Immunology and Etiology Of Type 1 Diabetes

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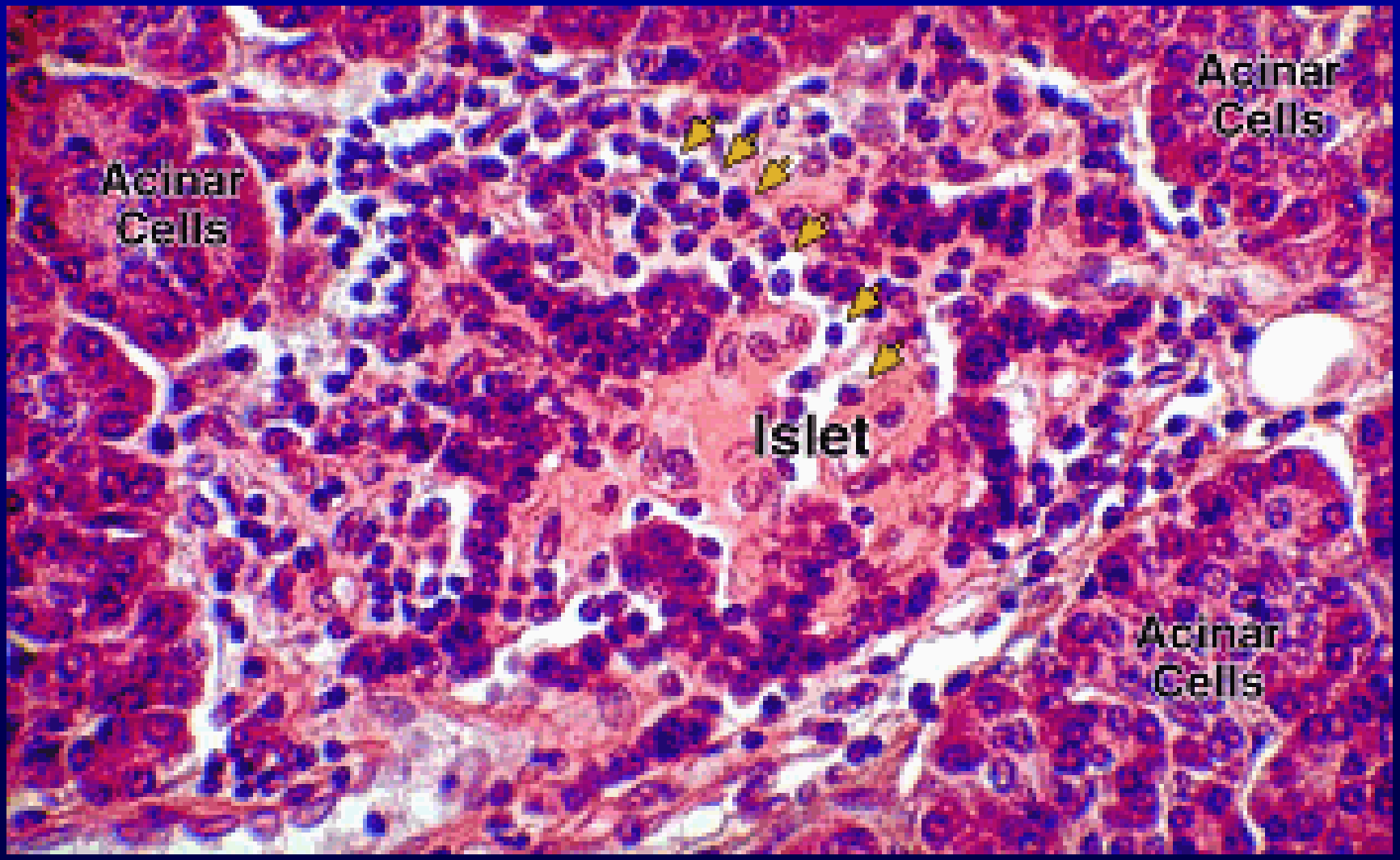
Overview

- Current understanding of pathogenesis
- Genetics of type 1 diabetes
- Diabetes prediction
- Diabetes prevention
- Ethical issues
- Questions

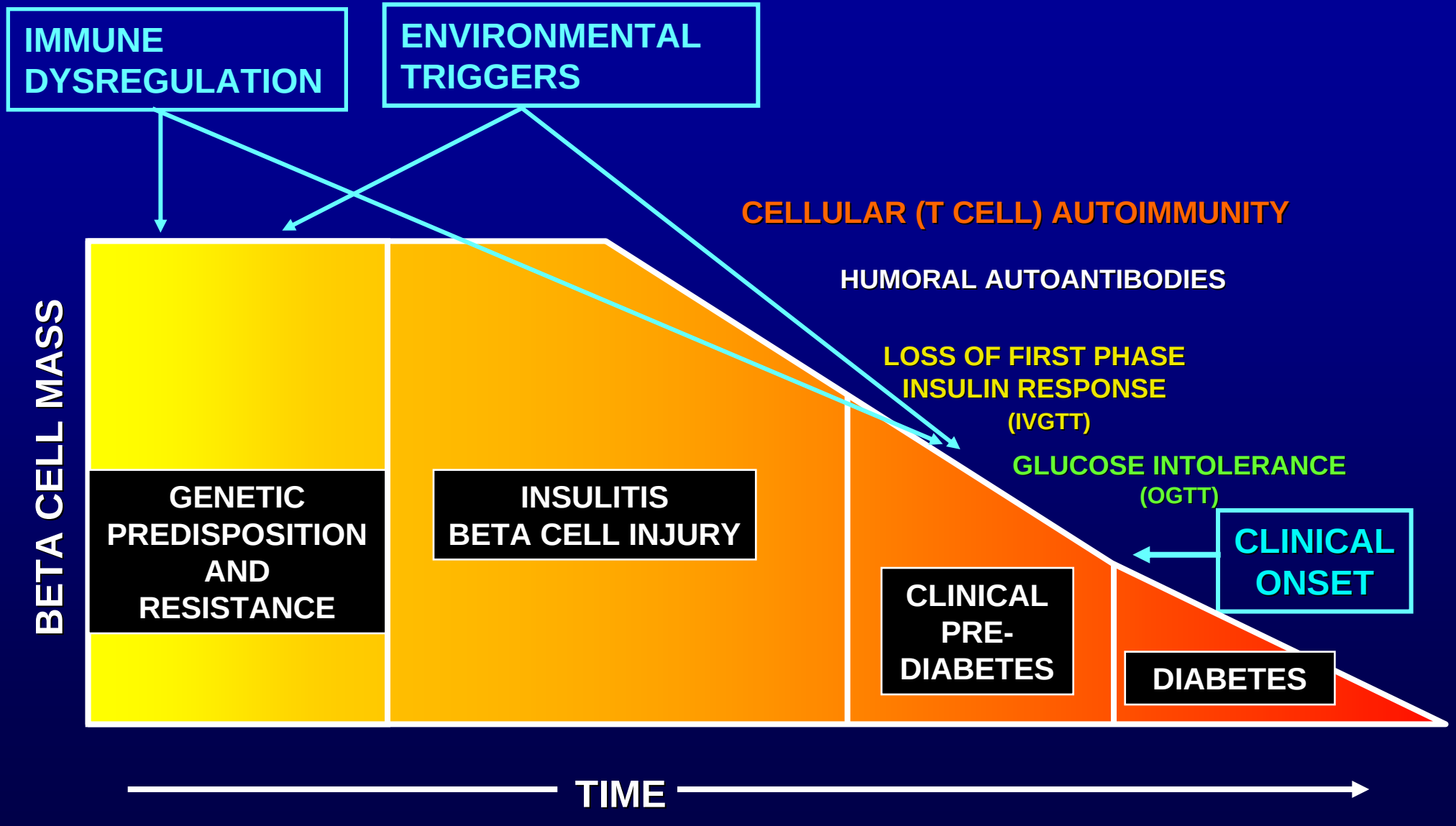
Type 1 Diabetes Pathogenesis

Type 1 Diabetes

- Autoimmune condition resulting in destruction of ß cells of the pancreas
- Leads to life-long insulin requirement
- Peak age of onset prior to puberty, range 3 moths to 50+ years
- Incidence 27/100,000 in those under 20 years of age in Ontario

