

Great strides in T1D treatment, but how close is the cure?



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1. **Overview:**
 - A. Diabetes definitions: Type 1 and Type 2 diabetes, the beta cell, islets of Langerhans
 - B. Problem scope/epidemiology
2. **“Standing on the shoulders of giants”:**
 - A. Discovery of insulin
 - B. Diabetes Control and Complications Trial (and follow up)
3. **Disease Pathogenesis-** “the Eisenbarth model”
4. **Recent NIDDK efforts & lessons:** “If at first you don’t succeed...”
 - A. Isolated islet and pancreas transplant studies
 - B. Efforts to promote recovery of pancreatic function
 - C. Do adult human beta cells divide in vivo?
5. **Future plans:** New beta cell sources, early intervention trial

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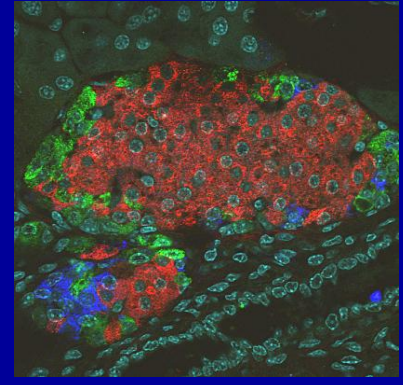
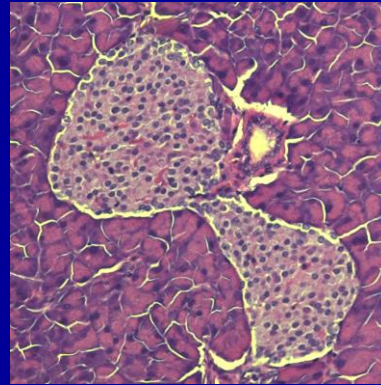
Alain Baron

Patrick Nelson

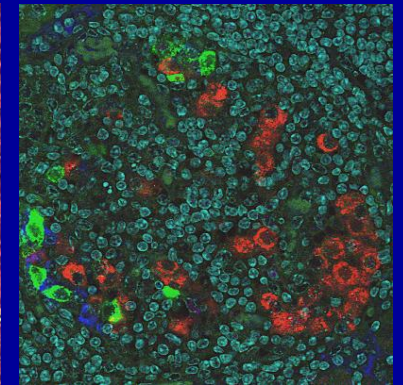
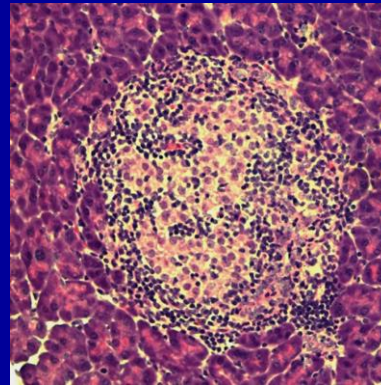
Kim Chen

Definitions

- ◆ Diabetes mellitus: “sweet siphon”
- ◆ Islets of Langerhans, and beta cells



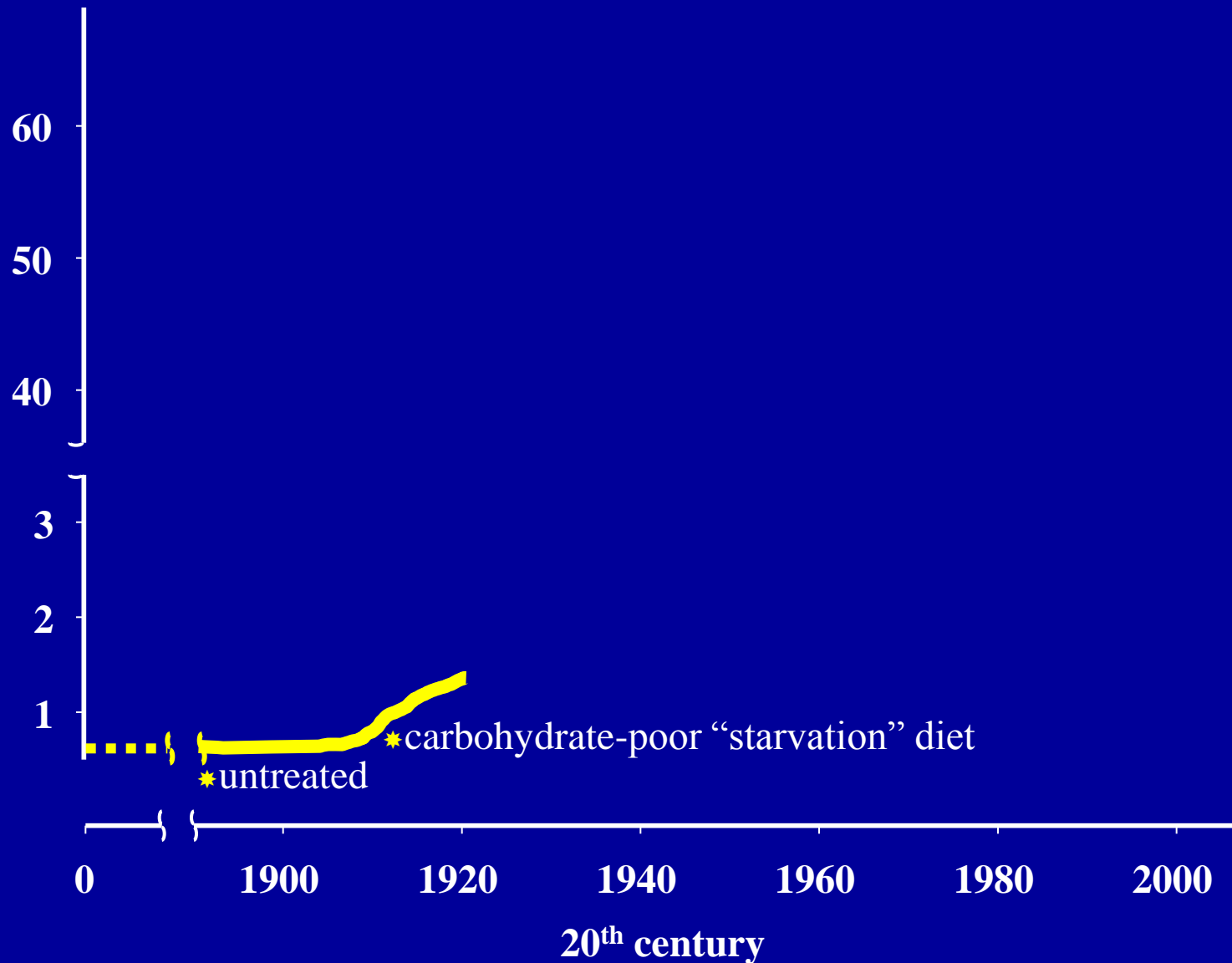
- ◆ Type 1 diabetes- autoimmune
=> beta cells killed
- ◆ Type 2 diabetes- insulin resistance
& beta cell failure



Problem scope

- ◆ 22 million Americans afflicted, incidence increasing
- ◆ Approximately 10% have type 1, >90% with type 2
- ◆ Expensive! \$174B in 2007
- ◆ Leading cause of blindness, kidney failure, & premature mortality.

Life expectancy after diabetes diagnosed (years)





Sir Frederick G.
Banting, M.D.

The dramatic story of insulin's discovery

Medical school at the University of Toronto cut short due to WWI.

1916: Banting joins Canadian Army Medical Corps and serves in France

1919: Returns from France, awarded military cross for heroism under fire

1919-1921: Worked as a general practitioner in London, Ontario

The idea: Preparing for a October 31, 1920 lecture on pancreatic anatomy....

SURGERY, GYNECOLOGY AND OBSTETRICS
AN INTERNATIONAL MAGAZINE, PUBLISHED MONTHLY

VOLUME XXXI NOVEMBER, 1920 NUMBER 5

THE RELATION OF THE ISLETS OF LANGERHANS TO DIABETES WITH SPECIAL REFERENCE TO CASES OF PANCREATIC LITHIASIS

By MOSES BARRON, M.D., MINNEAPOLIS, MINNESOTA
From the Department of Pathology, University of Minnesota, Minneapolis, Minnesota

ANY reference to the pancreas as secreting a hormone necessary for the utilization of sugar by the tissues of the body is misleading, as that function is, accurately speaking, exercised by only a very small portion of the organ, the so-called "islets" of Langerhans; so that what is generally under-

gagni and Cawley recognized the condition in 1765 and 1778 respectively. Opie (35) found two cases in 1,500 autopsies. Rindfleisch (39) found 3 cases in a series of 2,000 autopsies. Zins (45) in 1903 collected only about 70 cases from the literature. Of these, 7 had been diagnosed clinically. Einhorn (10)

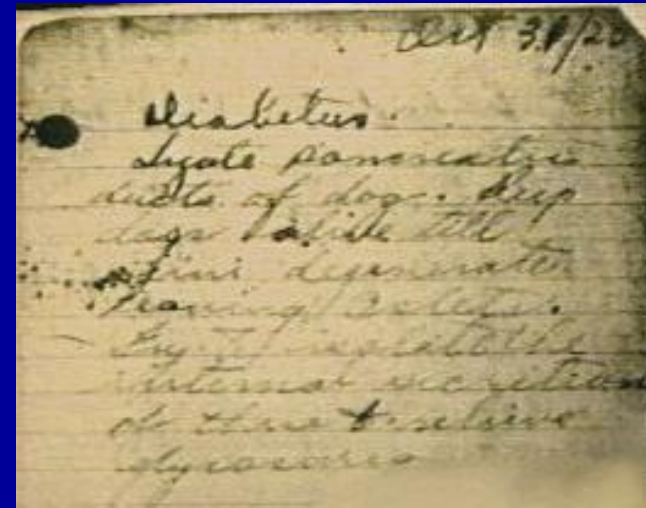
“Any reference to the pancreas as secreting a hormone necessary for the utilization of sugar by the tissues of the body is misleading, as that function is, accurately speaking, exercised by only a very small portion of the organ, the so-called “islets” of Langerhans...”

Moses Barron, M.D.

Banting writes in his notebook, “Oct 31, ’20

Diabetes

Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretion of these to relieve glycosuria.”





