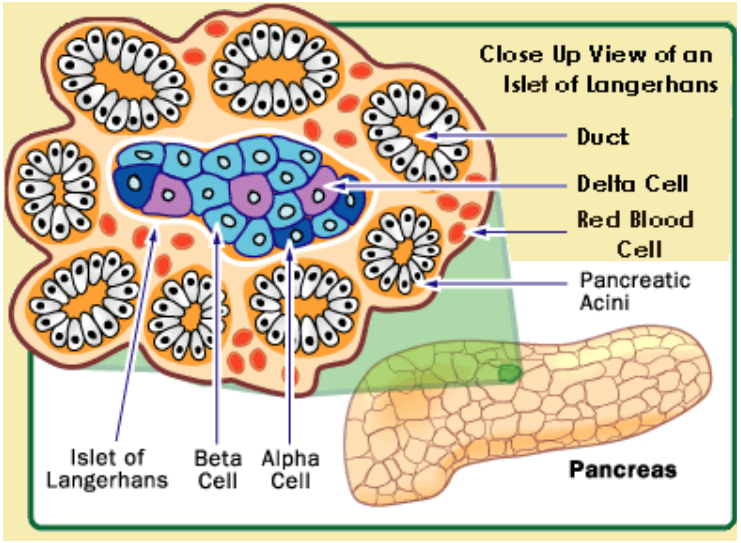
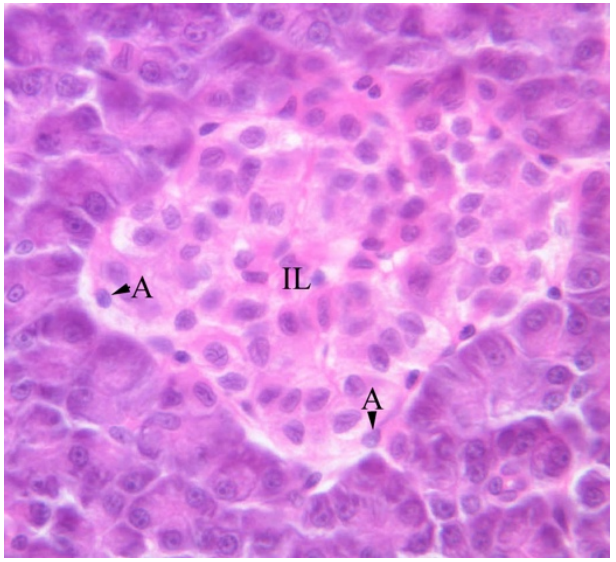
ENDOKRİN PANKREAS TÜMÖR DIŞI PATOLOJİLERİ:
DİABETES MELLİTUS





Prof. Dr. Işınsu Kuzu
Patoloji Anabilim Dalı

Dönem III
23 MART 2017

DİYABETES MELLİTUS

Ortak bulgusu hiperglisemi ile karakterli bir grup metabolik hastalık

Hiperglisemi sebebi insülin salınıımı veya/ve işlevi bozukluğudur.

Kronik hiperglisemi ile çoklu organ hasarları ve işlev bozuklukları ortaya çıkmaktadır.

TANI

- Rastgele ölçülen kan şekeri 200mg/dl den yüksek
- Açlık kan şekeri 126 mg/dl den fazla
- Anormal şeker yükleme testi sonuçları: standart karbonhidrat yüklemesini (75gr) takiben iki saat sonra 200 mg/dl den fazla kan şekeri olması.
- Glisiye Hemoglobin düzeyinin %6,5 dan yüksek olması

Sınıflama

- Tip 1 Diyabet: Pankreatik Beta hücre yıkımı ve **mutlak insülin eksikliği**. Tüm olguların %5-10 nu. 20 yaş altı kişilerin en sık sebebi
- Tip 2 Diyabet: Periferde insüline direnç ve beta hücrelerinin yetersiz insülin yapmasıyla oluşan **"bağıl insülin yetmezliği"**. Olguların %90-95'inde Erişkinlerde sık ancak obezite ile birlikte gençlerde artış

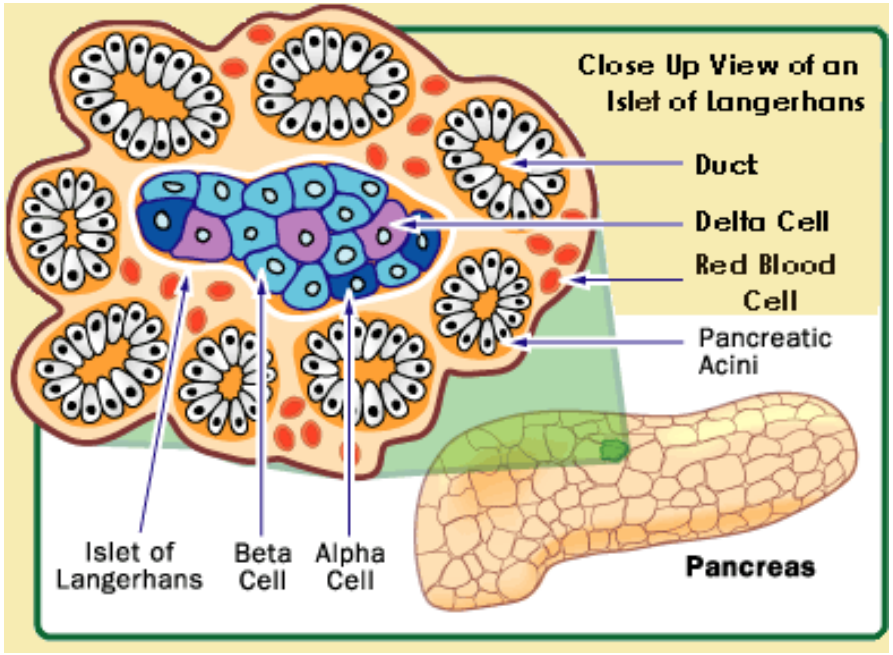
Table 24-6. Classification of Diabetes Mellitus

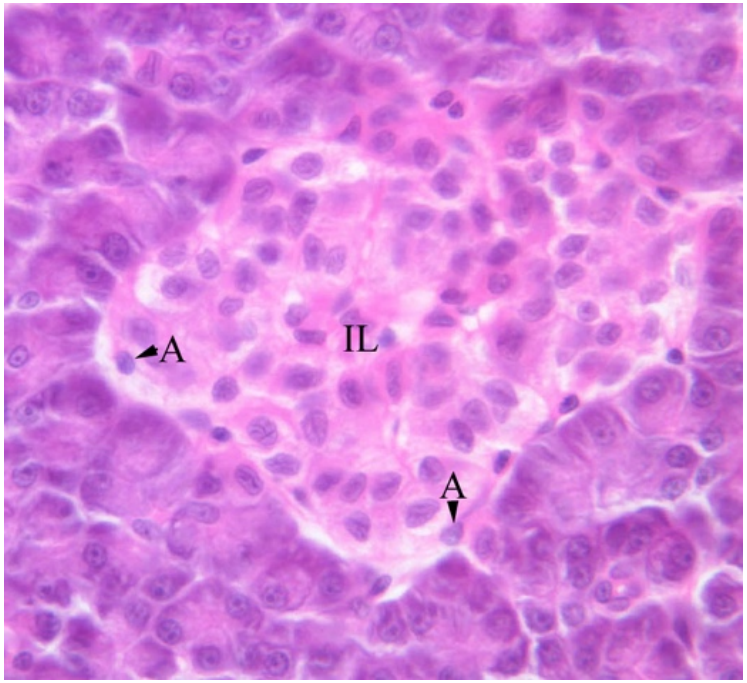
1. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated
Idiopathic
2. Type 2 diabetes (combination of insulin resistance and β-cell dysfunction)
3. Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY), caused by mutations in:
Hepatocyte nuclear factor 4α (*HNF4A*), MODY1
Glucokinase (*GCK*), MODY2
Hepatocyte nuclear factor 1α (*HNF1A*), MODY3
Pancreatic and duodenal homeobox 1 (*PDX1*), MODY4
Hepatocyte nuclear factor 1α (*HNF1B*), MODY5
Neurogenic differentiation factor 1 (*NEUROD1*), MODY6
Neonatal diabetes (activating mutations in *KCNJ11* and *ABCC8*, encoding Kir6.2 and SUR1, respectively)
Maternally inherited diabetes and deafness (MIDD) due to mitochondrial DNA mutations (m.3243A→G)
Defects in proinsulin conversion
Insulin gene mutations
4. Genetic defects in insulin action
Type A insulin resistance
Lipoatrophic diabetes, including mutations in *PPARG*

