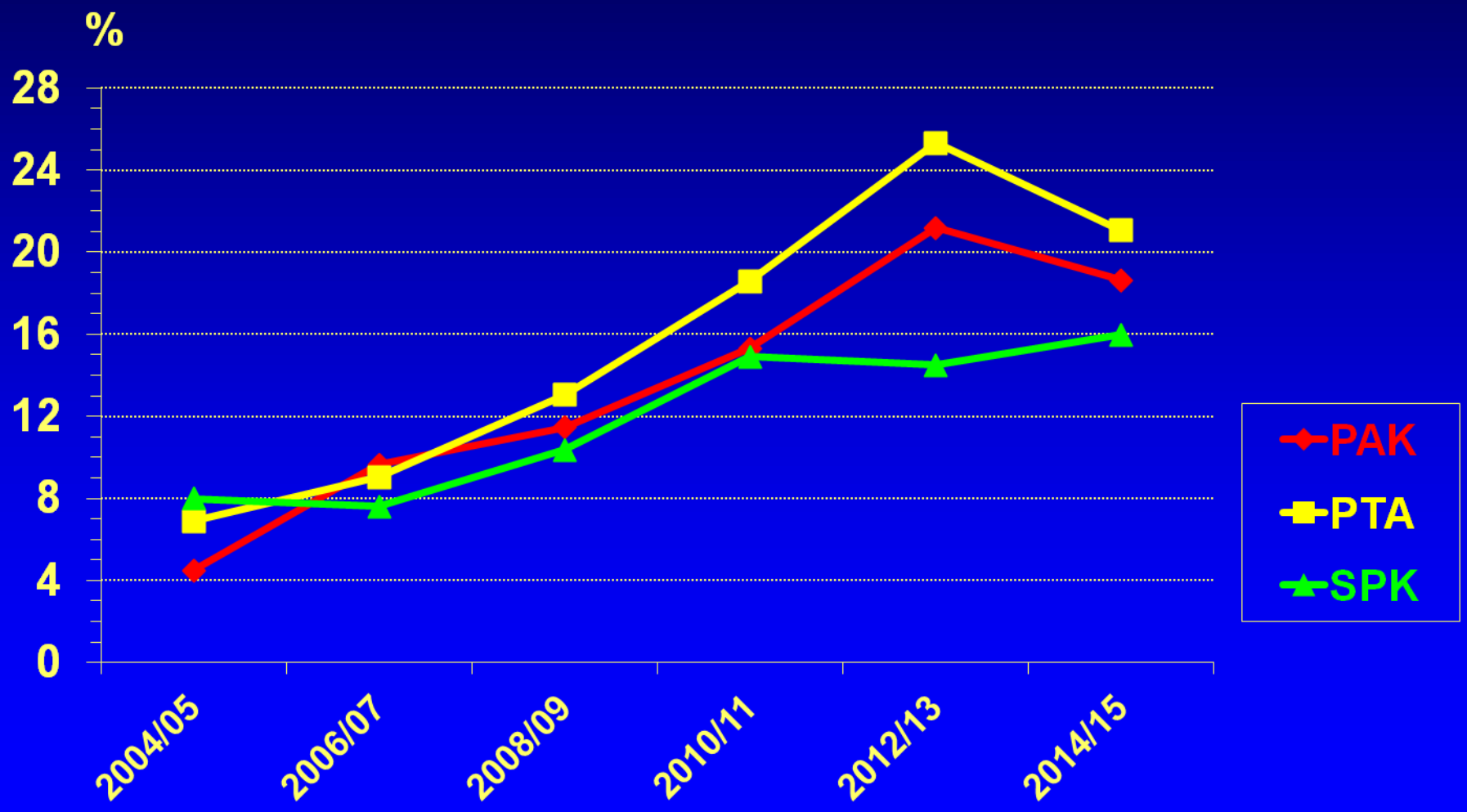
HLA A,B,DR Mismatching

USA Primary DD Pancreas Transplants 1/1/1988 – 12/31/2015



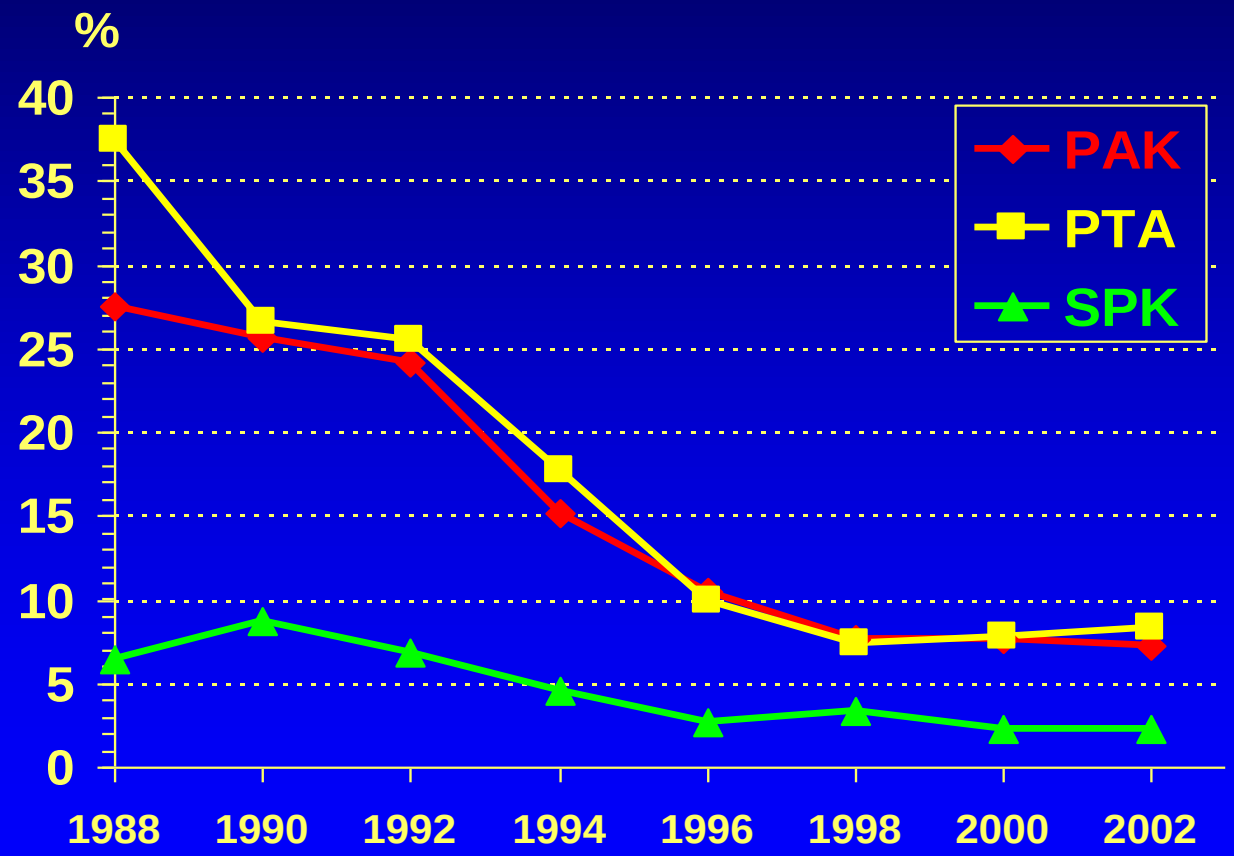
cPRA levels > 20%

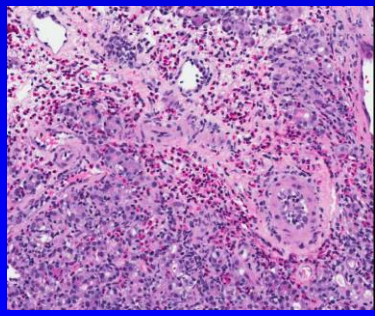
USA DD Primary Pancreas Transplants 1/1/2004 – 12/31/2015



