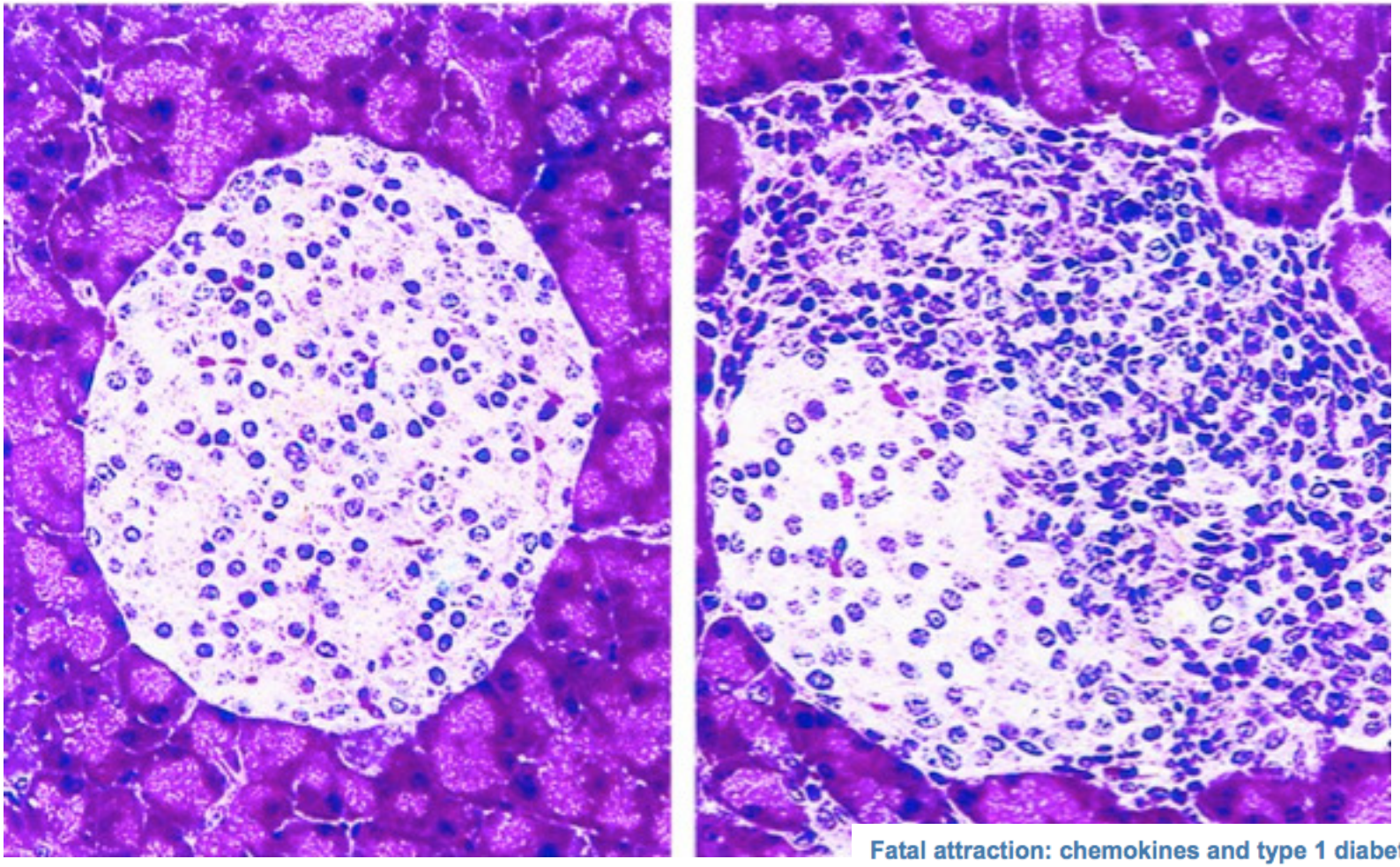
Är diabetes mellitus en autoimmun sjukdom?

Olle Korsgren

Type 1 Diabetes is currently regarded as a T cell mediated autoimmune disease, a notion expressed in over 50 000 scientific publications.

Acute onset TID NOD mouse



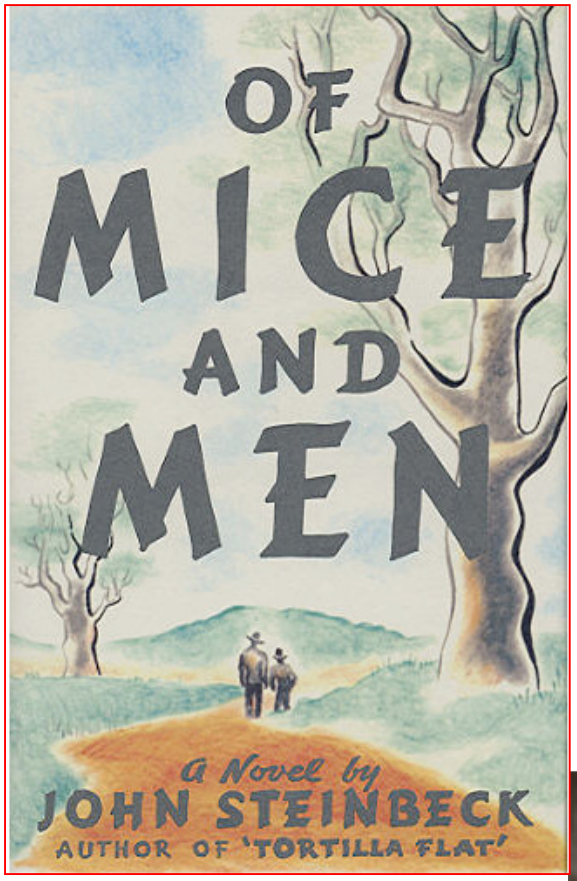
Fatal attraction: chemokines and type 1 diabetes

Mark A. Atkinson, S. Brian Wilson

Published in **Volume 110, Issue 11**

J Clin Invest. 2002; 110(11):1611 doi:10.1172/JCI17311

Mice ≠ Men

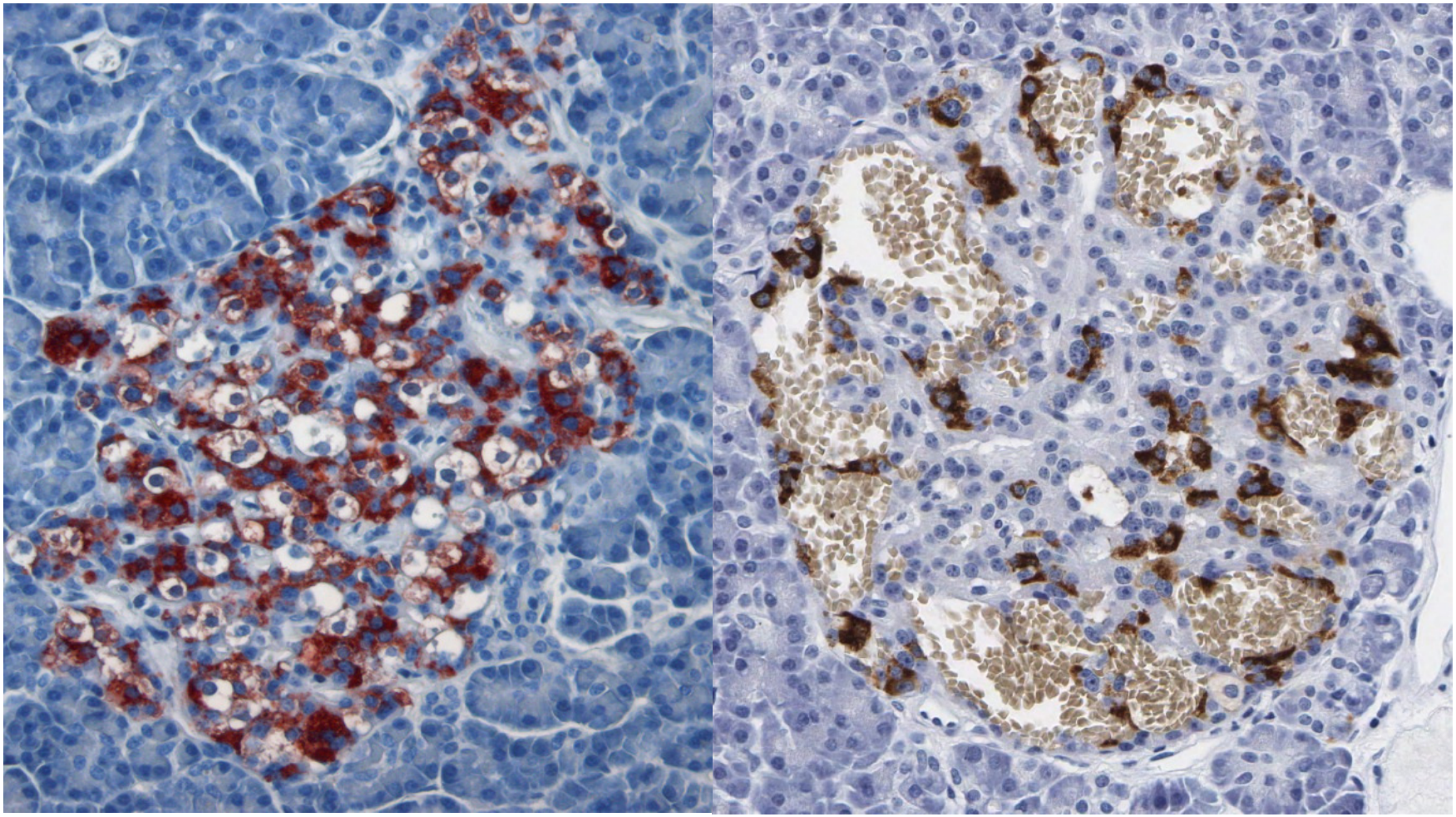

OF
MICE
AND
MEN
A Novel by
JOHN STEINBECK
AUTHOR OF 'TORTILLA FLAT'

Acute T1D case #1

Swollen Beta cells

Intra-islet bleedings

(hydroptic degeneration)



Described more than 100 years ago!

Swollen Beta cells bleedings (hydroptic degeneration)

Intra-islet

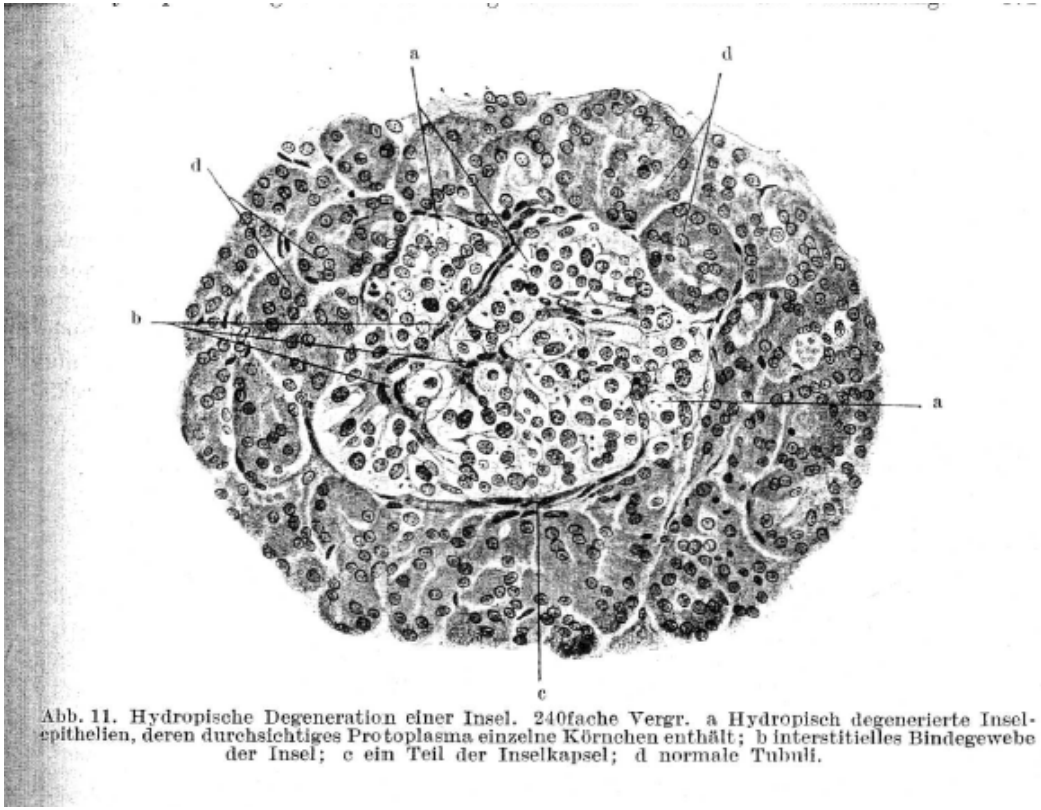
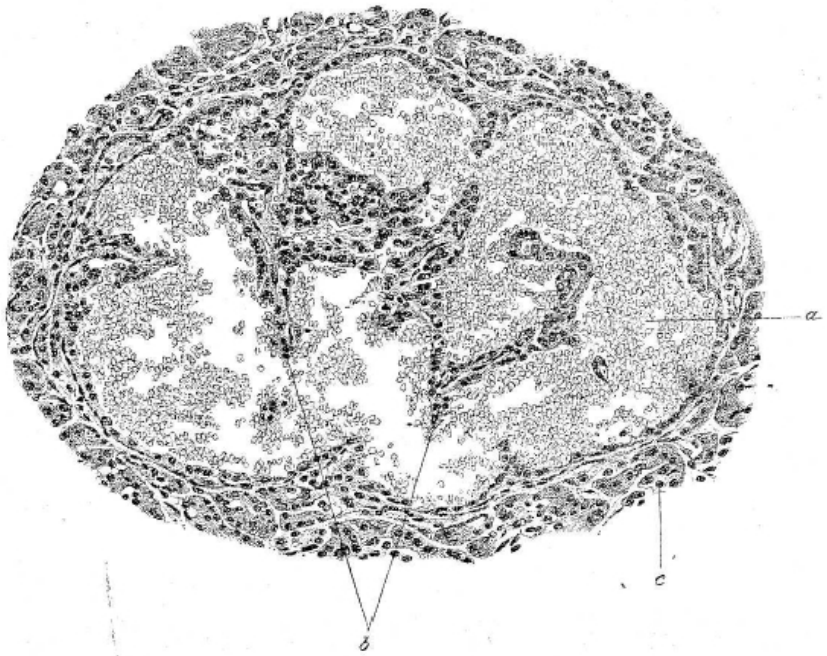


Abb. 11. Hydropische Degeneration einer Insel. 240fache Vergr. a Hydropisch degenerierte Inselepithelien, deren durchsichtiges Protoplasma einzelne Körnchen enthält; b interstitielles Bindegewebe der Insel; c ein Teil der Inselkapsel; d normale Tubuli.

Fig. 4.



Langerhans'sche Insel, nahezu ganz durch Hämorrhagien zerstör
a Blutextravasate; *b* Reste der Epithelzellenbalken.

Weichselbaum 1910

Weichselbaum 1902

Islets 3:4, 1-8; July/August 2011; ©2011 Landes Bioscience

Insulitis in human type 1 diabetes

The quest for an elusive lesion

Peter In't Veld

Department of Pathology; Diabetes Research Center; Free University of Brussels (VUB); Vrije Universiteit Brussel; Brussels, Belgium

Table 2. Incidence of insulitis in n = 213 type 1 diabetic patients stratified according to age at onset and duration of disease

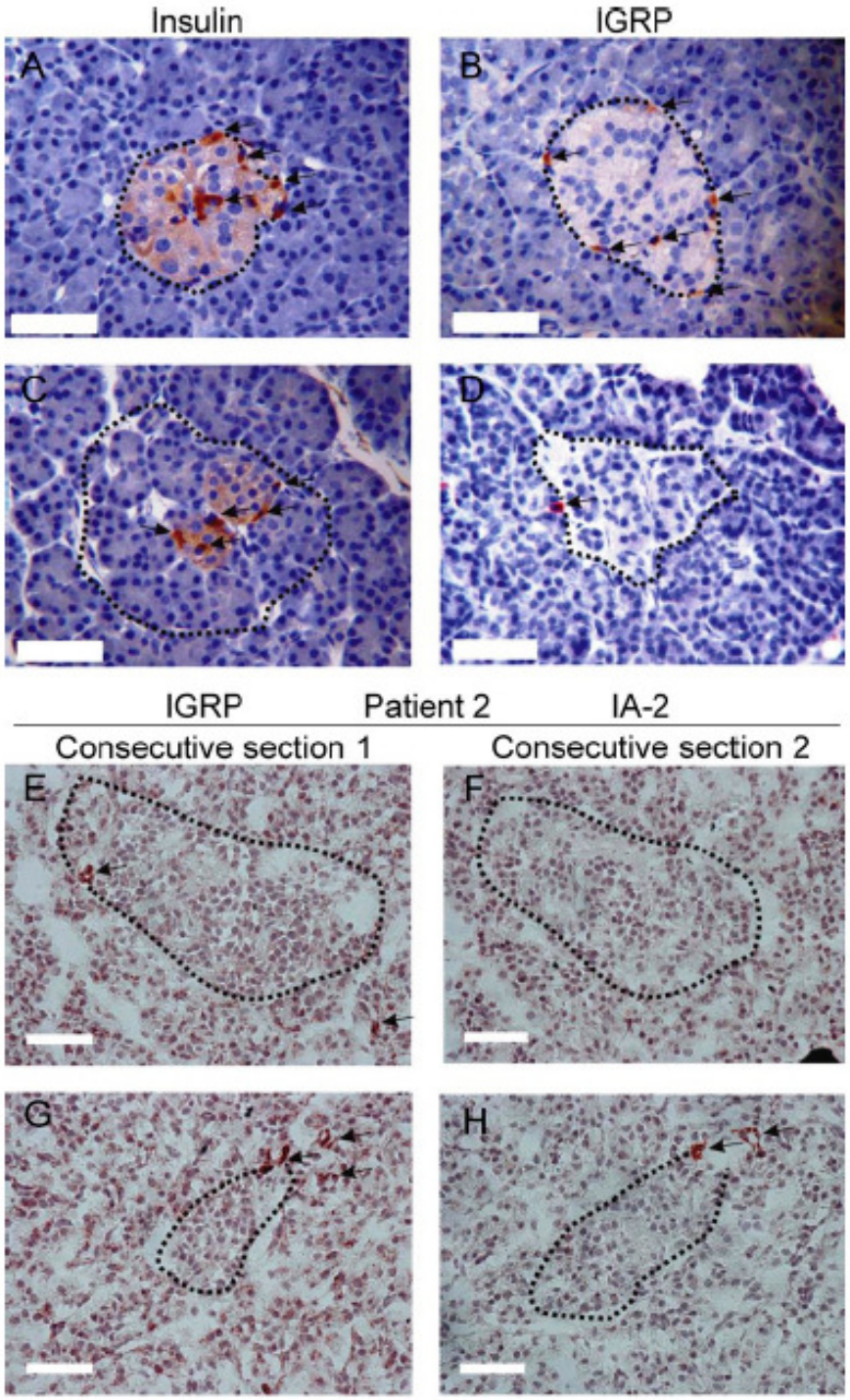
	Duration of disease			
Age at onset (yrs)	**≤1 month**	**>1 month–≤1 year**	**>1 year**	**Total**
0–14	19/26 (73)	12/20 (60)	3/81 (4)	34/127 (27)
15–39	5/17* (29)	5/18** (28)	1/51 (2)	11/86 (13)
total	24/43 (56)	17/38 (45)	4/132 (3)	45/213 (21)

Data are expressed as fraction of patients with insulitis (percentage). Combined patient data from population-based studies (refs. 12–15, 29, 37, 47–49). Significance of differences versus the age group 0–14 yrs was calculated using a chi-square test: *$p < 0.01$; **$p < 0.05$.

