Diabetes mellitus

Aetiology and Pathogenesis, Specific complications

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Diabetes mellitus

- chronic metabolic and endocrine disorder
- due to insuficiency of insulin action
- blood glucose level -permanent increased hyperglycaemia and glycosuria

in Czech Rep.: more than 9,5%=960.000 diabetics

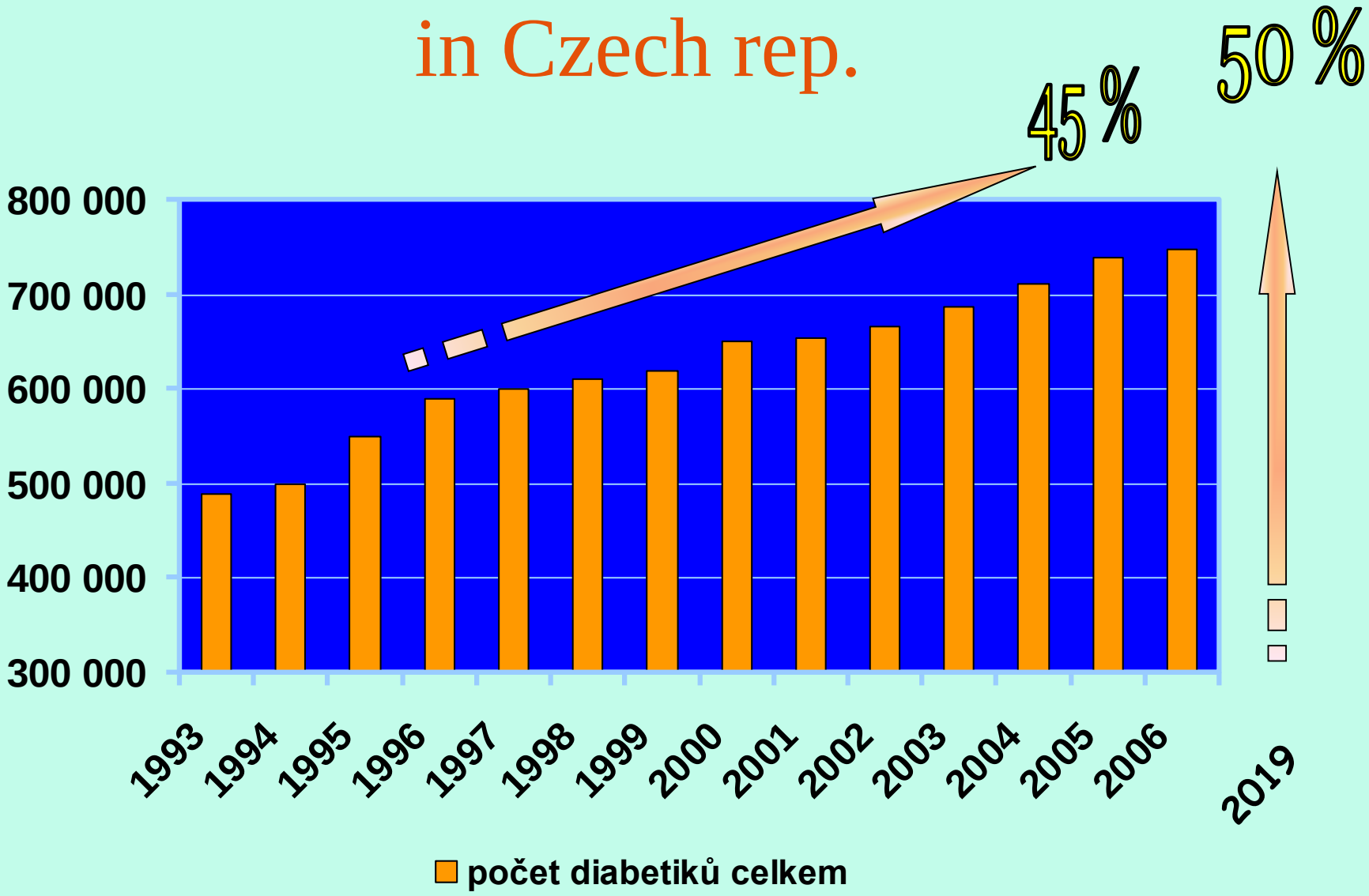
-92% DM type 2

1995- 504.000 diabetics, 1975- 250.000

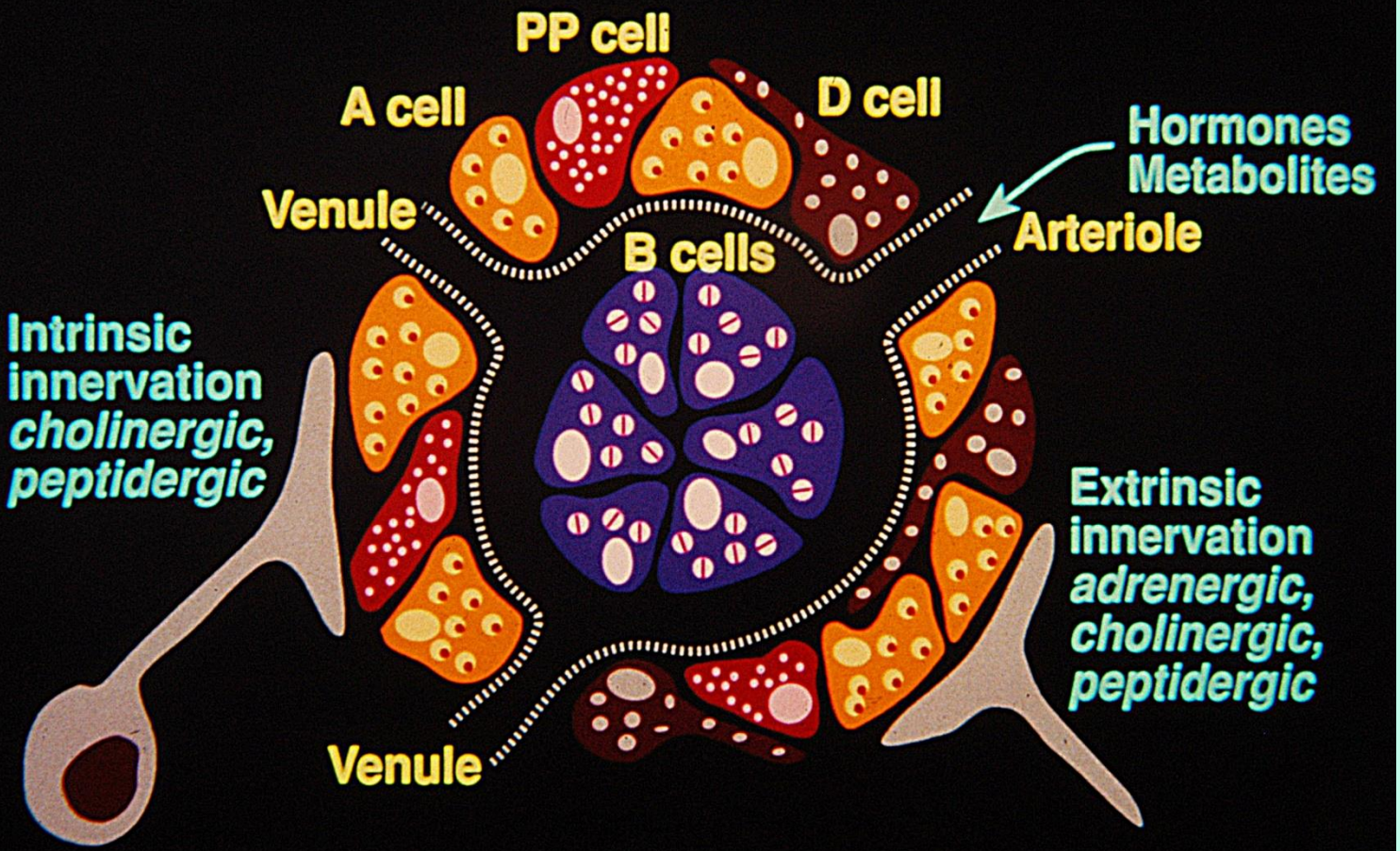
children: 4,3% till 15 y., 6,9% till 6 y.

USA: 11% > 20r., 28% >65r. (prediab.50% > 65r, 35% > 20r.)

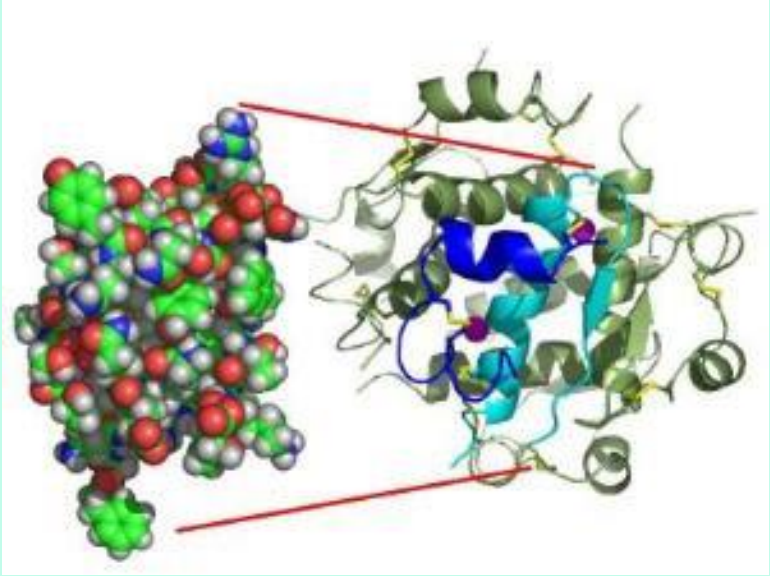
Number of treated diabetic patients in Czech rep.