1-Yr Immunological Graft Loss

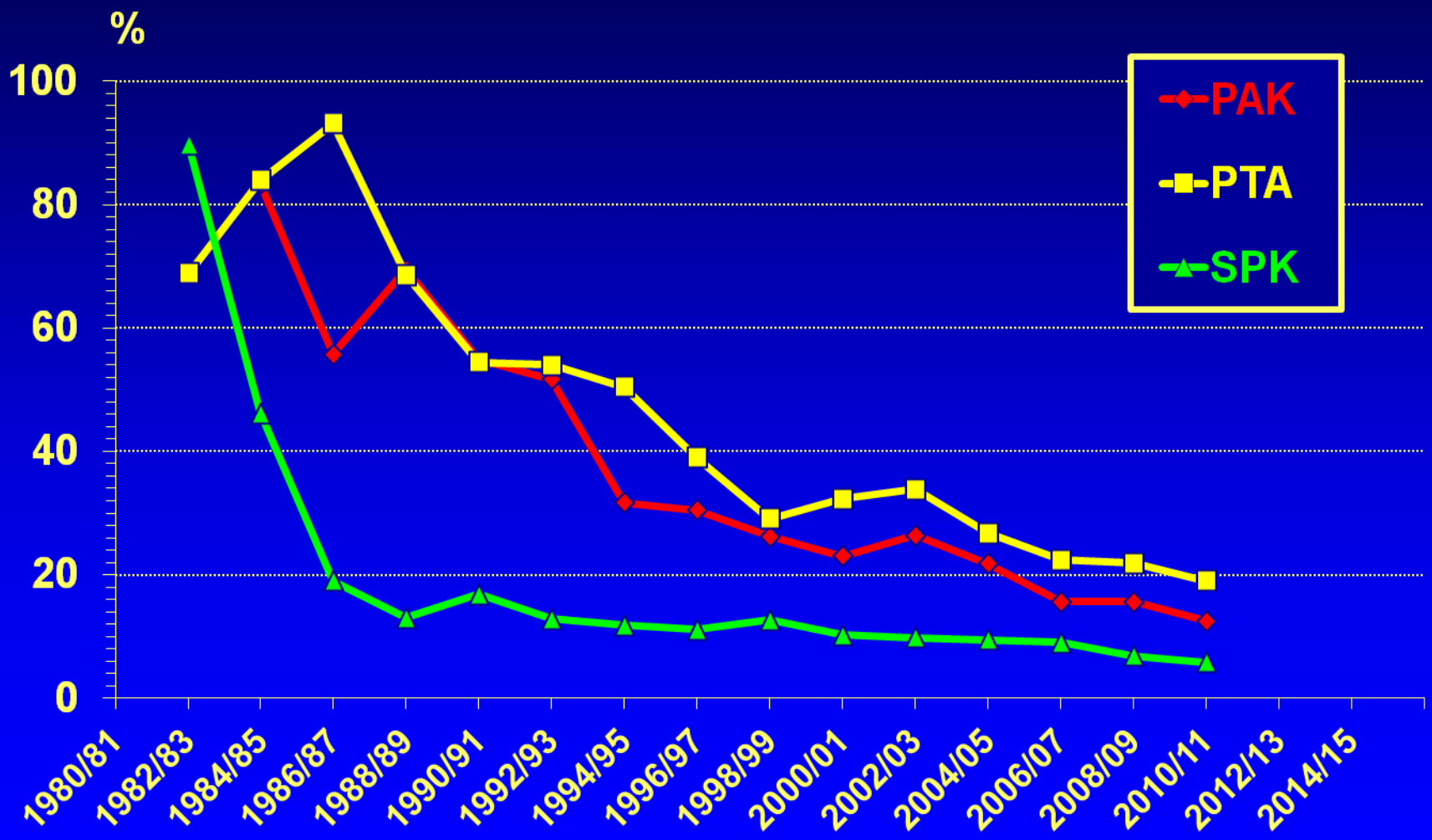
USA DD Primary Pancreas Transplants, 10/1/1988 – 12/31/2003





5-Year Immunologic Graft Loss

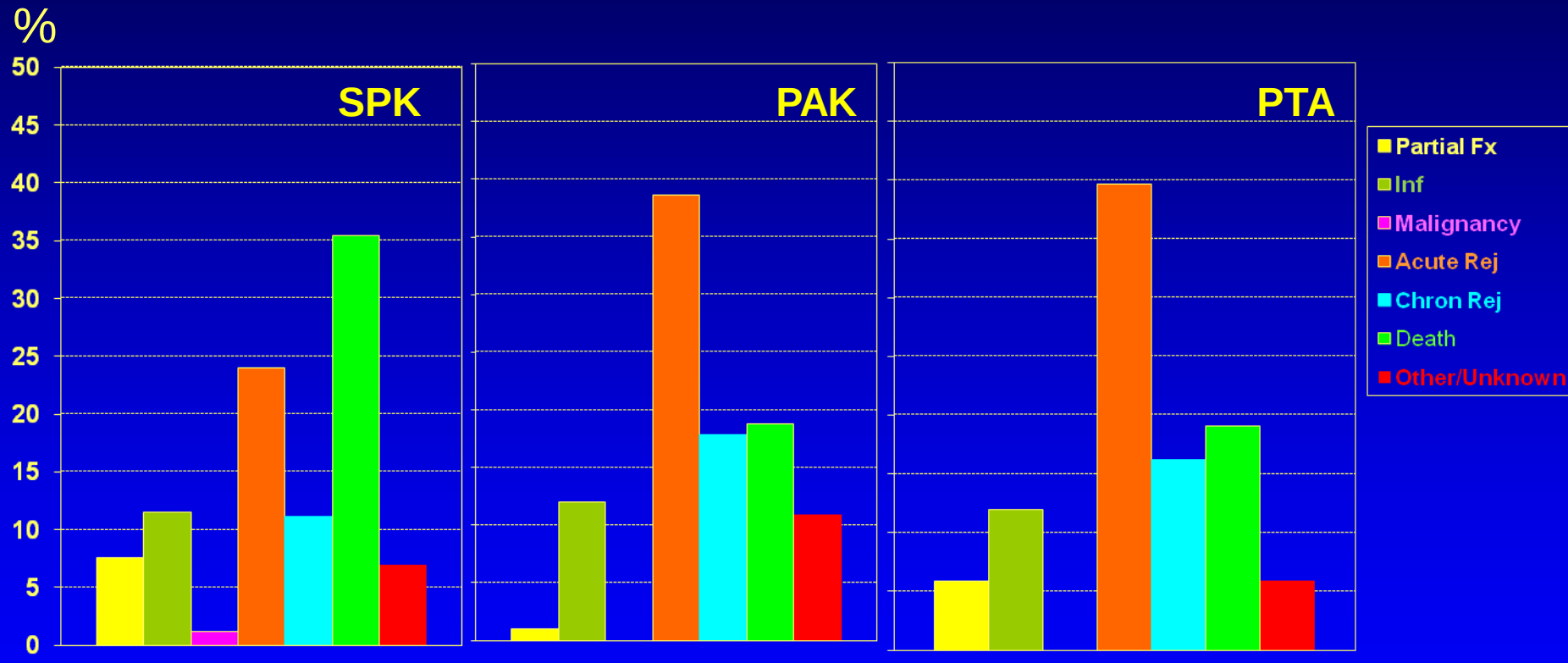
USA DD Primary TS Pancreas Transplants, 1/1/1980 – 12/31/2015



