# THE MEDICAL BENEFITS OF PANCREATIC TRANSPLANTATION

*Carlos E. Marroquin, M.D., F.A.C.S.*
*Chief, Transplant and Hepatobiliary Surgery*
*Department of Surgery*

THE University of Vermont MEDICAL CENTER

# Learning Objectives

- Describe historic events in the development of diabetes
- Become familiar with the physiology of insulin
- Define different types of diabetics and patients who would benefit from a kidney and pancreas transplant
- Define major morbidities associated with diabetes
- Define treatment options for patients with diabetes
- Describe sequelae of diabetes and effect of transplantation

# Definition

**Diabetes Mellitus (DM):**

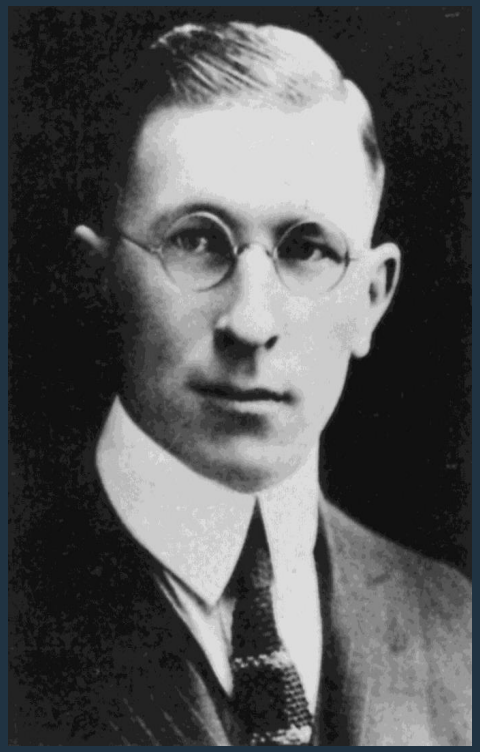
a group of common metabolic disorders that share the characteristic of high blood sugar due to reduced (or absent) insulin secretion, decreased glucose utilization, and/or increased glucose production.

# Discovering Insulin

Fredrick Grant Banting

- In the fall of 1920 Dr. Frederick Banting had an idea that would unlock the mystery of the dreaded diabetes disorder.
- Before this, a diagnosis of diabetes meant wasting away to a certain death.

# Discovering Insulin



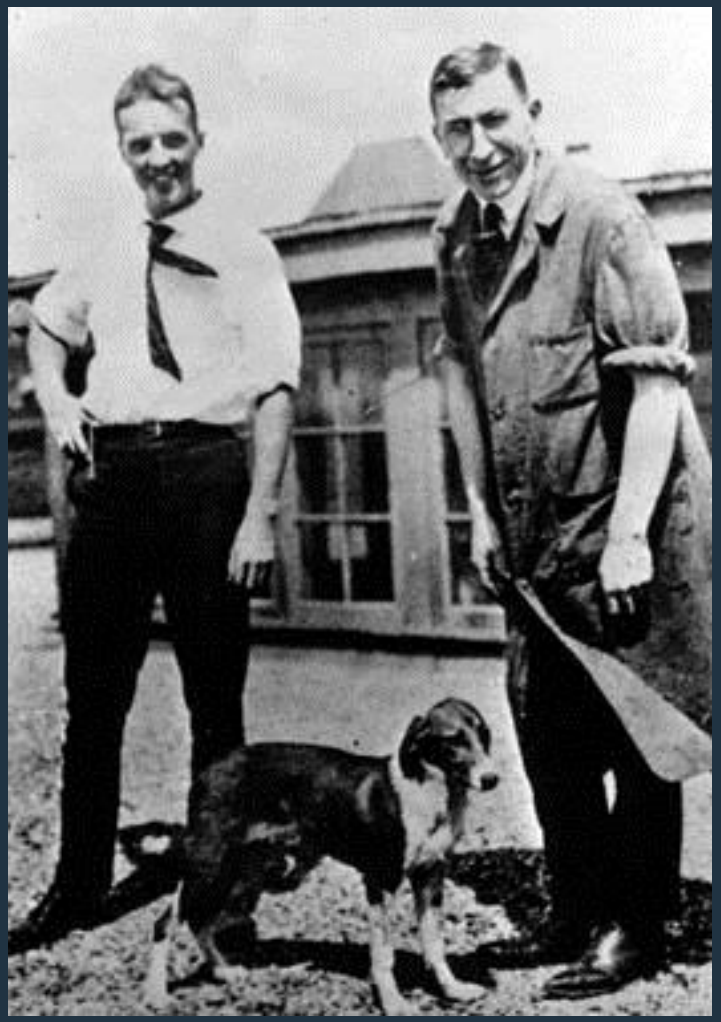
Fredrick Grant Banting

Charles Herbert Best

- Working at a University of Toronto laboratory, in 1921, Fred Banting and Charles Best were able to make a pancreatic extract which had anti diabetic characteristics.

# Discovering Insulin

They were successful in testing their extract on diabetic dogs.



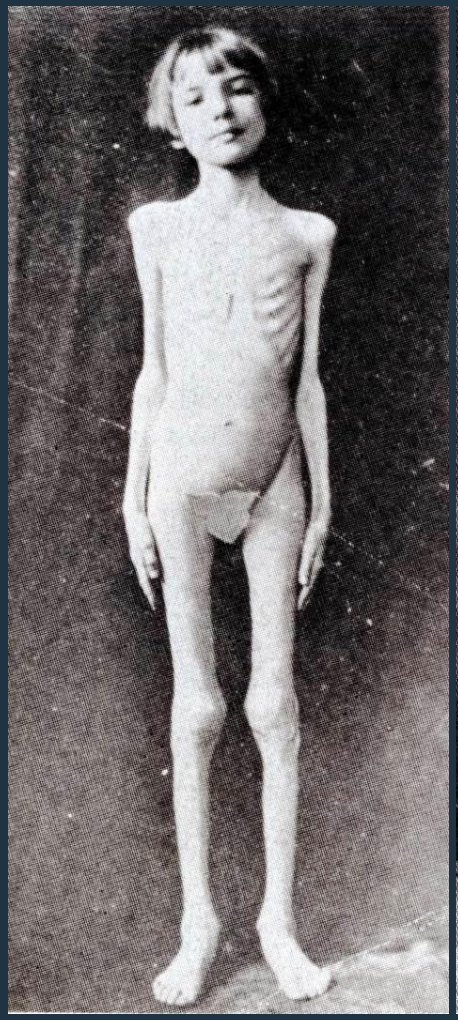
# Discovering Insulin

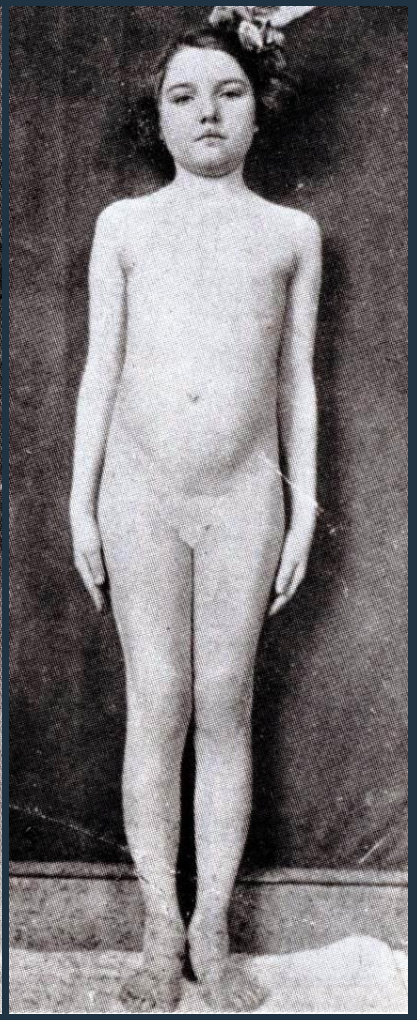
John J R Macleod

James B Collip

- Professor J. J. R. MacLeod provided the lab space and scientific direction to Banting and Best.
- Macleod put his entire research team to work on the production and purification of insulin.
- J.B. Collip joined the team and with his technical expertise the four were able to purify insulin for use on diabetic patients.

