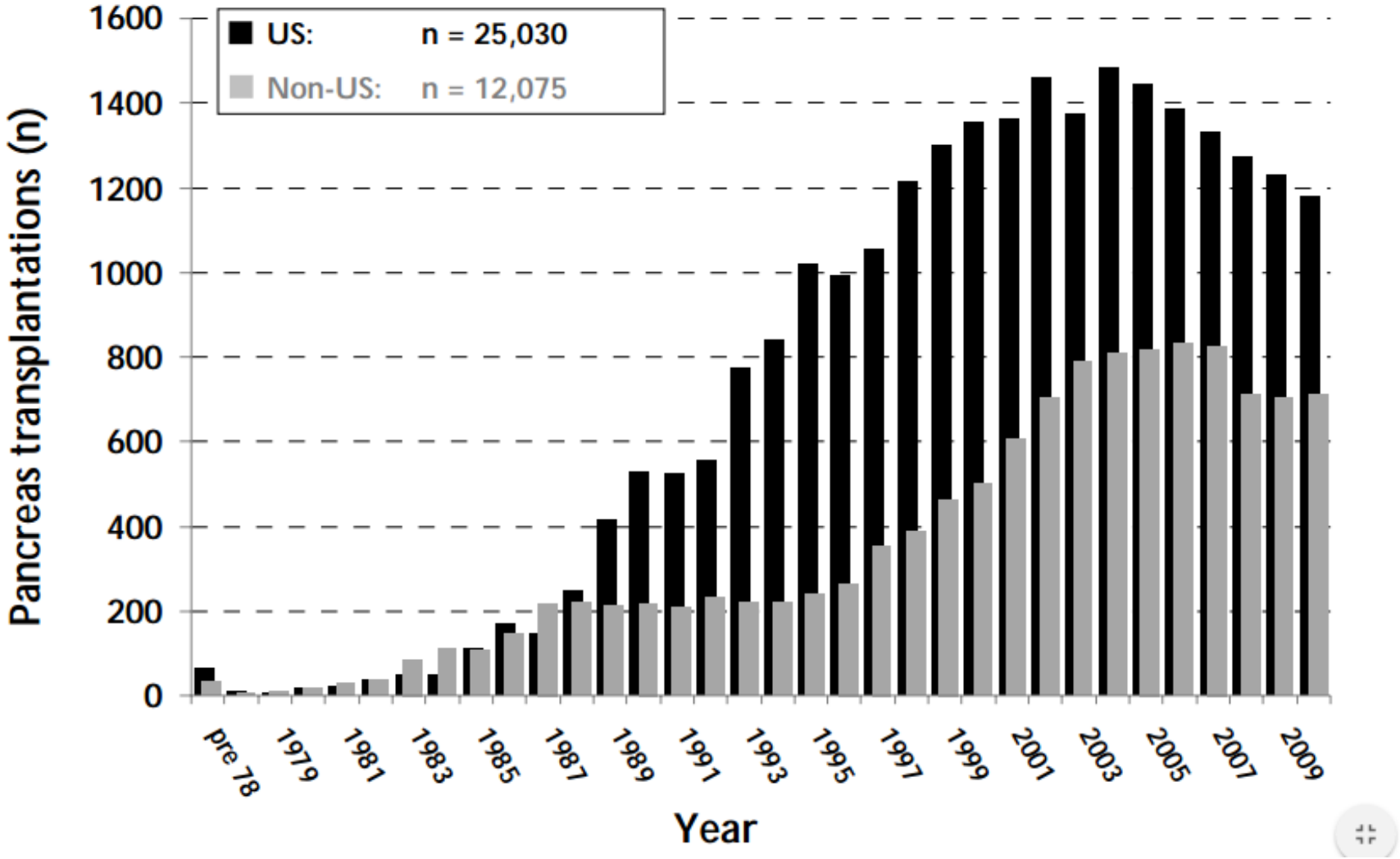
PANCREAS AND PANCREATIC ISLETS TRANSPLANTATION

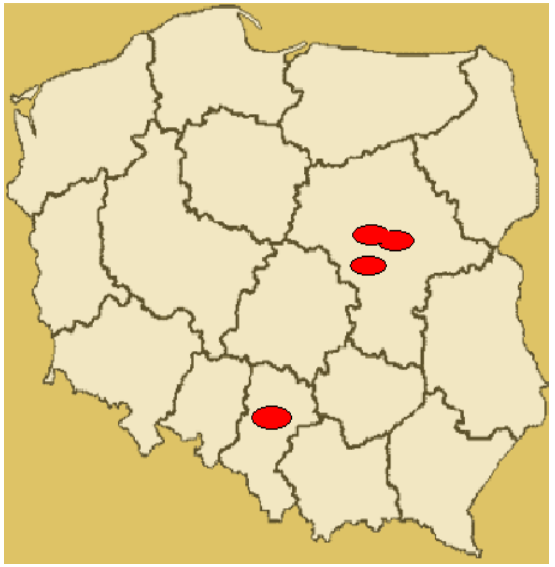
Annual number of pancreas transplantations reported to UNOS/IPTR, 1966-2010