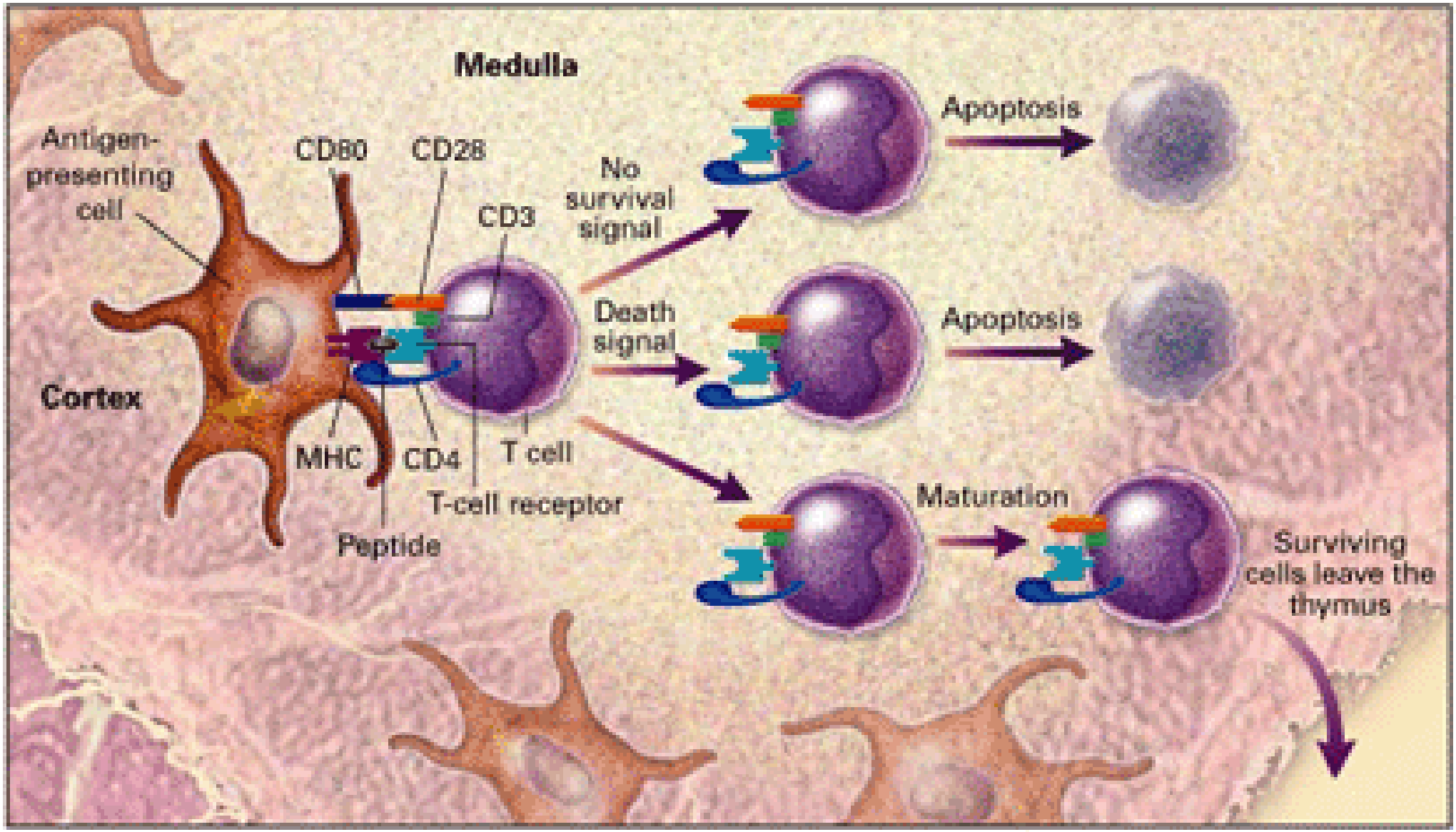

Acinar Cells
Acinar Cells
Islet
Acinar Cells

Natural History of Type 1 Diabetes

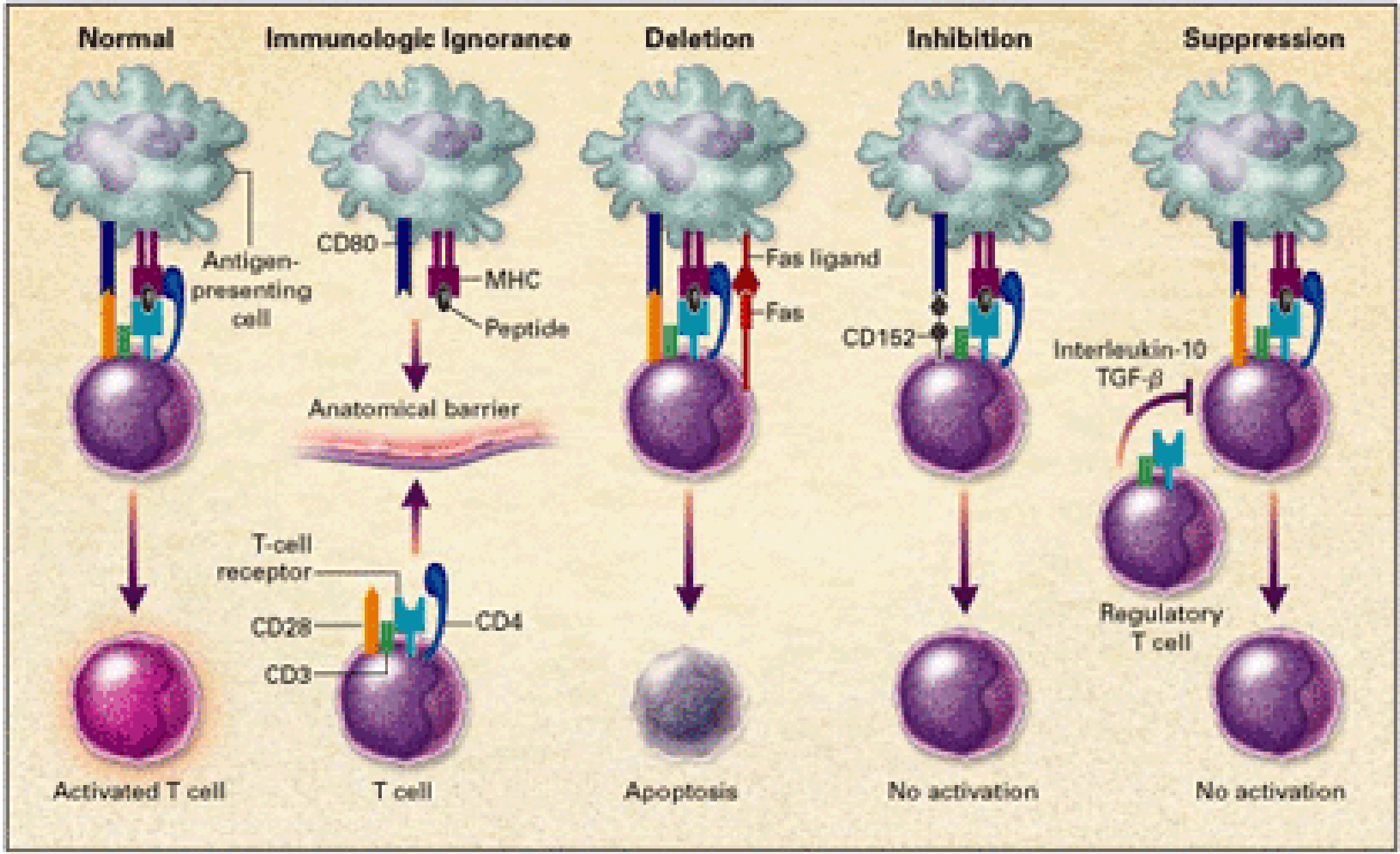


Immune Tolerance

- Immune system is “educated” to become tolerant of self and prevent autoimmunity
- Immature T cells die in the thymus if they bind too weakly or strongly to peptide-MHC
- Also occurs outside thymus



NEJM 2001 Mitchison



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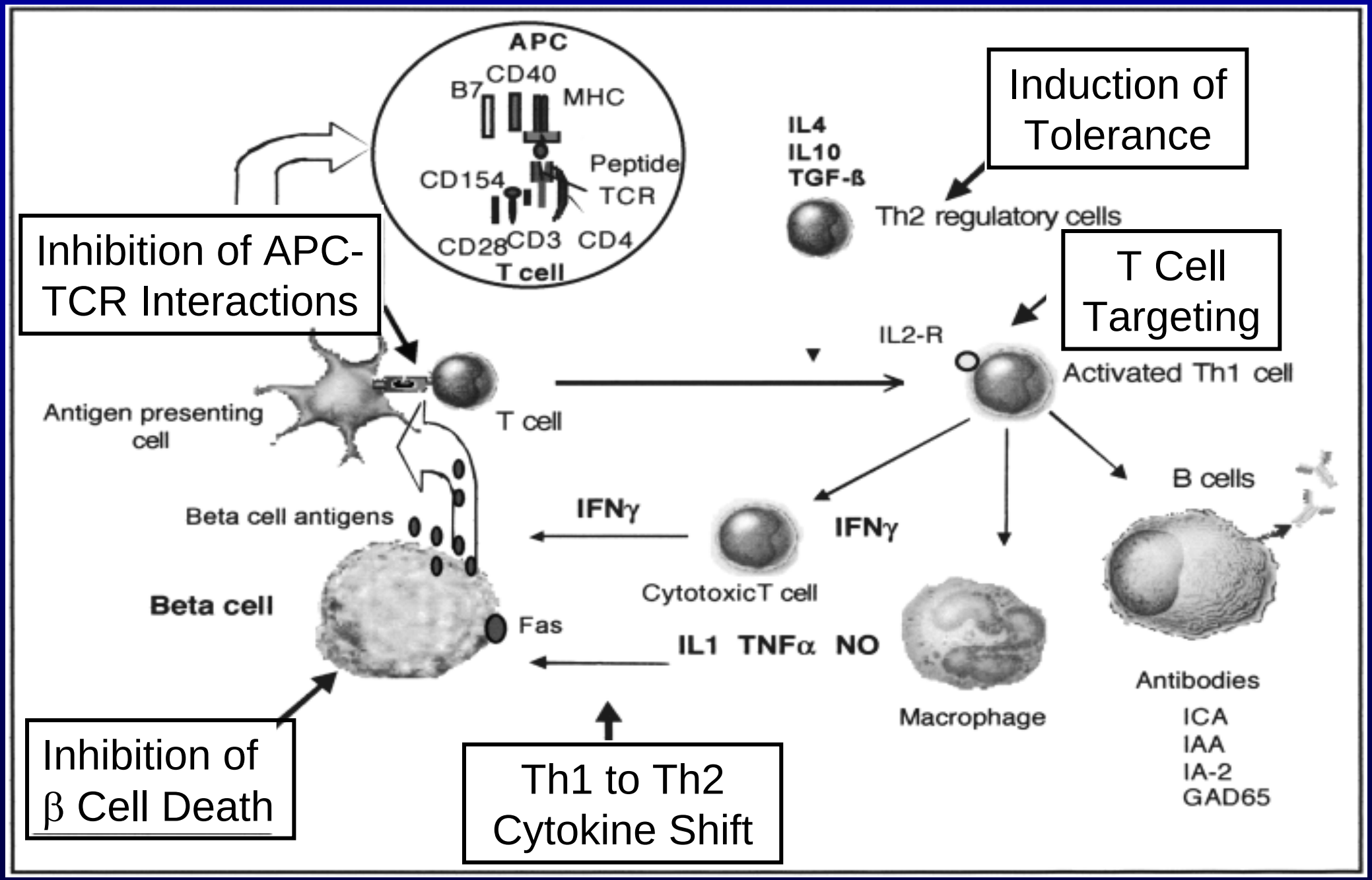


Thivolet, Clin Endo 2001

Genetics of Type 1 Diabetes

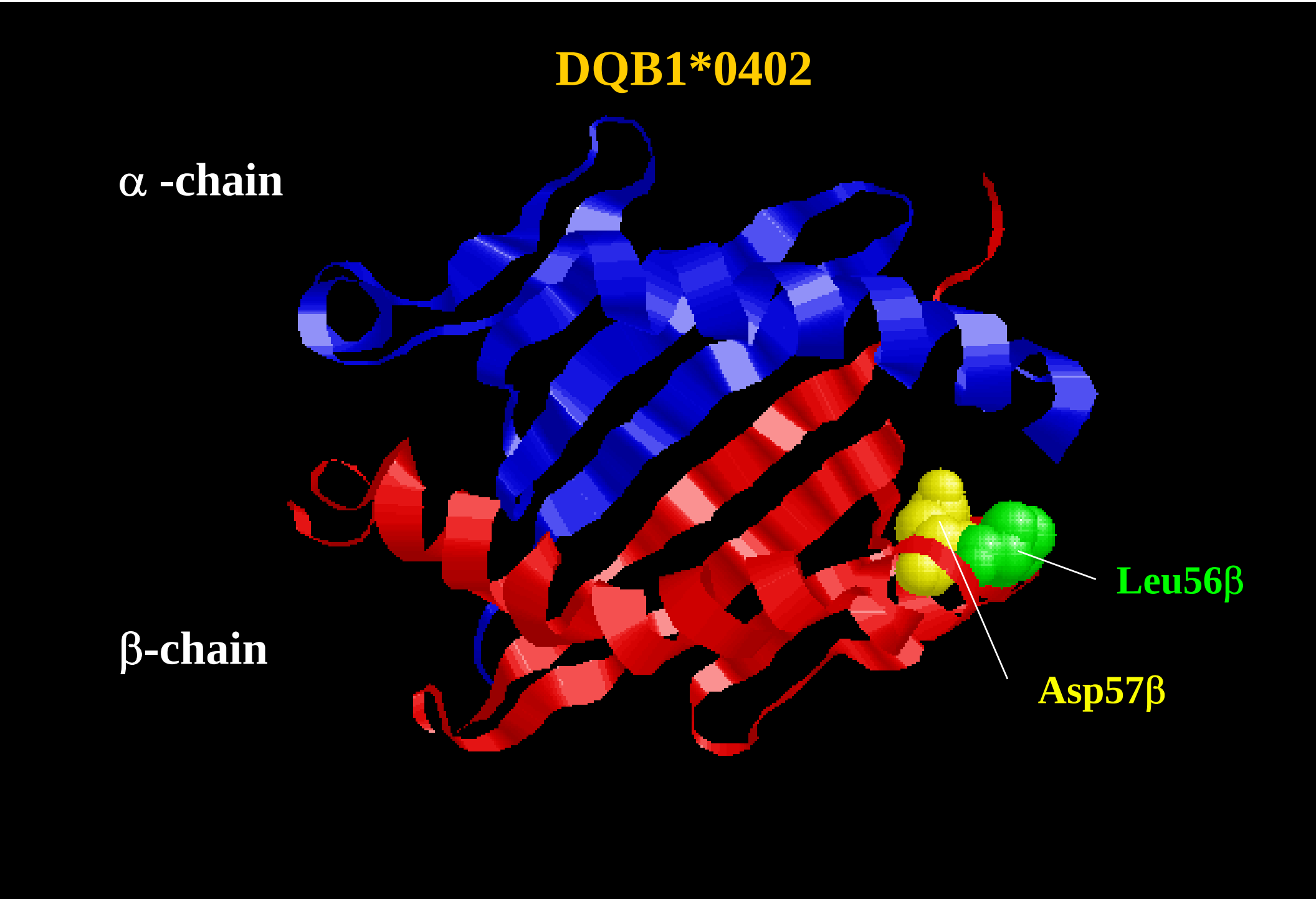
Familial Risk

Risk Group	Type 1 Diabetes
General Population	0.4%
Maternal Offspring	1 to 4%
Paternal Offspring	6 to 9%
Siblings	5 to 6%
Monozygotic Twins	33 to 50%