# Treatment:  Insulin injections (since 1922)





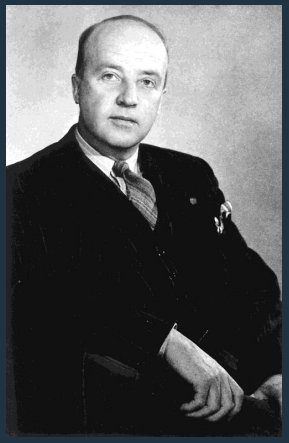
- The first tests were conducted on Leonard Thompson in early 1922.
- These were a spectacular success.
- Some patients in a diabetic coma made miraculous recoveries.
- Elizabeth Hughes Gossett; born 1907
- Received over 42,000 insulin injections before her death in 1981 at the age of 74

# Discovering Insulin

## Nobel Laureates 1923

Fredrick Grant Banting

John J R Macleod

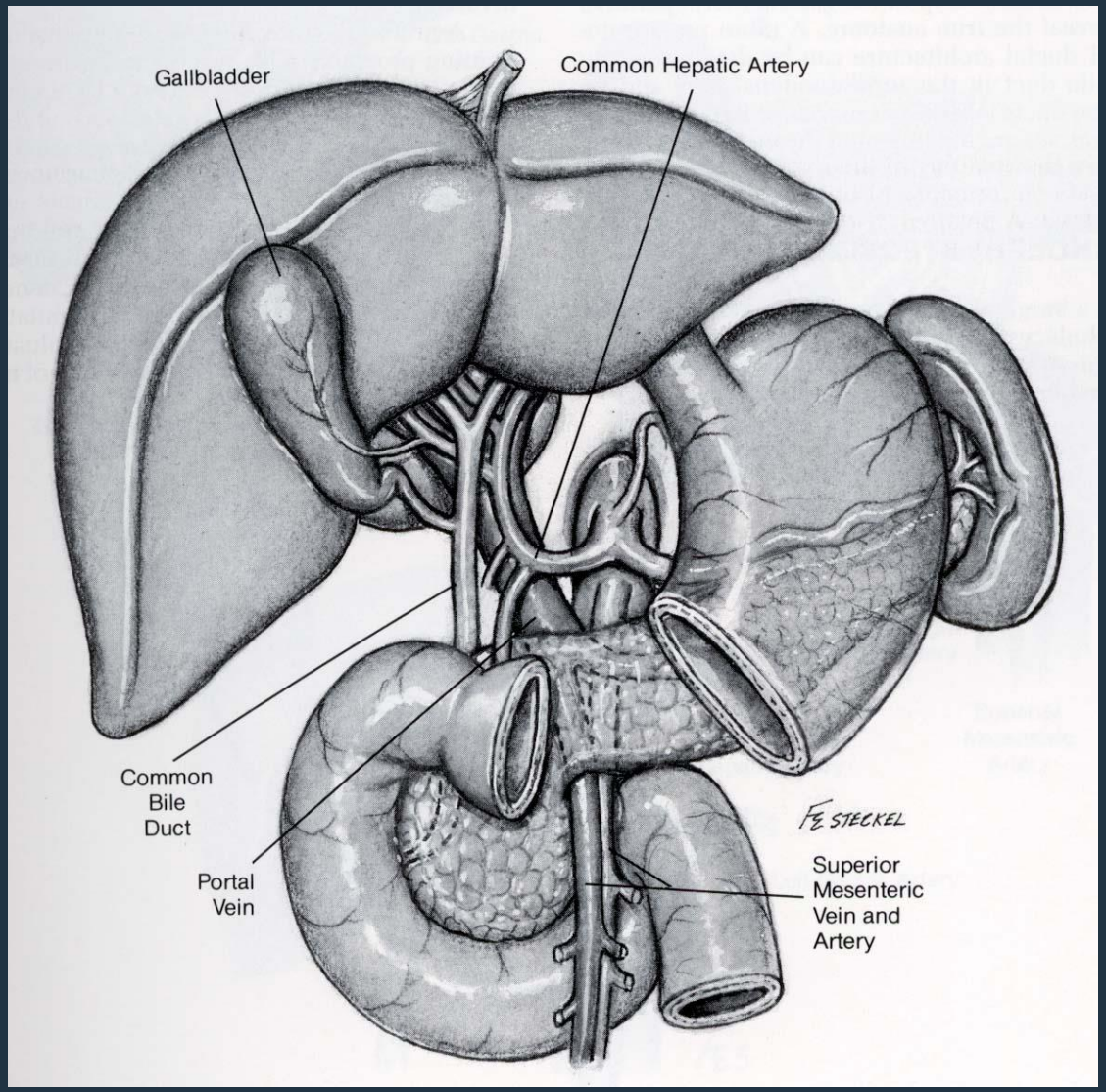


Charles Herbert Best

# Physiologic Considerations

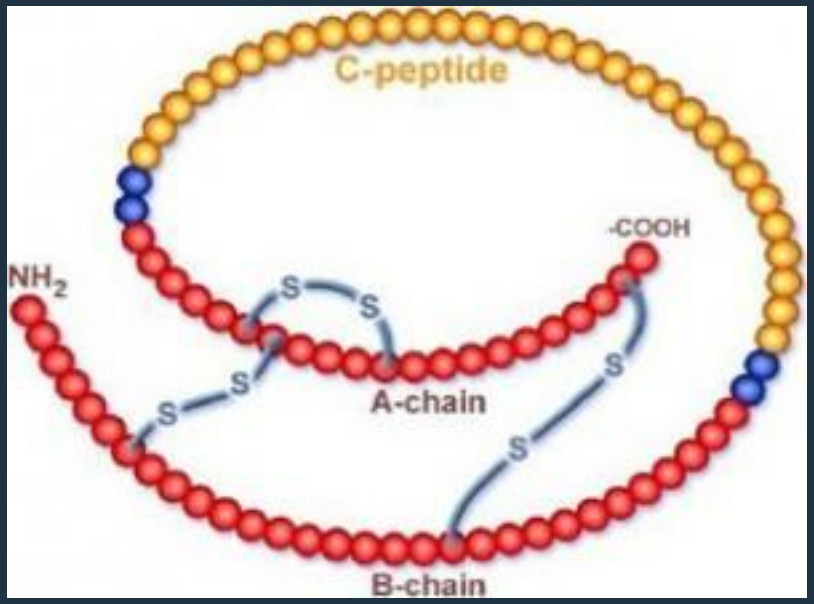
- Glucose is the primary stimulator of insulin secretion via glucose transporters located on the β-cells
- Intact insulin binds to insulin receptors that promote the active transport of glucose across most cells, particularly skeletal muscle and adipose tissue compartments
- Insulin is released into the portal venous circulation where ~ 50% is cleared during first pass metabolism in the liver

# Portal venous drainage of the pancreas



# Physiologic Considerations

- Insulin is the critical factor necessary for the maintenance of glucose homeostasis
  - Initially synthesized as pre-proinsulin
  - The amino terminus is cleaved to produce pro-insulin
  - Further cleavage removes c-peptide fragment producing insulin (A and B chains, 21 and 30 aa, respectively)



# Physiologic Considerations

- 2% of pancreatic mass is devoted to endocrine function
- Islets of Langerhans within the pancreas contain cells that synthesize and release hormones
- $10^6$ islets in the average human pancreas
  - Most located in the body and tail
- Islets contain 5 major cells types (α, β, δ, ε, PP)
- The **insulin**-producing β-cells comprise 75% of an islet's mass

# DIABETES MELLITUS

## CURRENT CLASSIFICATION SYSTEM

- Type 1A
- Type 1B
- Type 2
- Gestational
- Other specific types

# Type 1 Diabetes Mellitus*

## 1A:

- Autoimmune destruction of β-cells
- 90% of cases occur before age 30

## 1B:

- Idiopathic β-cell destruction
  - No evidence of an immunologic process
- Uncommon
- More common in African- and Asian Americans

***Rx: Insulin replacement therapy**

# Type 2 Diabetes Mellitus*

- Heterogeneous group of disorders characterized by some combination of insulin resistance, impaired insulin secretion, and increased glucose production
- Associated with increased age and BMI
- Increasing incidence in adolescents due to increasing obesity

*Rx: Diet modification, weight loss, oral agents, insulin

# Gestational Diabetes

- Glucose intolerance due to insulin resistance associated with the metabolic changes of late pregnancy
- Complicates 4% of pregnancies in the US
- Most women revert to normal glucose tolerance after delivery
- Imparts a ~50 to 80 % lifetime risk of developing DM