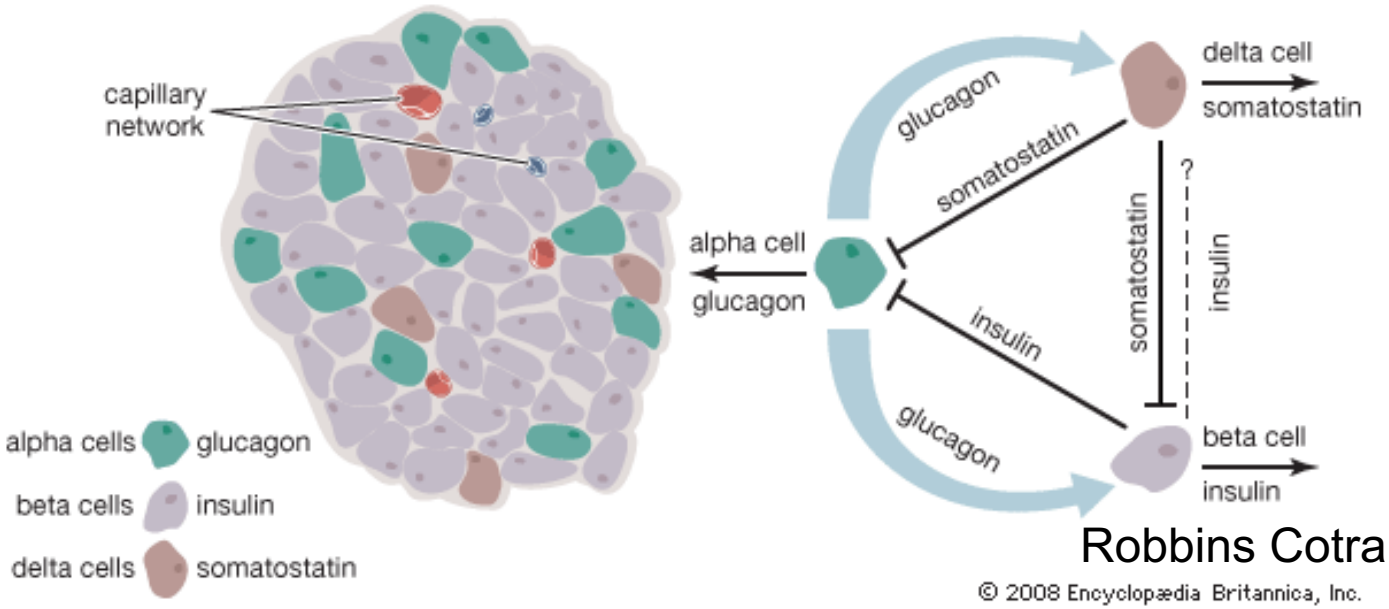
5. Exocrine pancreatic defects
Chronic pancreatitis
Pancreatectomy/trauma
Neoplasia
Cystic fibrosis
Hemachromatosis
Fibrocalculous pancreatopathy
6. Endocrinopathies
Acromegaly
Cushing syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma

7. Infections
Cytomegalovirus
Coxsackie B virus
Congenital rubella
8. Drugs
Glucocorticoids
Thyroid hormone
Interferon-α
Protease inhibitors
β-adrenergic agonists
Thiazides
Nicotinic acid
Phenytoin (Dilantin)
Vacor

9. Genetic syndromes associated with diabetes
Down syndrome
Kleinfelter syndrome
Turner syndrome
Prader-Willi syndrome
10. Gestational diabetes mellitus







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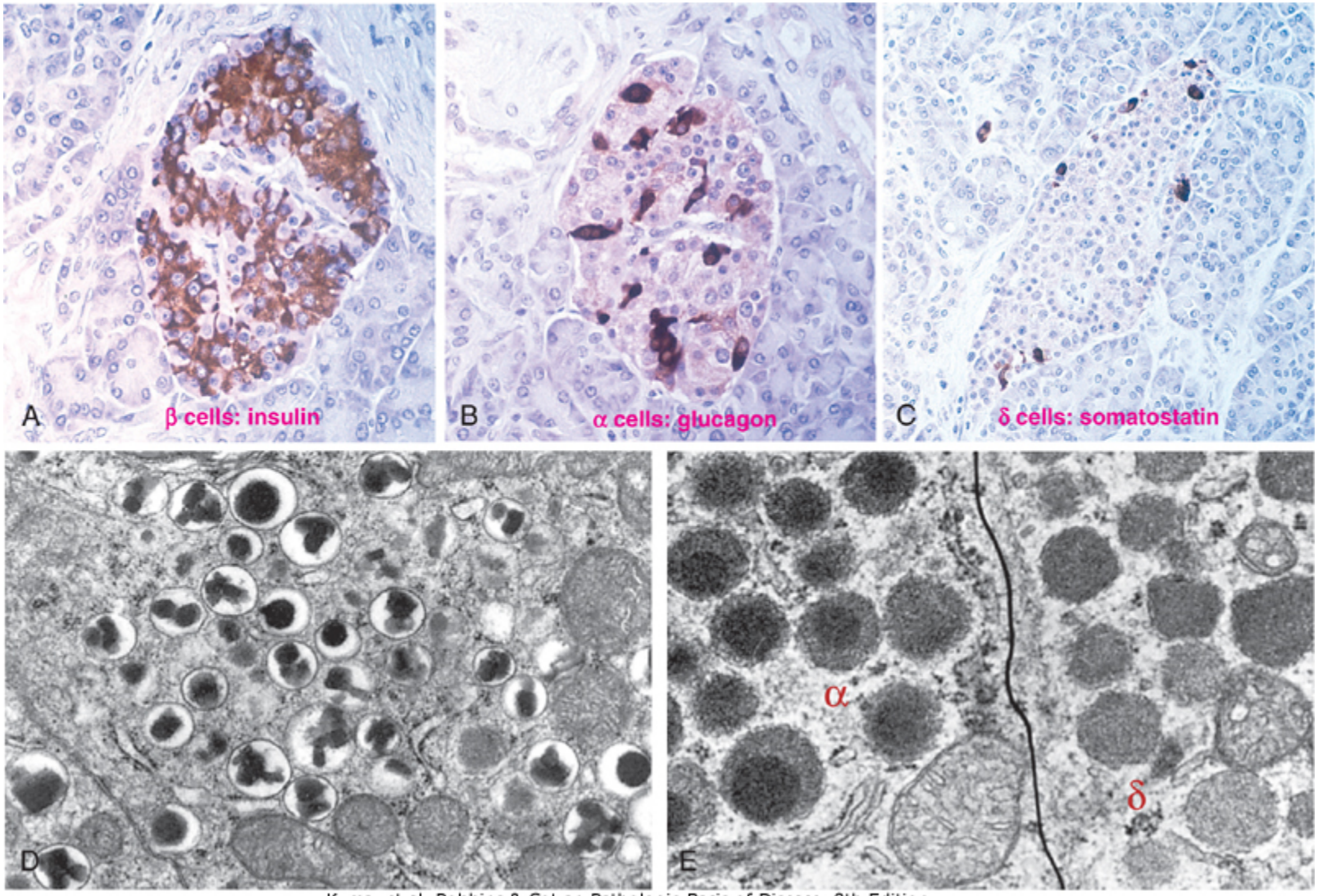
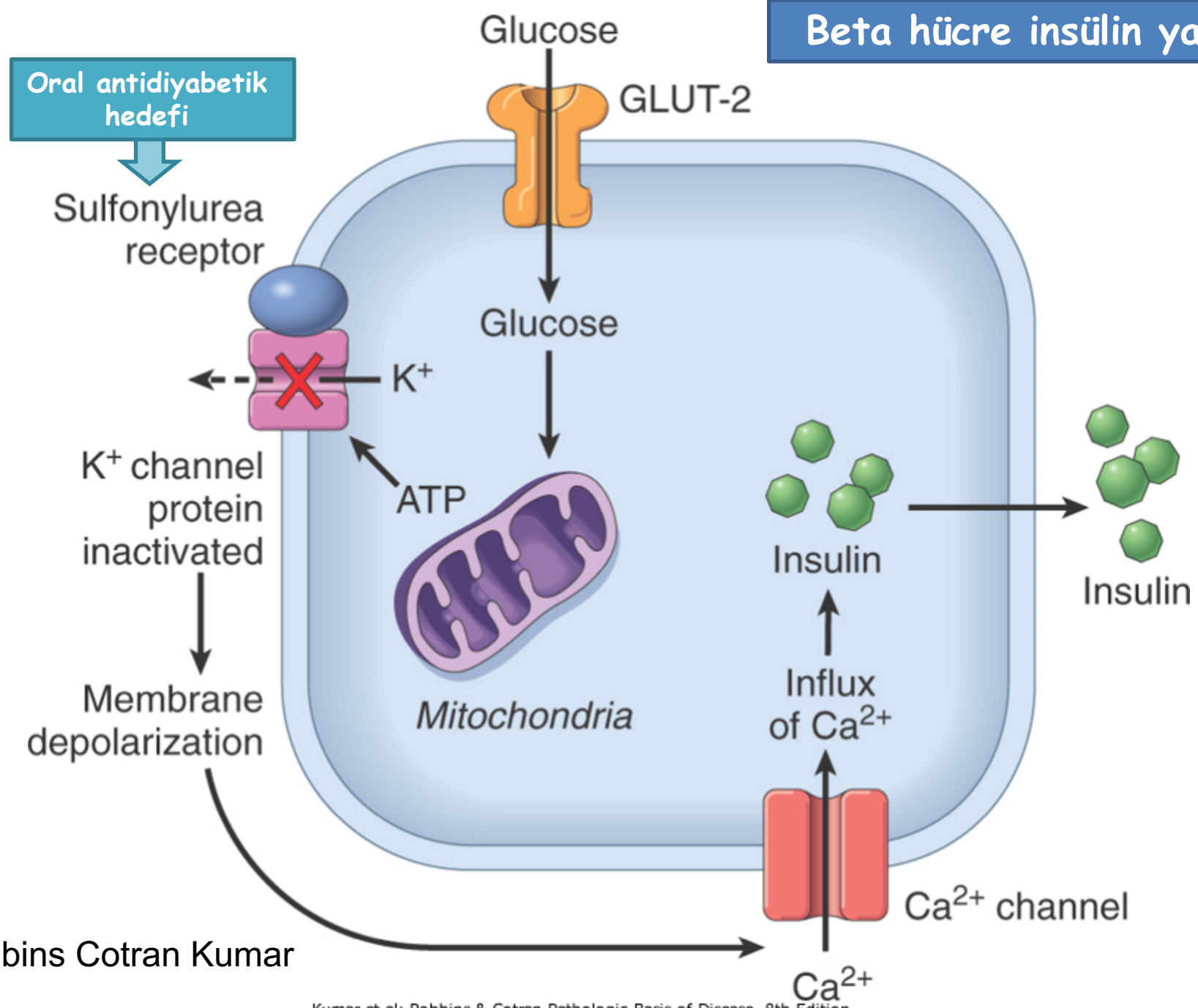