Causes of Pancreas Graft Failure

3 - <12 Month Posttransplant

USA Primary DD Pancreas Transplants 1/1/2010 – 12/31/2015

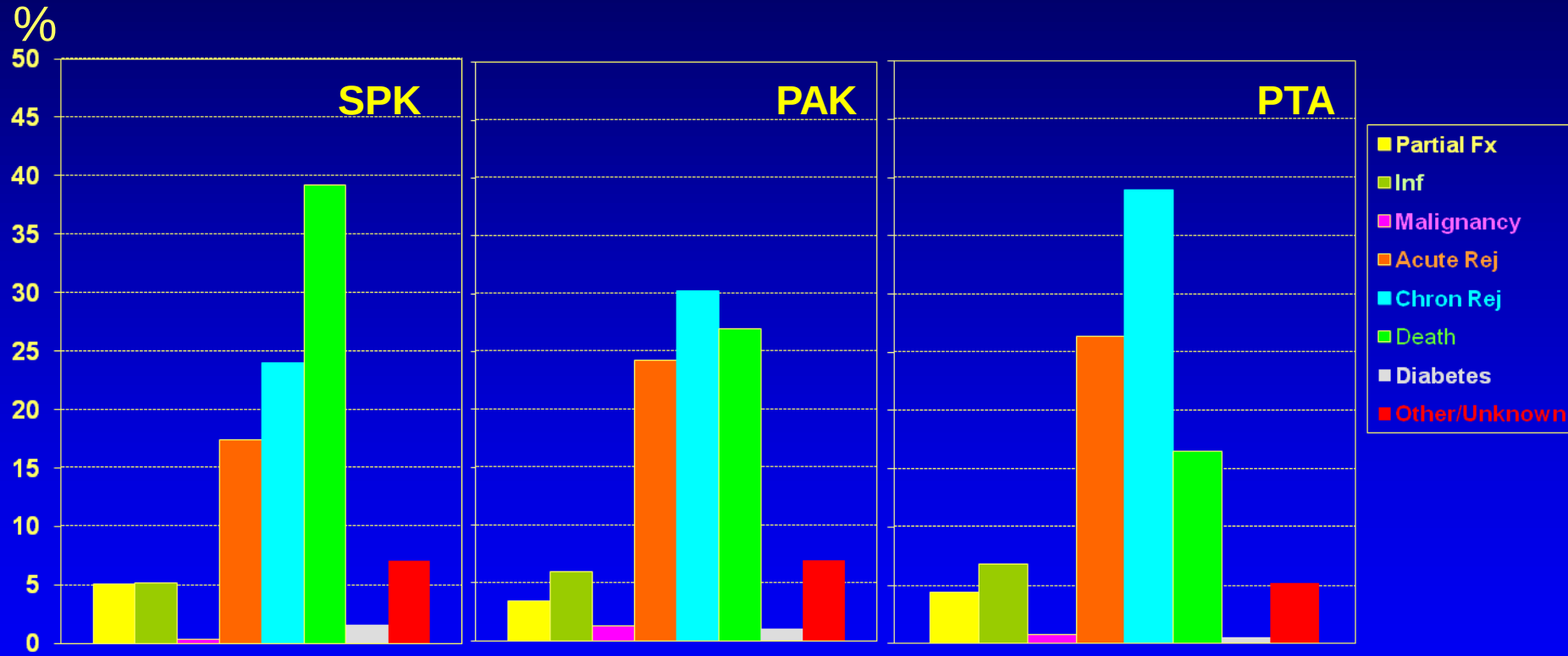


Pancreas Graft Failure Cause

Causes of Pancreas Graft Failure

≥ 1 - 5 Years Posttransplant

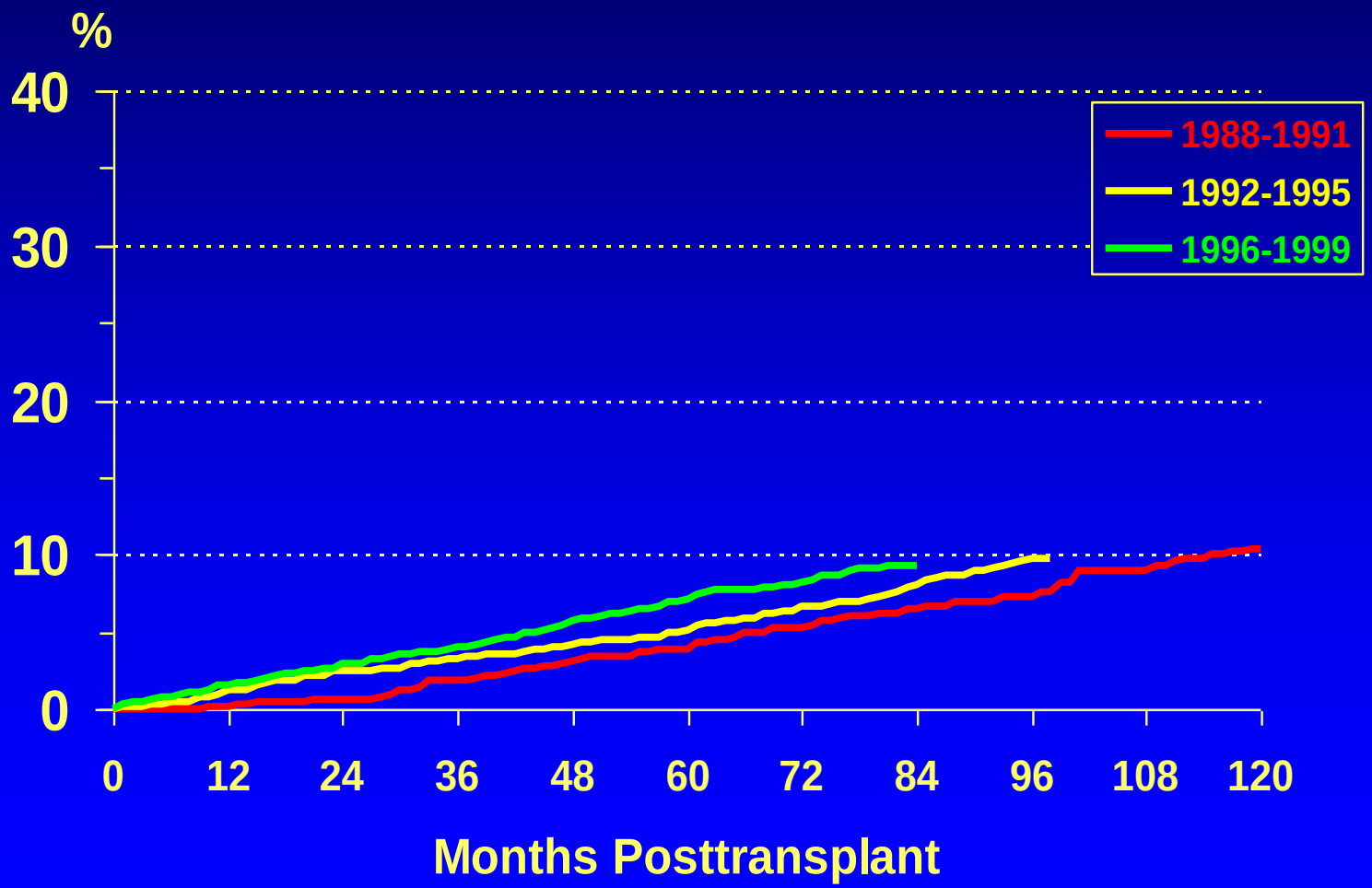
USA Primary DD Pancreas Transplants 1/1/2000 – 12/31/2015



Pancreas Graft Failure Cause

SPK Pancreas Graft Loss due to Chronic Rejection

USA DD TS Primary Pancreas Transplants, 1/1/1988 – 12/31/1999



0041-1337/03/7606-918/0
TRANSPLANTATION

Vol. 76, 918–923, No. 6, September 27, 2003
Printed in U.S.A.