# Other Causes of Diabetes

- Genetic defects in β-cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas (chronic pancreatitis, surgical resection, cystic fibrosis, etc.)
- Infections (rubella, CMV, coxsackie)
- Endocrinopathies
- Genetic syndromes

# TYPE 1 DIABETES MELLITUS

## PATHOGENESIS

Genetic predisposition

↓

Environmental trigger (viral, toxin, dietary)

↓

Autoimmunity (isletitis)

↓

β-cell destruction

# Diabetes Mellitus

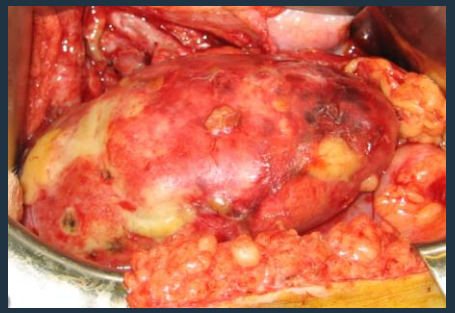
## Public Health Problem:

- 17 to 20 million diabetics in the US
- 1.5 to 2 million type 1 diabetics

# Diabetes Mellitus

## Public Health Problem:

- Significant cause of morbidity and mortality
- Quadruples the risk of heart disease and strokes
- Average decrease in life expectancy of at least 20 years
- **Leading cause of:**
  - **Blindness**
  - **Kidney disease**
  - **Amputation**



# Diabetes Mellitus

## Economic Problem:

- US Economic impact is $174 billion 2007
- $121 B direct medical costs and $53 B indirect costs
- 25% of Medicare dollars are utilized to treat diabetics

# ETIOLOGY OF COMPLICATIONS

- Multifactorial
- Glucose reduced to sorbitol by aldol reductase
- Glycosylation of proteins

# Sequelae of Diabetes

- **NEPHROPATHY: 35% incidence; most common indication for kidney transplantation**
- **RETINOPATHY: 40% incidence within 20 years of diagnosis; leading cause of blindness in the US**
- **PERIPHERAL NEUROPATHY: 70% incidence; producing numbness, paresthesias, pain, and gait disturbances**

# Sequelae of Diabetes

**PERIPHERAL VASCULAR DISEASE:**

- 80% of major, non-traumatic lower extremity amputations are performed in diabetics

**AUTONOMIC NEUROPATHY:**

- Gastroparesis
- Enteropathy
- Colopathy
- Diarrhea
- Orthostatic hypotension

# TREATMENT OPTIONS

## MEDICAL MANAGEMENT

- Best insulin therapy
- Insulin pump

## TRANSPLANTATION

- Whole organ
- Living donor segmental
- Islet cell

# Diabetes Control and Complications Trial

## 1441 insulin-dependent diabetics were followed for an average of 6.5 years

- Randomly assigned to one of 2 groups:
  - (a) conventional insulin therapy
  - (b) Intensive insulin therapy

- Results: Intensive therapy...

  **Delayed the onset and progression of nephropathy, retinopathy, and neuropathy.**

**NIDDK, 1983 - 1993**

# PANCREAS TRANSPLANTATION

- First performed in 1966, Kelly and Lillehei, University of Minnesota.
- Introduction of the cyclosporine (Borel, 1983) resulted in dramatic increases in organ and patient survival.
- Improvements in surgical techniques (early ‘80’s).

# Types of Procedures Performed

## Simultaneous Pancreas-Kidney Transplantation (SPK)

- SPK: most commonly performed
- 60% organ survival at 10 years

## Pancreas-After-Kidney Transplantation (PAK)

- PAK: performed in patients with successful renal transplant
- 50% organ survival at 5 years

## Pancreas-Transplantation-Alone (PTA)

- PTA: least commonly performed
- Patients are transplanted before the onset of nephropathy

# STATISTICS:

## THE WAITING LIST (3/27/2015)

- Kidney – 109,652
- Kidney-Pancreas – 2,068
- Pancreas – 1,090

## TRANSPLANTS PERFORMED - 2014

- Kidney – 17,106
- Kidney-Pancreas – 709
- Pancreas – 245

UNOS, April 2015

# CRITERIA FOR PANCREAS TRANSPLANT LISTING

- Type 1 diabetes mellitus (c-peptide absent)
- 18 - 50 years of age
- End stage renal disease (SPK, GFR < 20ml/min)
- BMI < 28 kg/$m^2$
- Functioning renal transplant (PAK, GFR > 60 ml/min)
- No medical contraindications (cardiac, etc.)
- No surgical contraindications
- Remote or no history of malignancy

