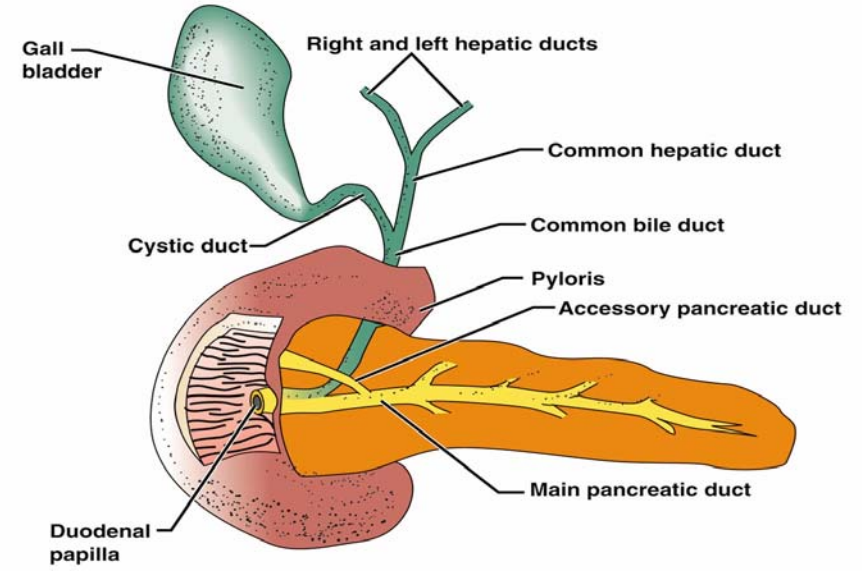
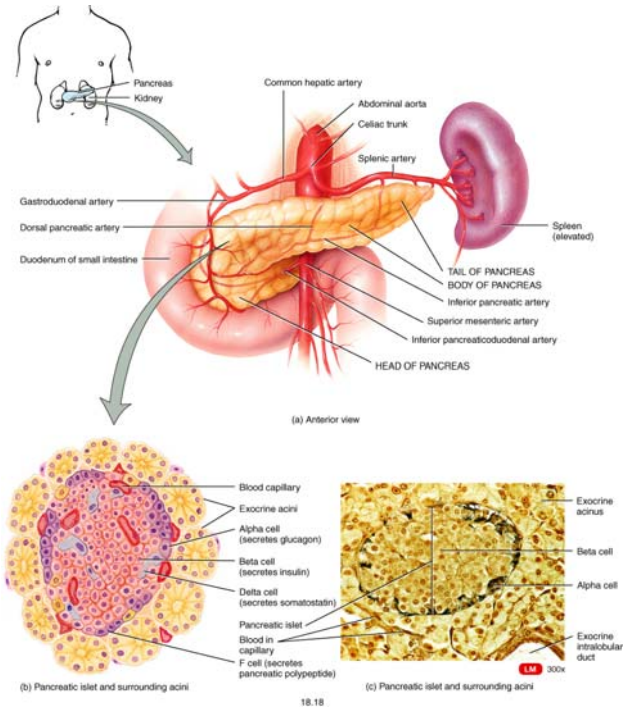
Pancreas

Rodolfo T. Rafael,MD.

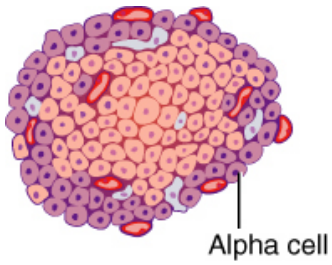


Anatomy

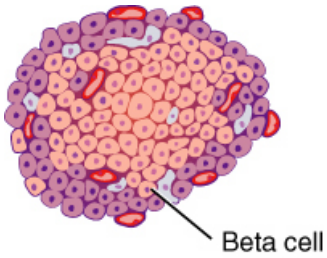
- 100g- pancreas
- 1 g- islets
- 99%- pancreatic juice→ duodenum
- 1%- endocrine function
- 200,000- 1,000,000 islets per pancreas



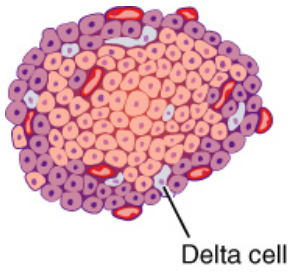
- Three Cell Types
  - A cells
    - glucagon
  - B cells
    - insulin
  - D cells
    - somatostatin and possibly gastrin
    - Zollinger- Ellison Syndrome



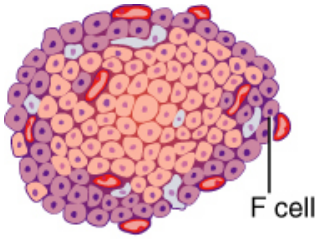
18.T09a



18.T09b



18.T09c



18.T09d

- derived from GUT
- Gut wall contains cell that secrete glucagon-like hormone, somatostatin and gastrin

Insulin

- Chemistry and Biosynthesis
- Regulation of Insulin Secretion
- Physiological Effects of Insulin
- Receptor and its Regulation