Structure of a pancreatic islet



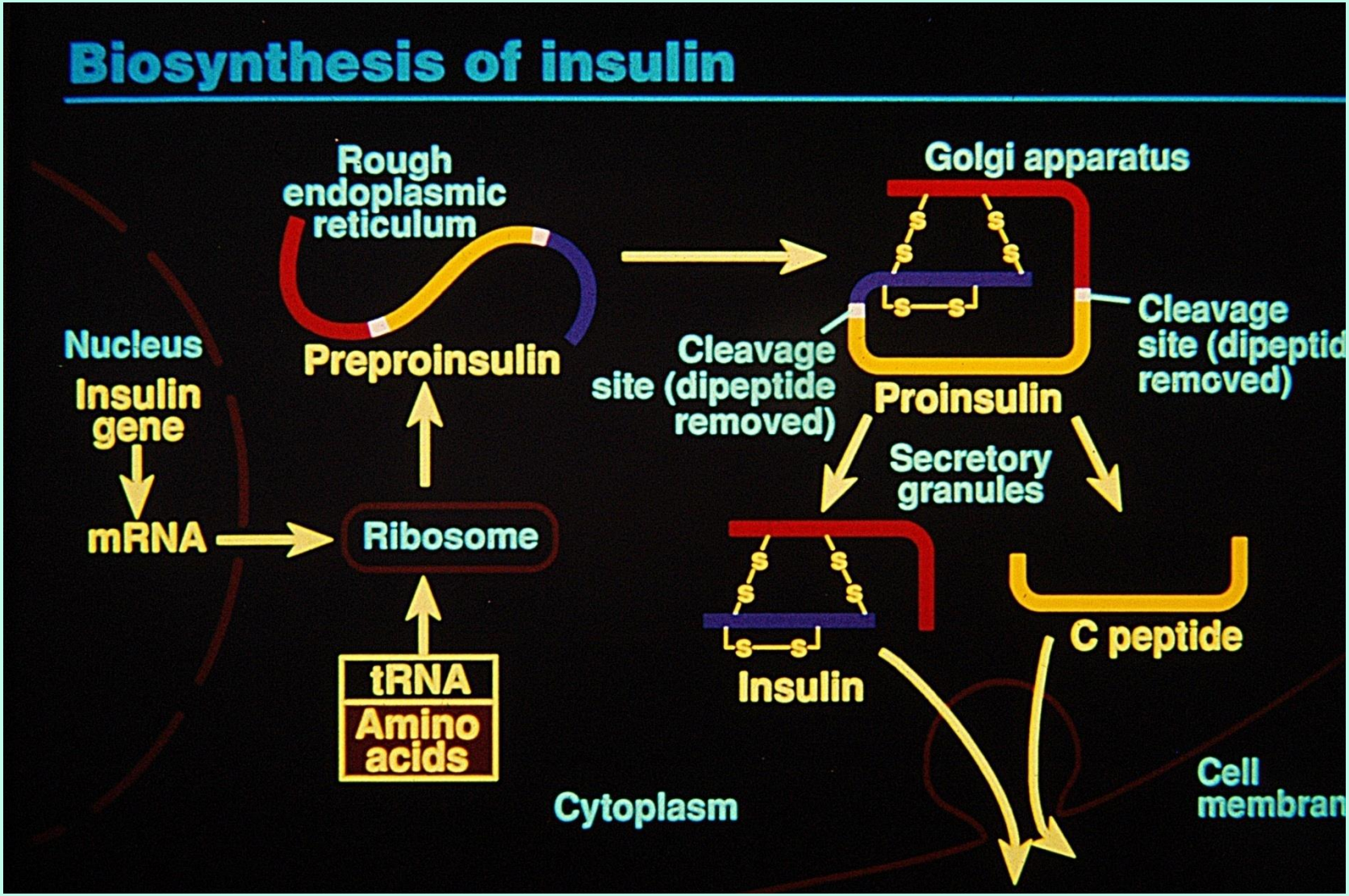
Biosynthesis of insulin



Gen-11-th chromosoma

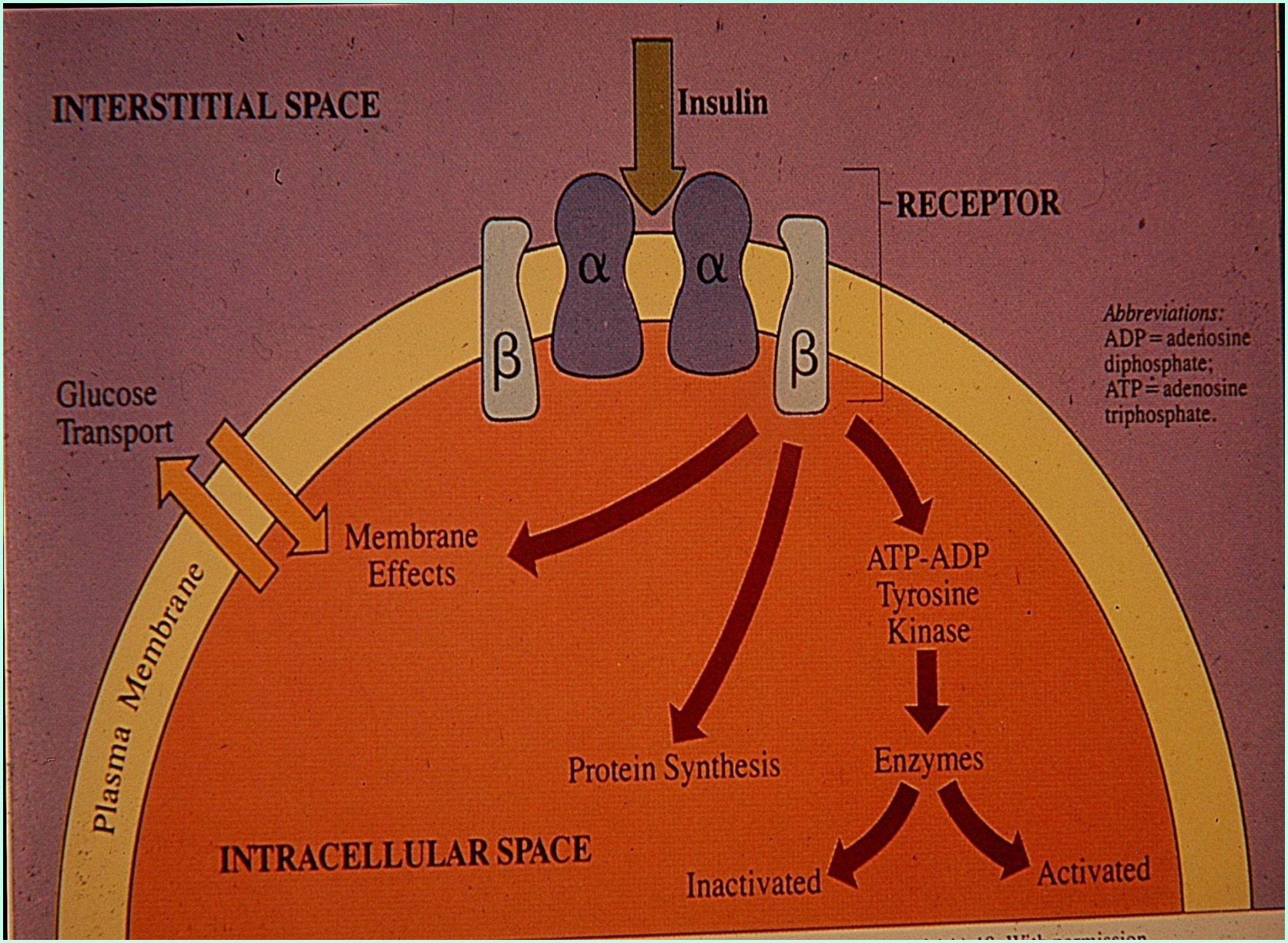
- preproinsulin
- proinsulin
- insulin + C peptid (30-120 min)
- receptors

-depends on insulin level, p.o. antidiabetic drugs


Biosynthesis of insulin
Rough endoplasmic reticulum
Golgi apparatus
Nucleus
Insulin gene
Preproinsulin
Cleavage site (dipeptide removed)
Proinsulin
Cleavage site (dipeptid removed)
mRNA
Ribosome
Secretory granules
tRNA
Amino acids
Insulin
C peptide
Cytoplasm
Cell membran