HLA Genetics

- Sibling risk 15x greater than general population
- 60% of risk explained by HLA
- 96% of Canadian children with diabetes HLA DR3 &/or 4 (46% in population)
- Linked to nature of amino acid in DQ allele

DQB1*0402



Other Genes

- 5’ region of insulin gene
- CTLA-4 gene
- Linkage or association with 20 regions of the genome
- Same regions also found in other autoimmune diseases
- Not clinically useful at present

Prediction of Diabetes

Prediction

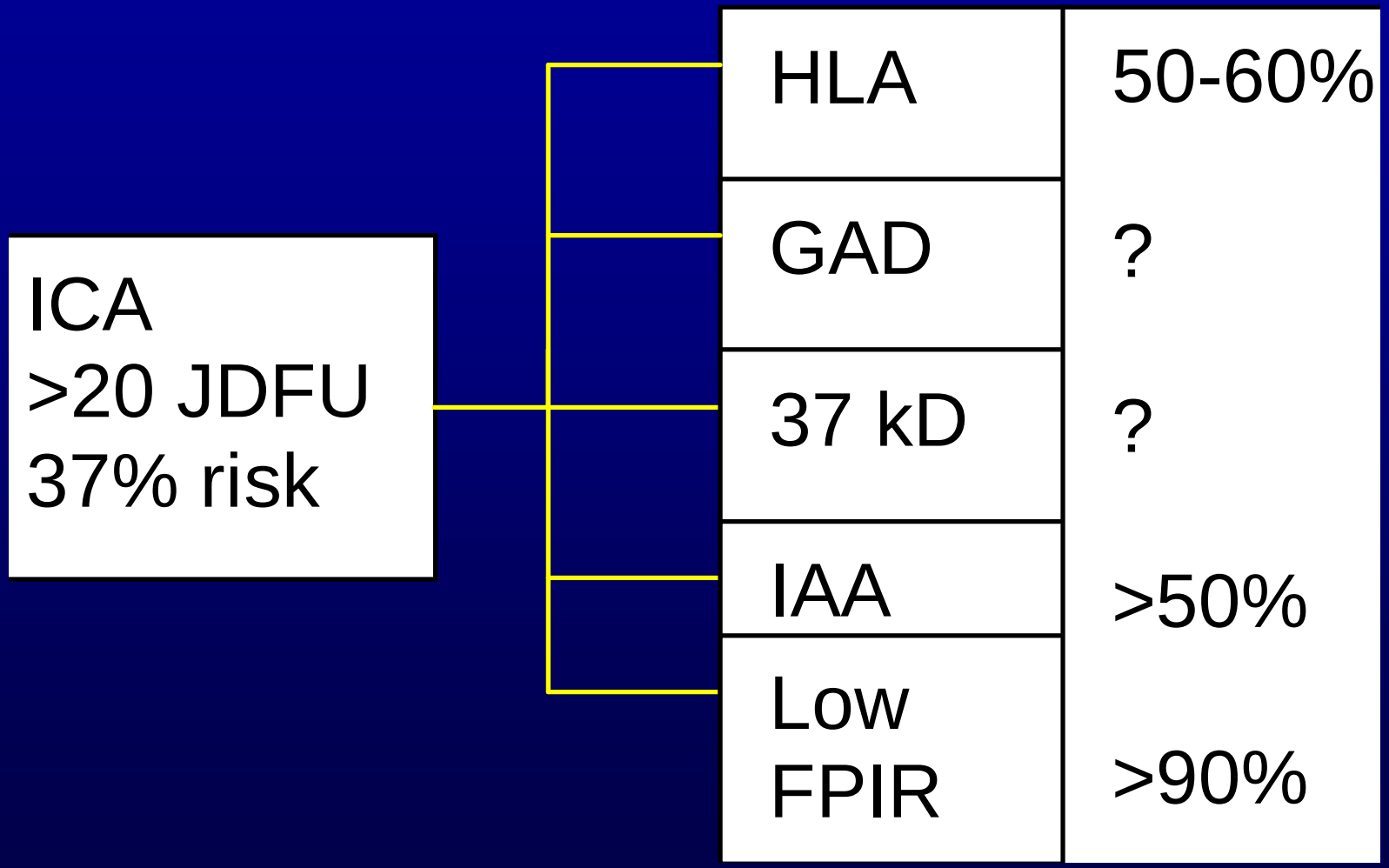
- Based on studies of first degree relatives
- Antibodies measured, often over many years with follow-up to diabetes
- First phase insulin secretion often assessed as a measure of β cell mass

Islet Antibodies

- *GAD (glutamic acid decarboxylase)
  - Enzyme in insulin processing
- *IA-2 (ICA512)
  - tyrosine phosphatase, “38 kD antigen”
- *insulin - β cell specific
- Islet cell antibodies (ICA) – non-specific antibody