Elizabeth & Charles Evan Hughes, 1916

Born 1907

Diabetes diagnosed 1919

age 11

weight 75 pounds, height 5' 00"

Allen treatment 1919 => 1922

age 15

weight 45 pounds

August, 1922: insulin begun

“Simply too wonderful for words”

January, 1923- 105 pounds

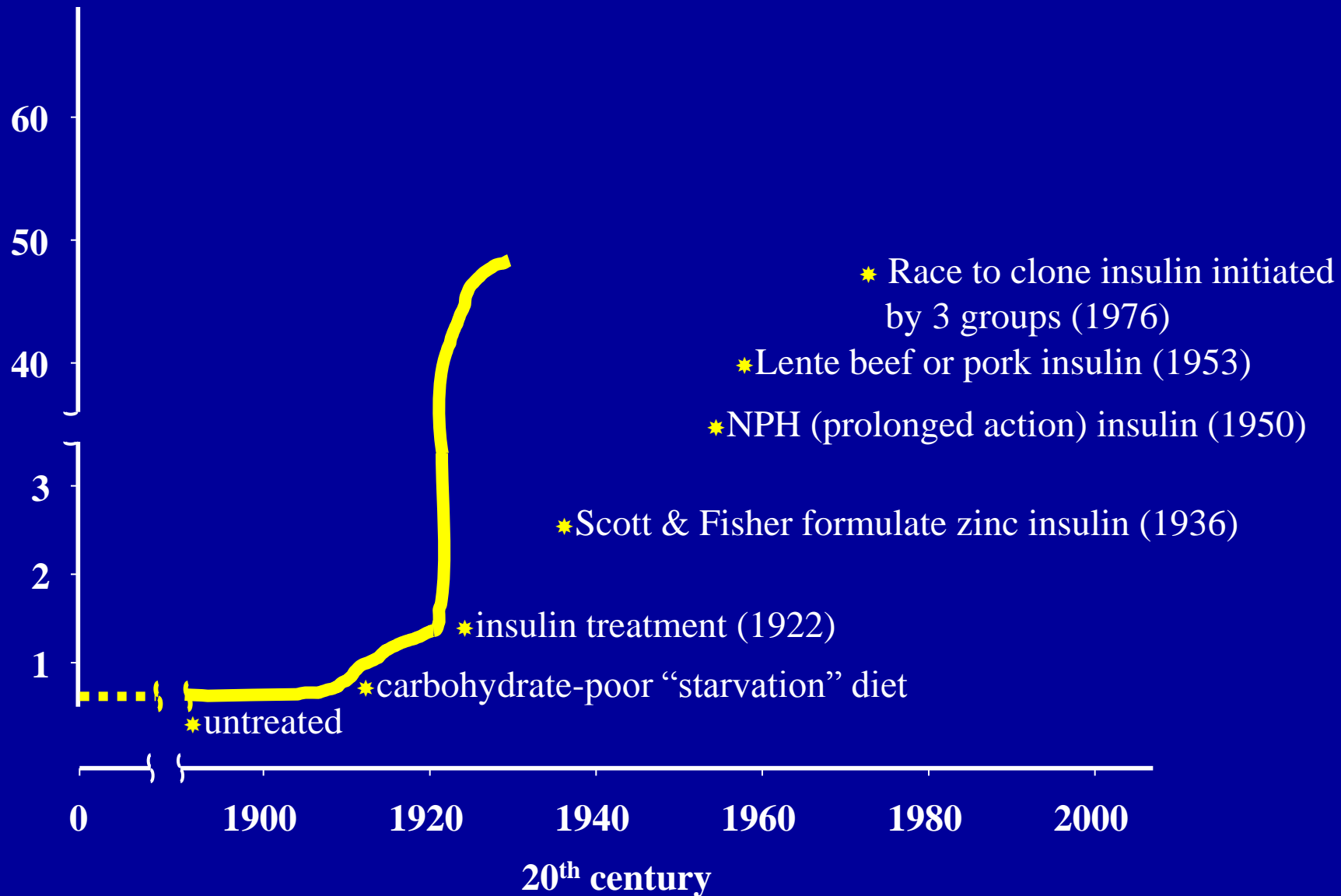
The rest of the story:

Barnard

3 children

Died at 74 years in 1981

Life expectancy diabetes diagnosis (years)



T1D: a T-cell mediated autoimmune illness

- ◆ Serologic evidence of anti-islet immune reaction months to years prior to disease onset (anti-islet cell antibodies: GAD, IA2, insulin, ZnT8)
- ◆ Islets infiltrated by immune cells (“insulitis”) at disease onset
- ◆ Strong genetic component (in particular HLA) with ~ 50% concordance among identical twins. Nearly all susceptibility associated genes regulate immune function
- ◆ Immune interventions at disease onset can prolong “honeymoon”
- ◆ Transplant experience between identical twins: even years after disease onset, rapid disease recurrence when the pancreas is replaced

Dr. Sutherland's "Do Over" Experiment



Diagnosed with
T1DM as a child



No diabetes!

Identical
twins



At least 15 years after sister with
diabetes diagnosed

- No anti-islet antibodies
- Normal glucose tolerance test

Will transplanting
half the non-
diabetic sister's
pancreas to the
sister with diabetes
result in a cure?

T1DM rapidly recurs in pancreas transplant recipients if donor is a discordant identical twin

	1	2	3	4
Age when given transplant	26	26	36	31
T1DM duration	22	17	27	21
Immunosuppression?	none	delayed	delayed	Azathioprine + CyA
Other factors	prev kidney tx			
Pancreas biopsy	insulitis	insulitis	insulitis	OK
Graft function	lost in 5 wks	lost in 6 wks	lost in 12 wks	Insulin at 38 mo
ICA results (Joslin)				
Pre-tx	1 g	neg	- -	neg
Post-tx				
1 wk				
2 wks				
6 wks				
8-9 wks		+/-*	+	neg
11 wks			++	
16 wks			+++	

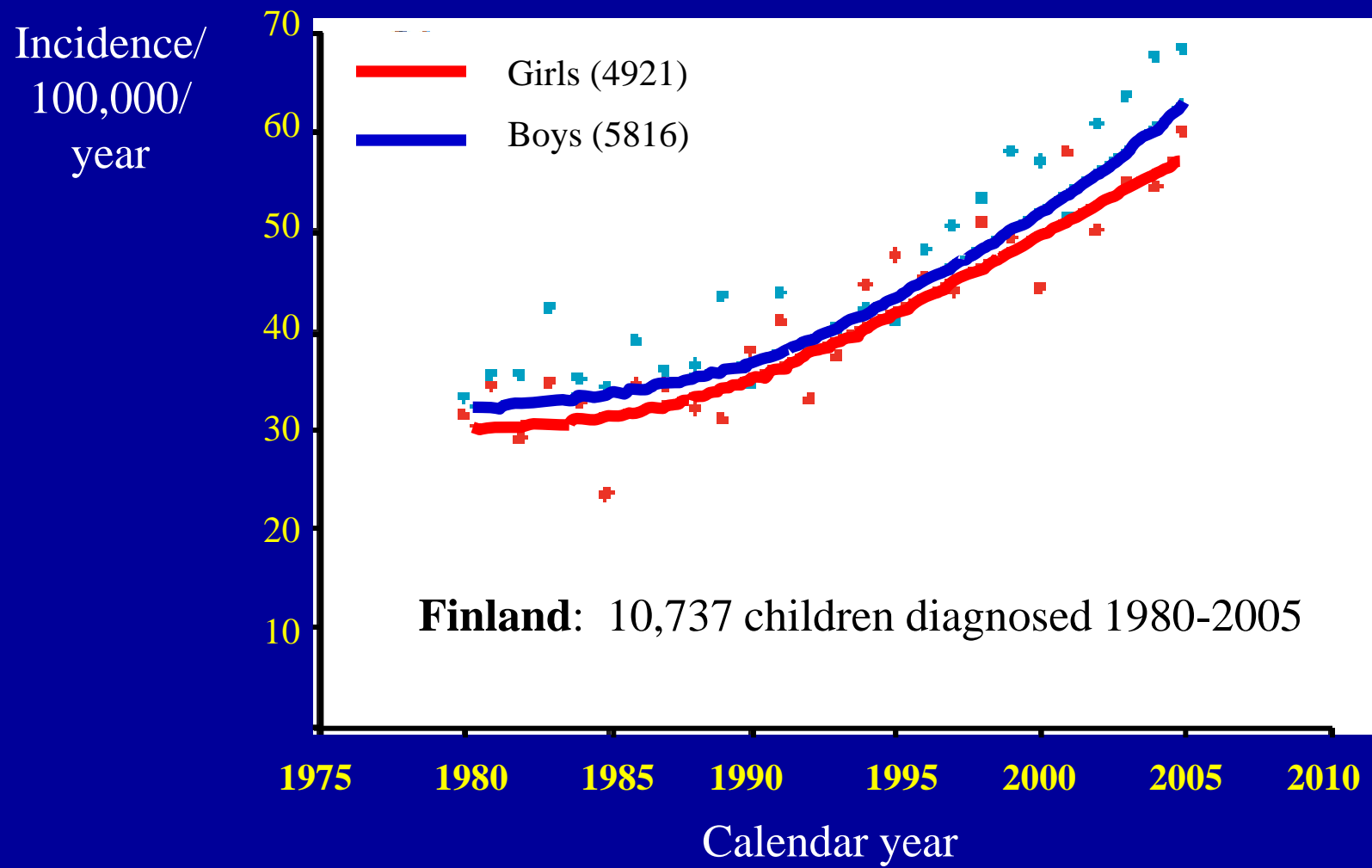
Note rapid immunological destruction when islets replaced, relative to typical primary onset

* Positive ICA confirmed in NIH assay

Sutherland et al. *Trans. Assoc. Am. Phys.* **97**: 80-87, 1984

Sutherland et al. *Diabetes* **38** (suppl 1): 85-87, 1989

Type 1 diabetes incidence is increasing!