No "insulitis"

	< 1 month	> 1 month -1 year
Age 0-14	27 %	40 %
Age 15-39	71 %	72 %

(Insulitis defined as ≥ 5 CD45 cells in ≥ 3 islets)



8+ cells/islet ets counted)	Islet HLA class I (pattern)	Tetramer reactivity[a] (pattern)
8.8 (160)	Positive	Insulin, IGRP (monospecific)
8.4 (125)	Positive	Insulin, IGRP (monospecific)
<1 (128)		-mismatched control (no staining)
3.5 (116)	Positive	Insulin
4.1 (150)	Positive	Insulin
3.2 (140)	Positive	IGRP
4.3 (40)	Positive	IGRP, IA-2, insulin (mono-/multispecific)
1.5 (70)		No staining
6.5 (20)		GAD65, pplAPP, insulin (multispecific)
9.4 (30)	Positive (tail region only)	IGRP, GAD65, PPI, insulin, IA-2 (mono-/multispecific)
3.5 (20)	Positive (lobular)	No staining

5.16 CD8+ cells/islet

4.73 CD8+ cells/islet

nd PPI in Siena. Patients 2, 4, 5, and 6 were stained for reactivity against IGRP, insulin, PPI, IA-2,

Ania Skowera,[1] Kristin Ladell,[2] James E. McLaren,[2] Garry Dolton,[2] Katherine K. Matthews,[2,3] Emma Gostick,[2] Deborah Kronenberg-Versteeg,[1] Martin Eichmann,[1] Robin R. Knight,[1] Susanne Heck,[4] Jake Powrie,[5] Polly J. Bingley,[6] Colin M. Dayan,[7] John J. Miles,[2,3,8] Andrew K. Sewell,[2] David A. Price,[2] and Mark Peakman[1]

β-Cell–Specific CD8 T Cell Phenotype in Type 1 Diabetes Reflects Chronic Autoantigen Exposure

Diabetes 2015;64:916–925 | DOI: 10.2337/db14-0332

Autoreactive CD8 T cells play a central role in the destruction of pancreatic islet β-cells that leads to type 1 diabetes, yet the key features of this immune-mediated process remain poorly defined. In this study, we combined high-definition polychromatic flow cytometry with ultrasensitive peptide–human leukocyte antigen class I tetramer staining to quantify and characterize β-cell–specific CD8 T cell populations in patients with recent-onset type 1 diabetes and healthy control subjects. Remarkably, we found that β-cell–specific CD8 T cell frequencies in peripheral blood were similar between subject groups. In contrast to healthy control subjects, however, patients with newly diagnosed type 1 diabetes displayed hallmarks of antigen-driven expansion uniquely within the β-cell–specific CD8 T cell compartment. Molecular analysis of selected β-cell–specific CD8 T cell populations further revealed highly skewed oligoclonal T cell receptor repertoires comprising exclusively private clonotypes. Collectively, these data identify novel and distinctive features of disease-relevant CD8 T cells that inform the immunopathogenesis of type 1 diabetes.

nature immunology

Structural basis for the killing of human beta cells by CD8+ T cells in type 1 diabetes

Anna M Bulek[1,9], David K Cole[1,9], Ania Skowera[2,3,9], Garry Dolton[1], Stephanie Gras[4], Florian Madura[1], Anna Fuller[1], John J Miles[1,5], Emma Gostick[1], David A Price[1], Jan W Drijfhout[6], Robin R Knight[2], Guo C Huang[7], Nikolai Lissin[8], Peter E Molloy[8], Linda Wooldridge[1], Bent K Jakobsen[8], Jamie Rossjohn[1,4], Mark Peakman[2,3,9], Pierre J Rizkallah[1,9] & Andrew K Sewell[1,9]

NATURE IMMUNOLOGY VOLUME 13 NUMBER 3 MARCH 2012

peptide–MHC class II[17,24], the affinity of this MHC class I–restricted autoreactive TCR was very low and within the overall spectrum of TCR-pMHCI interactions for which biophysical data are available. Indeed, to our knowledge, this is the lowest TCR-pMHC affinity recorded for any natural human agonist ligand.

A Single Autoimmune T Cell Receptor Recognizes More Than a Million Different Peptides*[S]

Received for publication, August 3, 2011, and in revised form, November 14, 2011 Published, JBC Papers in Press, November 18, 2011, DOI 10.1074/jbc.M111.289488

Linda Wooldridge[‡1,2], **Julia Ekeruche-Makinde**[‡1], **Hugo A. van den Berg**[§1], **Anna Skowera**[¶‖3], **John J. Miles**[‡4], **Mai Ping Tan**[‡], **Garry Dolton**[‡3], **Mathew Clement**[‡], **Sian Llewellyn-Lacey**[‡], **David A. Price**[‡3], **Mark Peakman**[¶‖3], **and Andrew K. Sewell**[‡3,5]

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 2, pp. 1168–1177, January 6, 2012

The promiscuity of autoreactive TRC

ysis to reveal that a single patient-derived autoimmune CD8$^+$ T cell clone of pathogenic relevance in human type I diabetes recognizes >one million distinct decamer peptides in the context of a single MHC class I molecule. A large number of peptides

is 100-fold better than the index. Almost 10 million peptides are within a factor 1,000 of the optimal agonist, but such weak agonists will not generally be physiologically significant unless presented at very high copy numbers. Taken

Acta path. microbiol. scand. Sect. A, *85*: 699–706, 1977

AN AUTOPSY STUDY OF THE ISLETS OF LANGERHANS IN ACUTE-ONSET JUVENILE DIABETES MELLITUS

KARSTEN JUNKER, JØRN EGEBERG, HANS KROMANN, JØRN NERUP

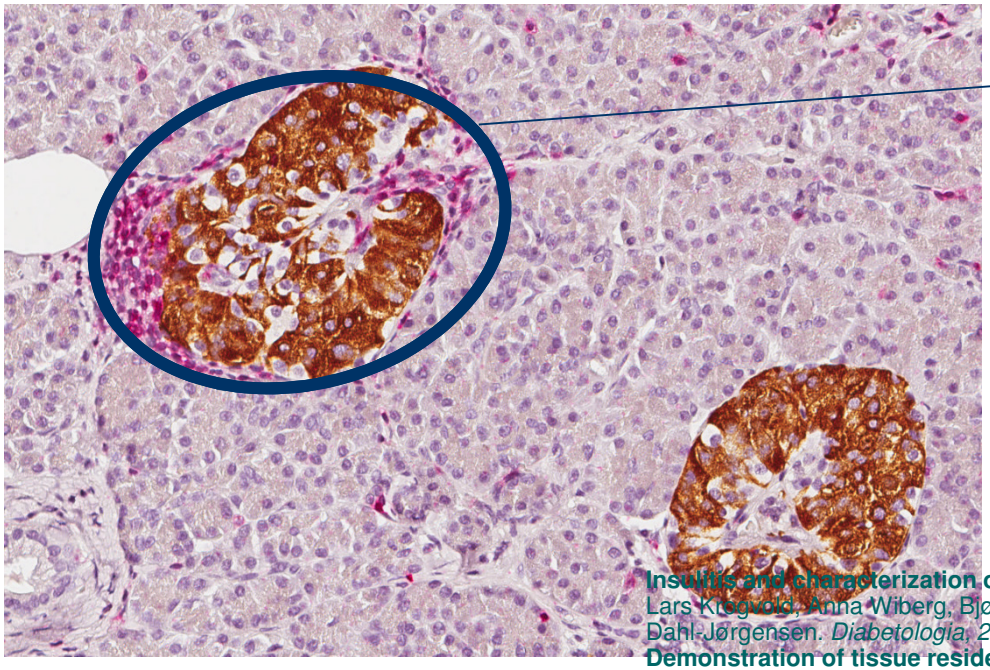
crine pancreatic tissue. In none of the cases was the insulitis mentioned in the original autopsy records.

Question the clinical importance of ≥5 immune cells in ≥ 3 islets with ultra-low-affinity present in equal numbers in T2D and often not reported in autopsy records

Insulitis in human diabetes: a histological evaluation of donor pancreases
by M. Lundberg, P. Seiron, S. Ingvast, O. Korsgren, O. Skog. Diabetologia 2016 In Press

Characteristics of T cells in insulitic lesions

- Few T cells in few islets, heterogeneously distributed
- Most (~60-80%) CD3 positive cells are located in the periphery of the islets (peri-insulitis)
- "No" CD8+ T cell is CD69+ ("no activated cytotoxic T cells")
- "No" MAIT cells
- 40% of all CD8+ T cells have a phenotype of "tissue resident T cells" (part of protective immunity).



LCM and transcriptome analysis of T cells in insulitic islets show little resemblance with T cells in allograft rejection

Insulitis and characterization of infiltrating T cells in surgical pancreatic tail resections from patients at ons
Lars Krogvold, Anna Wiberg, Bjørn Edwin, Trond Buanes, Frode Lars Jahnsen, Kristian F Hanssen, Erik Larsson, C
Dahl-Jørgensen. *Diabetologia, 2015*

Demonstration of tissue resident memory CD8 T cells in insulitic lesions in patients with recent onset type 1 diabetes
Enida Kuric, Peter Seiron, Lars Krogvold, Bjørn Edwin, Trond Buanes, Kristian F Hanssen, Oskar Skog, Knut Dahl-Jørgensen, Olle Korsgren
Am J Pathol 2016 In Press

Long-lived epithelial immunity by tissue-resident memory T (T_{RM}) cells in the absence of persisting local antigen presentation

Laura K. Mackay, Angus T. Stock, Joel Z. Ma, Claerwen M. Jones, Stephen J. Kent, Scott N. Mueller, William R. Heath, Francis R. Carbone[1], and Thomas Gebhardt[1]

Department of Microbiology and Immunology, University of Melbourne, Melbourne 3010, Australia

Edited* by Michael J. Bevan, University of Washington, Seattle, WA, and approved March 26, 2012 (received for review February 8, 2012)

Although circulating memory T cells provide enhanced protection against pathogen challenge, they often fail to do so if infection is localized to peripheral or extralymphoid compartments. In those cases, it is T cells already resident at the site of virus challenge that offer superior immune protection. These tissue-resident memory T (T_{RM}) cells are identified by their expression of the α-chain from the integrin α_E(CD103)β_7, and can exist in disequilibrium with the blood, remaining in the local environment long after peripheral infections subside. In this study, we demonstrate that long-lived intraepithelial CD103$^+$CD8$^+$ T_{RM} cells can be generated in the absence of in situ antigen recognition. Local inflammation in skin and mucosa alone resulted in enhanced recruitment of effector populations and their conversion to the T_{RM} phenotype. The CD8$^+$ T_{RM} cells lodged in these barrier tissues provided long-lived protection against local challenge with herpes simplex virus in skin and vagina challenge models, and were clearly superior to the circulating memory T-cell cohort. The results demonstrate that peripheral T_{RM} cells can be generated and survive in the absence of local antigen presentation and provide a powerful means of achieving immune protection against peripheral infection.

determine whether we could embed memory T cells in peripheral sites in the absence of ongoing antigen stimulation, and in so doing, exploit T_{RM} cells to provide effective barrier immune protection.

Results

Circulating CD8$^+$ Memory T Cells Do Not Control Skin Infection with HSV. Certain peripheral infections are efficiently eliminated by effector CD8$^+$ T cells but are less well controlled by their memory counterparts (3, 4, 9, 20). We wanted to address whether skin infection with herpes simplex virus (HSV) exhibited a similar pattern of circulating memory cell resistance. To this end, we vaccinated C57BL/6 mice with a recombinant influenza virus that contains the immunodominant determinant from the HSV glycoprotein B (gB) molecule (flu.gB) to generate cohorts with effector (day 10 after vaccination) or memory (day 30 after vaccination) T-cell populations in the circulation. When challenged by HSV skin infection, mice recently immunized with the recombinant flu.gB showed marked protection, with strongly reduced viral loads in the inoculation site compared with non-immunized controls (Fig. 1*A*). This protection was also associated

nature immunology

Memory T cells in nonlymphoid tissue that provide enhanced local immunity during infection with herpes simplex virus

Thomas Gebhardt, Linda M Wakim, Liv Eidsmo, Patrick C Reading, William R Heath & Francis R Carbone

Effective immunity is dependent on long-surviving memory T cells. Various memory subsets make distinct contributions to immune protection, especially in peripheral infection. It has been suggested that T cells in nonlymphoid tissues are important during local infection, although their relationship with populations in the circulation remains poorly defined. Here we describe a unique memory T cell subset present after acute infection with herpes simplex virus that remained resident in the skin and in latently infected sensory ganglia. These T cells were in disequilibrium with the circulating lymphocyte pool and controlled new infection with this virus. Thus, these cells represent an example of tissue-resident memory T cells that can provide protective immunity at points of pathogen entry.

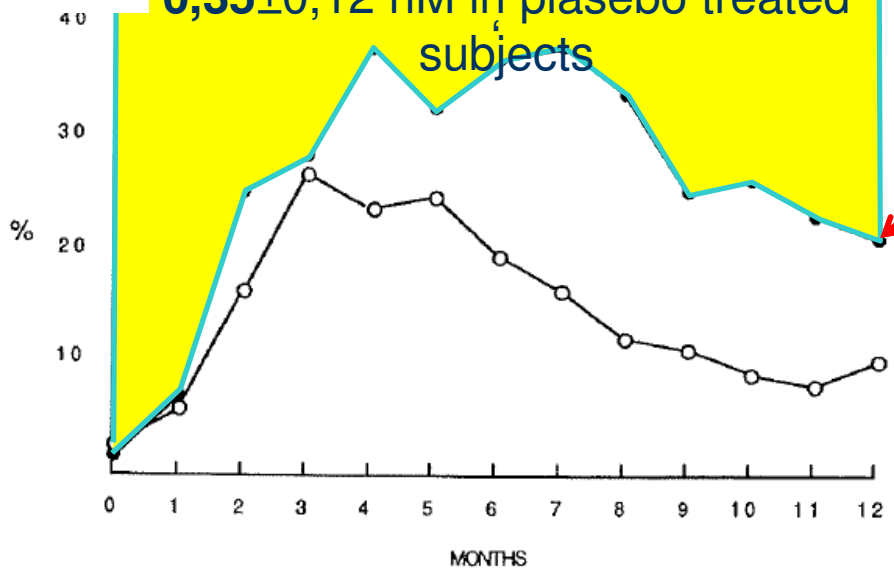
Cyclosporin-Induced Remission of IDDM After Early Intervention

Association of 1 yr of Cyclosporin Treatment With Enhanced Insulin Secretion

THE CANADIAN-EUROPEAN RANDOMIZED CONTROL TRIAL GROUP

Diabetes 37:1574–82, 1988

Stimulated C-peptide at 1 year was: **0,46**±0,13 nM in CsA treated subjects
and
0,35±0,12 nM in plasebo treated subjects



CsA treated subjects

Plasebo treated subjects

FIG. 1. Non-insulin-receiving remission rates in cyclosporin-treated (●) and placebo-treated (○) groups of patients at intervals through 1 yr.

Type 1 Diabetes

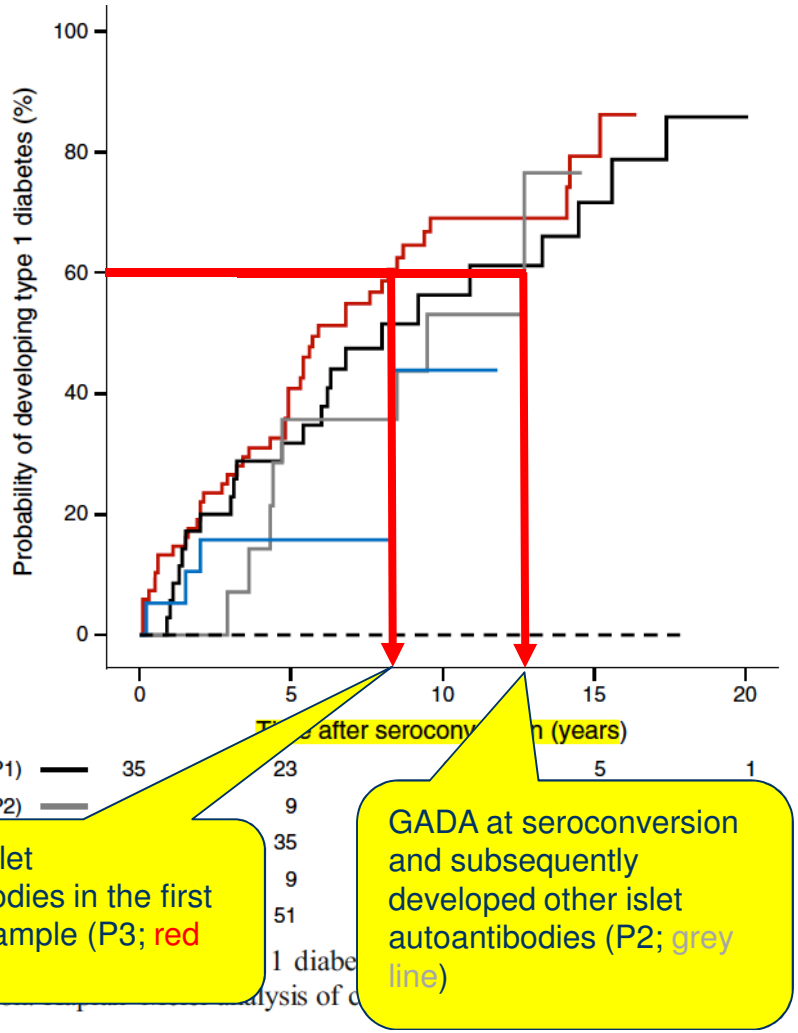
The natural history of type 1 diabetes argues against a role of autoreactive T cells

Diabetologia (2015) 58:2317–2323
DOI 10.1007/s00125-015-3672-y

ARTICLE

Islet autoantibody phenotypes and incidence in children at increased risk for type 1 diabetes

Eleni Z. Giannopoulou[1] · Christiane Winkler[1,2] · Ruth Chmiel[1] · Claudia Matzke[1] · Marlon Scholz[1] · Andreas Beyerlein[1] · Peter Achenbach[1,2] · Ezio Bonifacio[3,4,5] · Anette-G. Ziegler[1,2]



Prevalence of Residual Beta-cell Function in Insulin-Dependent Diabetics in Relation to Duration of Diabetes

, C. Binder, M.D., P. McNair, M.D.,*
Transbøl, M.D.,† Copenhagen

DIABETES 27 (Suppl. 1):262-64, 1978.

