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Pancreas Transplantation

Tayyab S. Diwan, MD

Surgical Director of Pancreas Transplantation

Division of Transplantation

University of Cincinnati

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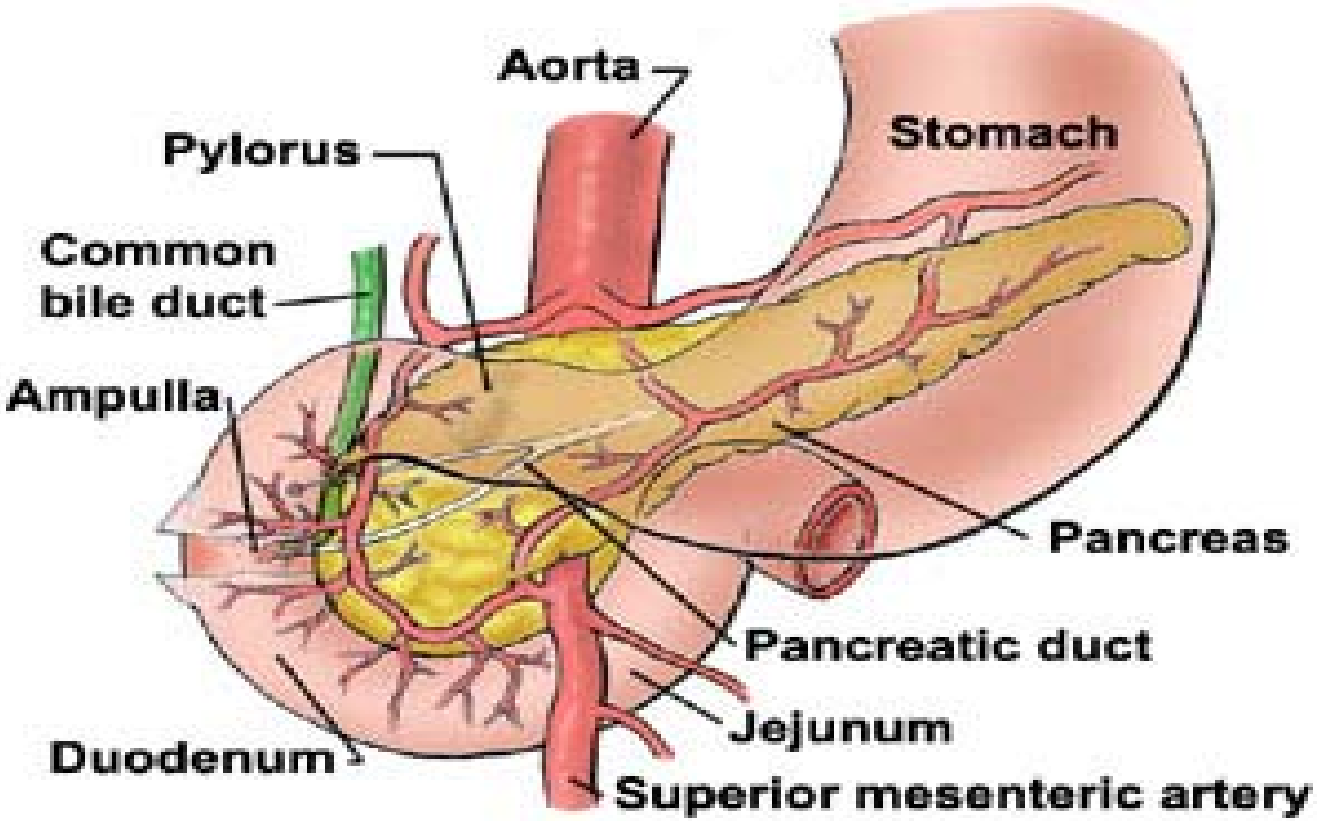
Pancreas Anatomy



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Pancreas Physiology

- Exocrine
  - Digestion of lipids and proteins
  - Pre-Cursors: Trypsinogen, chymotrypsinogen, lipase and amylase
  - Enterokinase bound to enterocytes in the duodenum

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Pancreas Physiology

- Endocrine
  - Regulate serum blood sugar
  - Islets of Langerhans
    - B-cells produce Insulin
      - stimulates cells to use glucose
    - A-cells produce Glucagon
      - increases serum gulcose by binding to hepatocyte receptors
      - Glycogen to glucose

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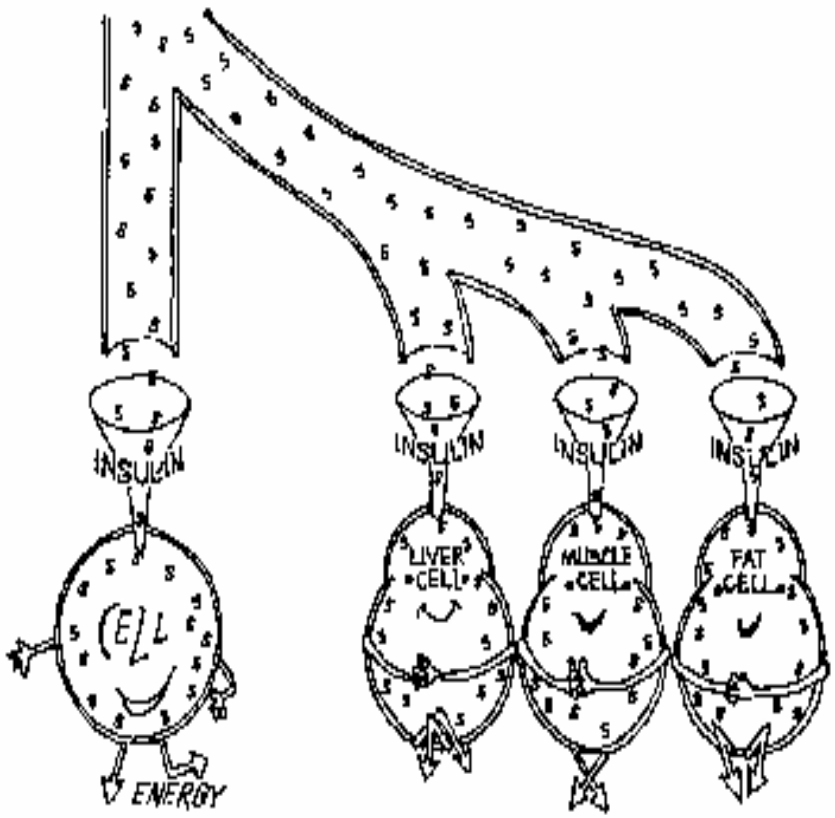
The Role of Insulin



- Polypeptide that regulates carbohydrate metabolism
- Allows cells to use serum glucose
- Inhibits liver glycogen breakdown

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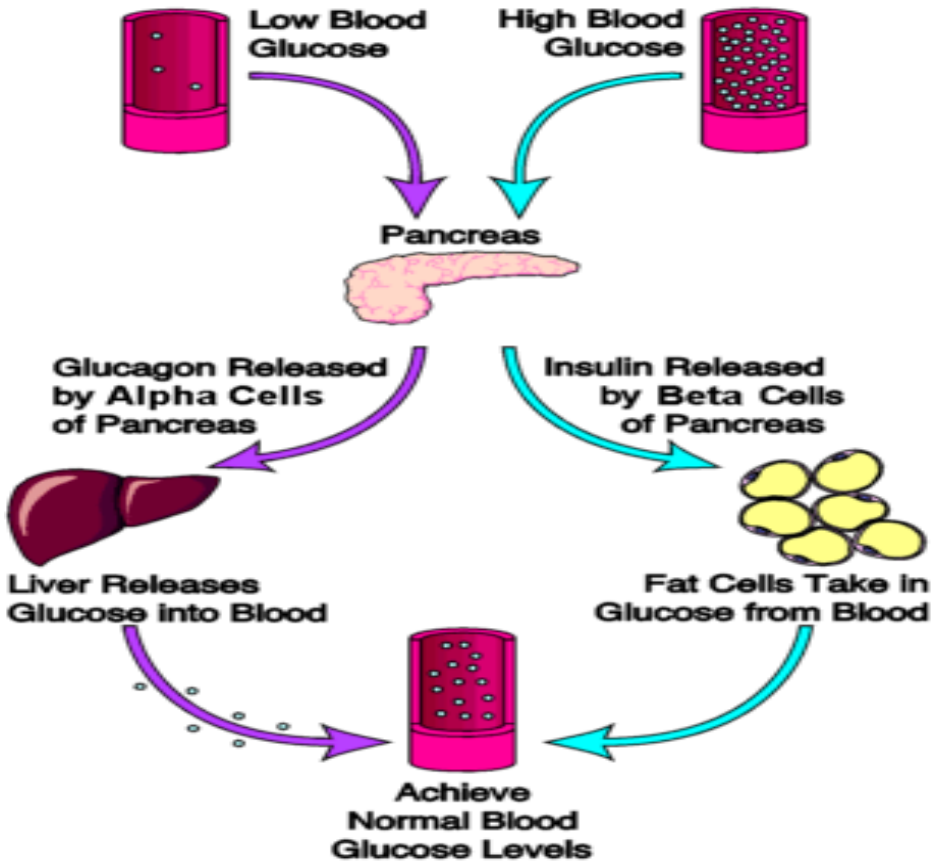
Pancreas Physiology



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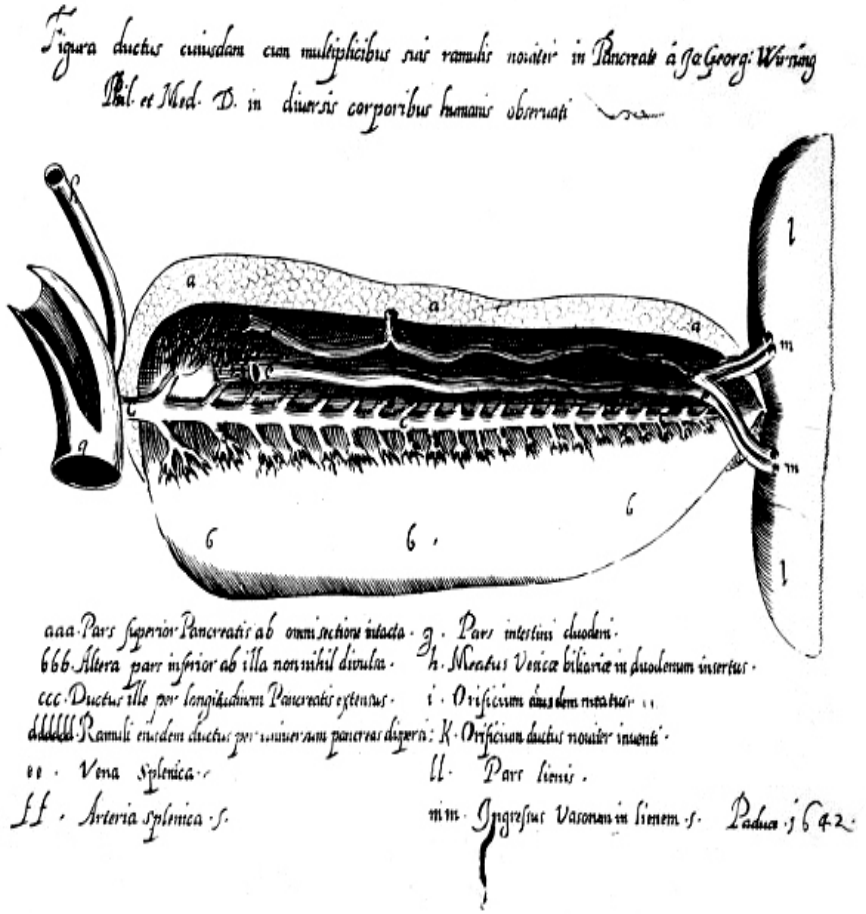
History of the Pancreas

- Discovered by Herophilus, Greek anatomist and surgeon, in 336 BC
- 400 years later Ephesus, Greek anatomist-surgeon, rediscovered the organ and named in ‘Pan-Kreas’
- Galen (138-201AD): ‘Physician to the Gladiators’ and the Roman Emperor
  - Pancreas serves as a cushion to blood vessels
  - No further scientific investigation until the 18th century

History of the Pancreas

- Johann Wirsung, in 1642, discovers the pancreatic duct in Italy
- Paul Langerhans, in 1869, a student at the Berlin Institute of Pathology, describes histology
- Late 1800's introduce aseptic operative technique advancing research in human and animal models