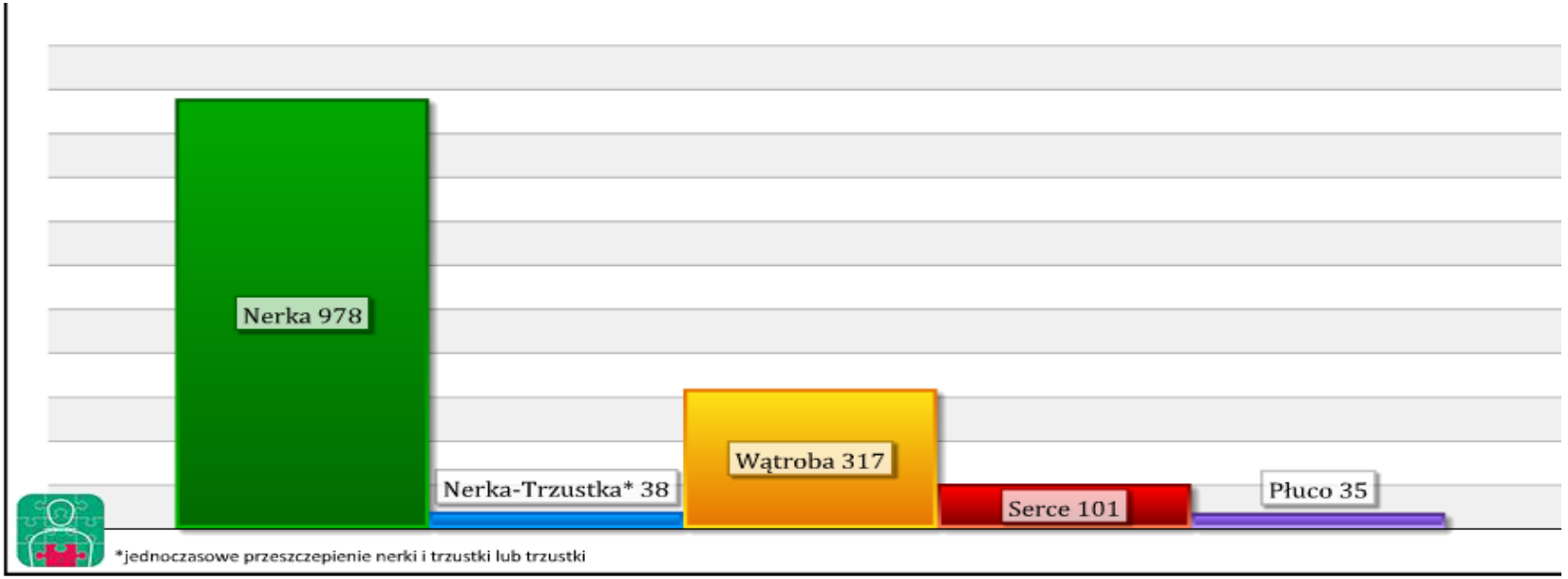


Pancreas transplantation

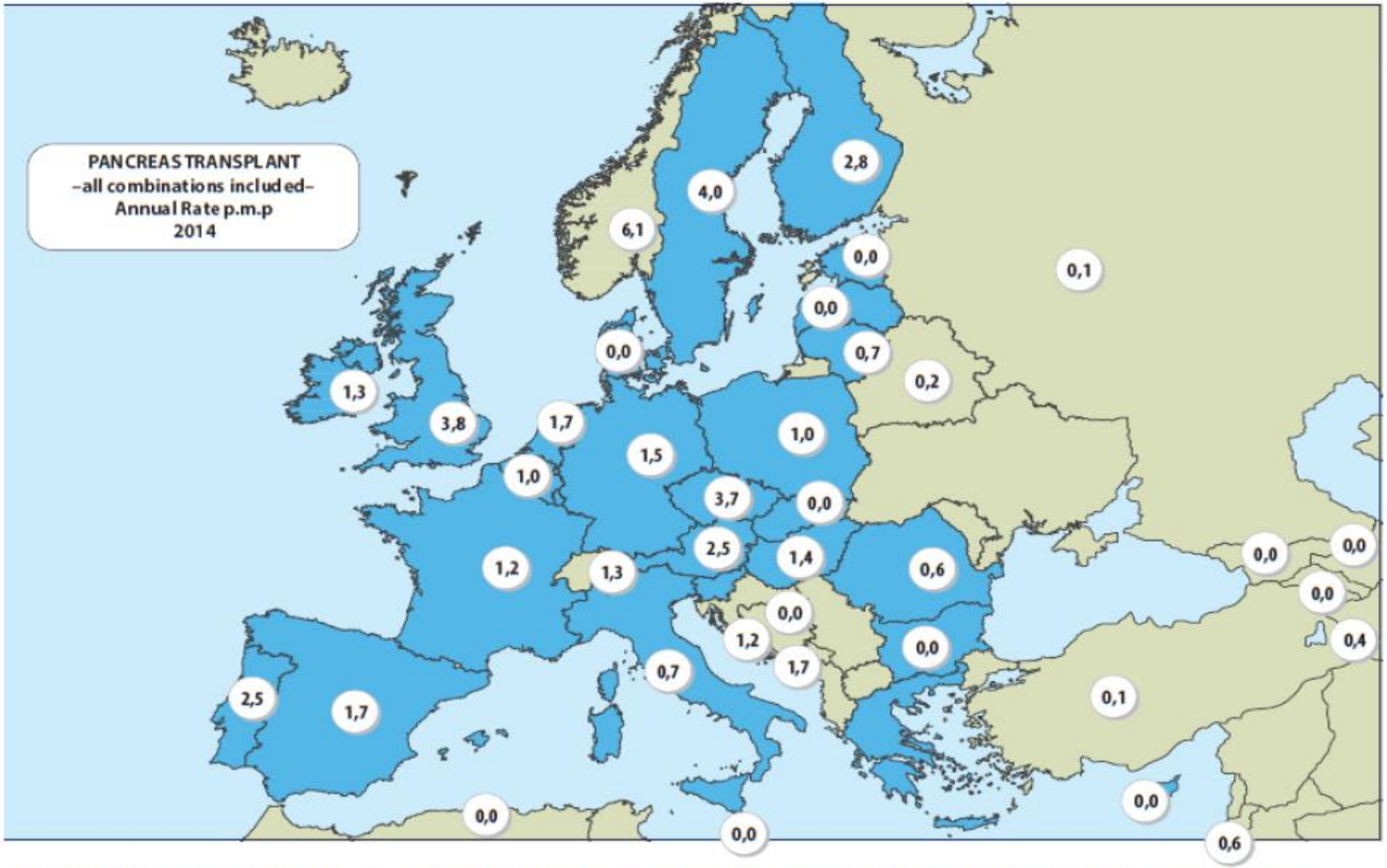
1. pancreas transplantation in the world :
R.Lillehei and W. Kelly 1968 USA

1. successful pancreas transplantation in Poland:
J. Szmidt 1988





Pancreas transplantation in Europe



Council of Europe and Organización Nacional de Trasplantes, et al. Newsletter Transplant. International figures on donation and transplantation 2014. http://www.ont.es/publicaciones/Documents/NEWSLETTER_2015_CE.pdf. Accessed 19/04/2016.

Pancreas transplantation -goals

- restore glucose-regulated endogenous insulin secretion
- arrest the progression of the complications of diabetes
-improve quality of life

Pancreas transplantation - modalities

SPKTx – *simultaneous pancreas-kidney transplant* (75%)

PAK – *pancreas after kidney* (12%)

PTA – *pancreas transplant alone (7%)*

Pancreas transplantation - indications

- **SPKTx –** type 1/ type 2 diabetics with secondary complications and uremia (chronic renal failure in pre-dialysis or on dialysis with creatinine clearance <20mL/min)

  On insulin **AND** C-peptide ≤2 ng/mL **OR**

  On insulin **AND** C-peptide >2 ng/mL **AND** BMI ≤30 kg/m^2

PAK – *pancreas after kidney* type 1 diabetics with a normal kidney transplant function function (eGFR min > 55ml/min)

PTA – *pancreas transplant alone* type 1 diabetics who are not uremic

Pancreas transplantation - indications

- Patients (age range between 18 and 55 years) without substantial renal disease are candidates for pancreas transplantation alone if they have:

  a history of frequent, acute, severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis),

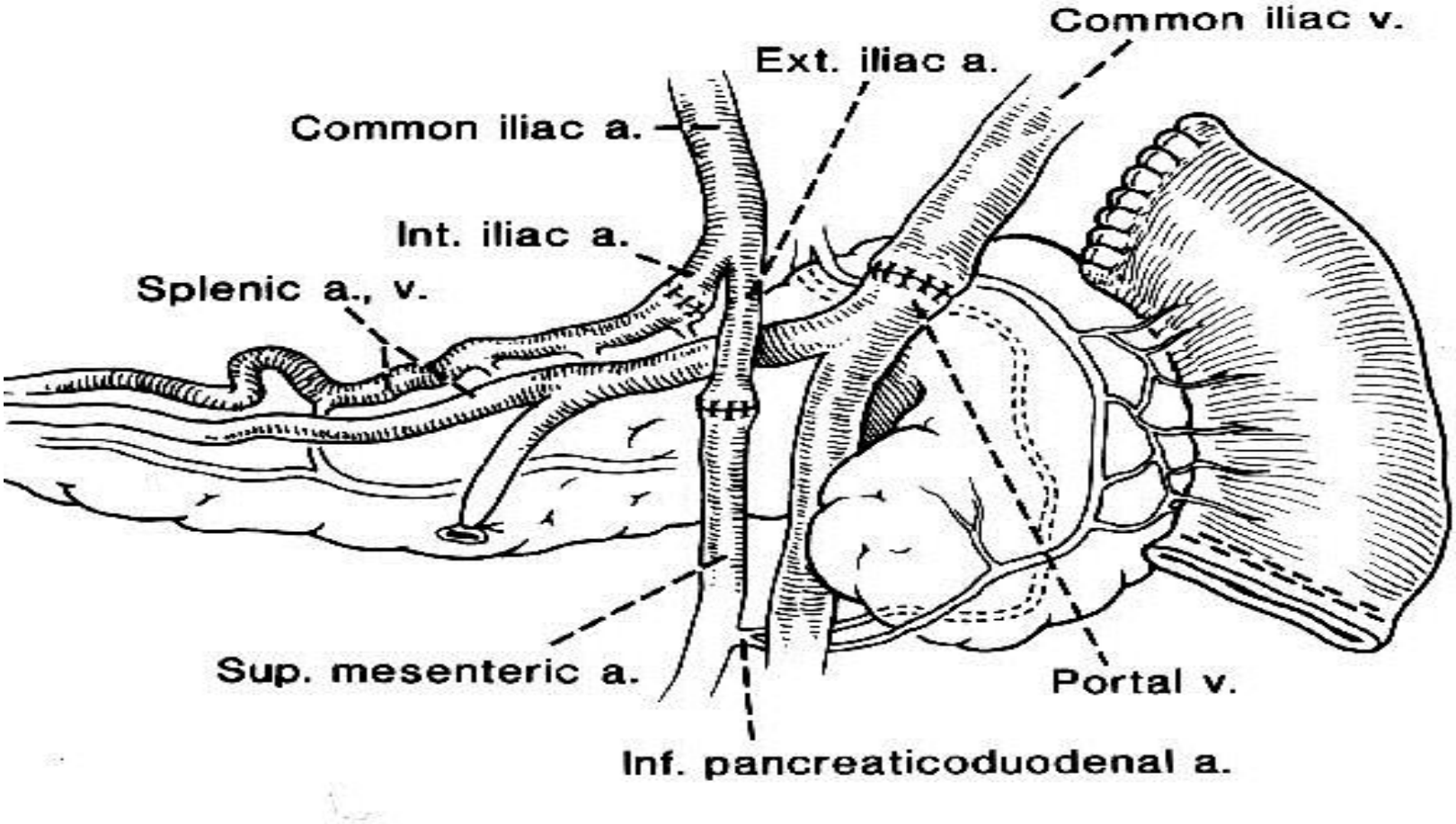
  incapacitating clinical and emotional problems with exogenous insulin therapy,