Insulin

- Chemistry and Biosynthesis
  - Two polypeptide Chains
    - 21 residues
    - 30 residues
      - joined by 2 disulfide bridges
  - 9,000 MW
  - Proinsulin
    - primary gene product
    - single polypeptide chain of 86 residues
    - Converted to insulin
      - endopeptidase
      - carboxypeptidase

Insulin

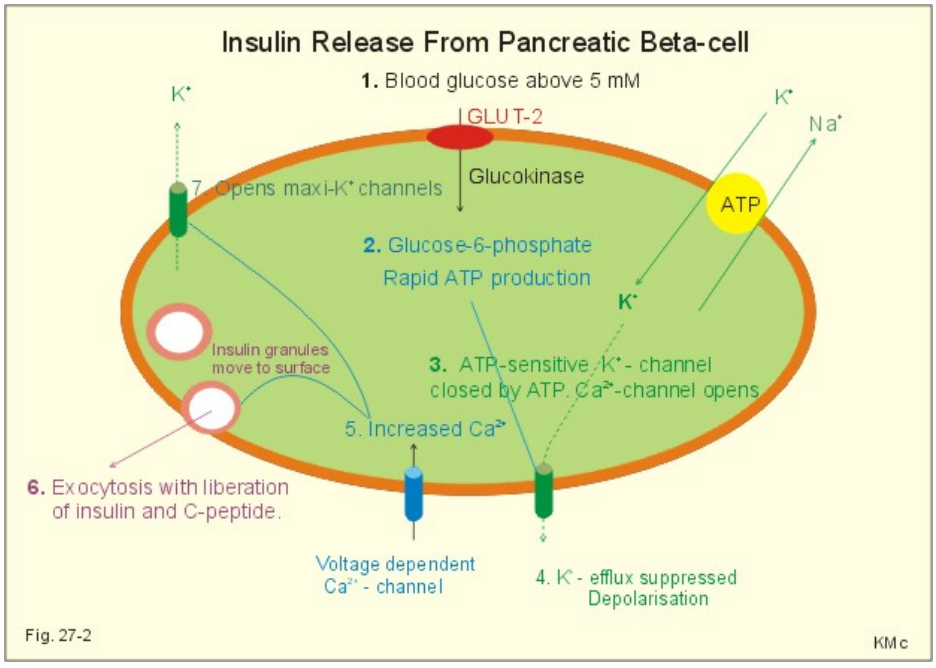
- Regulation of Insulin Secretion
  - 24 U/day- fasting state
  - 5-10x
  - Pancreatectomized patients
    - 50-60 U/day

Insulin

- Regulation of Insulin Secretion
  - Stimulation- Direct
  - Stimulation- Indirect
  - Inhibition

Insulin

- Regulation of Insulin Secretion
  - Stimulation- Direct
    - Glucose
    - Amino acids
    - Ketone bodies
    - Fatty acids
    - GI Hormones (secretin, gastrin, pancreozymin) anticipatory effect
    - Glucagon
    - Acetylcholine
    - Beta- adrenergic agents (isoproterenol)
    - Alpha- adrenergic blocking agents (phentolamine)
    - Sulfonylureas



Insulin

- Regulation of Insulin Secretion
  - Stimulation- Indirect

    Any agent that raises blood glucose levels (induce peripheral effects of insulin)
    - Growth Hormone
    - Glucocorticoids
    - Estrogenic Hormones
    - Progestational hormones
    - Parathyroid Hormones

Insulin

- Regulation of Insulin Secretion
  - Inhibition
    - Alpha- adrenergic agents (epinephrine, norepinephrine)
    - Beta- Blocking agents
    - Diphenylhydantoin
    - Diazoxide
    - Degraded by all tissues but liver (50%) dominant and folled by kidney (25%)

Insulin

- Physiological Effects of Insulin
  - Glucose Metabolism
  - Fat Metabolism
  - Amino acid and Protein Metabolism

Insulin

- Physiological Effects of Insulin
  - Glucose Metabolism
    - liver
      - increases glucose phosphorylation
      - increases glycogen synthesis
      - decreases glycogenolysis
    - Acutely, insulin modifies activity of the enzymes it regulates
    - Chronic Insulin Deficiency- leads to changes in the amount of the enzymes involved at a control points
    - Glucose uptake also stimulated in muscle (and glycogenesis) and adipose tissue (and glycogenesis).

Insulin

- Physiological Effects of Insulin
  - Fat Metabolism
    - Adipose Tissue
      - increase lipogenosis
      - decrease lipolysis
    - Liver
      - *Insulin Deficiency*→ fatty acid synthesis is reduced→ decreased availability of NADPH, decreased activity of fatty acid synthetase→ low citrate
        - » FFA delivery to liver is increased, acetyl CoA is shunted to acetoacetate → KETOSIS

Insulin

- Physiological Effects of Insulin
  - Amino acid and Protein Metabolism
    - Increased amino acid transport
    - increased protein synthesis

Insulin

- Receptor and its Regulation
  - Insulin receptors on target cells serve two major functions:
    - Specific recognition of insulin molecules amongst other circulating hormones and substrates
    - Triggering of a chain of intracellular events→ increased transport of substrates or altered enzymes
  - Insulin receptor is believed to be a glycoprotein with a molecular weight 150,000- 300,000 daltons
  - The number of insulin receptors per cell is estimated to vary between 50,000 and 250,000
  - Maximal biologic effects are observed when only a small proportions of insulin receptors are occupied.