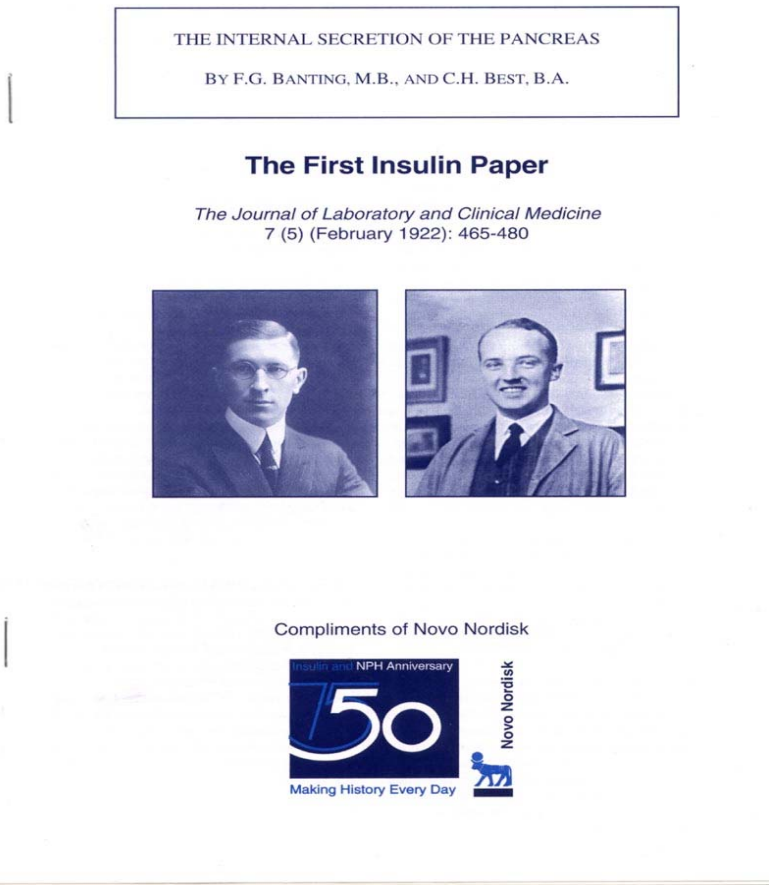


History of the Pancreas and DM

- Frederick Banting and Charles Best, in 1921 at the Univ of Toronto credited with the discovery of insulin
- Working from JJR Macleod's lab, James Bertram Collip, PhD extracted the insulin

History of Pancreas and DM

- No IRB…No Problem
- 6 months after 1st successful dog
- 14 yo Leonard Thompson injected with purified dog insulin



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History of Pancreas and DM

- The Canadian aftermath….
- Banting and Macleod were awarded the Nobel Prize in less than 3 years
- Thompson went on to work in a chemical factory, taking 85 units/d, until died of pneumonia at 46 years
- The University of Toronto was unable to keep up with the production of insulin and gave unlicensed control to Eli Lilly of Indianapolis, Indiana (within 18 mo)

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Diabetes Mellitus

- Condition of chronic hyperglycemia
  - Type I
  - Type II
  - Gestational DM
- Derived from the Greek
  - Diabetes: a siphon
  - Mellitus: sweet
  - Insipidus: that which has no flavor

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Modern Diagnosis of Diabetes

- National Diabetes Data Group and World Health Organization
- Symptoms of DM and nonfasting BS >200 mg/dL (sx: polyuria, polydipsia and unexplained wt loss)
- Fasting (no calories >8h) BS >126
- BS > 200, 2h after 75g glucose load

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Type I Diabetes Mellitus

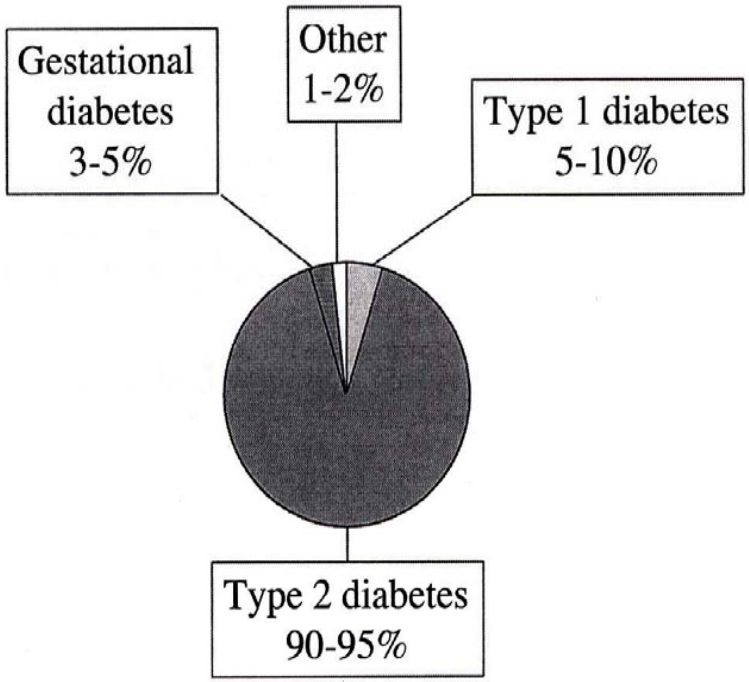

FIGURE 1.1. Types of diabetes. (Data are based on estimates of diabetes in the United States in 1998 by the Centers for Disease Control and Prevention.[4])

- Since 1997, no longer called IDDM
- Disease of absolute insulin deficiency
- Combo of genetic and environmental
- Autoimmune disorder
- May be triggered by viral infection
- Most common chronic disorder among child

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Type II Diabetes Mellitus

- Insulin resistance, inc BS, insulin deficiency and obesity
- Unlike Type I, no ketoacidosis
- Pathophysiology
  - Obesity, sedentary lifestyle
  - Inc hepatic glucose
  - Dec glucose transport
  - Impaired Bcell fxn due to loss of response to hyperglycemia

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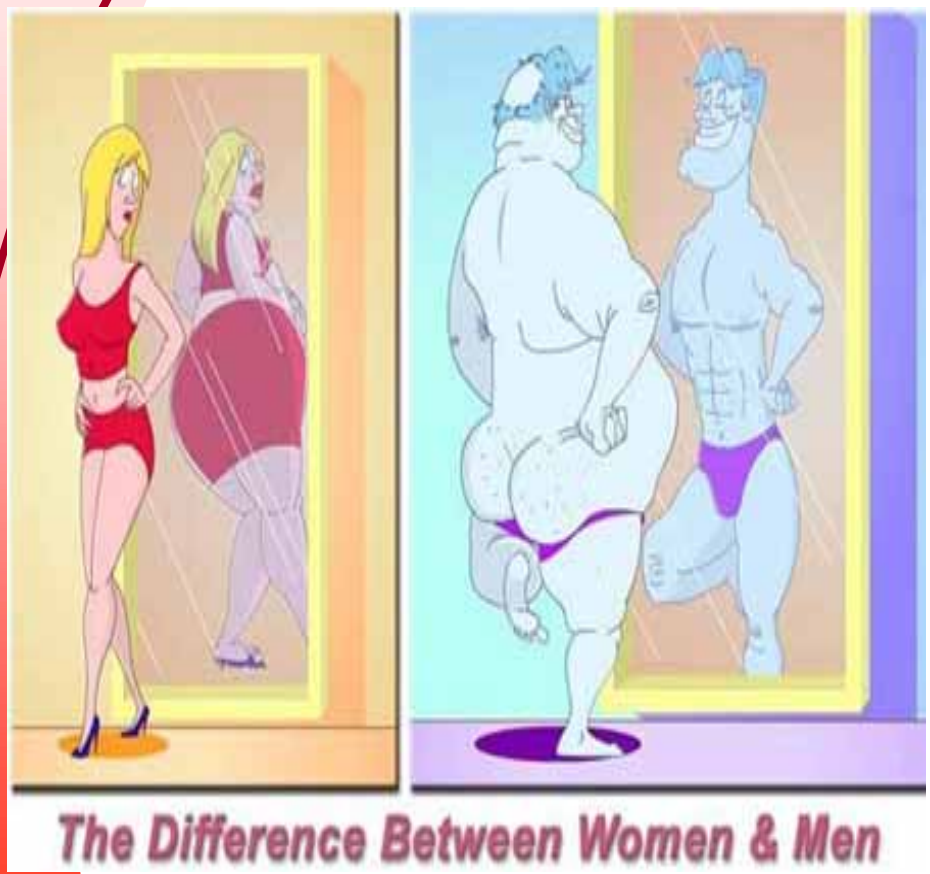
Type II Diabetes Mellitus



- Presents in middle age
- Other causes
  - Hemochromatosis
  - Polycystic ovary syn
  - Steroids
- Genetic link
- Type II DM results in obesity and obesity in Type II DM
- 20% of the US population >65 years is Type II Diabetic!!

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Type I vs Type II Diabetes

	Type I	Type II
Onset	<40 yrs	>40 yrs
Weight	Thin	Overweight
Sx	Sudden	Slowly
Insulin	None	Decreased
Insulin Req	Must take	May Require

Chronic Complications

- Macroangiopathic
- Ischemic HD
- CVA
- PVD
  - Foot ulcers
  - amputation
- Microangiopathic
- Retinopathy
  - Blindness
- Peripheral Neuropathy
  - Foot ulcers
  - Infection/gangrene
  - Amputation
- Nephropathy
  - ESRD

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U.S. Burden of DM Complications

- Diabetic Retinopathy
  - #1 cause of blindness in adults
  - 24,000 newly blind/year
- Diabetic Nephropathy
  - #1 cause of ESRD: 43% of new cases
  - 38,160 developed ESRD in 1999
  - 114,478 with DM underwent HD or Txp
- Diabetic Neuropathy
  - 60 to 70% of DM have mild to severe
  - Major factor leading to LE amputation

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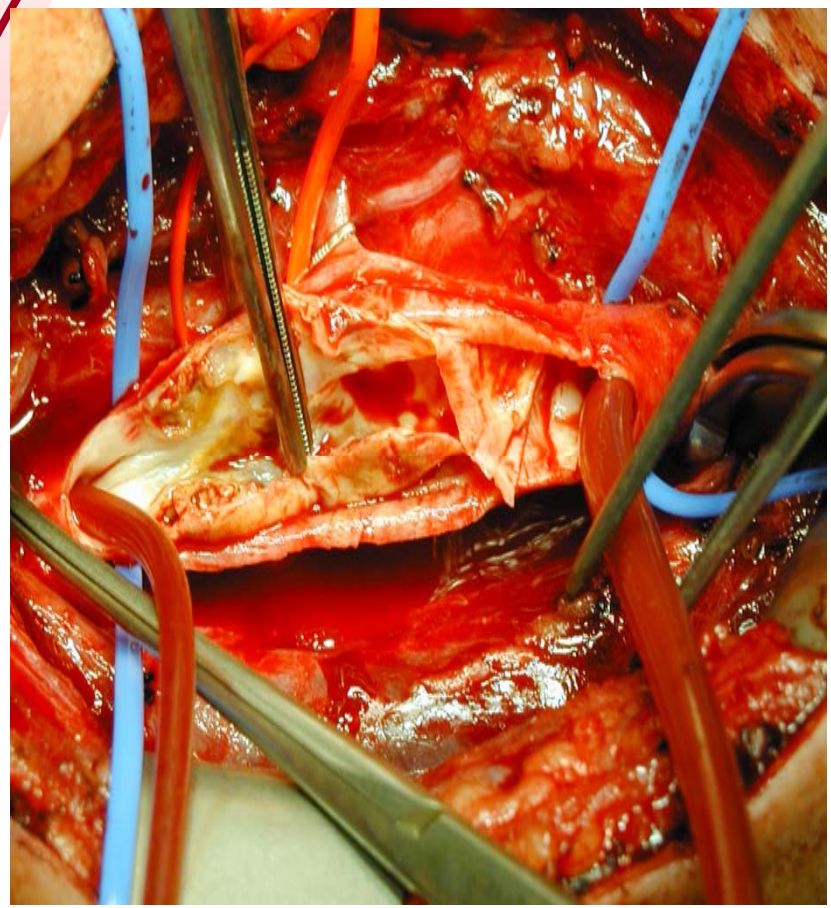
U.S. Burden of DM Complications



- Diabetic Amputations
  - #1 cause of nontrauma amp
  - 60% of all amps
- Diabetic Vascular Dz
  - 2-6X more likely to have HD
  - 2-4X more likely to have CVA
  - 73% of adults with DM BP > 130/80 or meds
  - 75% of all DM deaths due to CVD