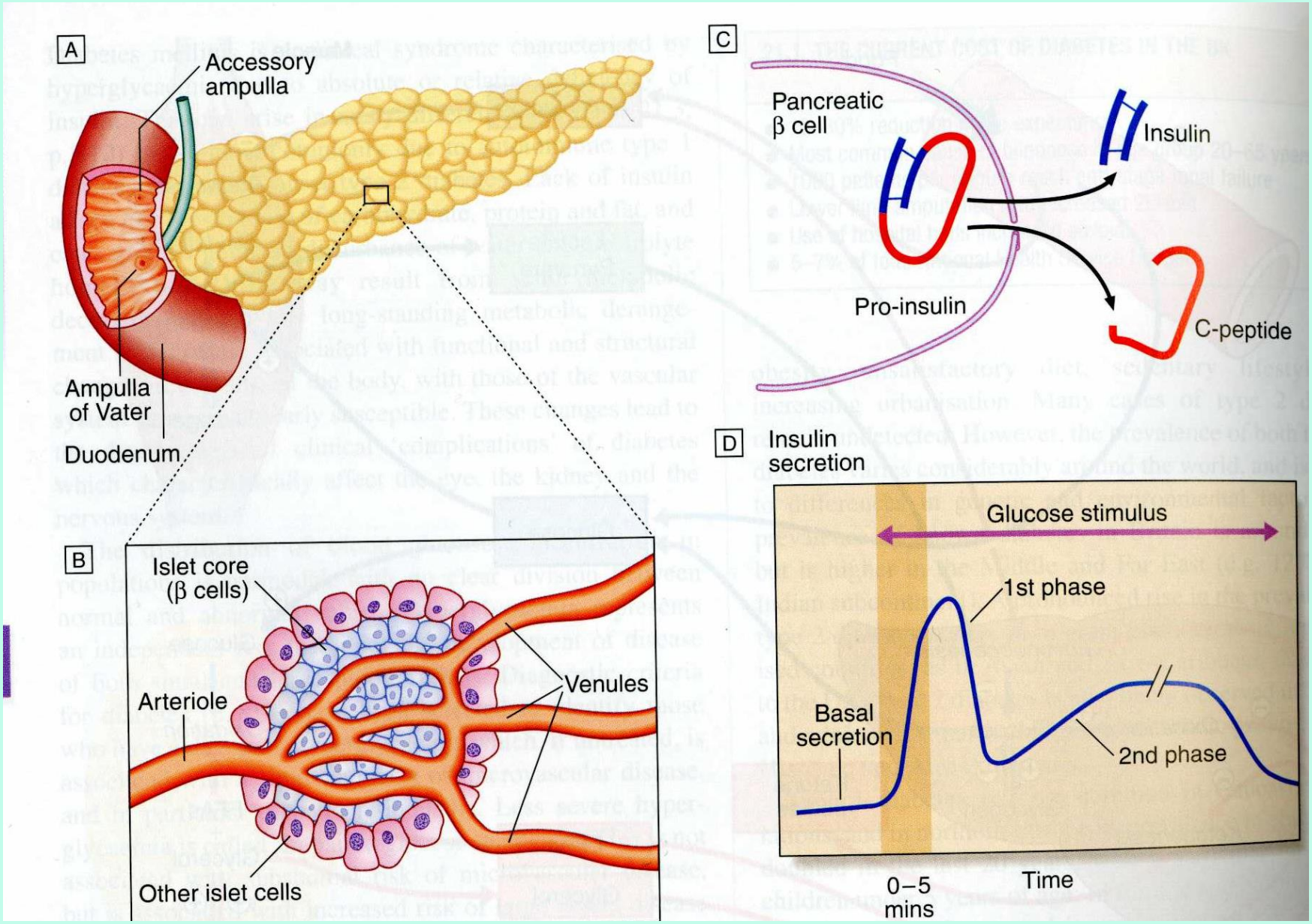
Primary structure of human insulin

	B30	A8	A10
Human	Thr	Thr	Ile
Porcine	Ala	Thr	Ile
Bovine	Ala	Ala	Val


INTERSTITIAL SPACE
Insulin
RECEPTOR
α
α
β
β
Abbreviations:
ADP = adenosine diphosphate;
ATP = adenosine triphosphate.
Glucose Transport
Membrane Effects
ATP-ADP Tyrosine Kinase
Plasma Membrane
Protein Synthesis
Enzymes
INTRACELLULAR SPACE
Inactivated
Activated

Insulin secretion

- **Basal**- cca 20 U/day
- **Stimulated**- after secretional stimuli
  - fast, first phase - mediated through hormons (GIP,GLP-1) - 5-10 min
  - prolonged, second phase - depends on nutritional stimuli, takes all the time of its duration, max 2-3 h.



Davidson´s Principles,Practice of Medicine

Lower action of insulin 1

- absence of insulin output in B-cells
- defect in synthesis of ins. /proins., decrease ins.production, output of faulty insulin
- insulin releasing defect
- defect due to antibodies
- defect of ins.action in target organs (receptors)
- defect in insulin degradation
- increased action of insulin´s antagonists

→ **hyperglycaemia**

Lower action of insulin 2

- Reduction of intra-cell transport of glucose
- increase in gluconeogenesis
  decrease in glycolysis in liver
- increase in glycogenolysis

→ **hyperglycaemia**

Insulin action

Increased intra-cell transport of glu, aminoacids,K,Mg,Ca

- of glucose-transporters GLUT-4
- 30-60% gl utilized in liver

➔ Stimulation of anabolic and block of catabolic processes in organism

Insulin actions 1

Liver:

- increase in synthesis of glycogen - anabol.effect
- increased intake of glu into the cells and its utilisation in peripherie
- decrease in glukoneogenesis a glykogenolysis

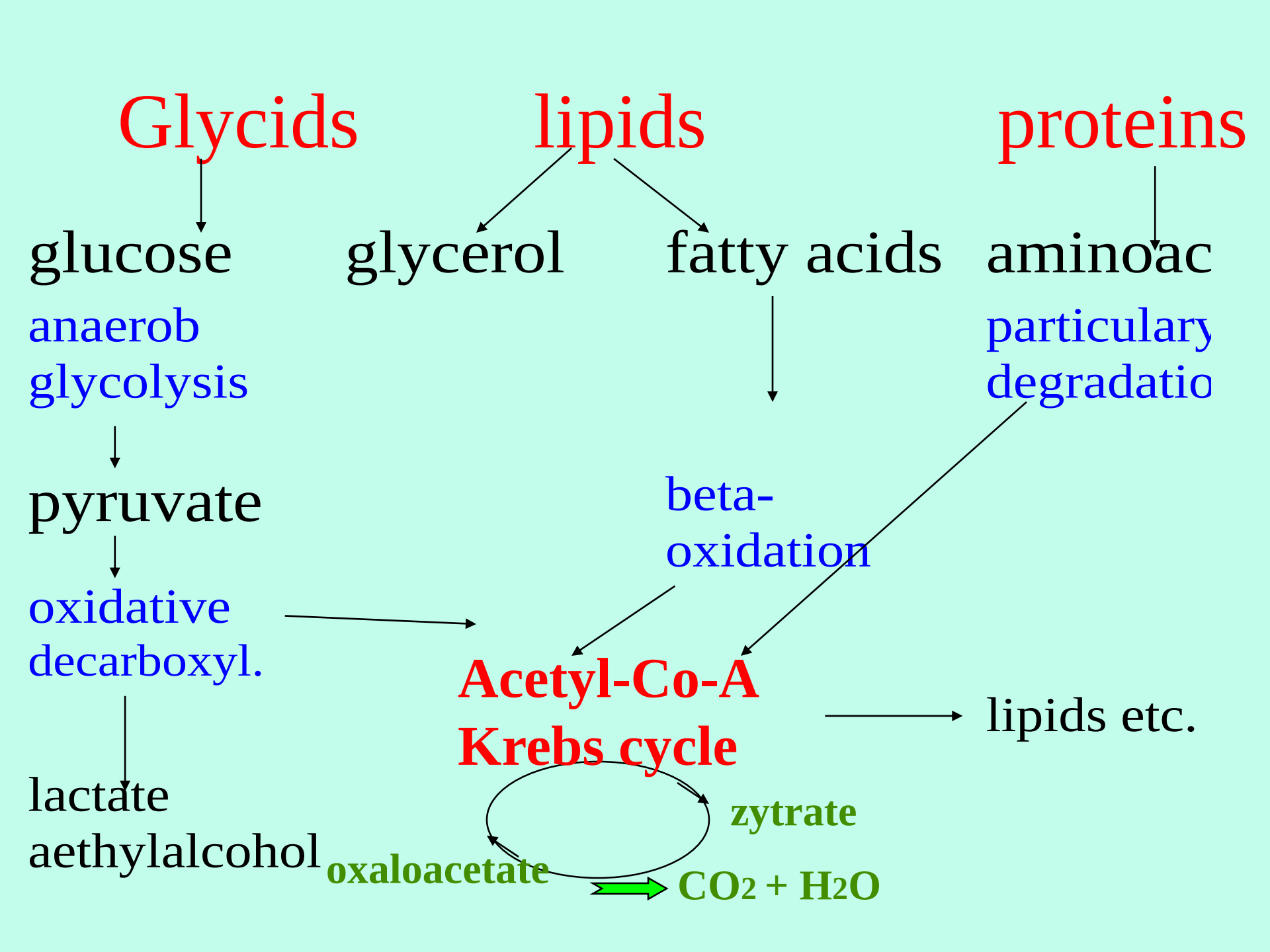
  - anticatabol.effect

- decreased glycaemia

Insulin actions 2

- increase in synthesis of lipids- lipogenesis
  decreased lipolysis- antilipolytic action
  antiketogen. action

- increase in synthesis of proteins-anabol. action
  increase in RNA syntesis
  decreased proteolysis- anticatabol. action


Glycids
lipids
proteins
glucose
glycerol
fatty acids
aminoac
anaerob
glycolysis
particulary
degradatio
pyruvate
beta-
oxidation
oxidative
decarboxyl.
Acetyl-Co-A
Krebs cycle
lipids etc.
lactate
aethylalcohol
zytrate
oxaloacetate
CO2 + H2O

Insulin deficiency 1

- In corporal cells

block of gluc. and aminoacids - transport intracell.

- In liver

↑ glykogenolysis

↑ glukoneogenesis

↑ proteolysis

↑ occur. of amnoacids

↓ peripheral gluc.utilisation

↓ proteosynthesis

↑ production of glu

↑ production of urea

↑ production of fat and lipoproteins

↑ production ketoacids

Insulin deficiency 2

- In fatty tissue
  - ↑ lipolysis
  - ↓ lipogenesis
  - → ↑ fatty acids
- In muscle
  preferential utilisation of proteins and fets
  - → ↑ offer of aminoacids and fatty acids for liver

Contraregulatory hormones

- Glukagon-A increases glycogen-splitting in liver
- STH,GH decreases glucose utilisation
- ACTH increases glucocort.
- Glucocorticoids increases glukoneogenesis, stim.of insulin, decreases peripheral glucose utilisation
- Adrenalin increases glykogenolysis in muscle, decreases insulin secretion
- Hormons of thyreoid gland
- Somatostatin -D decreases insulin secretion
  Pancreatic polypeptid ,VIP , Amylin -B decreases insulin secretion

DM classification 1

1 DM type 1 a) immune

absolute insulin deficit b) idiopatic

LADA, brittle

2 DM type 2 insulin resistance

relative insulin deficit

DM classification 2

3 Other specific types

- genetic defects of B-cells function: MODY

(autosomal domin. inheritance ,younger age,asthenics,without insulin necessity.)