  and consistent failure of insulin-based management to prevent acute complications.

- Patients (age range between 18 and 55 years) with ESRD who have had or plan to have a kidney transplant

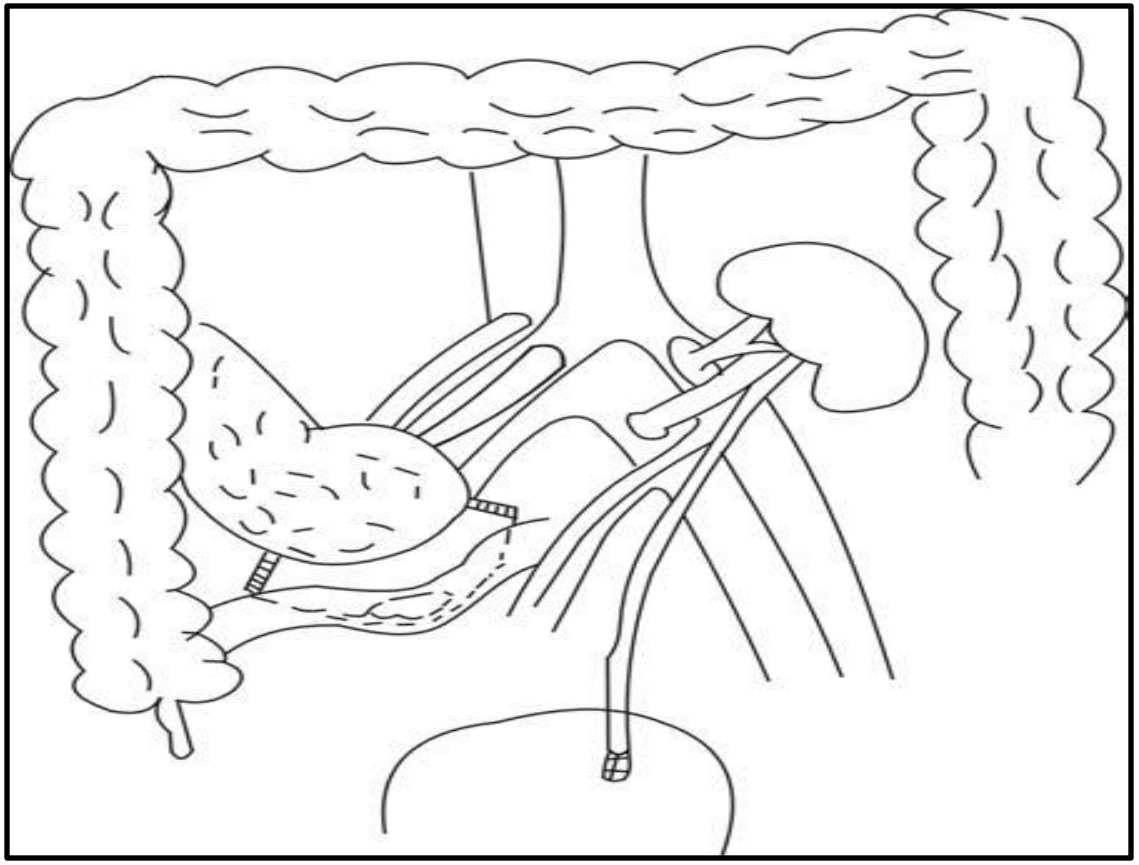
Pancreas transplantation – donor selection

- age range between 5-45 years (USA < 40-35 years)
- the weight of the donor should be between 30 and 50kg if there is retrieval of the pancreas without the liver, and >50kg if both pancreas and liver are procured
- blood compatibility in the ABO system
- negative crossmatching
- HLAmatching
- BMI <30



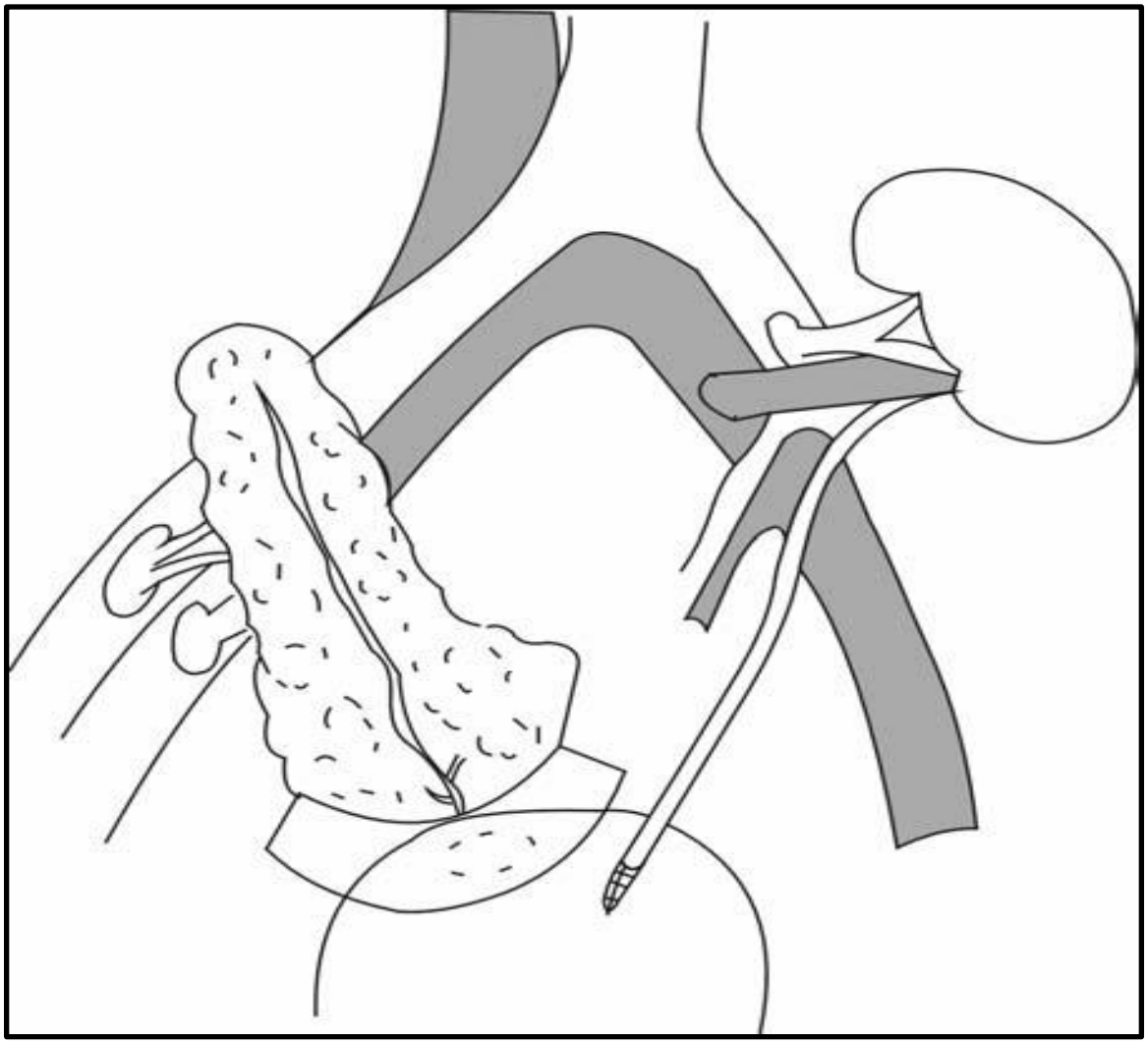
mobilization of the portal vein, vascular Y graft reconstruction (iliac arteries from the donor with the pancreatic graft superior mesenteric artery and splenic artery) arterial anastomosis to a branch of the iliac artery and venous anastomosis to a branch of the iliac vein