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The Fiscal Consequence of DM

- 15 million US with DM (5.9% of pop)
- 800,000 new cases per year
- 2002 total US cost of DM $132 billion
  - 10% of total US healthcare expenditure
- Per capita cost of health care
  - With DM $13,243
  - Without DM $2560

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Treatment of Diabetes

- 1970s: 1 daily injection
  - 3 strict meals
  - Urine testing of BS
- 1990s:
  - Insulins are highly purified by genetic engineering and recombinant DNA
  - BS measuring and administration improved
  - Dietary guidelines are flexible

Treatment of Diabetes

- Current Advances
  - Rapid acting insulin analogs (lispro, aspart)
  - Long acting (glargine)
  - Biguanides (metformin)
  - Glitazones (rosiglitazone)
  - A-glucosidase inhibitors (acarbose)
- End-Stage advance
  - Laser photocoagulation
  - Hemodialysis / renal transplant
  - HTN and hyperlipidemia control
  - Surgical and invasive management of vascular disease
- Research, governmental funding, organizations and public awareness

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Limitations of Treatment of DM

- Diabetic Control and Complications Trial (DCCT)
  - 1984 to 1993 in 1441 Type I diabetics
  - reduction in risk continued until HbA1c reached nl
  - Intensive therapy patients improved health and lifestyle
- Intensive Therapy
  - multi-injection (short and long-acting)
  - Balance of intake, activity and insulin dosing
  - Freq monitoring
  - Defined goals (HbA1c <6 and fast BS 70 to 140)
  - Freq interact between healthcare worker and patient
  - Pt education and counseling

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Limitations of Treatment of DM

- Exogenous insulin *cannot* normalize blood sugar
  - Day-to-day variations
  - DCCT average HbA1c 7.0%
- Intensive therapy reduces, but does not eliminate risk of DM complications
- Cost
  - Therapy is $4000 to $8000 per year
  - Does not include the cost of secondary complications
- Hypoglycemia

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Severe Hypoglycemia

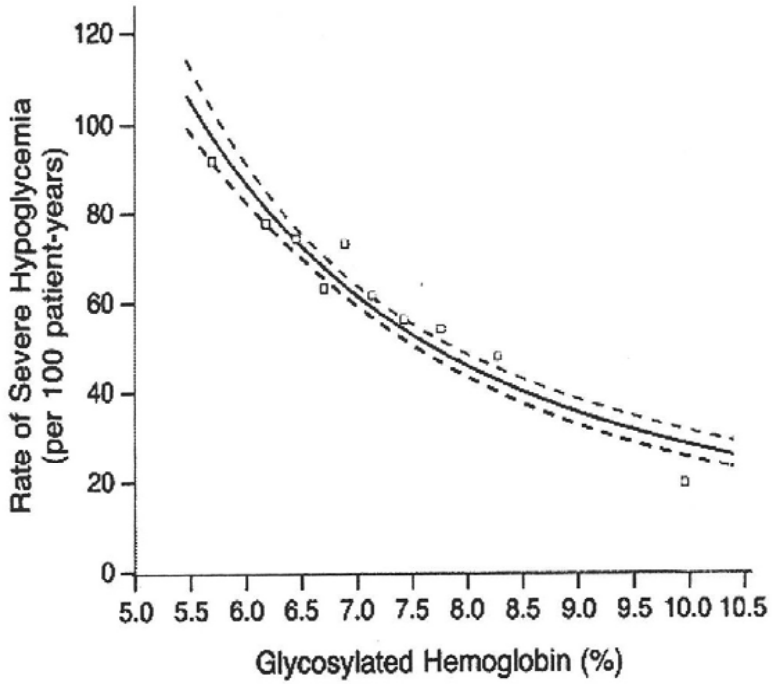

FIGURE 3.5. Rates of severe hypoglycemia in the intensively treated cohort from the DCCT. Overall, rates of hypoglycemia were threefold higher in the intensively treated subjects when compared to the standard therapy cohort and increased steadily as lower HbA1c levels were achieved. (Reprinted with permission from Diabetes Control and Complications Trial Research Group.[1] Copyright © 1993 Massachusetts Medical Society. All rights reserved.)

- Exogenous insulin
  - Absorbed irrespective of BS
- Gluc-counterregulation
  - Low BS usually results in glucagon
  - Glucagon stimulates catecholamine
- Fear of hypoglycemia
- Risk of permanent injury to self and others
- Lifestyle alteration

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Pancreas Transplantation

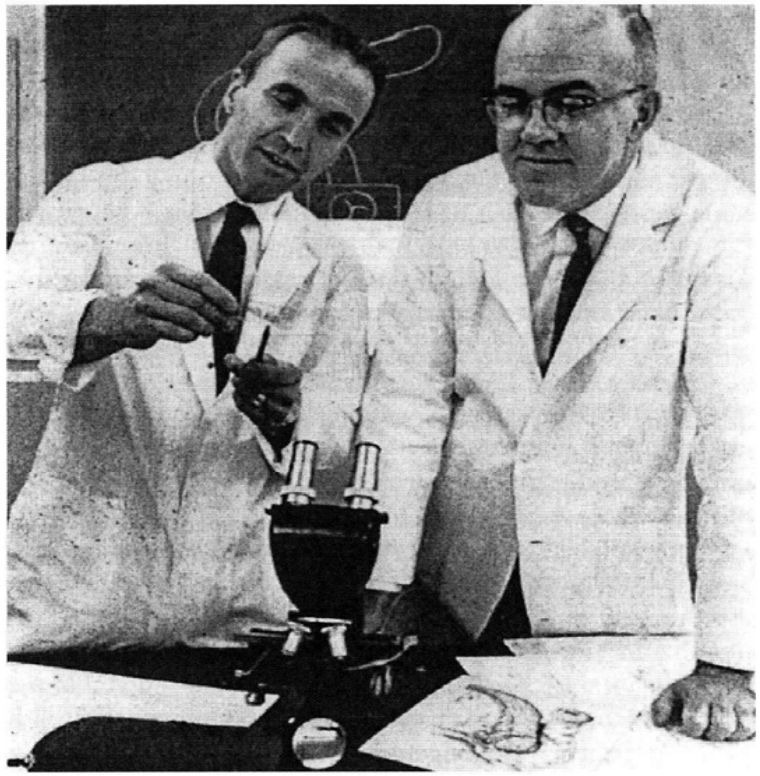

FIGURE 4.1. Richard Lillehei, left, and William Kelly, right, discussing a pancreas graft histology report. On the desk, the schematic drawing of the second ever performed pancreas transplant (see text). On the board, a schematic drawing of the pancreaticoduodenal graft anatomy.

- First SPK, Dec 1966 by Williaqm Kelly and Richard Lillehei at the Univ of Minnesota
- 28 yo female
  - AZA, pred, XRT
  - Leak POD 7
  - Removed 45d

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Pancreas Transplantation

Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy

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Patients suffering from terminal renal failure due to diabetes mellitus are not good candidates for either renal allotransplantation or chronic hemodialysis because they suffer from a systemic disease which is not corrected by either procedure. Moreover, the increased susceptibility to infection of these patients adds still greater risks to these procedures. Yet these drawbacks might be overcome by simultaneous allotransplantation of the cadaveric kidney and pancreas. Such a procedure is presently not indicated for patients with the usual form of diabetes mellitus, occurring first in adulthood without lethal complications. But those patients afflicted with diabetes mellitus of juvenile onset, where there is usually an absolute lack of insulin accompanied with terminal renal failure, are justifiably candidates for renal and pancreatic allotransplantation, since there is presently nothing else to offer them. While this is the primary reason for carrying out such procedures, the dividends in new knowledge about diabetes and insulin metabolism may also be great.

The problem of pancreas transplantation has been under study by various investigators for a number of years.[1-5, 7-10] Similarly working separately on the dog in the laboratory, Merkel with Kelly and Largiader, Lyons, Manax, and Idezuki with Lillehei have succeeded in producing short-term successful pancreas transplants to be reported elsewhere which corrected the hyperglycemia and glycosuria of pancreatectomy-induced diabetes. Since a more favorable response to renal homotransplantation occurs in man than in the dog, it was felt that a similar result might be achieved in the case of the pancreas.

Accordingly two patients with diabetes mellitus and renal failure have recently undergone operations wherein simultaneous

Supported by United States Public Health Service Grant No. AI-06063 for Studies of Allograft Tolerance Induction in Man.
Presented in Discussion at the Surgery Physiology Conference, University Hospitals, University of Minnesota, Minneapolis, Minn., Feb. 21, 1967.
Received for publication Feb. 20, 1967.

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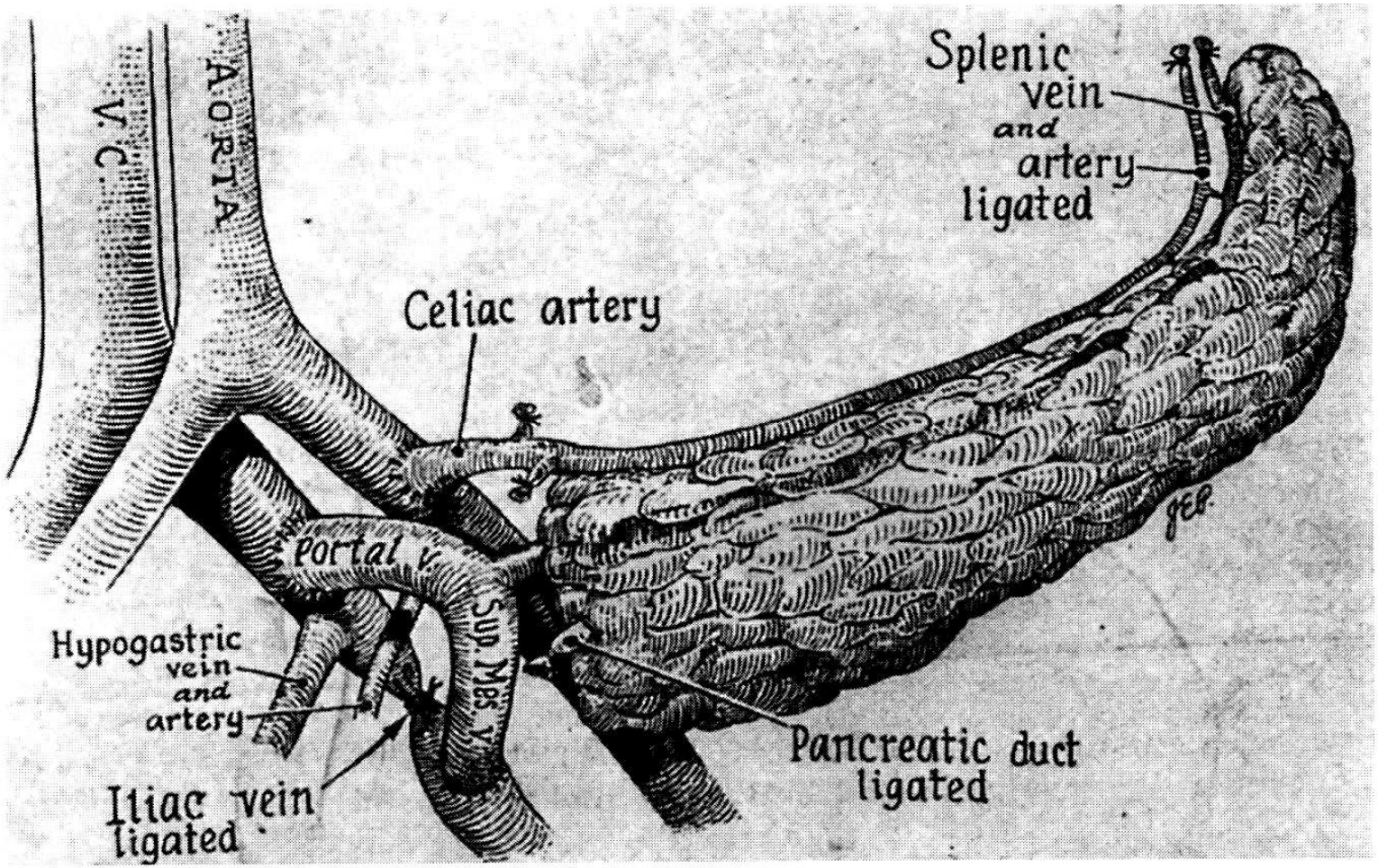
Pancreas Transplantation