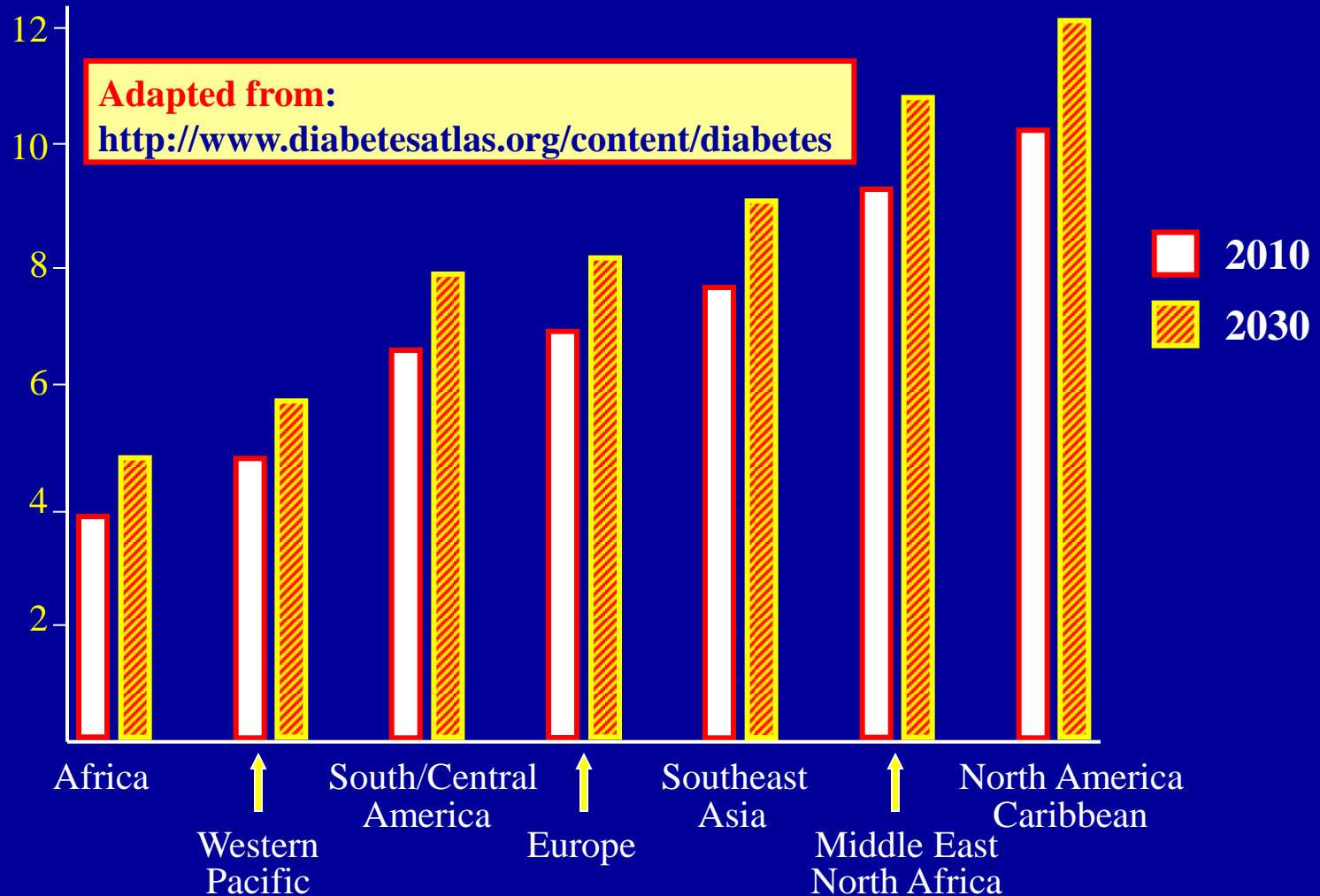


Diabetes (types 1 & 2): worldwide epidemic

In 2010 ~**285 million** (6.6% of adults) will have diabetes (~ 70% in low/middle-income countries)

By 2030, without successful preventive programs, ~**438 million** (7.8% of adults) will have diabetes

Estimated diabetes prevalence by region for ages 20-79 years (%)



The “Glucose Hypothesis”

Treatment that normalizes blood glucose will prevent or delay the long term complications of diabetes mellitus

1441 patients with type 1 diabetes mellitus:

	<u>Retinopathy?</u>	
	Yes	No
<u>Intensive Therapy</u>	25%	25%
Conventional	25%	25%

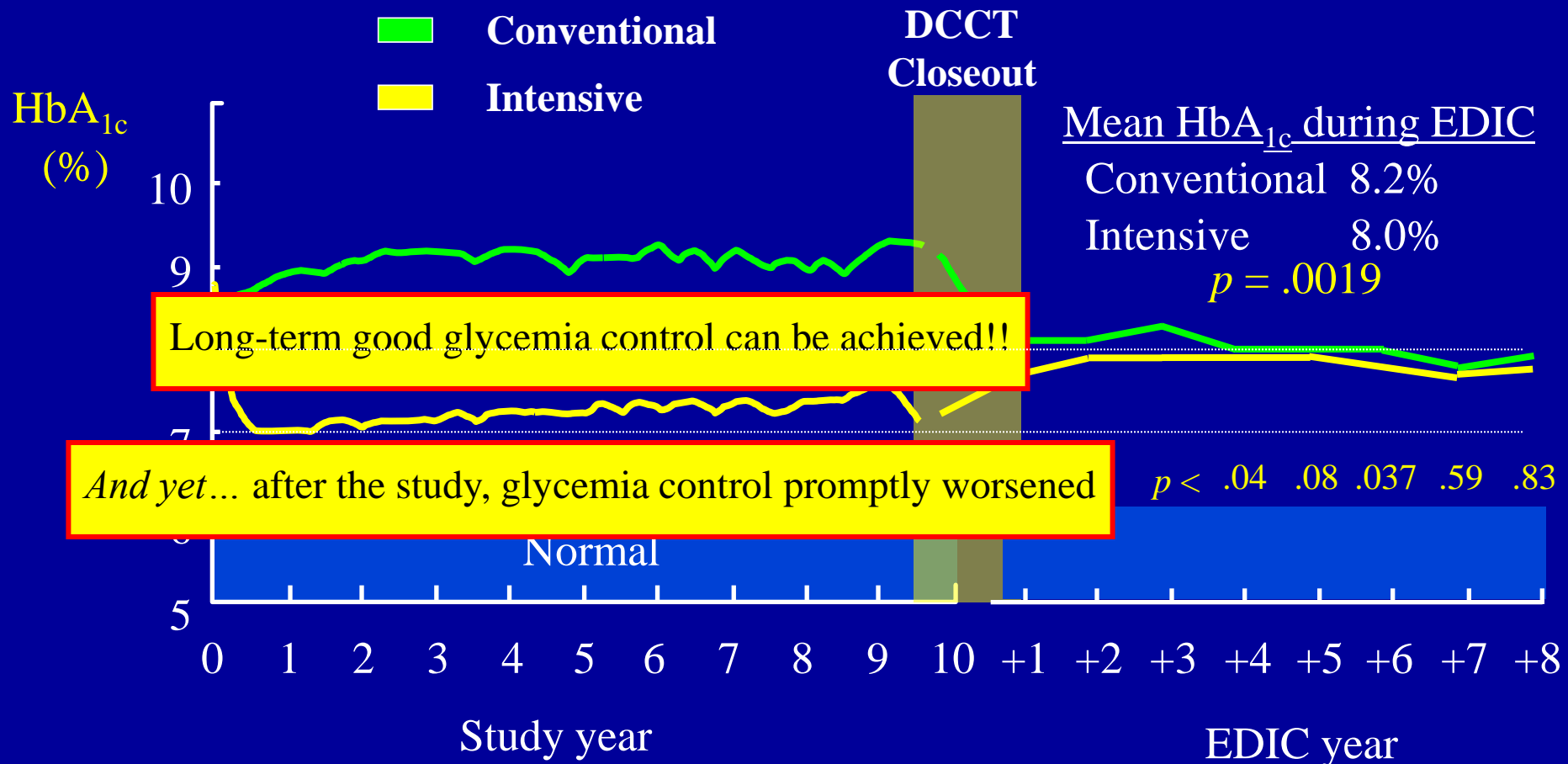
Better glycemia control reduced the risk of clinically meaningful:

- ◆ Retinopathy 76% ($P \leq 0.002$)
- ◆ Nephropathy 54% ($P < 0.04$)
- ◆ Neuropathy 60% ($P \leq 0.002$)
- ◆ Cardiovascular endpoints 57% ($P \leq 0.007$)

Diabetes Control & Complications Trial Research Group. *NEJM*. **329**: p977-86, 1993.