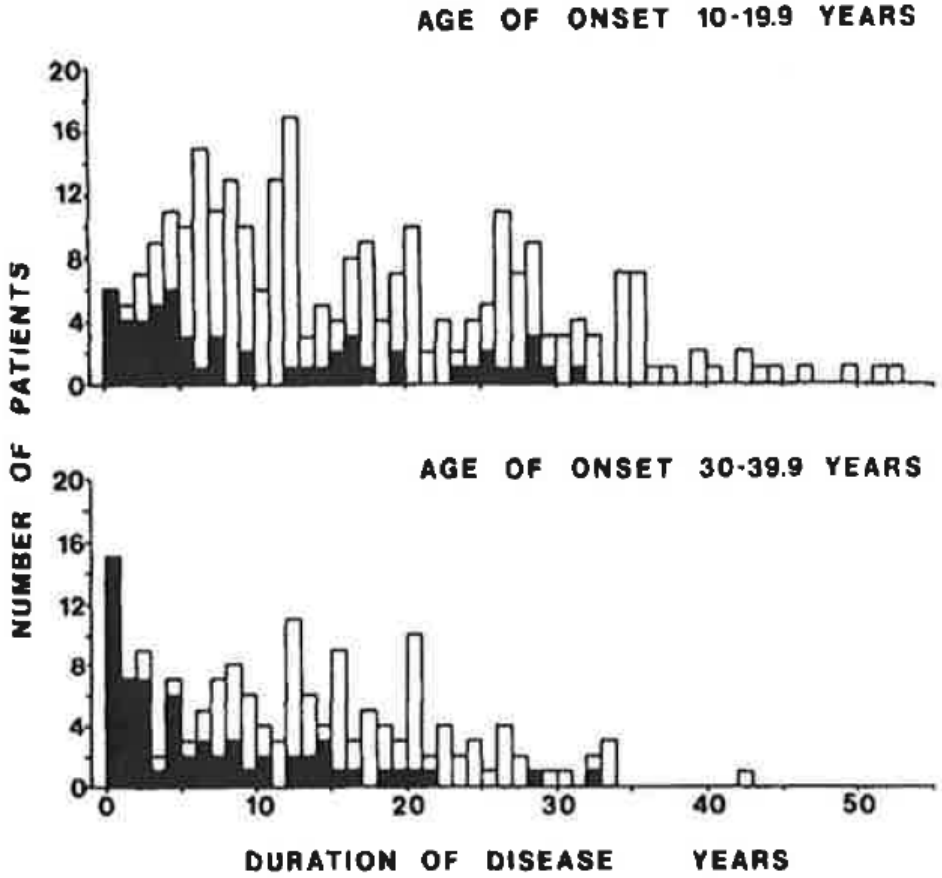


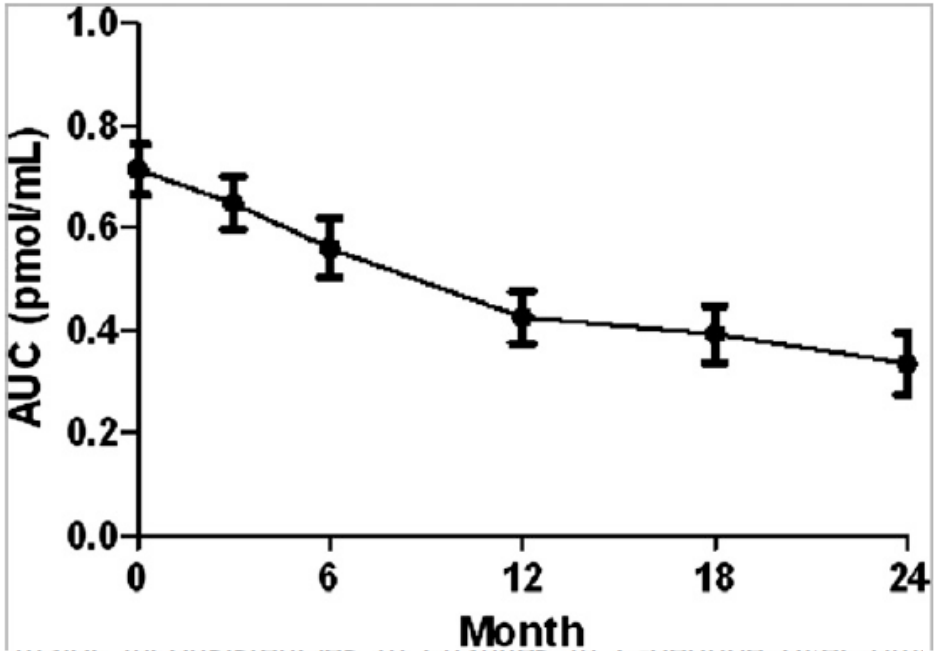
FIG. 1. Distribution of patients in the early- and late-onset groups by one-year intervals of duration of diabetes. Black areas illustrate number of patients with residual beta-cell function.

The natural history of T1D show a gradual loss of c-peptide over a period of several years

This is not in agreement with a T cell dependent beta cell destruction

cf. rejection of a transplanted organ and elimination of a viral infection

Interpretation of clinical trials to alter the decline in β-cell function after diagnosis of type 1 diabetes depends on a robust understanding of the natural history of disease. Combining data from the Type 1 Diabetes TrialNet studies, we describe the natural history of β-cell function from shortly after diagnosis through 2 years post study randomization, assess the degree of variability between patients, and investigate factors that may be related to C-peptide preservation or loss. We found that 93% of individuals have detectable C-peptide 2 years from diagnosis. In 11% of subjects, there was no significant fall from baseline by 2 years. There was a biphasic decline in C-peptide; the C-peptide slope was −0.0245 pmol/mL/month (95% CI −0.0271 to −0.0215) through the first 12 months and −0.0079 (−0.0113 to −0.0050) from 12 to 24 months ($P < 0.001$). This pattern of fall in C-peptide over time has implications for understanding trial results in which effects of therapy are most pronounced early and raises the possibility that there are time-dependent differences in pathophysiology. The robust data on the C-peptide obtained under clinical trial conditions should be used in planning and interpretation of clinical trials. ***Diabetes*** **61:2066–2073, 2012**



Even if the clinical onset of Type 1 Diabetes (T1D) is usually abrupt, the injurious processes that eventually cause the disease seem to have been in place for many years.

Also, there is only a gradual loss of the remaining insulin-producing cells after T1D diagnosis, as evidenced by a decline in c-peptide over a period of several years in most subjects. Importantly, the long-lasting beta cells remain functional even several decades after diagnosis of T1D.

These clinical observations suggest a mild disease process occurring over several years and should be viewed in relation to the total beta cell mass of only 0.2 – 1.5 g in non-diabetic adults.

Type 1 Diabetes

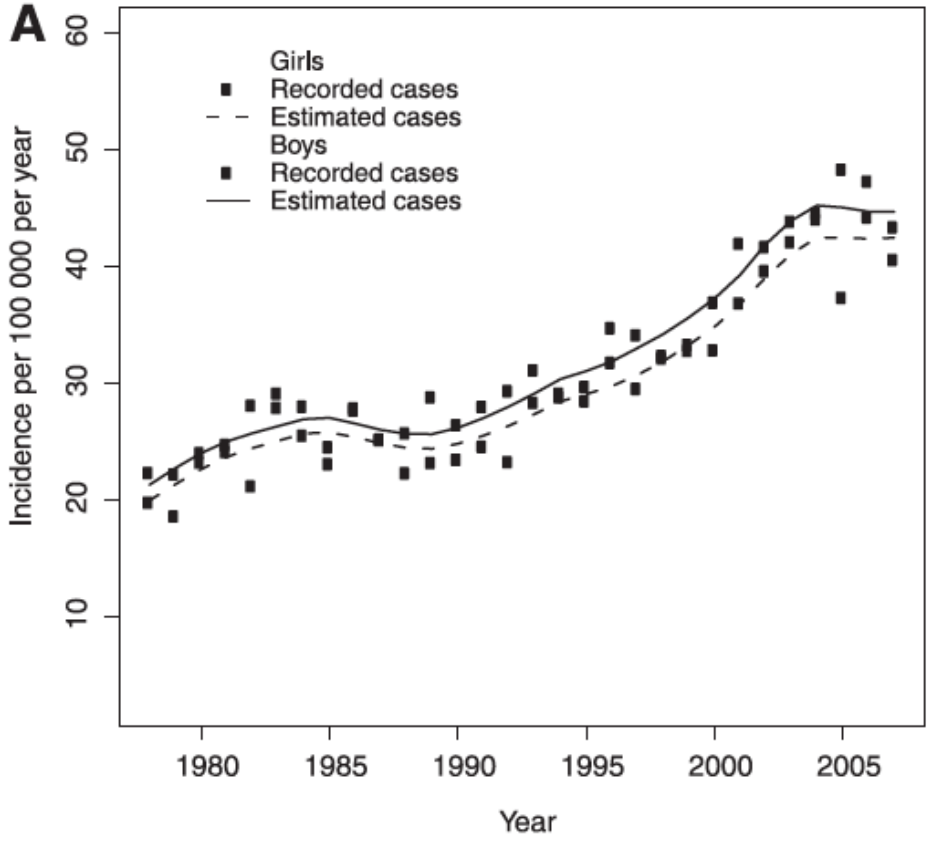
The importance of the environment

Thirty Years of Prospective Nationwide Incidence of Childhood Type 1 Diabetes

The Accelerating Increase by Time Tends to Level Off in Sweden

Yonas Berhan,[1] Ingeborg Waernbaum,[2] Torbjörn Lind,[1] Anna Möllsten,[1] and Gisela Dahlquist,[1] for the Swedish Childhood Diabetes Study Group*

***Diabetes* 60:577–581, 2011**



Trends in High-Risk HLA Susceptibility Genes Among Colorado Youth With Type 1 Diabetes

Kendra Vehik, mph, phd[1]
Richard F. Hamman, md, drph[1]
Dennis Lezotte, phd[1]
Jill M. Norris, mph, phd[1]
Georgeanna J. Klingensmith, md[1,2]
Marian Rewers, md, phd[1,2]
Dana Dabelea, md, phd[1]

OBJECTIVE — Type 1 diabetes is associated with a wide spectrum of susceptibility and protective genotypes within the HLA class II system. It has been reported that adults diagnosed with youth-onset type 1 diabetes more recently have been found to have fewer classical high-risk HLA class II genotypes than those diagnosed several decades ago. We hypothesized that such temporal trends in the distribution of HLA-DR, DQ genotypes would be evident, and perhaps even stronger, among 5- to 17-year-old Hispanic and non-Hispanic white (NHW) youth diagnosed with type 1 diabetes in Colorado between 1978 and 2004.

RESEARCH DESIGN AND METHODS — HLA-DR, DQ was typed using PCR and sequence-specific oligonucleotide hybridization in 100 youth diagnosed during the period of 1978–1988 and 264 diagnosed during 2002–2004. Logistic regression was used to adjust for confounders and assess temporal trends.

RESULTS — The frequency of the highest-risk genotype (DRB1*03-DQB1*02/DRB1*04-DQB1*03) was higher (39%) in children diagnosed during the period 1978–1988 than in those diagnosed during 2002–2004 (28%). A similar pattern was observed in NHWs and Hispanics.

CONCLUSIONS — We found that high-risk HLA genotypes are becoming less frequent over time in youth with type 1 diabetes of NHW and Hispanic origin. This temporal trend may suggest that increasing environmental exposure is now able to trigger type 1 diabetes in subjects who are less genetically susceptible.

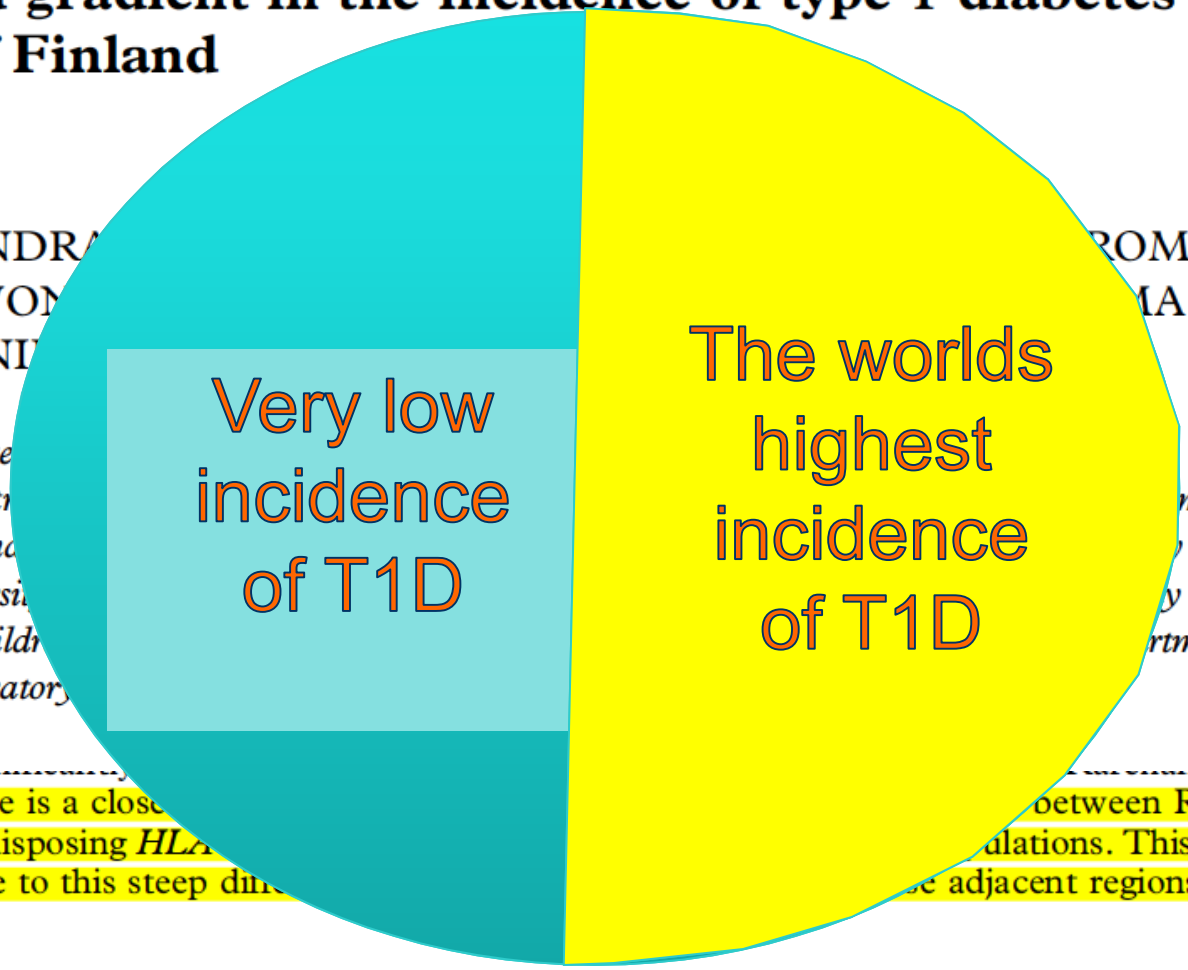
Diabetes Care 31:1392–1396, 2008

Annals of Medicine, 2005; 37: 67–72

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

A six-fold gradient in the incidence of type 1 diabetes at the eastern border of Finland



ANITA KONDR ROMANOV[2],
AINO KARVON IA ILONEN[1,5],
MIKAEL KNI

[1]*Juvenile Diabete* [2]*Department of Pediatrics,*
University of Pet mpere, Medical School,
Tampere, Finland Center and Department of
Virology, Universi y Hospital, Tampere, Finland,
[7]*Hospital for Child rtment of Clinical Microbiology,*
Centre for Laborator

Conclusions. There is a close between Russian Karelia and Finland, although the predisposing *HLA* ulations. This suggests that environmental factors contribute to this steep di e adjacent regions.

Pediatric Diabetes 2011
doi: 10.1111/j.1399-5448.2011.00783.x

Pediatric Diabetes

Original Article

Prevalence and characteristics of diabetes among Somali children and adolescents living in Helsinki, Finland

Oilinki T, Otonkoski T, Ilonen J, Knip M, Miettinen PJ. Prevalence and characteristics of diabetes among Somali children and adolescents living in Helsinki, Finland.
Pediatric Diabetes 2011.

T Oilinki[a], T Otonkoski[a,b], J Ilonen[c,d], M Knip[a,e,f] and PJ Miettinen[a,b]

Risk for T1D is associated to being born in a high incidence area, but not associated to T1D risk HLA

ORIGINAL ARTICLE

Cesarean Section and Interferon-Induced Helicase Gene Polymorphisms Combine to Increase Childhood Type 1 Diabetes Risk

Ezio Bonifacio,[1,2] Katharina Warncke,[2,3] Christiane Winkler,[4] Maike Wallner,[5] and Anette-G. Ziegler[2,4,5]

Diabetes 60:3300–3306, 2011

RESULTS—Children delivered by cesarean section (n = 495) had more than twofold higher risk for type 1 diabetes than children born by vaginal delivery (hazard ratio [HR] 2.5; 95% CI 1.4–4.3; P = 0.001).

Diabetes During Diarrhea-Associated Hemolytic Uremic Syndrome

A systematic review and meta-analysis

RITA S. SURI, MD[1]
WILLIAM F. CLARK, MD[1]
NICK BARROWMAN, PHD[2]
JEFFREY L. MAHON, MD, MSC[3,4]
HEATHER R. THIESSEN-PHILBROOK, MMATH[1]
M. PATRICIA ROSAS-ARELLANO, MD, PHD[1]
KELLY ZARNKE, MD, MSC[3,5]
JOCELYN S. GARLAND, MD[6]
AMIT X. GARG, MD, MA, PHD[1,3]

Diabetes Care 28:2556–2562, 2005

OBJECTIVE — To quantify the incidence of diabetes during the acute phase of diarrhea-associated hemolytic uremic syndrome (D+HUS) and to identify features associated with its development.