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Selection Criteria

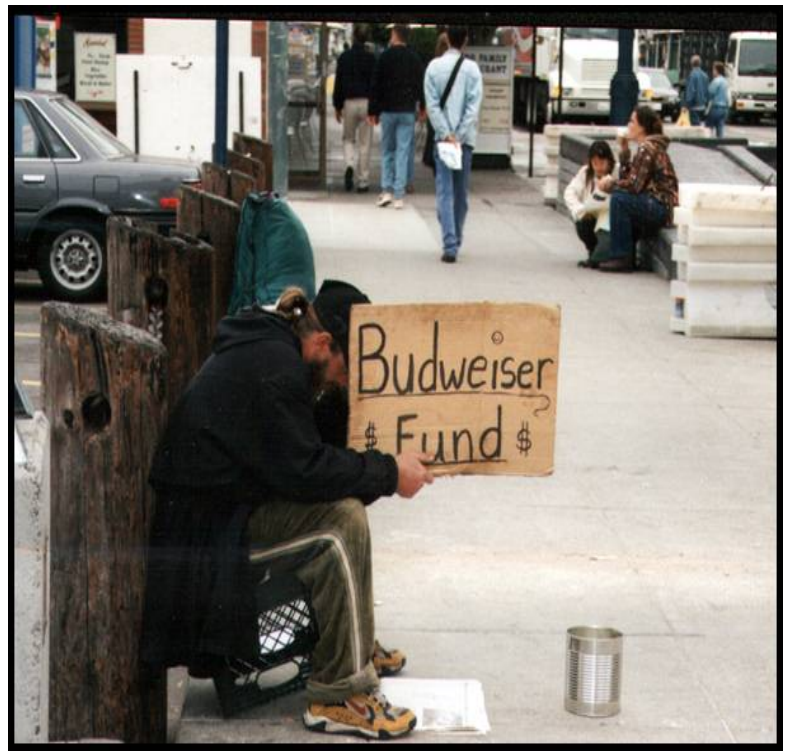
- Indications:
  - DM requiring insulin (c-peptide <0.6ng.ml signifies type 1)*
  - Frequent/severe hypoglycemic episodes
  - Recurrent hospitalizations for hypoglycemia
  - Early development of secondary diabetic complications (relative)
  - Inability to manage DM by standard insulin regimens

Selection Criteria

- Absolute Contraindications:
  - Unwilling or unable to comply to post-transplant care
  - Anatomical reasons
  - Significant active infectious disease
    - HIV
    - Carries, UTI, line sepsis, chronic pulm
    - Hep B and C

Selection Criteria

- Absolute Contraindications:
  - Active malignant neoplasm
  - Severe cardio, pulm, neuro, metabolic, or rheumatologic dz prohibiting safe administration of general anesthesia
  - Severe immune deficiency state that is untreated or unresponsive to tx



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Selection Criteria

- Relative Contraindications:
  - Active psych dz, chemical dependency, non-compliance with med tx, or social challenges
  - h/o Treated malignancy
  - h/o Treated severe infectious dz
  - h/o immune deficiency state
  - Morbid obesity (BMI>40)
  - Multiple medical comorbidities increasing risk of death within 1st 5yrs after txp

Selection Criteria

- Relative Contraindications:
  - Single cardio, pulm, neuro, metabolic, or rheumatologic dz increasing risk of mortality within 1st 5 yrs after txp
  - Estimated life expectancy with successful txp 2-5 yrs.

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Types of Pancreas Transplantation

- Simultaneous Panc and Kidney transplant (SPK)
- Pancreas after Kidney (PAK)
- Pancreas Txp Alone (PTA)
  - Preserved renal fxn
  - Rapid fluctuations in BS
  - Freq episodes of DKA
  - Hypoglycemic unawareness

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Medical Evaluation

- Cardiac
  - #1 cause of death after txp
  - Noninvasive- poor predictive value
  - Dobutamine stress if young and asx
  - Coronary angiogram
  - Risk of renal failure
  - >75% lesion treated
- PV Evaluation
  - Extensive PVD and heterotopic txp
  - History and PE
  - Noninvasive study
    - MRA
    - Duplex
  - Arteriogram-risk of renal failure

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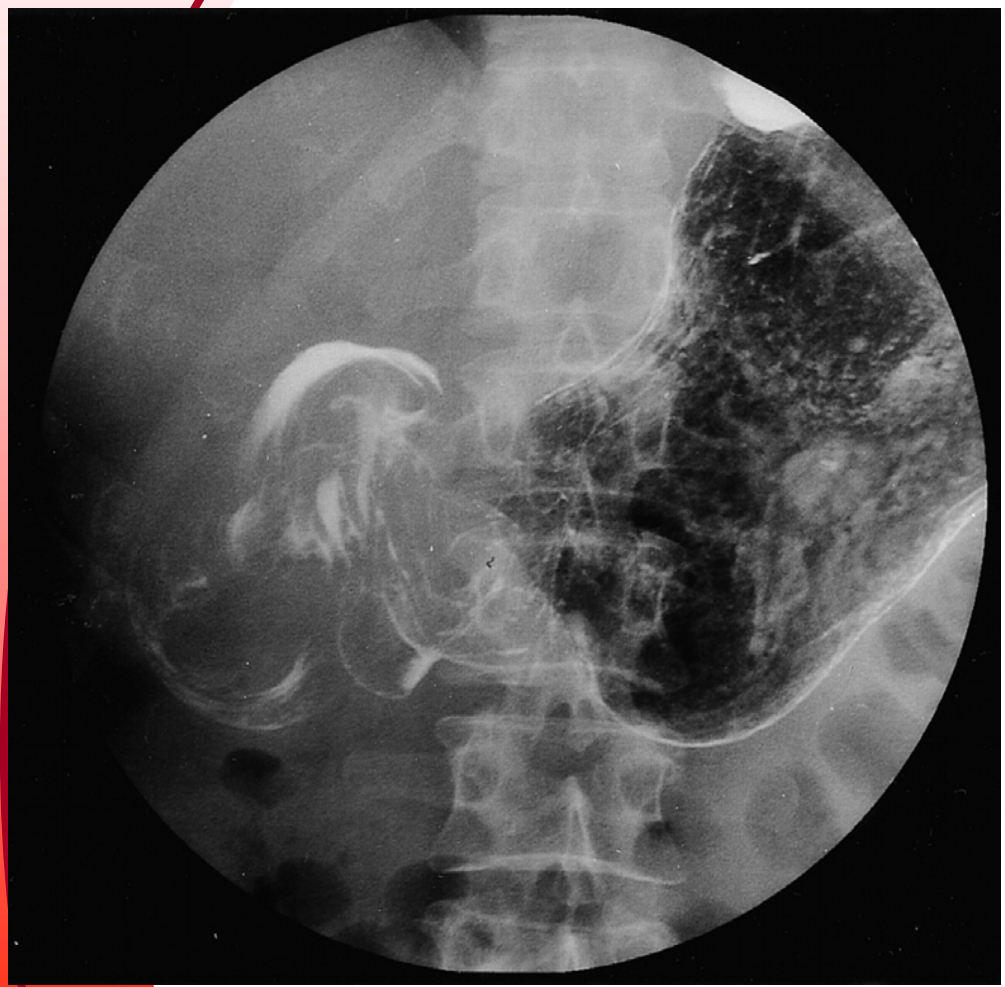
Medical Evaluation



- Other Evaluation
  - Immunologic
  - Respiratory
  - Urologic
    - Neurogenic bladder
  - Bone
    - Mineral density scan
  - Nutritional
  - Education

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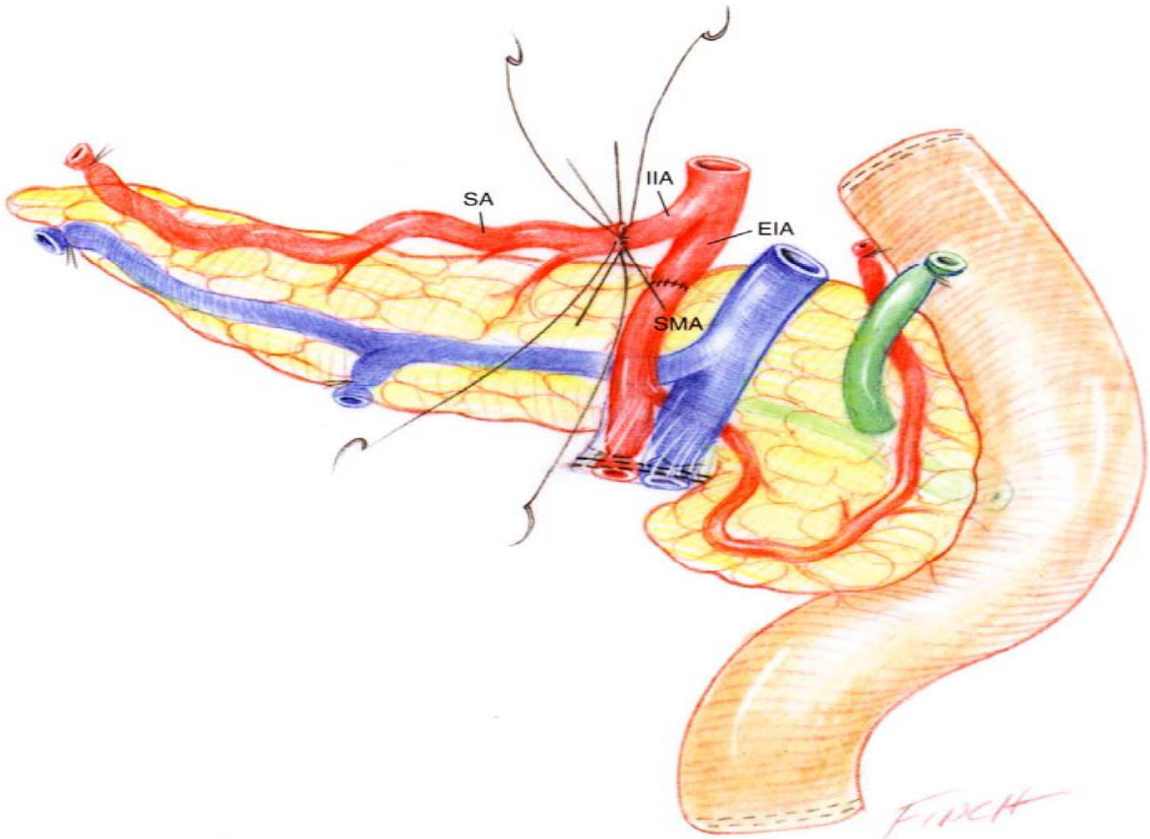
“Benching the Panky”