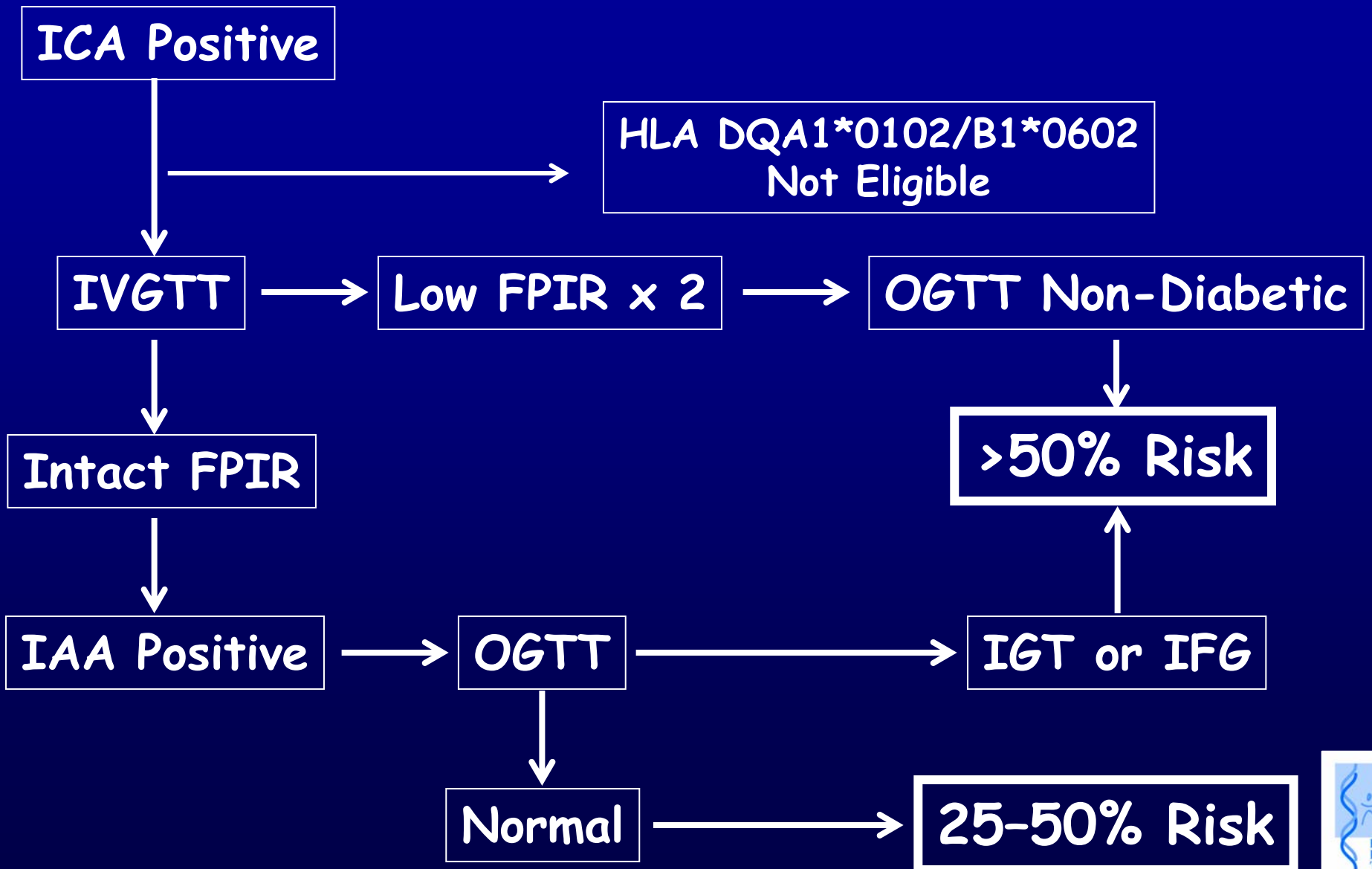
* Can be easily measured and quantified

Diabetes Prediction in 1993

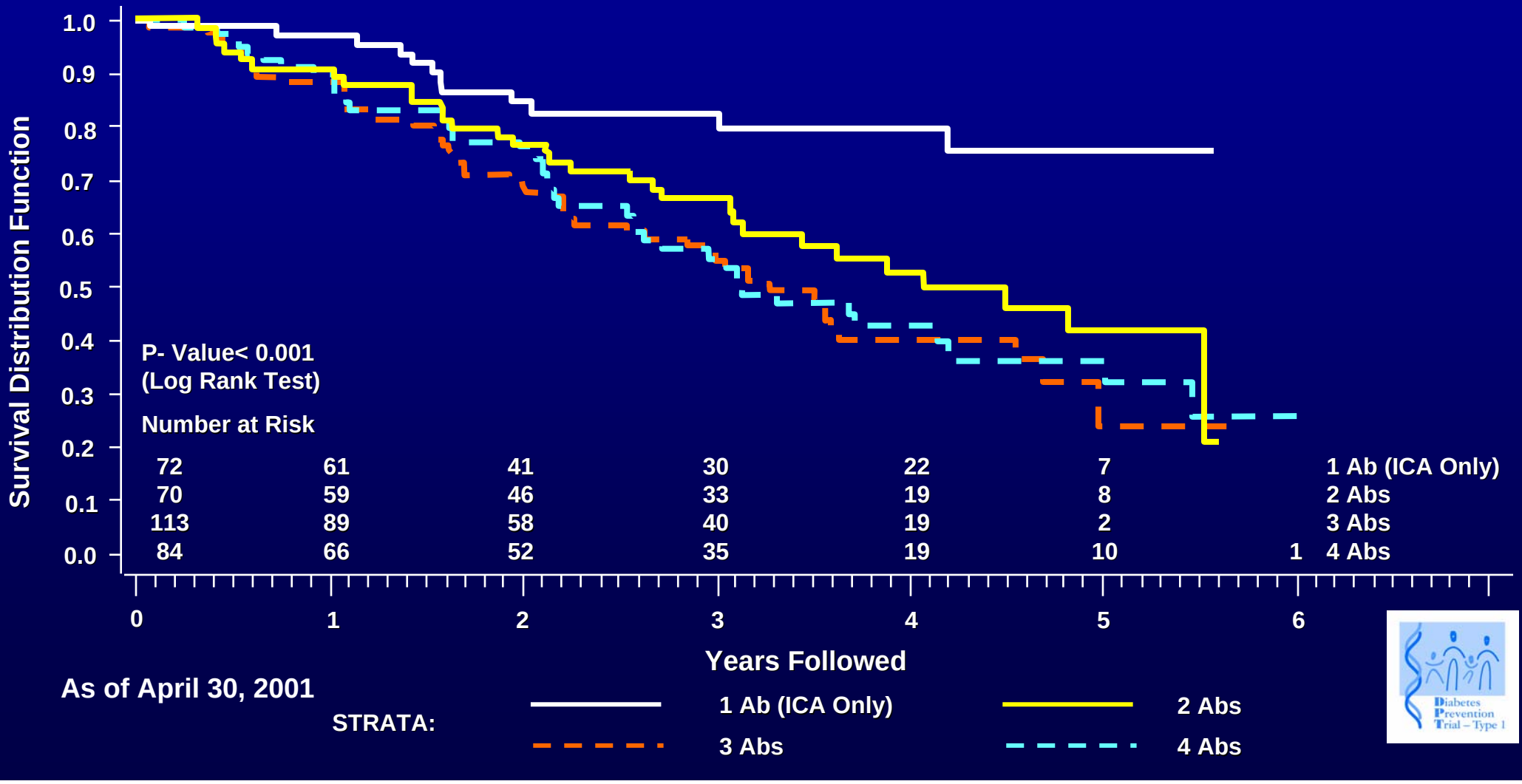


Bingley, Diabetes 1993

DPT-1 Diabetes Prediction



DPT-1 Parenteral Study – Time to Diabetes By Number of Confirmed Antibodies



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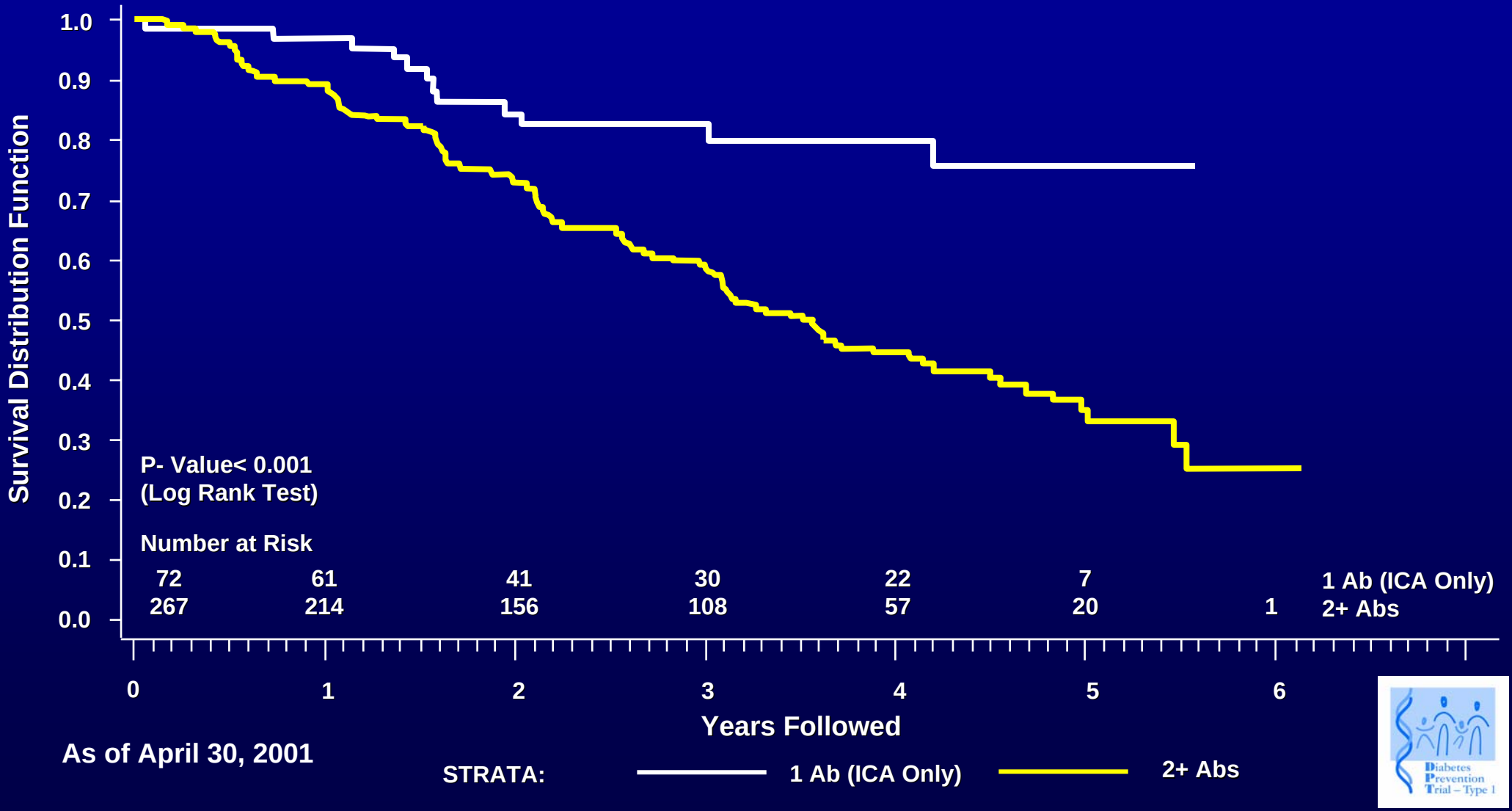
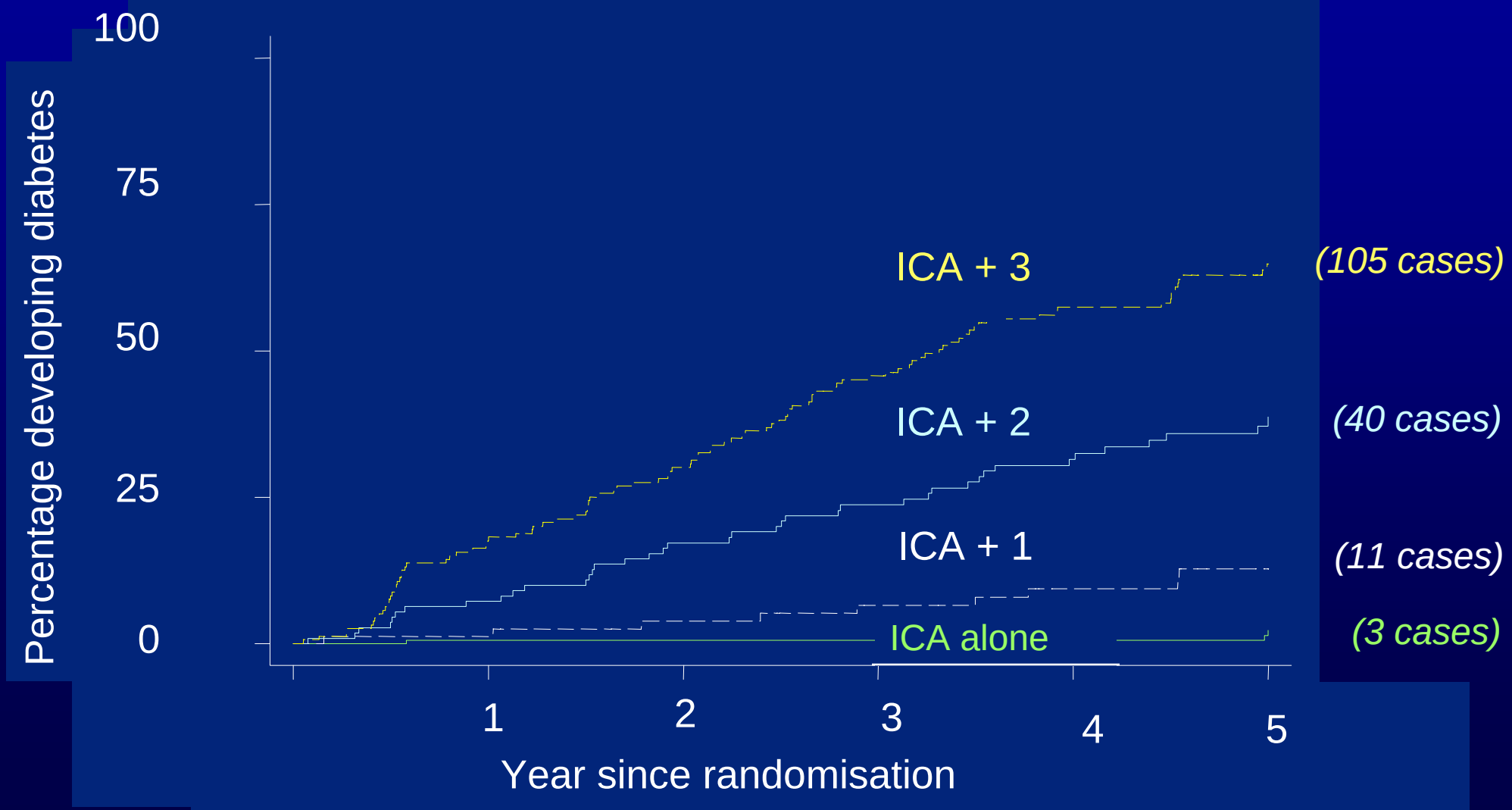
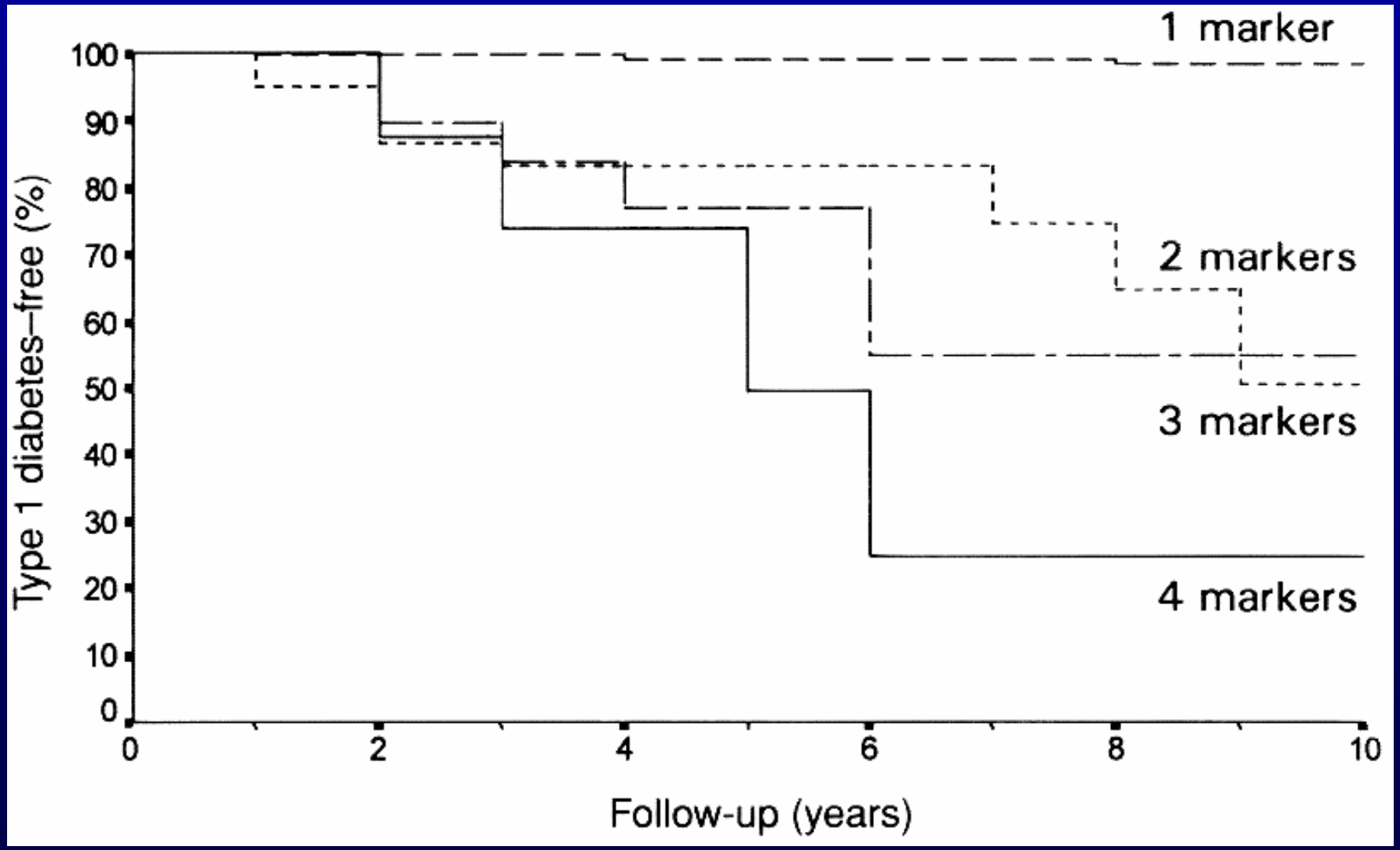