Insulin

- Receptor and its Regulation
  - Circulating monocyte specifically bind insulin and mirror the condition of insulin receptors in conventional target tissues.
    - Erythrocytes have also been identified as a site of insulin receptors
  - In some patients
    - failure of adequate insulin secretion
    - hyperinsulinemia→ defect in tissue responsiveness to insulin
    - Receptor-Deficient Disease States
      - Obesity
      - MODY (Type II)
      - Severe Insulin Resistance and Acanthosis Nigricans
      - Uremia
      - Growth Hormone Excess
      - Glucocorticoid excess

Insulin

- Receptor and its Regulation
  - Regulation of Receptor Number
    1. Plasma insulin concentration (basal state)
       a. Hyperinsulenemia- decrease
       b. Hypoinsulinemia- increase
    2. Weight reduction in obese- increase
    3. Sulfonylureas- increase
    4. Improvement in physical fitness- increase
  - Circumstances are now recognized in which there is a clear cut dissociation between insulin action and insulin receptor function
  - Receptor antibodies→ "Autoimmune Diabetes"

Glucagon

- Chemistry and Assay
- Regulation of Secretion
- Physiologic Effects

Glucagon

- Chemistry and Assay
  - alpha cells
  - single polypeptide chain of 29 residues (MW 3485) with no cross-linkages
  - Pancreas and plasma contain “big” glucagon (MW 9,000) and also lower MW fragments→ PROHORMONES

Glucagon

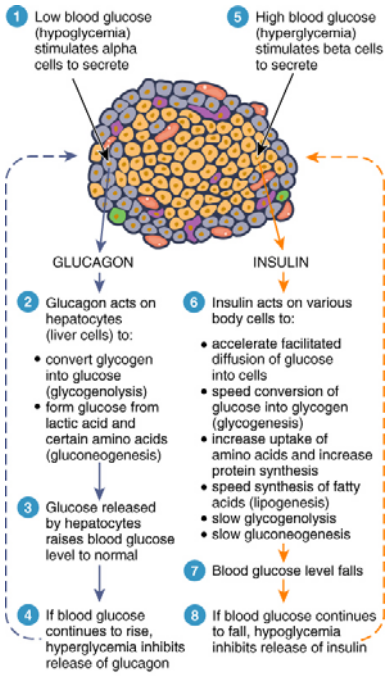
- Regulation of Secretion
  - Stimulation
    - Hypoglycemia
    - Amino acids
    - Pancreozymin
    - Catecholamines
    - Exercise
  - Inhibition
    - Hyperglycemia
    - Insulin
    - Free Fatty Acids

Glucagon

- Physiologic Effects
  - Stimulates Hepatic Gluconeogenesis by:
    - Deactivation of pyruvate kinase
    - Increase in uptake of amino acids
  - Stimulates hepatic glycogenolysis by:
    - activation of phosphorylase
    - deactivation of glycogen synthase
  - Stimulates lipolysis in adipose tissue via cAMP- dependent protein kinase
  - Stimulate insulin release

Somatostatin

- tetradecapeptide
- Guillemin
  - hypothalamus→ potent inhibitor of growth hormone
- suppress both insulin and glucagon release



18.19

Diabetes Mellitus

Introduction

- Diabetes mellitus (sweet urine)
- 3% of world population, 100 million people
- Commonest non communicable disease
- High Morbidity & mortality

Diabetes Mellitus

- Disorder of metabolism (Carb, Prot & Fat)
- Due to Absolute or relative deficiency of insulin.
- Characterized by hyperglycemia.
- Clinically : Polyuria, Polydypsia, Polyphagia.

Classification

- Primary DM.
  - Type I – IDDM / Juvenile – 10%.
  - Type II – NIDDM /Adult onset – 80%.
  - MODY – 5% maturity onset - young - Genetic
- Secondary DM – islet destruction.
  - Infectious – congenital rubella, CMV.
  - Pancreatitis/tumors/Hemochromatosis.
  - Endocrinopathy, gestational DM, downs.
  - Drugs – Corticosteroids.