- genetic defects of insulin action
- disease of exocrine part of pancreas
- endocrinopathies
- drugs induced
- viral infection (cong. rubeola, CMV, …)
- rare immunologically caused
- other genetic sy (Down, Klinefelter, …)

4 Gestational DM

	I	II
~~Age of manifestation~~	~~childhood-40~~	~~middle, older, >40~~
habitus	asthenic	hyperstenic
haplotyps	DR3,DR4,DQ	-
ins.synthesis	- 0	norm.
insulinaemia	- 0	norm,
autoantibodies	+	-
response on PAD	-	+
glycaemia	brittle	relat. stable
onset of disorder	quick /weeks/	slow (months-years)
symptoms	severe	mild or none
ketoacidosis	+	
insulin therapy	+	PAD, diet, insulin-resistance
vascul.complications	micro	macro

Pathogenesis of DM 1.type

Eisenbarth´s scheme

1. Genetic susceptibility

DR3,DR4

2. Initiating mechanism

Coxackie B
mumps, rubeolla, CMV
EBV

3. Incipient insulitis

/ICA,ICSA,IA-2,GADA/
/IAA,PAA,ICSTA/

4. Full developed insulitis (80%)

5.Manifestation of diabetes

6. No secretion of endogenous insulin

↳ DM 1.type

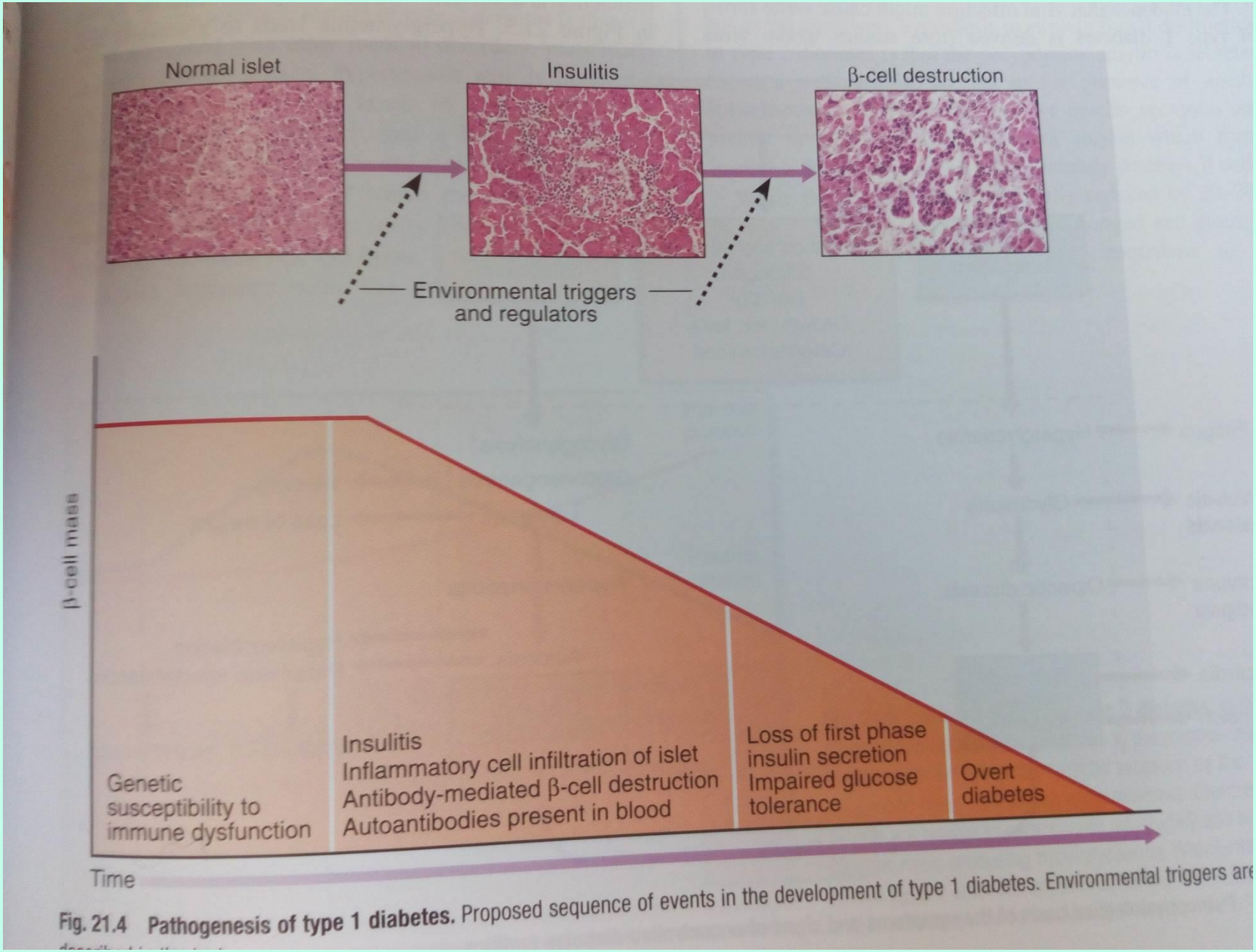


Fig. 21.4 Pathogenesis of type 1 diabetes. Proposed sequence of events in the development of type 1 diabetes. Environmental triggers are

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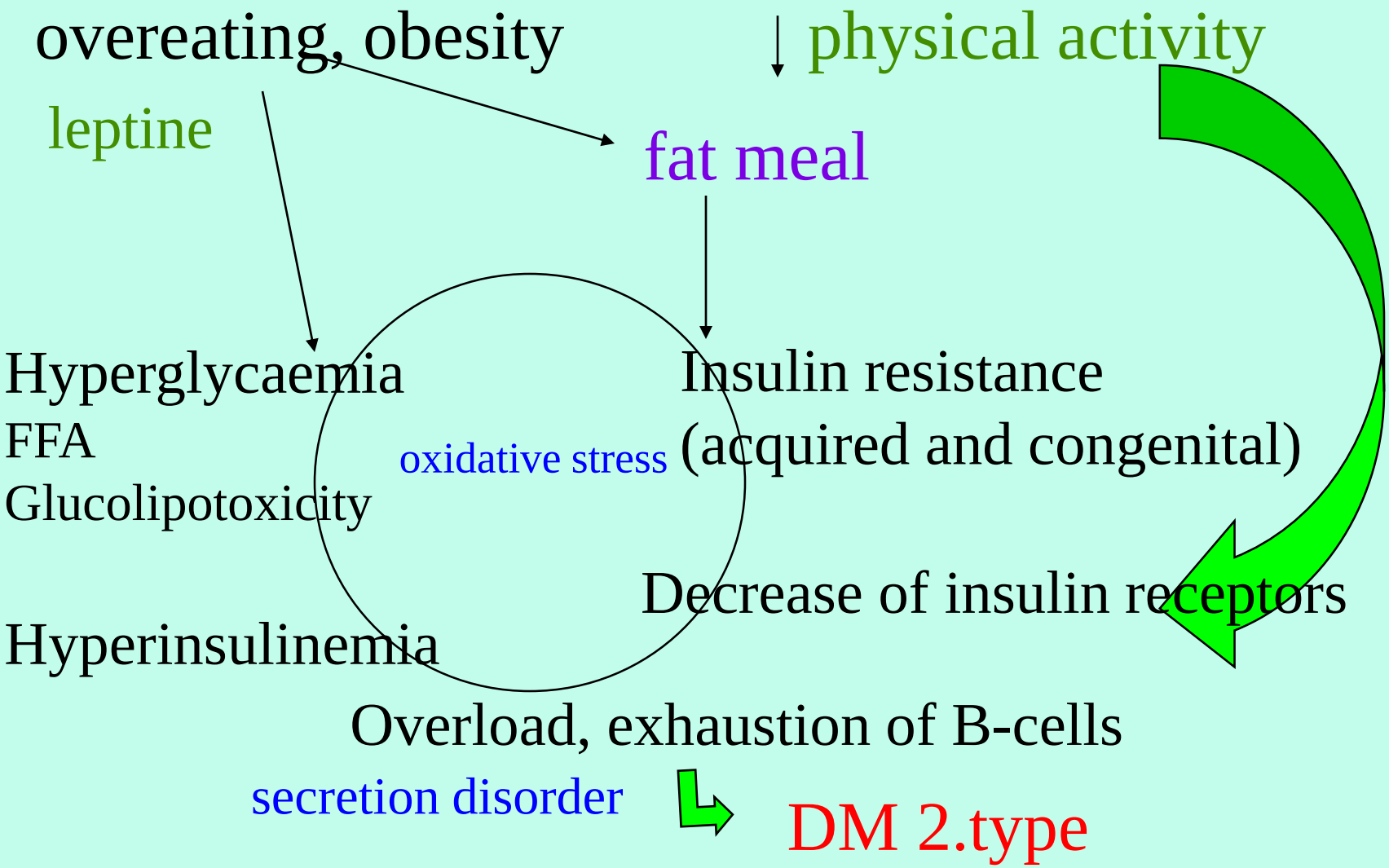
Pathogenesis of DM 2. type

(polygenic type of heredity-except MODY))



DM 2.type -contributing factors

fett meals

nutrition - overeating

high age

live style - stress, infection, operation
acute endangering situations
reduction of movement

alcohol - pancreatitis, cirhosis hepatis

iatrogenic DM - corticosteroids, thiazids,
contraceptivs

gravidity

endocrine disorders

DG criteria

Clin.symptoms	fasting gly	gly/pp.	dg
thirst,polydipsia, polyuria, weight loss, total disability infection(skin,genitals) poorly healing wounds suddenly developed complication	> 7,0	> 11,1	DM
	< 7,0	5,7-11,1 increased FPG, prediabetes	IGT
No clin. sympt.	< 5,6	< 7,8	norm

Oral glucose tolerance test
oGTT

	norm.	IGT	DM
fasting value	< 5,6	insignificant	>7
2-hour value	< 7,8	7,8- 11,0	>11,1

Laboratory examinations

Glycaemia -fasting value glycosuria
-postprandial value ketonuria
-glycaemic profil

Glycated hemoglobin (HbA_1C)

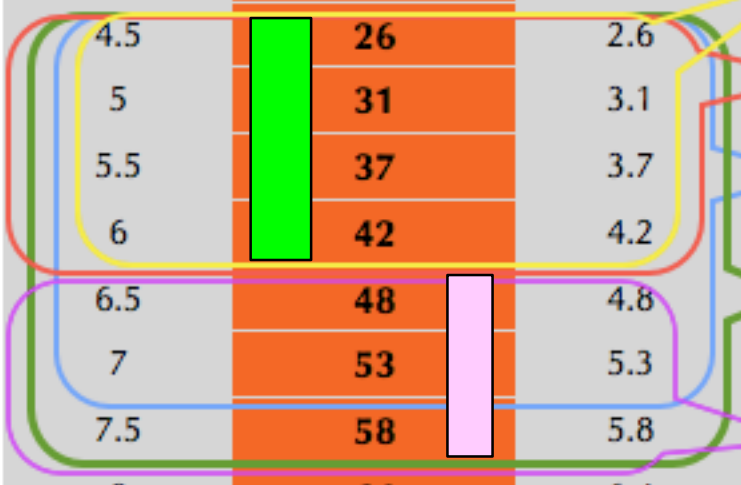
(fructosamin)