Robbins Cotran Kumar

Beta hücre insülin yapımı



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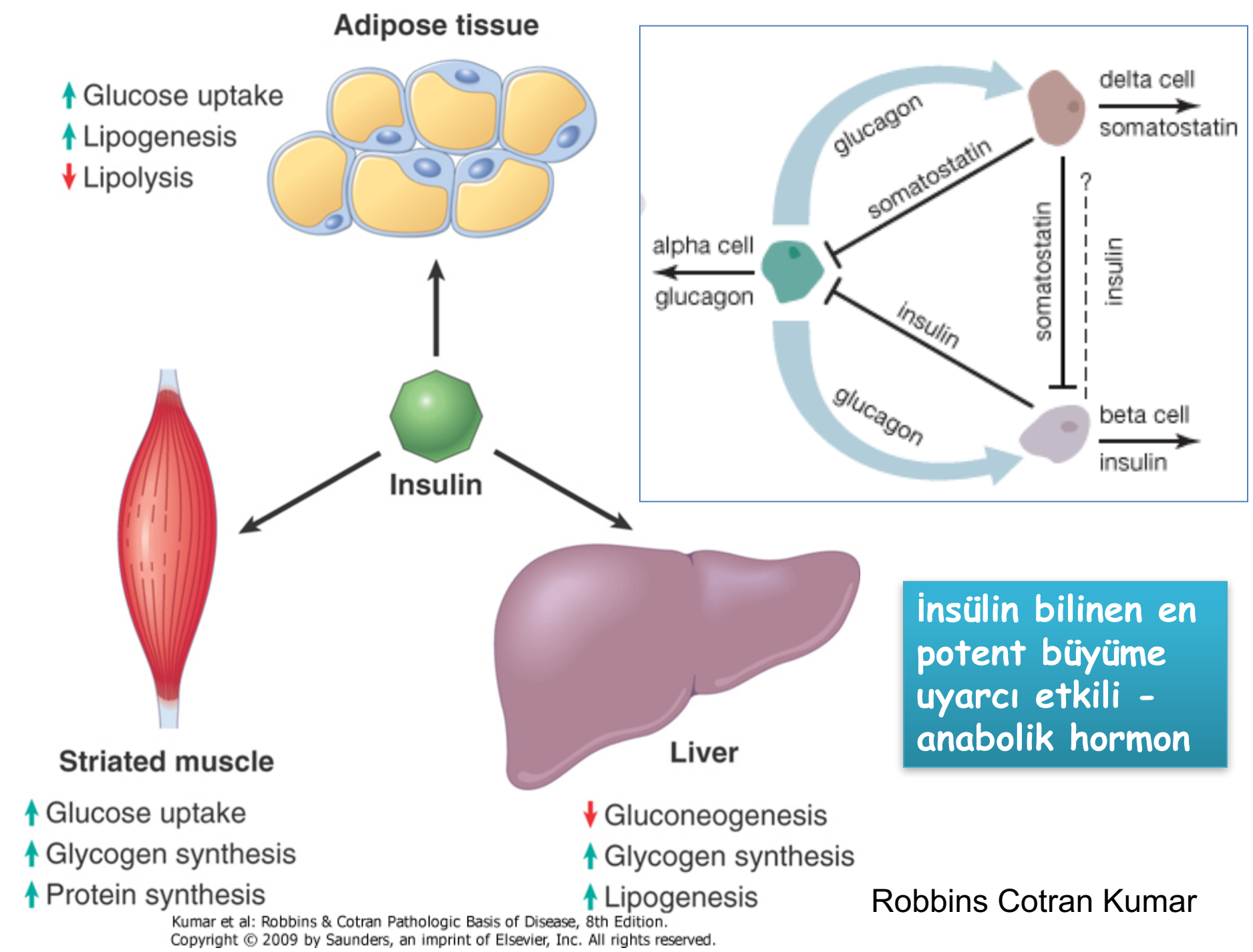
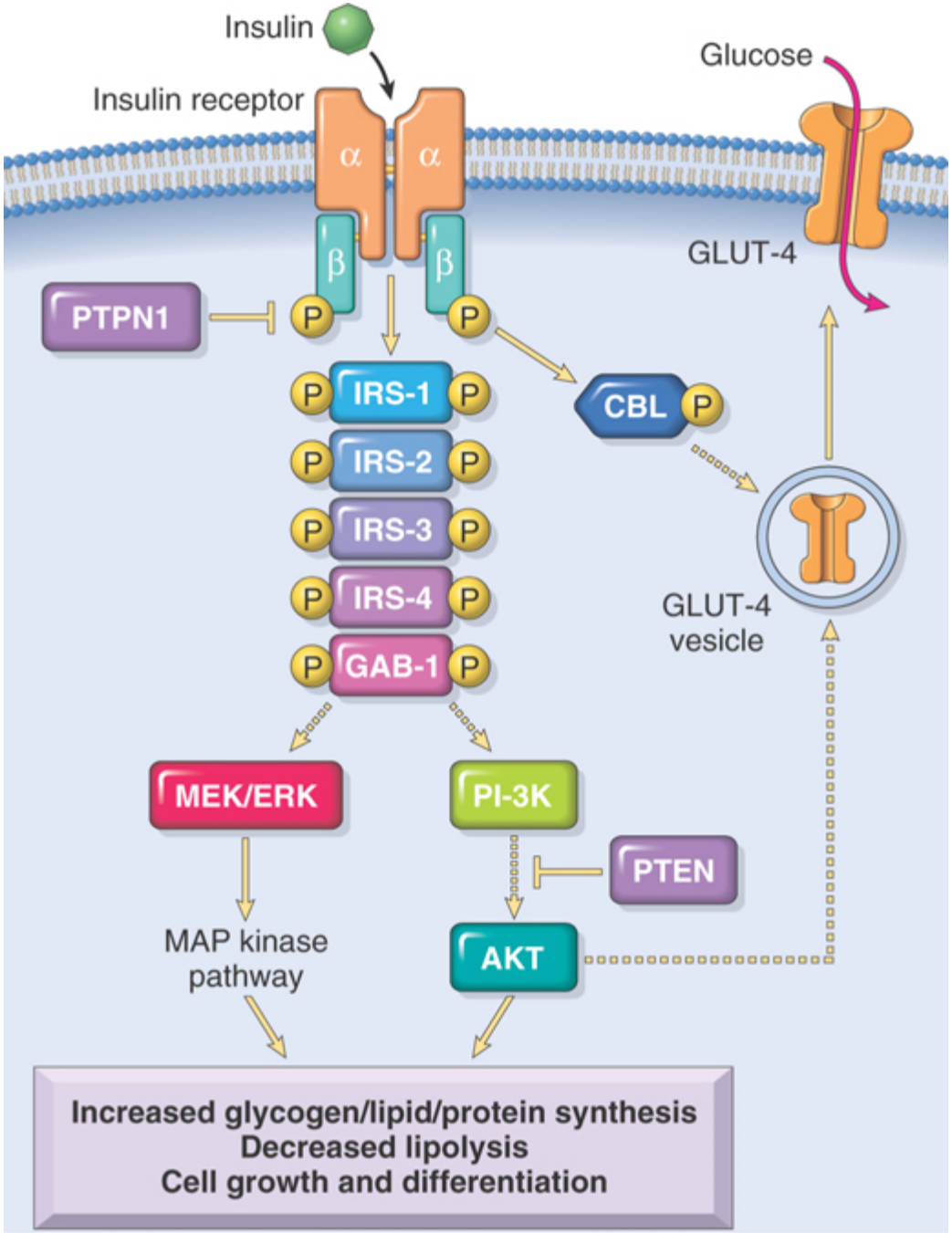