Classification

- Type I Diabetes (*insulin-dependent diabetes mellitus*, IDDM)
  - characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life
  - onset occurs predominantly in childhood
  - probably has some genetic predisposition and is likely autoimmune-mediated

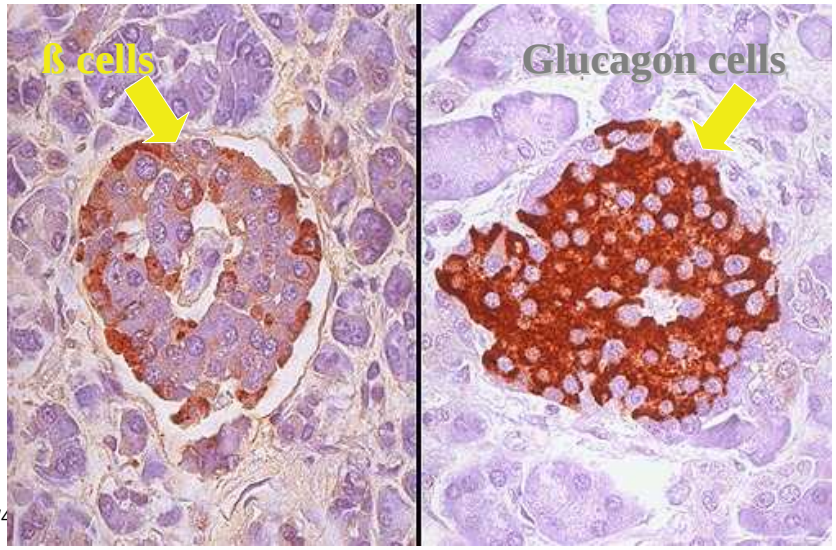
Classification

- Type II Diabetes (*non-insulin-dependent diabetes mellitus*, NIDDM)
  - patients are not insulin dependent and rarely develop ketosis
  - generally occurs after age 40, and there is a high incidence of associated obesity
  - insulin secretion generally adequate; insulin resistance is present
  - no associated genetic predisposition

Classification

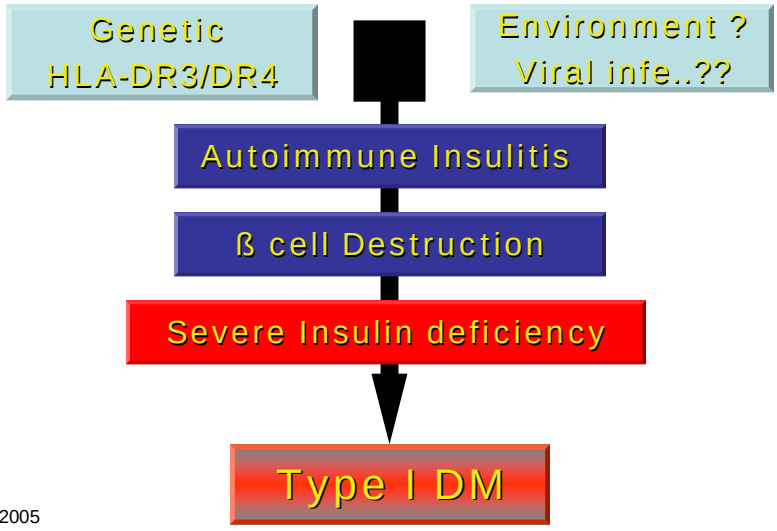
- Secondary Diabetes
  - occurs in response to other disease processes:
    - exocrine pancreatic disease (cystic fibrosis)
    - Cushing syndrome
    - poison ingestion (rodenticides)

Normal Pancreatic Islets:



3/4

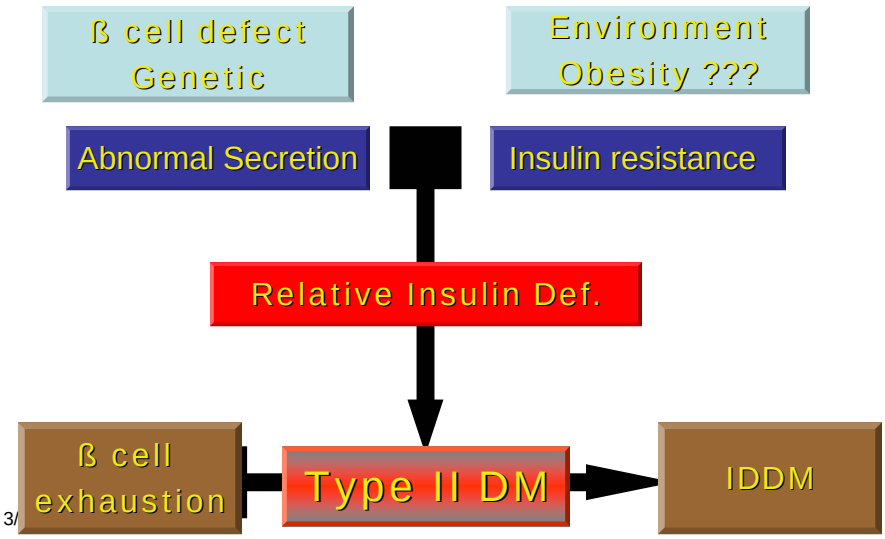
Pathogenesis of Type I DM



3/4/2005

40

Pathogenesis of Type II DM



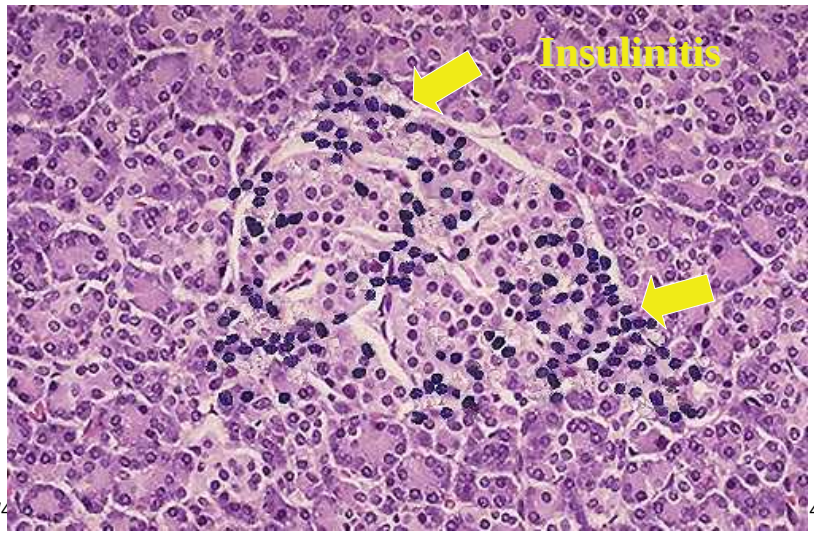
Type-I

- Age: < 40 Years
- Duration: Weeks
- Ketonuria: Common
- Insulin- Dependent
- Autoantibody: Yes
- Family History: No
- Insulin levels: very low
- Islets: Insulitis
- Complications:
  - Acute & Metabolic

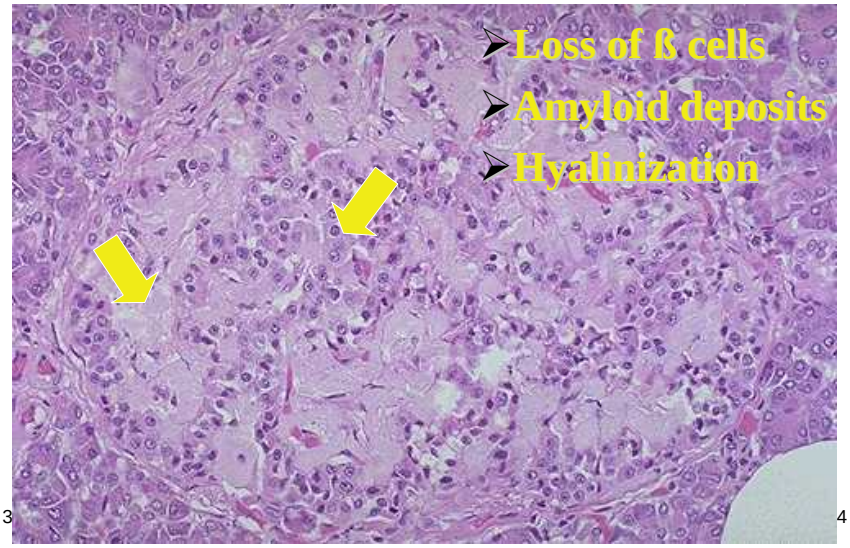
Type-II

- > 40 Years
- Months to years
- Rare
- Independent *
- No
- Yes
- Normal or high *
- Normal / Exhaustion
- Complications
  - Late and vascular.

Insulitis – Type I



Islets in Type II Diabetes:



Type I Diabetes Mellitus: Epidemiology

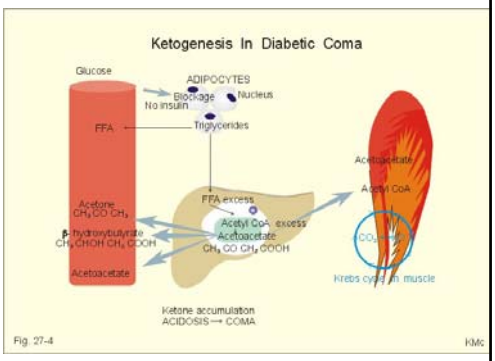
- Prevalence of IDDM among school-age children in the US is 1.9 per 1000
- The annual incidence in the US is about 12 - 15 new cases per 100,000
- Male to female ratio is equal
- Among African-Americans, the occurrence of IDDM is about 20 - 30% of that seen in Caucasian-Americans

Type I Diabetes Mellitus: Epidemiology

- Peaks of presentation occur at 5 - 7 years of age and at adolescence
- Newly recognized cases appear with greater frequency in the autumn and winter
- Definite increased incidence of IDDM in children with congenital rubella syndrome

Ketogenesis

- Triglycerides are liberated from adipose tissue, and the concentration of free fatty acids (FFA) in the blood is elevated.
- FFA are broken down to fatty acyl carnitine within the liver cells, and this molecule is converted to acetyl CoA, which in turn reach the mitochondria, where ketone bodies (aceto-acetate, acetone, β-hydroxybutyrate) are formed
- The breath of the patient smell by acetone, and there is ketosis in the urine.
- The concentration of ketone bodies in the blood passes *5 mM*, and when pH falls below 7, there is life-threatening or terminal coma