# PANCREAS DONOR EVALUATION

Age

Weight

Serologies

No history of DM

Social risk factors

Mode of death

Hemodynamics

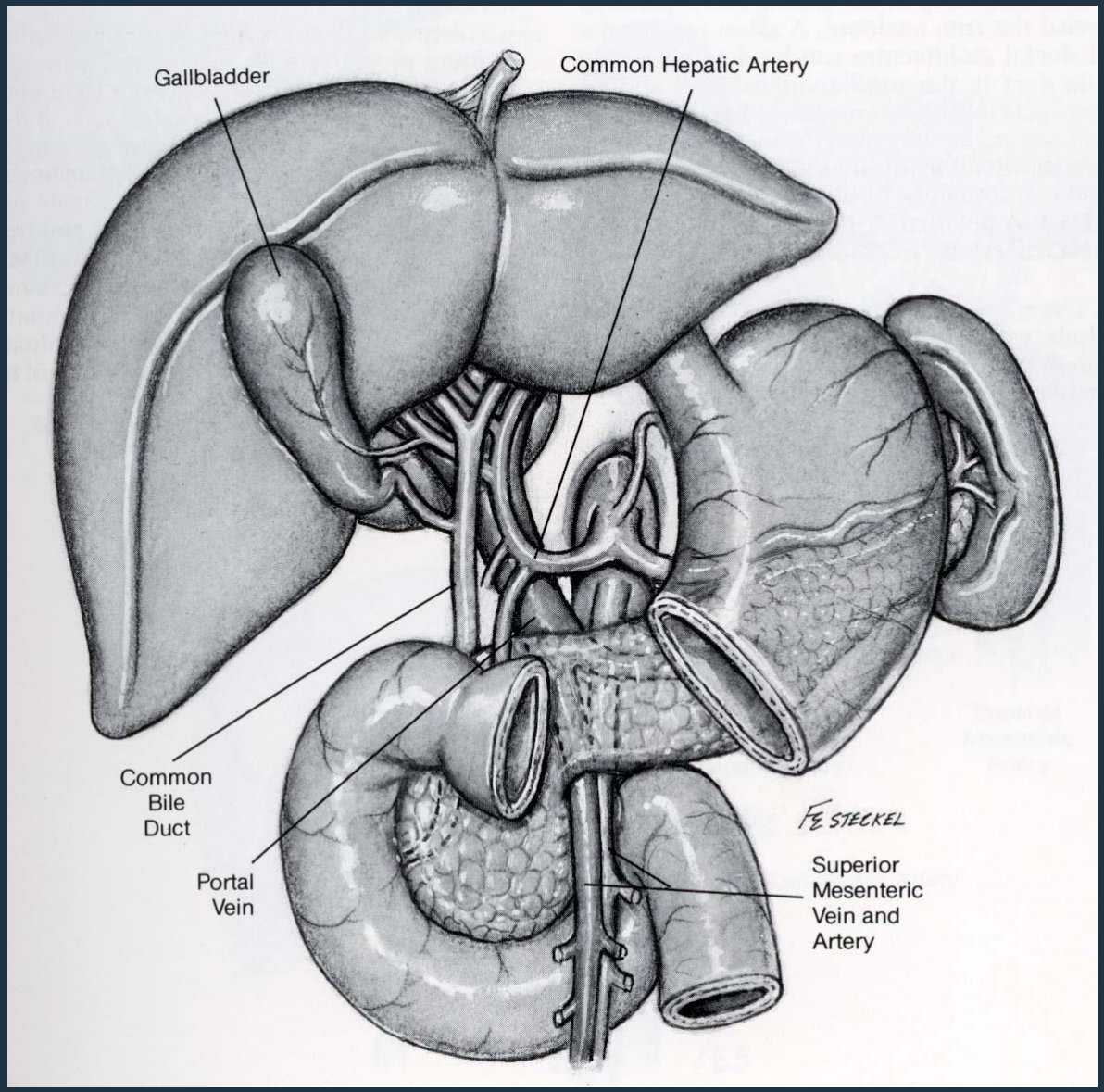
Electrolyte balance

Careful recovery

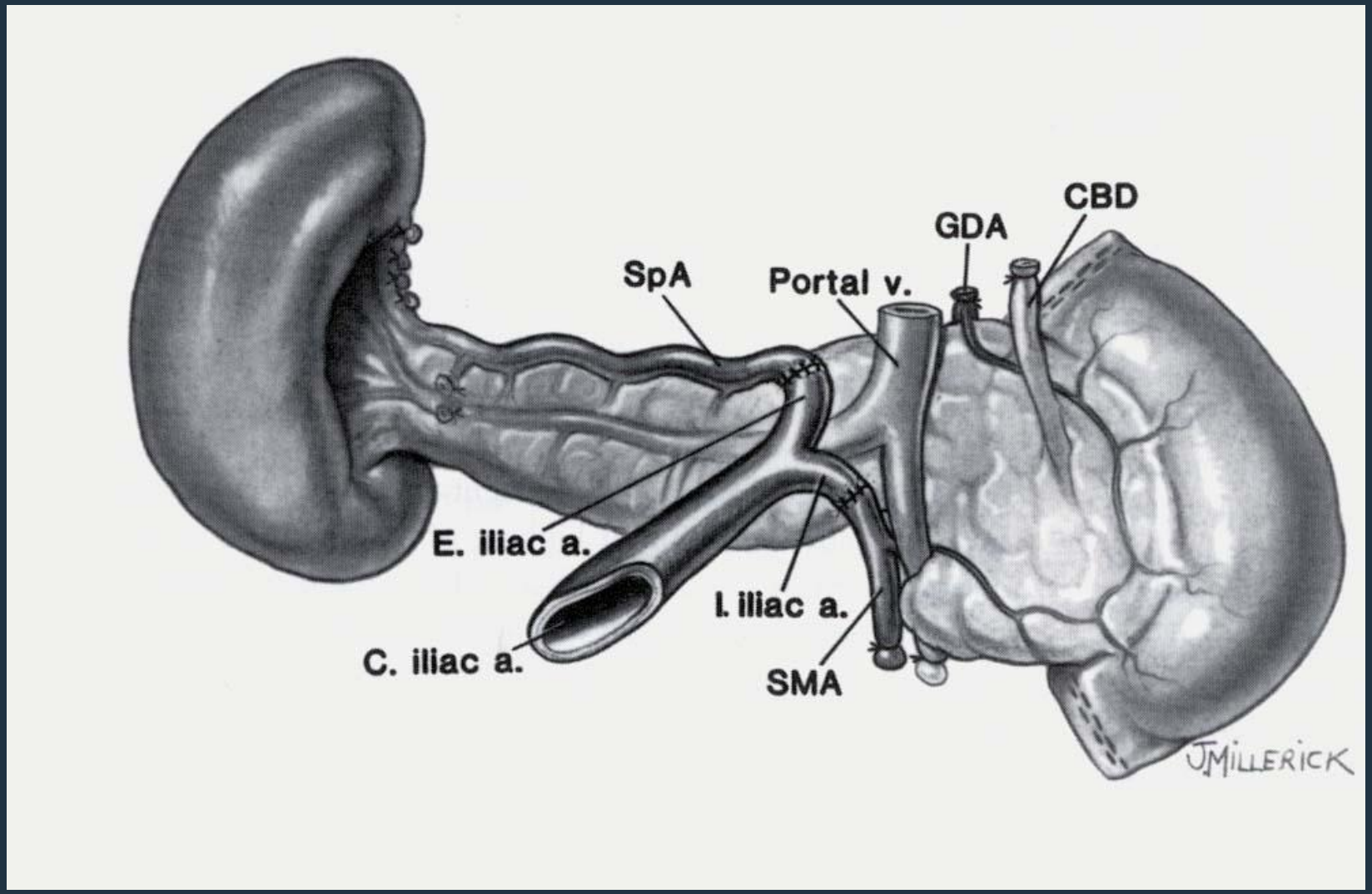
Meticulous back table examination

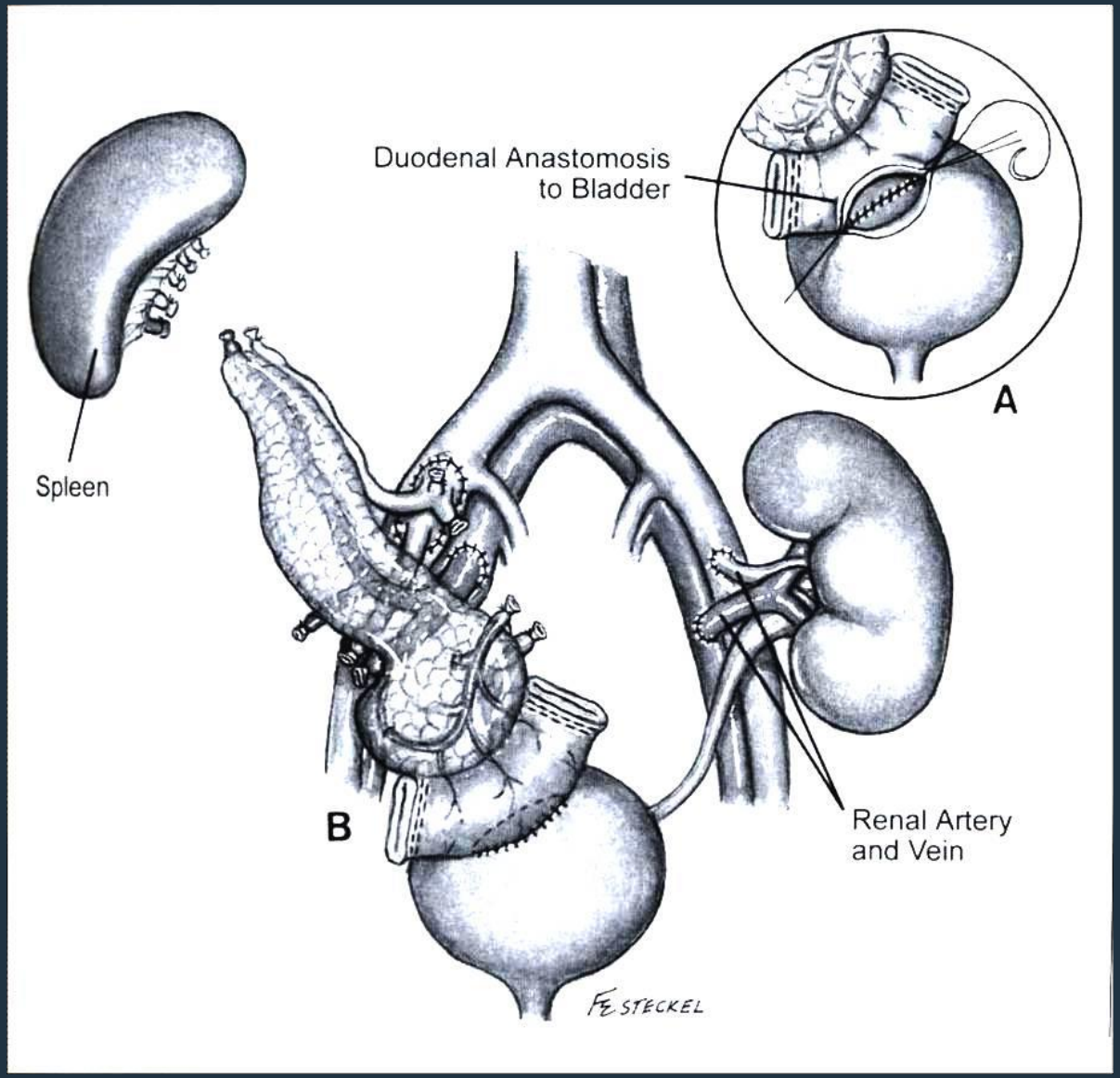
Careful graft preparation (in the cold)