CHRONIC REJECTION: THE NEXT MAJOR CHALLENGE FOR PANCREAS TRANSPLANT RECIPIENTS

ABHINAV HUMAR,[1] KHALID KHWAJA, THIAGARAJAN RAMCHARAN, MASSIMO ASOLATI, RAJA KANDASWAMY, RAINER W. G. GRUESSNER, DAVID E. R. SUTHERLAND, AND ANGELIKA C. GRUESSNER

Objective. **With newer immunosuppressive agents, acute rejection and graft loss resulting from acute rejection have become less common for pancreas transplant recipients. As long-term graft survival rates have improved, an increasing number of grafts are being lost to chronic rejection (CR). We studied the**

creased after all types of abdominal and thoracic transplants. A better understanding of donor and recipient risk factors, coupled with improvements in preservation and surgical techniques, also helped decrease the incidence of graft loss to technical complications.

TABLE 1. Causes of graft loss

	SPK (%)	PAK (%)	PTA (%)	Total (%)
Still functioning	230 (71.6)	267 (68.6)	146 (71.6)	643 (70.3)
Technical failure	48 (15.0)	49 (12.6)	21 (10.3)	118 (12.9)
Chronic rejection	12 (3.7)	45 (11.6)	23 (11.3)	80 (8.8)
Acute rejection	1 (0.3)	7 (1.8)	6 (2.9)	14 (1.5)
Death with function	26 (8.1)	19 (4.9)	6 (2.9)	51 (5.6)
Primary nonfunction	2 (0.6)	1 (0.3)	1 (0.5)	4 (0.4)
Other/unknown	2 (0.6)	1 (0.3)	1 (0.5)	4 (0.4)
Total	321	389 (0.3)	204	914

PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney transplant.

Risk Factors

TABLE 2. Multivariate analysis of risk factors for CR after pancreas transplants

Risk factor		RR	*P* Value
Acute rejection	Yes (vs. no)	4.41	<0.0001
Transplant category	PTA or PAK (vs. SPK)	3.02	0.002
CMV infection	Yes (vs. no)	2.41	0.001
Retransplant	Yes (vs. no)	2.27	0.004
PRA >20	Yes (vs. no)	1.73	0.10
Recipient age (yr)	≤45 (vs. >45)	—	NS
Number of mismatches at A locus	1 or 2 (vs. 0)	—	NS
Number of mismatches at B locus	1 or 2 (vs. 0)	1.68	0.04
Number of mismatches at DR locus	1 or 2 (vs. 0)	—	NS
Immunosuppression	MMF (vs. other)	—	NS
Immunosuppression	Sirolimus (vs. other)	—	NS

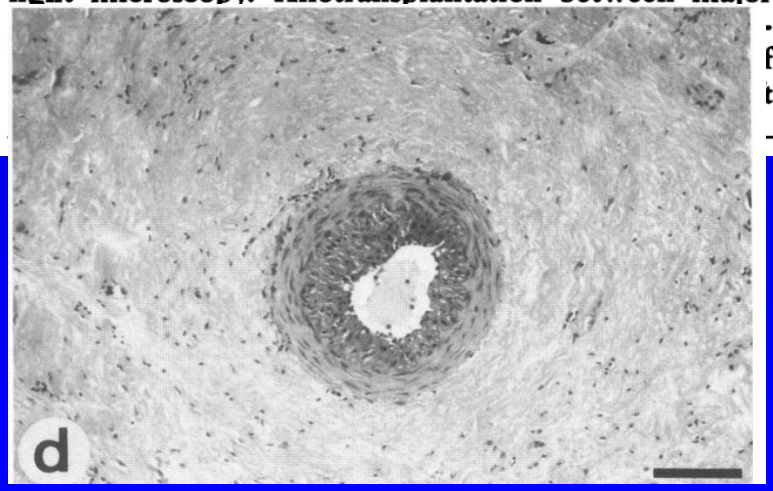
CMV, cytomegalovirus; PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney transplant; PRA, panel-reactive antibody; CR, chronic rejection; NS, not significant; RR, relative risk.

Distinct Histologic Patterns of Acute, Prolonged, and Chronic Rejection in Vascularized Rat Pancreas Allografts

BIRTE STEINIGER, MD, and JÜRGEN KLEMPNAUER, MD

From the Centre of Anatomy and Department of Abdominal and Transplantation Surgery, Medical School, Hannover, Federal Republic of Germany

In a model of pancreas whole organ transplantation in streptozotocin diabetic rats distinct histologic patterns of acute, prolonged and chronic rejection were defined by light microscopy. Allotransplantation between major



morphology. The impact of surgical techniques with preserved and suppressed exocrine secretion on graft histology was sequentially assessed in pancreas isograft recipients. MHC incompability was associated with acute rejection, non-MHC disparity with prolonged rejection and RT1.C mismatch with chronic rejection. (Am J Pathol 1986, 124:253–262)

American Journal of Pathology, Vol. 138, No. 2, February 1991

Longitudinal Histopathologic Assessment of Rejection After Bladder-drained Canine Pancreas Allograft Transplantation

R. D. M. Allen,* J. M. Grierson,* H. Ekberg,†
W. J. Hawthorne,† P. Williamson,*
S. A. Deane,† J. R. Chapman,* G. J. Stewart,*
and J. M. Little†

From the Pancreas Transplant Research Gro
Department of Surgery,† University of Sydne
Hospital, Sydney, Australia

lems of graft pancreatitis and vascular thrombosis. Furthermore serum and urine markers of rejection either occur late or are unreliable and are prone to misinterpreta-

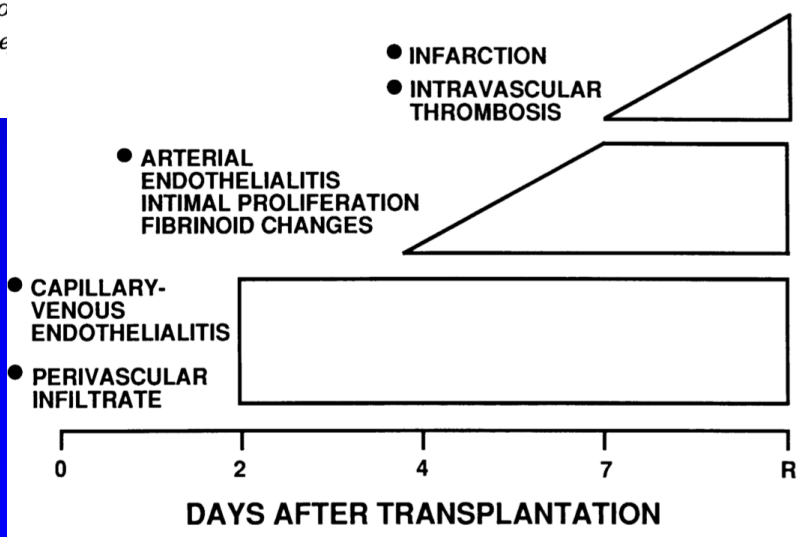


Figure 6. *Summary of vascular changes, unmodified by immunosuppression, seen after canine pancreas allograft transplantation (R, rejection).*