Type I Diabetes Mellitus: Pathophysiology

- DKA results in altered lipid metabolism
  - increased concentrations of total lipids, cholesterol, triglycerides, and free fatty acids
  - free fatty acids are shunted into ketone body formation due to lack of insulin; the rate of formation exceeds the capacity for their peripheral utilization and renal excretion leading to accumulation of ketoacids, and therefore metabolic acidosis

Type I Diabetes Mellitus: Pathophysiology

- With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose

Type I Diabetes Mellitus: Clinical Manifestations

- Classic presentation of diabetes in children is a history of polyuria, polydipsia, polyphagia, and weight loss, usually for up to one month
- Laboratory findings include glucosuria, ketonuria, hyperglycemia, ketonemia, and metabolic acidosis. Serum amylase may be elevated. Leukocytosis is common

Type I Diabetes Mellitus: Clinical Manifestations

- Keotacidosis is responsible for the initial presentation of up to 25% of children
  - early manifestations are mild and include vomiting, polyuria, and dehydration
  - More severe cases include Kussmaul respirations, odor of acetone on the breath
  - abdominal pain or rigidity may be present and mimic acute appendicitis or pancreatitis
  - cerebral obtundation and coma ultimately ensue

Type I Diabetes Mellitus: Diagnosis

- Diagnosis of IDDM is dependent on the demonstration of hyperglycemia in association with glucosuria with or without ketonuria
- DKA must be differentiated from acidosis and coma due to other causes:
  - hypoglycemia, uremia, gastroenteritis with metabolic acidosis, lactic acidosis, salicylate intoxication, encephalitis

Type I Diabetes Mellitus: Diagnosis

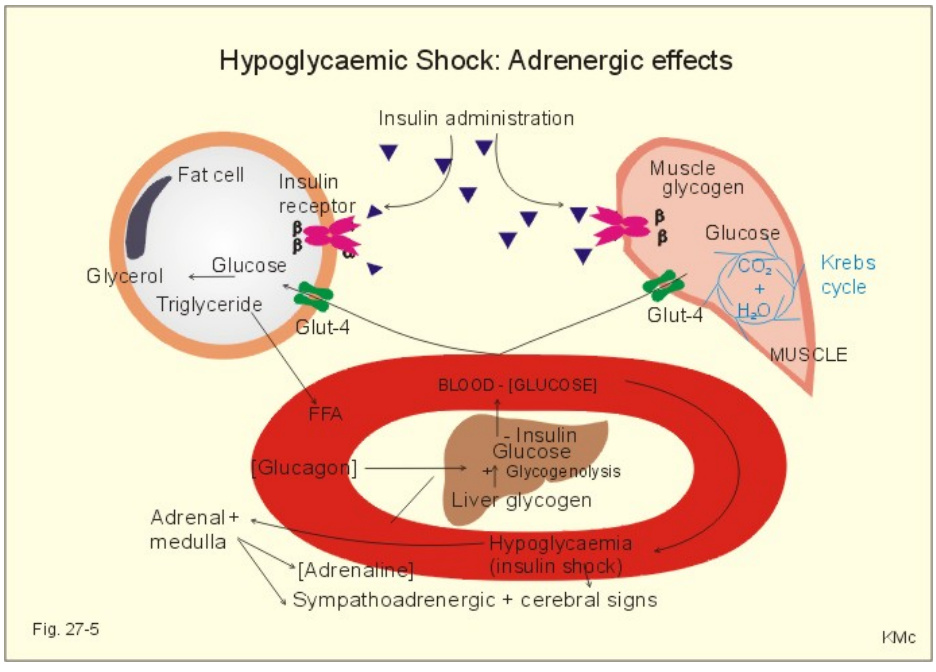
- DKA exists when there is hyperglycemia (> 300 mg/dL), ketonemia, acidosis, glucosuria, and ketonuria

Type I Diabetes Mellitus: Treatment

- Insulin is used to treat ***acidosis***, not ***hyperglycemia***
  - insulin should *never* be stopped if ongoing acidosis persists
- When the acidosis is corrected, the continuous insulin infusion may be discontinued and subcutaneous insulin initiated
- With the regimen, DKA usually is usually fully corrected in 36 to 48 hours

Type I Diabetes Mellitus: Treatment

- Hypoglycemic Reactions (Insulin Shock)
  - symptoms and signs include pallor, sweating, apprehension, trembling, tachycardia, hunger, drowsiness, mental confusion, diplopia, headache, seizures, coma, death
  - management includes administration (if conscious) of carbohydrate-containing snack or drink
  - glucagon 0.5 mg is administered to an unconscious or vomiting child