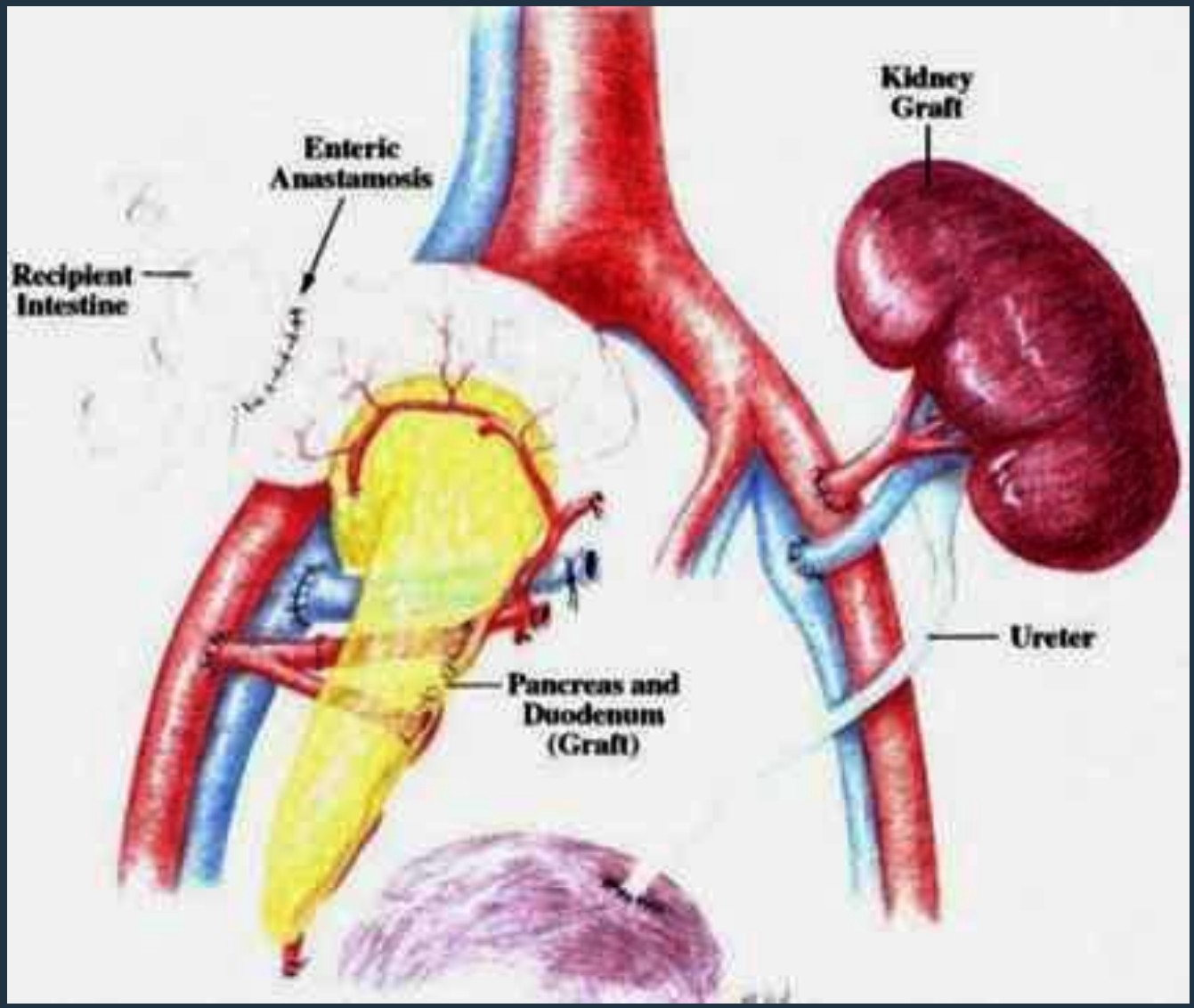
# Careful recovery



# Meticulous back table preparation




Duodenal Anastomosis
to Bladder
A
Spleen
B
Renal Artery
and Vein
FE STECKEL


Kidney
Graft
Enteric
Anastamosis
Recipient
Intestine
Ureter
Pancreas and
Duodenum
(Graft)

# PANCREAS TRANSPLANTATION

## POSTOPERATIVE COMPLICATIONS

Leak
Thrombosis
Infection
Graft Pancreatitis
Metabolic derangements
Lymphoproliferative Disorder (PTLD)