C peptid

Insulinaemia = IRI insulin antibodies (IA2,GADA)

biochemistry tests, lipids

DCCT	IFCC (mmol/mol)	IFCC %
4	20	2.0
4.5	26	2.6
5	31	3.1
5.5	37	3.7
6	42	4.2
6.5	48	4.8
7	53	5.3
7.5	58	5.8
8	64	6.4
8.5	69	6.9
9	75	7.5
9.5	80	8.0
10	86	8.6
10.5	91	9.1
11	97	9.7
11.5	102	10.2
12	108	10.8
12.5	113	11.3
13	119	11.9



zdraví lidé: 28-42 mmol/mol

ČDS: výborná kompenzace: <45 mmol/mol

ADA doporučení: <7.0% (DCCT)

ISPAD doporučení: < 58 mmol/mol

ČDS: uspokojivá kompenzace: <60 mmol/mol

Complications

- Acute ~ hypoglycaemic coma
  ~ hyperglycaemic coma -with ketoacidosis
  - hyperosmolar without ketoacidosis
  ~ laktacidotic coma
- Chronic

- Imunoallergic - local (lipodystrophia)

	hypo	hyper
start	sudden	slow
symptoms	nervosity shivering,agitation, hunger,sweating	nausea, vomitus, dehydration
insulin administration	precede	sometimes miss
thirst	-	+
cognition lost	sudden	slow
skin	wet	dry
skin turgor	normal	decreased
eyeball´s tonus	normal	soft
breathing	normal	profound-Kussmaul
breath	without aceton	aceton
glycaemia	low	high
gl/u	-	++
ac/u	-	+

Complications

- Acute

- Chronic a/ specific

  ~ microangiopathy- retina, kidney, foot

  ~ neuropathy

  b/ nonspecific

~ makroangiopathy ~ dermatol. dis. ~ liver ~ other

- Imunoallergic

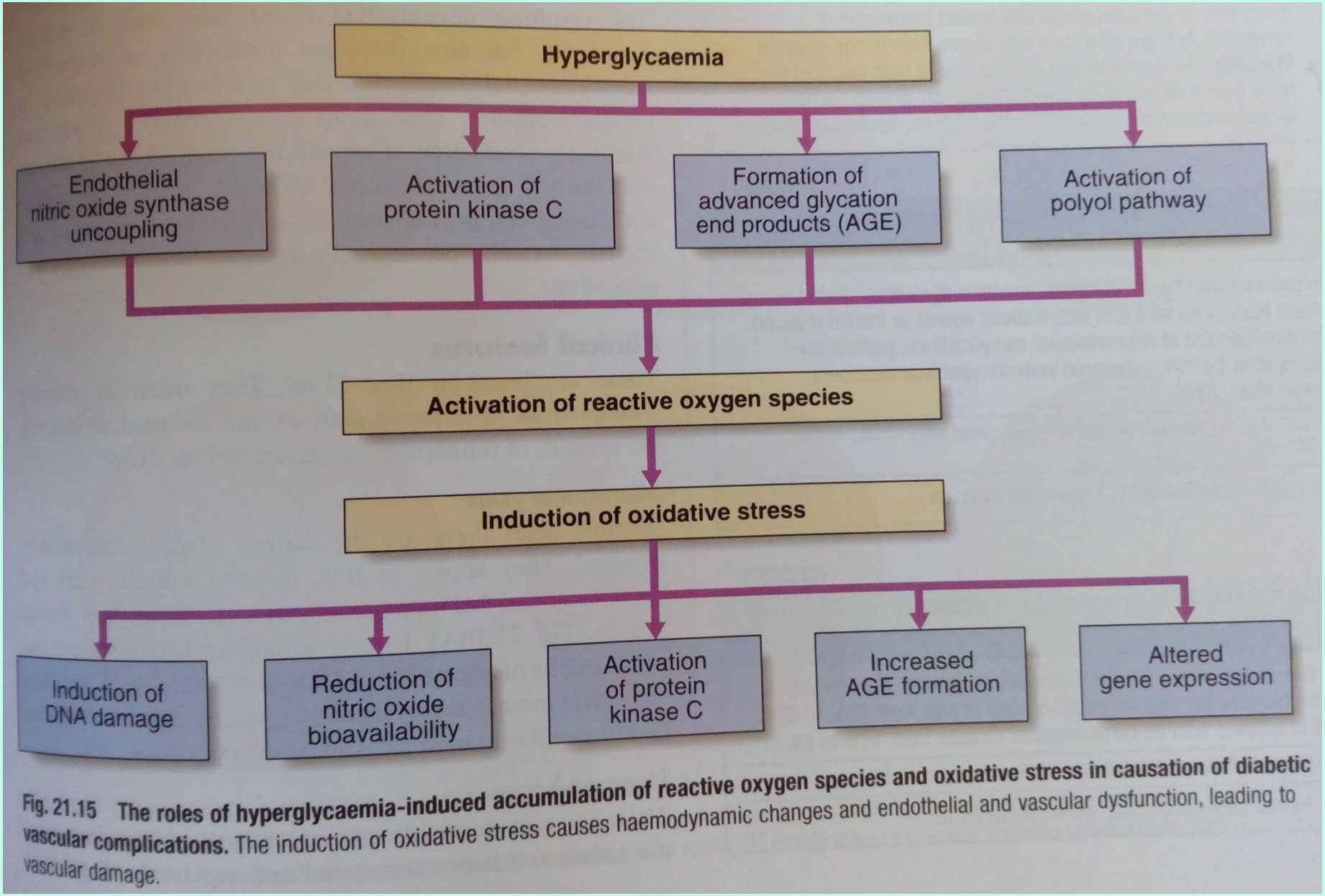


Fig. 21.15 The roles of hyperglycaemia-induced accumulation of reactive oxygen species and oxidative stress in causation of diabetic vascular complications. The induction of oxidative stress causes haemodynamic changes and endothelial and vascular dysfunction, leading to vascular damage.

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Cardiovascular mortality

3x ↑ in diabetics than nondiabetics

37x ↑ in diabetics with nephropathy than nondiabetics with nephropathy

Results of UKPDS

decrease in microvascular complications

about **25%**

due to HbA_1C improvement

from 7,9 to 7,0%

(act. from 64 to 54 mmol/mol)

Diabetic neuropathy

- Peripheral neuropathy-abnormal and decreased sensation ('glove and stocking' distribution)

  diabetic foot (neuropathy + angiopathy)

  Charcot's Joint - neuropathic arthropathy
- Autonomic neuropathy - digestive system, urinary tract, sex organs,..
- mononeuritis
- Diabetic amyotrophy - muscle weakness due to neuropathy

Diabetic retinopathy

- Nonproliferative retinopathy
- Macular edema
- Proliferative retinopathy

  growth of friable and poor-quality new blood vessels in the retina
- which can lead to severe vision loss or blindness (most common cause of blindness among non-elderly adults)

Diabetic nephropathy

- serious microangiopatic late complication of diabetes
- one of the most frequent causes of diabetics preterm death
- occurs in both types of diabetes
  - in 1/3 by type 1, less by type 2

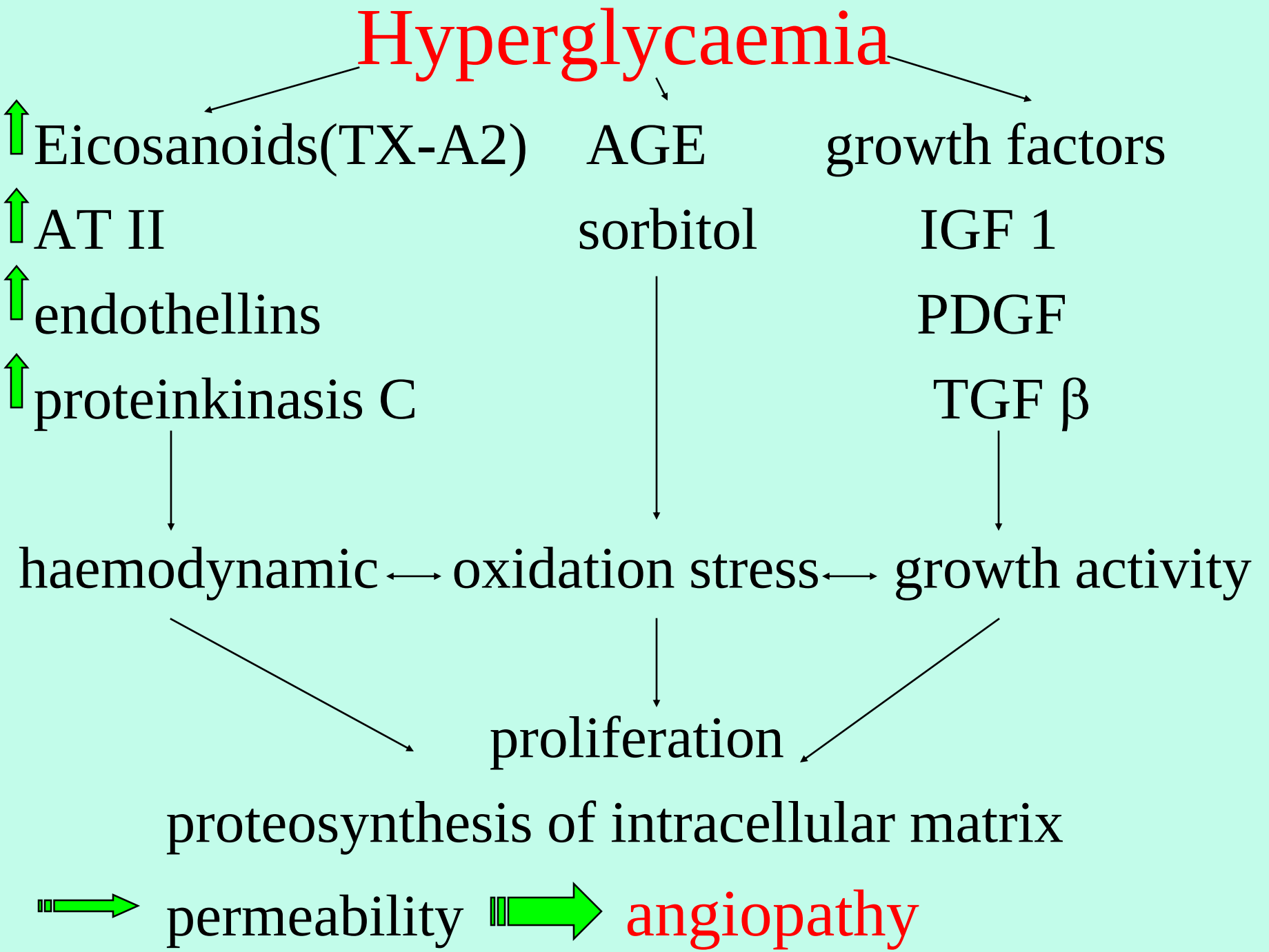
Diabetic nephropathy

- chronic progressive renal disease
- proteinuria
- hypertensis
- gradual decrease of renal functions

