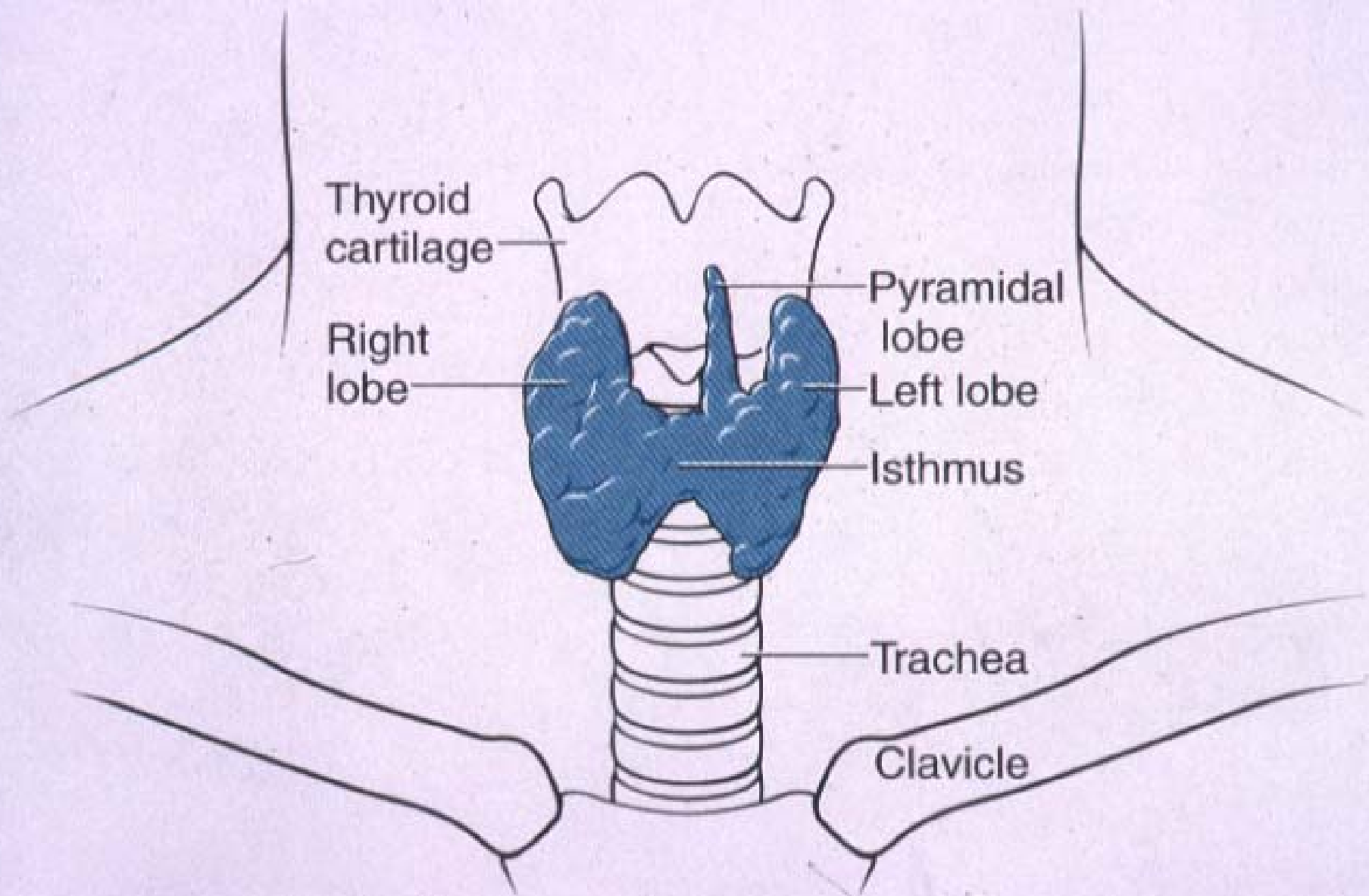


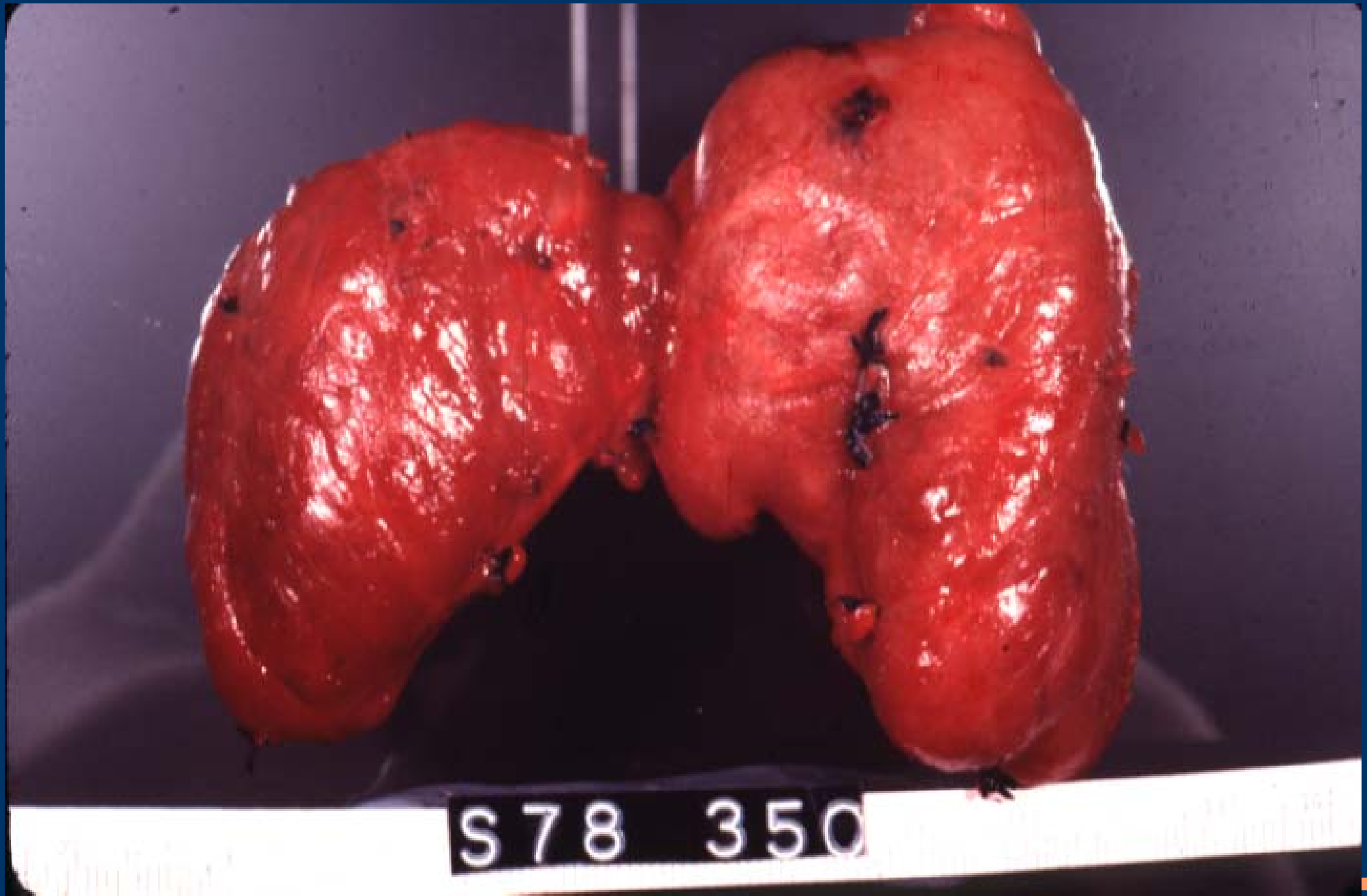
Clinical Correlates in Endocrinology

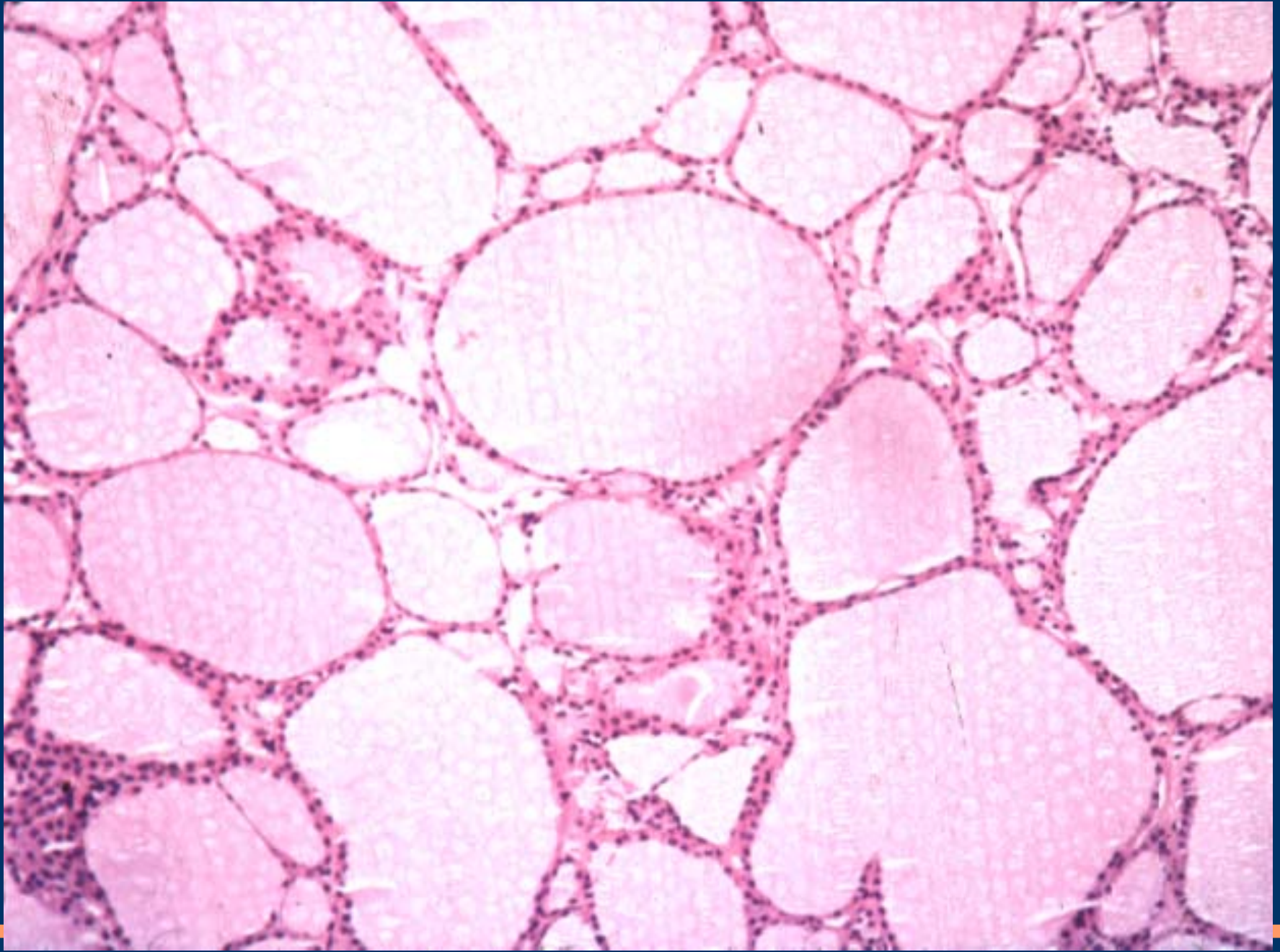
Ronald E. Cirullo, M.D., PhD.
Oregon Medical Group
Endocrinology