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

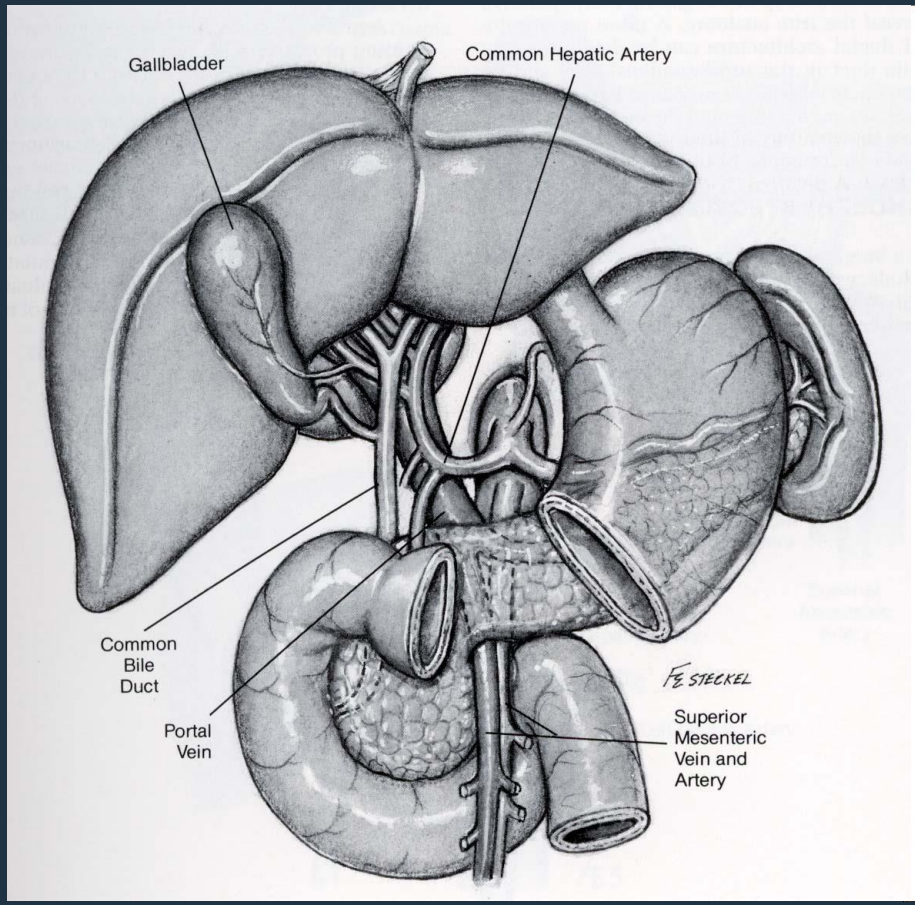
**SYSTEMIC VENOUS DRAINAGE:**

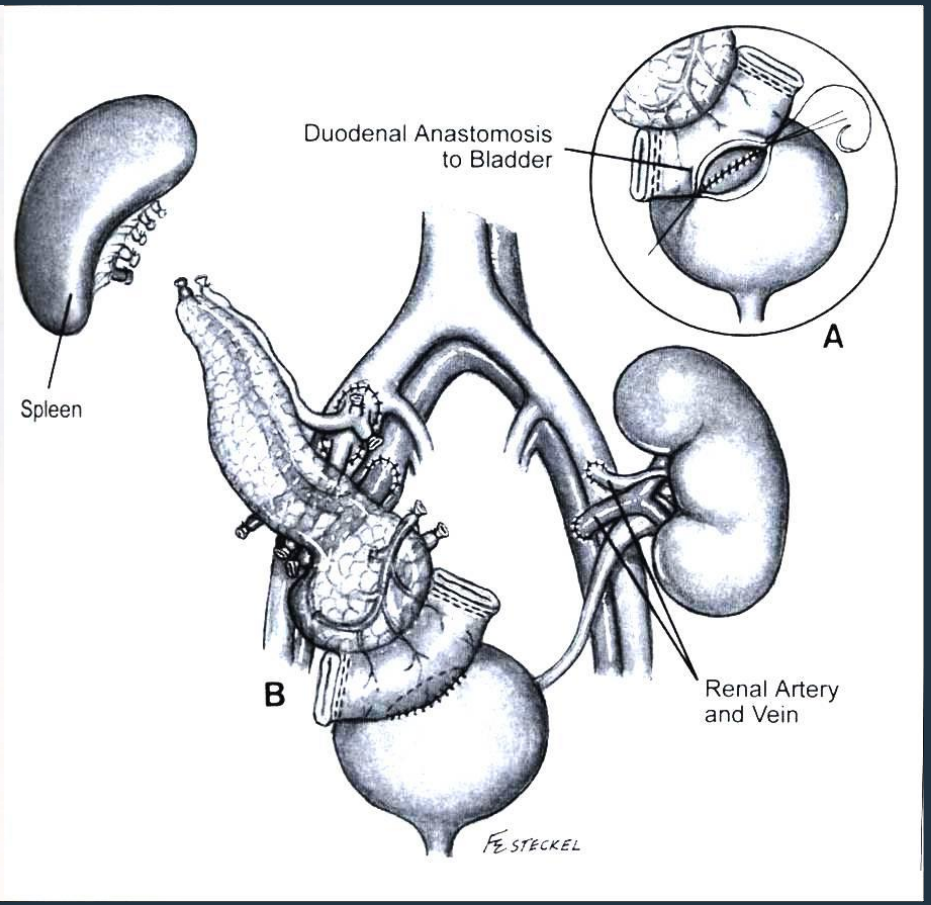
- Anastomosis of donor portal vein to IVC or native common iliac vein.
- Insulin enters the systemic venous circulation and bypasses the liver; net result is **hyperinsulinemia**.

**PORTAL VENOUS DRAINAGE:**

- Anastomosis of donor portal vein to native SMV
- Insulin enters native portal system and undergoes 1st pass metabolism in the liver; net result is **insulin homeostasis**.

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS




**PORTAL VENOUS DRAINAGE**

**SYSTEMIC VENOUS DRAINAGE**

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

- In a native pancreas, 40 to 85% of pancreatic insulin is extracted by the liver during the first passage

- Basal insulin levels are 3 times higher in systemically drained pancreas transplants when compared to controls

- Insulin response to a glucose challenge is 2 to 4 times higher in systemically drained pancreas transplant recipients when compared to controls

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

**Hyperinsulinemia as an independent risk factor for ischemic heart disease**

- **Blood sampled from 2103 males aged 45 to 76 with no history of coronary heart disease.**
- **114 patients had 1st ischemic event within the next 5 yrs.**
- **Fasting insulin concentrations were significantly higher in the study group than in the control group.**

**Despres, *NEJM*, 1996**

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

## Hyperinsulinemia as an independent risk factor for ischemic heart disease

- Excluded men with diabetes
- Adjustments by multivariate analysis:
  - Plasma triglyceride
  - Apolipoprotein B
  - LDL cholesterol
  - HDL cholesterol concentrations

- No decrease in the association between high fasting insulin concentrations and the risk of ischemic heart disease.

- **Insulin appears to contribute to cardiovascular morbidity**

Despres, *NEJM*, 1996

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance

- 2 groups of 32 healthy, normotensive, non-obese subjects with normal glucose tolerance

  Group 1: hyper-insulinemic (>2 SD above the mean)

  Group 2: normo-insulinemic (≤1 SD of the mean)

- Hyperinsulinemic group:
  - ✓higher glucose levels after oral glucose challenge
  - ✓higher fasting plasma triglyceride levels
  - ✓lower high-density lipoprotein cholesterol concentrations
  - ✓higher systolic/diastolic blood pressures

- Conclusion: hyper-insulinemia increases risk factors for coronary artery disease

Zavaroni, *NEJM*, 1989

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

- Prospective studies of healthy subjects have shown that hyperinsulinemia is an independent risk factor for coronary heart disease.

- Hyperinsulinemia is associated with dyslipidemias including high TG and low HDL levels.

- Experimental and clinical studies have yielded mixed data in the transplant setting.

# VENOUS DRAINAGE OF THE TRANSPLANTED PANCREAS

**CONCLUSIONS:**

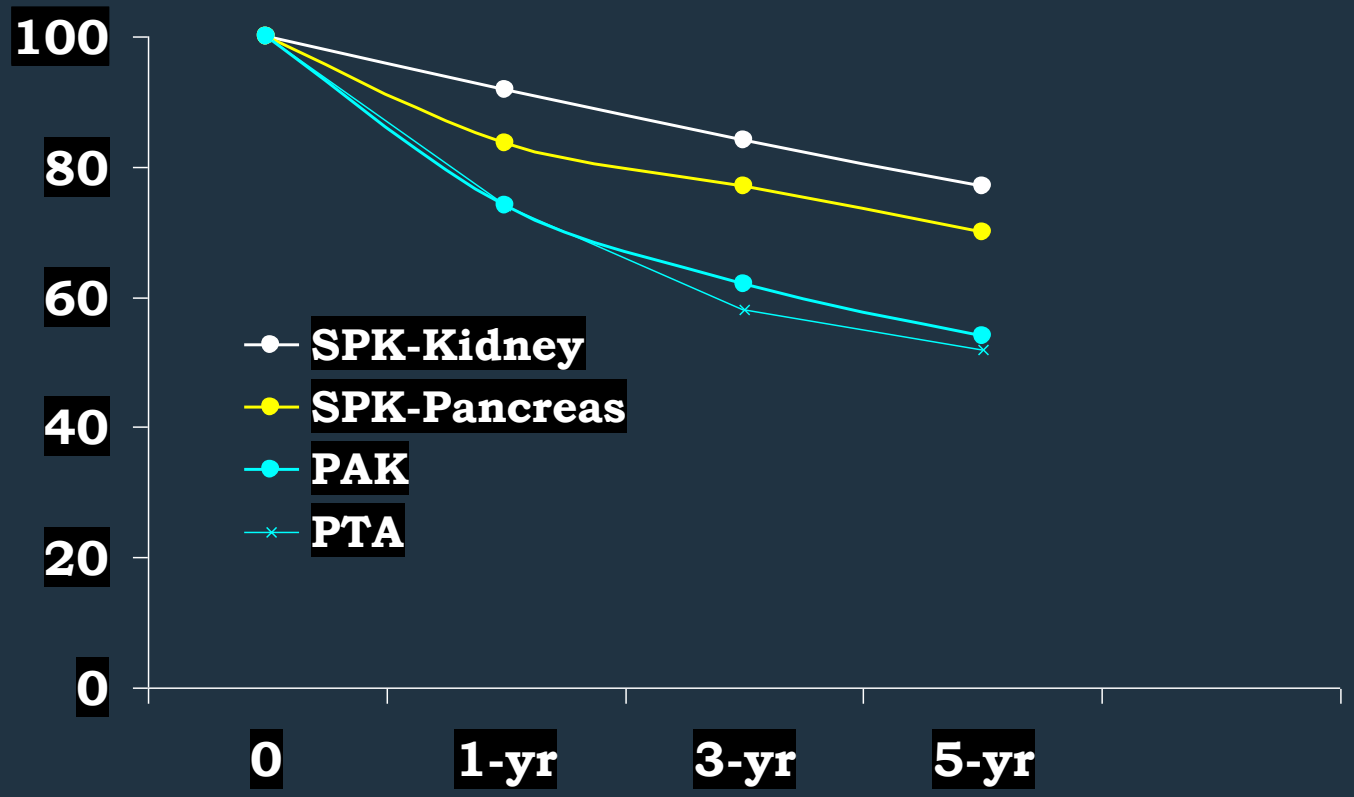
- **Glucose homeostasis is maintained regardless of method of venous drainage.**
- **Hyperinsulinema is likely due to decreased insulin clearance.**
- **Hyperinsulinemia may be secondary to the immunosuppressant agents.**
- **Over time there appears to be a compensatory reduction in insulin secretion following transplantation.**

**Which type of transplant is superior; SPK, PAK, or PTA???**

**Is SPK transplantation superior to kidney transplantation alone in Type 1 diabetics?**

# PANCREAS TRANSPLANTATION

## ALLOGRAFT SURVIVAL DATA




OPTN/STR – 2000 - 2005

# PATIENT SURVIVAL
# TYPE 1 DIABETICS


Mohan et al., Br J Surg, 2003

# Half-Life Analysis of Pancreas and Kidney Transplants

The United Network for Organ Sharing Scientific Registry was reviewed for the period from January 1, 1988 to December 31, 1996.