Etiopathogenesis

Factors important for the developement of DN:

- poor glycemic control
- hypertensis


Hyperglycaemia
Eicosanoids(TX-A2)
AT II
endothellins
proteinkinasis C
AGE
sorbitol
growth factors
IGF 1
PDGF
TGF β
haemodynamic
oxidation stress
growth activity
proliferation
proteosynthesis of intracellular matrix
permeability
angiopathy

Microalbuminuria

Definition:

MAU - excretion of alb/U,
which exceeds upper limit
of referential range for nondiabetics

Normally non detectable
with diagnostic proteinuric strips

Stages of diabetic nephropathy

(Mogensen 1993)

Stage	Duration of DM-years	Laboratory	GF	Compli-cations
1.Latent	**at the same time with dg of DM**	**norm**	**hyperfiltration**	**0**

hypertrophic

hyperfunctional

reversible by the strict control of gly

Stages of diabetic nephropathy

(Mogensen 1993)

Stage	Duration of DM-years	Laboratory	GF	Compli-cations
2.Incipient	2 - 6	a)MAU intermitent -after phys.exer.	norm.	0
	7 - 15	b)MAU permanent 30-300 mg/24h		

a) hyperfiltration reduction by the gly control, antihypert. drugs: reduction of MAU

b) reduction of MAU, decrease of GFR prevention

Stages of diabetic nephropathy

(Mogensen 1993)

Stage of	Duration DM-years	Laboratory	GF	Compli-cations
3.**Manifest**	**15 - 20**	**PU>500 mg/ 24/h**	**about 1ml/ min/month**	**retinopathy neuropathy**

gly control: ireversible

antihypertonic drugs: deceleration of progression

Stages of diabetic nephropathy

(Mogensen 1993)

Stage	Duration of DM-years	Laboratory	GF	Compli-cations
4. Chronic renal insuficiency	> 20	↑ S-krea ↑ S-urea ↑ S-uric acid	↓	progression of vascular compl.

End stage kidney

ACE inhibitors, RAS blockers

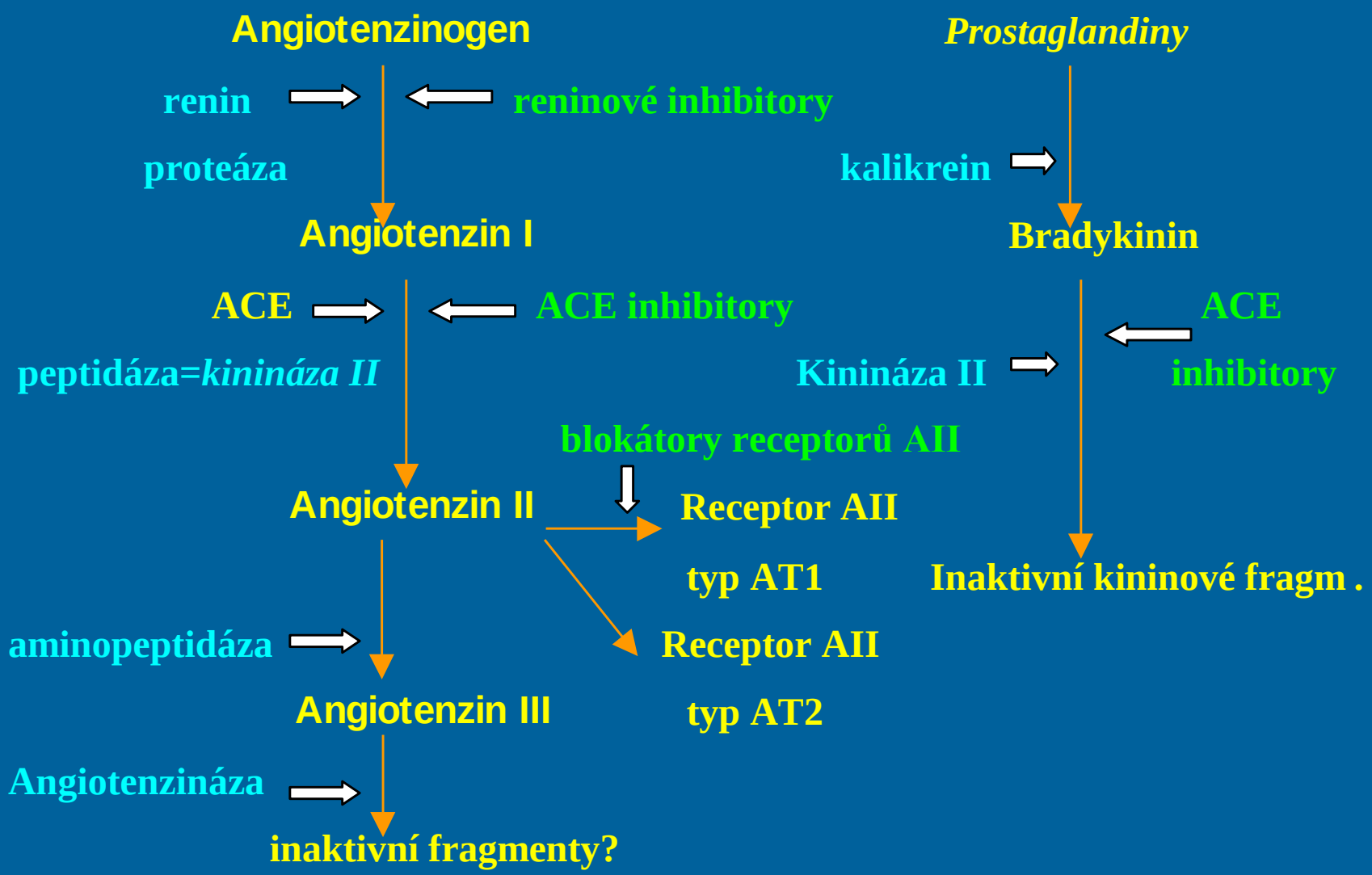
Effect: **antihypertensive**

cardioprotective

vasoprotective

- **in diabetics: action metabolic, antiproliferative, paracrine and specific nephroprotective .**

Renin-angiotenzinový systém



Therapy algoritm in diabetics with MAU

Diabetes control N → control correction

correct? Y ↓

Start of therapy RAS blockers

↓

Undesirable effects/ pregnancy- Y → stop. Other antihypert. drugs

N ↓

TK<130/85+decrease MAU-N → therapy of hypert. (add)

Y ↓

Repeat MAU each 3-6 m. → Risk factor elimination

↓

Goal:stable GFR. Stable/decreasing MAU. BP.