insülin bilinen en potent büyüme uyarıcı etkili - anabolik hormon

Robbins Cotran Kumar



insülin bilinen en potent büyüme uyarıcı etkili - anabolik hormon

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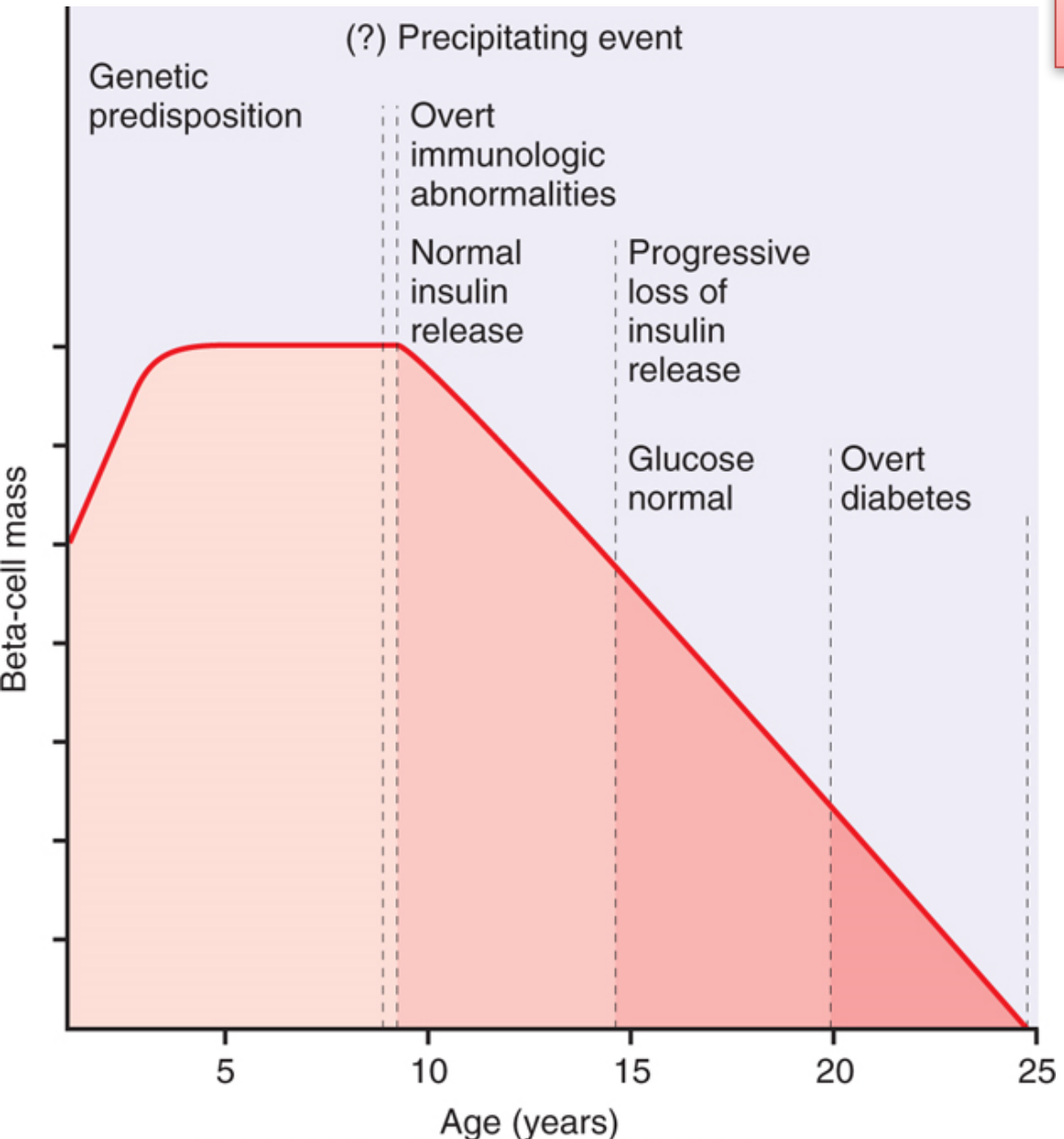
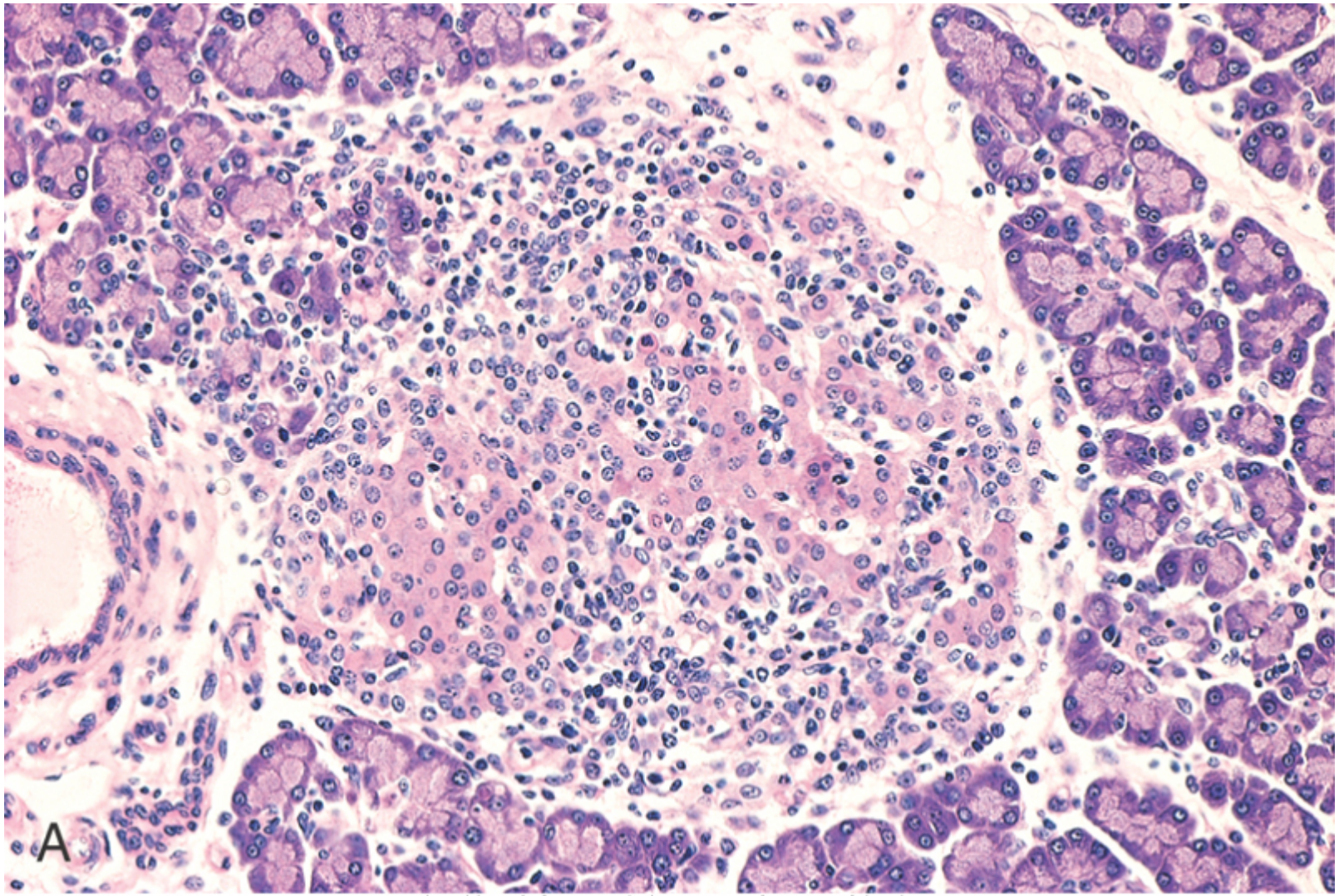
TİP I DİYABET (Jüvenil Diyabet)



GENETİK YATKINLIK
(6q21)
(HLA DR3, DR4, DQ8)
+
ÇEVRESEL FAKTÖRLER
Viral enfeksiyonlar
kabakulak, kızamık,
coxackie B, CMV

T hücrelerinde Self tolerans bozukluğu

TİP I DİYABET



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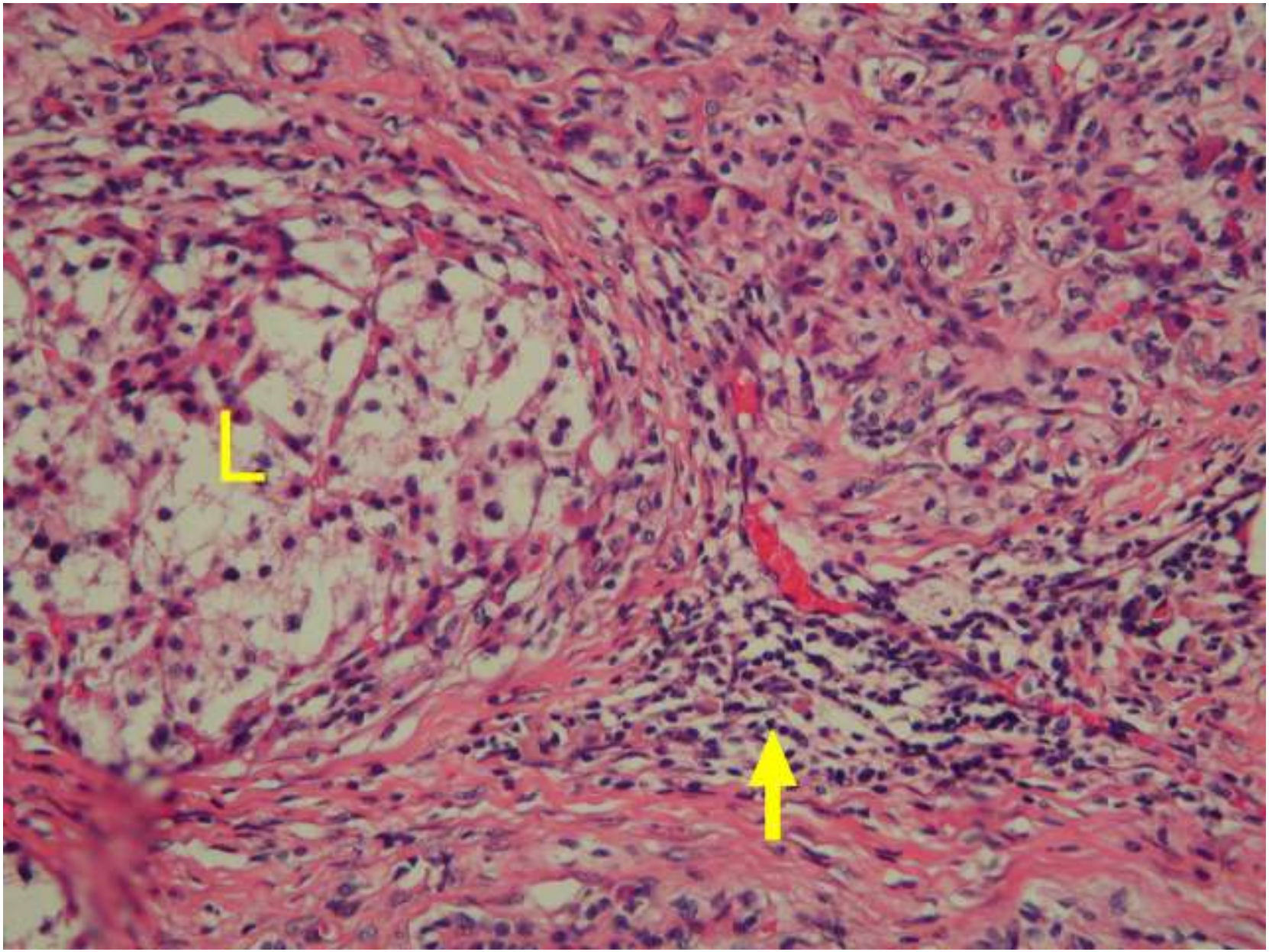


TİP II DİYABET

Genetik yatkınlık **Çevresel faktörler**

1- İnsülin direnci: Şişmanlık (%80 Obez)

2- Beta hücre disfonksiyonu

1- İnsülin direnci:

* Beslenme sonrası glukozun kas hücresine girmesi, glikojen sentezi azalır. - Yüksek postprandial glikoz düzeyi

•Yağ dokusunda lipoprotein lipaz enzim inhibisyon defekti: Kanda serbest yağ asitlerinde artış ----insülin direncinde artış .