## Analysis of pancreatic graft and patient half-life

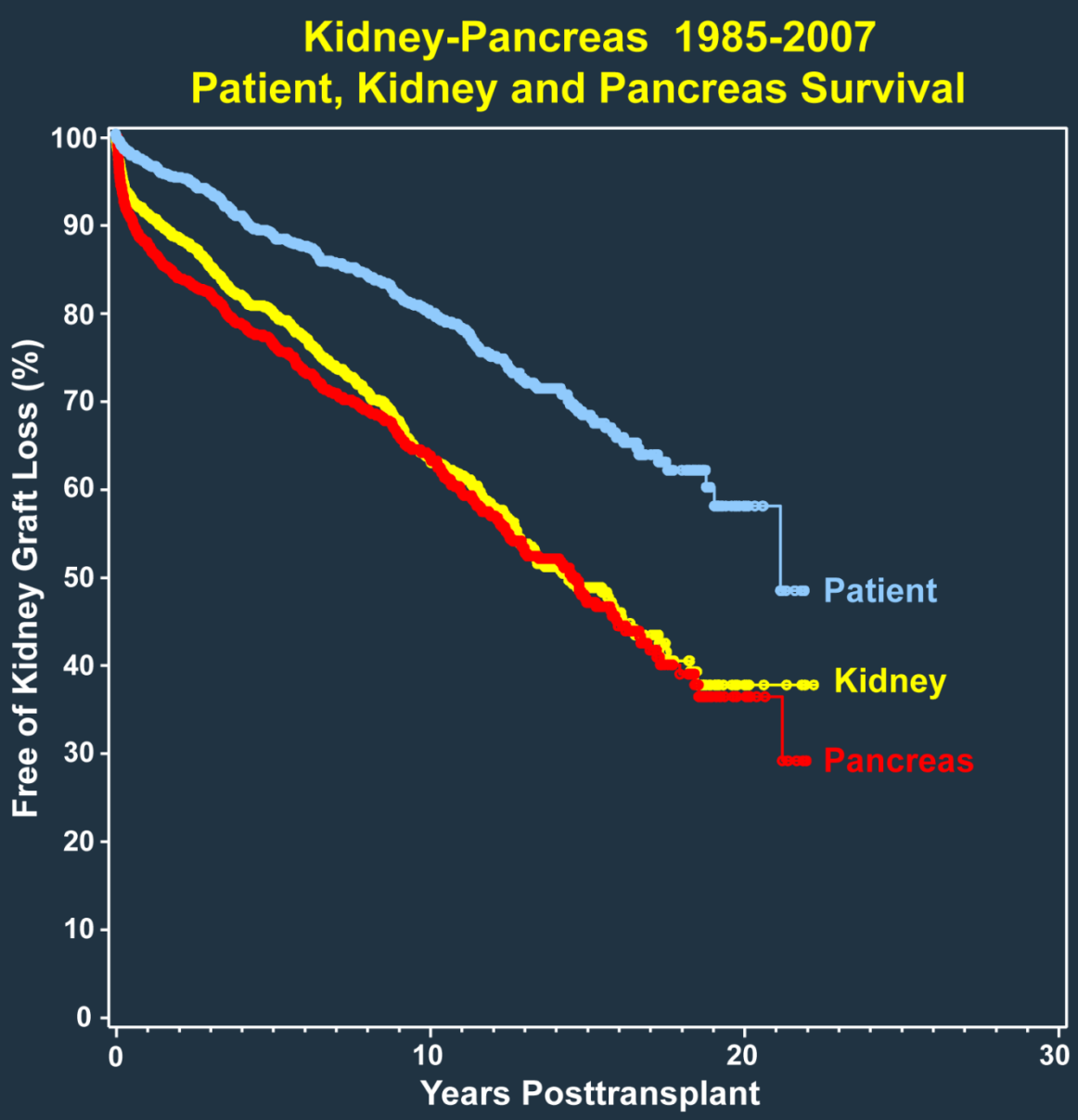
| Group | n | Survival half-life (years) | 95% CI |
|---|---|---|---|
| Graft PAK/PTA | 692 | 2.5 | 2.0–2.9 |
| Graft SPK | 4780 | 11.2 | 10.7–11.9 |
| Patient PAK/PTA | 521 | NC | NC |
| Patient SPK | 4719 | NC | NC |

Marroquin et al. *Transplantation* 2005;80: 272–275

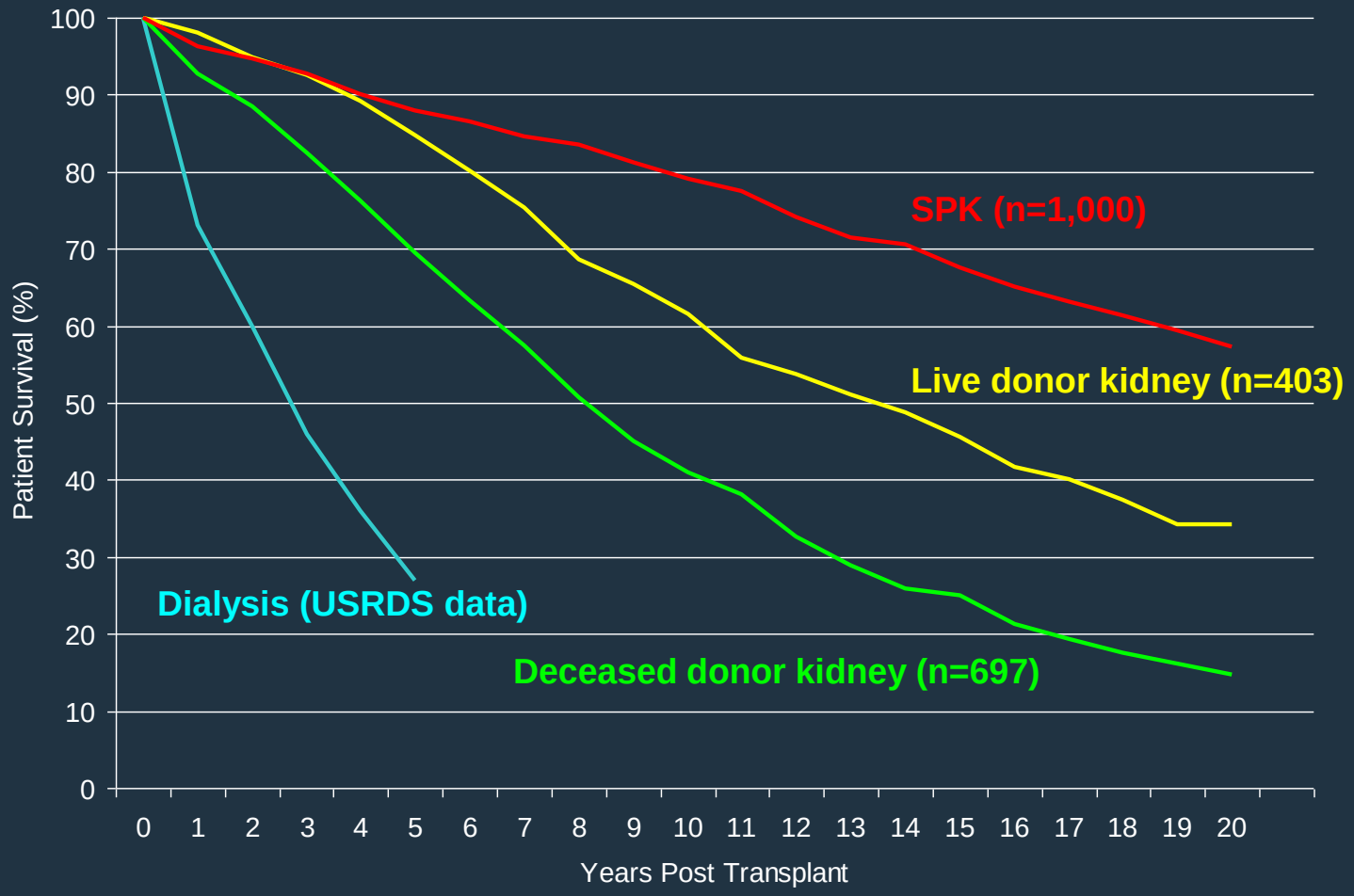
# One Thousand Simultaneous Pancreas-Kidney Transplants At a Single Center With 22-year Follow-up.