Enteric drainage of pancreatic exocrine secretion of the graft (side-to-side duodenojejunal anastomosis)

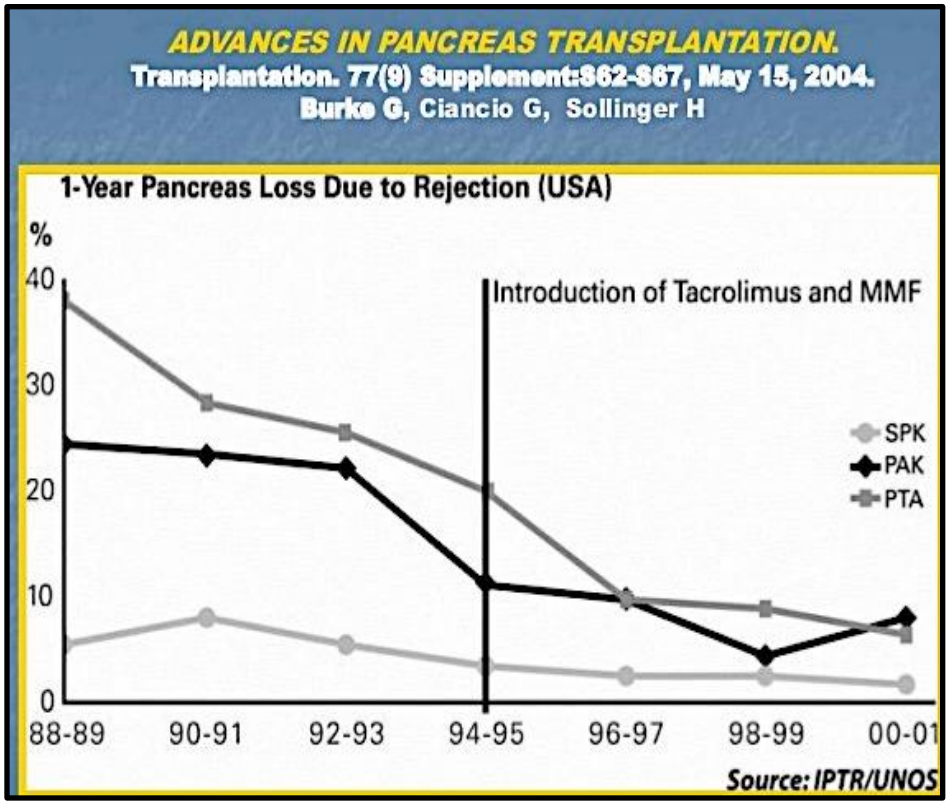


The pancreatic implant is preferentially performed in the right iliac fossa of the recipient, since the right iliac vessels are more accessible.

Bladder drainage of pancreatic exocrine secretion of the graft (side-to-side duodenovesical anastomosis)