RESEARCH DESIGN AND METHODS — A systematic review and meta-analysis of articles assessing diabetes during D+HUS was conducted. Relevant citations were identified from Medline, Embase, and Institute for Scientific Information Citation Index databases. Bibliographies of relevant articles were hand searched. All articles were independently reviewed for inclusion and data abstraction by two authors.

RESULTS — Twenty-one studies from six countries were included. Only 2 studies reported a standard definition of diabetes; 14 defined diabetes as hyperglycemia requiring insulin. The incidence of diabetes during the acute phase of D+HUS could be quantified in a subset of 1,139 children from 13 studies (1966–1998, age 0.2–16 years) and ranged from 0 to 15%, with a pooled incidence of 3.2% (95% CI 1.3–5.1, random-effects model, significant heterogeneity among studies, $P = 0.007$). Children who developed diabetes were more likely to have severe disease (e.g., presence of coma or seizures, need for dialysis) and had higher mortality than those without diabetes. Twenty-three percent of those who developed diabetes acutely died, and 38% of survivors required long-term insulin (median follow-up 12 months). Recurrence of diabetes was possible up to 60 months after initial recovery.

CONCLUSIONS — Children with D+HUS should be observed for diabetes during their acute illness. Consideration should be given to long-term screening of D+HUS survivors for diabetes.

Incidence of T1D: 3.3%

Type 1 Diabetes

A disease affecting both the exocrine and endocrine pancreas

Demonstration of islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients

Ken T. Coppieters,[1] Francesco Dotta,[2] Natalie Amirian,[1]
Peter D. Campbell,[3] Thomas W.H. Kay,[3] Mark A. Atkinson,[4]
Bart O. Roep,[5] and Matthias G. von Herrath[1]

[1]Type 1
[2]Diabet
and Fo
Siena
[3]St Vincent's Institute, Fitzroy 3065, Victoria, Australia
[4]D
Fl
[5]D

In total, only 4 (2 recent onset and 2 longstanding cases) of the 45 subjects included in the study by Coppieters et al showed insulitis, defined as more than 5 CD8+ T cells within the islets

Supplementary information provided for the nPOD cases show that of the 22 subjects below 20 years of age 16 (72%) had obvious signs of pancreatitis and inflammation in the exocrine pancreas, and of the 11 subjects above 20 years of age 7 (63%) showed affection of the exocrine pancreas.

sity of Siena
esville,
etherlands
uary 2, 2012

Pathologic Anatomy of the Pancreas in Juvenile Diabetes Mellitus

Willy Gepts, M.D., Brussels, Belgium

DIABETES *14*:619-33, October 1965.

Lesions of the exocrine pancreas. Lesions of the acinar tissue were frequent in the pancreases of juvenile diabetics (tables 5 and 6). In the acute cases, the findings comprised mostly focal or diffuse lesions of acute pancreatitis. These lesions were centered around the excretory canals, which were distended by the secretion product (dyschylia).

Pancreas
Vol. 27, No. 1, pp. 26–30

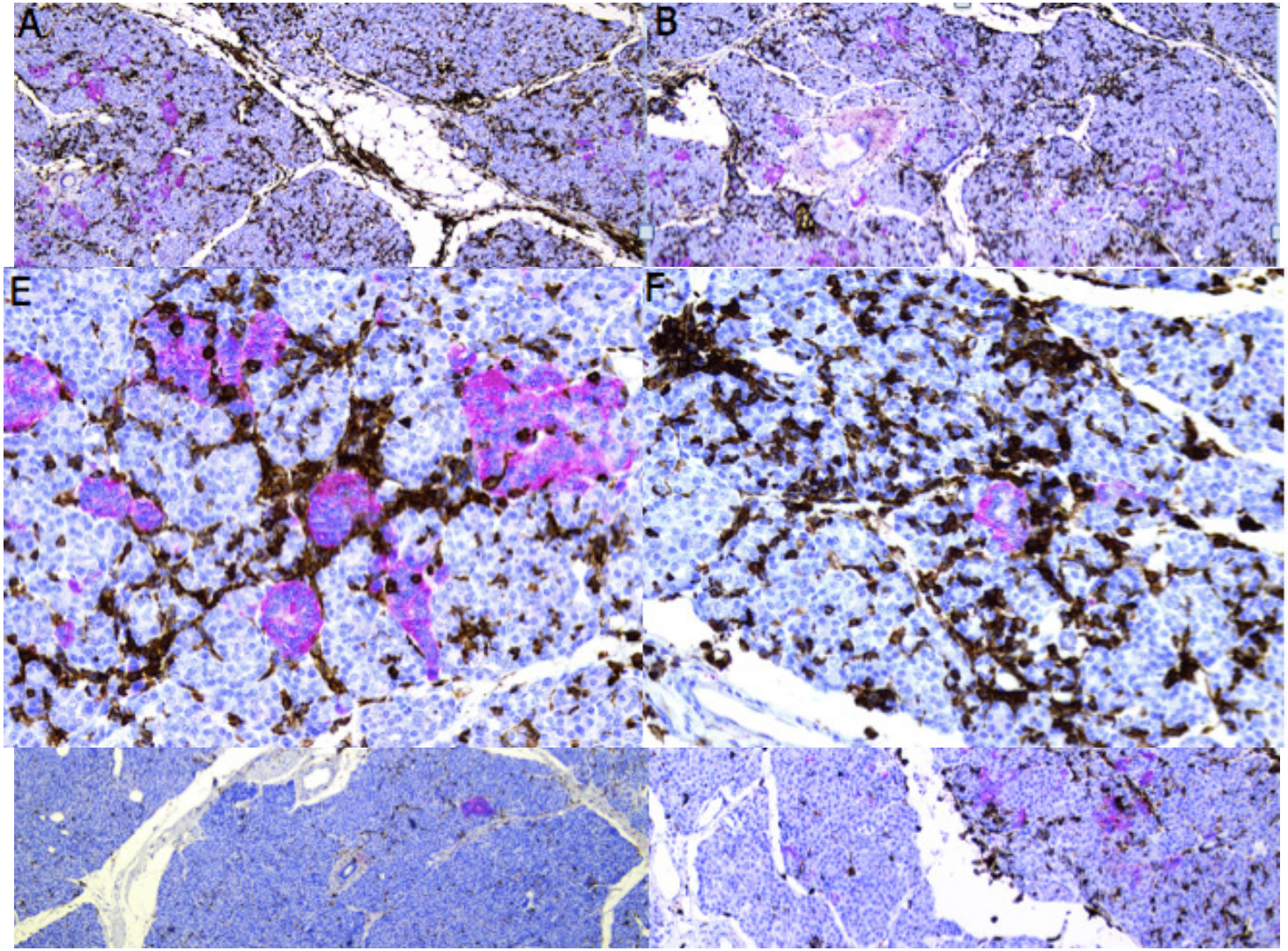
High Prevalence of Autoantibodies Against Carbonic Anhydrase II and Lactoferrin in Type 1 Diabetes: Concept of Autoimmune Exocrinopathy and Endocrinopathy of the Pancreas

*Takao Taniguchi, †Kazuichi Okazaki, *Motozumi Okamoto, *Shuji Seko, *Junnya Tanaka, ‡Kazushige Uchida, §Kazuaki Nagashima, §Takeshi Kurose, §Yuichiro Yamada, ‡Tsutomu Chiba, and §Yutaka Seino

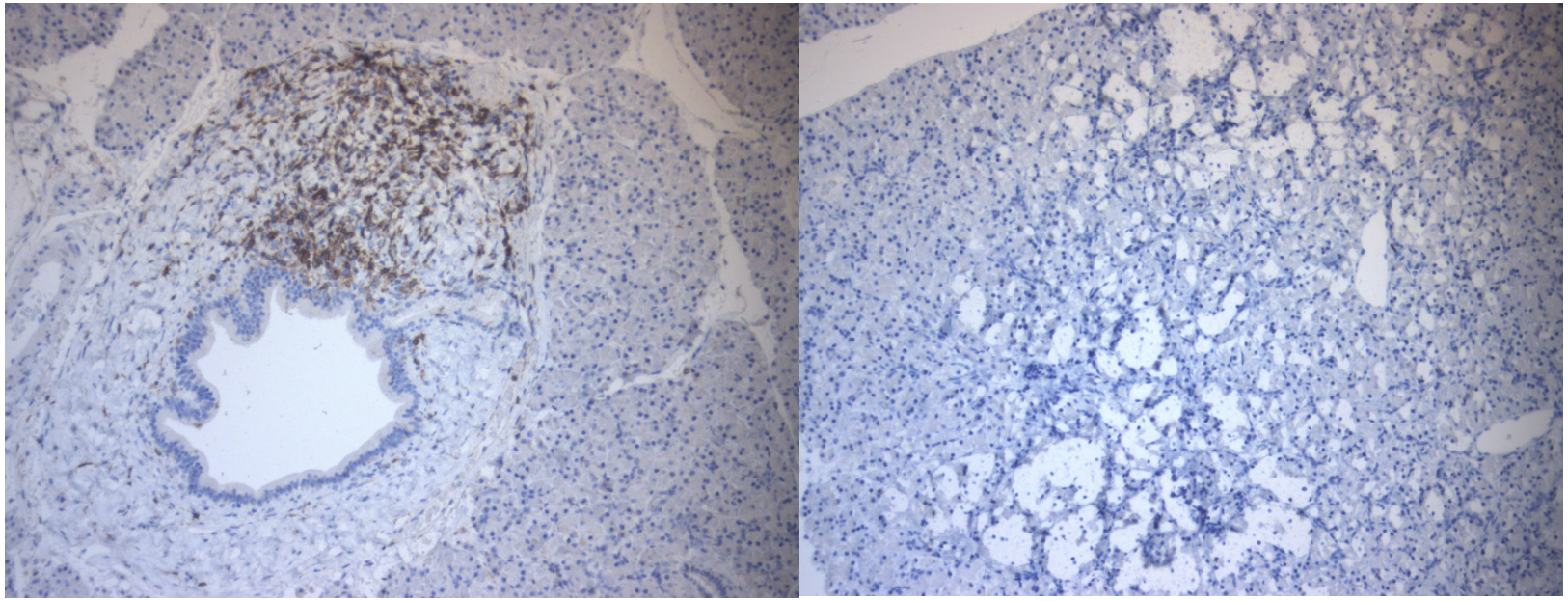
**Department of Internal Medicine, Ohtsu Red Cross Hospital, Shiga, Japan, †The Third Department of Internal Medicine, Kansai Medical University, Osaka, Japan, ‡Department of Endoscopic Medicine and Gastroenterology, Kyoto University Faculty of Medicine, Kyoto, Japan, and §Department of Diabetes and Clinical Nutrition, Kyoto University Faculty of Medicine, Kyoto, Japan*

Introduction: Dysfunction of the exocrine as well as the endocrine pancreas has been reported in type 1 diabetes. Lymphocytic infiltration of the exocrine pancreas is observed in approximately half of Japanese type 1 diabetic patients. **Aims:** To investigate the involvement of autoimmunity against the exocrine pancreas in type 1 diabetes. **Methodology:** We examined autoantibodies against human carbonic anhydrase II (ACA) and lactoferrin (ALF), antigens in the pancreatic duct cells and the pancreatic acinus, respectively, in 43 type 1 diabetic patients and 20 type 2 diabetic patients using the enzyme-linked immunosorbent assay method. **Results:** Of 43 type 1 diabetic patients, ACA was detected in 28 patients (65%) and ALF was detected in 29 patients (67%). One or both of the antibodies were detected in 33 type 1 diabetic patients (77%). In contrast, neither ACA nor ALF were detected in type 2 diabetic patients. **Conclusions:** The high prevalence of both ACA and ALF strongly suggests the involvement of autoimmunity against the exocrine pancreas as well as the endocrine pancreas in some type 1 diabetic patients. We propose that these conditions be referred to as autoimmune exocrinopathy and endocrinopathy of the pancreas. **Key Words:** type 1 diabetes, exocrine gland, autoantibody, autoimmune pancreatitis

CD45+ cells infiltrate the human pancreas at onset of T1D (human T1D 2 days after first symptoms)

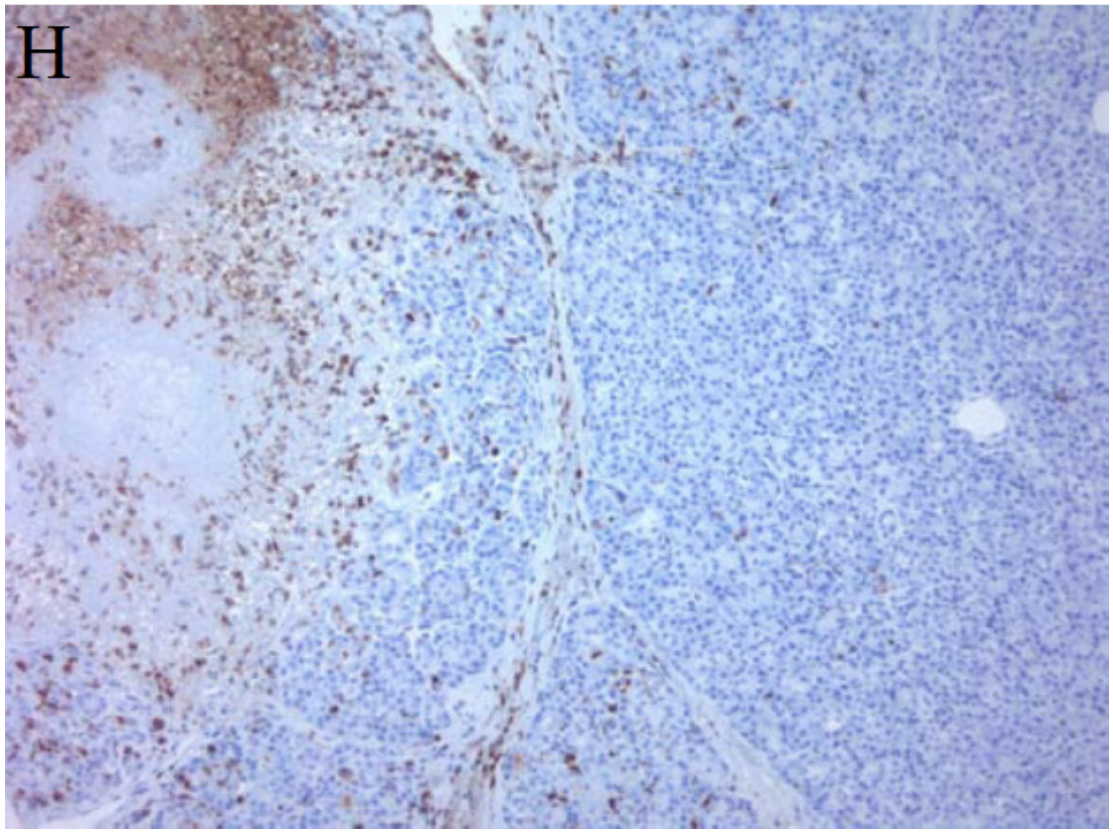


Human T1D 6 wks after onset



Human: Acute onset T1D

Necrotic lesions and accumulation of neutrophil granulocytes in one lobe but not in the adjacent lobe



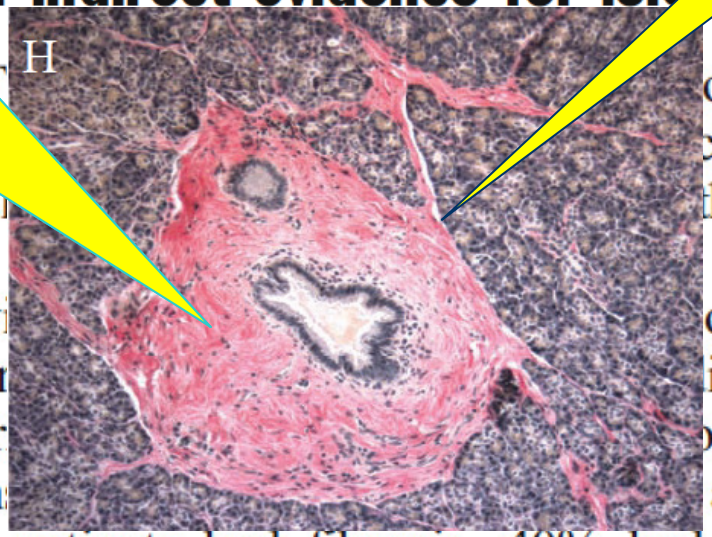
Diabetologia (2005) 48: 2221–2228
DOI 10.1007/s00125-005-1949-2

Where new islets are formed!?

End-stage of periductal inflammation

han · A. E. Butler · R. A. Rizza ·

a cell apoptosis in patients wit long-standing es: indirect evidence for islet regeneration?



ore commonly
cts, which had
than in control
subjects.

As previ observed pancreatic fibr iabetes. In its mildest for nly, but when more exten areas. All type 1 diabetic patients had fibrosis, 40% had periductal fibrosis (grade 1 or 2) only, and 60% of cases had periductal fibrosis extending to interlobular pancreas. In contrast, only one of the control subjects had any pancreatic fibrosis detected, which was also periductal, but was less extensive than in any of the diabetic patients.

Noninvasive imaging of pancreatic islet inflammation in type 1A diabetes patients

Jason L. Gaglia,[1,2,3] Alexander R. Guimaraes,[2,4] Mukesh Harisinghani,[2,4] Stuart E. Turvey,[3] Richard Jackson,[3] Christophe Benoist,[1,3,5] Diane Mathis,[1,3,5,6] and Ralph Weissleder[2,4,5,6,7]

[1]Department of Pathology, Harvard Medical School, Boston, Massachusetts, USA. [2]Center for Systems Biology, Massachusetts General Hospital, Boston, Massachusetts, USA. [3]Joslin Diabetes Center and Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA. [4]Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA. [5]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. [6]Harvard Stem Cell Institute, Cambridge, Massachusetts, USA. [7]Department of Systems Biology, Harvard Medical School, Boston, Massachusetts, USA.