Thyroid

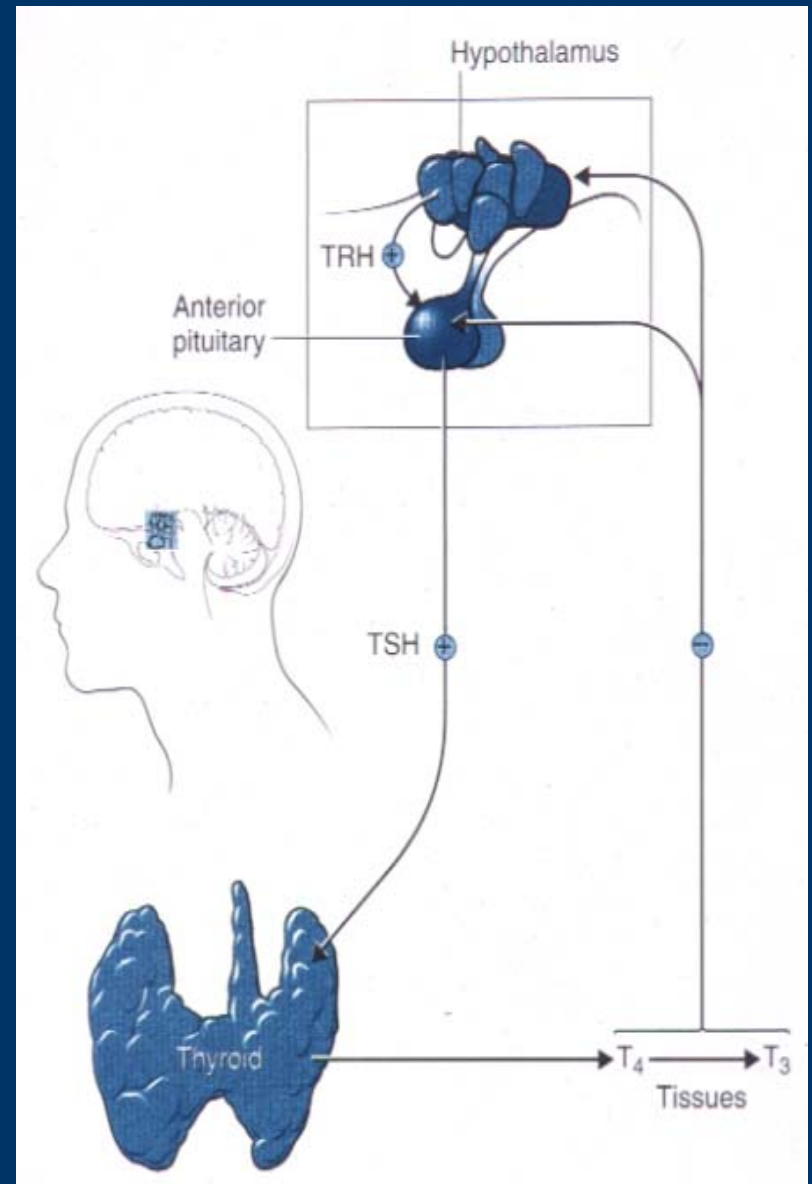
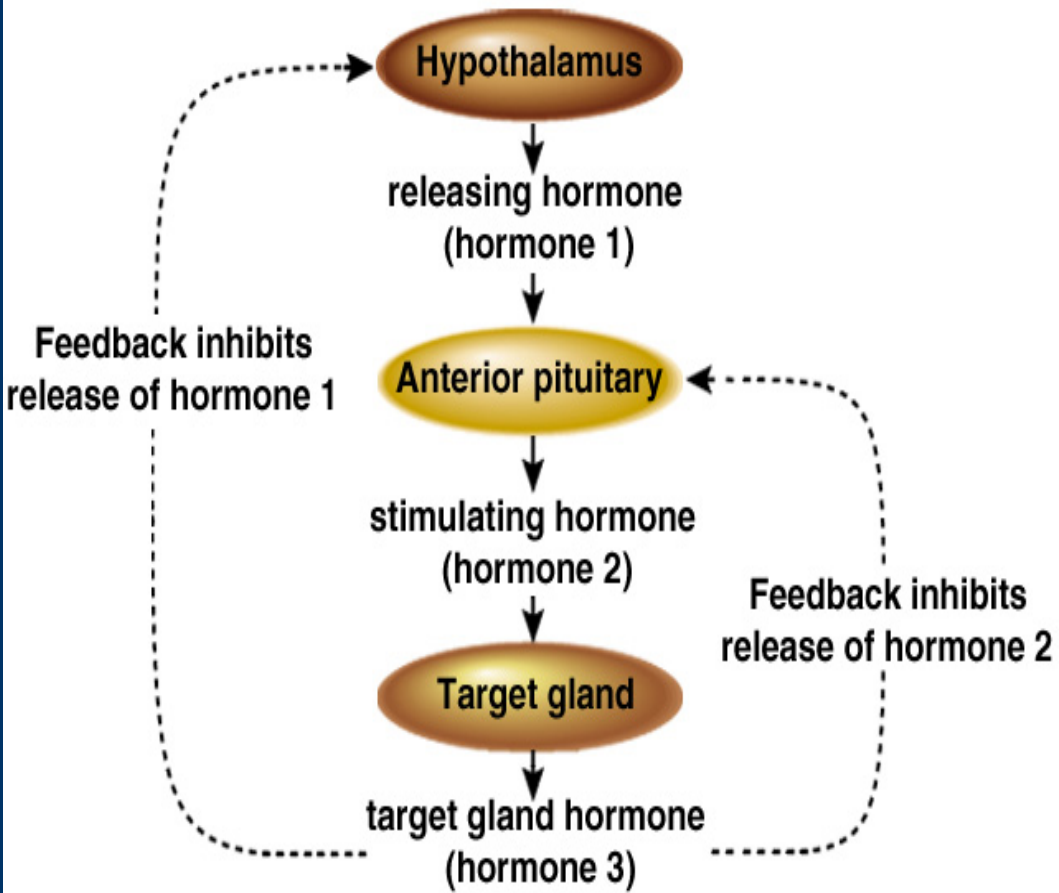
- Gross Description
 - Anterior and Inferior to Larynx
 - Bilobed Gland Arising Pharyngeal Epithelion
 - Microscopic Description
 - Spherical Follicles Lined by Cuboidal Epithelia [synthesizes hormone (T4)]
 - Colloid - Thyroglobulin [stores hormone (T4)]
 - Parafollicular "C" - Cells Secrete Calcitonin
-
-



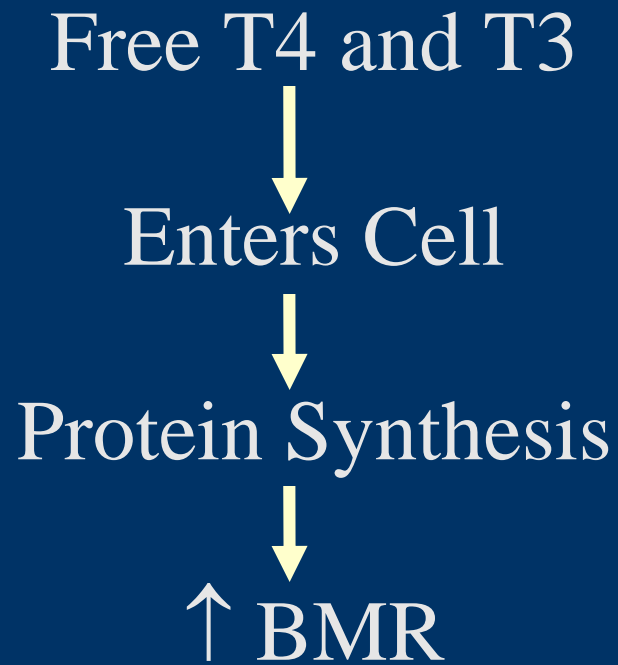




Endocrine Glands



Thyroid Hormone Metabolic Effect



Physiologic Effects of Thyroid Hormones

↑ BMR-----> ↑ Heat

Cardiovascular: ↑ HR & ↑ CO

GI - ↑ Motility

Skeletal - ↑ Bone Turnover

Neuromuscular - ↑
Contraction

Blood - ↑ RBC 2,3 DPG

Lipids

↑ Gluconeogenesis

↑ Cholesterol

Sympathetic Nervous System

↑ Beta - Adrenergic

↑ Catecholamines

Hypothyroidism - Adults

MYXEDEMA - Accumulation of Mucopoly-saccharide in skin and visceral sites resulting in non-pitting edema.

- Weight Gain
 - Muscle Cramps
 - Fatigue
 - Slowed Mentation
 - Slowed Speech
 - Cold Intolerance
 - Constipation
 - Cardiomegaly
 - Pericardial Effusion
-
-



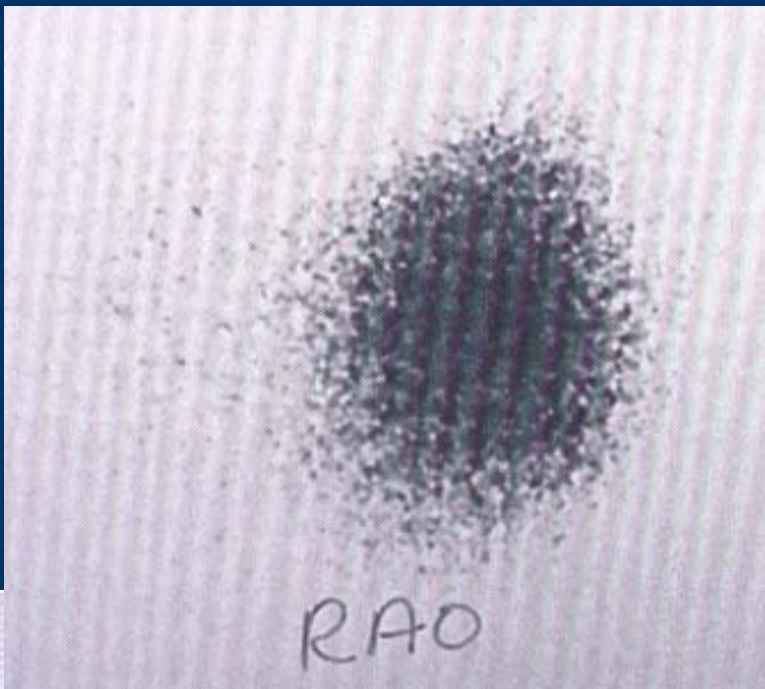
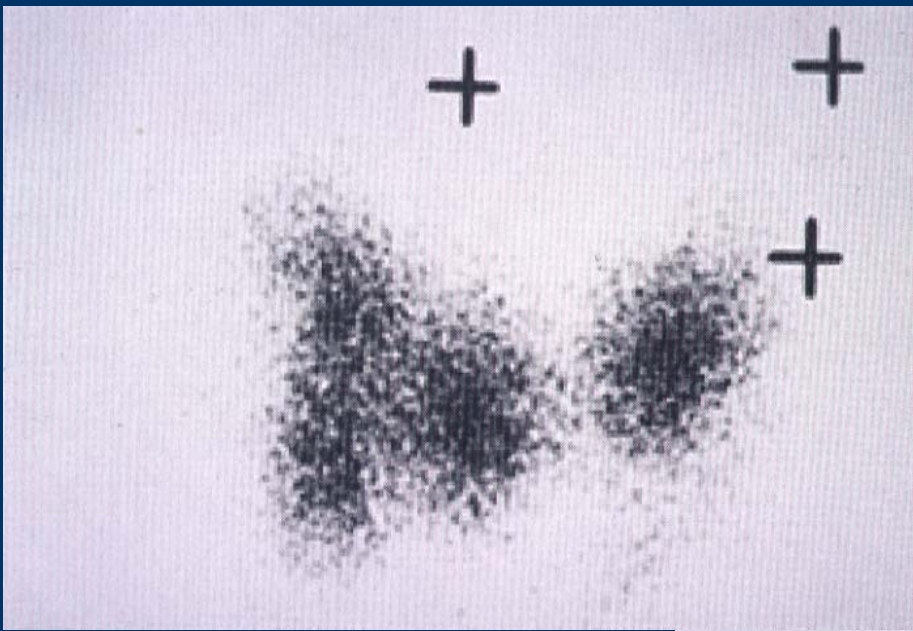
Thyrotoxicosis (↑ Thyroid Hormone)