Nathan et al. *NEJM* **353**: p2643-2653, 2005

Effect of Intensive Glycemic Control: HbA_{1c} Levels

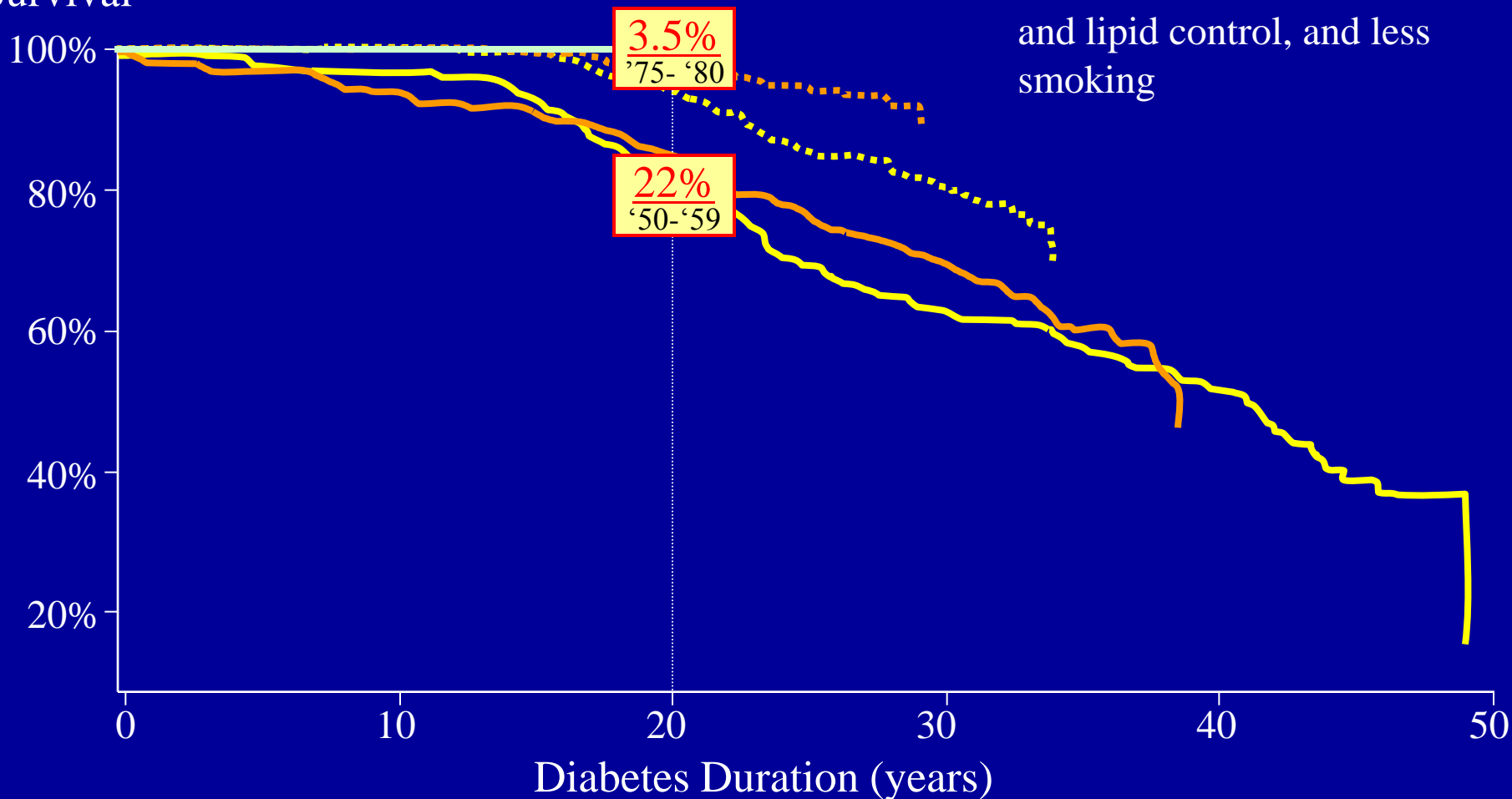


All cause T1DM mortality improving dramatically

Pittsburgh Epidemiology of Diabetes Complications Study

Pambianco, G. et al. *Diabetes* 55: 1463- 1469, 2006.

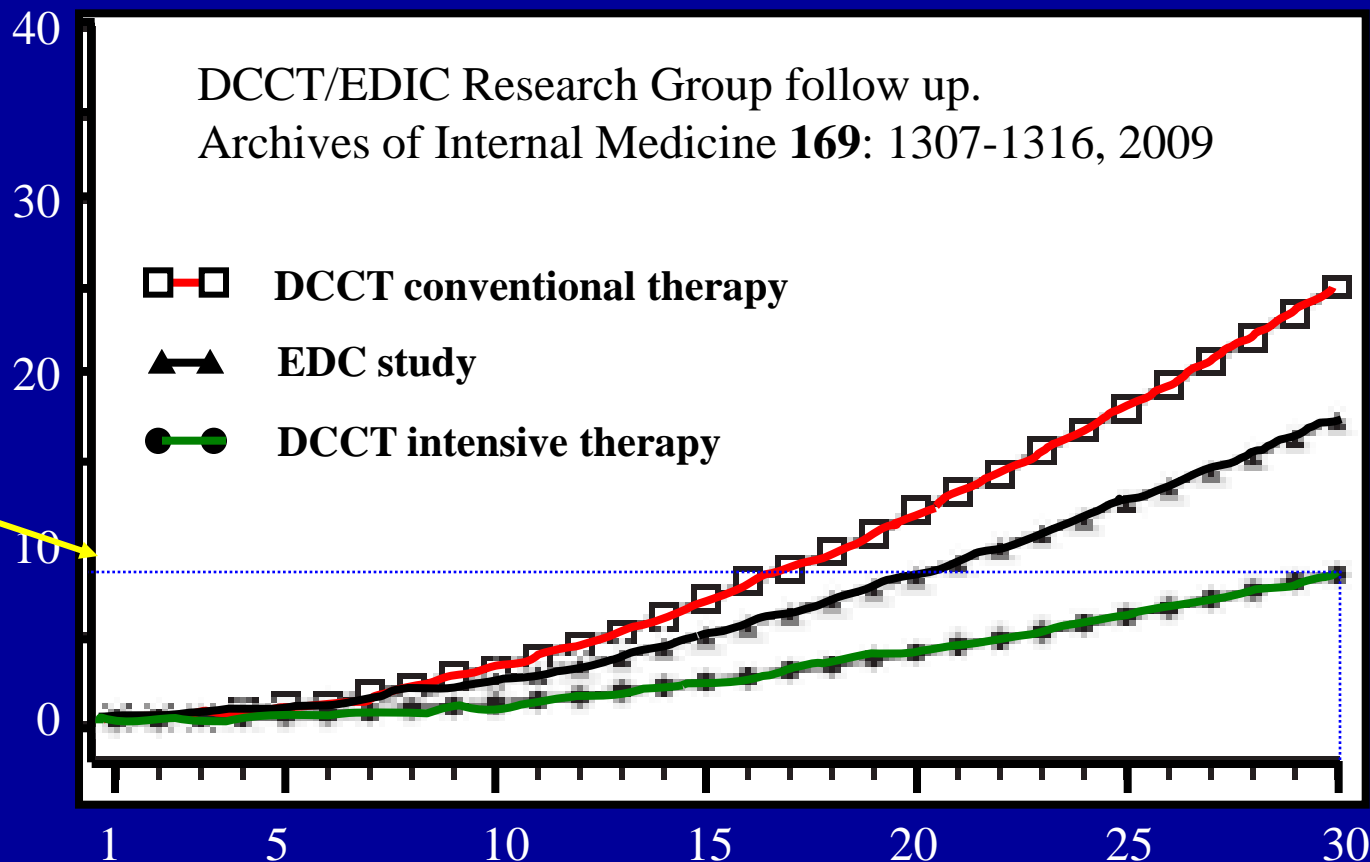
Cumulative
Survival



Improved prognosis for T1D: decreased end-organ complications (e.g. nephropathy)

Cumulative nephropathy incidence (%)

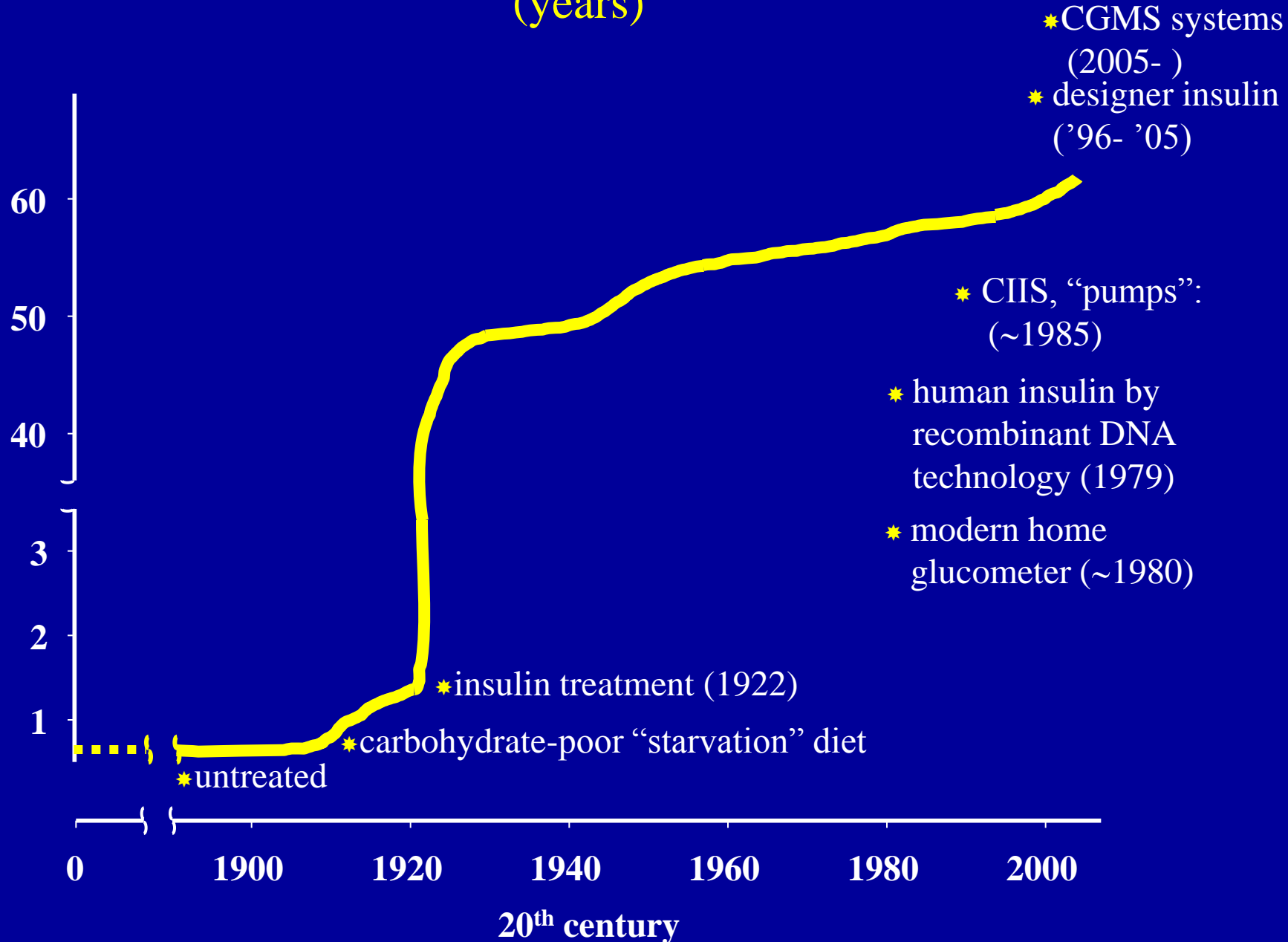
9% at 30 years



- **Defined as:** Albumin excretion rate of > 300 mg/d, serum creatinine > 2 mg/dL, dialysis or kidney transplant

Life expectancy following diabetes diagnosis

(years)



Sam Andersen- Joslin 84-Year Medalist!