Diabetes Prevention Trial – Type 1

Progression by Number of Antibodies - ENDIT



Prediction: Bart's Oxford Family Study



Bingley, Diabetes Care 1999

Diabetes Prediction 2005

- Screen for GAD, IA-2, IAA in <10yrs, perhaps ICA in those with one antibody
- Continue to eliminate low risk HLA haplotype
- Can select degree of risk by numbers of antibodies/ titre
- IVGTT rarely needed

Diabetes Prevention

Types of Prevention Strategies

- **Primary – prevent immune response**
  - **newborns**
- **Secondary – prevent progression from autoimmunity to diabetes**
  - **relatives**
- **Tertiary – intervene at disease onset to prevent ongoing β cell loss**
  - **new onset patients**

Primary Prevention

Cow's Milk Formula & Diabetes

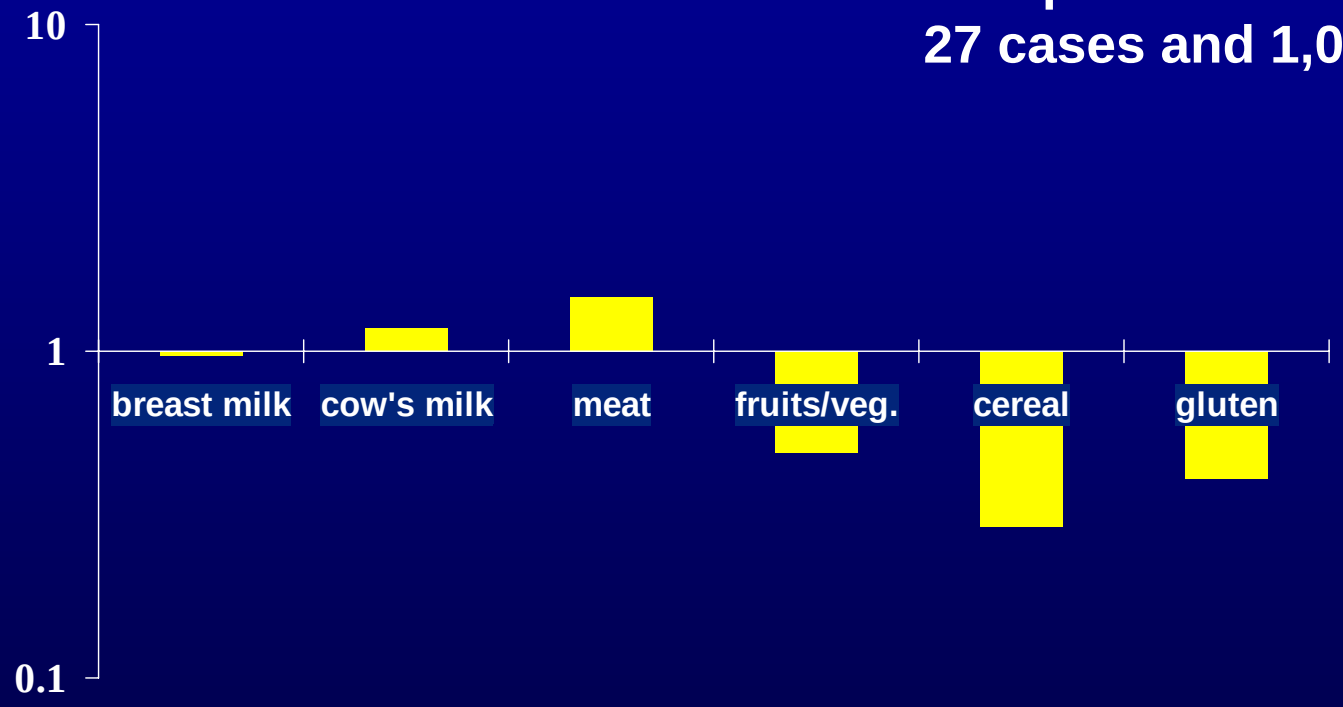
- Animal model experiments suggest that weaning to hydrolyzed protein formula protects
- Human data variable, may be slight increase in risk with cow's milk formula introduction before 3 to 4 months (OR=1.61)

Infant diet and beta-cell autoimmunity

Norris et al. DAISY 2000

Hazard Ratio

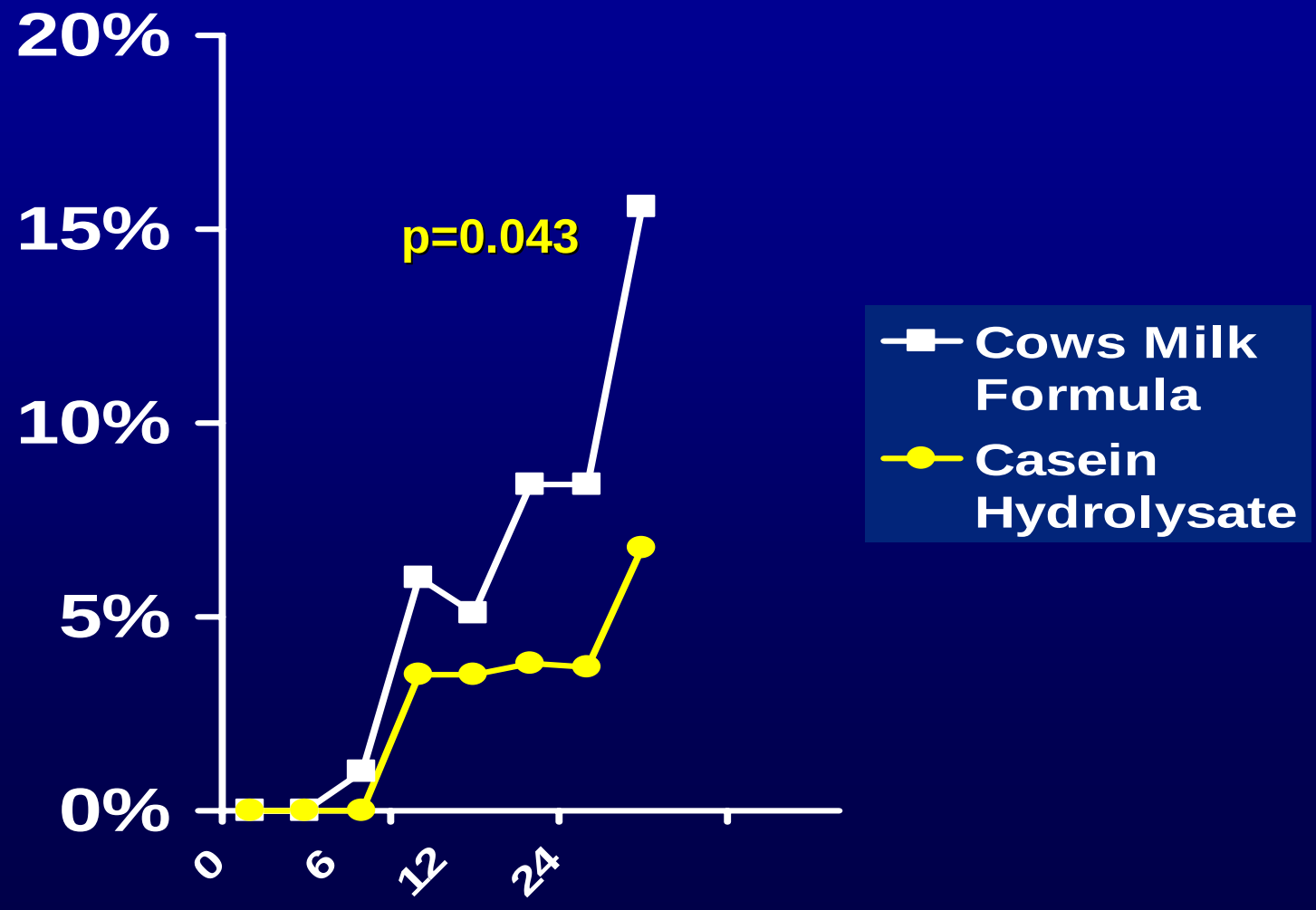
Prospective cohort study
27 cases and 1,022 controls



Adjusted for HLA-DR,DQ and relationship to type 1 diabetic person

Pilot for TRIGR 3-yr Follow-up Results

Seroconversion to 1+ Autoantibody



n=173

TRIGR Trial

- International multicentre trial, 17 Canadian sites
- Infants with relative with T1DM and risk HLA alleles randomized to cow's milk or hydrolysed protein formula prior to 8 months of age
- Sample size 2370
- Endpoint - islet antibodies to 10 years of age

Diabetes and Vitamin D

Study	Question	Outcome
Europe Case-control	Retrospective Infant vit D	OR 0.65
Norway Case-control	Retrospective Cod liver oil in pregnancy	OR 0.36
Finland Cohort	Prospective Infant vit D	RR 0.12 with high dose

Secondary Prevention

Hurdles for Prevention Trials

1. Finding subjects

2. Long duration of follow-up without surrogate markers of efficacy

3. Need promising interventions & multicentre trial infrastructure

Large Prevention Trials to Date

- **Diabetes Prevention Trial-Type 1 (DPT-1)**
  - **Parenteral insulin in high risk (>50%), oral insulin in intermediate risk (25 to 50%)**
- **European Nicotinamide Diabetes Intervention Trial (ENDIT)**
  - **Nicotinamide or placebo in all at risk**