•Endojen glukoz kaynağı Hepatik glukoneogenezin baskılanmasında yetersizlik

James S. Simmons Professor of Genetics & Metabolism, Chair, Department of Genetics & Complex Diseases, Harvard-MIT Broad Institute, Harvard Stem Cell Institute, Joslin Diabetes Center Boston, MA, ABD ghotamis@hsph.harvard.edu

Gökhan S. Hotamışlıgil, (24 Haziran 1962), Türk doktor ve bilimadamı.
1986 yılında Ankara Üniversitesi Tıp Fakültesi'nden mezun oldu,
2003 yılında Harvard Üniversitesi'nden profesör unvanını aldı.

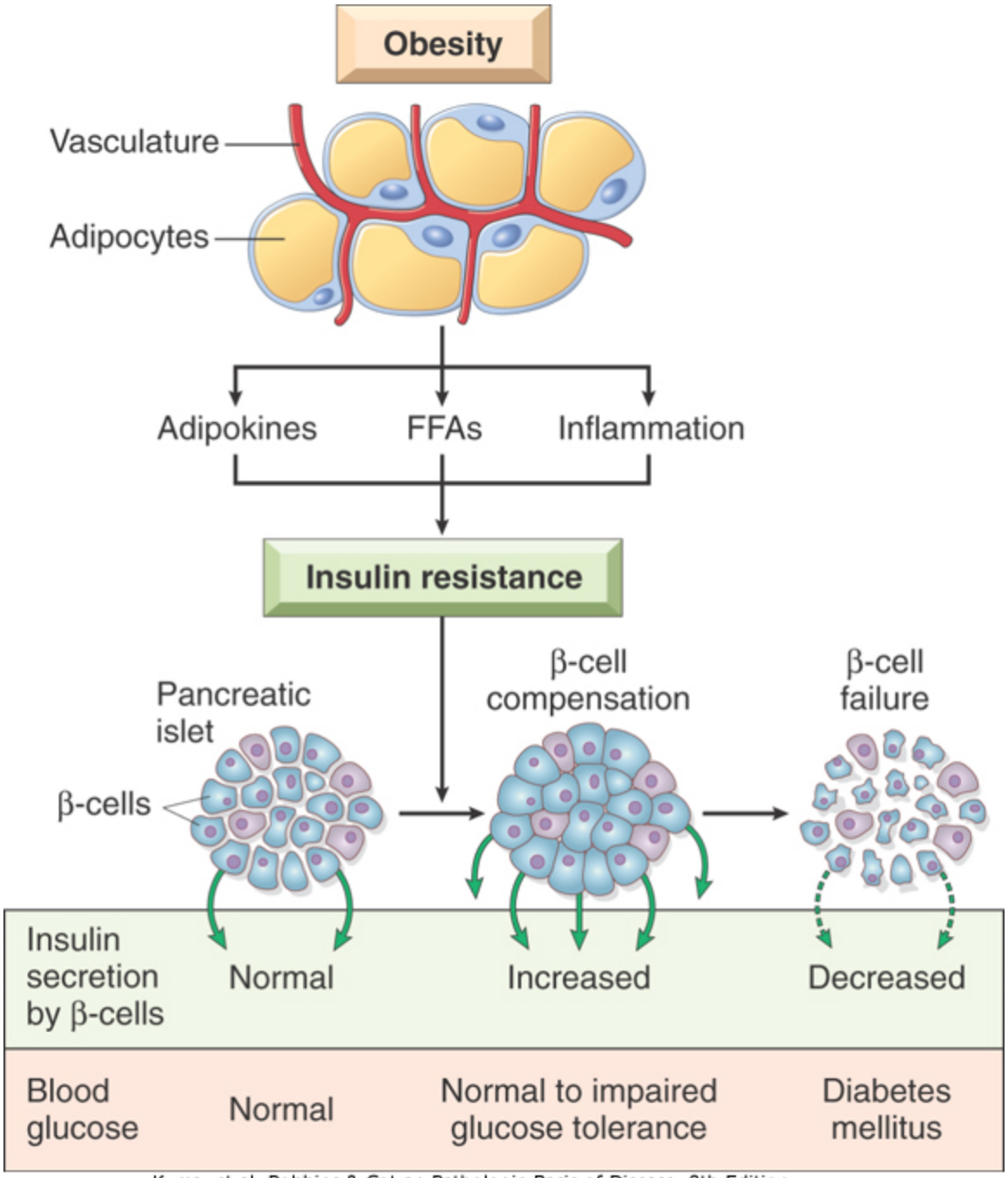
Şişmanlık, tip 2 diyabet ve metabolik sendromun moleküler mekanizmaları
, 2005 yılından beri Harvard Üniversitesi'nde görev yapıyor.
Prof. Dr. Gökhan Hotamışlıgil ve ekibi diyabet ve karaciğer yağlanması gibi hastalıkları durdurabilecek **"lipokin"** adlı bir hormon keşfetti.[1]
Obezite ve buna bağlı metabolik bozukluklarla ilgili çalışmaları ile tüm dünyada tıp bilimine büyük katkı sağlamıştır

1- Şişmanlık ve insülin direnci

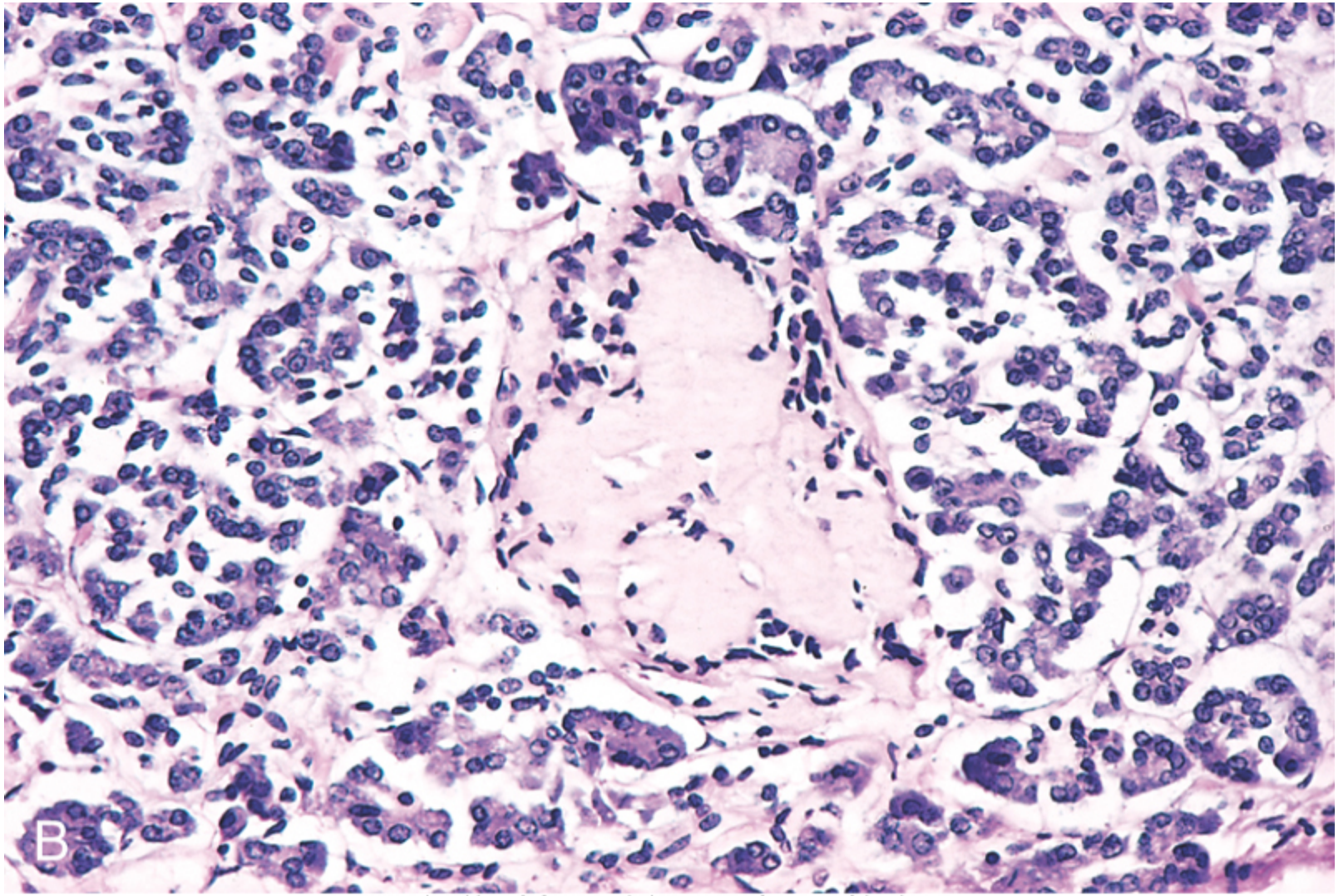
- Nonesterified fatty acids (NEFAs):
-Adipokinler (sitokinler):
yağ asidi oksdasyonu hızlanması, obezitede azalır
prohiperglisemik (resistin , retinol bağlayan protein)
Antihiperglisemik (leptin adiponektin)
- İnflamasyon: proinflamatuar sitokin salınımı artışı ile hücre stresi artar ve insülin direnci olur.
-Peroksizomal proliferator aktive reseptor gamma (PPAR g):
antihiperglisemik adipokinler artar.