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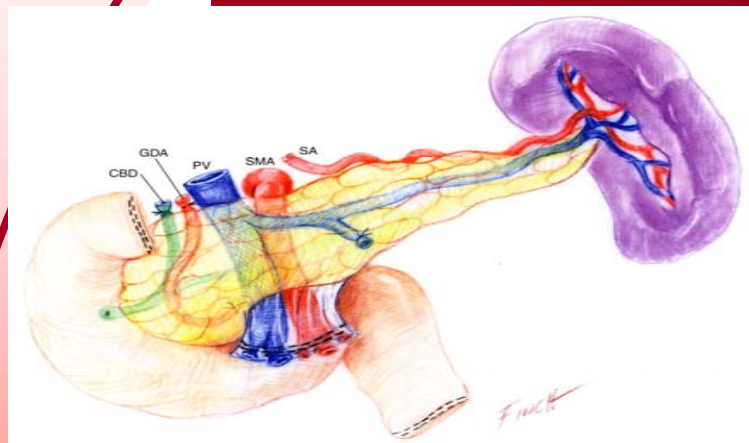
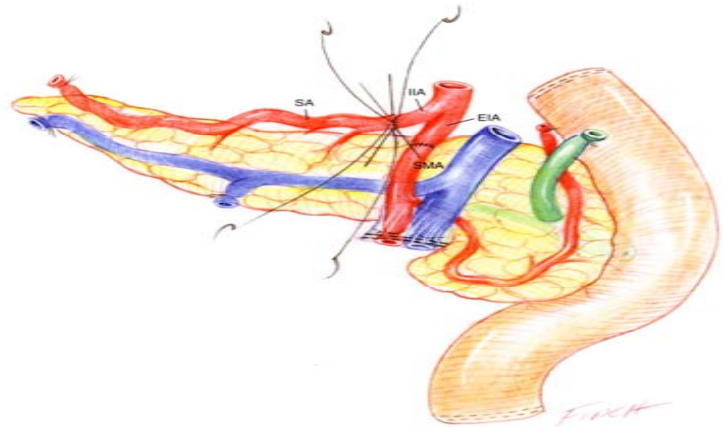
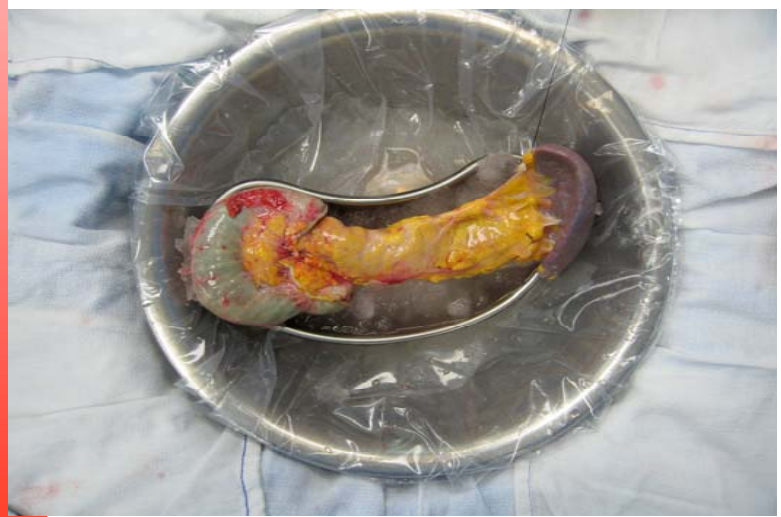
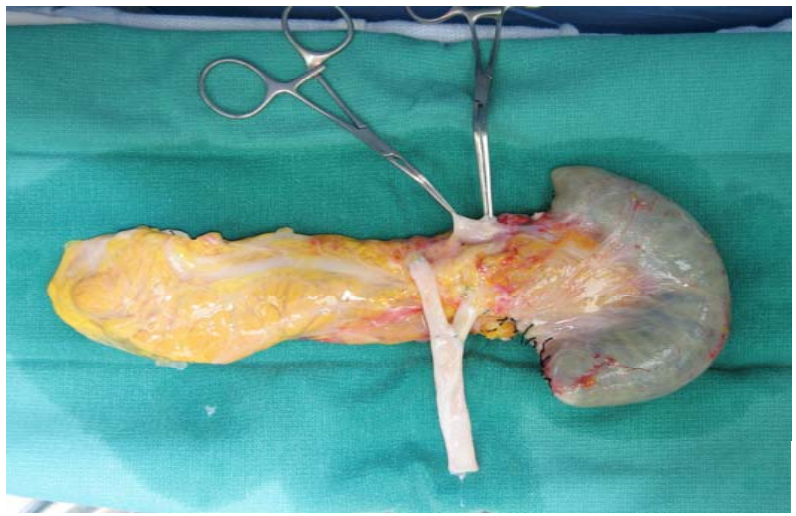
Pancreas Backtable









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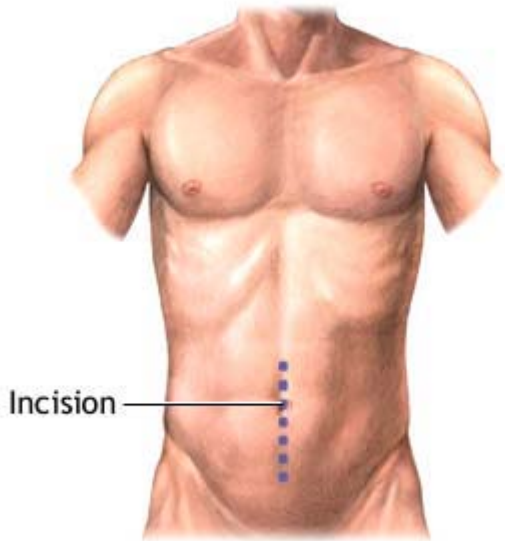
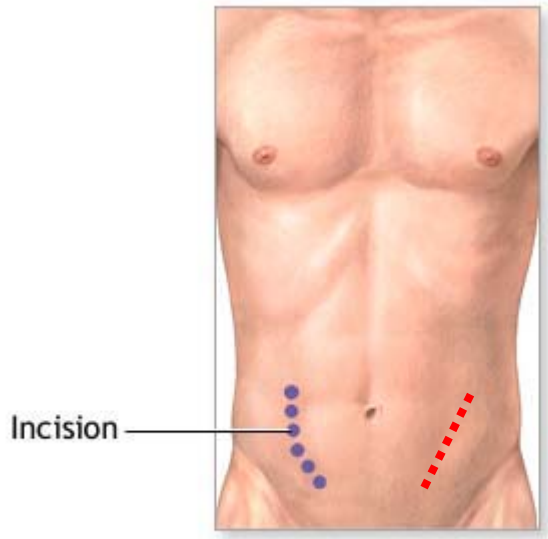
Surgical Procedure

- Can use midline incision or bilateral lower quadrant incisions



A.D.A.M.



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Surgical Procedure

- dissection of bilateral common/external iliac vein and artery
  - Pancreas anastomosed to IVC and common iliac artery
  - Kidney anastomosed to either IVC and CIA OR external iliac artery and vein

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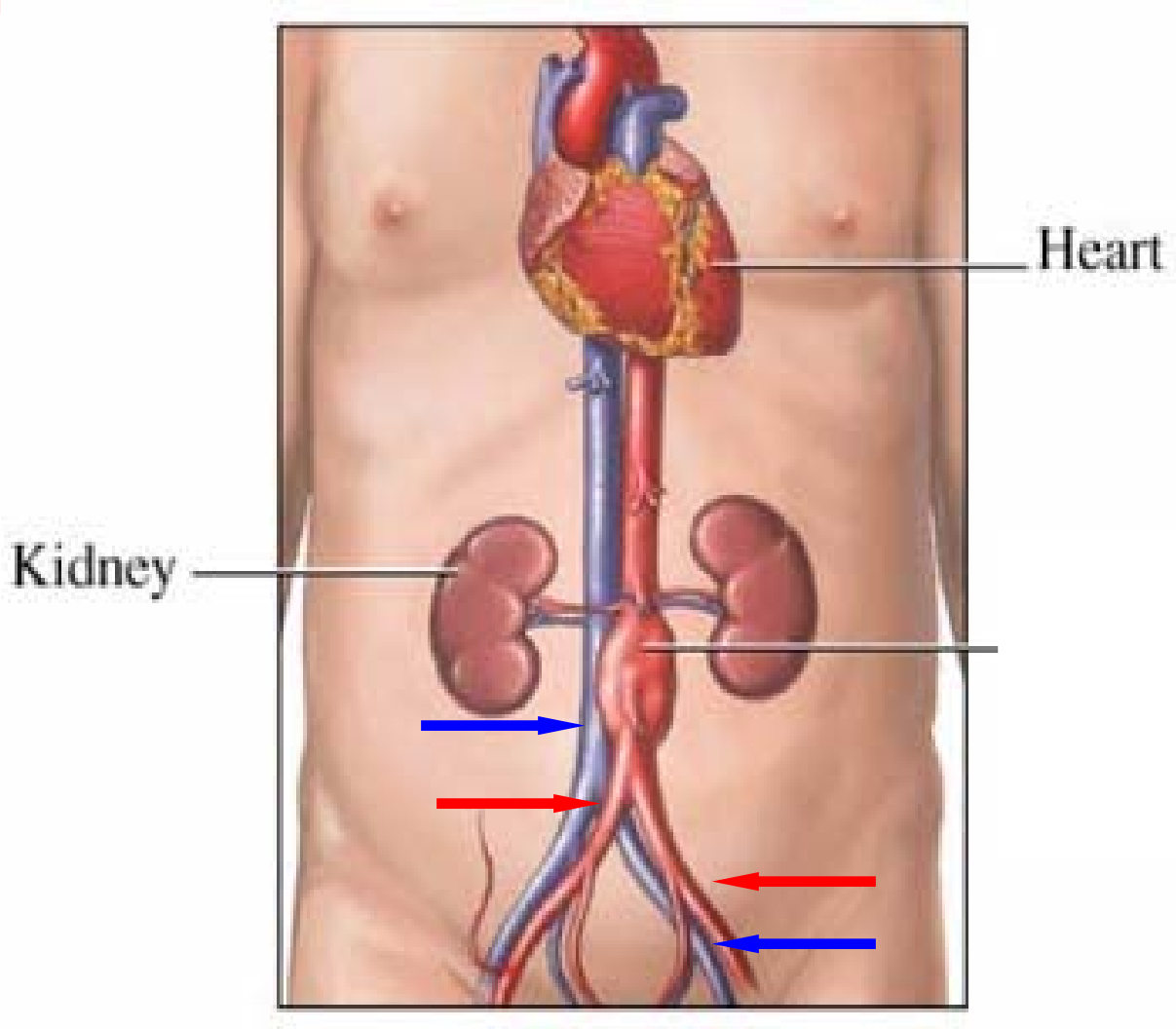
Surgical Procedure



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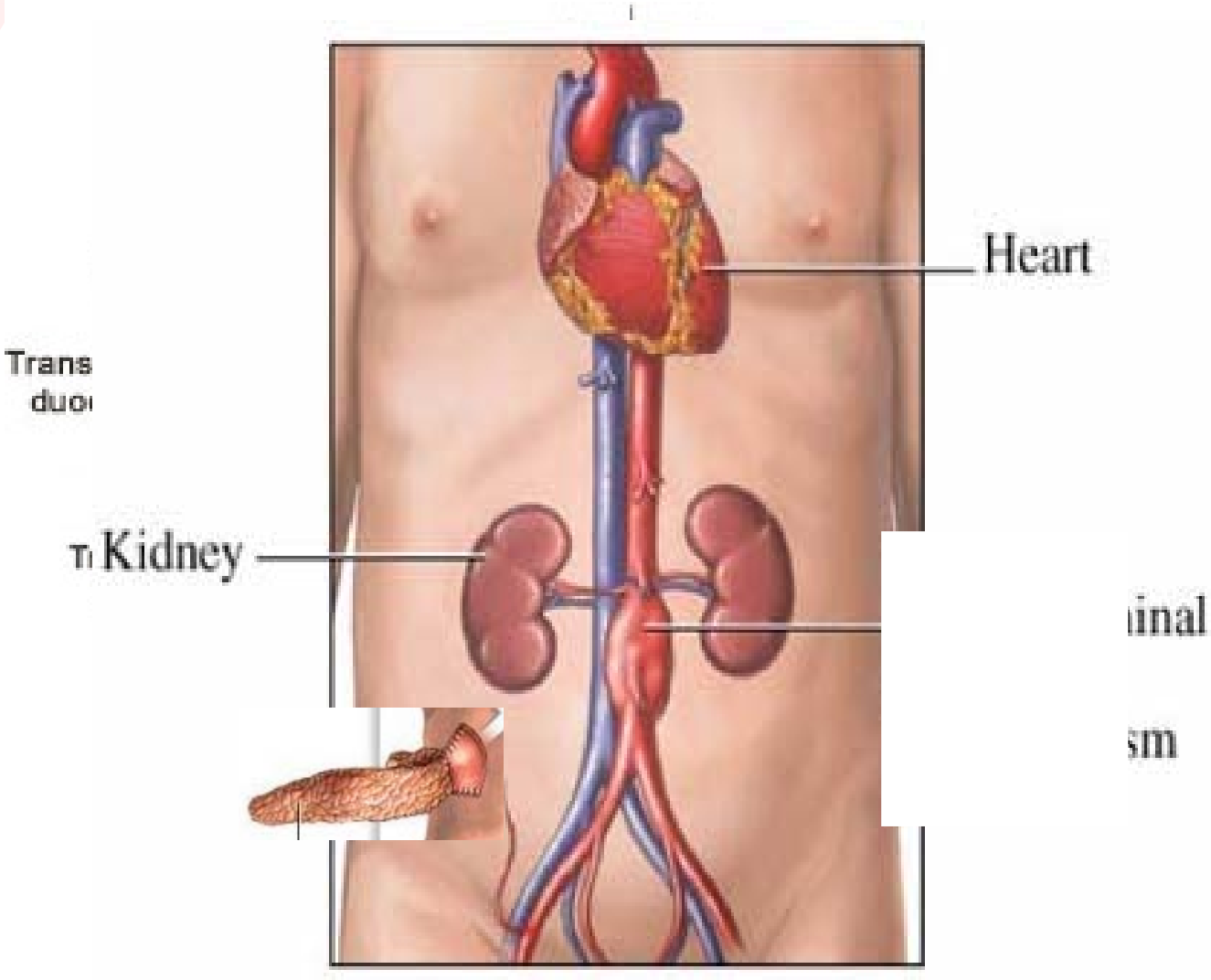
Surgical Procedure