DPT-1 Intervention Protocols

- **Parenteral Insulin**

  In Subjects with 5 year Risk of

  Type 1 Diabetes > 50%

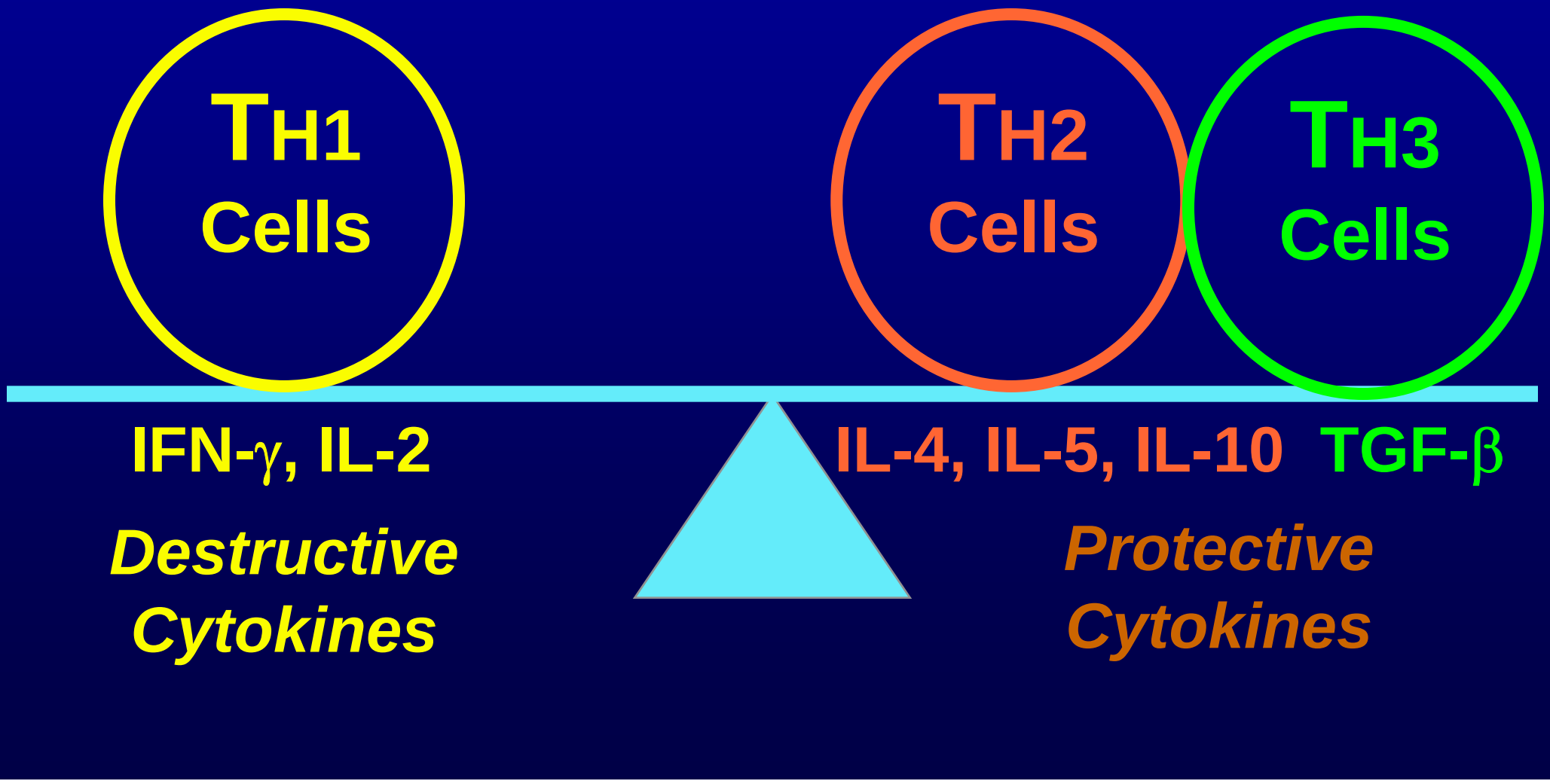
- **Oral Insulin**

  In Subjects with 5 year Risk of

  Type 1 Diabetes = 26-50%

Diabetes Prevention Trial – Type 1

Immunoregulation



DPT-1 Population

TARGET GROUP: NON-DIABETIC RELATIVES

- First-Degree Relatives
  - (Siblings, Parents, Children)
  - Age 3-45 years
- Second & Third Degree Relatives
  - (Cousins, Nieces, Nephews, Aunts, Uncles, Grandchildren)
  - Ages 3-20

*If ICA+ > 10 JDFU ---> STAGING

Diabetes Prevention Trial – Type 1

II. Staging: Multiple Criteria

- Genetic
  - –Protective HLA
- Immunologic
  - –ICA, IAA, GAD65 Ab, ICA-512 Ab
- Metabolic
  - –IVGTT Insulin Response, OGTT

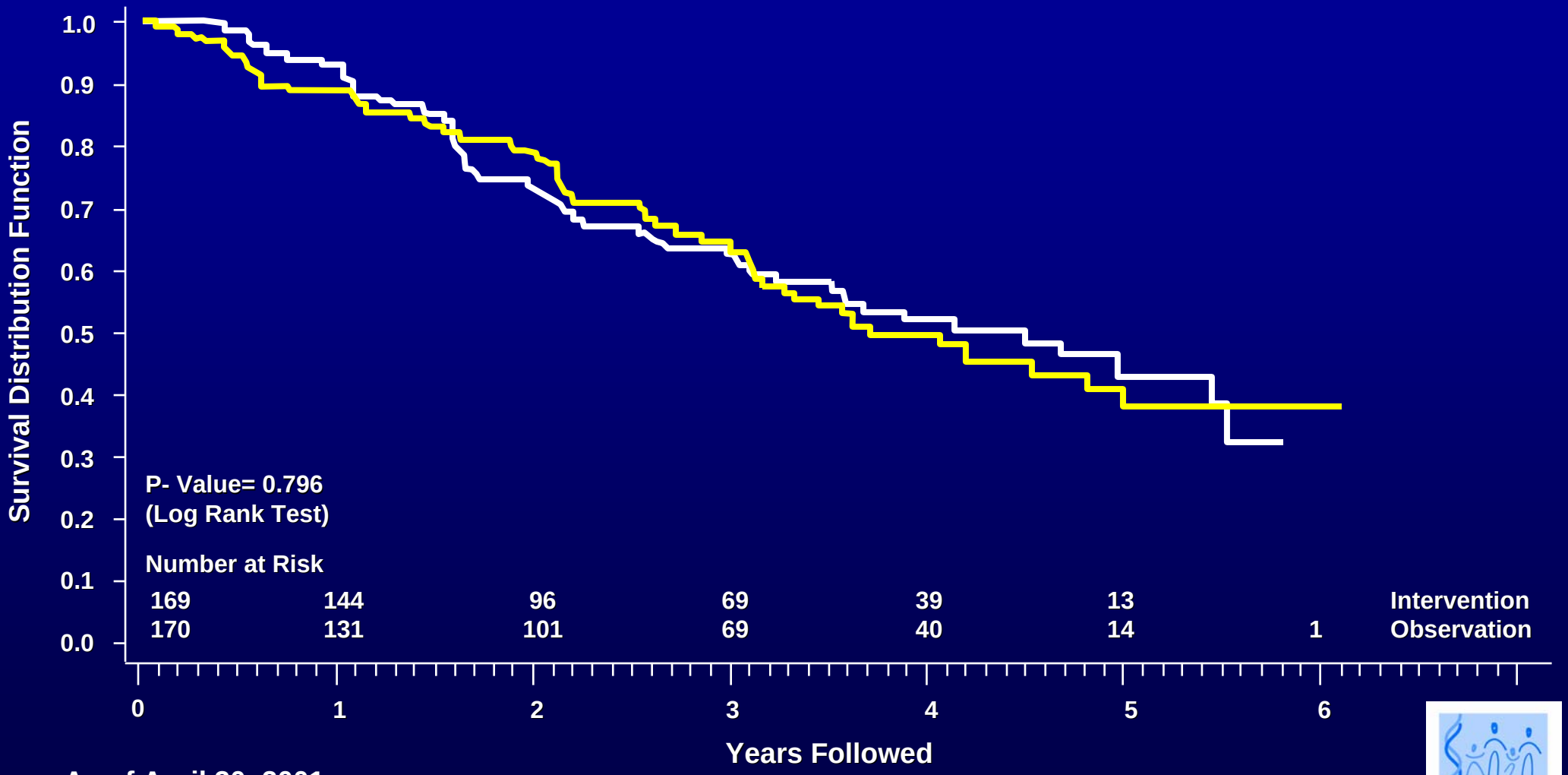
Diabetes Prevention Trial – Type 1

DPT-1 Results

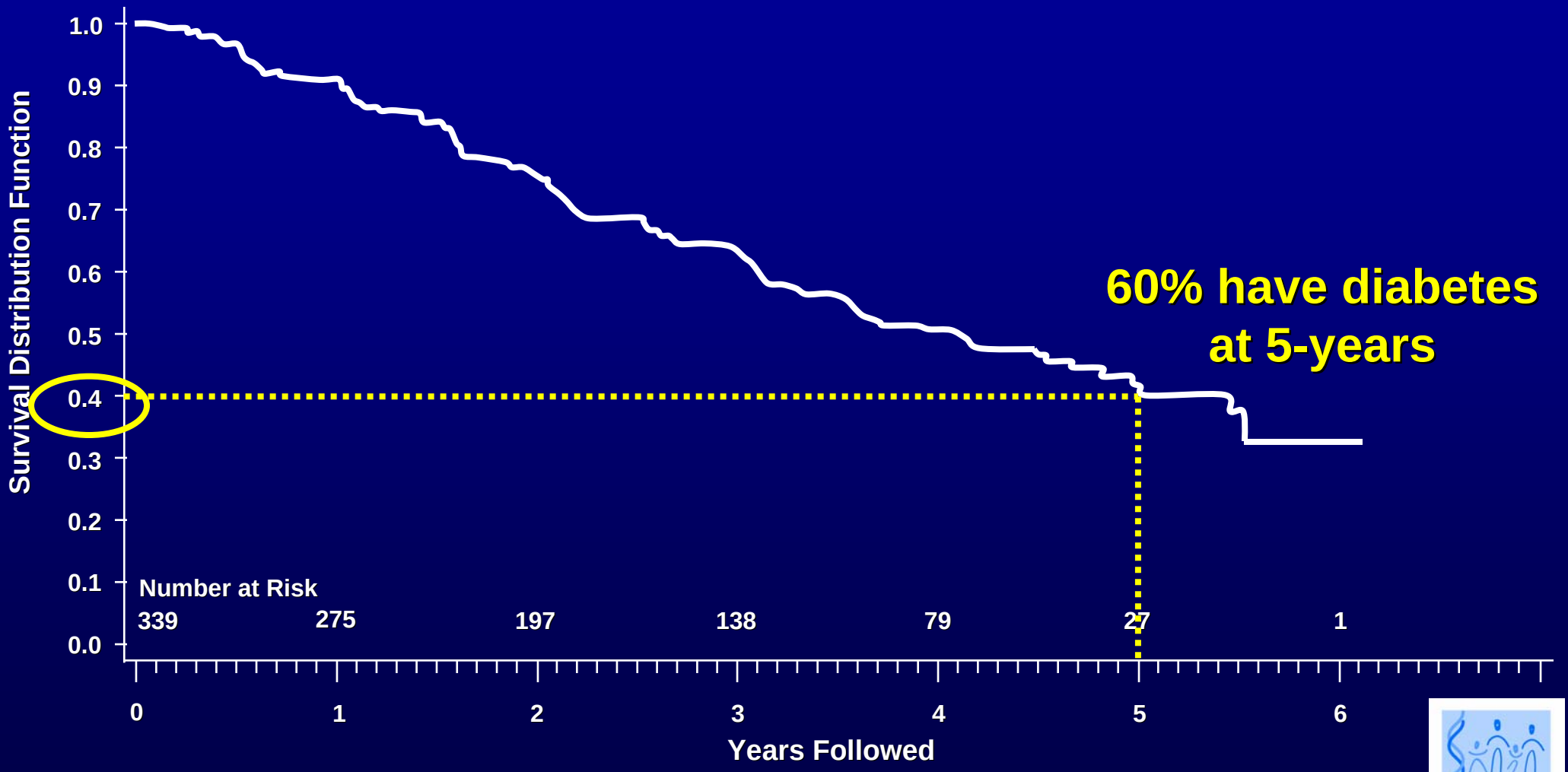
- 103,389 screened
- 339 randomized to Parenteral Trial, 372 to Oral Trial
- Parenteral trial showed no benefit
- Primary analysis of Oral Trial showed no benefit
- Subgroup analysis showed benefit in a group

Diabetes Prevention Trial – Type 1

DPT-1 Parenteral Study – Time to Diabetes By Treatment



DPT-1 Parenteral Study – Time to Diabetes



ENDIT

- Nictinamide or placebo in first degree relatives with islet cell antibody titre >20JDFU
- Animal studies and prevention study in New Zealand showed promising results
- Conducted in Europe and Canada with few sites in US