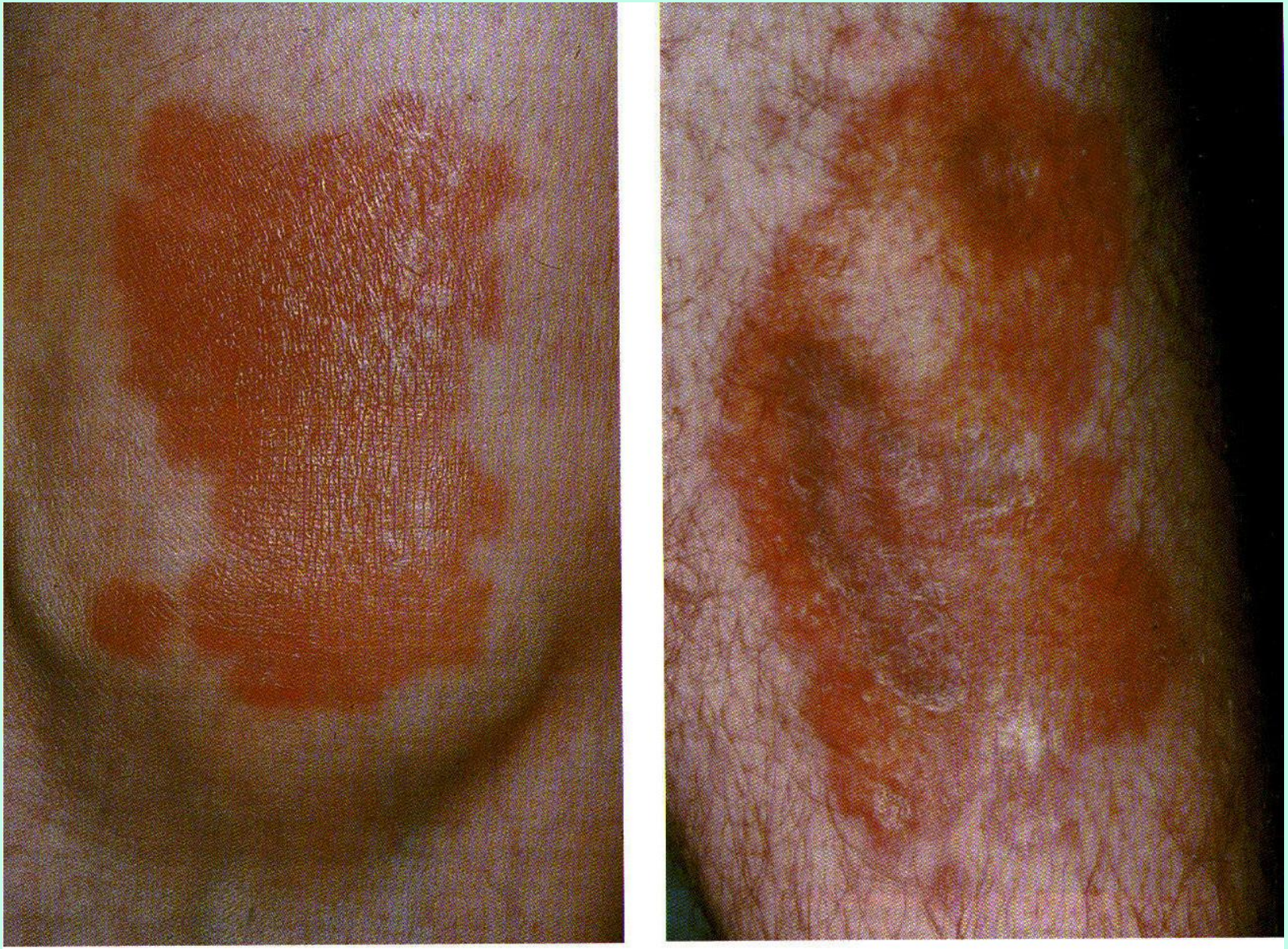
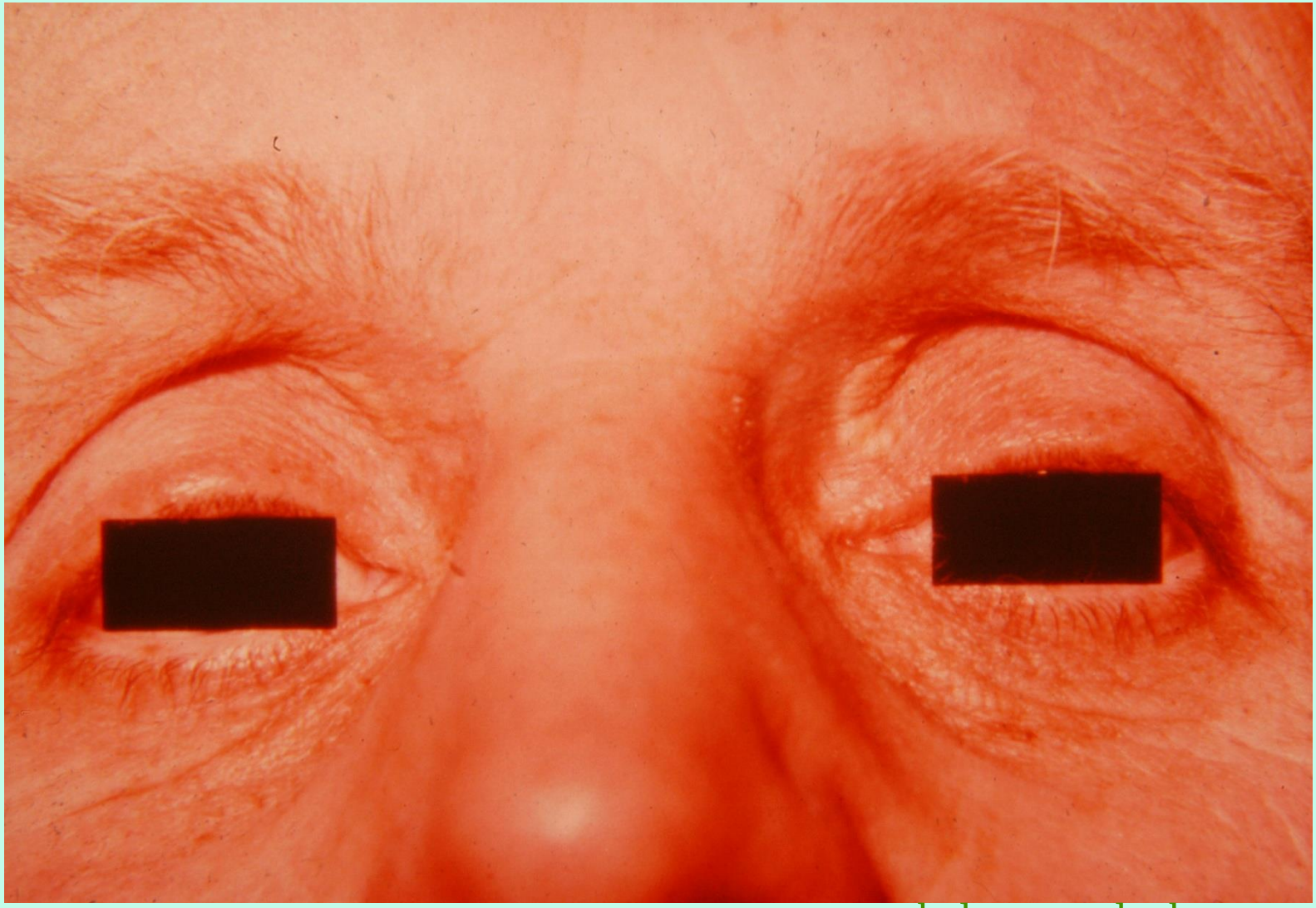
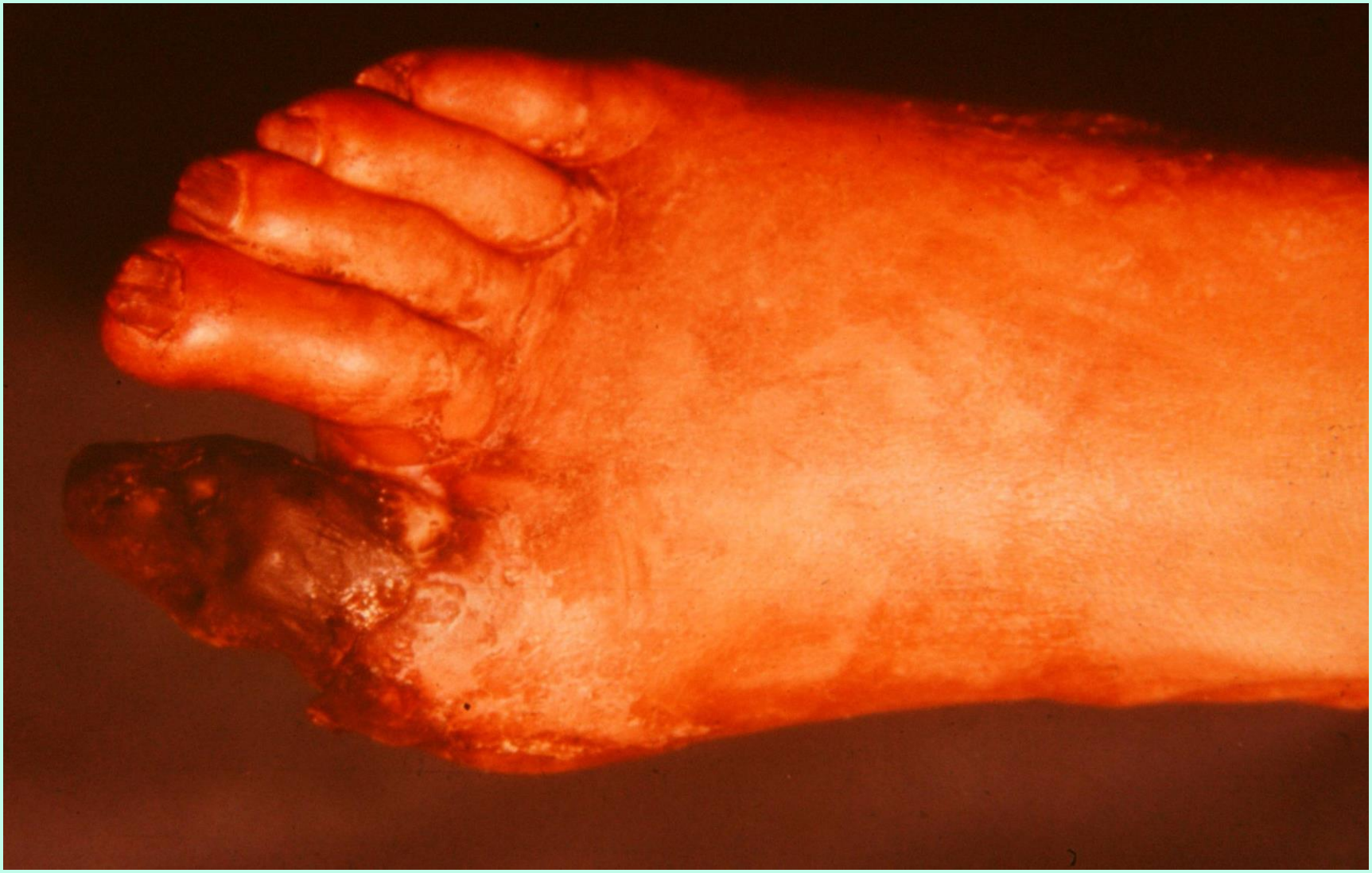