The Journal of Clinical Investigation

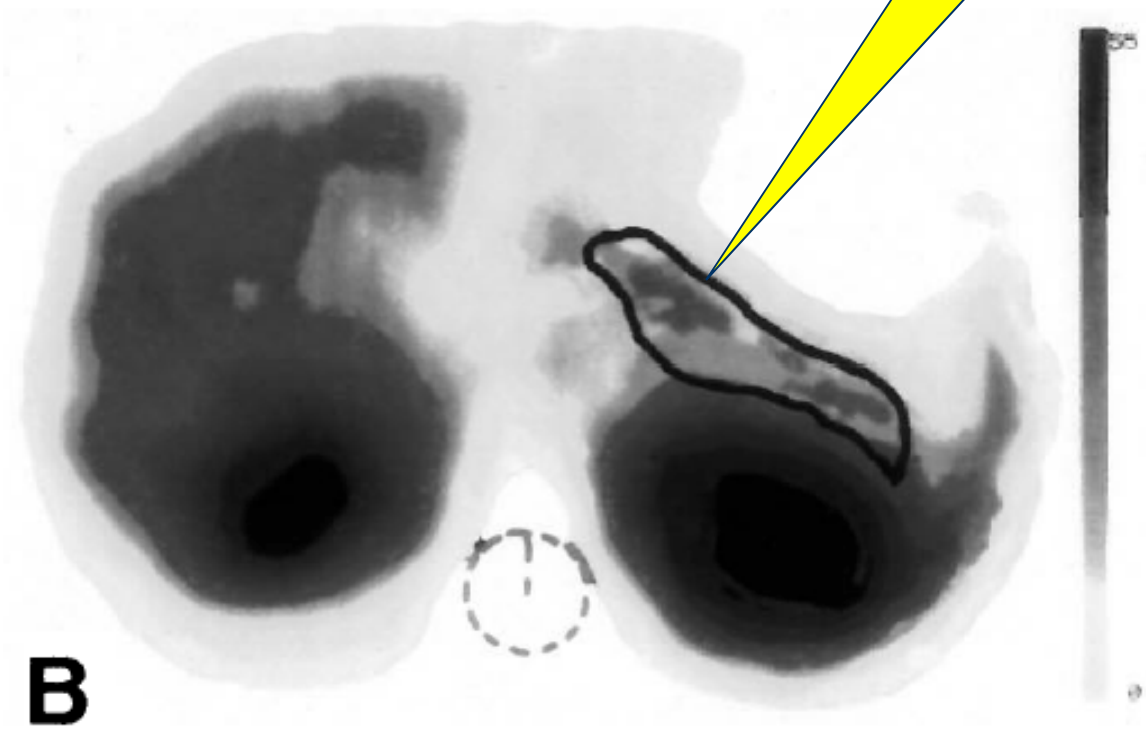
While our primary focus was on indicators of vascular integrity and leukocyte infiltration, we also measured pancreas volume, given that pancreatic atrophy is a characteristic observation in long-standing T1D, as evidenced by examination of pancreas volume at autopsy, by ultrasound, by CT, or via MRI (10–13). To control for the influences of body build on pancreatic volume, we calculated a pancreatic volume index (PVI) by dividing the pancreatic volume by body-surface area (12, 14). Mean PVI of the patients was 31% less than that of the controls (Figure 1).

Prognostic relevance of pancreatic uptake of technetium-99m labelled human polyclona in patients with type 1 diabetes

Raffaella Barone[1], Enrica Procaccini[1], Marco Chianelli[1], Alessio Annovazzi[1], Vincenzo F ...awa[2], Giampaolo Nardi[1], Giuseppe Ronga[1], Paolo Pozzilli[2,3], IMDIAB Study Group*, Alberto ...e[1]

Eur J Nucl Me ...(1998) 25:503–508

Inflammation and vascular-leakage in entire lobes, "**not insulitis**"

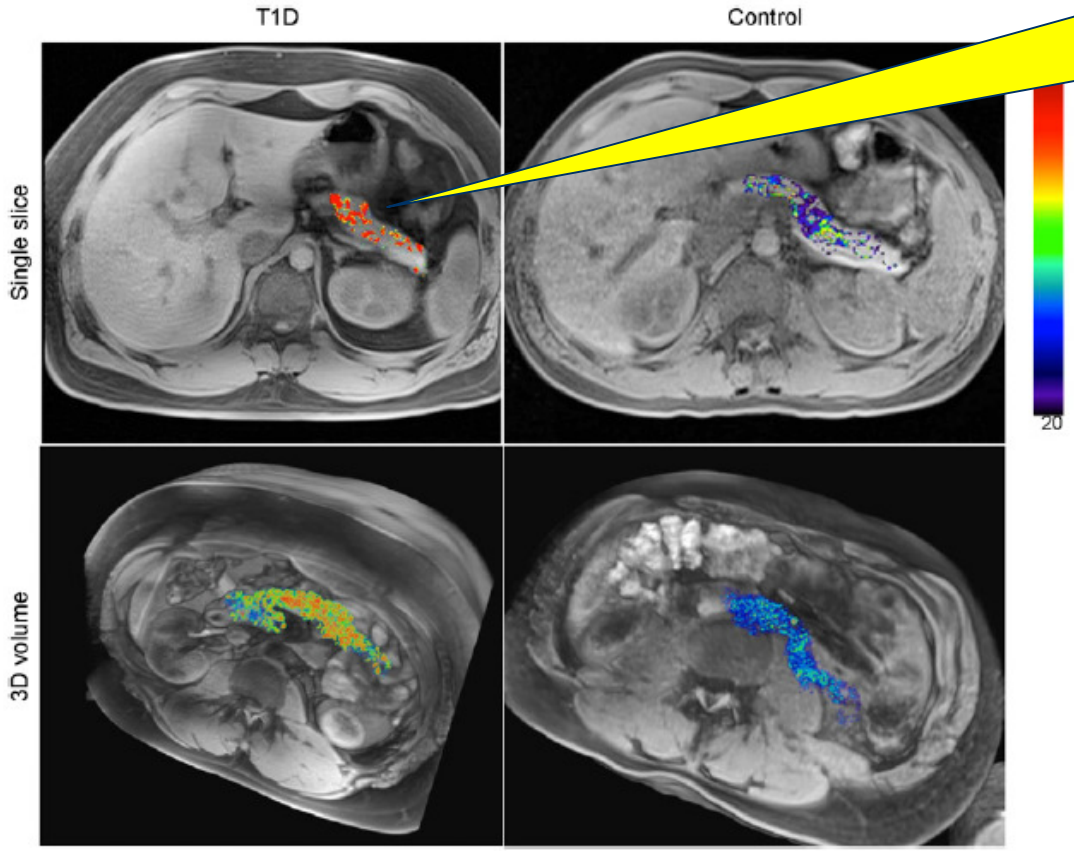


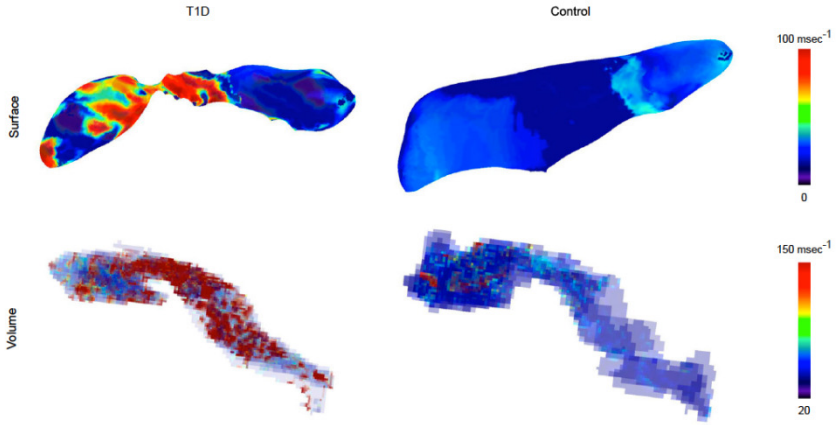
Noninvasive mapping of pancreatic inflammation in recent-onset type-1 diabetes patients

Jason L. Gaglia[a,1], Mukesh Harisinghani[b,c,1], Iman Aganj[c], Gregory R. Wojtkiewicz[b]
Christophe Benoist[d,e], Diane Mathis[d,e,2,3], and Ralph Weissleder[b,c,2,3]

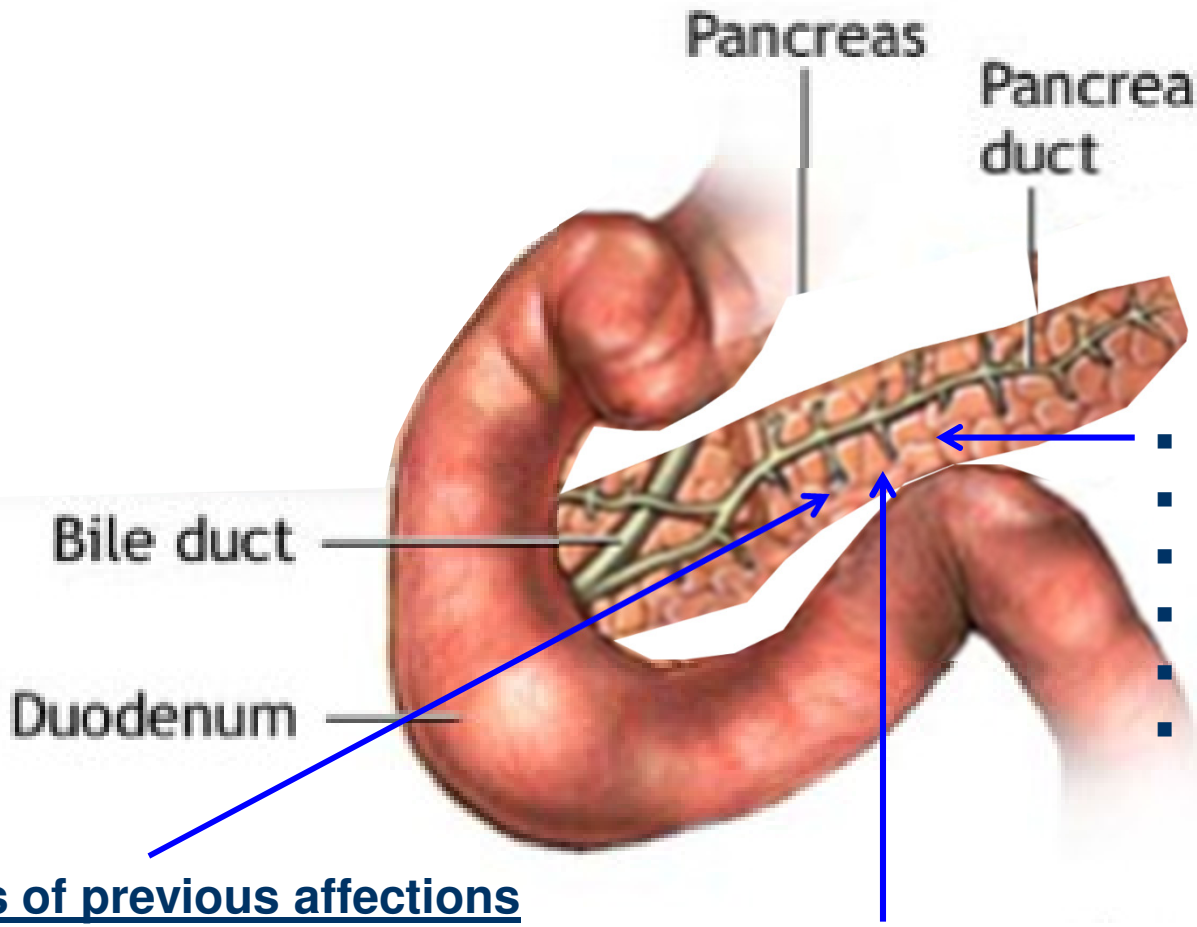
PNAS

Inflammation and vascular-leakage in entire lobes,
"not insulitis"





T1D: a focal disease affecting both the exocrine and the endocrine pancreas



Ongoing disease

- Inflammation
- Local pancreatitis
- Dying beta cells
- Hydroptic degeneratio
- Islet bleedings
- Discreet insulitis

Signs of previous affections

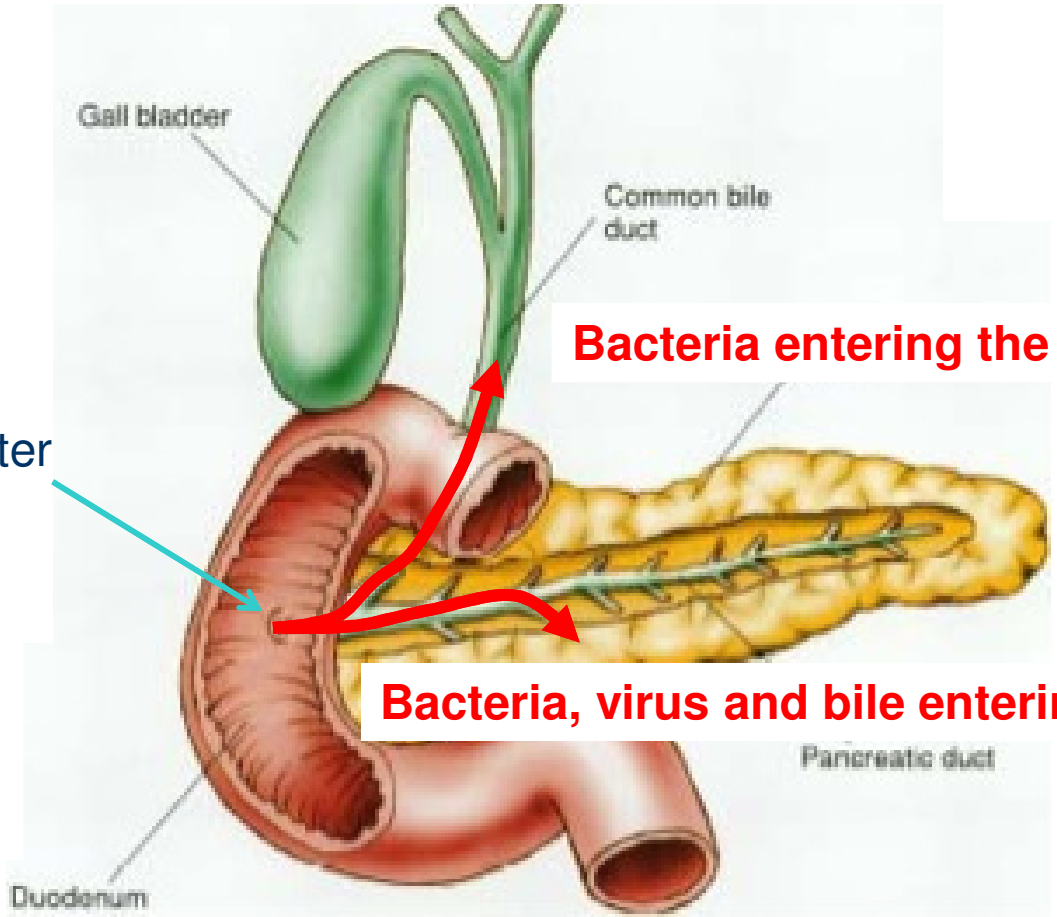
- Ductal fibrosis
- No inflammation
- Islets without beta cells

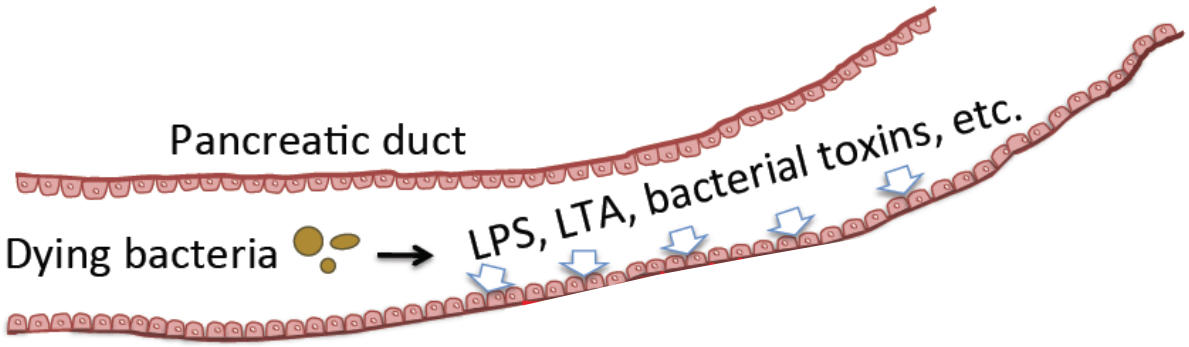
Normal pancreas without any signs of disease

- Normal exocine parenchyma
- Normal number of islet
- Normal number of beta cells

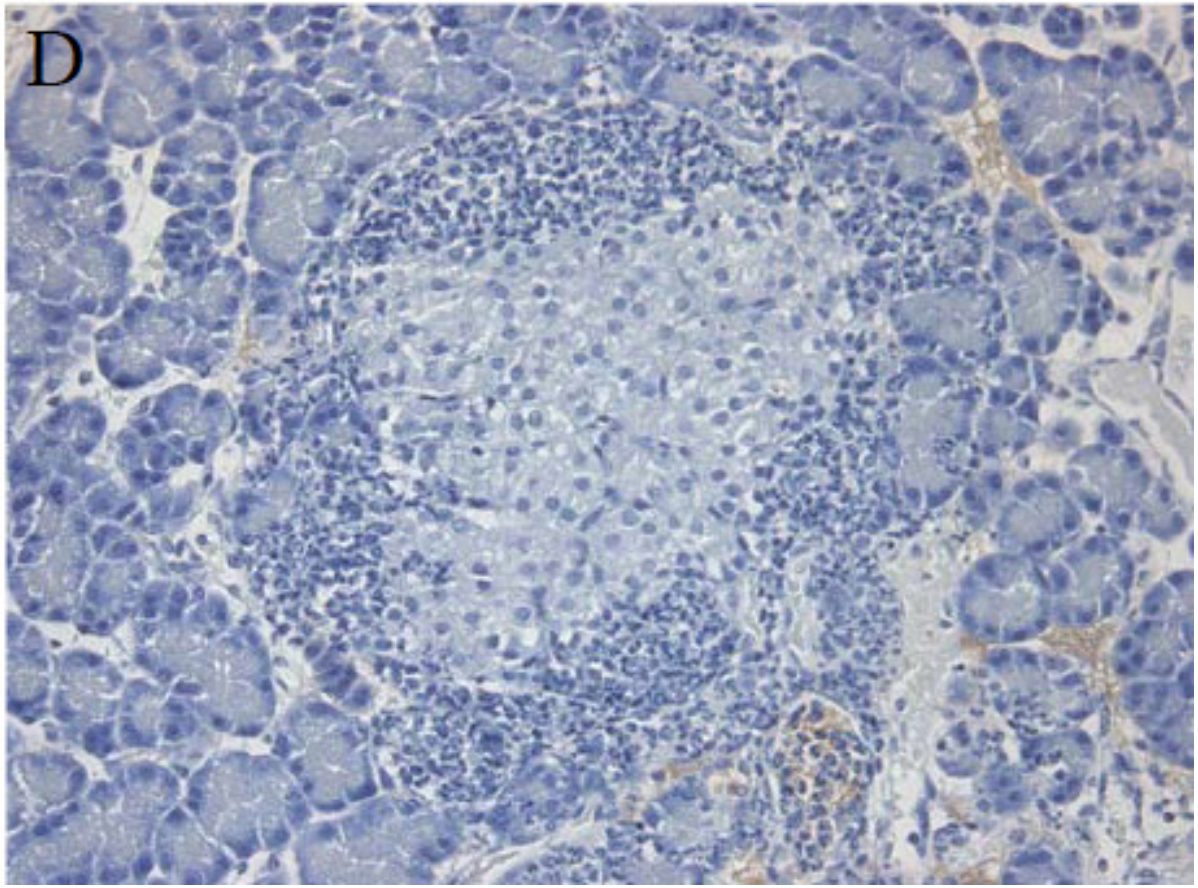
Hypothesis

T1D is an organ specific inflammatory disease triggered by repeated episodes of bacterial translocation from the intestine to the pancreatic ducts leading to a progressive loss of the insulin producing cells.