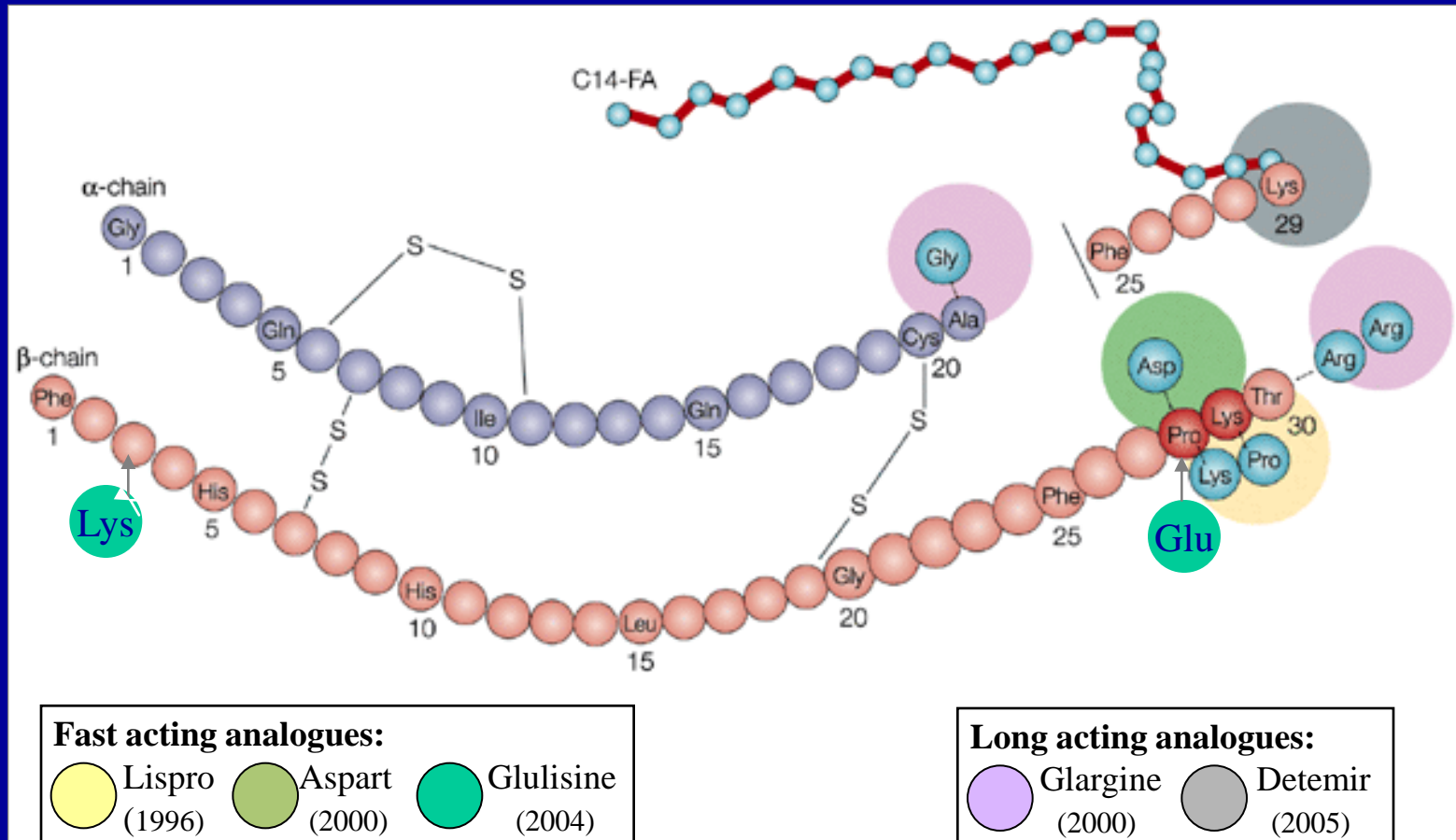
Diagnosed with diabetes in 1925



Slide courtesy of Dr. George L. King,
Joslin Diabetes Center

Creating Insulin Analogues

- ◆ Using recombinant DNA technology, insert modified human proinsulin gene into *Saccharomyces cerevisiae* (baker's yeast) or non-pathogenic *E. coli*
- ◆ AA substitutions generally in beta-chain B26-B30 since not necessary for insulin receptor recognition



Adapted from: *Nature Reviews Drug Discovery* **1**; 529-540, 2002

Diabetes Prevention Program (DPP)

NEJM 346:393, 2002

Patients at increased risk of diabetes (~10%/year)

Placebo
(N = 1082)

Metformin
(N = 1073)

Lifestyle
Change
(N = 1079)

Progression to diabetes?
2.8 year follow-up

Goals:
Low fat diet
7% weight loss
Exercise: 30 min/day
5 days/week

Relative to
control group

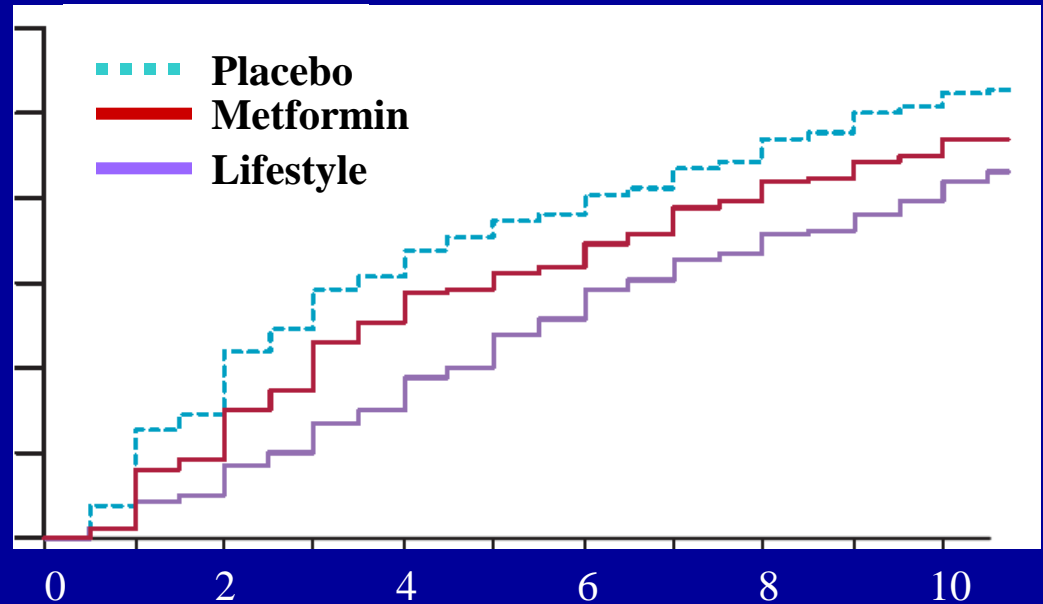
31% reduction
P < 0.001

58% reduction
P < 0.001

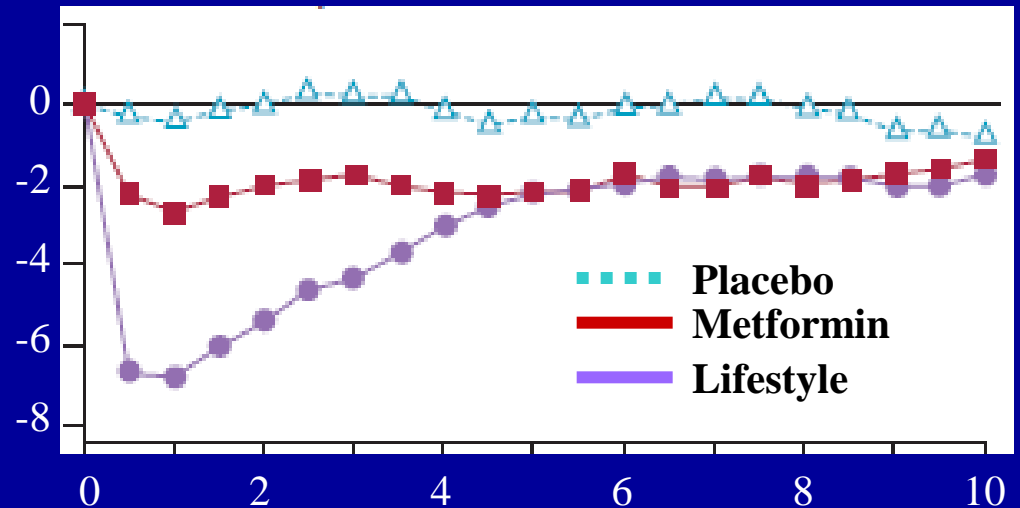
DPP 10 Year Follow up

2766 of the original 3150 continued follow up

Cumulative
Diabetes
Incidence
(%)



Weight
change
(Kg)



Can population-wide behaviors be modified?

Difficult, but not impossible. Recent examples*.

In “”Ask not what your country can do for you.....”

In

We must all do our part!

In A. Harold Schnitzer Diabetes Health Center

In 1. Outreach

2. Education

In 3. Treatment

In 4. Research

B. Each of you!

A. Watch your diet and weigh

B. Be active

C. Set an example.

*Lavizzo
childho

1. The F
1983
2. Natio
Drivi

3. “Perspectives in Disease Prevention and Health Promotion, Seat Belt Use- United States.” CDC MMWR, May 16, 1986.