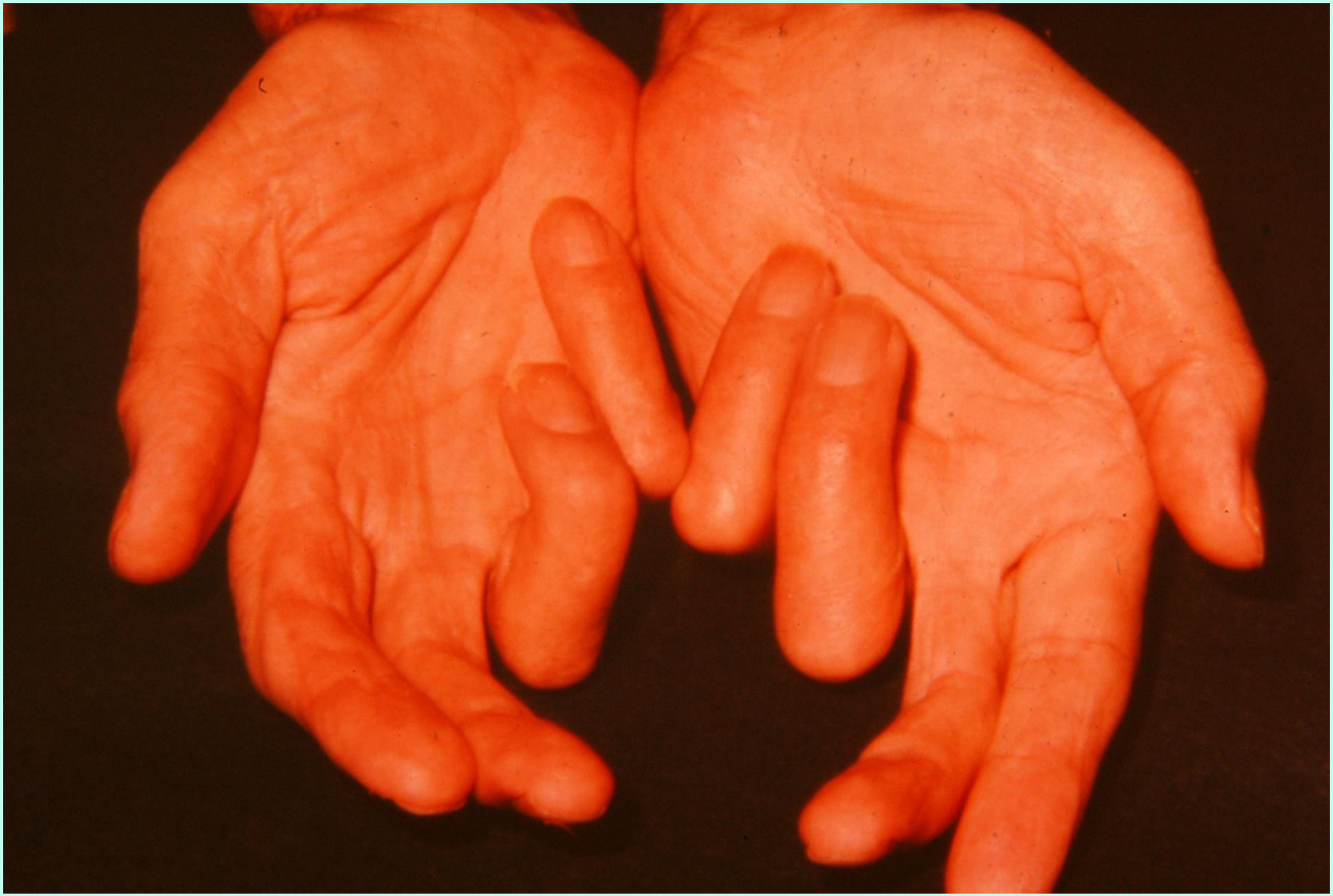
Fig. 60.1 Necrobiosis lipoidica diabeticorum (NLD). (a) An early lesion on an ankle, showing the erythematous stage. (b) A long-standing patch of NLD. Note the typical yellow, atrophic appearance with telangiectasia.



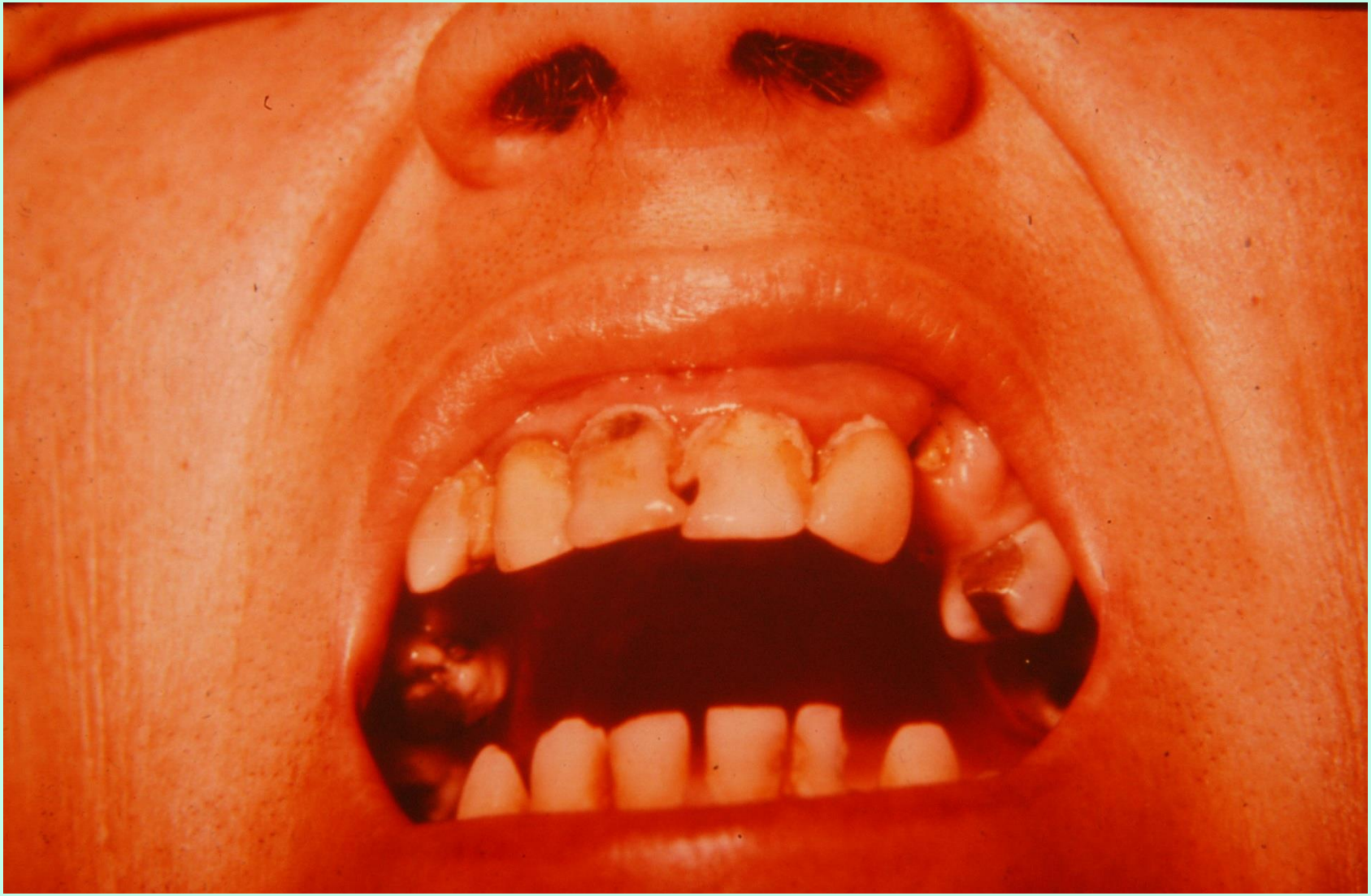
xanthelasma palpebrarum

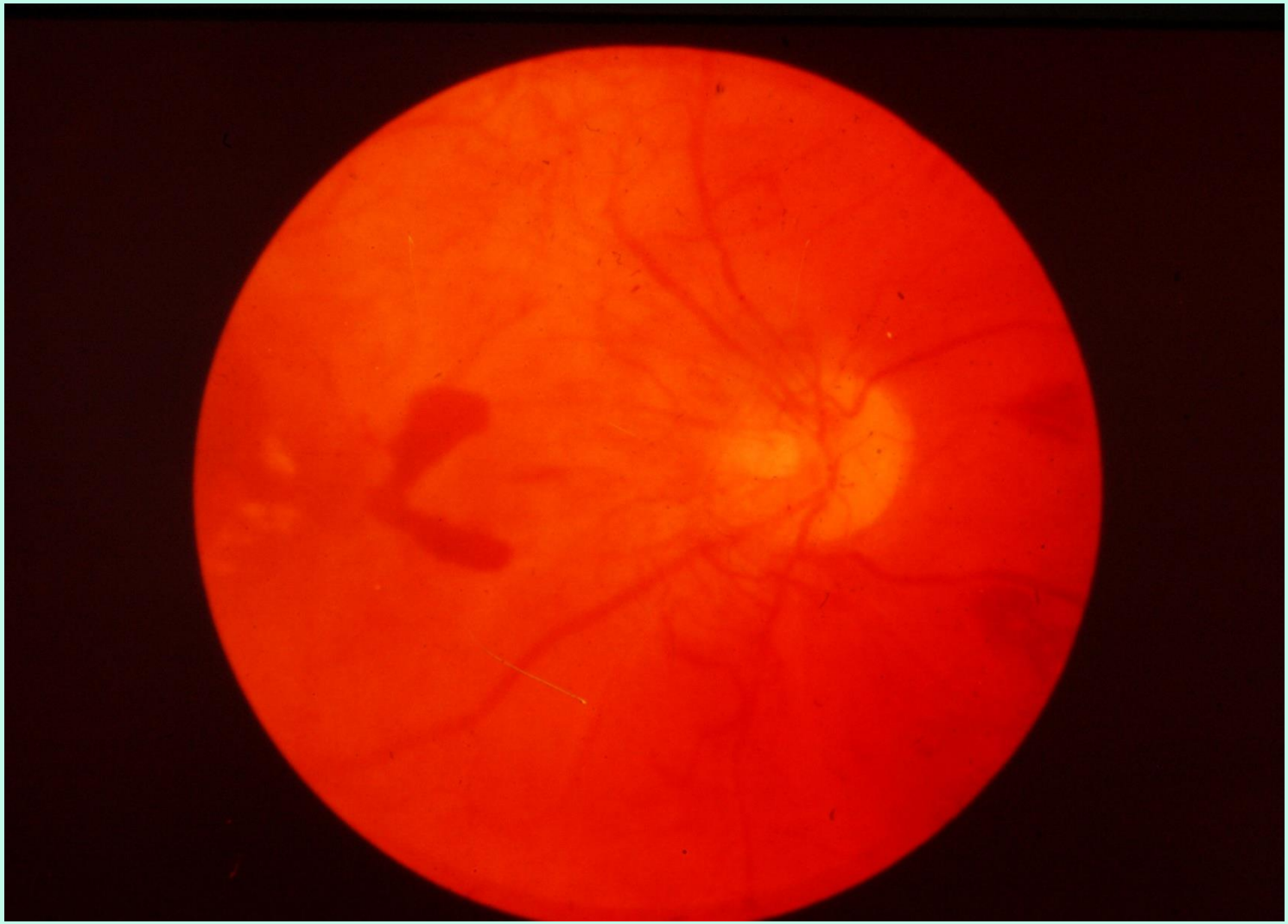


gangraena sicca



Dupuytrain´s contracture





vitreous hemorhagy