ENDIT Population Screened

Family members screened ~30,000

x 1.2 – 4.5%

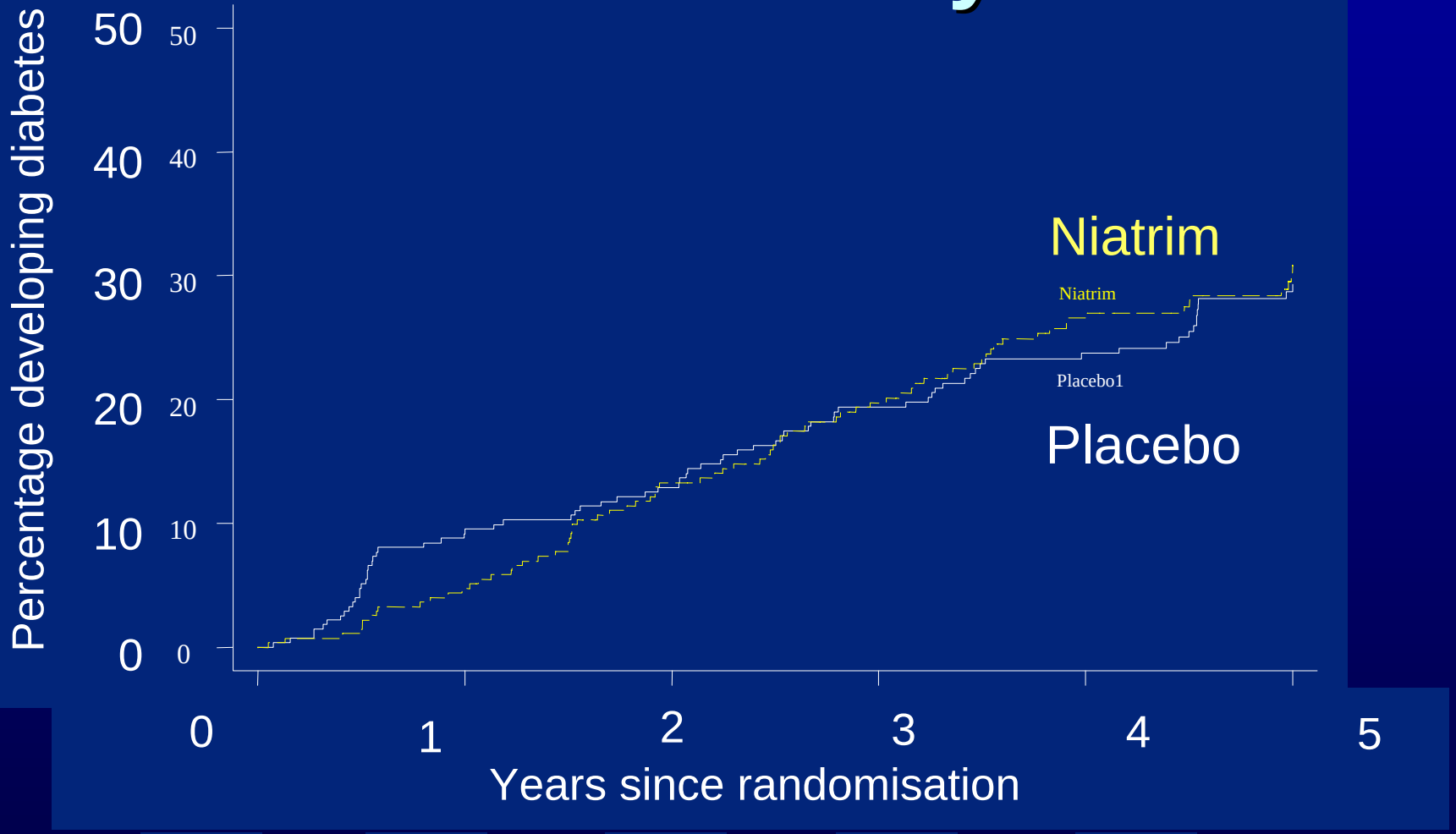
Eligible (ICA ≥ 20 JDF units) 1004

x 55%

Recruited 552

Overall Treatment Effect

Intention to treat analysis



Placebo	275	245	232	205	184	115
Niatrim	274	260	232	208	171	107

Tertiary Prevention

Benefits of New Onset Subjects

- Subjects easier to find
- Shorter studies
- Potential benefit to subjects
- If efficacious, likely to be so in prevention
- Feasibility shown

Effect of Residual β Cell Function

- 303 of DCCT subjects had C-peptide >0.2 pmol/L at entry
- Intensive therapy prolonged this

Factor	Relative Risk
Retinopathy	0.5
Hypoglycemia	0.38
A1c	Improved over 1st 4 yrs

Issues in New Onset Studies

- Defining preservation of C-peptide
  - Level, change in C-peptide & factors influencing it
- Effects of diabetes control
- Negative effects
  - Disease acceleration, psychological distress
  - Missing an intervention that only works early in disease course

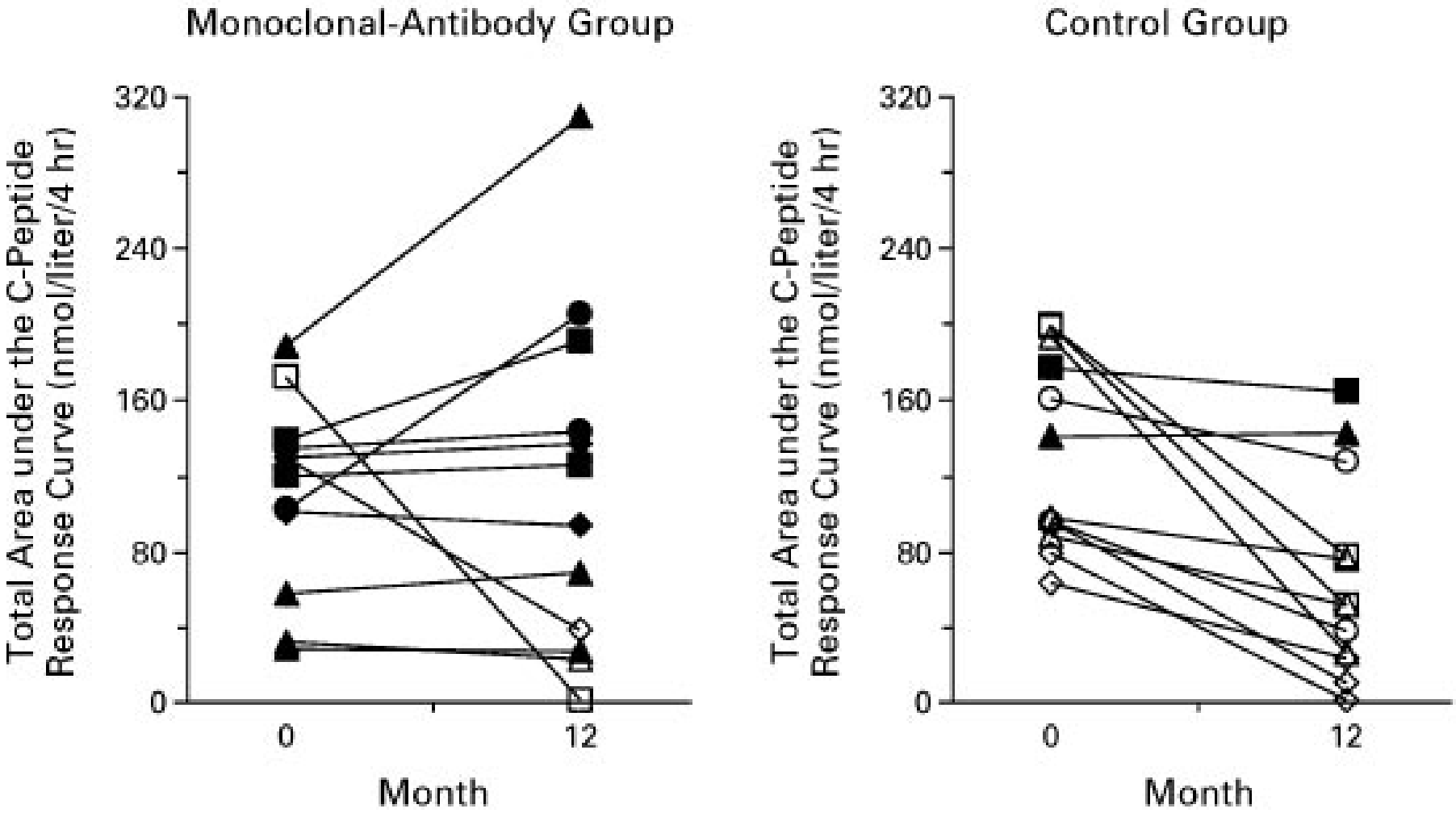
Tertiary Prevention Therapies

- Modified anti-CD3 (Herold 2002)
- DiaPep277 (Cohen 2001)

Approaches in New Onset Subjects

- Modified Anti-CD3 antibody
- Tolerance induction in NOD mice, effective at disease onset
  - 24 subjects & controls
  - Median age 13
  - 14 day course of antibody
  - Stable or improved C-peptide at 1 yr in 75% subjects, 17% controls

Anti-CD3 Effect on C-Peptide
Herold, NEJM 2002



Approaches in New Onset Subjects

- Antigen based peptide therapy – HSP 277 peptide
- Prevents diabetes in NOD, effective at disease onset
- 35 subjects and controls
- Mean age 29.3/23.1
- 3 injections given at 0, 1 and 6 mons
- Stable C-peptide over 10 mons, significantly better than controls

DiaPep Effect on Stimulated C-Peptide Cohen, Lancet 2001

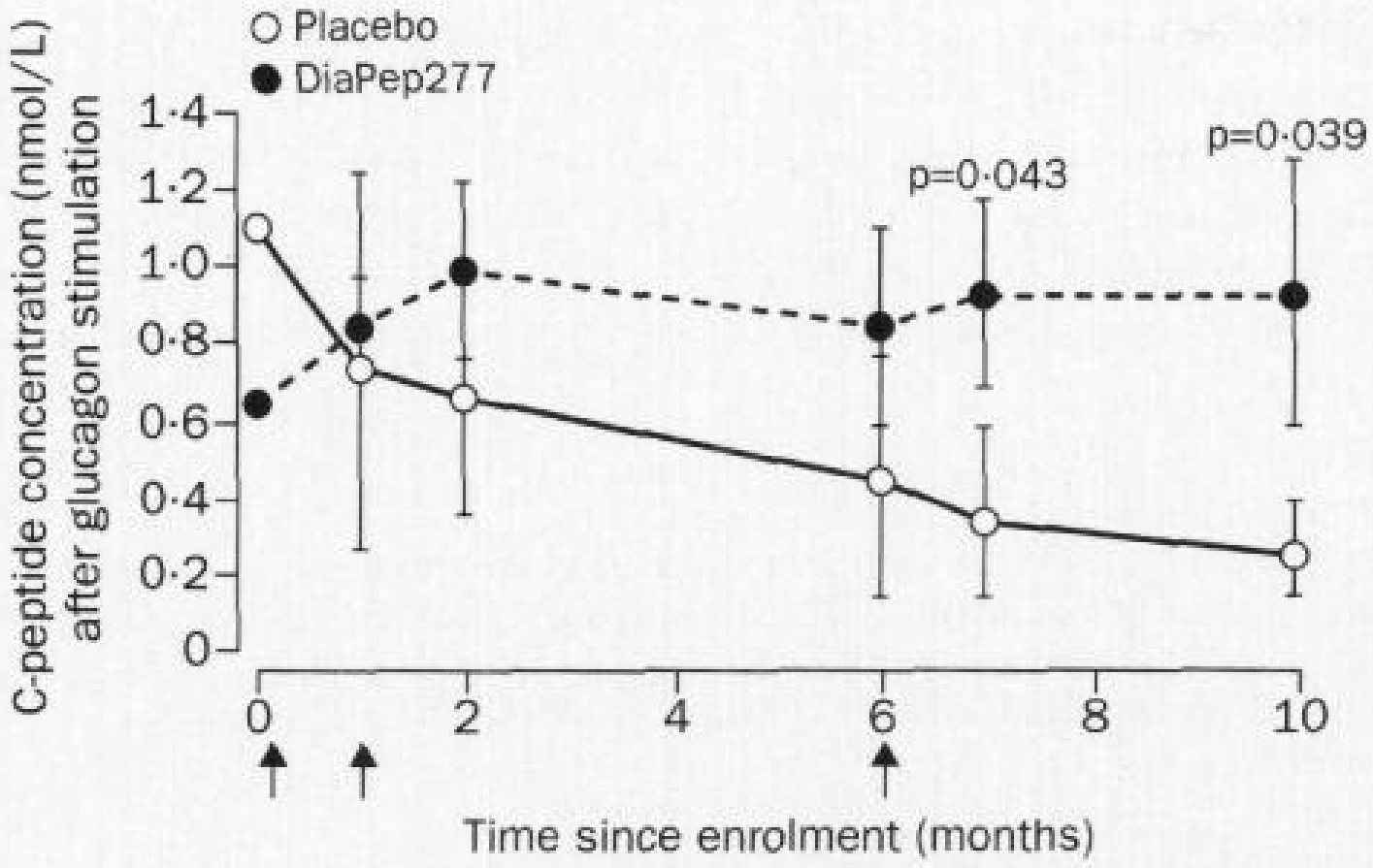


Figure 2: **Mean and SD stimulated C-peptide concentrations**
Arrows indicate times of treatment.