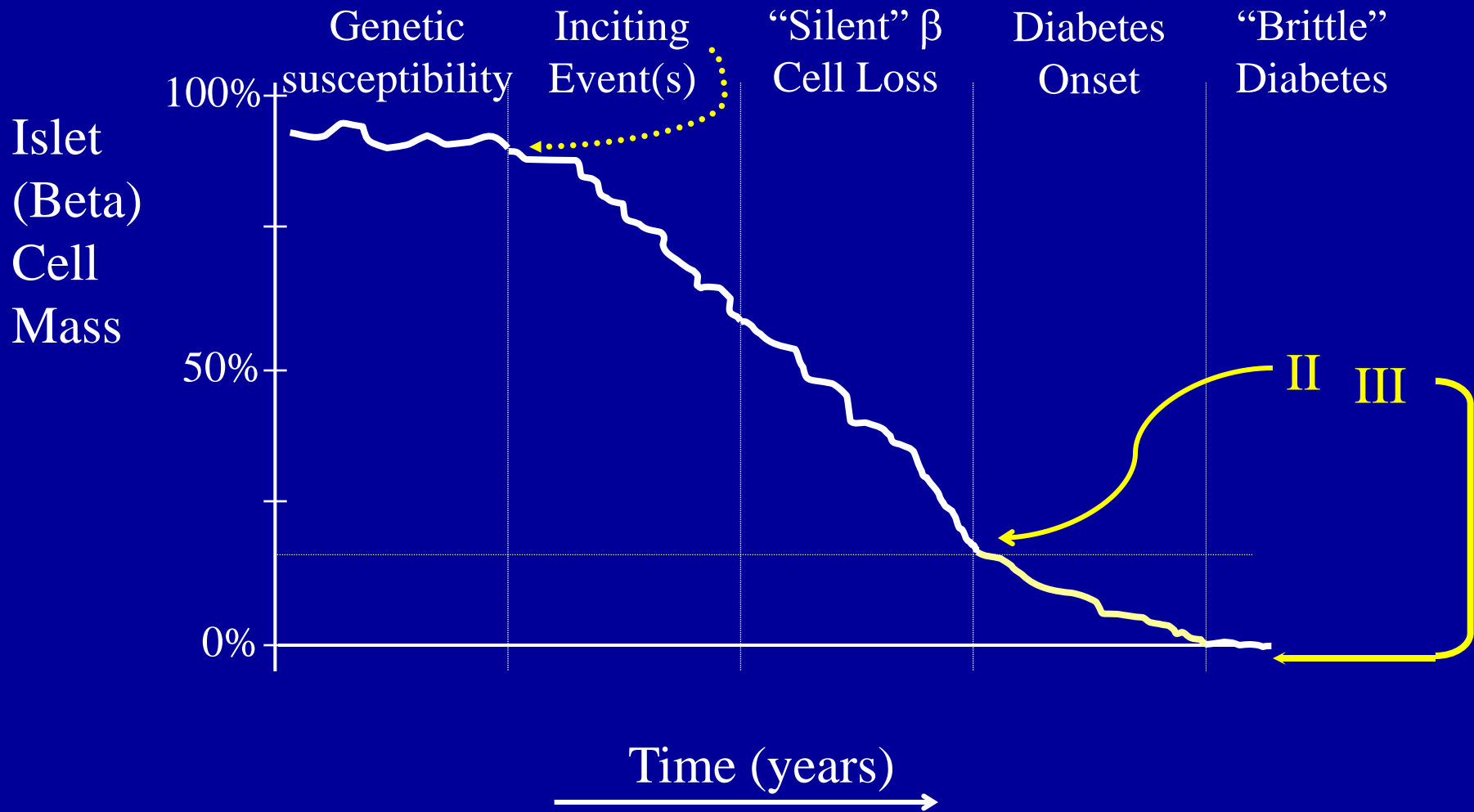
4. Tobacco Use Among Adults-United States, 2005. CDC MMWR Weekly, October 27, 2006

5. “Seat Belt Use Lags Among Rural Men.” USA Today, May 15, 2006 (citing NHTSA data)

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T1DM- a slowly progressive T-cell mediated autoimmune illness

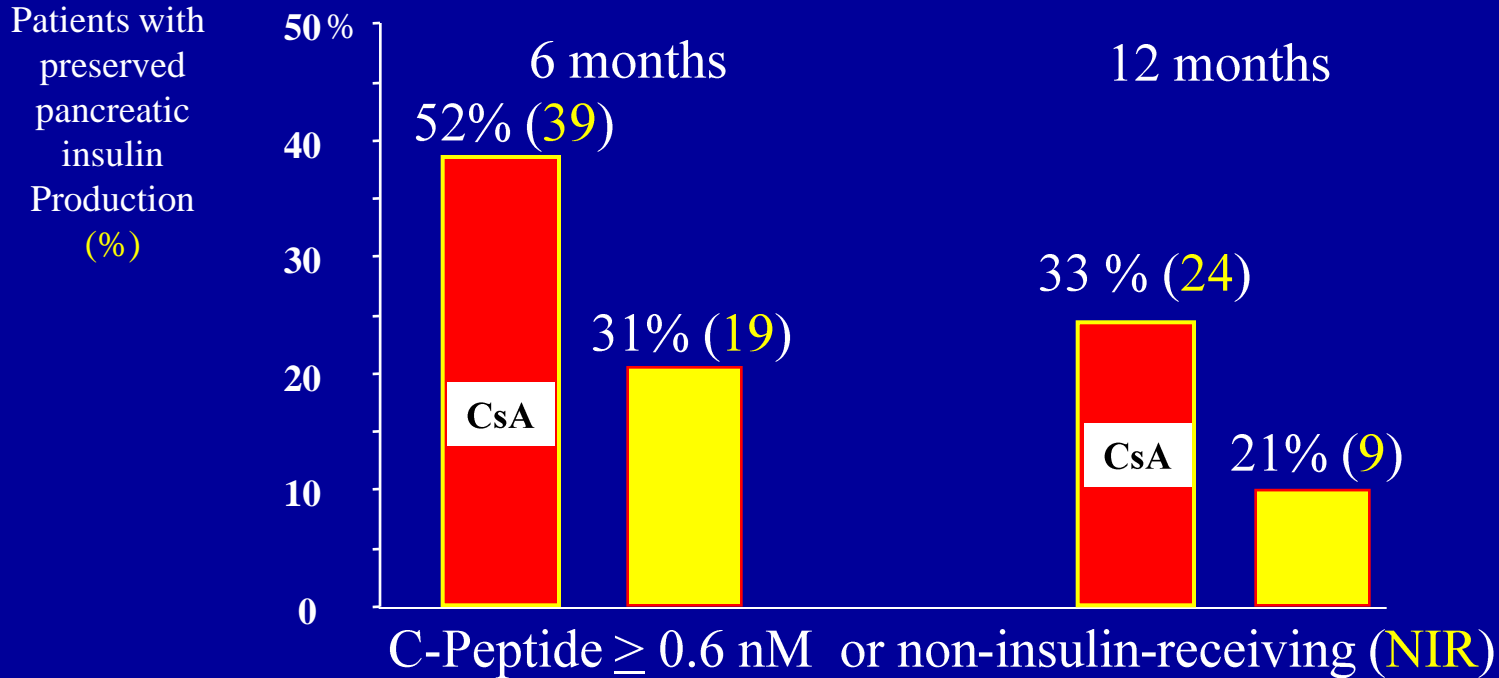


The Canadian-European Randomized Control Trial Group

Diabetes 37:1574, 1988

Inclusion: 188 patients with new onset 'IDDM'

Treatment: Placebo versus cyclosporin

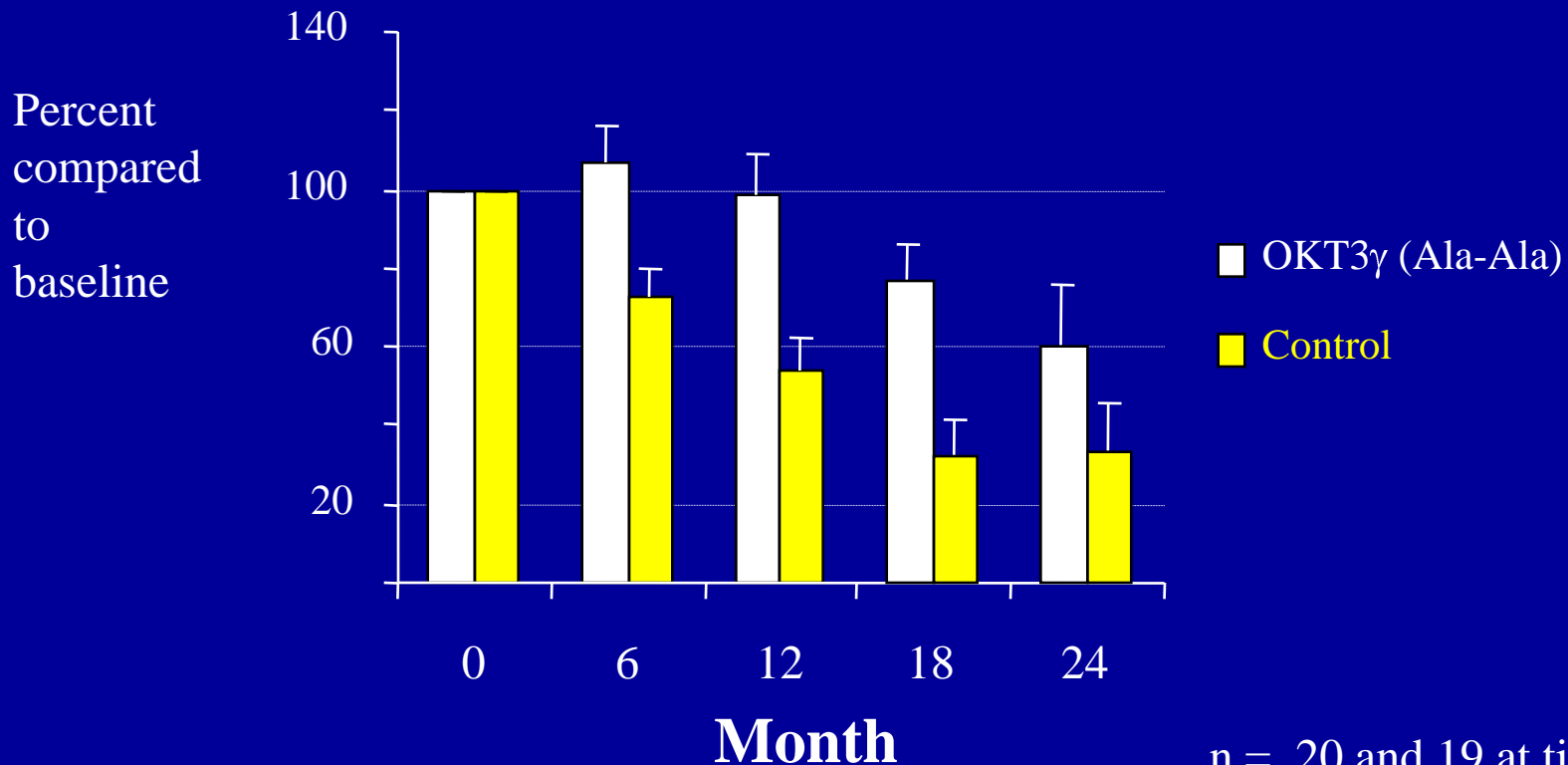


Creatinine Clearance = Kidney function

1.61 2.04

1.54 2.04 ml/s

Insulin area under the curve (AUC) response to a mixed meal treatment test as % baseline



n = 20 and 19 at time 0
20 and 19 at 6 months
18 and 13 at 18 months
14 and 10 at 24 months

The law of unintended consequences?