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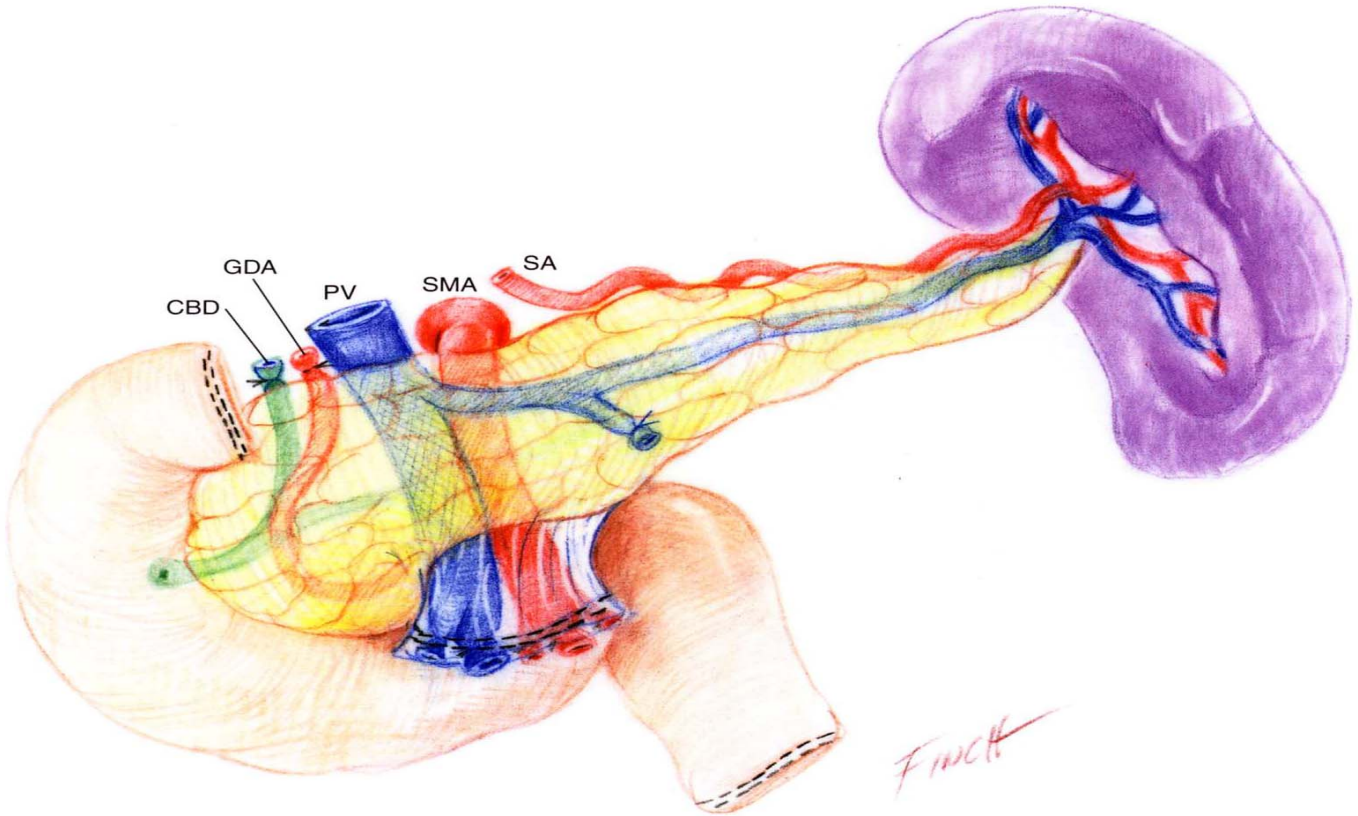
Recipient Procedure



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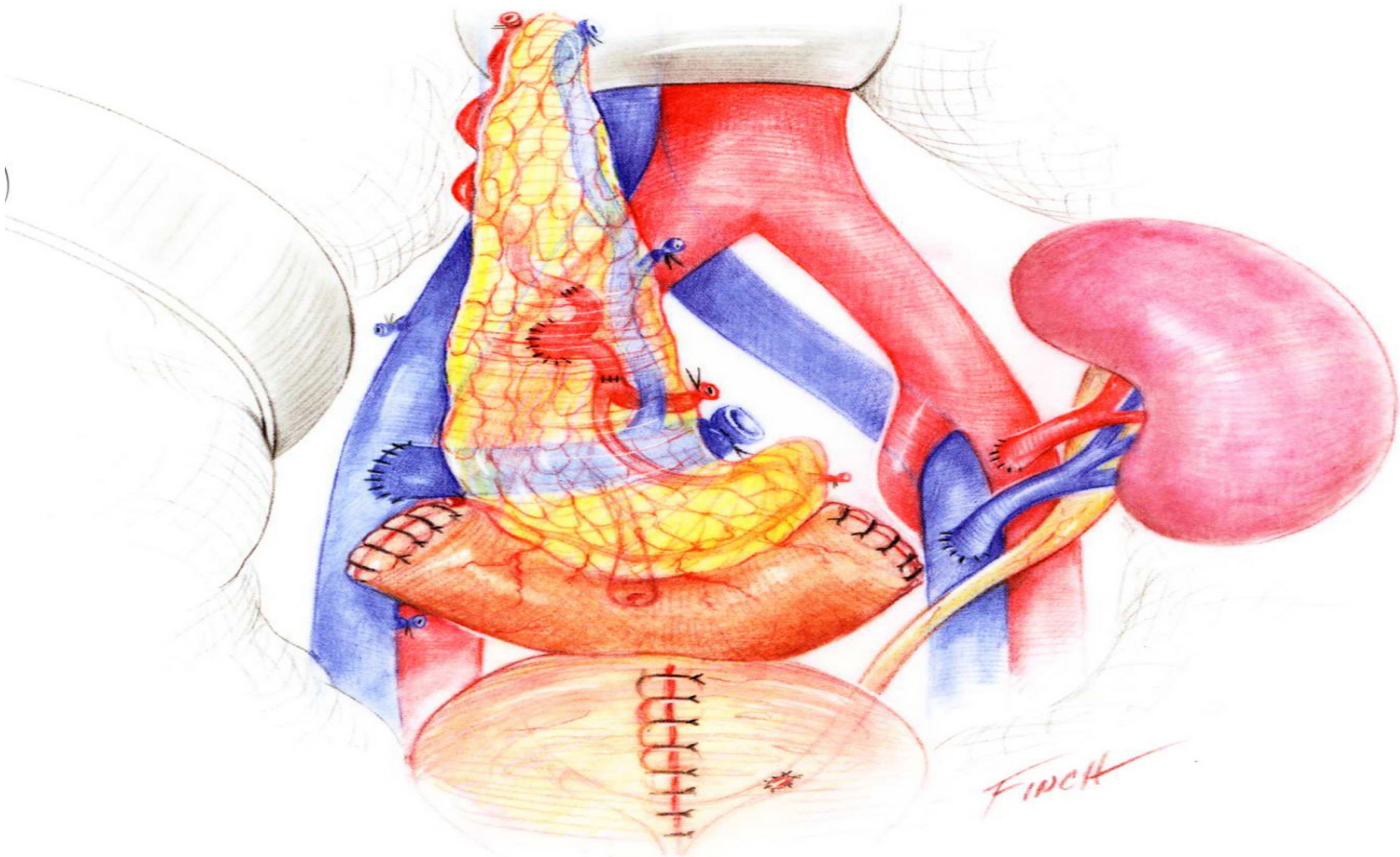

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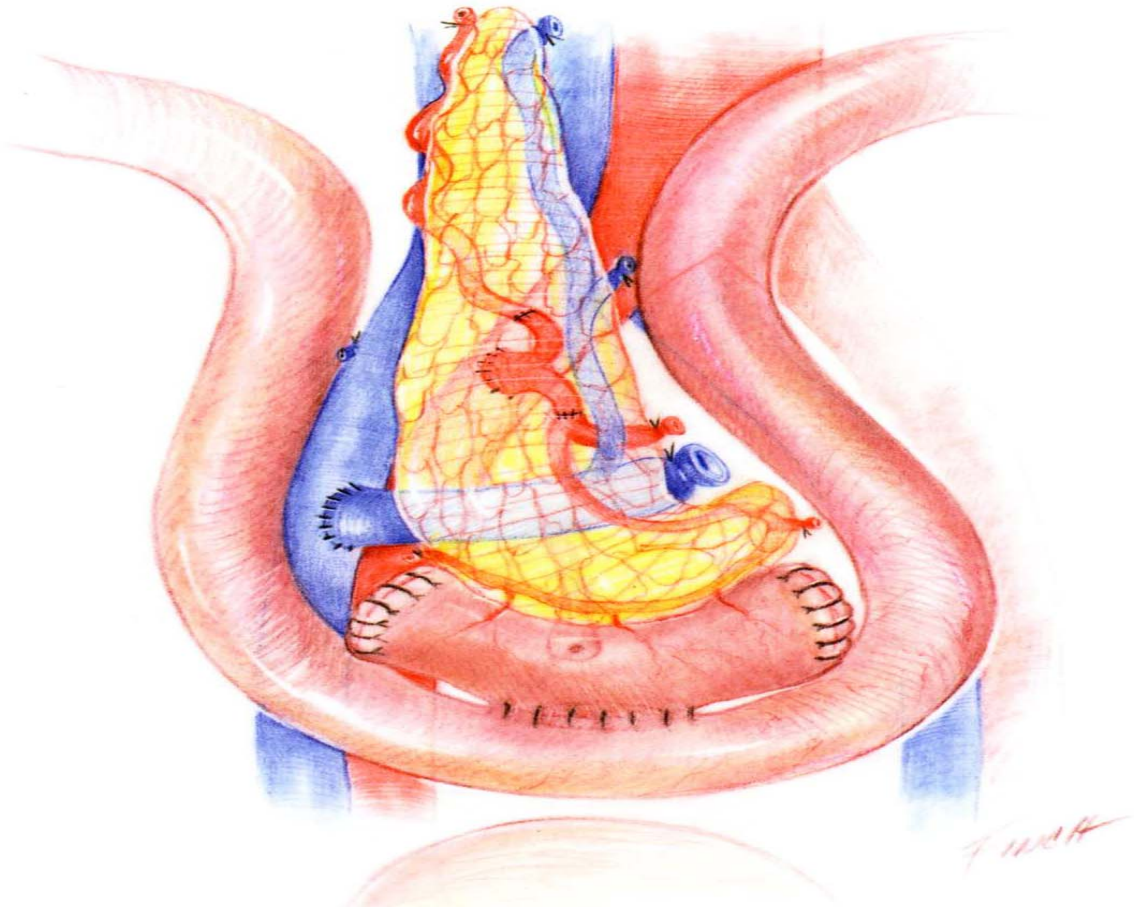