Common

- Grave's Disease
- Toxic Adenoma
- Toxic Multinodular Goiter

Less Common

Subacute Thyroiditis
Hashimoto's Thyroiditis -
Postpartum
Amiodarone



Thyrotoxicosis - Clinical Features

Sympathetic Nervous System

- Nervousness
- Tremor
- Tachycardia
- Palpitations
- Hyperreflexia
- Staring Gaze
- Warm Flush Skin

GI

- Hypermotility
 - Malabsorption
 - Diarrhea
 - Weight Loss
-
-

Grave's Disease

An autoimmune disorder in which a variety of autoantibodies cause a diffuse hyperfunctioning thyroid. Grave's disease is the most common cause of primary or endogenous hyperthyroidism.

- Primarily Women: 3rd to 4th Decade
 - Familial
 - HLA-DR3
-
-

Grave's Disease

- Thyrotoxicosis
 - Diffuse Thyroid Enlargement (Bruit)
 - Ophthalmology
 - Wide Staring Gaze
 - Lid Lag
 - Protuberant Eyes (Exophthalmos)
 - Pretibial Edema, Hyperpigmentation
-
-



Goiter

Goiter is simple enlargement of the thyroid due to TSH stimulation because of impaired (decreased) thyroid hormone (T3 or T4). Goiter is the most common thyroid disease worldwide.

Goiter

Endemic

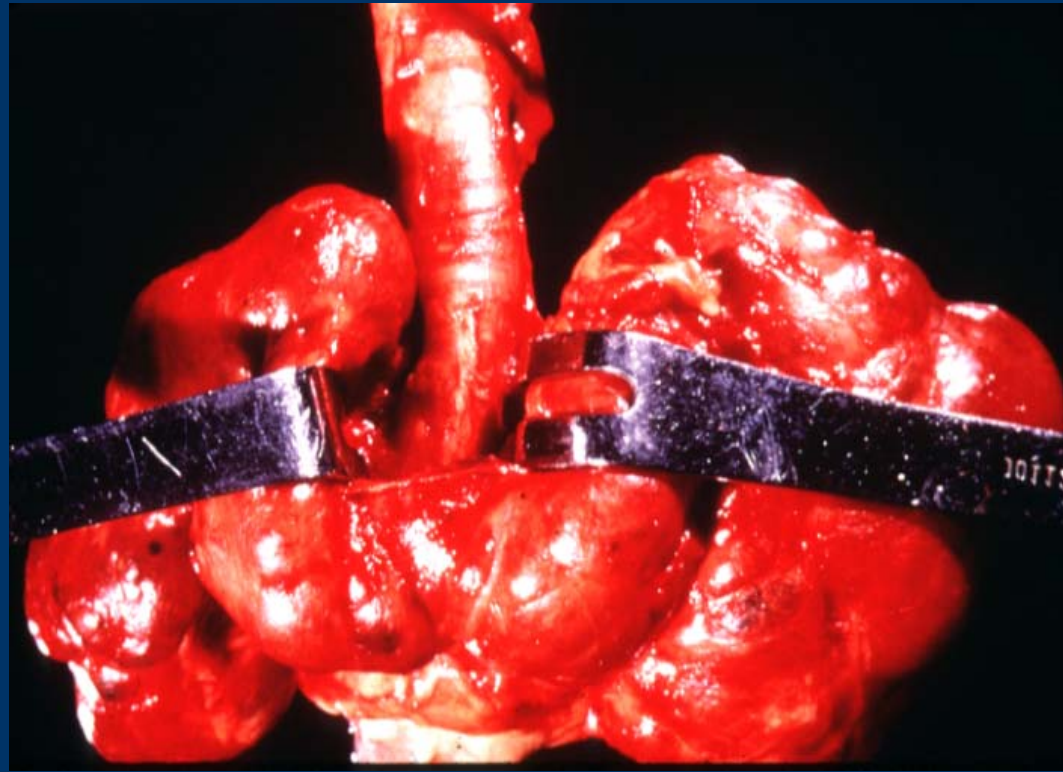
- ↓ I₂ - Mountainous Regions

Sporadic

Usually Unknown
Cruciferus Vegetables

- I₂ - 150ug/day
 - Average American Diet 250 to 750 ug/day
 - Iodine-----> Iodide
 - MIT + DIT-----Iodine Peroxidase-----> T4 or T3
-
-





Diabetes Mellitus



Diabetes Mellitus (DM)

DM is a chronic disorder of carbohydrate, fat, and protein metabolism. DM is characterized by hyperglycemia resulting from defects in insulin. The chronic hyperglycemia is associated with dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

- 13 Million in USA
 - 35,000 Annual Mortality
 - Type I - Life Time Risk ~ 0.5%
 - Type II - Life Time Risk ~ 5-7%
-
-

Criteria for Diagnosis of Diabetes Mellitus

Normoglycemia

FPG < 110

2-h PG* < 140

IFG or IGT

FPG \geq 110 & < 126 (IFG)†

2-h PG* \geq 140 & < 200 (IGT)†

Diabetes Mellitus

FPG \geq 126 (x2)†

2-h PG* \geq 200

Random >200

FPG = Fasting Plasma Glucose

PG* = Glucose Load of 75g

F = Fasting = No food - 8 hours

1FG = Impaired Fasting Glucose

IGT = Impaired Glucose

Tolerance

Blood Glucose & Various Hormones

Hormone

- Insulin
- Glucocorticoids
- Glucagon
- Growth Hormone
- Epinephrine

Action

- ↓ Glucose
- ↑ Glucose
- ↑ Glucose
- ↑ Glucose
- ↑ Glucose



Diabetic
Syndrome

Insulin - Metabolic Actions

Insulin is the **only*** hormone that ↓ blood glucose. Insulin travels to its target sites of liver, muscle, & fat cells. Glucose can enter these cells only with the aid of insulin. Insulin binds with a cellular receptor site to exert its effect.

***IGF-2**

Effects of Insulin

Carbohydrate

- ↑ Uptake of Glucose by Cells
- ↑ Liver Glycogen
- ↑ Pyruvate

Fat

- ↓ Breakdown of Fat
 - ↑ Formation of Fat
 - ↓ FFA
-
-

Genetics - DM

Type I - 15%

- Northern Europeans
- 40% Concordance
- 6% - 1st Order
- 95% HLA DR3
- DQB - Linkage

Type II - 85%

60-80% concordance in twins

No HLA association

Insulin Resistance

Relative Insulin

Deficiency

Clinical

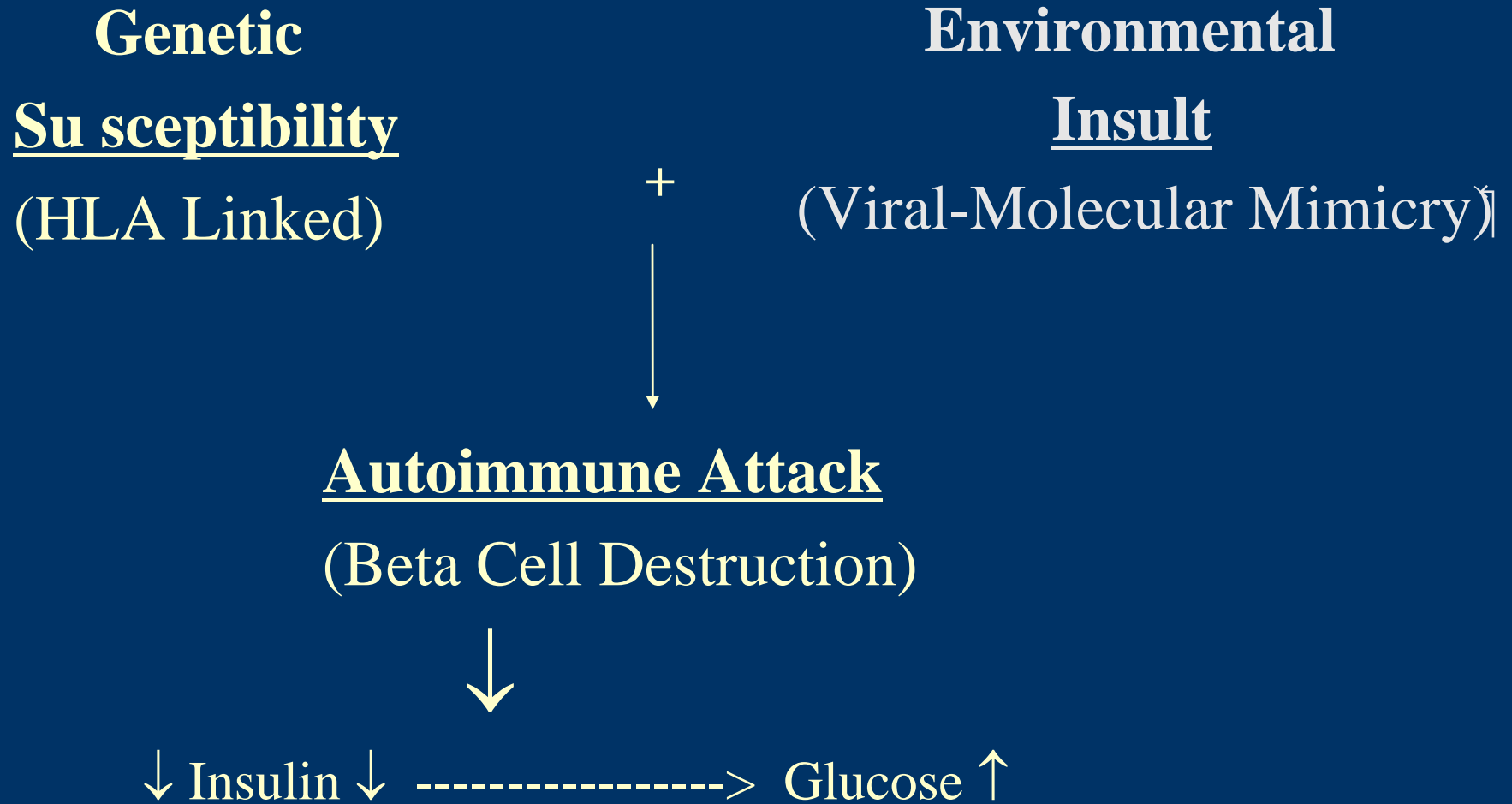
Type I - 15%

- <20 y/o
- Normal Weight
- ↓ Insulin
- Islet Cell Abs
- **Ketoacidosis - common**