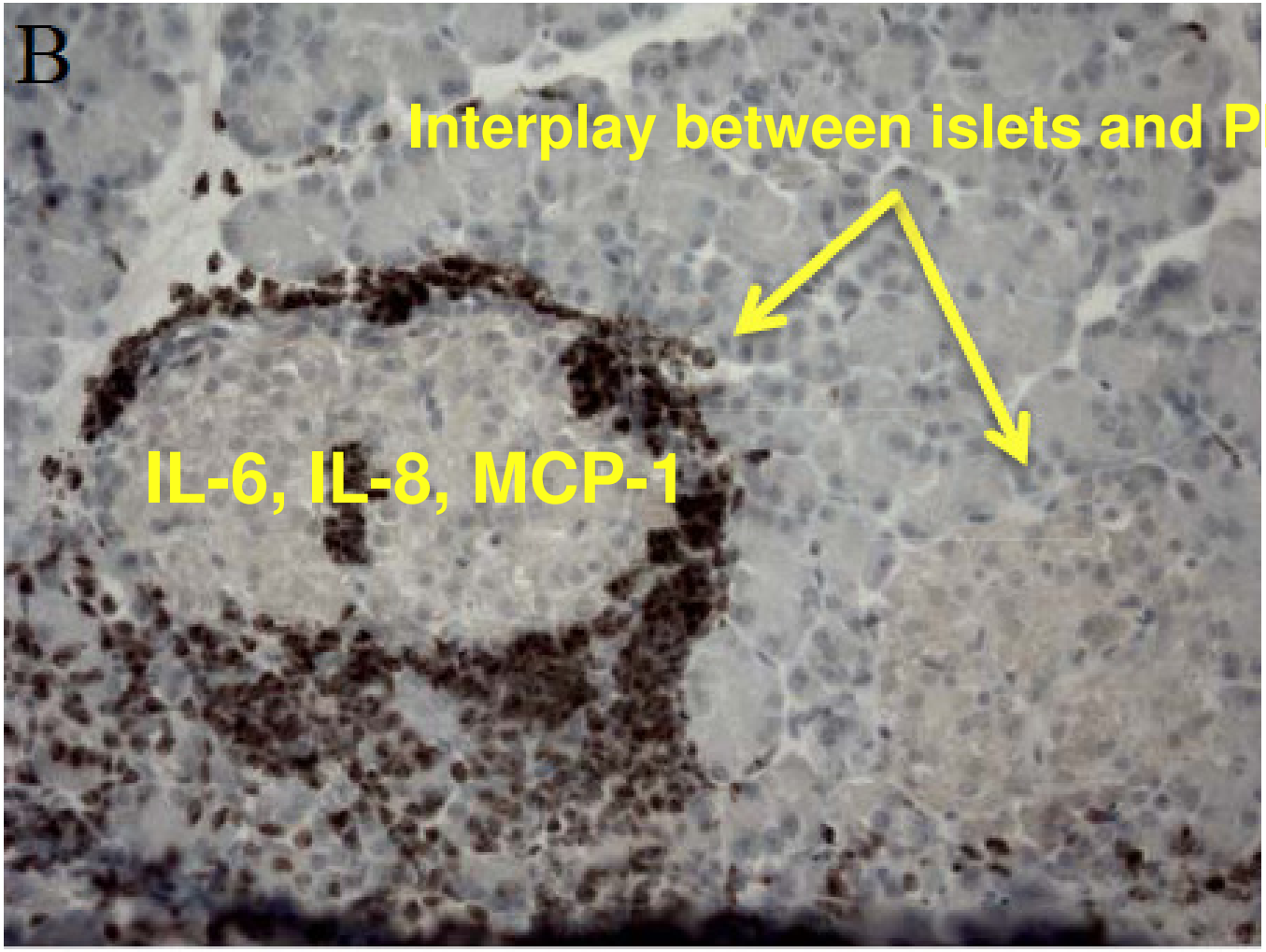

Gall bladder
Common bile duct
Papilla Vater
Bacteria entering the bile system
Bacteria, virus and bile entering the pancreas
Pancreatic duct
Duodenum
ADAM.

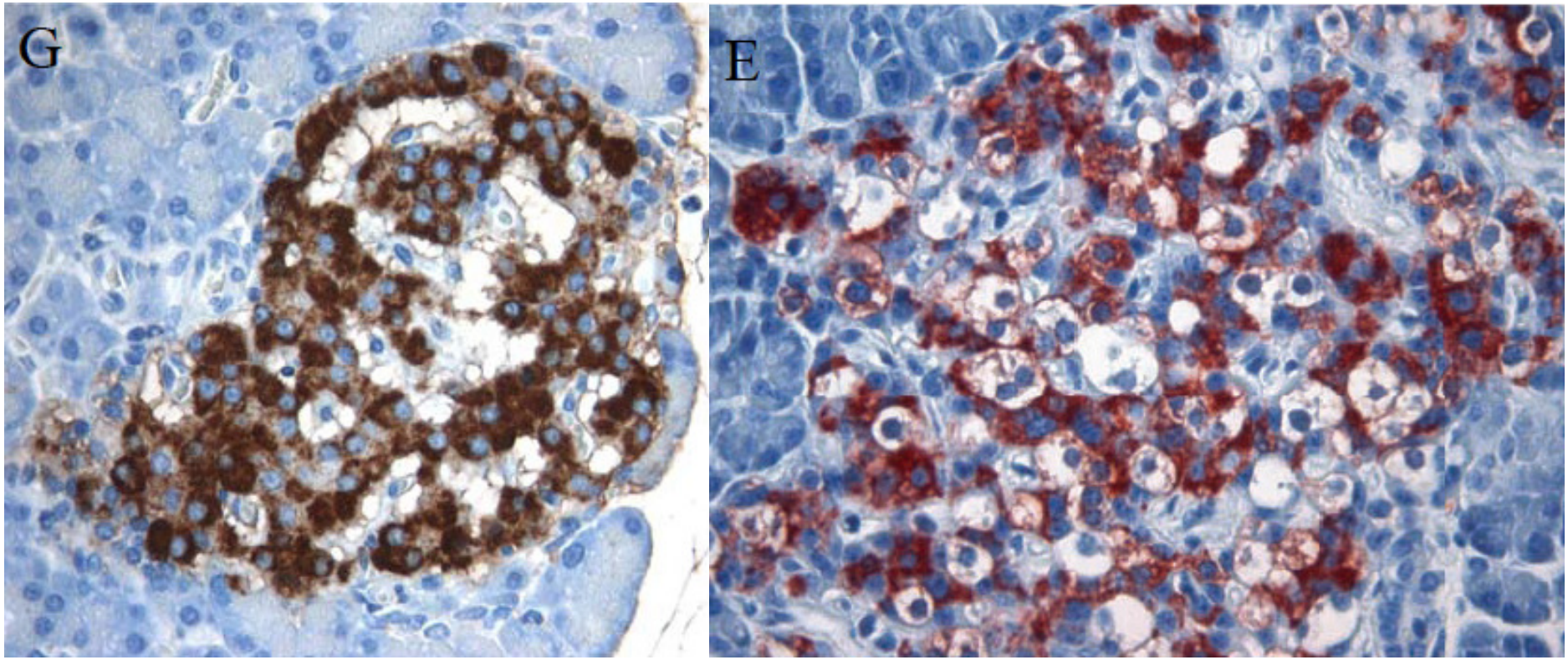

Pancreatic duct
Dying bacteria
LPS, LTA, bacterial toxins, etc.

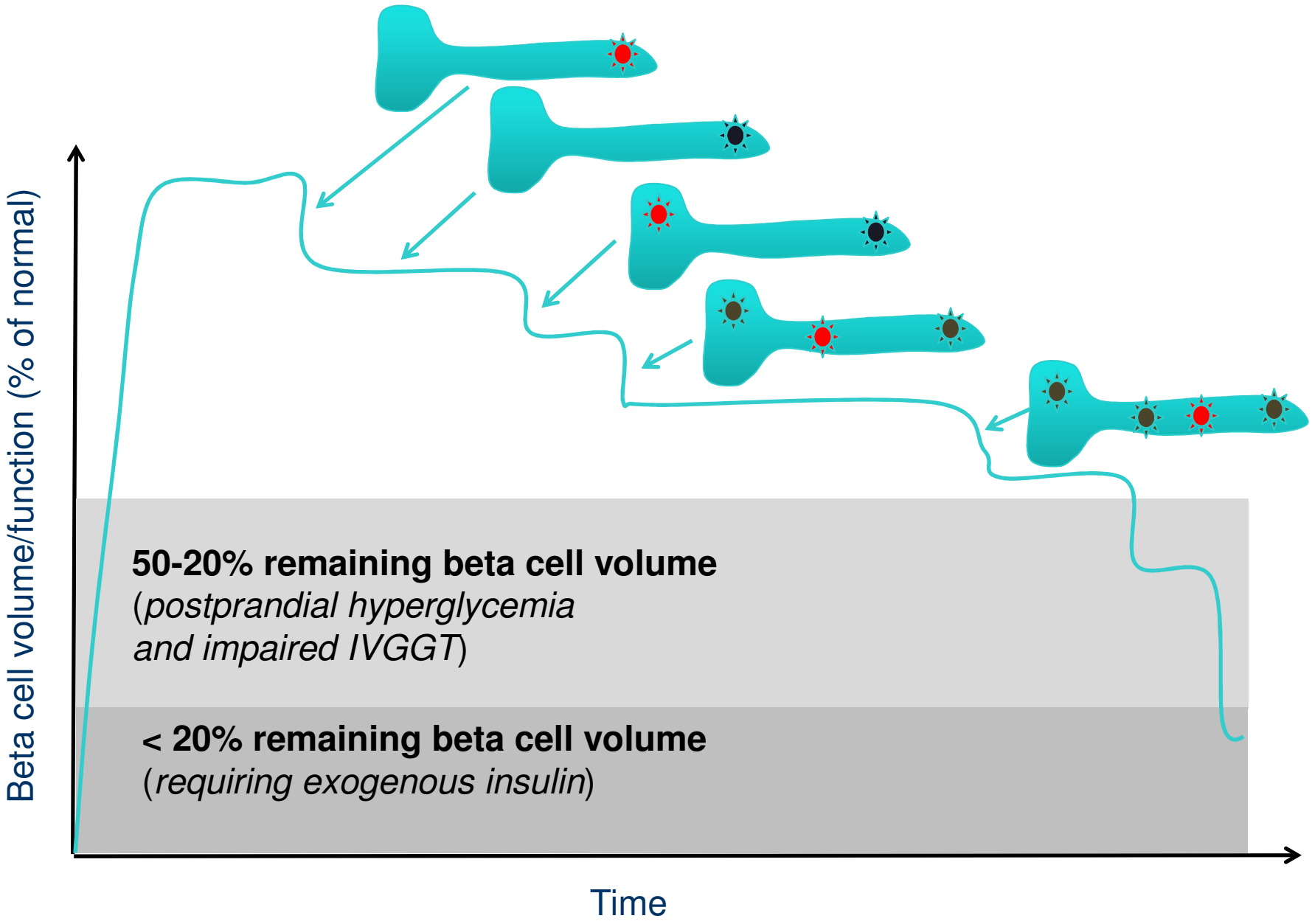
Rat 4 h after installation of dying bacteria in the ductal system



Rat 5 h after installation of dying bacteria in the ductal system




G
E

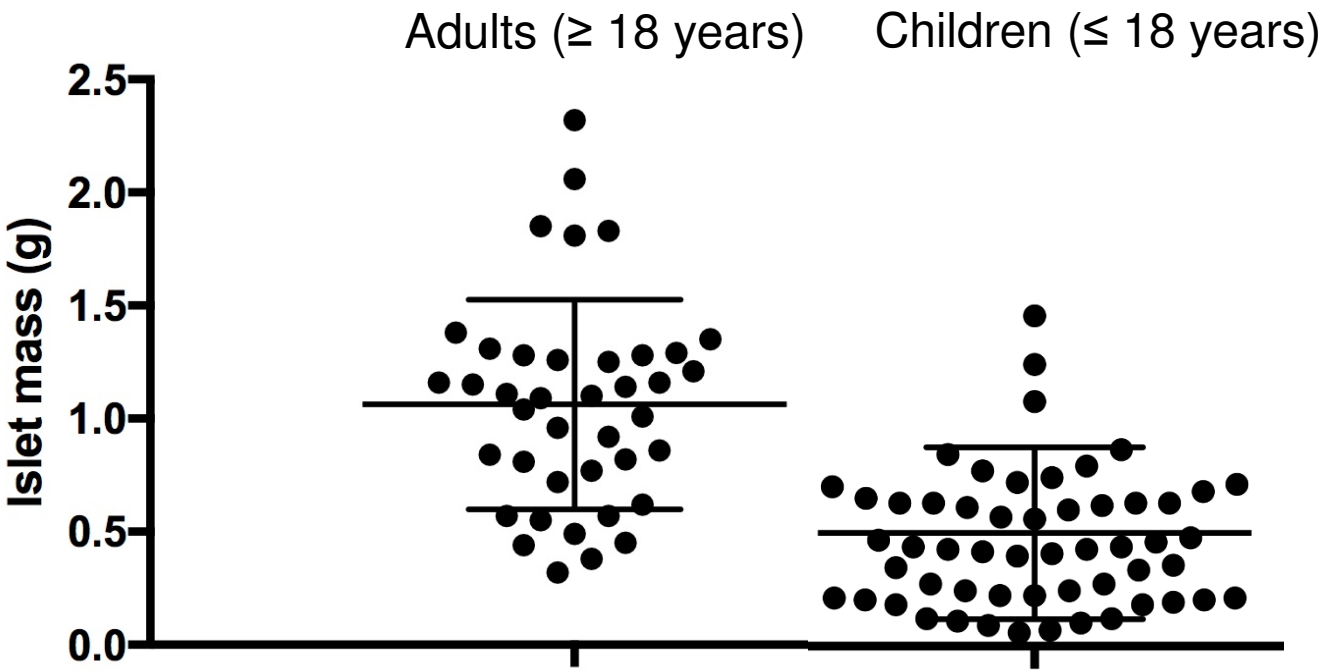

Beta cell volume/function (% of normal)
50-20% remaining beta cell volume
(postprandial hyperglycemia
and impaired IVGGT)
< 20% remaining beta cell volume
(requiring exogenous insulin)
Time

A QUANTITATIVE ESTIMATION OF THE PANCREATIC ISLET TISSUE[1]

By ROBERTSON F. OGILVIE

(From the Pathological Departments of the University and Royal Infirmary, Edinburgh)

Quarterly Journal of Medicine 1937: 28: 287- 300



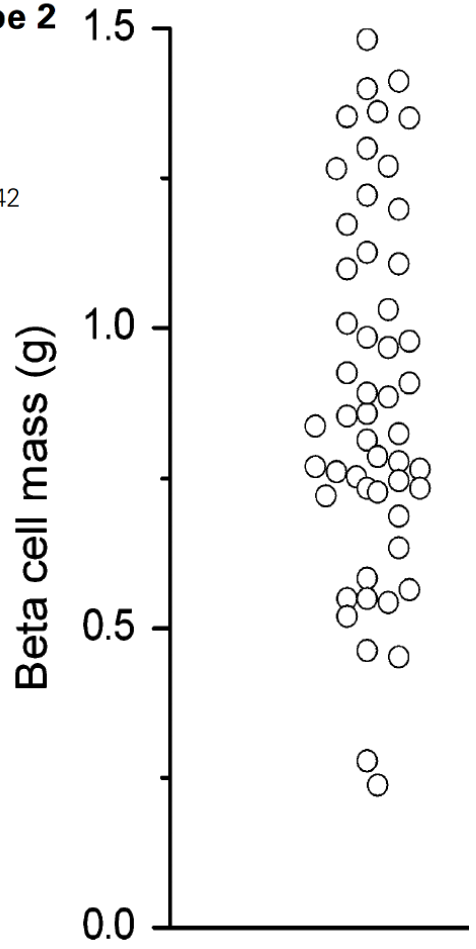
ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326