2- Beta Hücre fonksiyon kaybı :

Amiloid birikimi



TİP II DİYABET



Amiloid

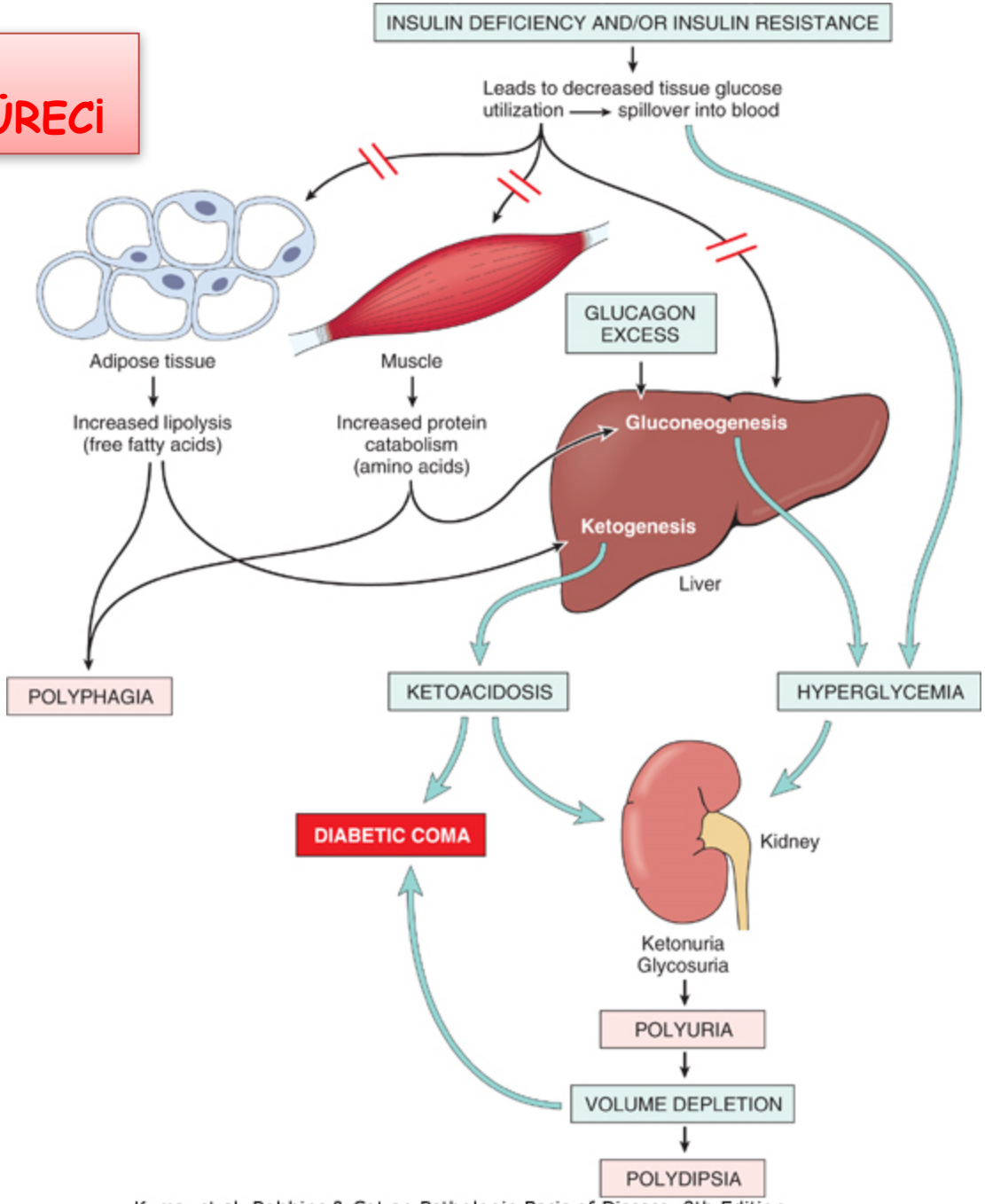
Klinik Tablo

- Poliüri
- Polidipsi
- Polifaji

- Diabetik ketoasidoz

En sık görülen akut metabolik Komplikasyonlar hipoglisemi ile olur

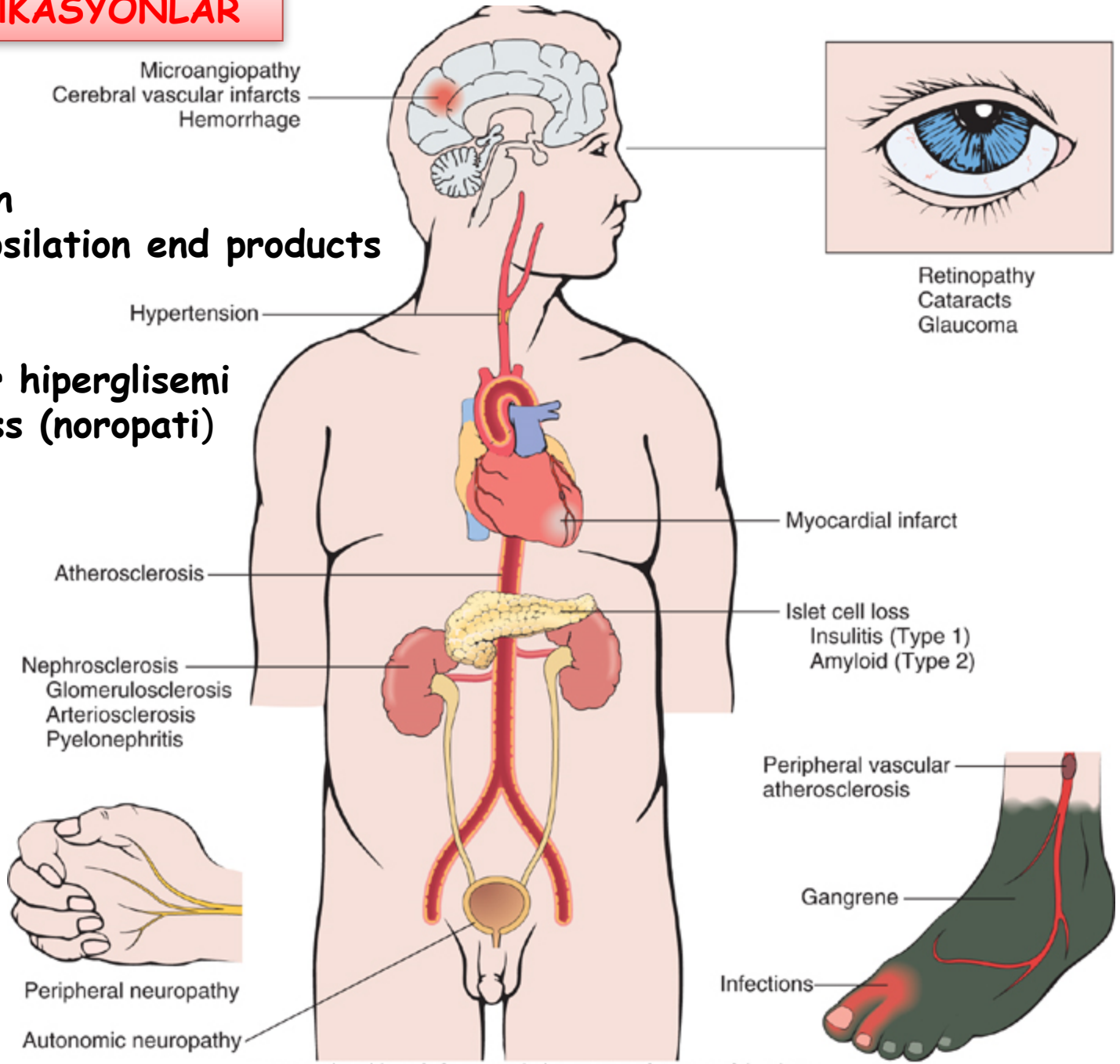