Type II - 85%

- >30 y/o
- Obesity
- N/ ↑ Insulin
- No islet cell abs
- **Ketoacidosis - Rare**
- Hyperosmolar Non-Ketotic Acidosis

Islet Cell Destruction in IDDM (Type I)



Diabetic Ketoacidosis (Type I - DM)

↓ Insulin--> ↑ Fat Breakdown--> ↑ Ketoacids--> Metabolic
(Ketone Bodies) Acidosis

Lab Findings

↓ pH

↑ Glucose
(600-800)†

↓ HCO_3^-

↑ Ketones

Diabetes - Type II - Risk Factors

- $FH_x(+)$ Previous IGT or IFG
 - Obesity: $>20\%$ IBW or $BMI \geq 27$ kg/mL \uparrow BP ($\geq 140-90$)
HDL ≤ 35 mg/dl
 - Race/Ethnicity Triglycerides ≥ 250 mg/dl
 - **Age ≥ 45** GDM or baby $> 9\%$
-
-

Diabetes Type II - NIDDM - Pathogenesis

Deranged Insulin Secretion

- Increased Insulin Secretion
- Delayed Insulin Secretion
- Deficiency of Insulin Secretion

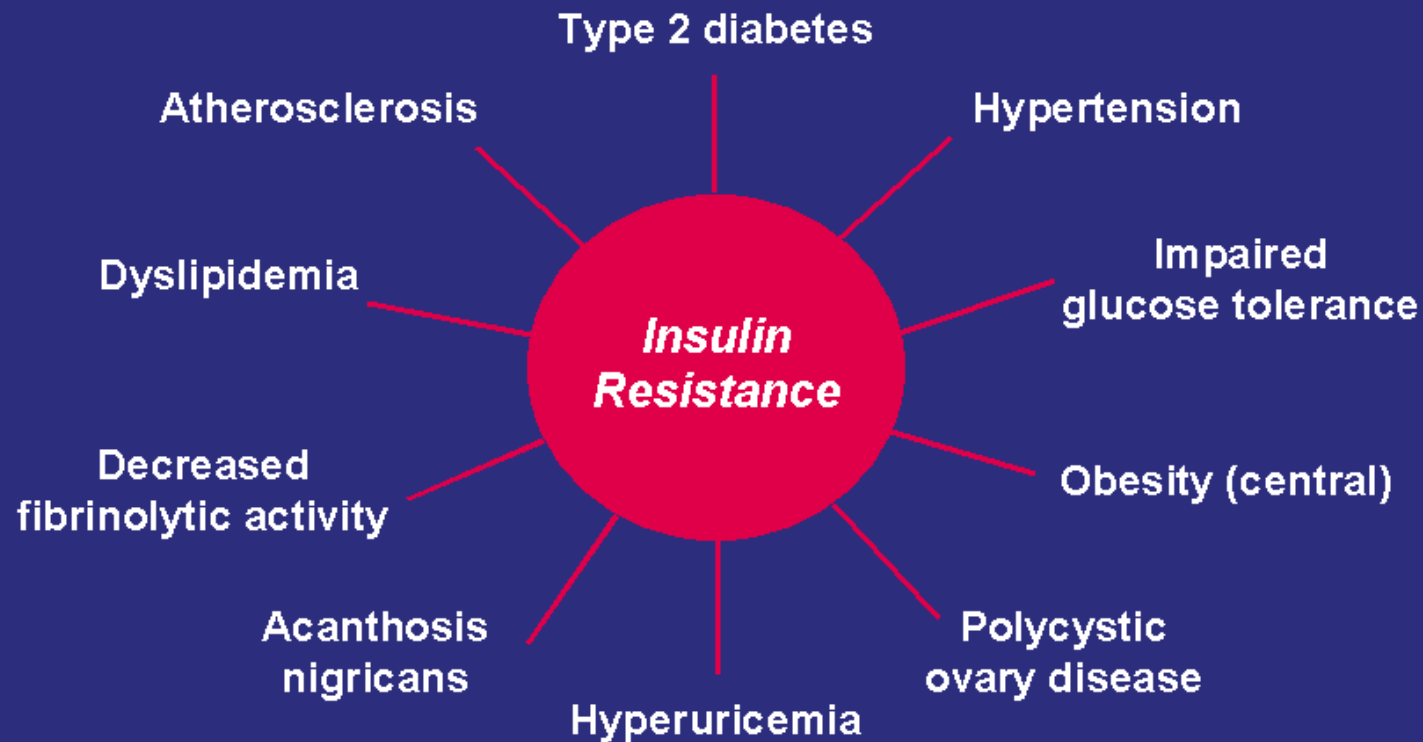
Insulin Resistance

- ↓ Number of Receptors
- Postreceptor Defects
- Reduced GLUTS

Obesity

- **80% Type II Obese**
 - ↓ Insulin
-
-

Insulin Resistance: Associated Conditions



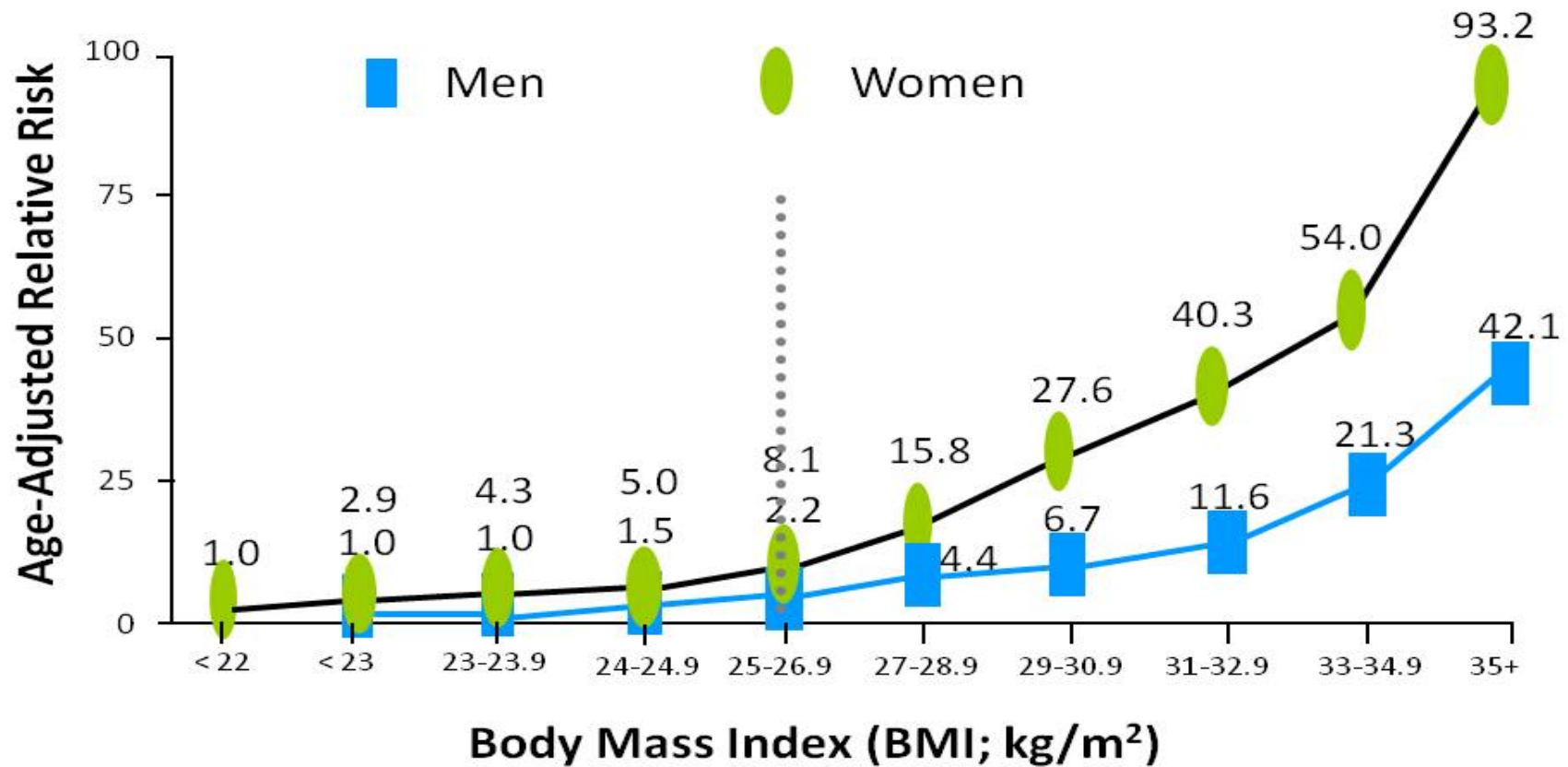
Adapted from Consensus Development Conference of the American Diabetes Association. *Diabetes Care*. 1998;21:310-314.



Body Mass Index

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight	Healthy					Overweight					Obese					Extremely obese							
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Relationship Between BMI and Risk for Type 2 Diabetes Mellitus



Chan J, et al. *Diabetes Care*. 1994;17:961-969.
Colditz G, et al. *Ann Intern Med*. 1995;122:481-486.

Complications of diabetes in the United States

Heart disease and stroke

- **Heart disease is the leading cause of diabetes-related deaths.** Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes.
- The risk for stroke is 2 to 4 times higher among people with diabetes.
- About 65% of deaths among people with diabetes are due to heart disease and stroke.

High blood pressure

- **About 73% of adults with diabetes have blood pressure greater than or equal to 130/80 mm Hg or use prescription medications for hypertension.**

Blindness

- **Diabetes is the leading cause of new cases of blindness among adults aged 20-74 years.**
 - Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year.
-
-

Kidney disease

- Diabetes is the leading cause of end-stage renal disease, accounting for 44 percent of new cases.
- In 2001, 42,813 people with diabetes began treatment for end-stage renal disease.
- In 2001, a total of 142,963 people with end-stage renal disease due to diabetes were living on chronic dialysis or with a kidney transplant.

Nervous system disease

- About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and other nerve problems.
- Severe forms of diabetic nerve disease are a major contributing cause of lower-extremity amputations.