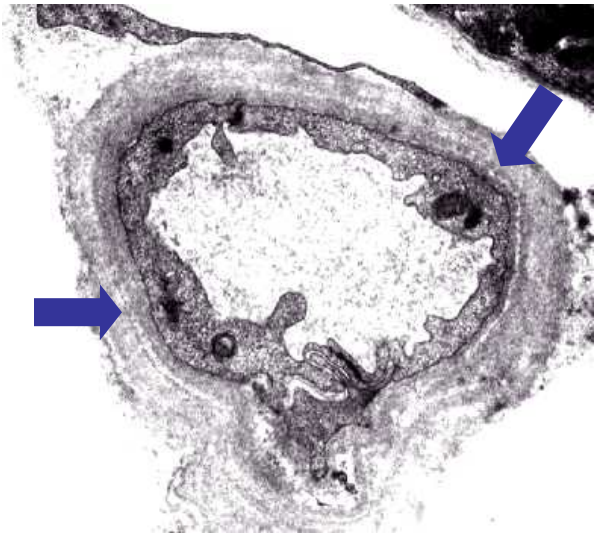
Complications:

- Short term Complications: (metabolic)
  - Hypoglycemia
  - Diabetic Ketoacidosis
  - Non Ketotic hyperosmolar diabetic coma
  - Lactic acidosis
- Long term Complications:(microangiopathy)
  - Angiopathy, Retinopathy, Nephropathy, Neurophathy

Pathogenesis of Microangiopathy:

- Long standing diabetes
- Combination of glucose with proteins - Particularly collagen in blood vessels - Glycosylation.
- Excess deposition of glycosylated type IV collagen in the basement membrane
- Thick and Leaky blood vessels.
- Chronic Ischemia & protein loss into tissues.
- Organ damage...

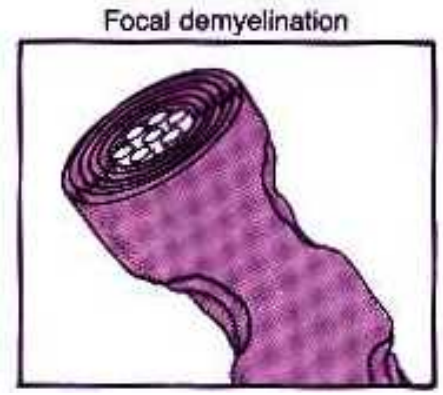
Microangiopathy



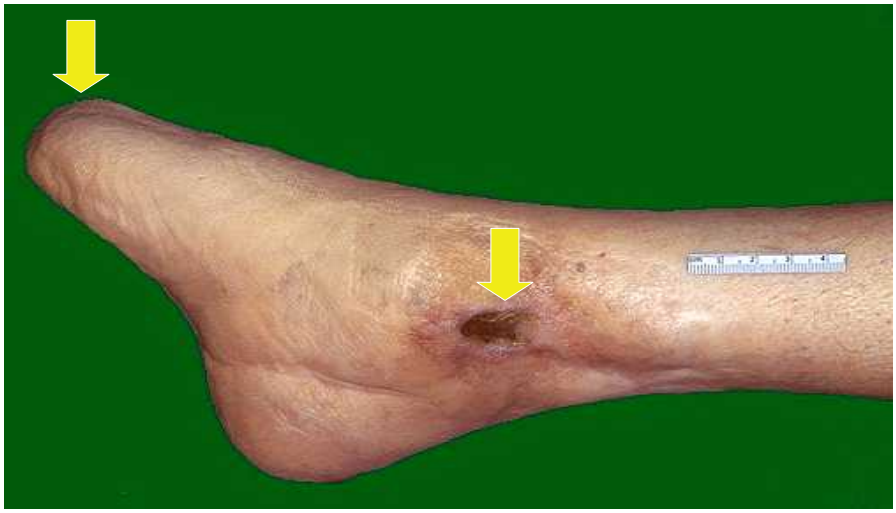
Long term Complications:

- Angiopathy
  - Atherosclerosis
  - Hyaline arteriolosclerosis
  - Diabetic microangiopathy
- Nephropathy
  - Nodular glomerulosclerosis
- Retinopathy
  - Non Proliferative & Proliferative
- Neuropathy
  - Peripheral axonal neuropathy