METABOLİK BOZUKLUK SÜRECİ

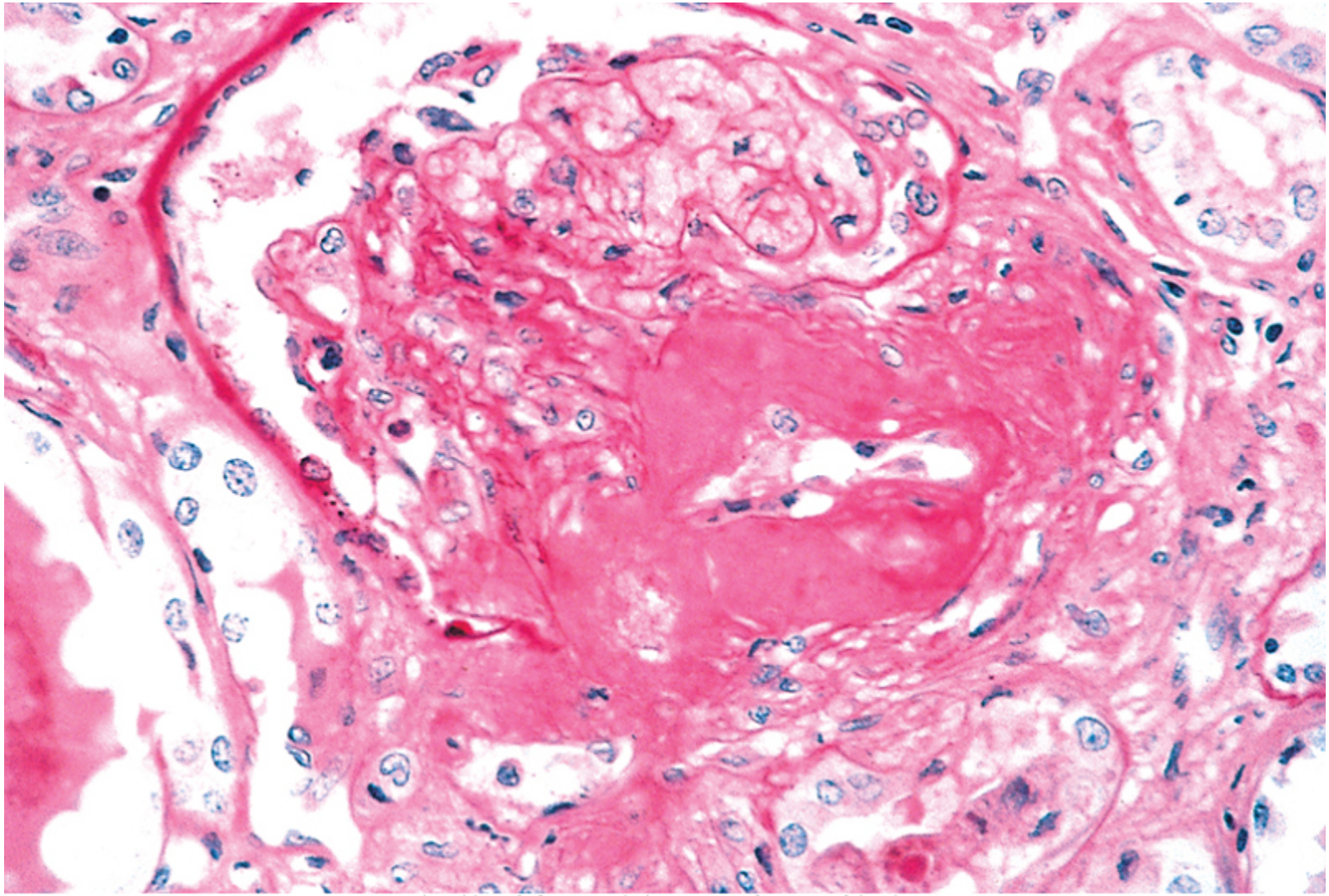


KRONİK KOMPLİKASYONLAR

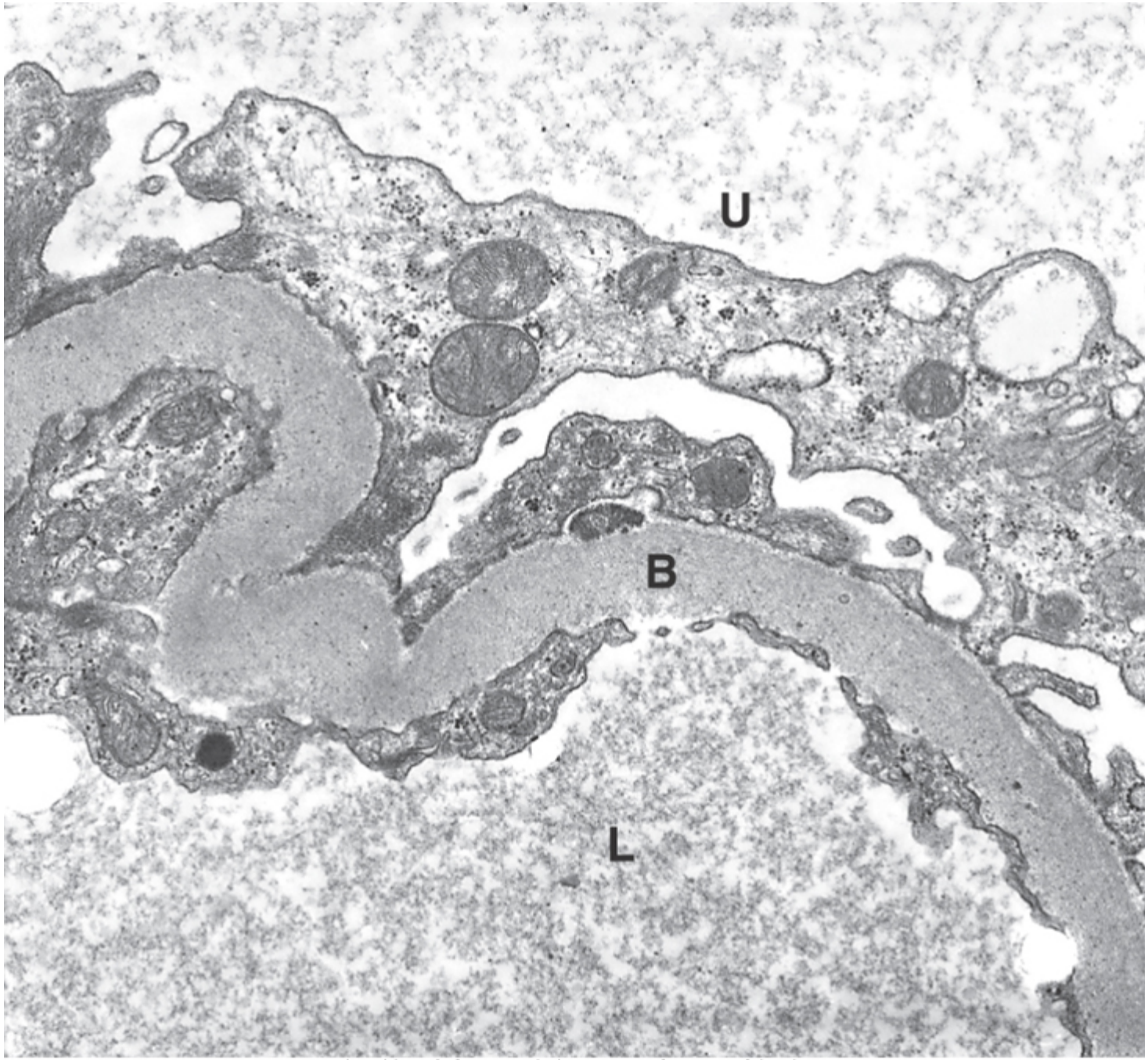
Glukotoksisite
1- Glikosilasyon
Advanced glycosilation end products (AGEs)

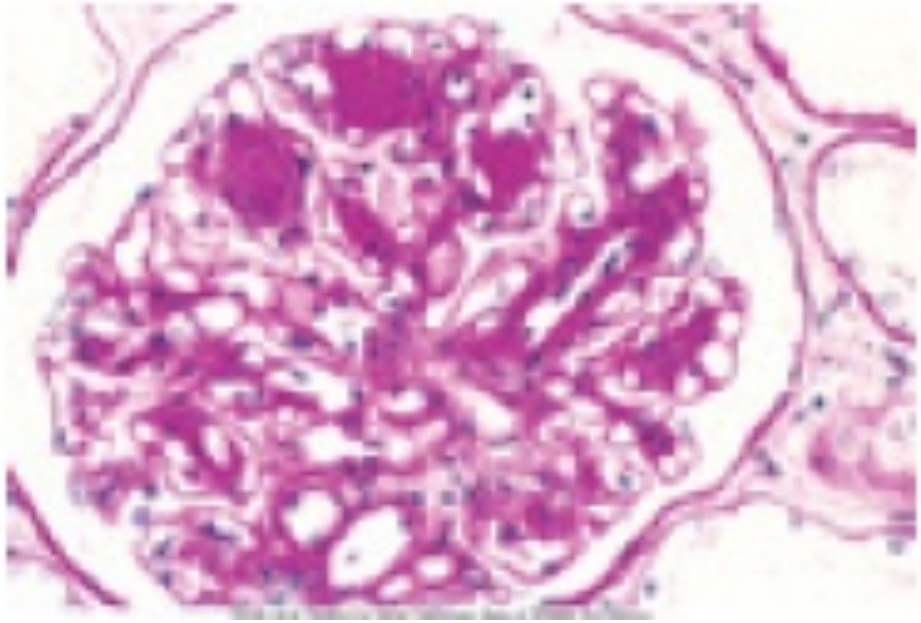
2- intraselluler hiperglisemi
Oksidatif stress (noropati)