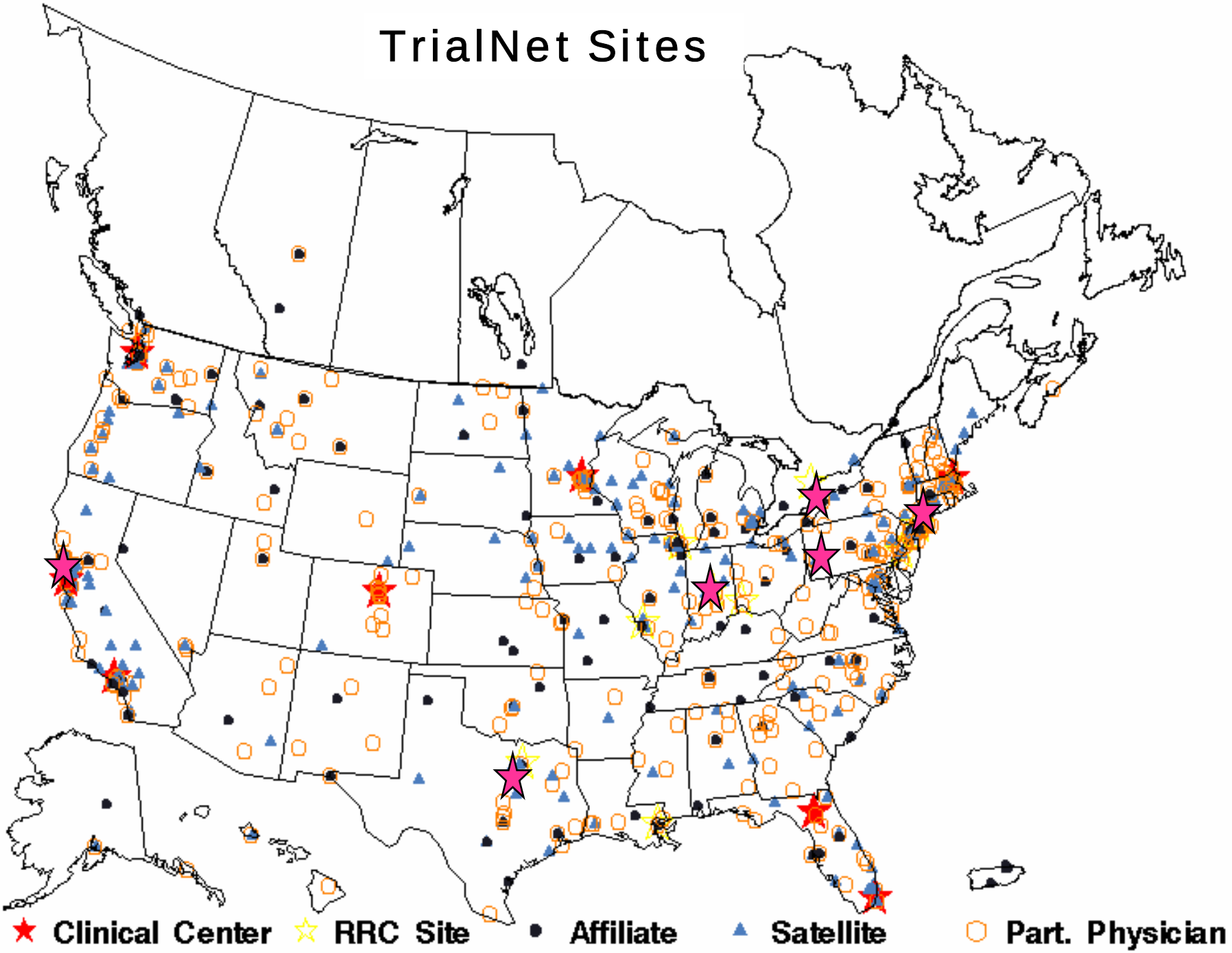

Type 1
Diabetes
TrialNet

TrialNet Goals

- Explore new therapies in:
  - New-onset type 1 diabetes
  - Relatives at risk of type 1 diabetes
  - Genetically high risk individuals
- Further define epidemiology, natural history, immune mechanisms, genetics and risk factors of type 1 diabetes

TrialNet Study Group

- Many DPT-1 investigators
- Basic immunologists, transplant physicians/surgeons
- Genetics, epidemiology
- Enhanced coordinating centre
- Link with Immune Tolerance Network for mechanistic studies and trials


TrialNet Sites
Clinical Center
RRC Site
Affiliate
Satellite
Part. Physician

Therapeutic Approaches

- Newer immunosuppressives
  - Less toxic, could induce tolerance
- Antigen based therapies
  - Peptides or modified proteins
  - Higher doses
- Diet based
  - Introduction of solid foods, ?gluten

Active TrialNet Studies

- Natural History
- MMF/DZB
- Assessment of Beta Cell Function
- Type 1 Diabetes Genetics Consortium

Natural History Study

- **PURPOSE:**
  - **To define how type 1 diabetes progresses prior to diagnosis**
  - **To identify participants for diabetes prevention trials**
- **WHO?**
  - **Relatives of those with type 1 diabetes**
  - **Parents, children, brothers, sisters up to age 45**
  - **Cousins, grandchildren, nieces, nephews, half siblings up to age 20**

Steps In Natural History Study

- Single blood test to measure diabetes autoantibodies
- If found, repeat antibodies and oral glucose tolerance test
- Follow-up with same testing every 6 months
- 1 antibody gives low risk of diabetes, 2 or more 40% risk over 5 years

Type 1 Diabetes Genetics Consortium

- Multicentre international effort to recruit 2500 families with 2 members with diabetes, their parents (and an unaffected sibling if possible)
- Search for diabetes susceptibility genes
- Create resource of DNA and cell lines for researchers worldwide

Improving Metabolic Assessments in T1DM Clinical Trials (MMTT vs GST)

- In trials of maintenance of insulin production after onset of diabetes, need to measure residual insulin production
- Many methods to test insulin production, but best method is not clear
- Comparing mixed meal (Boost) vs glucagon stimulation

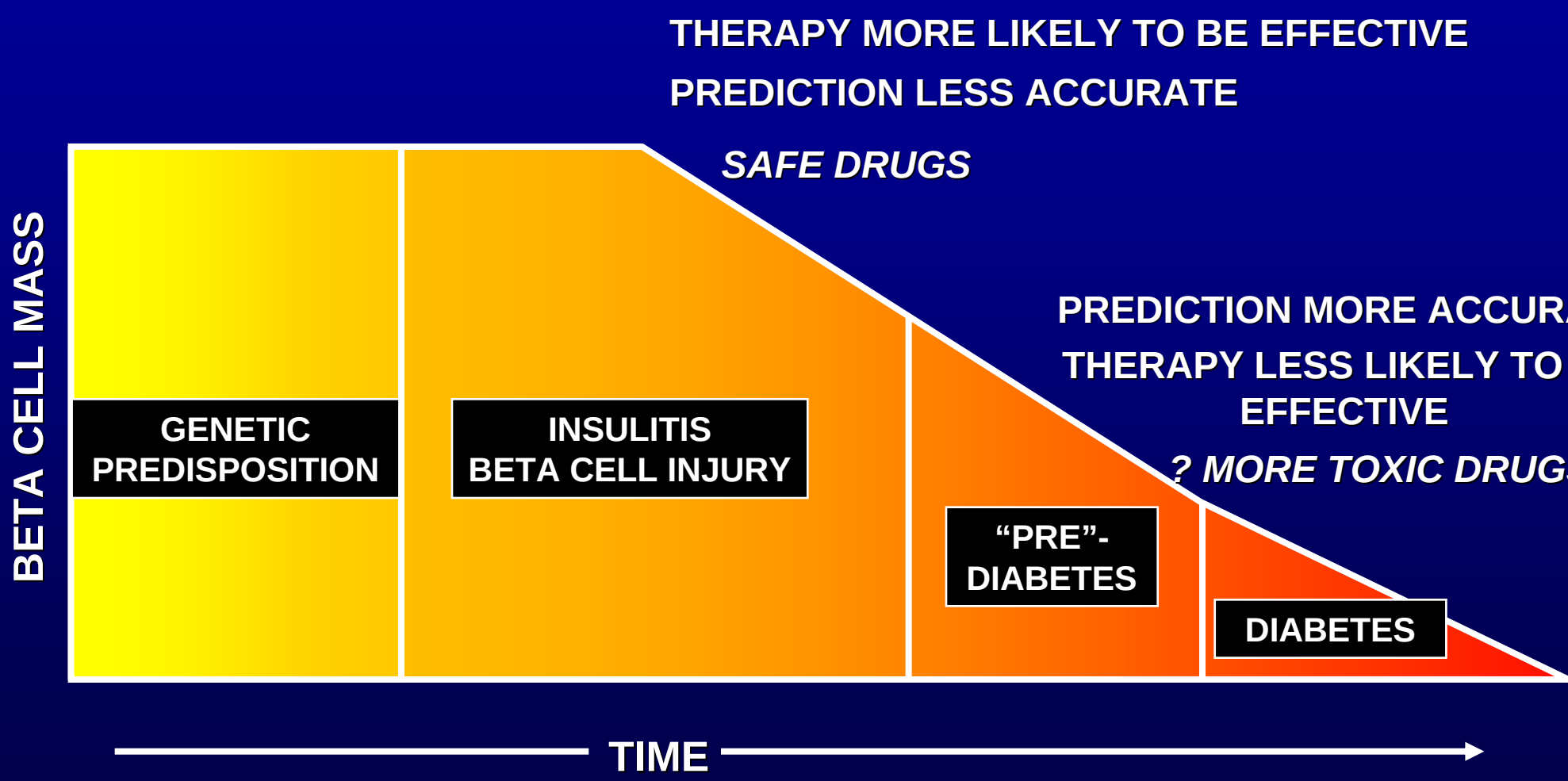
Preservation of Pancreatic Production of Insulin through Immunosuppression – 1

- Goal: to maintain insulin production after diabetes onset, using drugs that target active immune response
- Drugs:
  - Diclizamab (DZB) antibody to CD25, IL-2 receptor expressed on activated T cells
  - MMF – interferes with lymphocyte proliferation during an active immune response
- Not yet started in Canada, running in 6 centres in US

Interventions Under Consideration

- Immunosuppression
  - Anti-CD20
  - Anti-CD3 (Herold)
- Antigen-Based Therapies
  - Nasal Insulin
  - GAD
- Immunomodulation
  - Anti-CD3
  - IL-2 plus Sirolimus
  - IVIG plus Sirolimus
- Newborns
  - Nutritional Intervention: Vitamins D & E, Omega-3-Fatty Acids, Delay of Cereal

Therapeutic Dilemma



Ethical Issues

- "Attempts to prevent Type 1 diabetes are experimental and should be limited to research studies", CDA Clinical Practice Guidelines
- Newborn screening
  - Appropriate consent, harm of labeling
- Family members
  - Insurance issues, guilt, trials in children
- New onset
  - "Wishful thinking", distraction from good control, potential for harm

Conclusions

- Prediction improved
- Prevention trials unsuccessful to date
- Structure established for new prevention trials
- Promising new therapies to be tested