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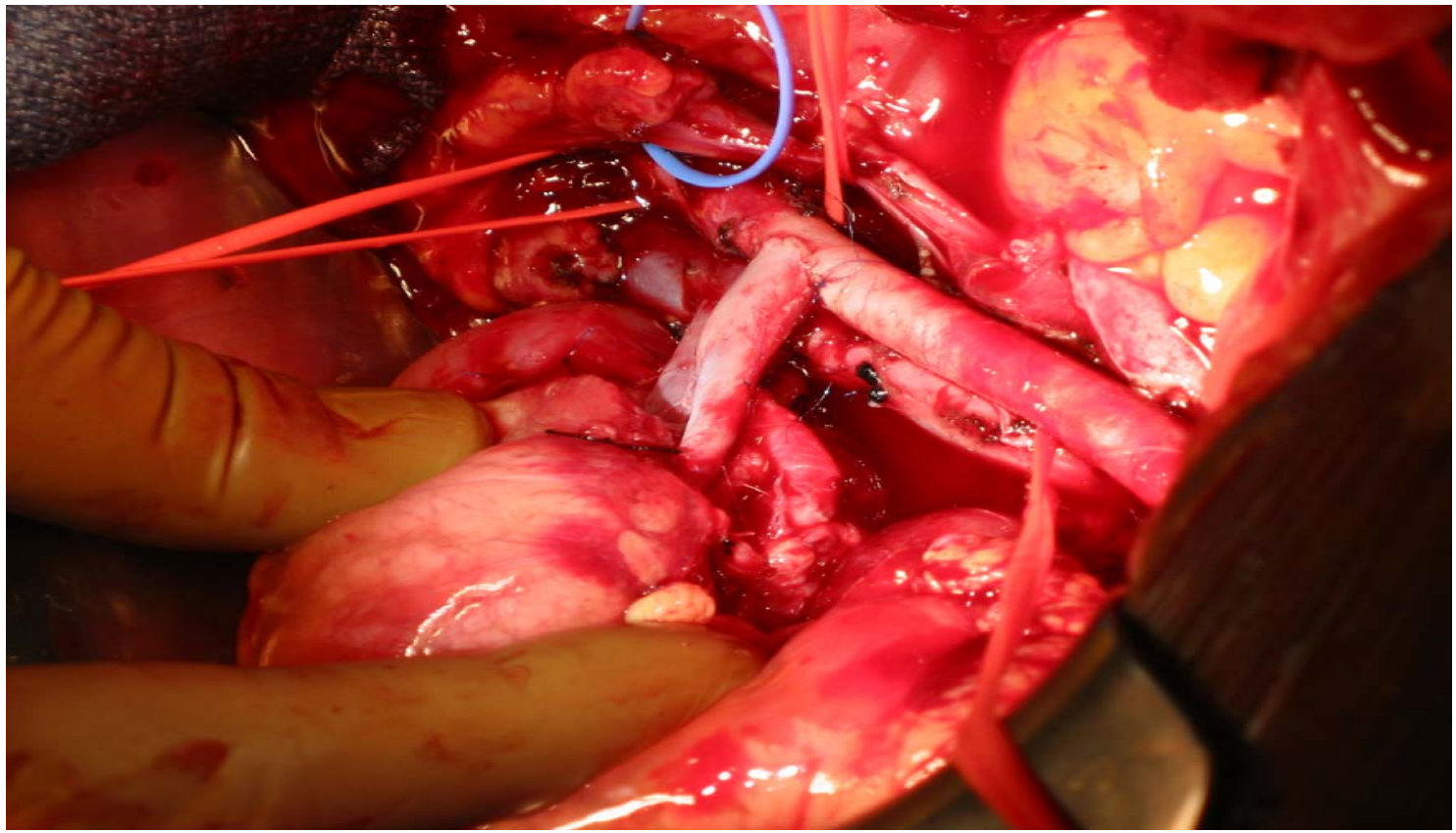


Post-Operative Course

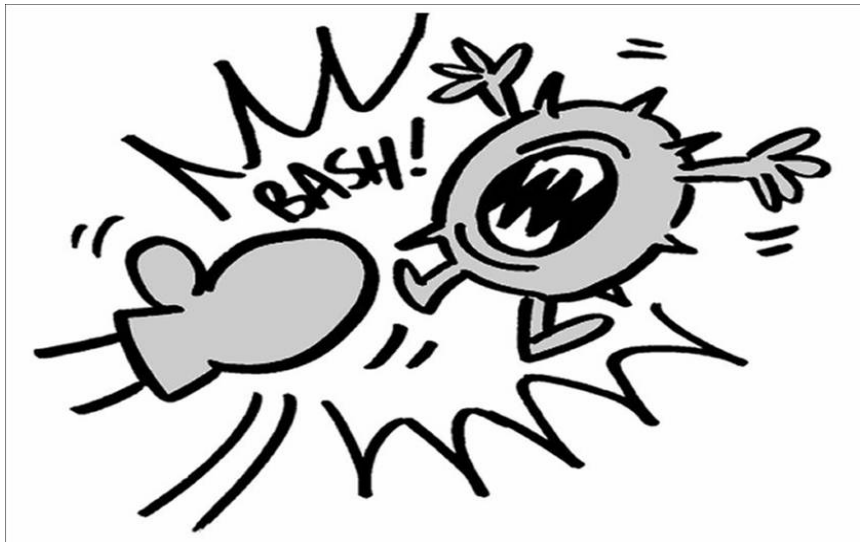
- Nearly all catastrophic events occur within 48hrs
- Standard ICU montioring for 24-48hrs
- q 1-2 hr serum BS
- Anticoagulation
- Insulin gtt
- UOP
- Albumin, mannitol

Post-Operative Course

- Day 2 to 7
  - Regular floor
  - Diet after bowel fxn returns
  - Dismiss POD 6-7
- Immunosuppression
  - Induction
  - Maintenance
  - Timing and dosing

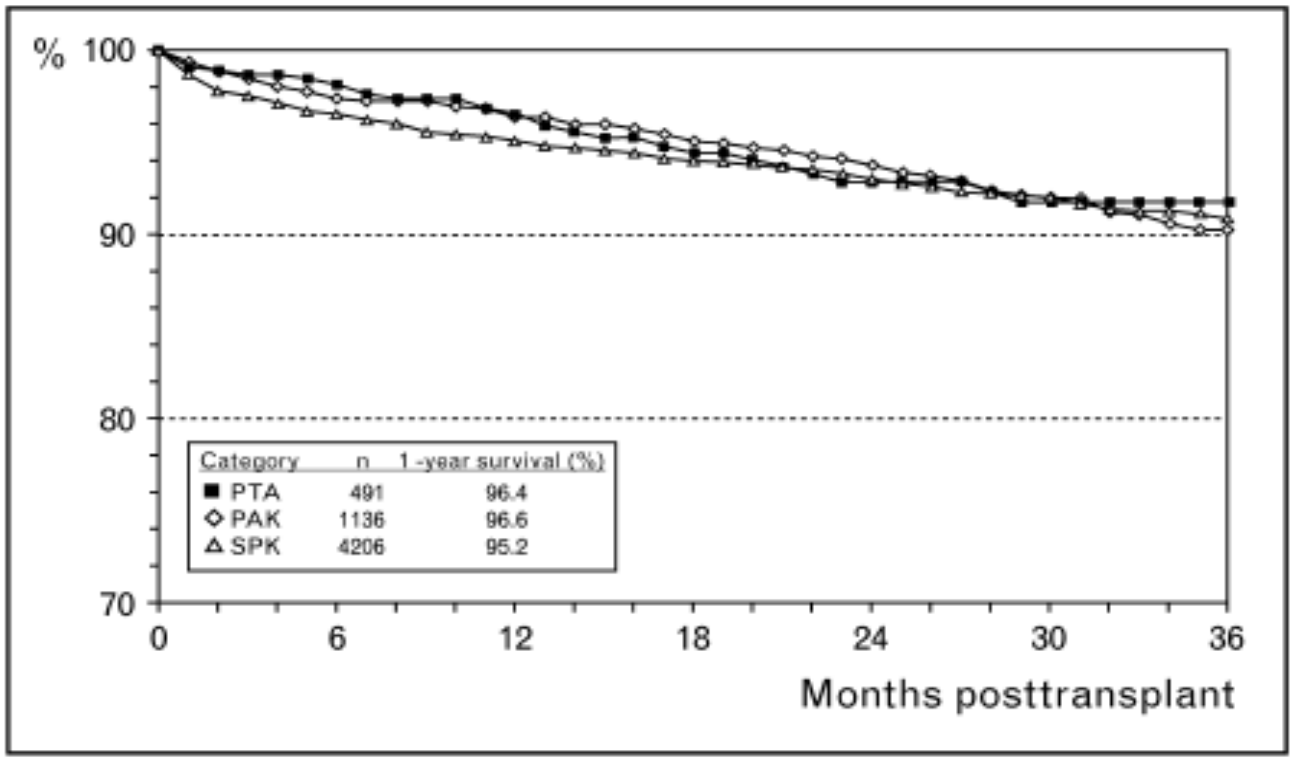
Immunosuppression

- Induction Therapy
  - T-Cell depleting antibodies (e.g. Campath, Thymoglobulin)
  - T-Cell non-depleting (e.g. daclizumab, basiliximab)
- Maintenance Therapy
  - Cellcept
  - Prograf or CSA
  - Prednisone



Outcomes

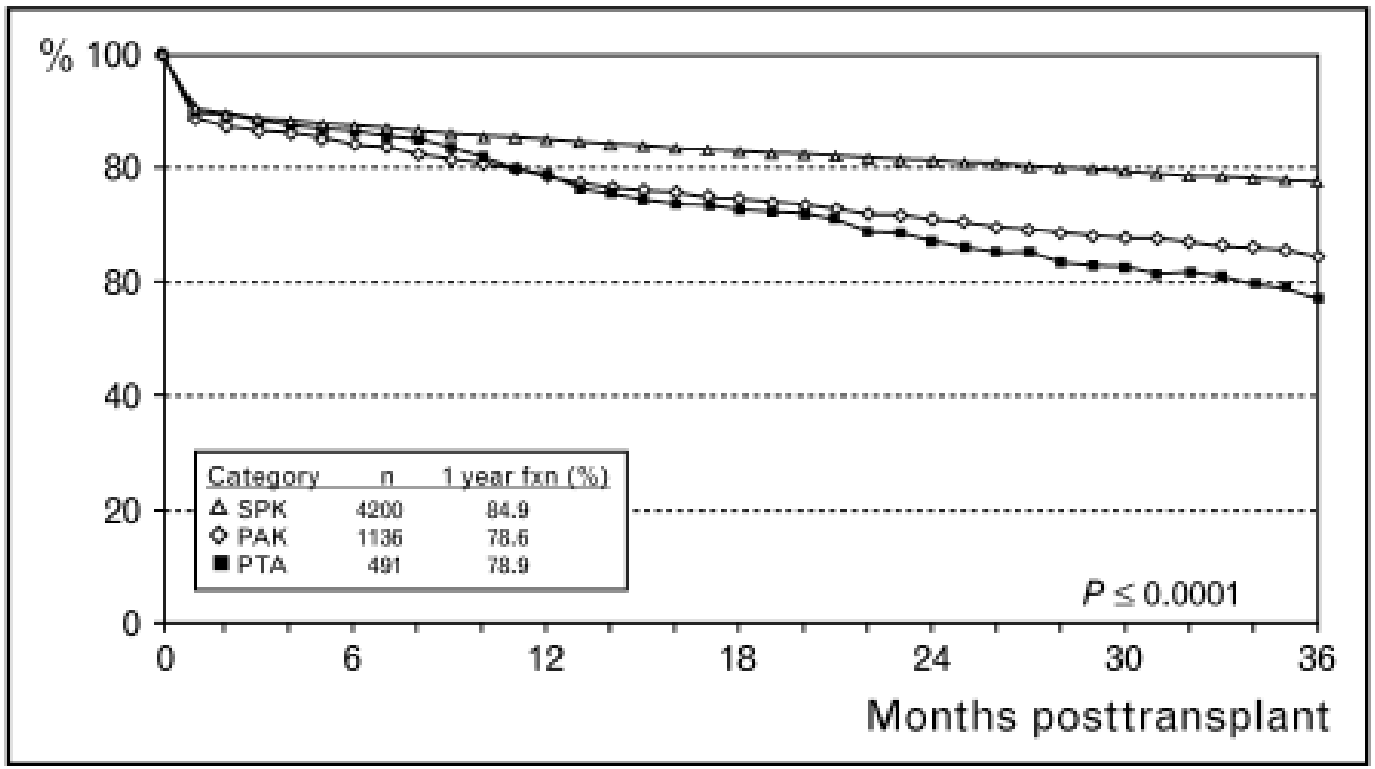
- Pt survival at 1yr >95%; 3yr >90%



Gruessner et al. 2010.