Clin Transplantation 1994: 8: 293–298
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Clinical Transplantation
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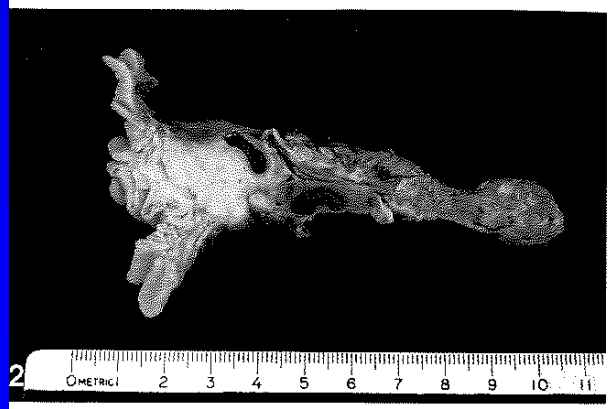
Morphologic features of chronic rejection in kidney and less commonly transplanted organs

Sibley RK. Morphologic features of chronic rejection in kidney and less commonly transplanted organs.
Clin Transplantation 1994: 8: 293–298. © Munksgaard, 1994

Richard K. Sibley

Department of Surgical Pathology, Stanford University Medical Center, Stanford, California, U.S.A.

Abstract: Chronic rejection is characterized by morphological evidence of destruction of the transplanted organ. The injury to the organ is associated with collagenization of variable degree. The destruction and fibrosis of the organ is probably the result of 1) direct alloimmune cytotoxic
jection) of the organ tissue, and 2)
to fibroproliferative endarteritis (i.e.,
linal morphological feature of chronic
liferative endarteritis, which is char-
othelial space due to a cellular fibrosis



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American Journal of Transplantation 2003; 3: 599–605
Blackwell Munksgaard

ISSN 1600-6135

Histological Grading of Chronic Pancreas Allograft Rejection/Graft Sclerosis

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Departments of [a] Pathology,[b] Medicine and [f] Surgery, University of Maryland, School of Medicine, Baltimore MD, USA
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[d] Department of Pathology, Johns Hopkins University

Introduction

Biopsy-proven chronic rejection (CR) is the largest single cause of late pancreas allograft loss (1–3). The clinical presentation of CR is nonspecific, with loss of glycemic control being the main feature. Hyperglycemia may develop progressively or may be unmasked by infection or other physiologic stresses (1). However, the clinical usefulness of this feature is limited since with the development of hyperglycemia due to chronic rejection, the beta cell function is in general already irretrievably lost (1). The diagnostic specificity of hyperglycemia is also

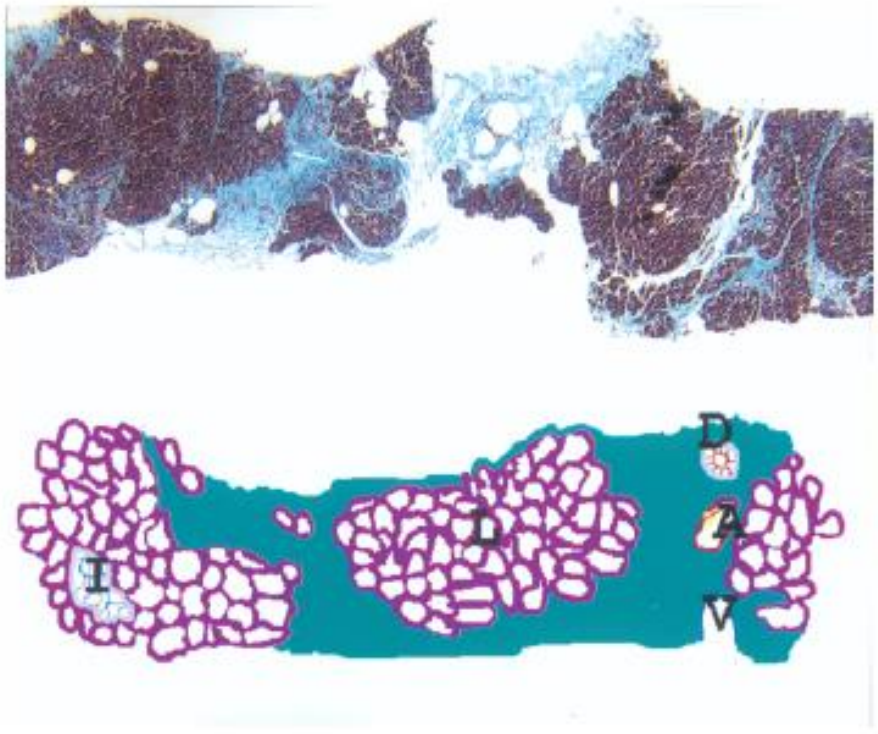


Figure2: Grade I – Mild chronic rejection/graft sclerosis. Expansion of fibrous septa (<30% of core surface). The lobules show peripheral erosion and fragmentation, but the central areas are intact.

Grade

0- 54 mths
1- 24 mths
2- 9 mths
3 – 1-2 mths

ACUTE AND CHRONIC REJECTION OVER TIME
IN A TYPICAL CASE OF GRAFT LOSS

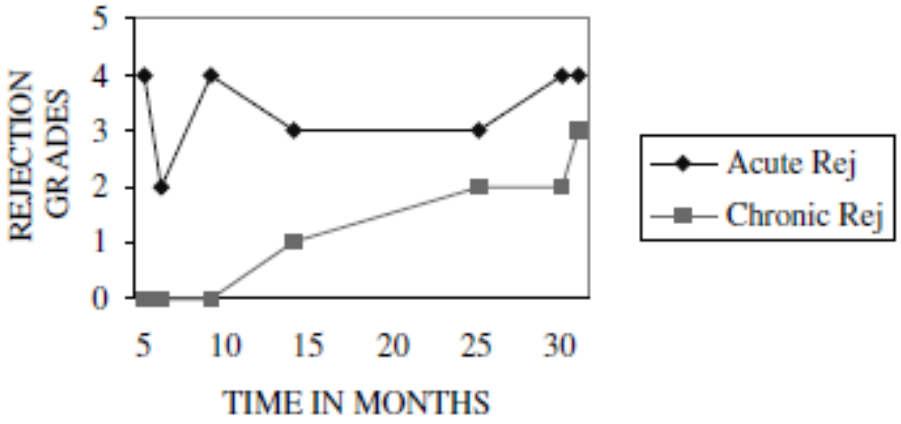
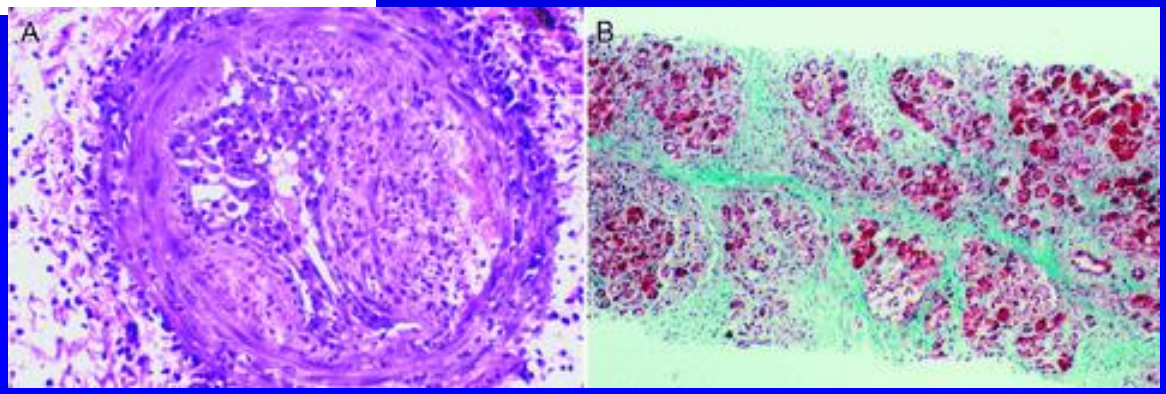