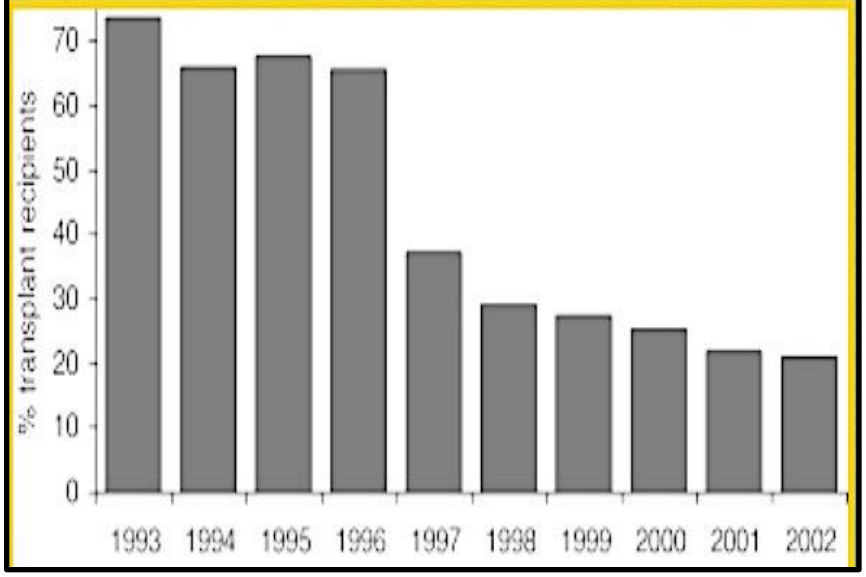


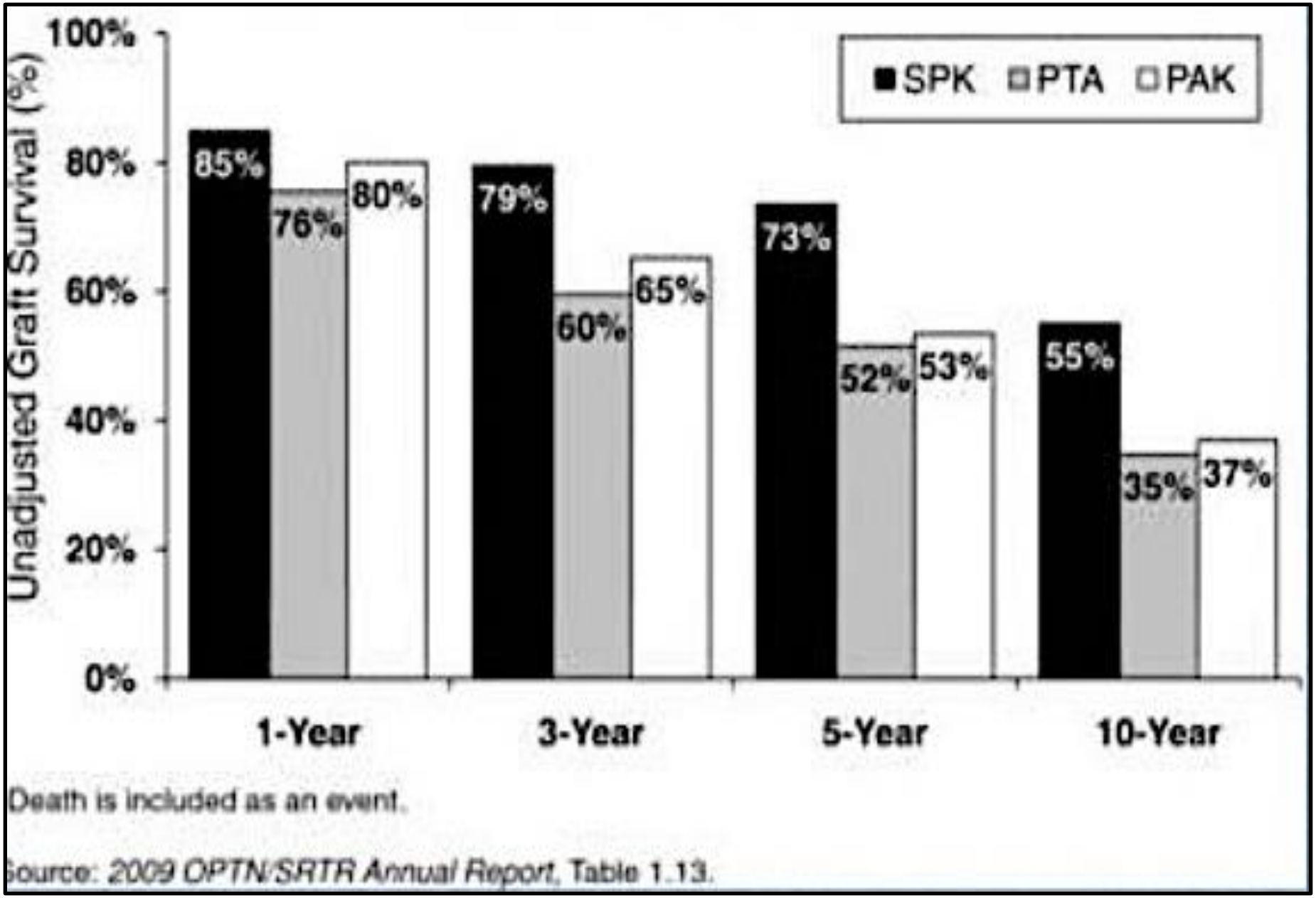
ADVANCES IN PANCREAS TRANSPLANTATION.
Transplantation. 77(9) Supplement:S62-S67, May 15, 2004.
Burke G, Ciancio G, Sollinger H



Incidence of rejection during first year among simultaneous kidney-pancreas recipients

American Journal of Transplantation 2005;5(Part 2):874-886





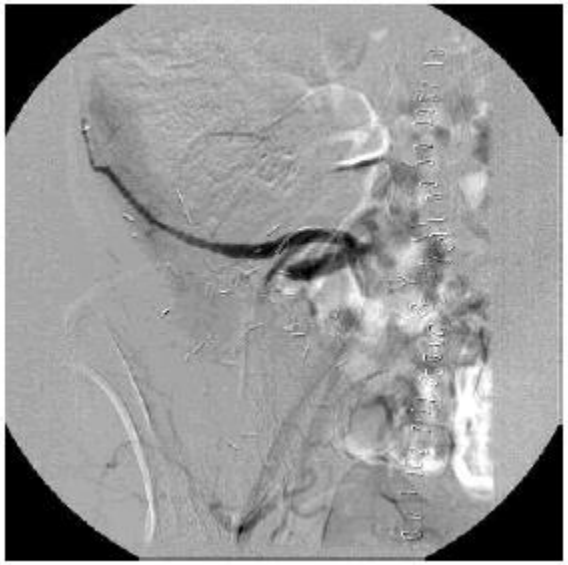
Death is included as an event.

Source: *2009 OPTN/SRTR Annual Report*, Table 1.13.

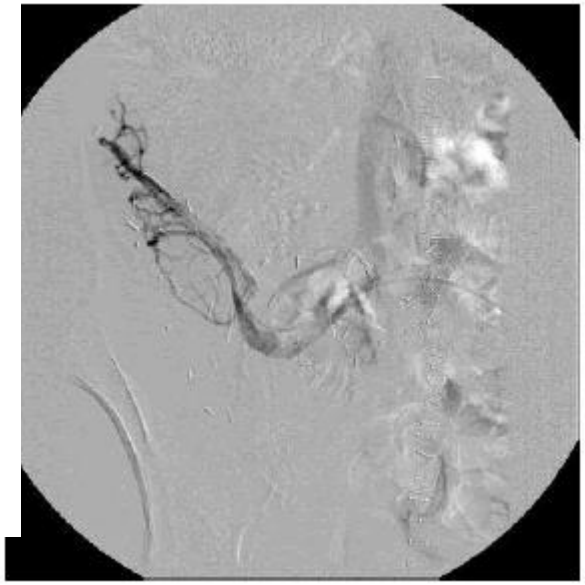
Early graft loss

defined as loss occurring within hours or days after surgery, usually results from:

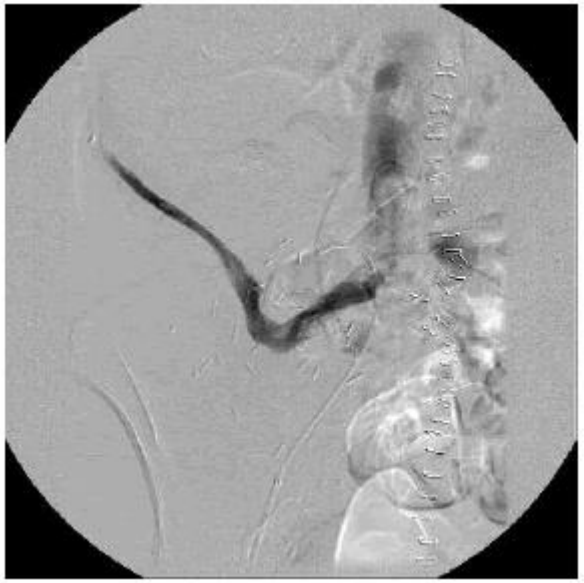
thrombosis (10%)
leaks,
bleeding,
infection,
pancreatitis



arterial inflow into the pancreatic transplant



extensive thrombus in the venous drainage of the pancreatic transplant



… after pulsed spray of thrombolytic into the vein

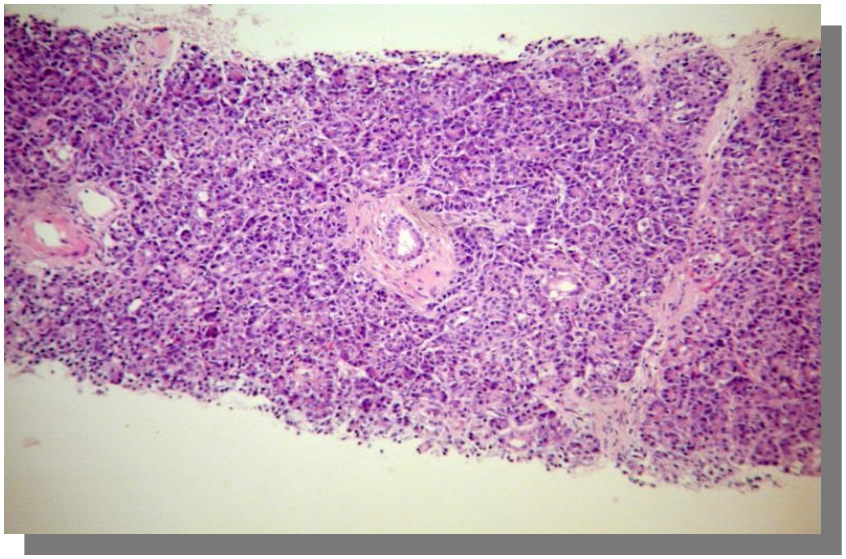
Asher J. et al.: ExpClinTrans2013

Rejection

The rejection of the pancreas graft is uncommon in the absence of concurrent kidney graft rejection (≤15 %)