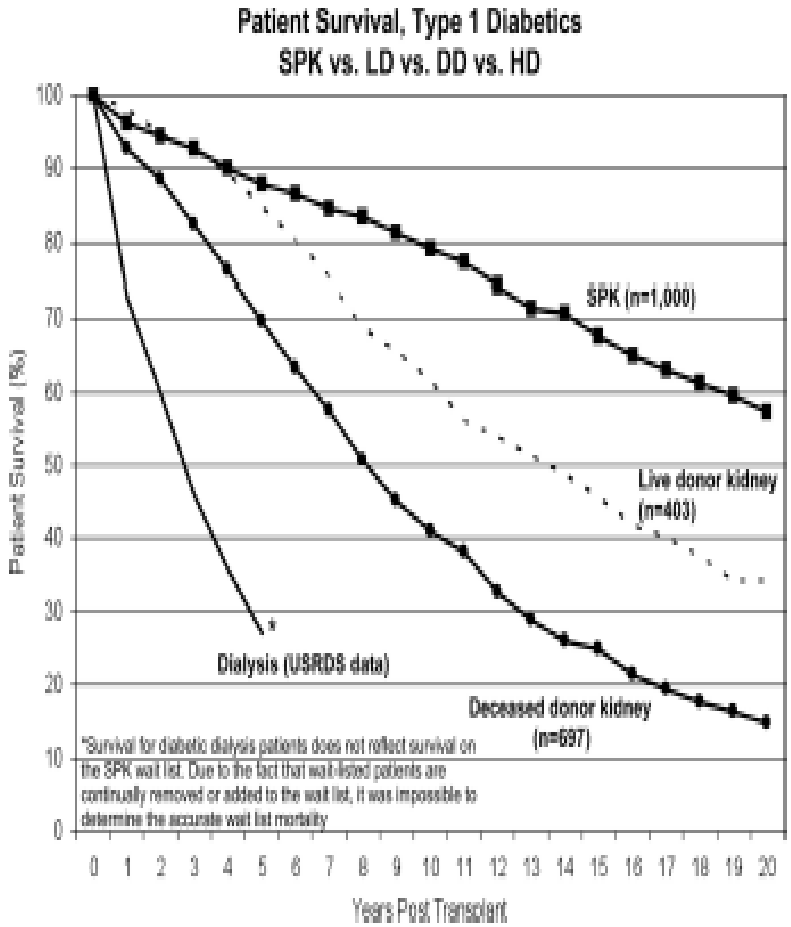
Outcomes

- Graft survival at 1 yr best in SPK



Gruessner et al. 2010.

Outcomes



- 1000 SPK from 1985-2007
- Pt survival 89%, 80%, and 58% 5-, 10-, 20-yr for SPK
- Survival for LDKT diverges from SPK at approx. 5yr
- Diabetic pts on dialysis have a very poor outcome

Sollinger et al. 2009.

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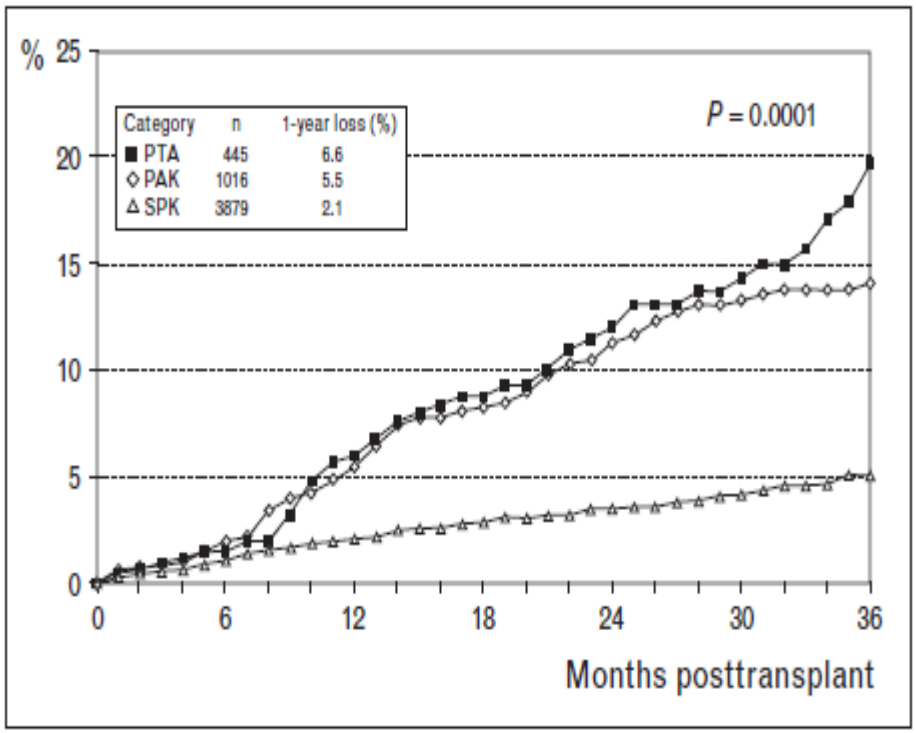
Complications

- Rejection
- Graft thrombosis
- Anastomotic leak
- Bleeding
- Infection
- Death

Rejection

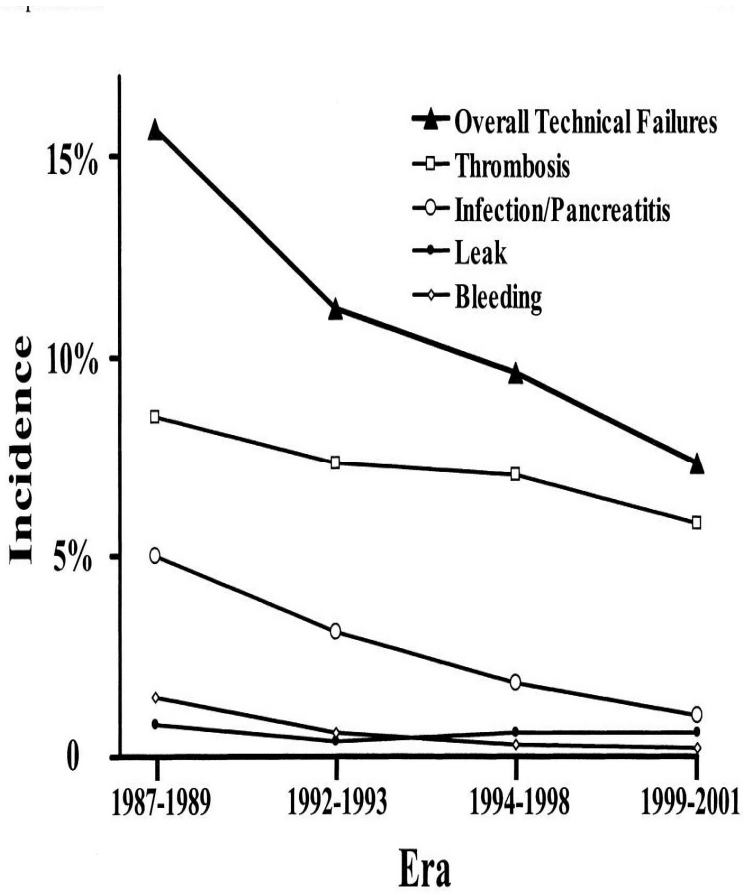


PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas–kidney.

- Increased rate of immunologic graft loss in PTA and PAK verus SPK
- Immunologic graft loss rates 2% for SPK; 6% for PTA and PAK
- Rate of graft loss from acute rejection peaked 3-12 months

Gruessner et al. 2010.

Surgical Complications



- Graft Thrombosis
  - SPK (5.5%), PAK (8.9%) and PTA (11.6%)
- Wound Infections
  - 11 to 18%
- Duodenal Leak
  - 4 to 9%
  - Enteric leaks graft survival worse than bladder drained
- Graft Pancreatitis
  - 35% of all pancreas txp
  - Always conservative management

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Anastomotic Leak

TABLE 9. Pancreatic Graft Loss

	Bladder N (%)	Enteric N (%)
Death with functioning graft	77 (19.7%)	48 (7.9%)
Rejection	47 (12.1%)	33 (5.4%)
Chronic graft loss, etiology undetermined	26 (6.7%)	18 (3.0%)
Graft thrombosis	9 (2.3%)	22 (3.6%)
Anastomotic enzyme leak	5 (1.3%)	16 (2.6%)
Insulin resistance	9 (2.3%)	11 (1.8%)
Infection	7 (1.8%)	5 (0.8%)
Bleeding	5 (1.3%)	3 (0.5%)
Pancreatitis	5 (1.3%)	3 (0.5%)
Noncompliance	1 (0.3%)	5 (0.8%)
Hemolytic uremic syndrome	0	1 (0.2%)
Initial poor function, graft loss <4 month posttransplant	0	1 (0.2%)
Primary nonfunction	1 (0.3%)	0
Other	2 (0.5%)	2 (0.3%)
Unknown	9 (2.3%)	15 (2.5%)
Total	203 (52.1%)	183 (30%)

Sollinger et al. 2009.

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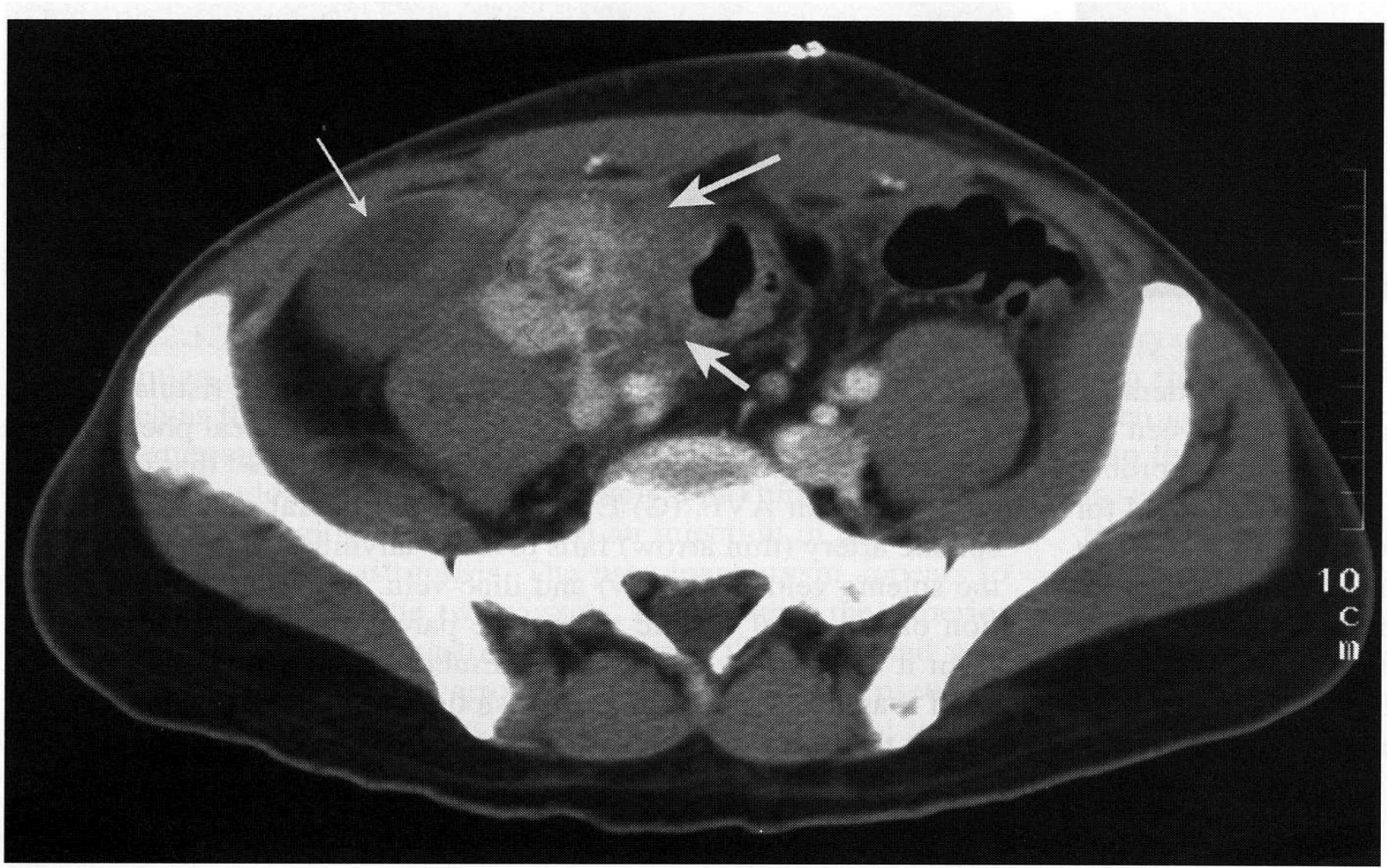
Duodenal (anastomotic) Leak



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Death

- Death with functioning graft is leading cause of graft loss
- This is for both kidney and pancreas transplant recipients
- Most common cause of death was cardio/cerebrovascular
- Highest risk of mortality is in first 90 days

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Conclusion

- Pancreas transplant is for morbidity secondary to diabetic complications; does not change mortality
- SPK has better outcomes and seems to have less complications
- Solitary pancreas transplant has lower graft survival mainly due to immunologic graft loss

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Conclusion

- Highest rate of mortality and complications occurs in first 90 days

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Thank You

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