Figure 6: Acute and chronic rejection grades in serial biopsies from a PTA recipient who lost graft function 34 months after transplantation. Repeated episodes of acute rejection (including late rejections) and several instances of acute rejection grade IV occurred over time. Chronic rejection/graft sclerosis was initially non-existent but gradually progressed, leading to loss of graft function.



Yonsei Medical Journal
Vol. 45, No. 6, pp. 1169 - 1172, 2004

Vanishing Pancreatic Grafts

Christopher Pivetti[1], In Chul Hong[1], Chang H. Yoo[1], Sun Lee[1], Kenny Kim[1], Gregory Emmanuel[1], Jason Kim[1], Romy Chung[1], Slawomir Niewiadomski[2], Paul Wolf[3], and R. F. Gittes[4]

From the [1]San Diego Microsurgical Institute, [2]Scripps Mercy Hospital, [3]University of California San Diego Medical Center, [4]Scripps Clinic.

Comparison of pancreaticoduodenal transplants (PDT) and duct-ligated pancreas transplant (DLPT) were performed using syngeneic and allogeneic studies in rats. Both DLPT and PDT allogeneic grafts showed mild rejection. DLPT groups showed disorganized pathology and acini replaced by fat. Eventually, massive fibrosis was seen in the Islets of Langerhans, as well as rejection cellular infiltrates. In both PDT groups, normal histology was observed in the same period. Thus the effect of duct occlusion is highly detrimental for the grafts.

Key Words: Pancreaticoduodenal transplants, duct-ligated pancreas transplants

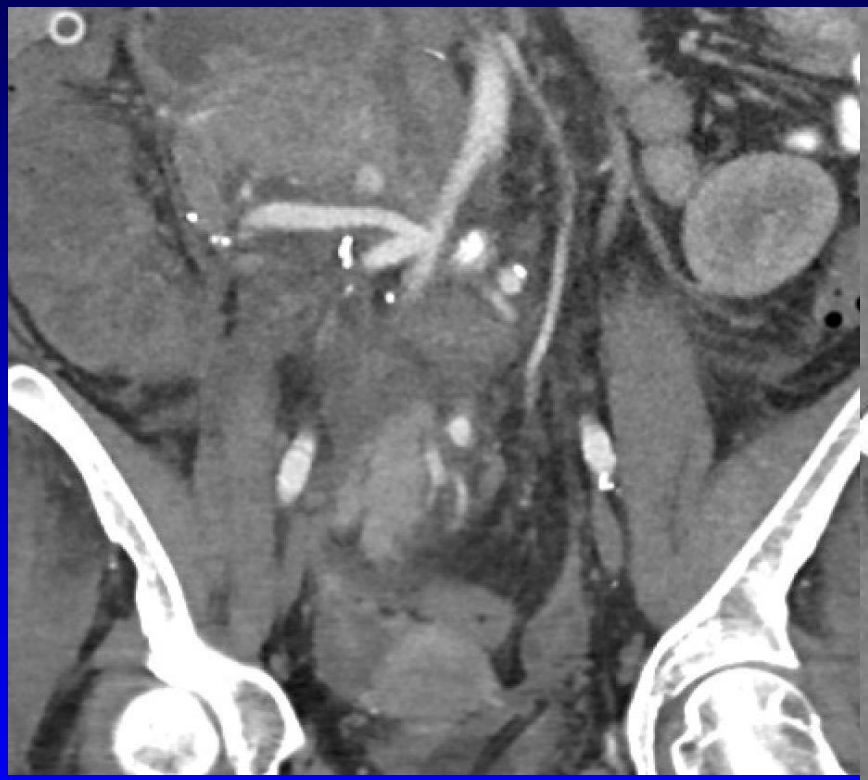
MATERIALS AND METHODS

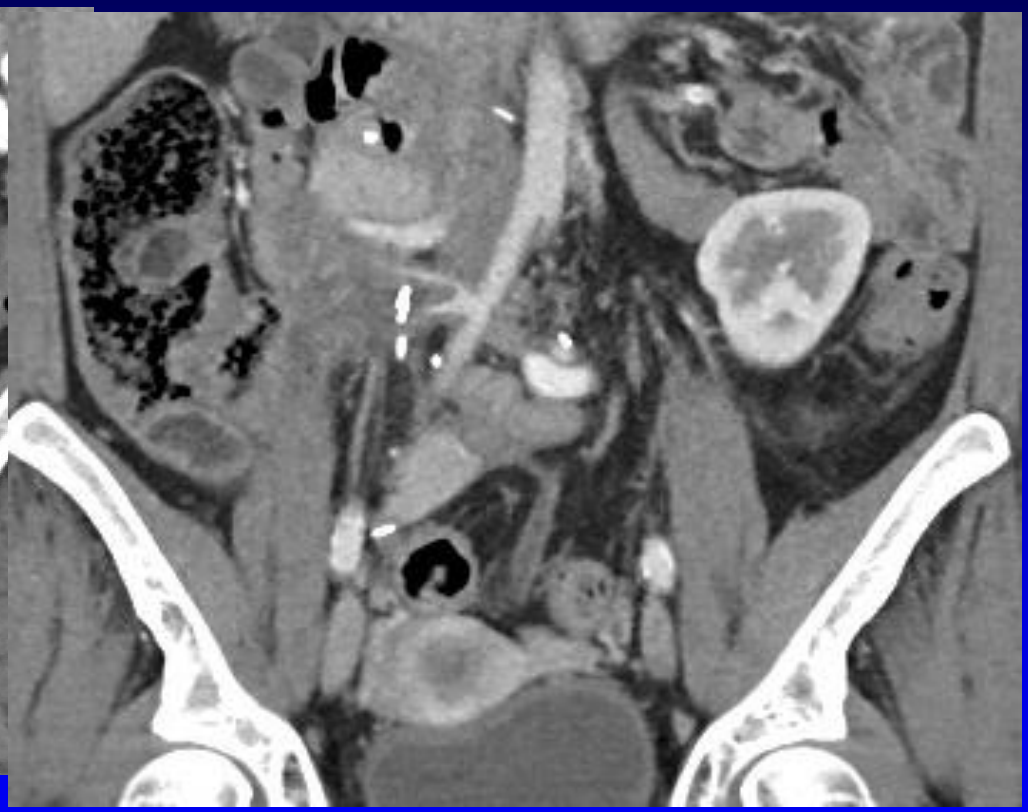
Lewis (LW) and Sprague Dawley (SD) rats, weighing 250g to 300g of mixed sex were employed for syngeneic and allogeneic studies, respectively. Though SD strains of rats were inbred at the San Diego Microsurgical Institute for over 15 generations, transplantation of solid organs (heart or pancreas) between SD strains still shows mild to moderate rejection phenomena. Grafts between