Pancreatic β-cell mass in European subjects with type 2 diabetes

J. Rahier,[1] Y. Guiot,[1] R. M. Goebbels,[1] C. Sempoux[1] and J. C. Henquin[2]

Diabetes, Obesity and Metabolism, **10** (Suppl. 4), 2008, 32–42



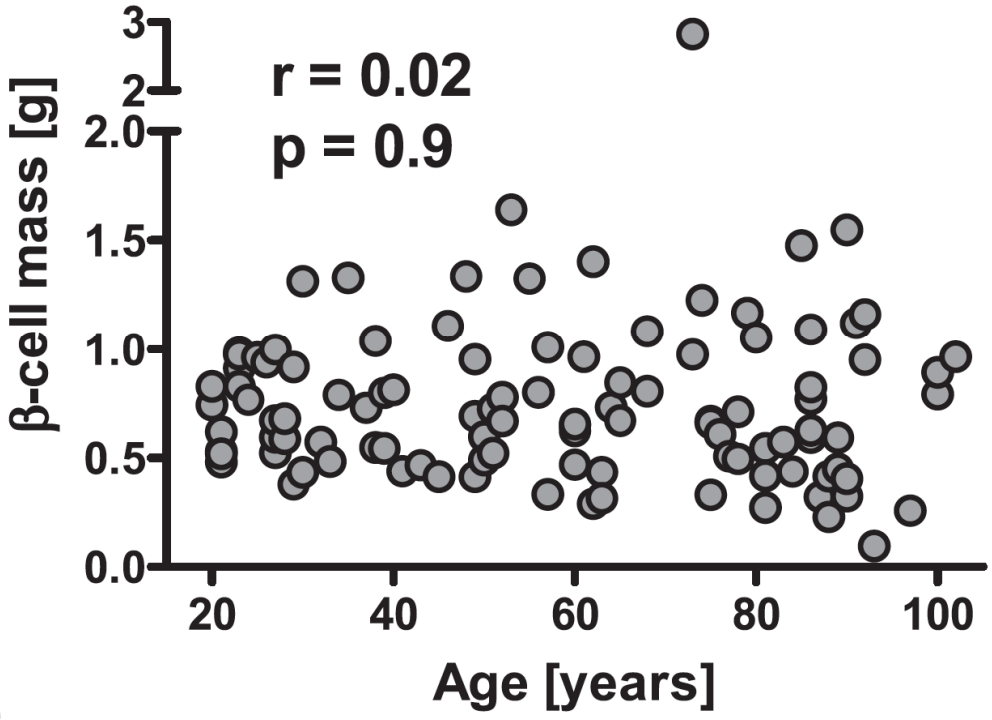
β-Cell Mass and Turnover in Humans

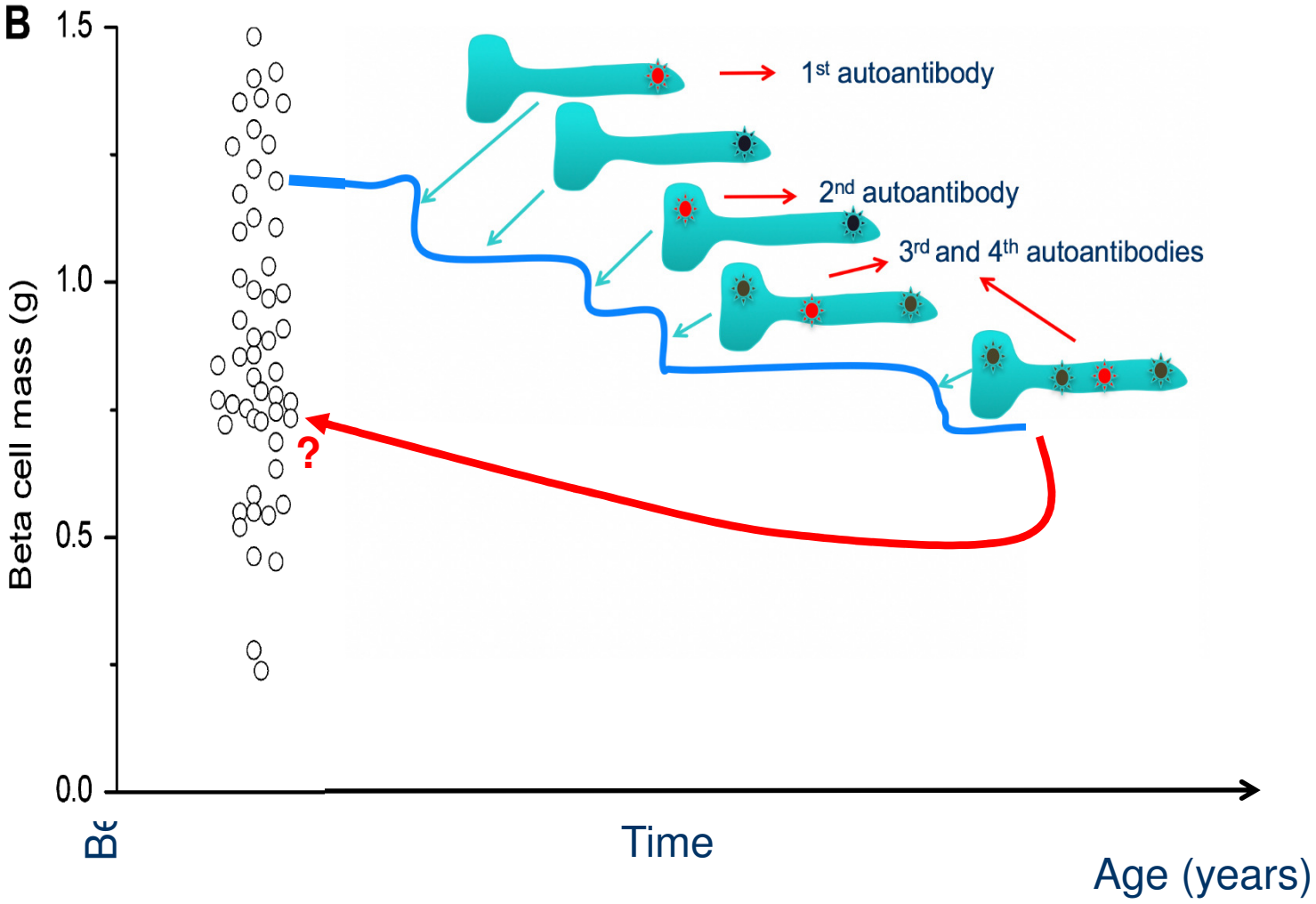
Effects of obesity and aging

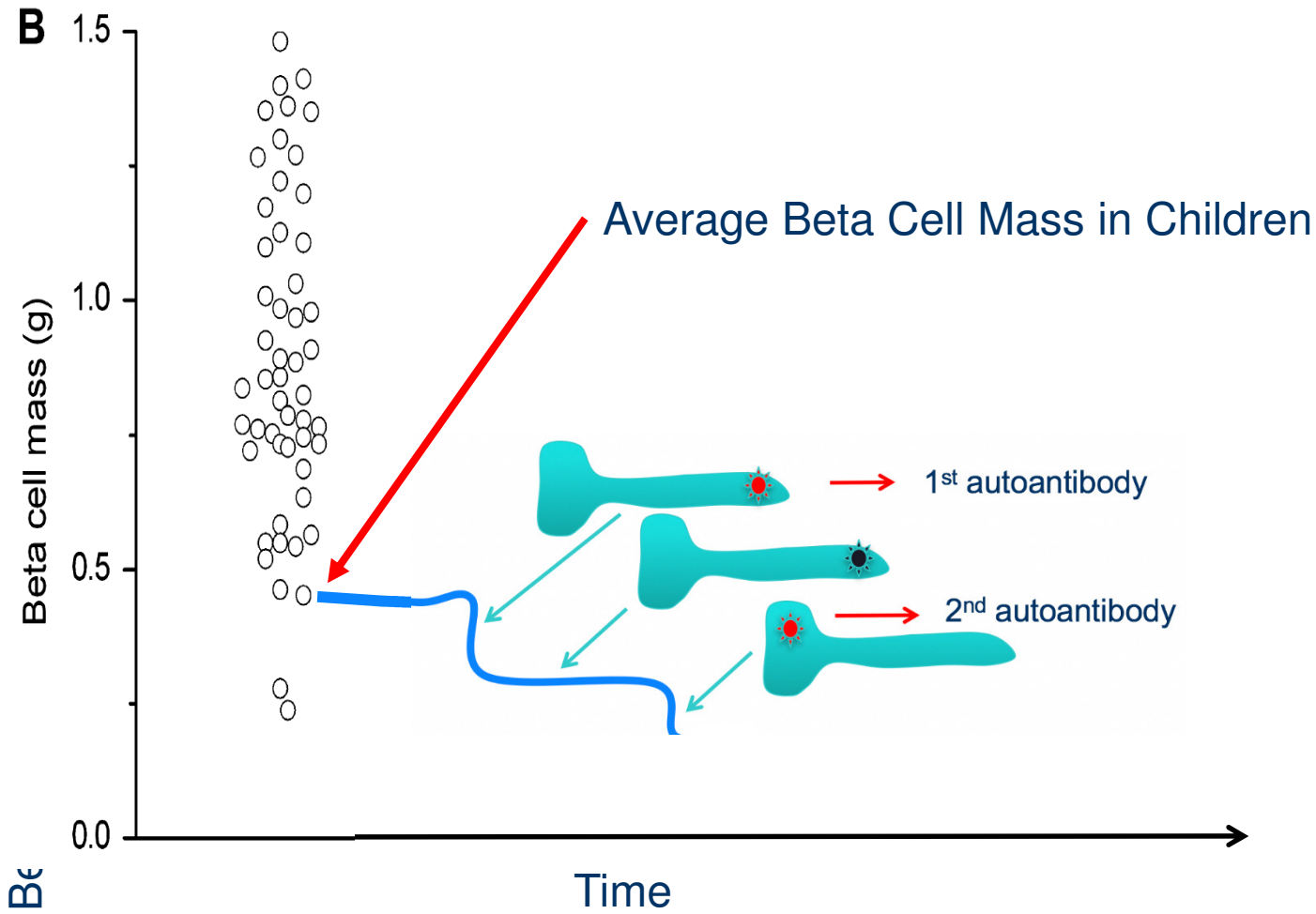
Yoshifumi Saisho, md[1]
Alexandra E. Butler, md[1]
Erica Manesso, phd[1]
David Elashoff, phd[2]
Robert A. Rizza, md[3]
Peter C. Butler, md[1]

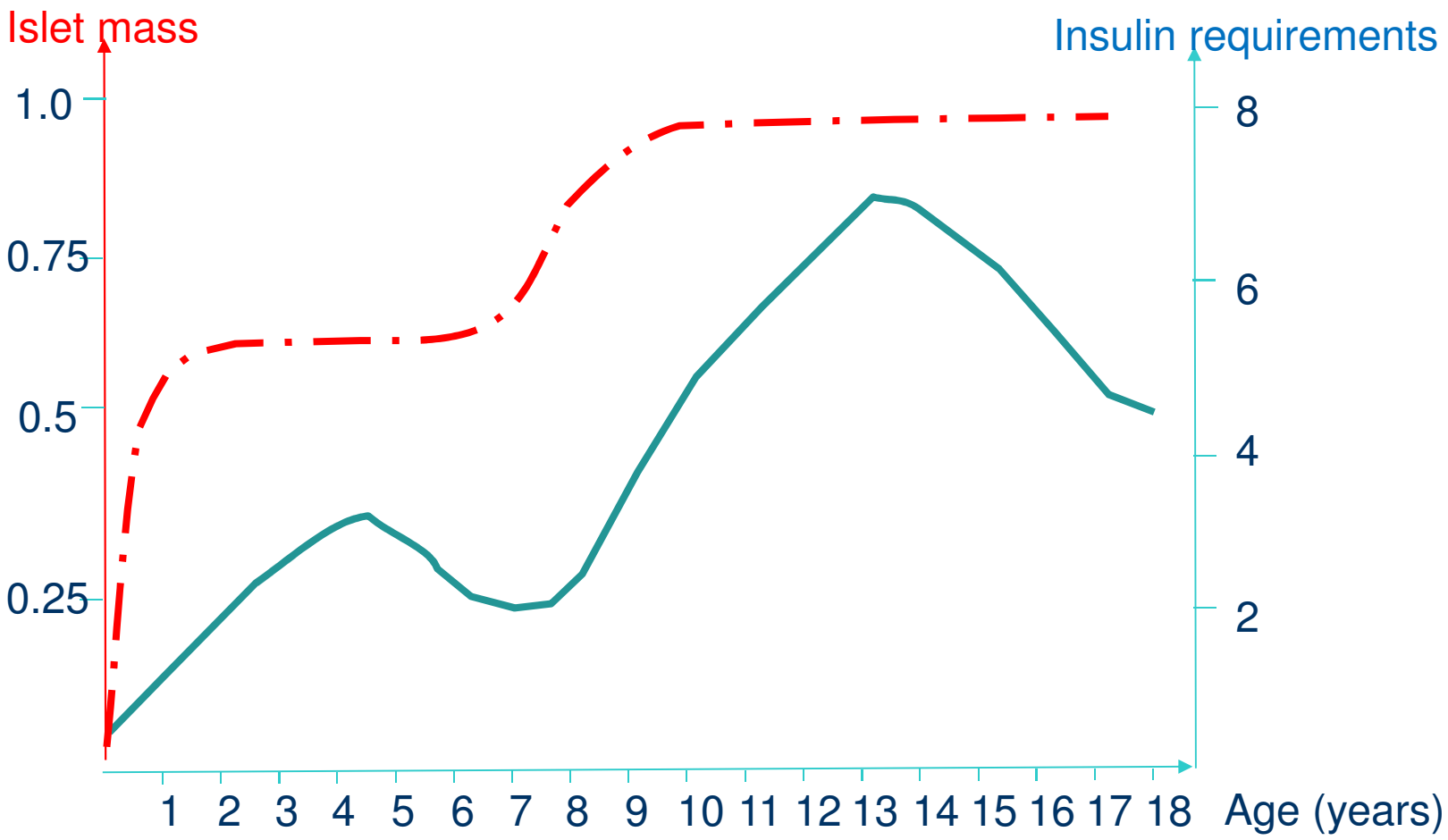
with age (3) but providing β-cell turnover.