Amputations

- More than 60% of nontraumatic lower-limb amputations occur among people with diabetes.
 - In 2000-2001, about 82,000 nontraumatic lower-limb amputations were performed annually among people with diabetes.
-
-

Deaths among people with diabetes, United States, 2000

- **Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2000.** This ranking is based on the 69,301 death certificates in which diabetes was listed as the underlying cause of death. Altogether, diabetes contributed to 213,062 deaths.
 - **Diabetes is likely to be underreported as a cause of death.** Studies have found that only about 35% to 40% of decedents with diabetes have diabetes listed anywhere on the death certificate and only about 10% to 15% have it listed as the underlying cause of death.
 - **Overall, the risk for death among people with diabetes is about 2 times that of people without diabetes.**
-
-

Economic Consequences of Diabetes in the United States, 1997

Total Annual Costs: \$98.2 billion*(2007 174 billion)

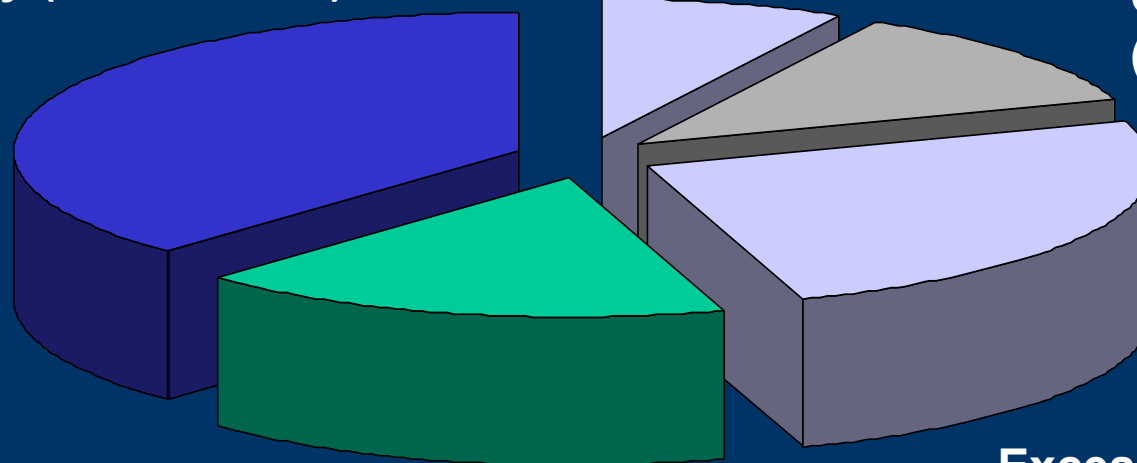
Indirect Costs = \$54.1 billion

Direct Costs = \$44.1 billion

Disability (\$37.1 billion)

**Diabetes/
Acute Glycemic Care
(\$7.7 billion)**

**Excess Prevalence of
Chronic Complications
(\$11.8 billion)**

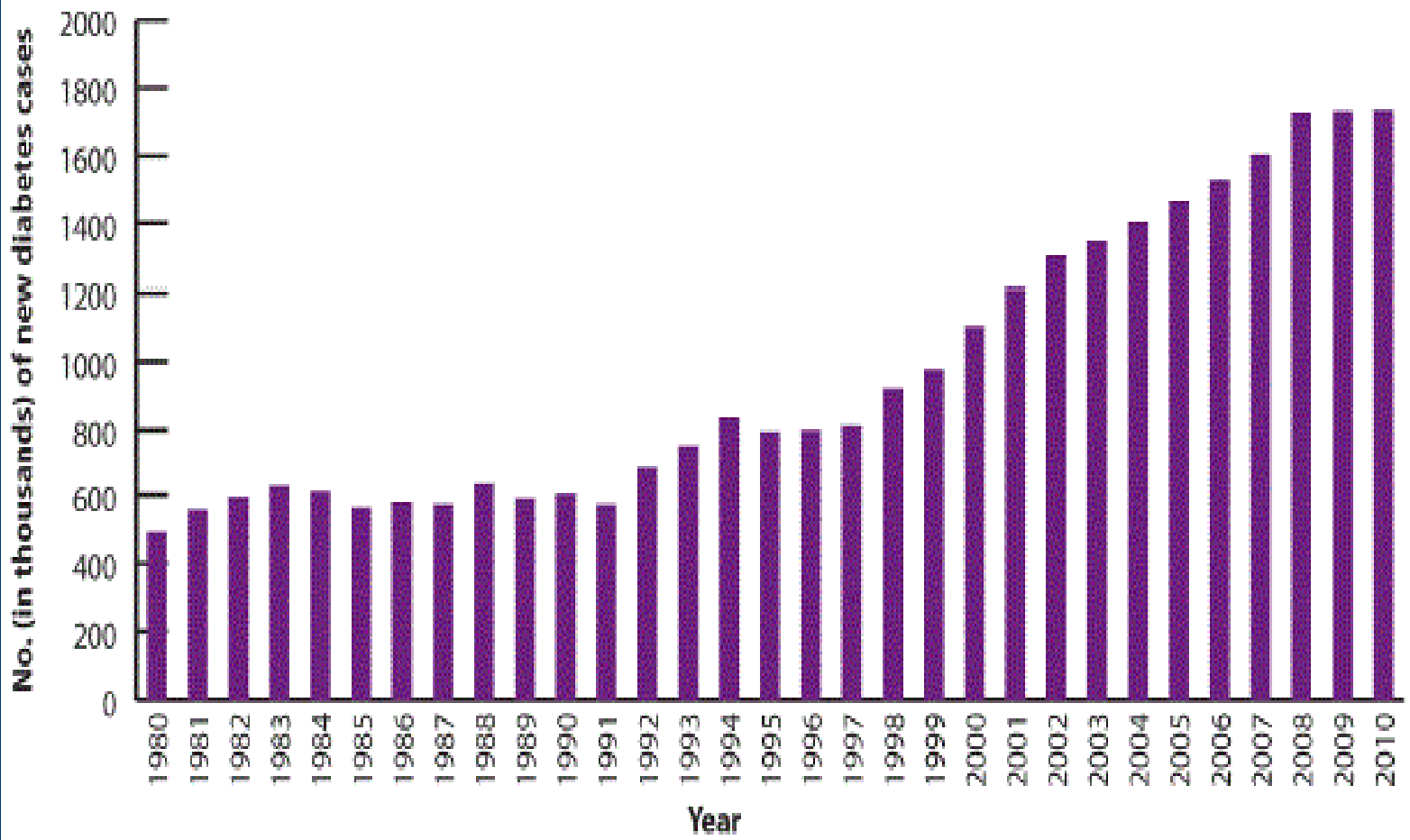


Premature Mortality (\$17.0 billion)