Vascular remodelling

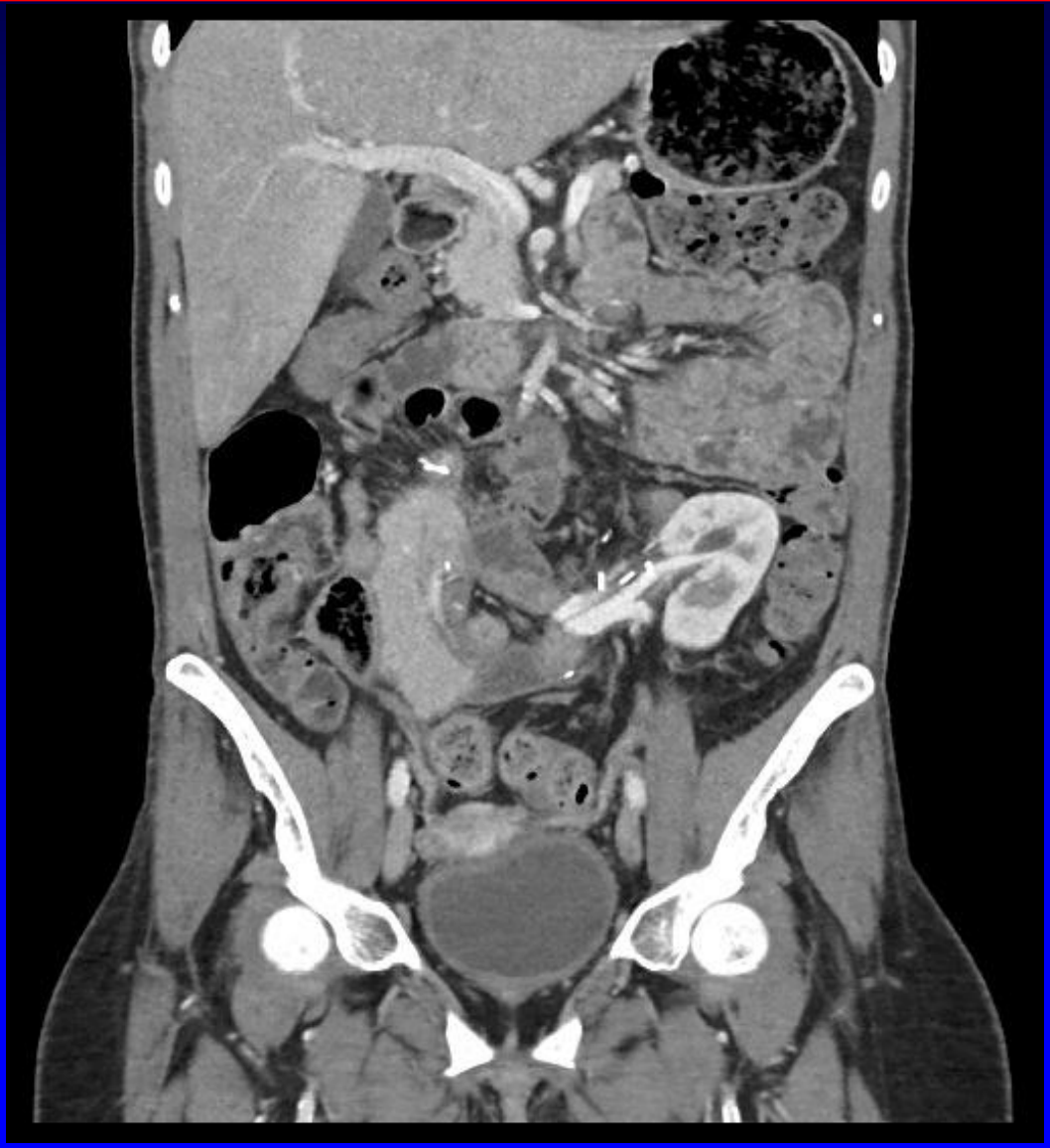
- Physiological process triggered by a number of insults
- Differs from pathological stenotic disease
  - Rejection
  - donor specific antibodies
- Incidental observation of pancreatic graft vessel narrowing necessitated further investigation after a change in practice on post-op imaging

SPK Arterial Early/Late



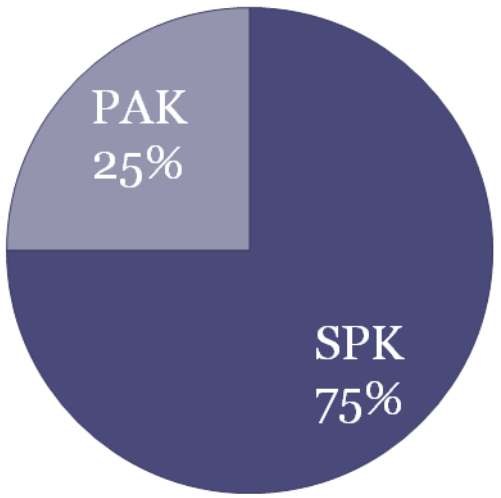


Renal Arterial Late



Results

- 8 patients
- 12 month period
- Standard immunosuppression
  - Alemtuzmab Tacrolimus, MM
- Surgical technique-Systemic



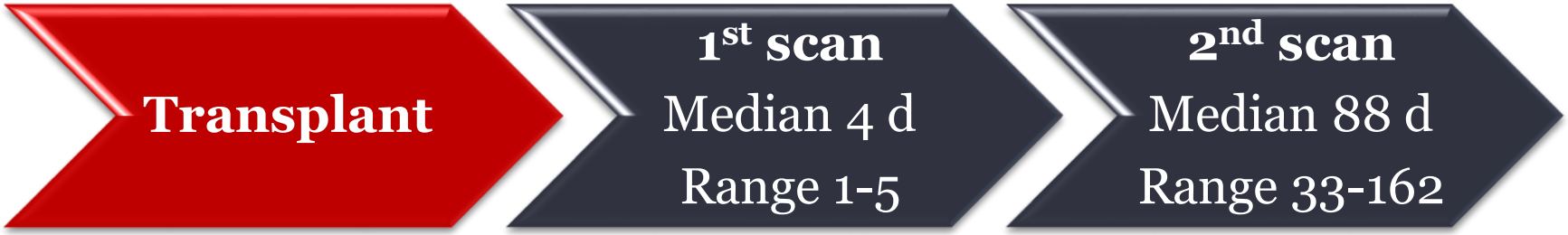
Characteristic	Statistic
Sex - M:F	7:1
Recipient age	Median 43 (32-55)
Donor age	28 (9-51)
CIT	9.8 (7.4-13.5)
Drainage – Enteric:Bladder	6:2