How do we define acceptable risk?

Recent examples & literature citations:

Cyclosporine/FK506 Mainstay of current anti-rejection regimens, associated with 7-21% risk of end-stage kidney disease 5 year post transplant (N Engl J Med. **349**:931-940, 2003)

Anti-CD154 Extremely promising anti-rejection approach in non-human

“...a mature immune response is characterized by redundancy, raising concern that selective blockade of one potential pathway to disease may simply prompt others to take its place. The induction of tolerance seems to be the most promising way forward: we are more likely to win this particular war by gaining the insight needed to negotiate with the immune system than by seeking to bomb it into submission.”

Edwin A.M. Gale, M.D.

N. Engl. J. Med., Vol 346: 1740-1741, 2002

Anti-CD32

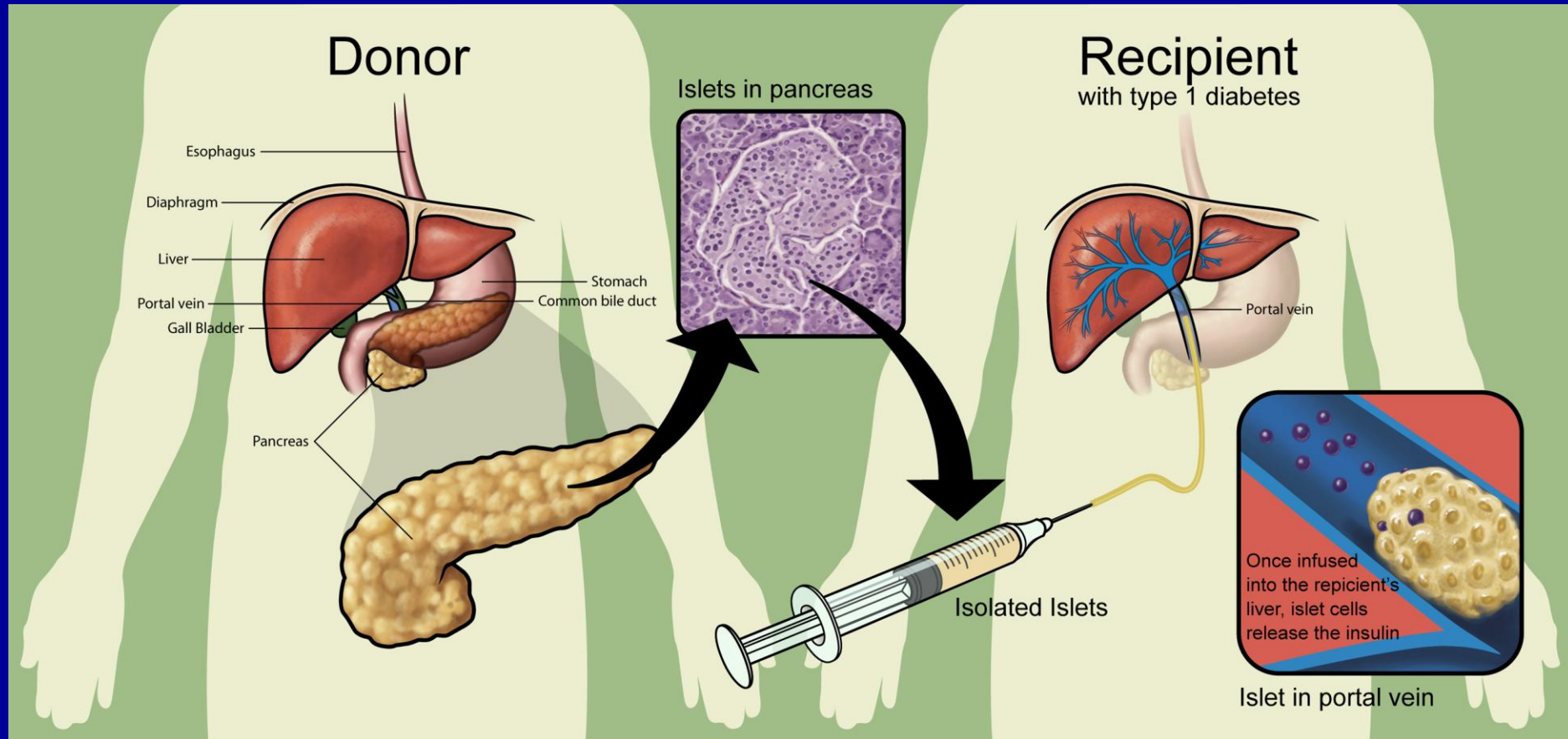
promising anti-rejection therapy to prevent calcineurin agent related kidney damage, but with late increased fungal infection risk (Transplant Proc; **37**:934-936, 2005)

Super islets via gene modification?

Great initial success in X-SCID gene therapy trial, but 4/11 subjects with late leukemia (Science; **307**:1544-1545, 2005)

Autologous bone marrow rescue???

Islet Transplantation Procedure

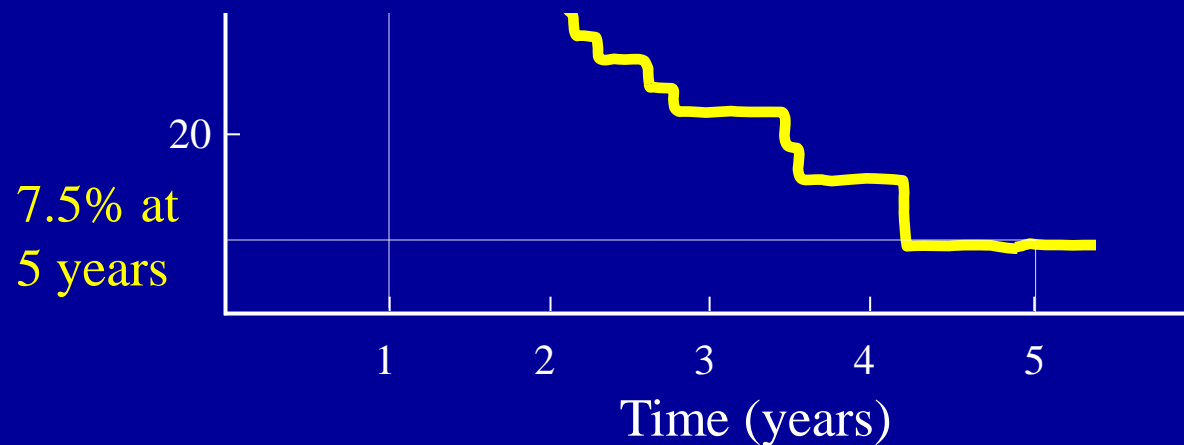


Edmonton Protocol Follow-up

Diabetes 2005; 54(7):2060-2069

But...with immunosuppressive agent toxicity:

	Pre-Transplant	One Year Post-Transplant	Most Recent
Creatinine Clearance (ml/min/1.73 m ²)	108 (96-120)	96 (78-108)	84 (66-102)
Albumin Excretion Rate (μg/min)	11	16	19
Serum Triglycerides (mmol/liter)	0.87±0.07	1.32±0.11	1.23±0.10

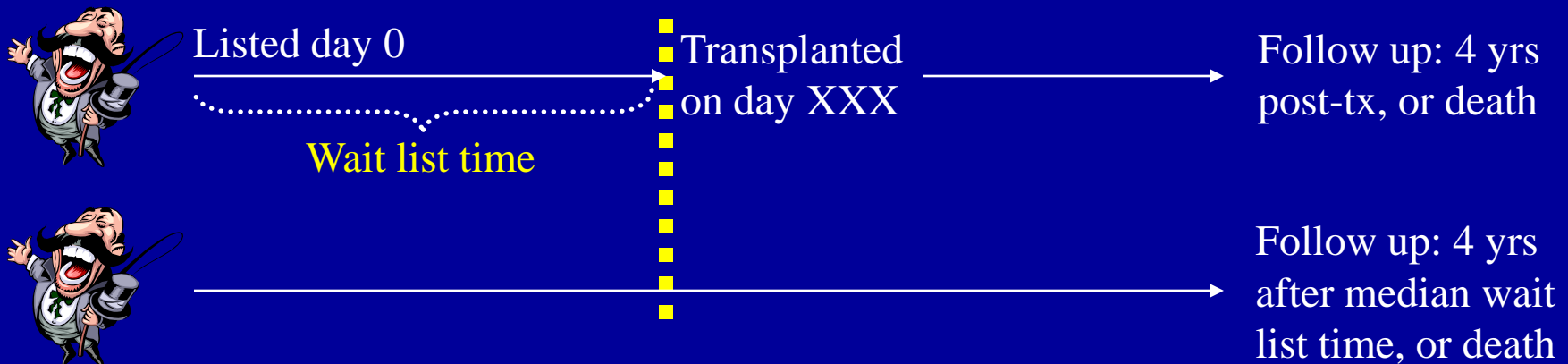


Patient # => 47 41 29 18 11 4

Does Pancreas Transplantation Improve Mortality?