**Excess Prevalence of
General Medical Conditions
(\$24.6 billion)**

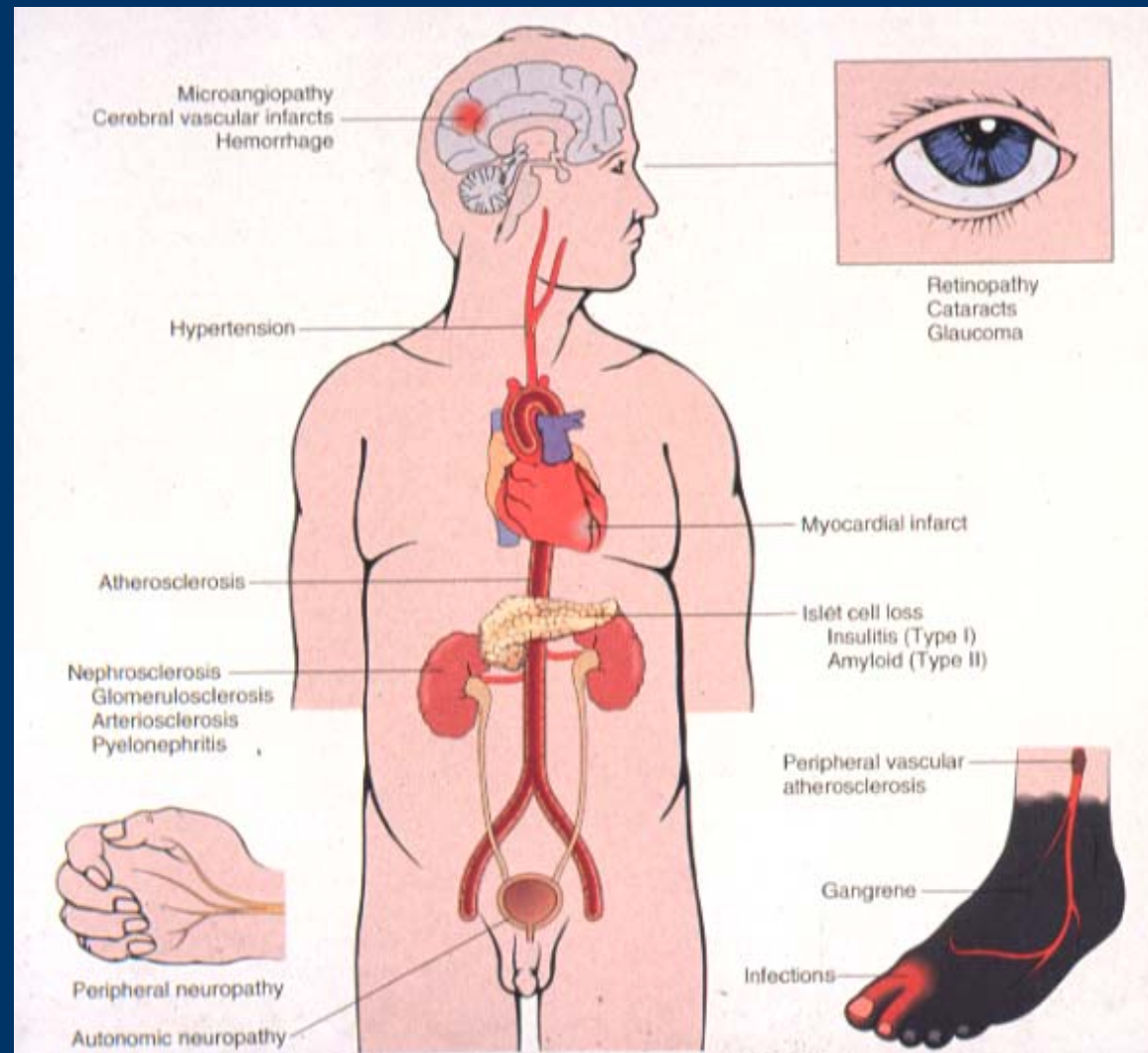
***1997 dollars.**

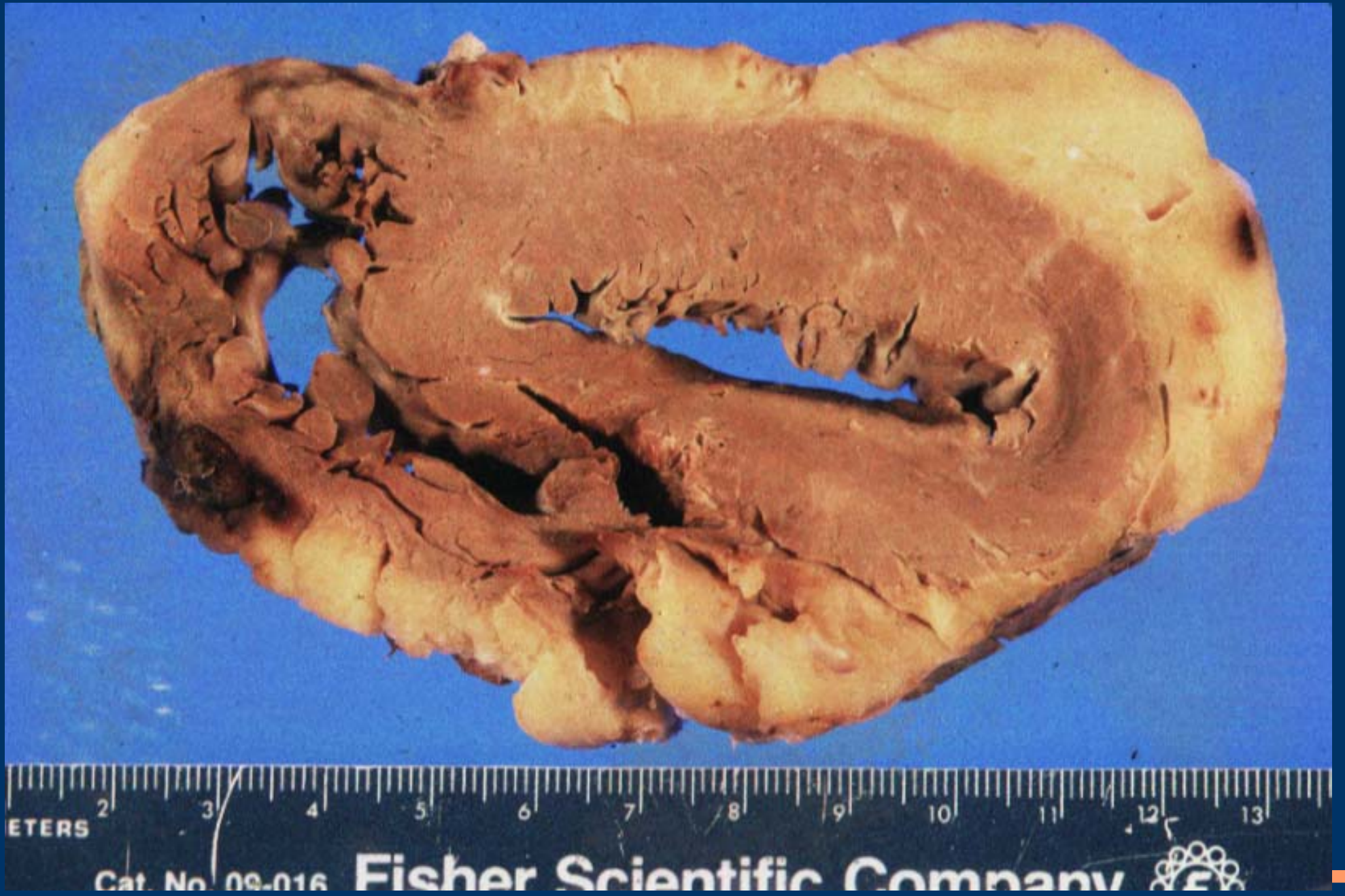
American Diabetes Association. *Diabetes Care*. 1998;21:296-309.



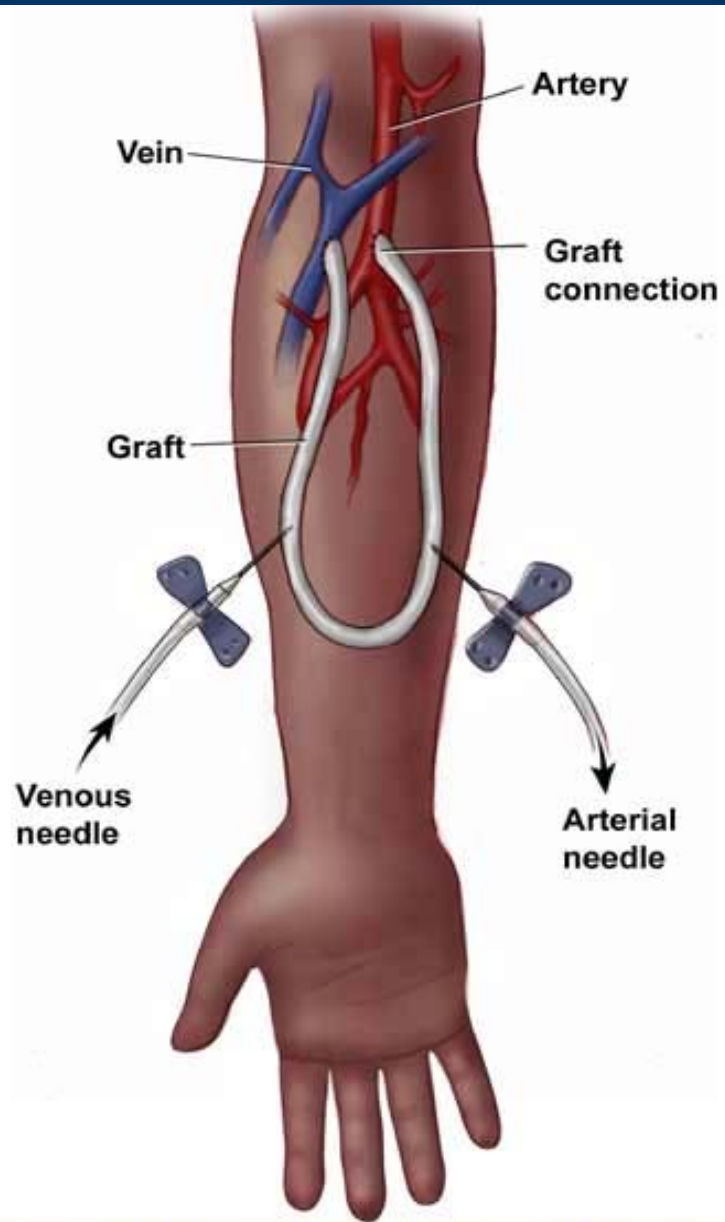
Complications of Diabetes Mellitus

- Microangiopathy
- Nephropathy
- Retinopathy
- Neuropathy

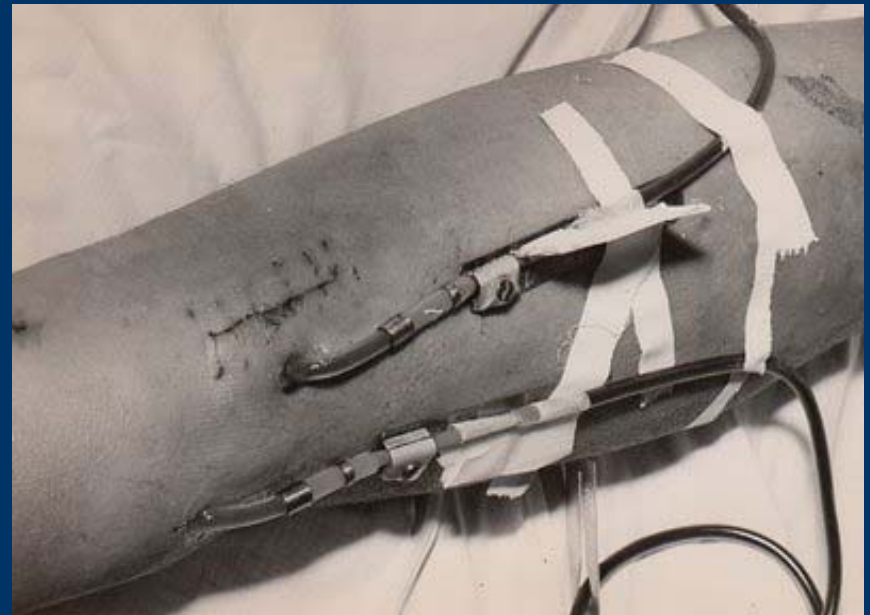


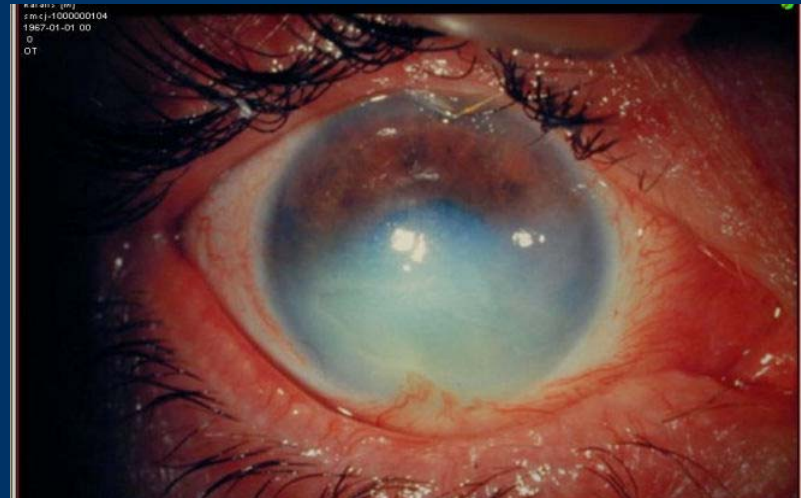
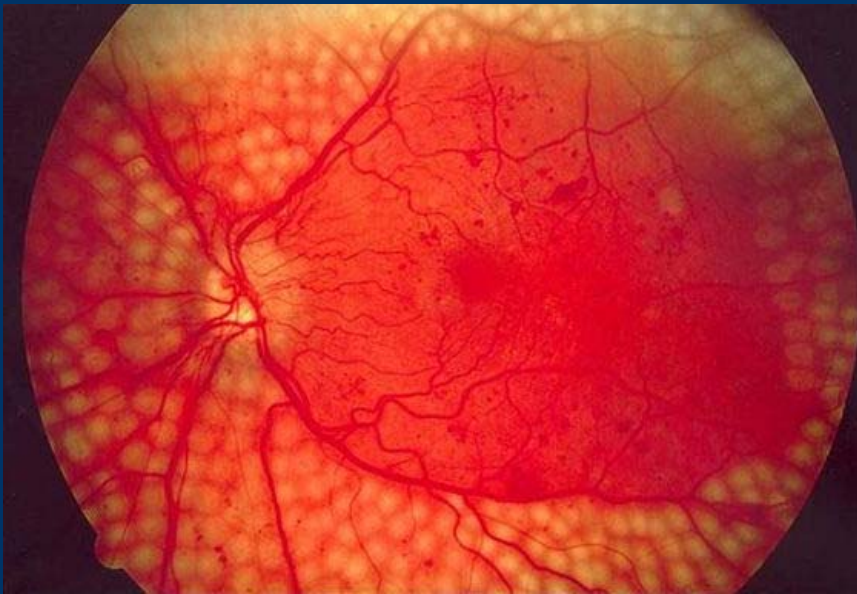
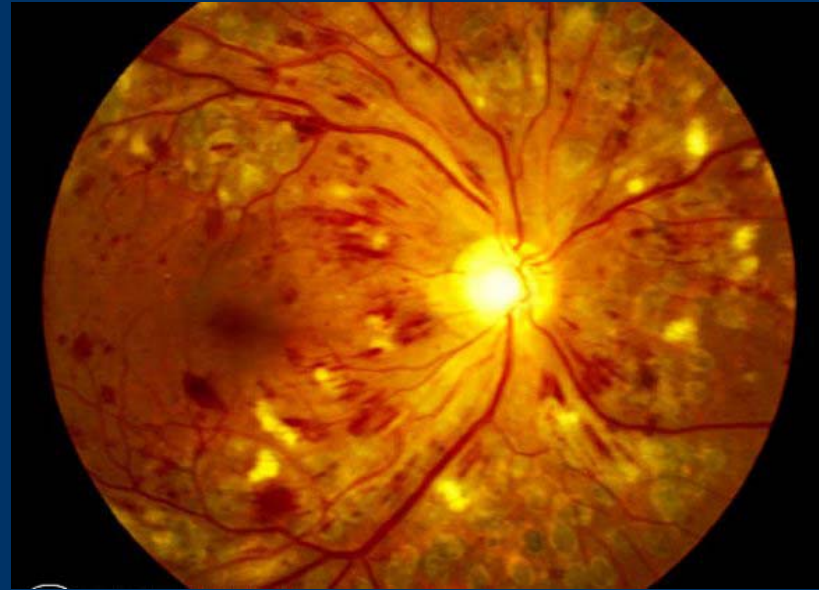
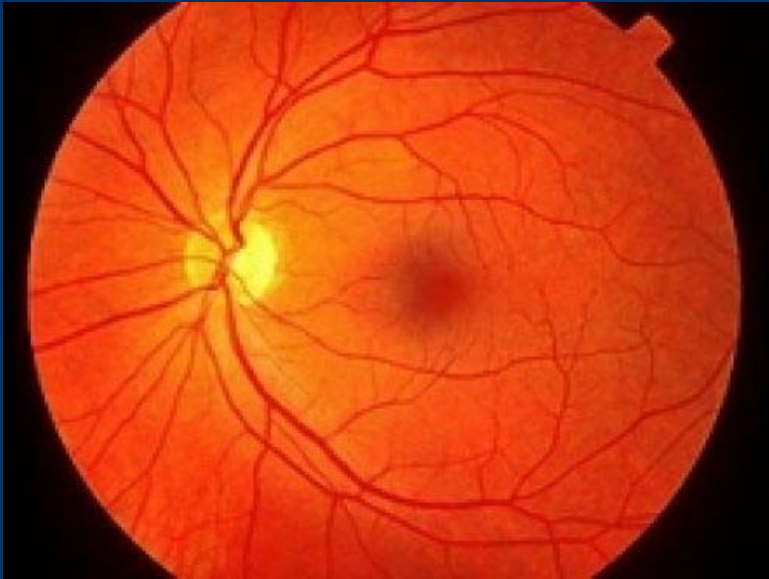