Increasing serum amylase concentrations → Increasing blood glucose concentrations

When rejection is suspected, a cystoscopic-guided transduodenal pancreatic biopsy is the procedure of choice

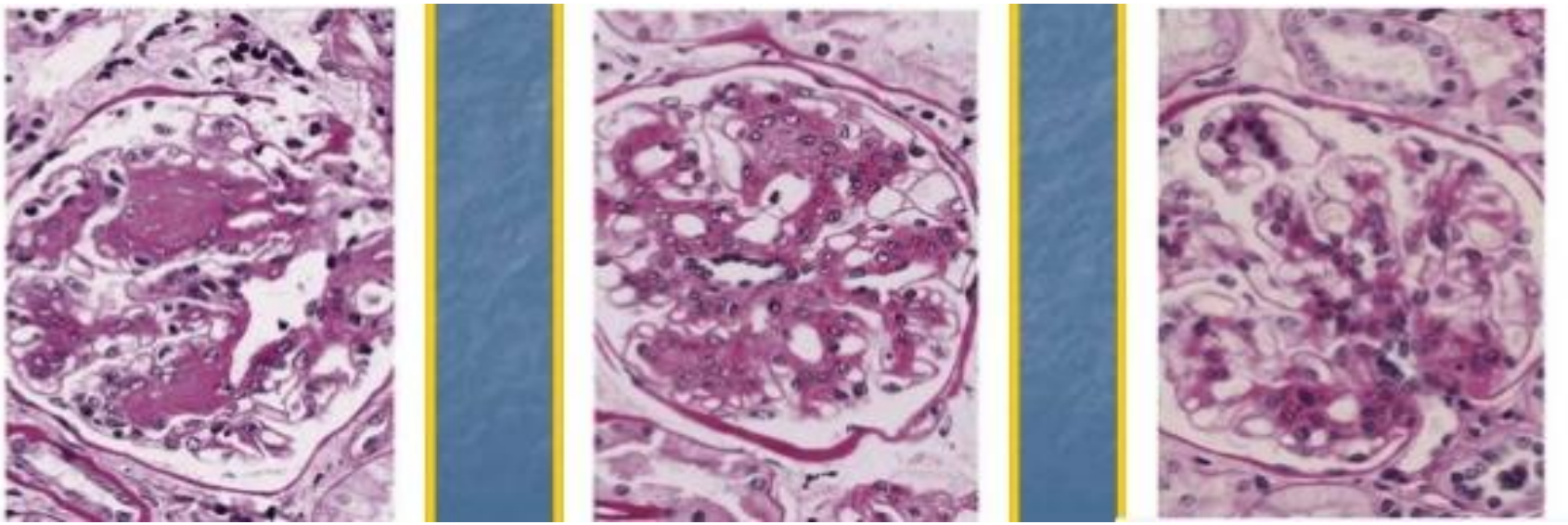


PTA > PAK > SPK

Effects on the chronic complications of diabetes

- Quality of life studies consistently demonstrate benefits, such as return to work and successful pregnancies.
- Life expectancy in patients with autonomic insufficiency is dramatically increased
- The velocity of motor and sensory nerve conduction as well as clinical neuropathy stabilizes

Effects on the chronic complications of diabetes



Renal structure becomes more normal, as reflected by diminished mesangial mass in patients receiving pancreas and kidney transplants versus those receiving a kidney alone and by improvement in native renal structure after 10 years

Fioretto P et al.: NEJM 1998

Later graft loss

death with functioning graft

chronic rejection

reccurent autoimmunity

insulin resistance (T2D)

chronic calcineurin inhibitor toxicity

graft pancreatitis in the absence of rejection

cytomegalovirus, PTLD and bacterial or fungal infection

ISLET TRANSPLANTATION

The first attempt at islet transplantation occurred in 1893 when Watson-Williams and Harsant transplanted minced sheep's pancreas into the subcutaneous tissue of a young boy with ketoacidosis

Insulin was first discovered through the efforts of Nobel Prize winners Banting and Best in the 1920s

The first to isolate islets was Polish Professor, Stanislaw Moskalewski, who prepared pancreatic islets in 1965 from a guinea pig for physiological study

First method of islet isolation and purification including the development of the Ricordi chamber by Camillo Ricordi in 1989

The first successful trial of human islet allotransplantation resulting in long-term reversal of diabetes was performed at the University of Pittsburgh in 1990

Pancreatic islets transplantation - indications

- type 1 diabetes (allo)
- chronic pancreatitis (auto)

Pancreatic islets transplantation -goals

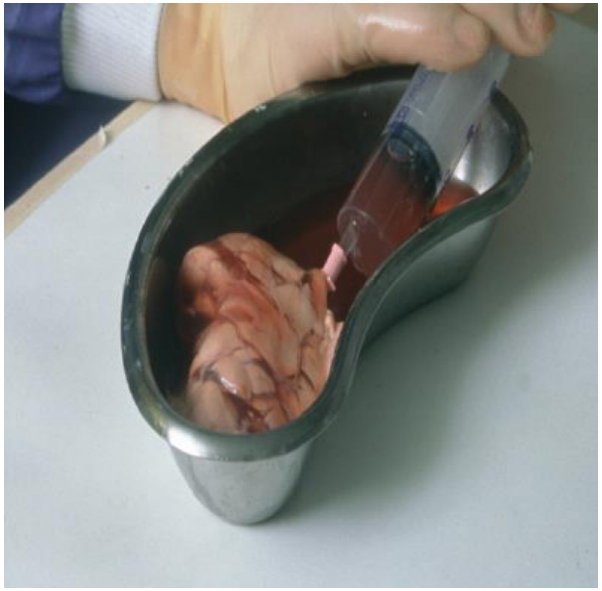
- optimal glycemic control without severe hypoglycemia, rather than insulin independence (HbA1c < 7%, C-peptide > 3 ng/mL)

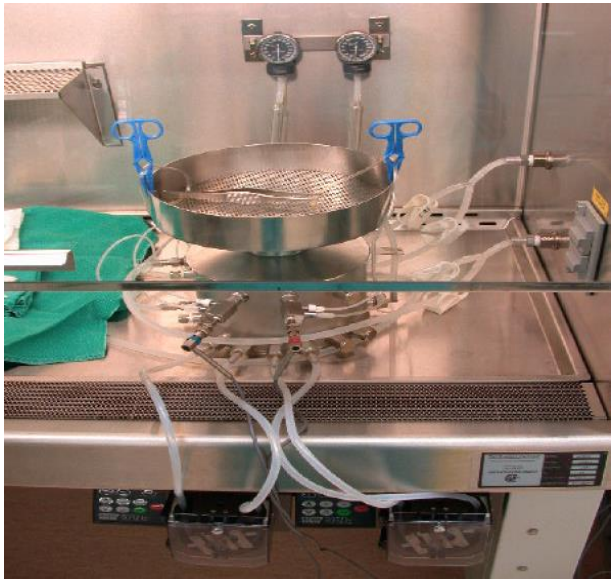
- arrest the progression of the complications of diabetes