Aims/methods

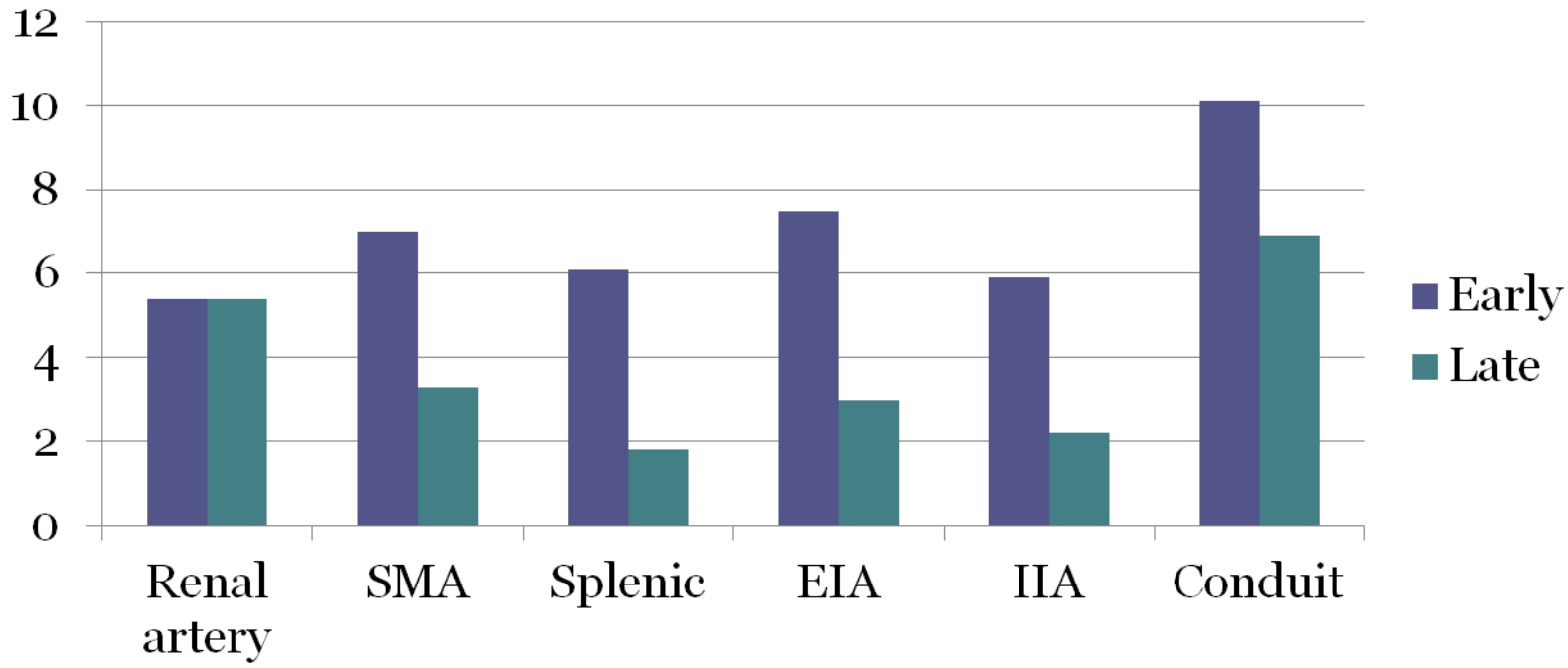
- Examine changes in axial/coronal diameters of the arterial conduit, external iliac artery (EIA), internal iliac artery (IIA), superior mesenteric artery (SMA), splenic artery (SA) and renal arteries
- Retrospective CT analysis
  - Measurements were made by experienced radiologists

Imaging timescales

- In 2012 CT angiography became routine for pancreas transplants in the early (<5 days) and late (< 6 months) post-transplant period



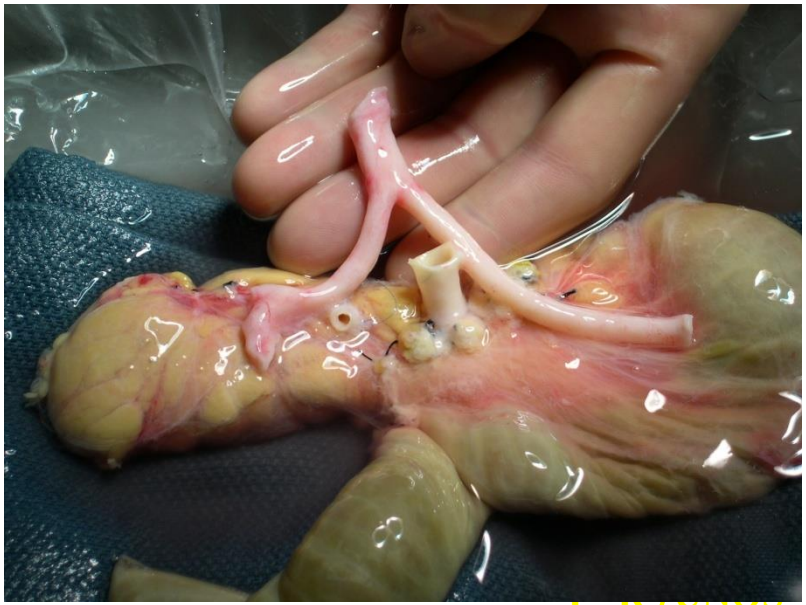
Mean Δ luminal diameter (mm)



Median % Δ (range)	0	-50 (40-70.4)	-60 (50-86.7)	-70.8 (0-80)	-57.8 (50-80)	-30.7 (0-77.8)
P value	n/a	<0.01	0.012	<0.01	<0.01	<0.01

Morbidity

- Acute rejection (n=1)
  - Resolved with steroids
  - Arterial branch thrombosis (n=2)
  - Anticoagulated
- Collection (n=2)
- Pancreatitis (n=1)



Follow up

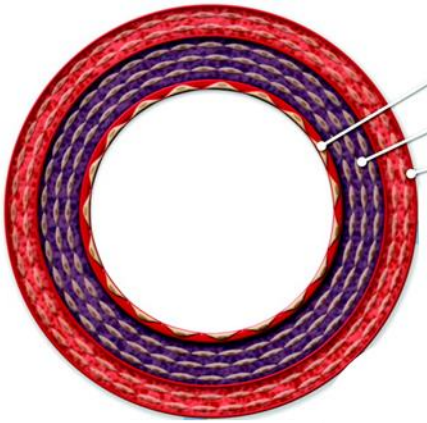
- All grafts functioning @ median follow up 15 months (range 10-21)
- All patients insulin independent
- 3 patients developed de novo DSA
- Occurs independently of DSA
- No CMV infections

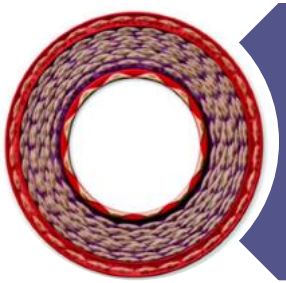
Summary

- Luminal narrowing of large pancreatic allograft vessels
  - No corresponding changes in renal arteries
- No apparent impact on short term graft function/survival
- ? Aetiology

Physiological remodelling	Pathological disease
• Compensatory due to reduced demand	• Stenotic vasculopathy • Immunological/rejection related

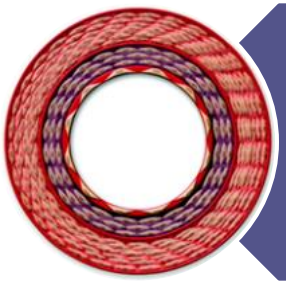
Transplant vasculopathy





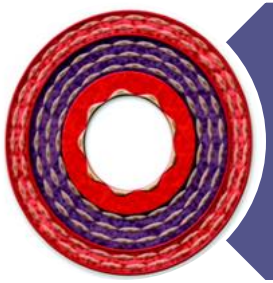
Increased medial tone

- secondary to reduced vasodilator production or response or increased vasoconstrictor activity
- ↑ wall shear stress



Adventitial fibrosis

- limit the ability of the perivascular ECM to positively remodel and will indirectly lead to luminal compromise



Intimal hyperplasia

- recruitment of inflammatory cells and SMLCs and elaboration of ECM

Clinical implications

- Risk of thrombosis
- Graft survival
- Therapeutic Modulation-anti-angiogenesis
- - PDGF, BMP4, A20, uric acid