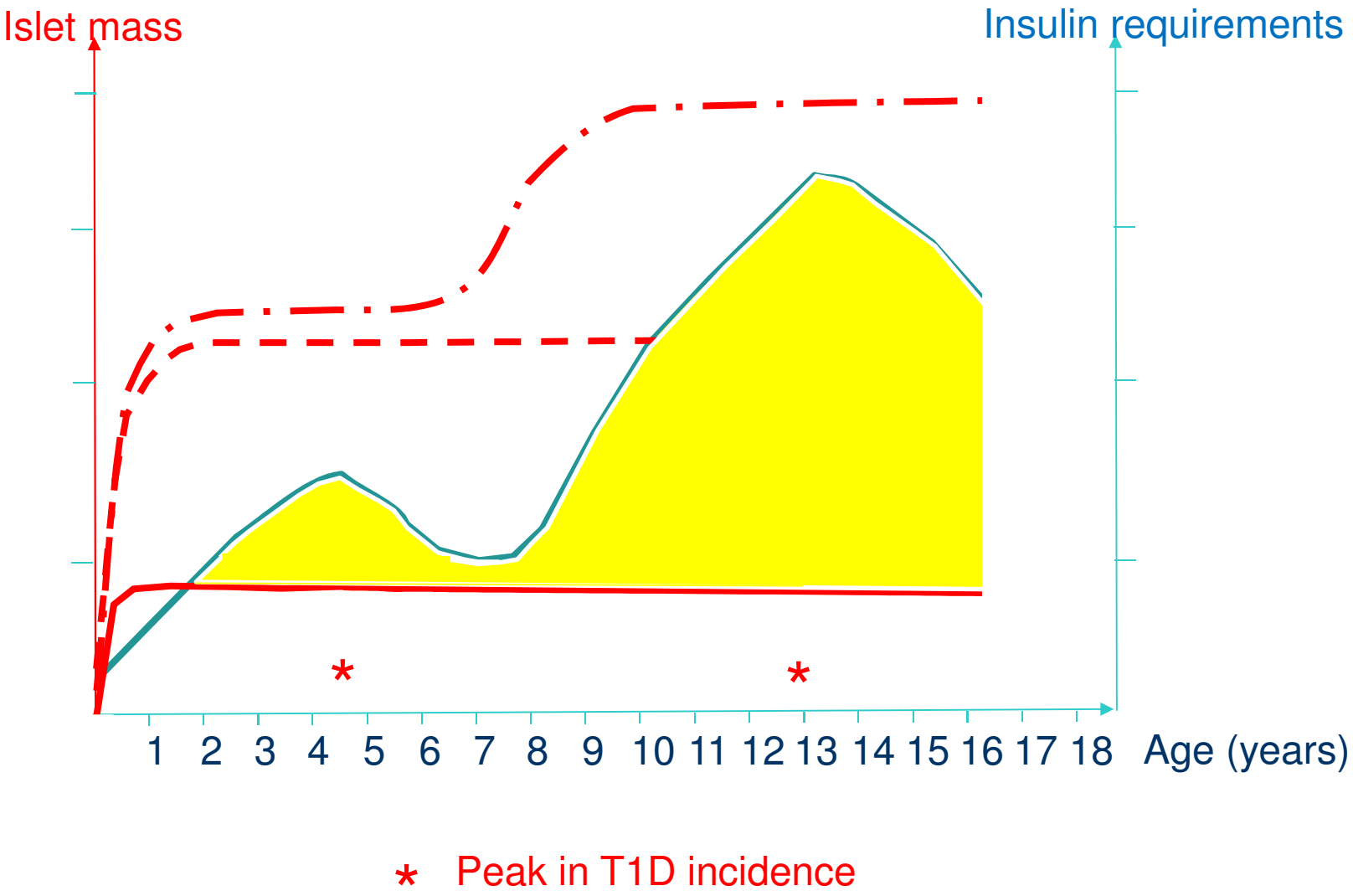
Diabetes Care 36:111–117, 2013

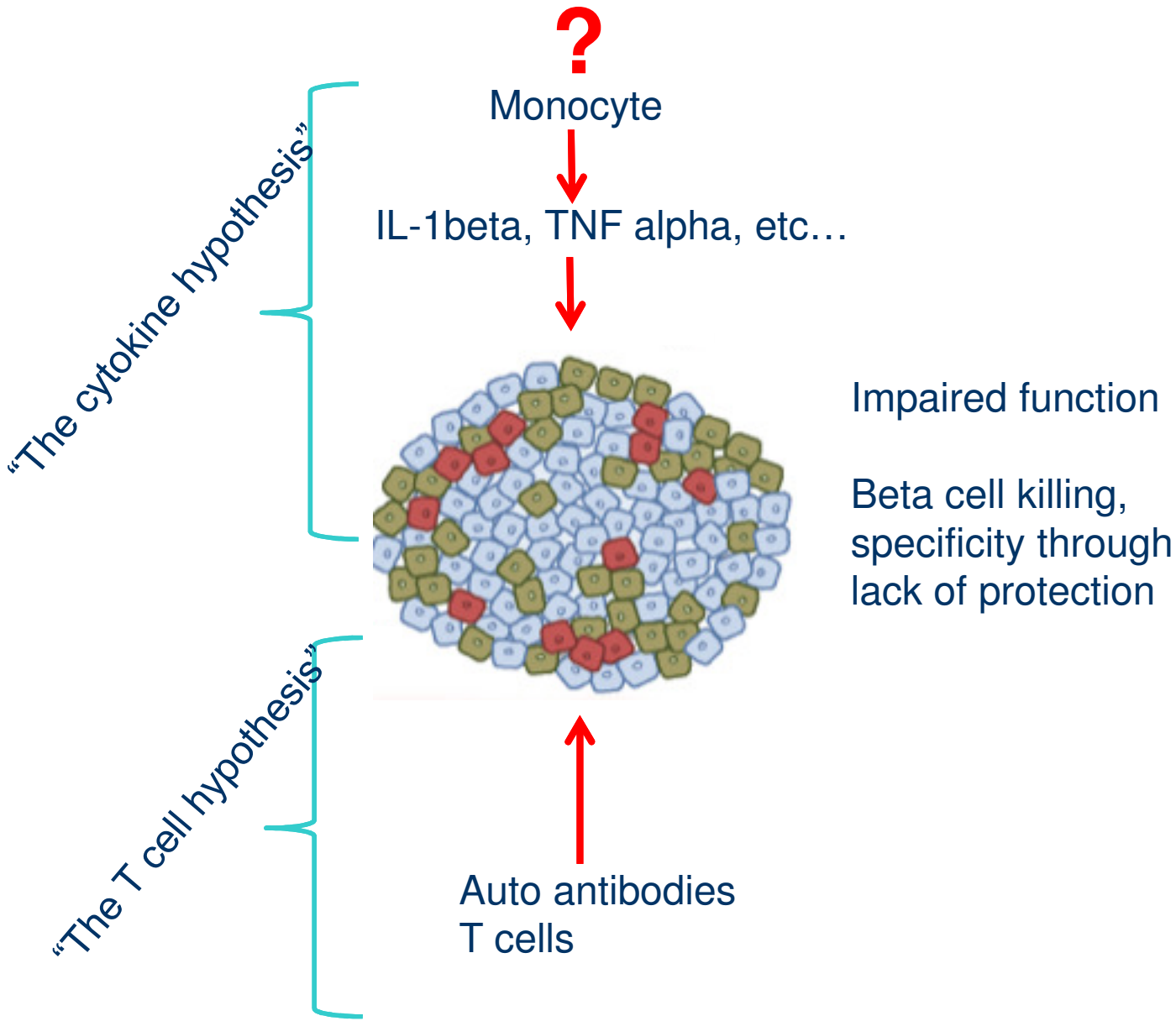


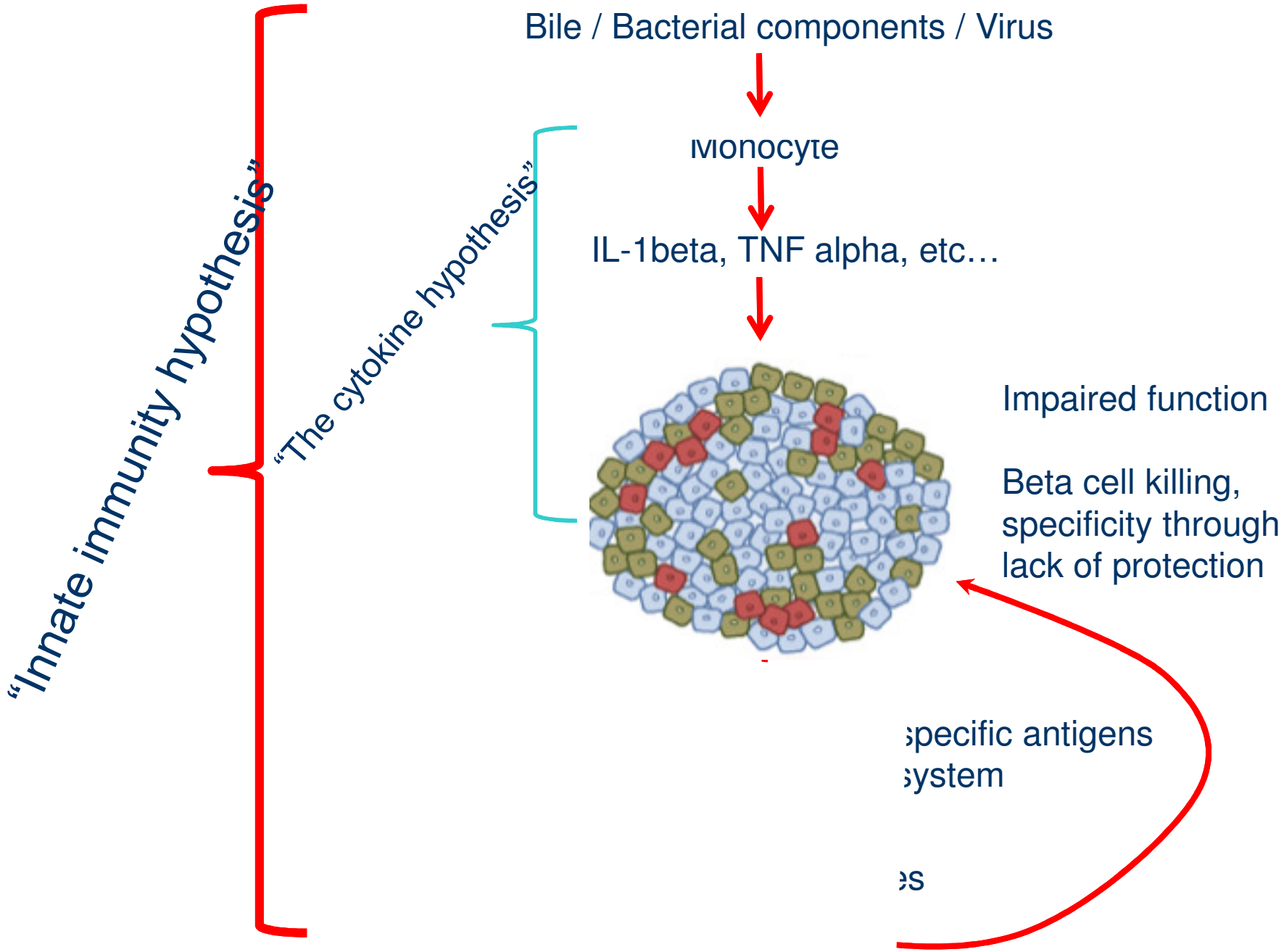

B
1.5
1.0
0.5
0.0
Beta cell mass (g)
1st autoantibody
2nd autoantibody
3rd and 4th autoantibodies
?
Time
Age (years)


B
1.5
1.0
0.5
0.0
Beta cell mass (g)
Average Beta Cell Mass in Children
1st autoantibody
2nd autoantibody
Time


Islet mass
Insulin requirements
1.0
0.75
0.5
0.25
8
6
4
2
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Age (years)


Islet mass
Insulin requirements
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Age (years)
* Peak in T1D incidence


?
Monocyte
IL-1beta, TNF alpha, etc…
"The cytokine hypothesis"
Impaired function
Beta cell killing, specificity through lack of protection
"The T cell hypothesis"
Auto antibodies
T cells


"Innate immunity hypothesis"
"The cytokine hypothesis"
Bile / Bacterial components / Virus
Monocyte
IL-1beta, TNF alpha, etc…
Impaired function
Beta cell killing, specificity through lack of protection
specific antigens
system
es

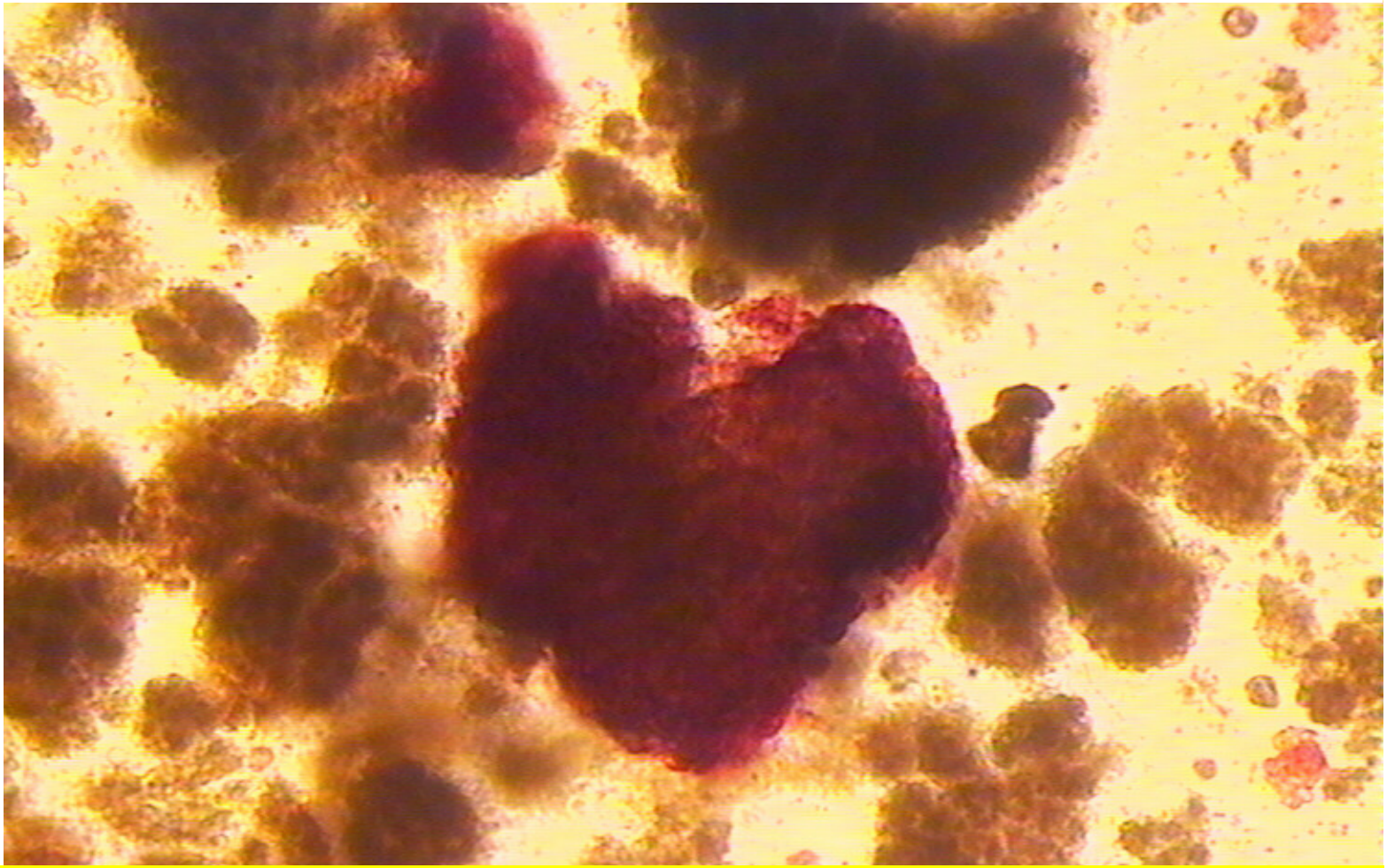
Why “all” T1D interventional studies fail?

The underlying hypothesis is not correct!

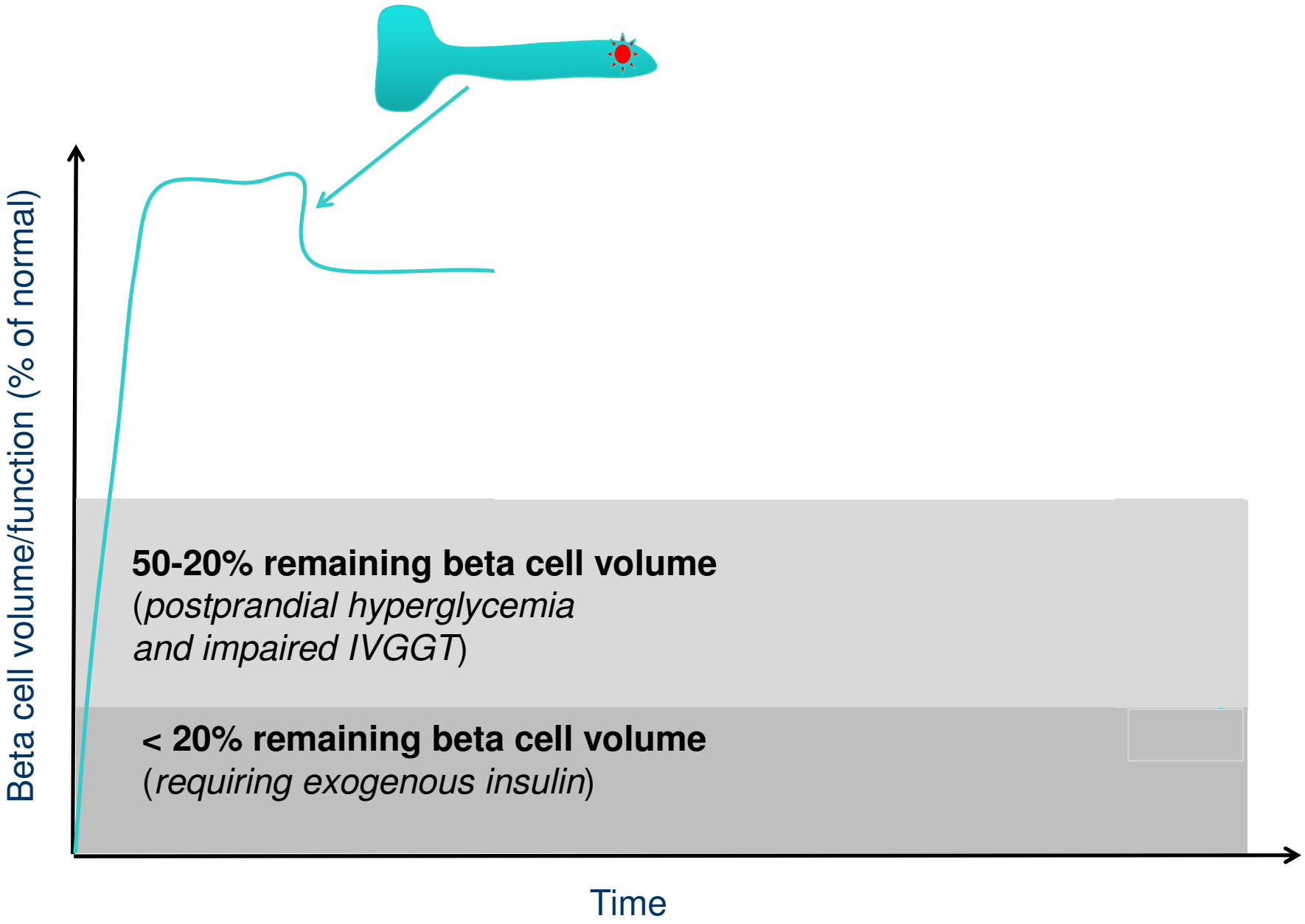
T1D is not a beta cell specific autoimmune disease mediated by autoreactive T cells.

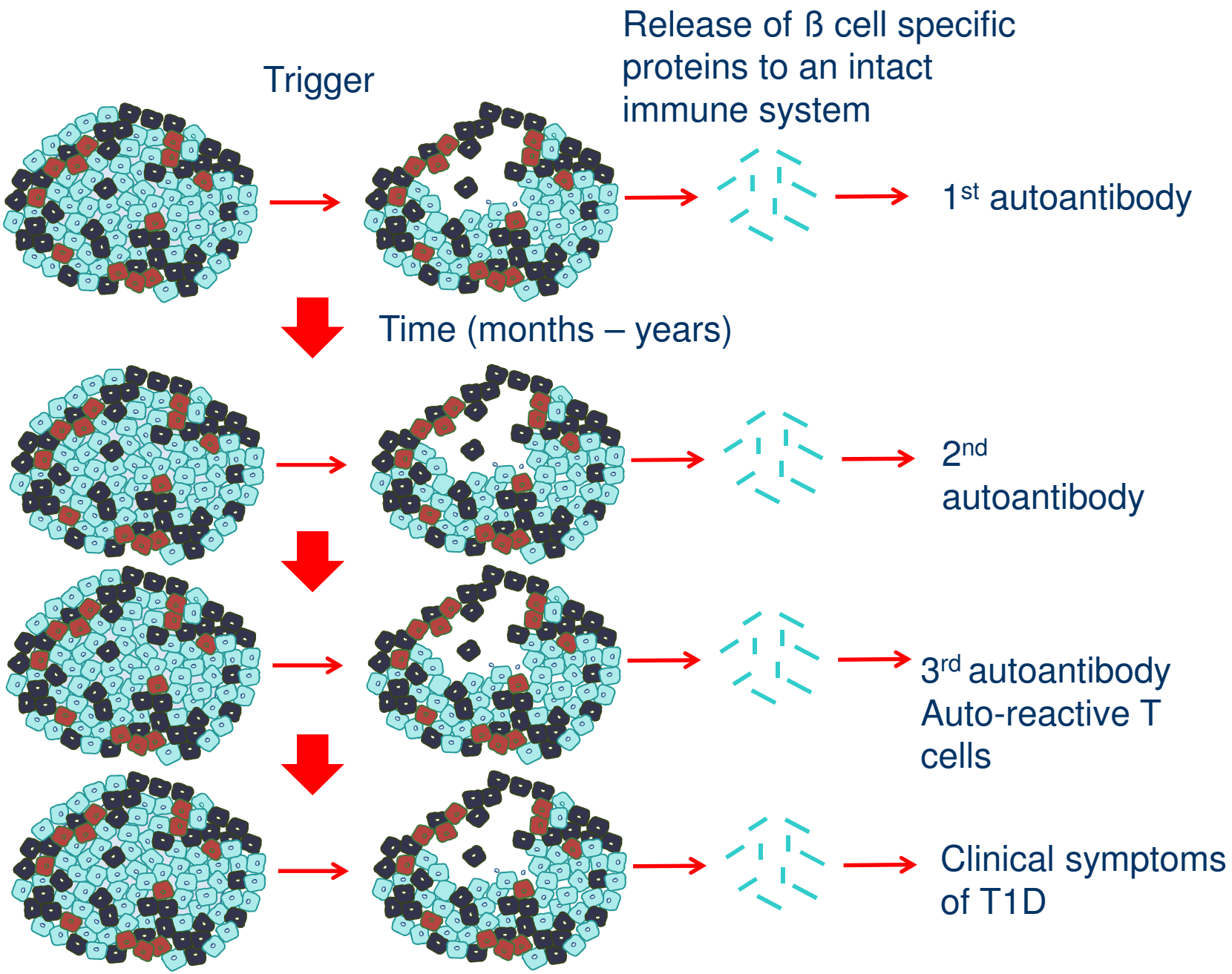
T1D is an organ specific innate inflammatory disease affecting the entire pancreas, potentially mediated by translocation of bacteria, viruses and bile from the intestine to the pancreatic ductal system.

The proposed model explains the “regional distribution of the disease within the pancreas” and includes the prevailing hypothesis for the etiology of T1D; the “cytokine hypothesis”, as well as superimposed “autoimmunity” and “glucose toxicity”!



The Nordic Network for Clinical Islet Transplantation
All national and international colleagues and friends
UU, UAS, VR, JDRF & NIH


Beta cell volume/function (% of normal)
50-20% remaining beta cell volume
(postprandial hyperglycemia
and impaired IVGGT)
< 20% remaining beta cell volume
(requiring exogenous insulin)
Time


Trigger
Release of ß cell specific proteins to an intact immune system
1st autoantibody
Time (months – years)
2nd autoantibody
3rd autoantibody
Auto-reactive T cells
Clinical symptoms of T1D

Human: Acute onset T1D

Neutrophil granulocytes accumulating in one lobe but not in the adjacent lobe