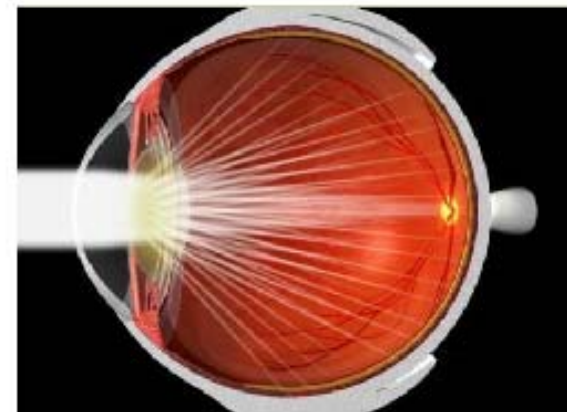
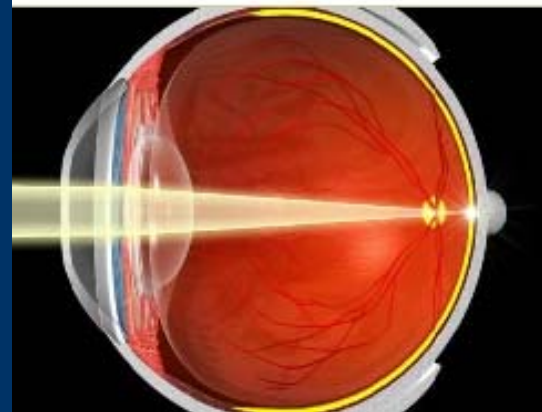




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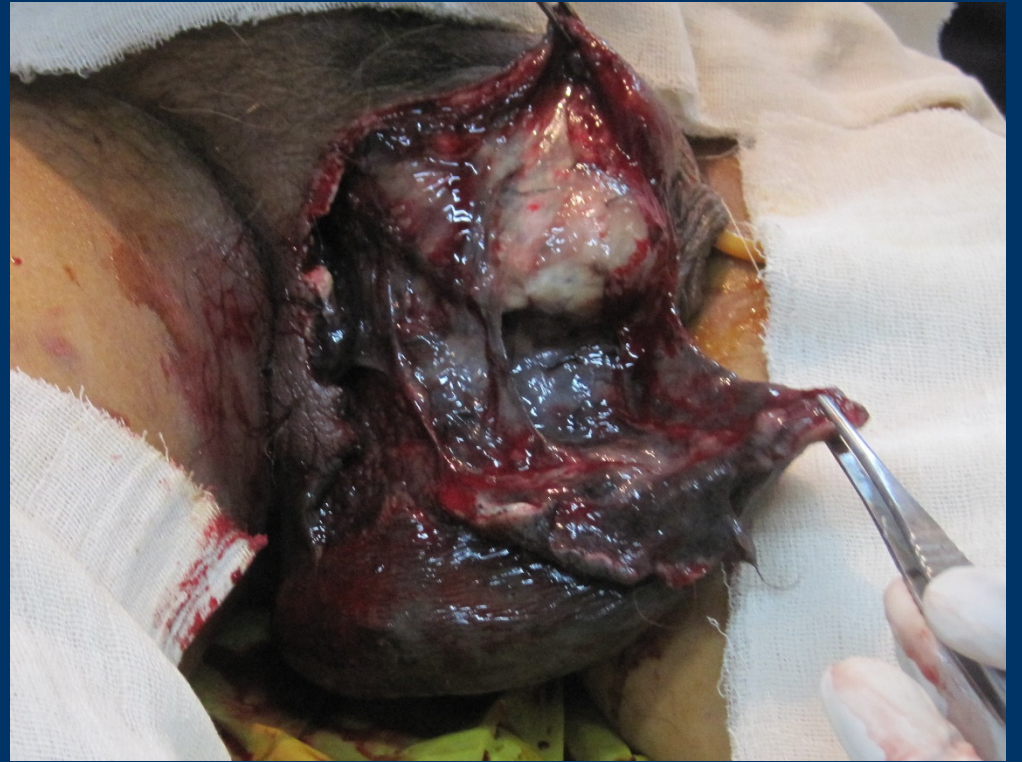




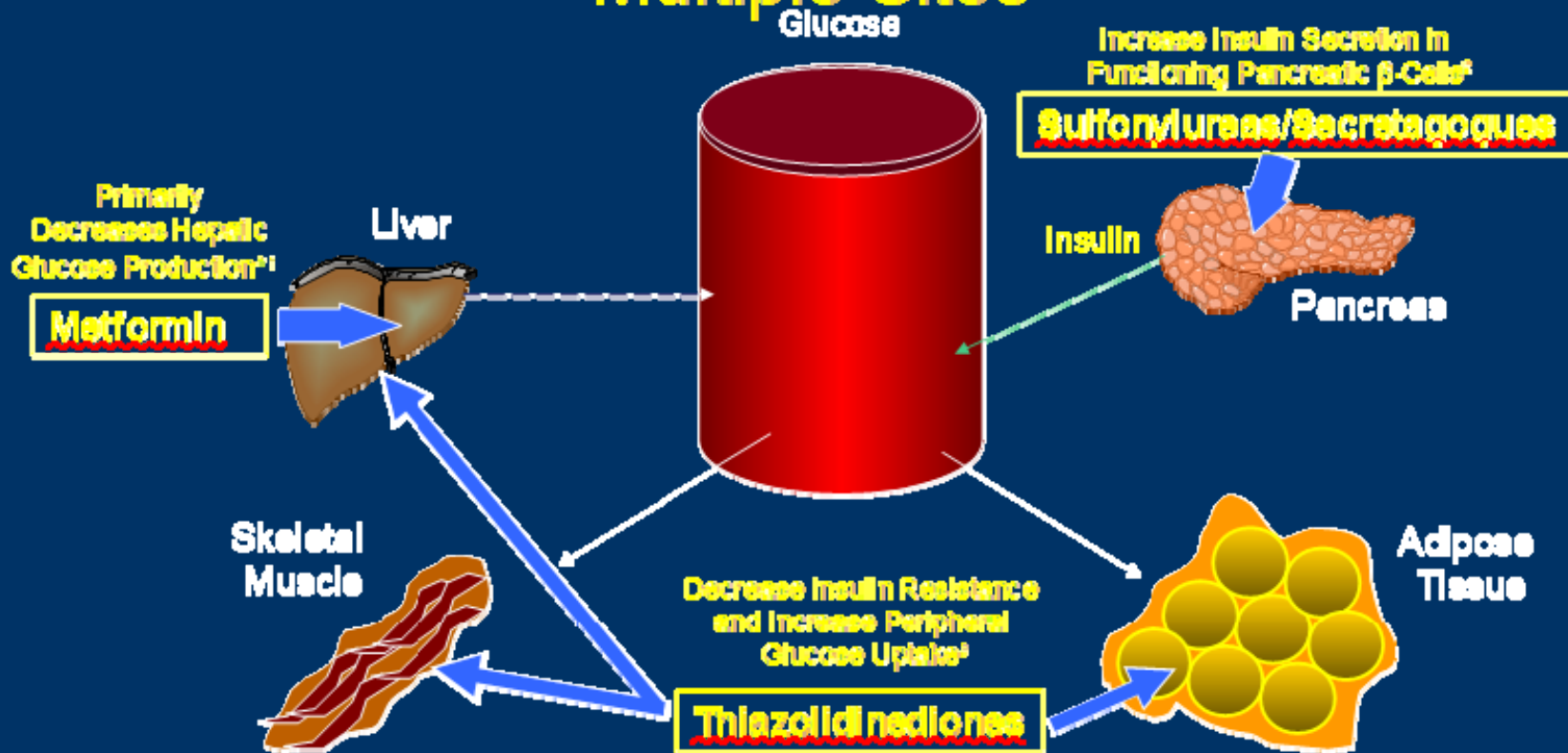








Therapy: Multiple Mechanisms of Action Targeting Multiple Sites



* Also decreases intestinal absorption of glucose and increases peripheral glucose uptake and utilization.

1. Glucophage [prescribing information]. Bristol-Myers Squibb.
2. Amaryl [prescribing information]. Aventis Pharmaceuticals.
3. AVANDIA[®] (rosiglitazone maleate) [prescribing information]. GlaxoSmithKline.