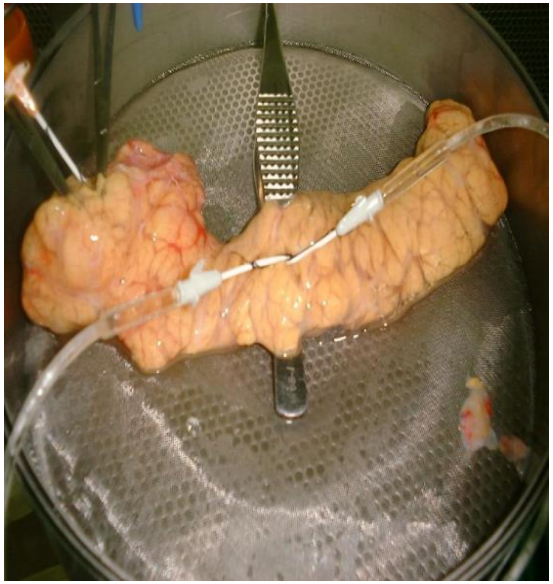
-improve quality of life

Islet isolation

The procurement of a donor pancreas with subsequent digestion and separation of the exocrine tissue and stroma from the islets. This is performed using enzyme degradation and density centrifugation

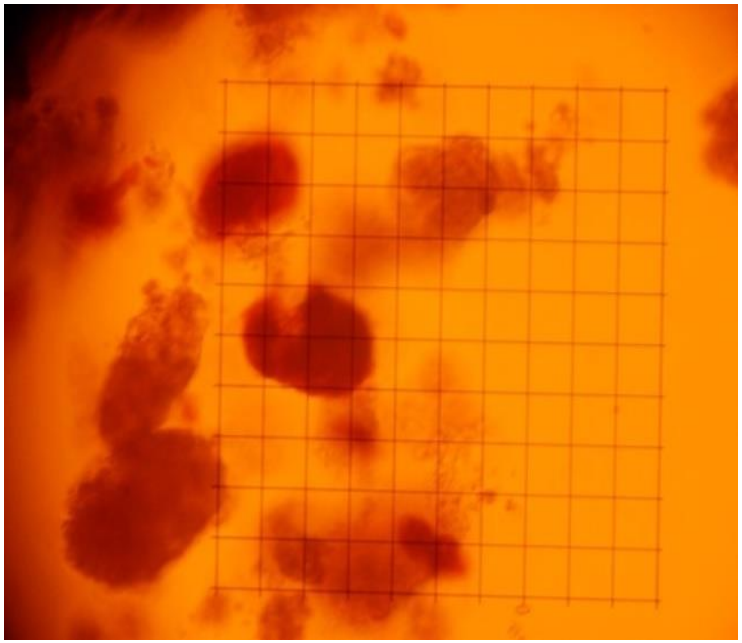


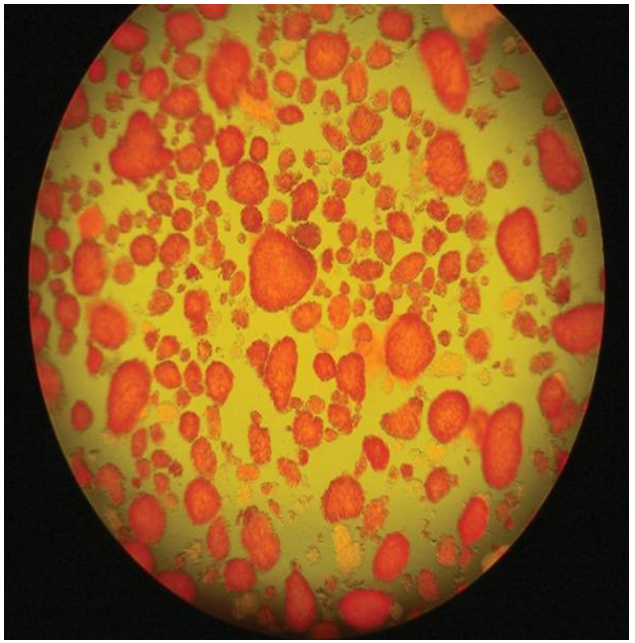




Islet isolation

Islet preparations that contain an adequate number of islets
(5000 islet equivalents per kilogram based on recipient weight
Insulin independence – 8000-9000ie/kg = multiple donors / obese donors).

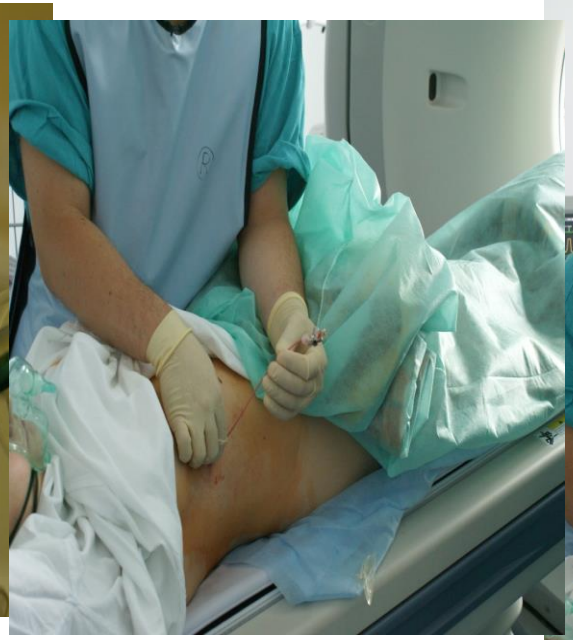


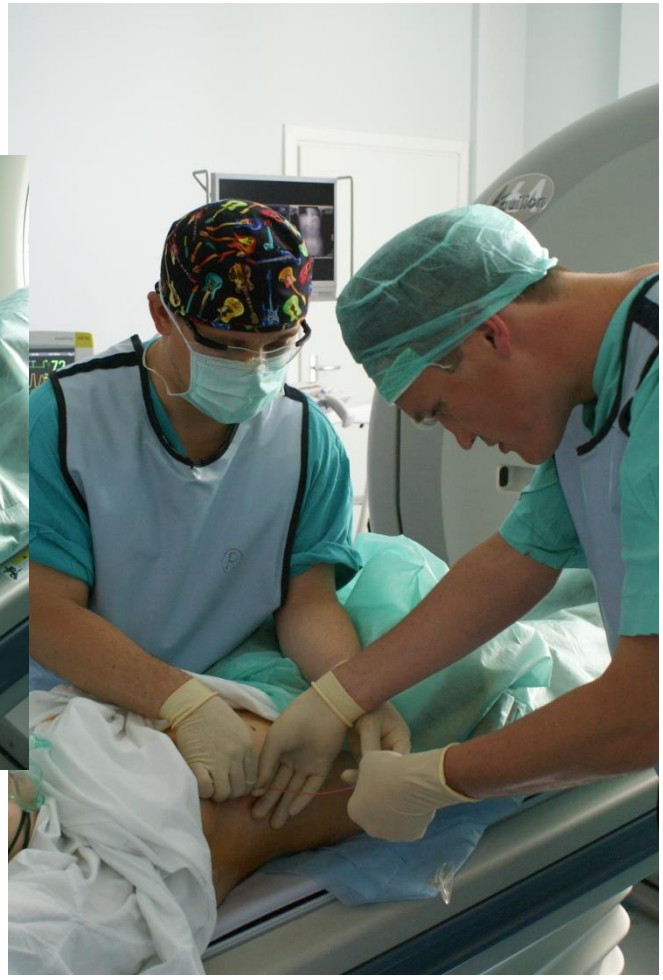


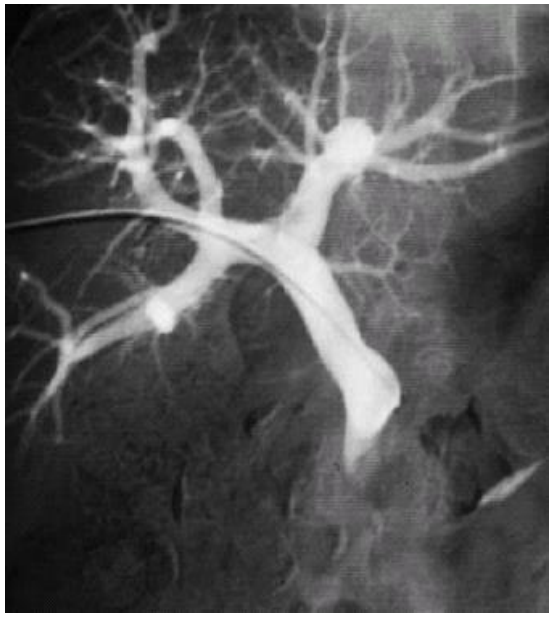
50-70 % of the islet mass can be lost during the purification process!!!.