*University of Wisconsin, Madison*

Ann Surg. 2009 Oct;250(4):618-30.


Kidney-Pancreas 1985-2007
Patient, Kidney and Pancreas Survival
Free of Kidney Graft Loss (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
Years Posttransplant
Patient
Kidney
Pancreas

# Patient Survival, Type 1 Diabetics
# SPK vs. LD vs. DD vs. HD



**What is the ultimate effect of transplantation on the secondary complications of diabetes???**

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEPHROPATHY

- Occurs in kidneys transplanted into diabetics
- Simultaneous pancreas transplantation prevents transplant nephropathy
- Animal studies have demonstrated that early histologic features of diabetic nephropathy are reversed if blood glucose levels are normalized

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEPHROPATHY

- Deceased donor with 17 year history of Type 1 DM with documented proteinuria

- Bx: diffuse glomerulosclerosis, thickening of mesangial matrix and capillary basement membrane

- Bx of both recipients 7 months post-op revealed normal mesangial matrix and capillary basement membrane

Abouna, *Lancet*, 1983

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEPHROPATHY

- 12 type 1 diabetics with functioning renal allografts were biopsied just prior to isolated pancreas transplantation
- Mild to moderate nephropathy was documented histologically
- No progression of nephropathy was noted in any pancreas transplant recipient (23 month to 10 year follow up)
- Progression of nephropathy was noted in diabetic controls who received kidney transplants alone

Sutherland, *NEJM*, 1989

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEPHROPATHY

- 8 type 1 diabetics without uremia but mild to advanced native diabetic nephropathy received isolated pancreas transplants

- No change in native nephropathy at 5 years

- Kidneys exhibited significant improvement to near-normal histology by 10 years

Sutherland, *NEJM*, 1998

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEUROPATHY

- 61 pancreas recipients (35 of whom were non-uremic) underwent motor and sensory testing at 12, 24, and 42 months post-transplant

- Motor nerve conduction velocities, strength testing, reflexes, and sensory functioning were improved when compared to a control group of type 1 diabetics

Kennedy, *NEJM*, 1990

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEUROPATHY

- 18 type 1 diabetics with polyneuropathy received simultaneous pancreas-kidney transplants
- Control group consisted of 18 diabetics who received renal transplants alone
- Peripheral nerve and autonomic function were measured 6, 12, 24, and 48 months post-op

Solders, *Diabetes*, 1992

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# NEUROPATHY

- **Both groups exhibited improvements in nerve conduction initially; however, further improvement was noted in the pancreas recipients only**

- **Autonomic function improved slightly after 48 months in both groups (no significant difference)**

Solders, *Diabetes*, 1992

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# RETINOPATHY

- 51 kidney-pancreas recipients compared to 21 diabetics who received kidney transplants alone
- Post transplant glycosylated hemoglobin was 6.4% versus 10.6%
- At 1-year follow-up, no significant difference noted in progression of retinopathy between the groups
- No benefit of combined transplant on advanced retinopathy

Sollinger, *Ophthalmology*, 1992

## SECONDARY COMPLICATIONS OF DIABETES MELLITUS

# MICROANGIOPATHY

- 28 recipients of simultaneous pancreas-kidney transplants compared to a group of 17 type 1 diabetics who received kidney transplants alone

- Peripheral microcirculation assessed by transcutaneous oxygen pressure measurements

- Only combined pancreas-kidney recipients exhibited an increase in transcutaneous oxygen pressure measurement following transplantation (4 year follow-up)

Abendroth, *Diabetologia*, 1991

# CARDIAC FUNCTION

- Comparison of cardiovascular outcomes in Type 1 diabetics receiving SPK (130 pts.), KTA (25 pts.), or no transplant (196 pts. on waiting list)

| | 7 Year Survival | Cardiovascular Death |
|---|---|---|
| SPK | 77.4% | 7.6% |
| KTA | 56.0% | 20.0% |
| WL | 39.6% | 16.1% |

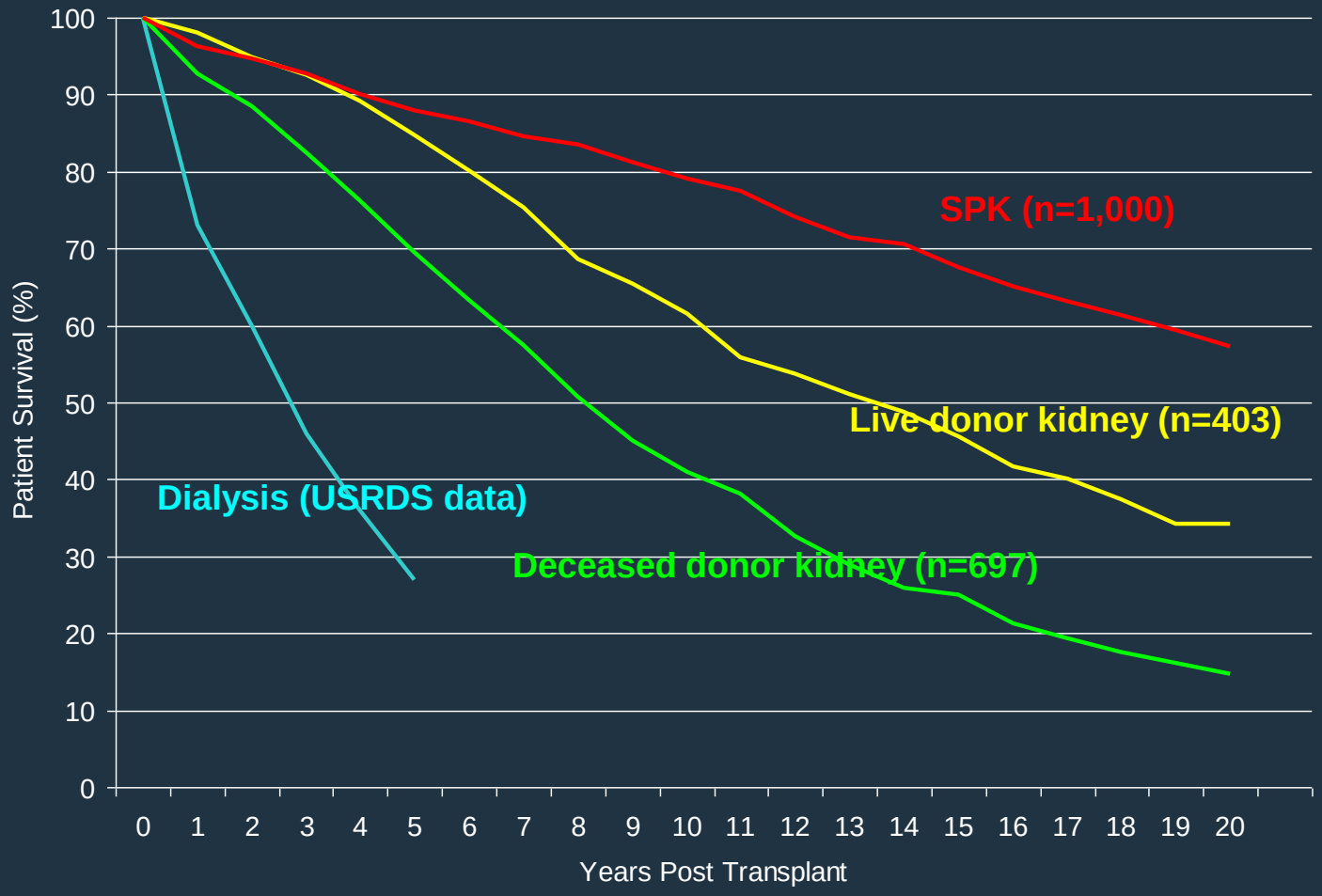
- Subsample of patients underwent radionuclide ventriculography

  Improvement in LV EF with SPK but not KTA

  Significant differences noted at 2 and 4 yrs.

La Rocca et al., Kidney Int, 2001

# Patient Survival, Type 1 Diabetics
# SPK vs. LD vs. DD vs. HD



## EFFECTS OF PANCREAS TRANSPLANTATION ON THE SECONDARY COMPLICATIONS OF DIABETES MELLITUS...

- Native nephropathy improves
- Transplant nephropathy is prevented
- Peripheral neuropathy improves
- Autonomic neuropathy improves
- Microangiopathy stabilizes and may improve
- Retinopathy stabilizes

**Thank You,**