Glucagon-Like Peptide-1

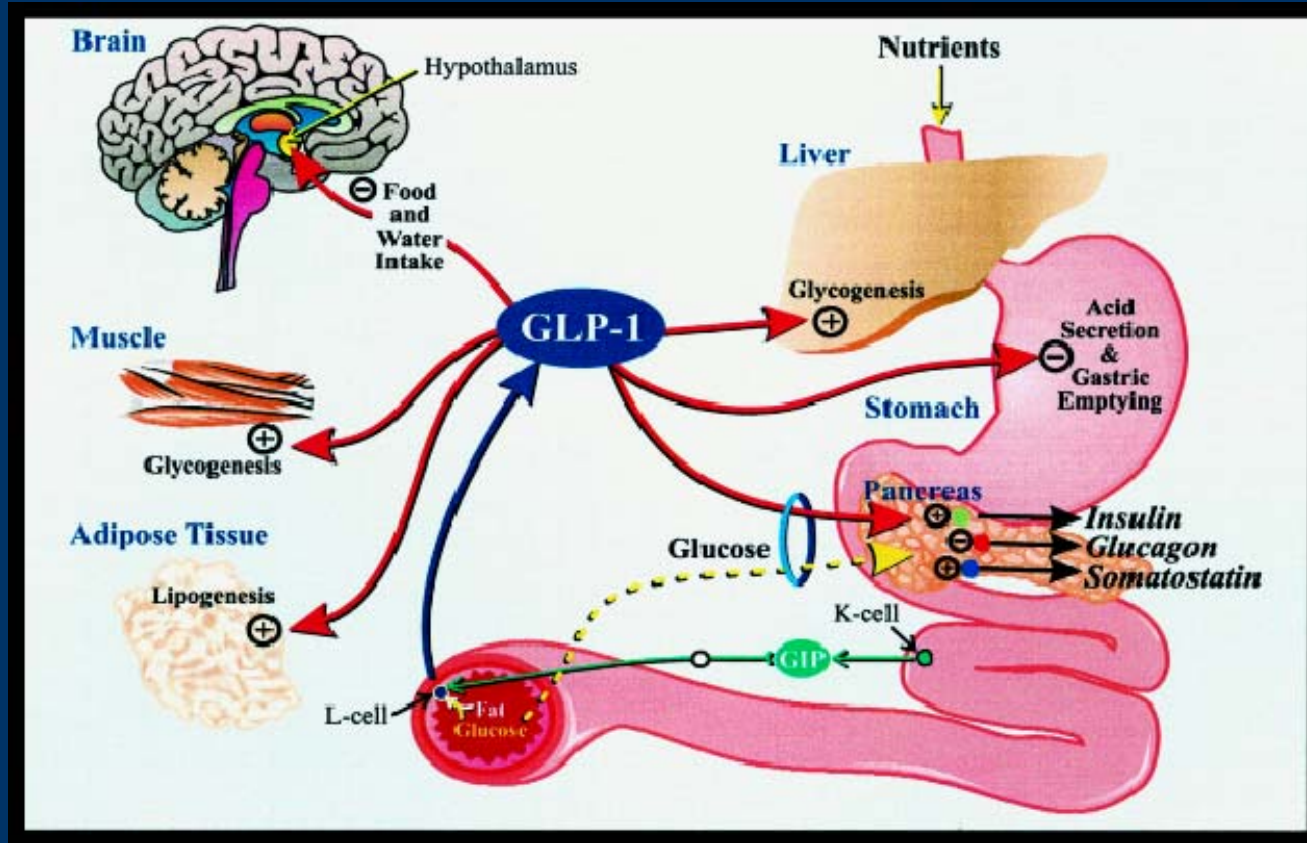


- Secreted from intestinal L-cells with meal ingestion
- In humans and animals
 - enhances glucose-stimulated insulin release
 - decreases glucagon release
 - slows gastric emptying
 - reduces food intake
- In animals and in vitro
 - increases insulin gene transcription
 - increases β -cell mass and β -cell differentiation

Drucker DJ. *Curr Pharm Des.* 2001;7:1399-1412.

Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.

Native GLP-1 is an intestinal hormone



DPP-IV Inhibitors

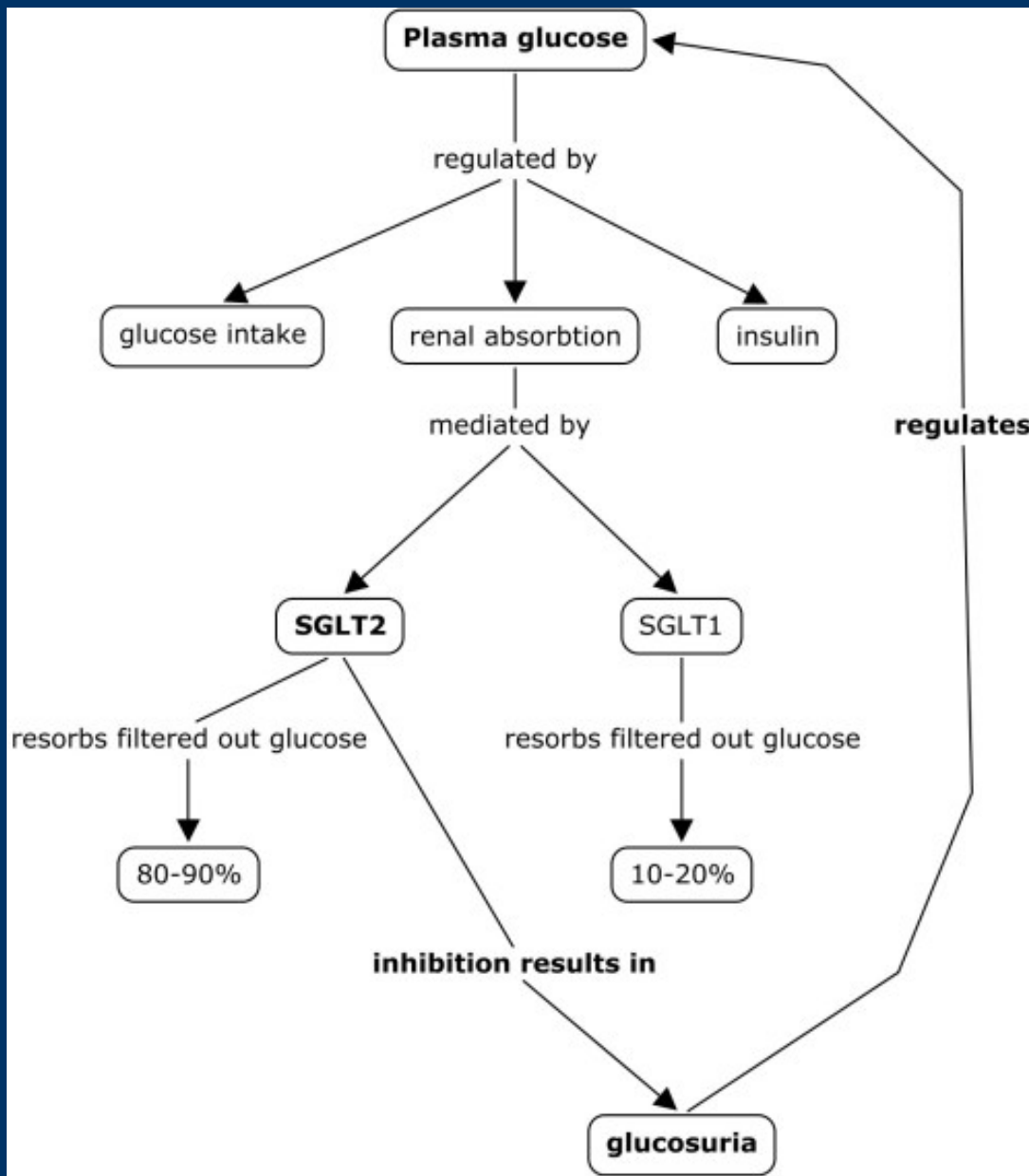
(dipeptidyl peptidase 4 (DPP-4) inhibitor)

- Potentially important in early DM2 to prevent deterioration of glucose metabolism
- Decrease rate of GLP-1 degradation
- Partially restore impaired insulin secretion
- Protect β -cells
- Oral DPP-IV inhibitors in phase 3 development
 - Sitagliptin
 - Vildagliptin

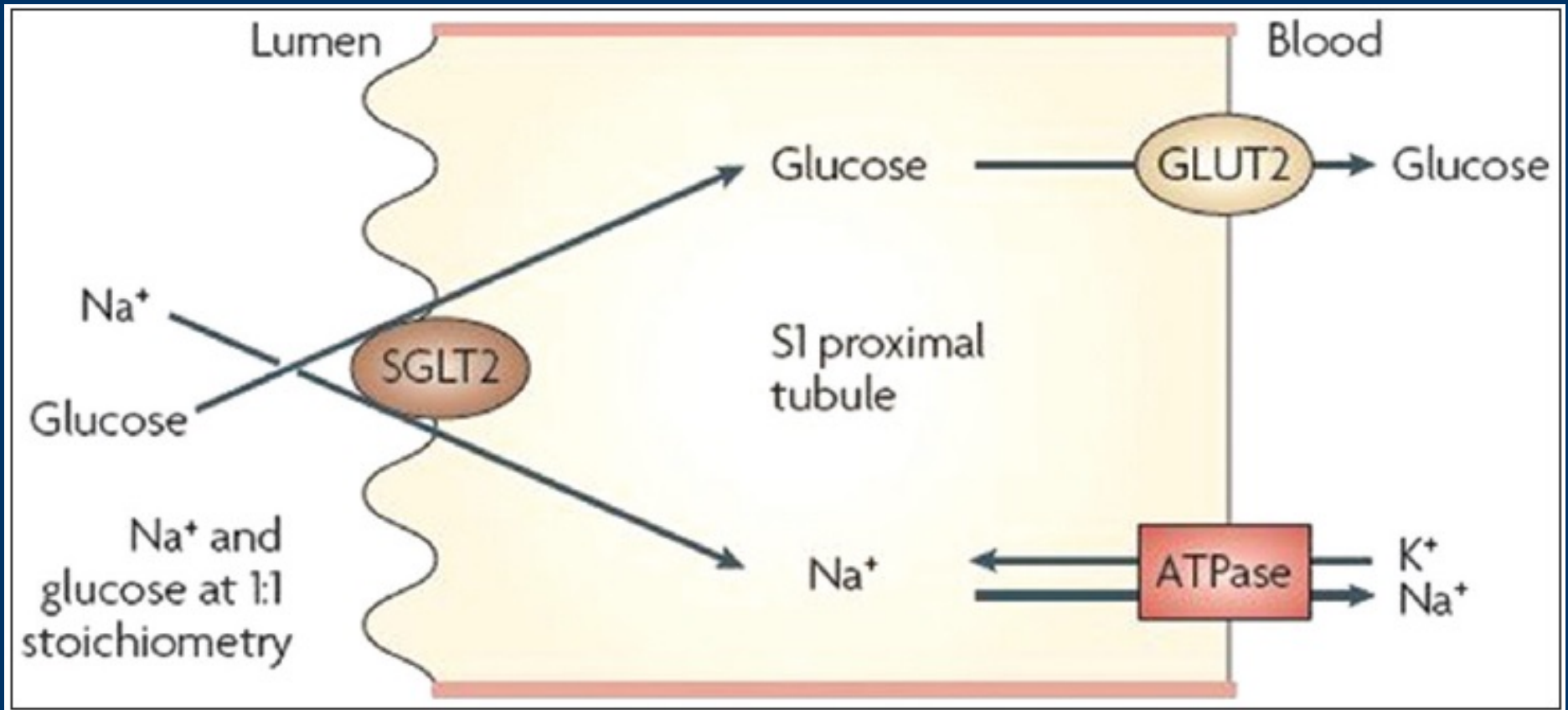
DPP-IV = dipeptidyl peptidase-IV

GLP-1 = glucagon-like peptide-1

Smith S, Heron A. *Nat Med* 2005;12:75-80.



Na⁺-glucose cotransporter type 2 (SGLT2)



Strictly Restrictive Procedures



• Non-Adjustable Gastric Banding (Molina)



• Adjustable Gastric Band-LapBand (Kuzmak)



• Horizontal Gastroplasty (Carey)



• Vertical Banded Gastroplasty (Mason)



• Silastic Ring Vertical Banded Gastroplasty (Laws)

Restrictive Procedures with some Malabsorption



• Gastric Bypass with Loop Gastro-Jejunostomy (Mason)



• Roux-en-Y Gastric Bypass (Torres)



• Transected Roux-en-Y Gastric Bypass (Miller)



• Laparoscopic Roux-en-Y Gastric Bypass (Wittgrove)



• Transected Silastic Ring Vertical Gastric Bypass (Fobi)

Malabsorptive Procedures with some Restriction



• Distal Roux-en-Y Gastric Bypass (Torres, Fobi)



• Bilio-pancreatic Diversion (Scopinaro)



• Bilio-pancreatic Diversion with Duodenal Switch (Hess)

Strictly Malabsorptive Procedures



• Jejunio-Ileal Bypass (JIB) End-to-End (Scott)



• Jejunio-Ileal Bypass (JIB) End-to-Side (Payne)