Methods:

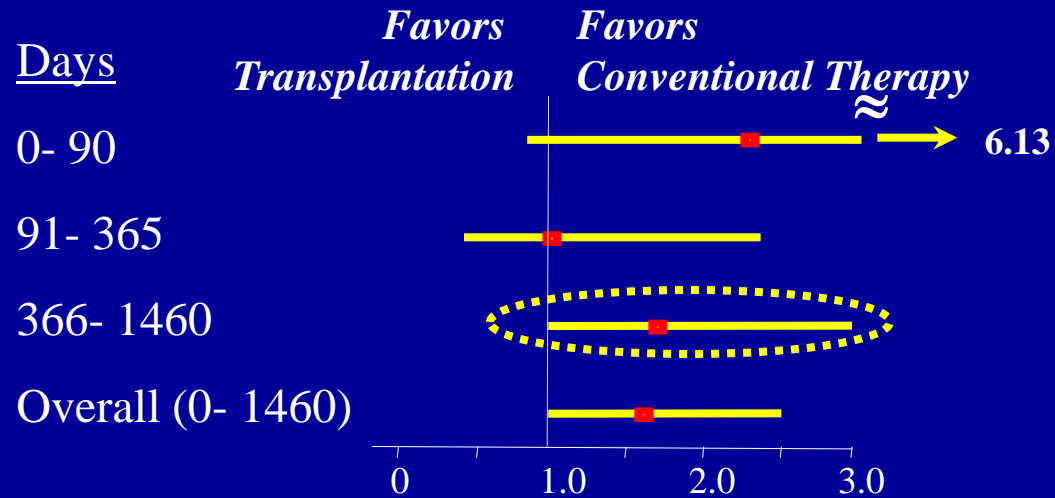
- UNOS national database, 1995 – 2000
- Patients subdivided according to procedure anticipated (PTA, PAK, SPK)
- Social Security Death Master File (SSDMF) searched for ALL patients once listed for a pancreas transplant
- Included ALL deaths (regardless of cause or timing)
- Cox hazard regression model for estimating mortality relative risk.



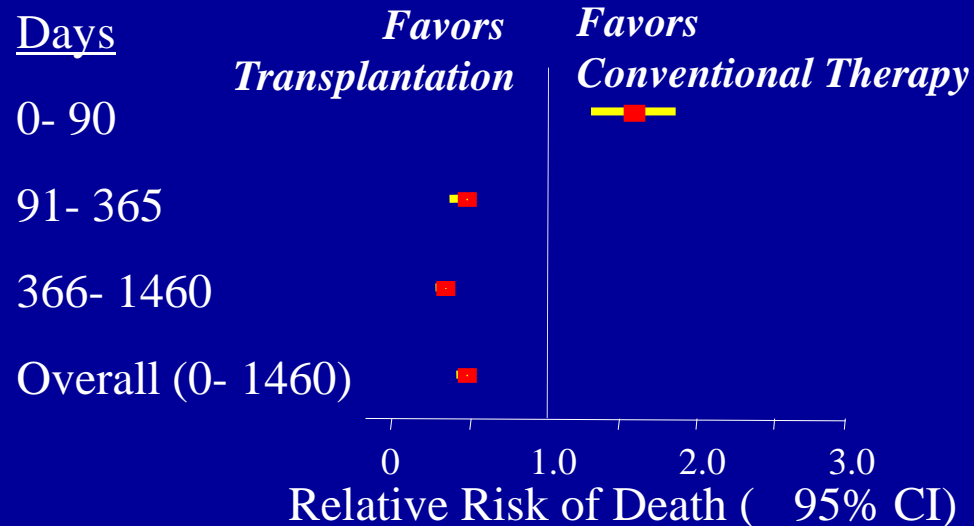
Solitary Pancreas Transplantation and Patient Survival

Journal of the American Medical Association (December 3, 2003).

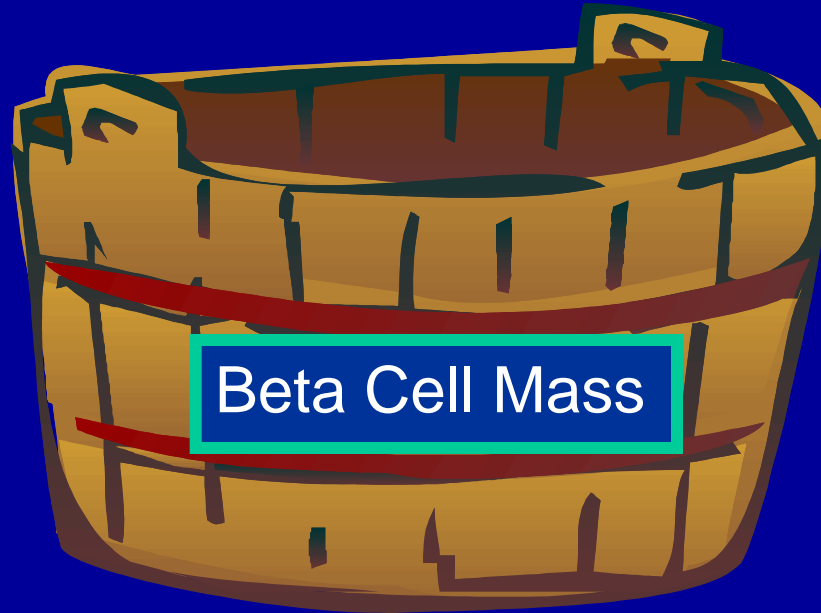
Pancreas-Transplant-Alone (n=672)



Simultaneous Pancreas-Kidney (n=9502)



Beta Cell Regeneration



Beta Cell Destruction

- Autoimmunity
- Metabolic abnormalities

Beta Cell Regeneration



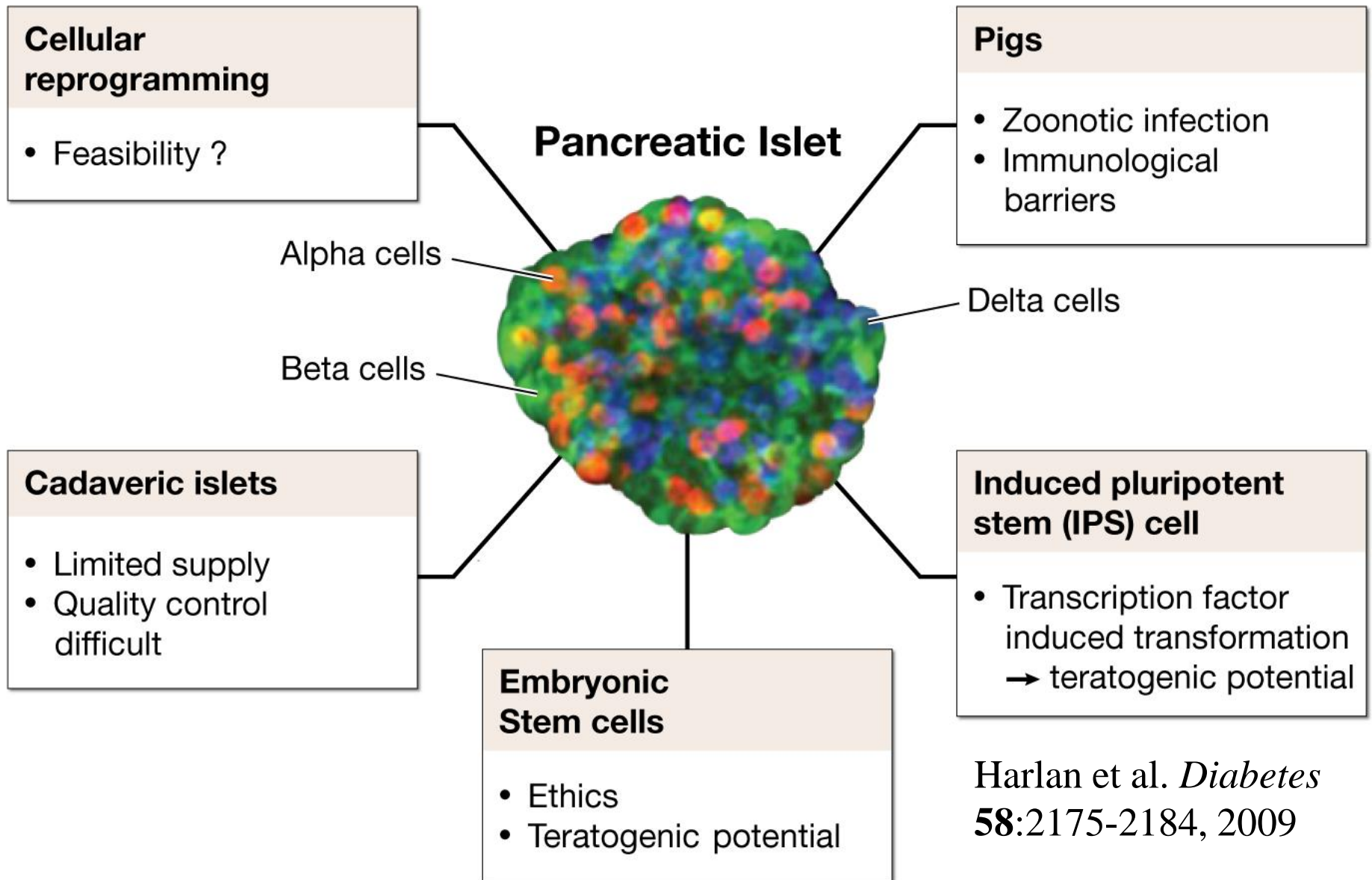
Liu EH, Digon BJ, Hirshberg B, et al.
Diabetologia 52: 1369-1380, 2009

If we cannot push the pancreas to regenerate new islet β -cells, then can we identify another source?

Beta Cell Destruction

- Autoimmunity
- Metabolic abnormalities

Potential Islet or “Islet-like” Sources



Harlan et al. *Diabetes*
58:2175-2184, 2009

Conclusions

- ◆ T1D is a T cell mediated autoimmune illness
- ◆ T1D prognosis has markedly improved, with dramatically improved survival since the 1960s. Any new therapy's risk: benefit must be carefully weighed.
- ◆ Minimal islet function is preserved in most patients with T1D, but no therapy yet shown to promote meaningful islet functional recovery
- ◆ Challenges for the future:
 1. Our progress was produced by research. Future progress will require continued research.
 2. We have the knowledge, tools, and skills to effectively treat diabetes now. We must structure our health care system to deliver that care.

“You must begin
with an ideal,
and end
with an ideal”

Sir Frederick G. Banting