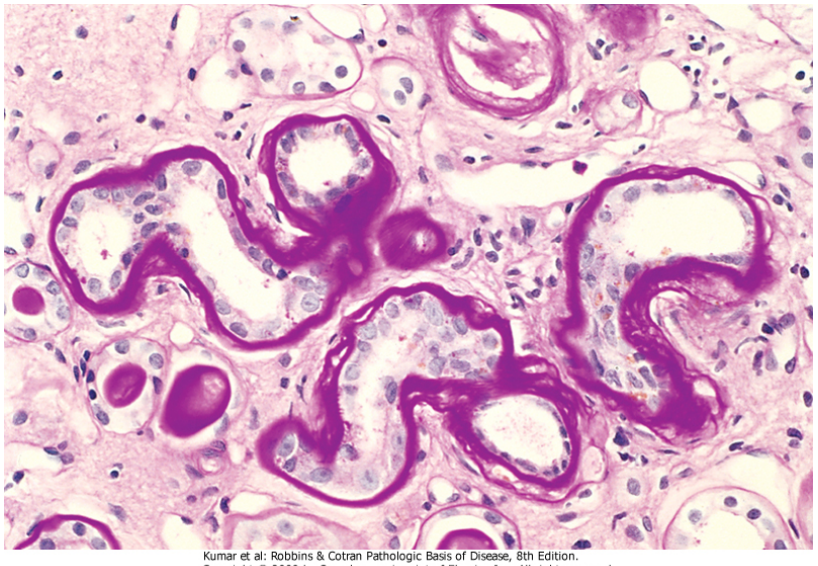


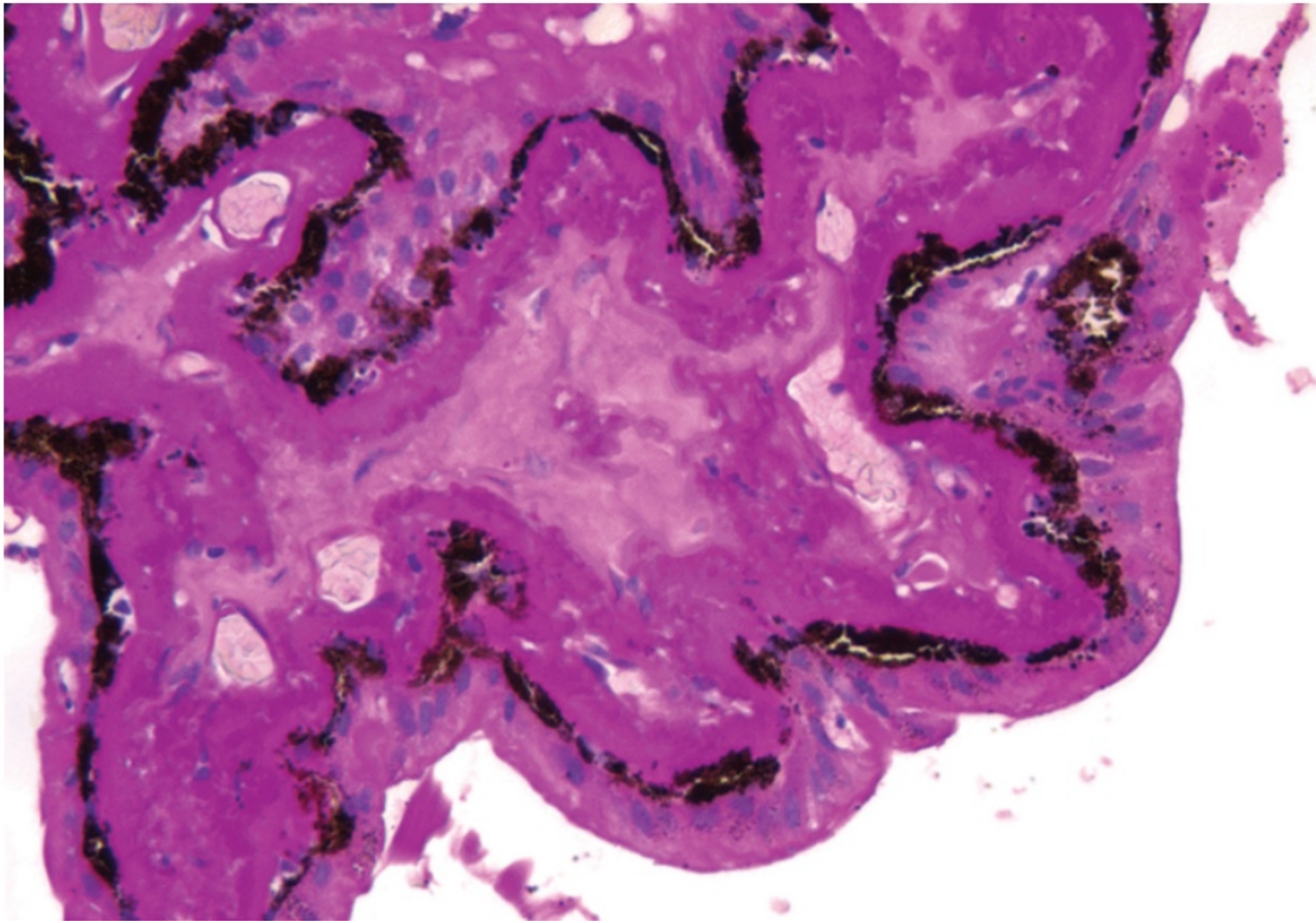
Hyalin arteriolosklerоz





Noduler Diffüz glomeruloskleroz Kimmelstiel Wilson





Renal glomeruloskleroz

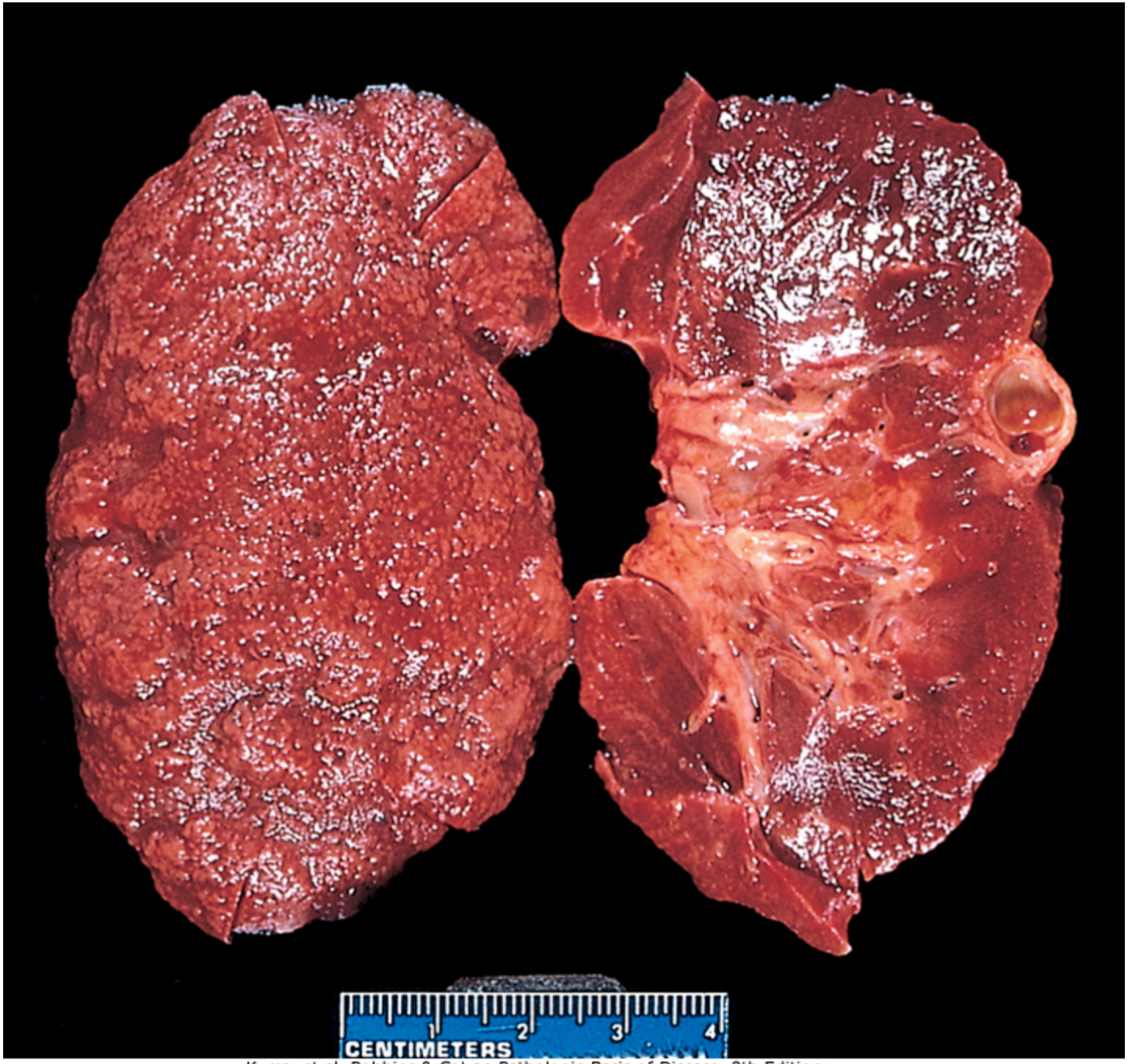


Table 24-7. Type 1 Versus Type 2 Diabetes Mellitus

Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
CLINICAL	
Onset: usually childhood and adolescence	Onset: usually adult; increasing incidence in childhood and adolescence
Normal weight or weight loss preceding diagnosis	Vast majority are obese (80%)
Progressive decrease in insulin levels	Increased blood insulin (early); normal or moderate decrease in insulin (late)
Circulating islet autoantibodies (anti-insulin, anti-GAD, anti-ICA512)	No islet auto-antibodies
Diabetic ketoacidosis in absence of insulin therapy	Nonketotic hyperosmolar coma more common
GENETICS	
Major linkage to MHC class I and II genes; also linked to polymorphisms in *CTLA4* and *PTPN22*, and insulin gene VNTRs	No HLA linkage; linkage to candidate diabetogenic and obesity-related genes (*TCF7L2*, *PPARG*, *FTO*, etc.)
PATHOGENESIS	
Dysfunction in regulatory T cells (Tregs) leading to breakdown in self-tolerance to islet auto-antigens	Insulin resistance in peripheral tissues, failure of compensation by β-cells
	Multiple obesity-associated factors (circulating nonesterified fatty acids, inflammatory mediators, adipocytokines) linked to pathogenesis of insulin resistance
PATHOLOGY	
Insulitis (inflammatory infiltrate of T cells and macrophages)	No insulitis; amyloid deposition in islets
β-cell depletion, islet atrophy	Mild β-cell depletion

HLA, human leukocyte antigen; MHC, major histocompatibility complex; VNTRs, variable number of tandem repeats.