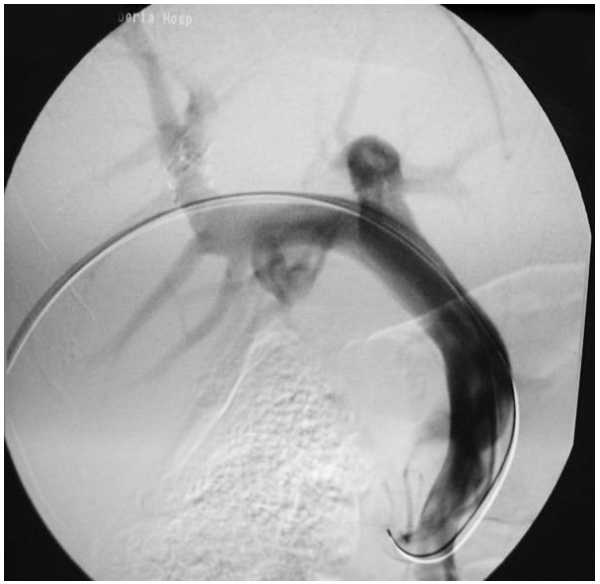
Islet transplantation

The majority of transplants involve percutaneous cannulation of a branch of the portal vein with subsequent gravity infusion of the islet preparation









Intrahepatic islet transplant grafts (auto or allografts):

- unable to secrete glucagon in response to sustained hypoglycemia
- exposed to environmental toxins and high immunosuppressive drug concentrations that can impair beta cell function
- must be purified to avoid injecting a large tissue volume into the liver (which may result in obstruction of portal flow and portal hypertension

Alternate sites: omentum, peritoneal cavity, bone marrow are being considered

Efforts to achieve successful islet transplantation

Transplantation with a sufficient amount of islets
- obese donors
- multiple donors
- older donors
- fetal pancreatic tissues

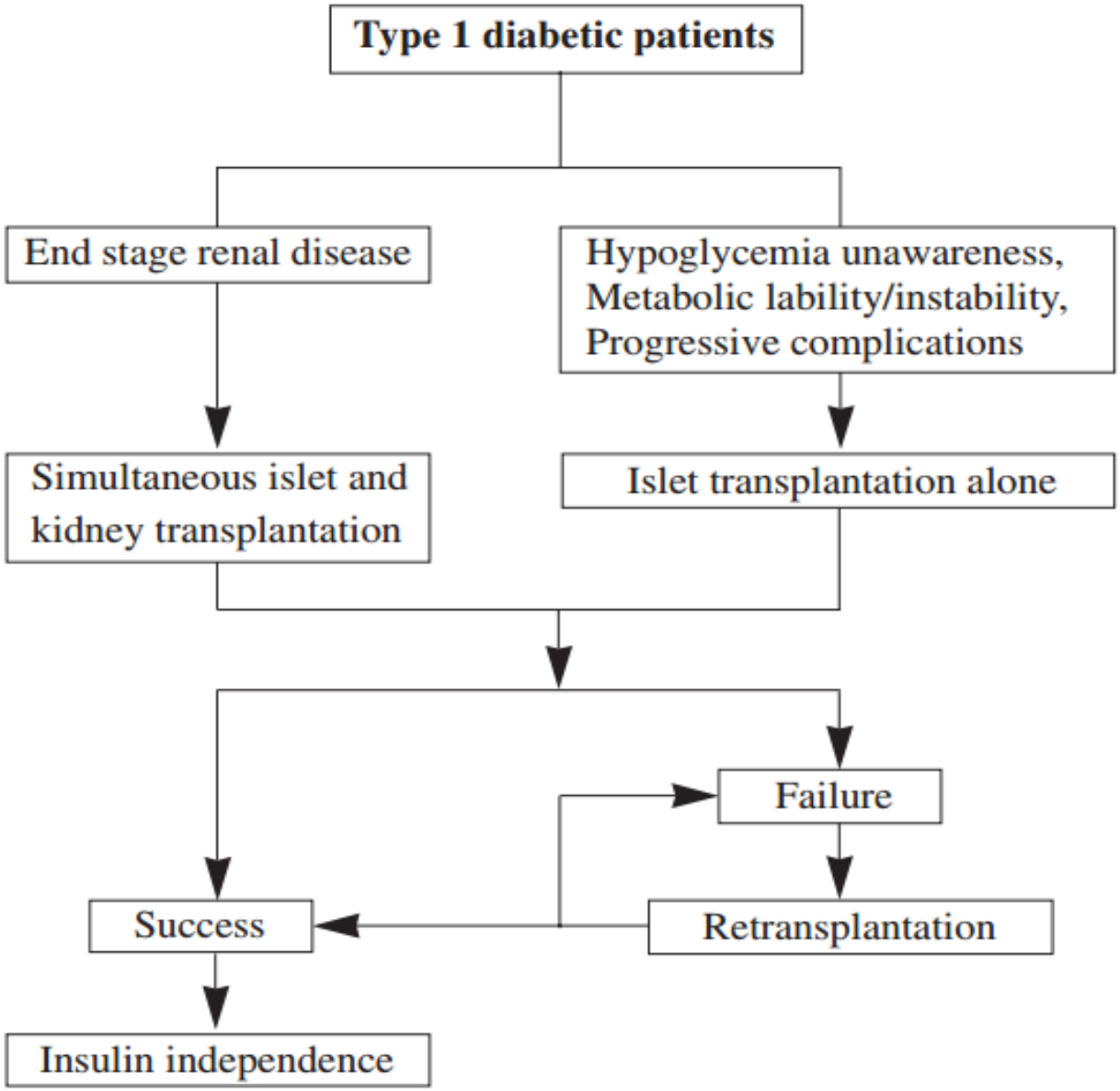
Modification of islet processing and preservation methods
- A two-layer (UW solution/perfluorochemical) method
- pancreas perfusion with collagenase
- islet culture before transplant
- cryopreservation

Searching for alternative islet sources
- animal islet tissues
- insulin-producing cell lines
- genetically engineered insulin-producing cells
- progenitor/stem cells B.

total pancreatectomy and islet autotransplantation (TPIAT)

Advantages:

- use of freshly isolated islets (often within three to four hours of pancreas resections) as opposed to the longer periods of time required to harvest islets from human donors
- absence of underlying autoimmune disease directed at beta cell destruction, as is present in type 1 diabetes
- absence of the need for immunosuppressive drugs, which are often toxic to beta cells


Type 1 diabetic patients
End stage renal disease
Hypoglycemia unawareness,
Metabolic lability/instability,
Progressive complications
Simultaneous islet and
kidney transplantation
Islet transplantation alone
Failure
Success
Retransplantation
Insulin independence