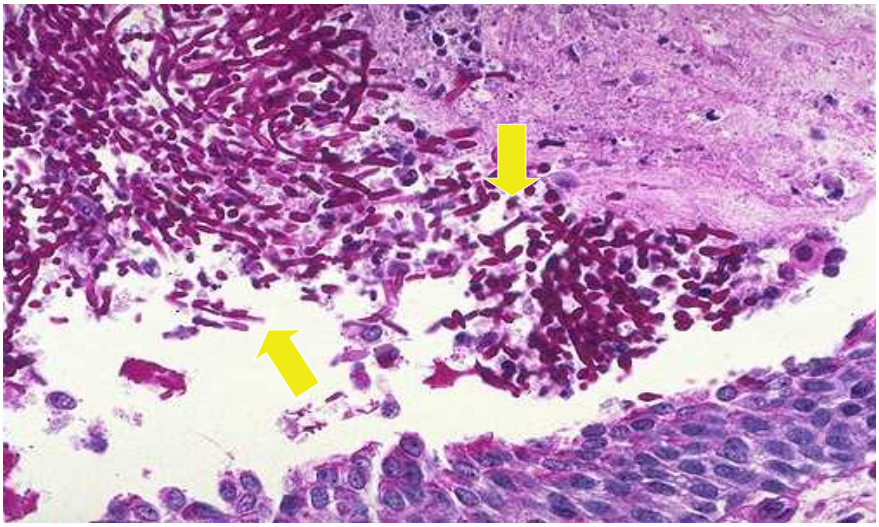
Neuropathy



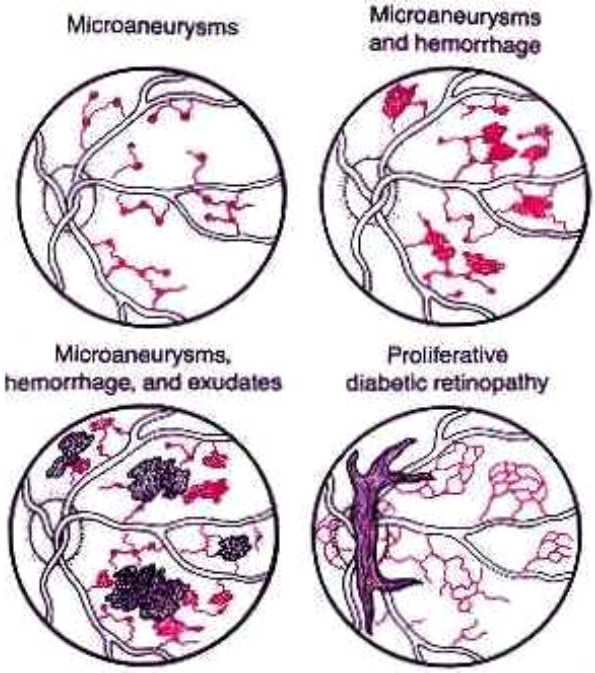
Diabetic Gangrene



Candidiasis

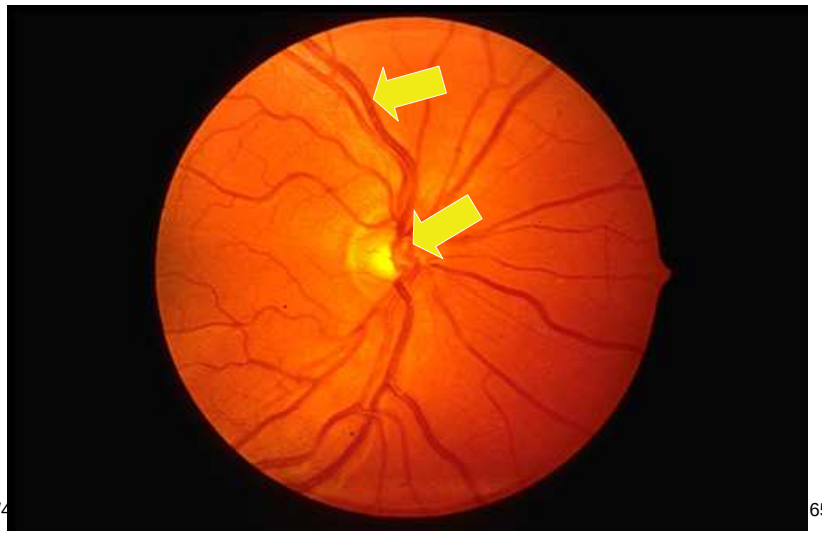


Pathogenesis of Retinopathy

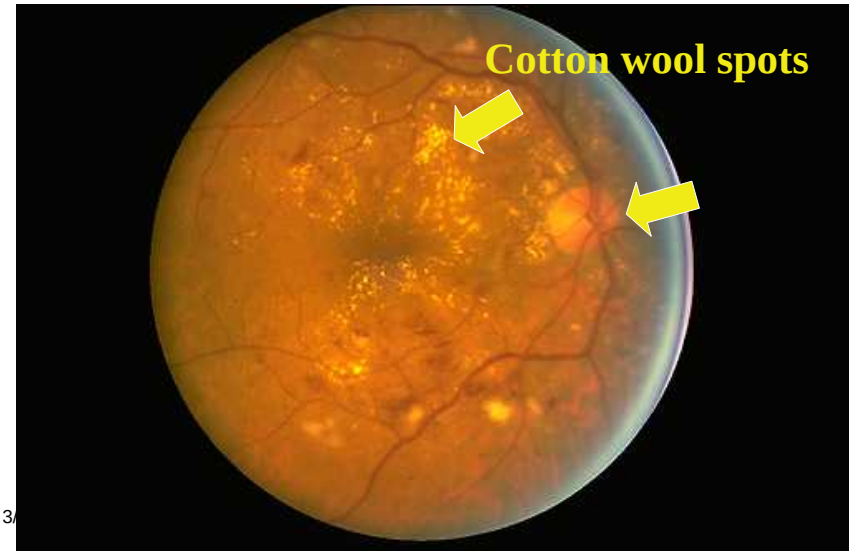


3/4/2005

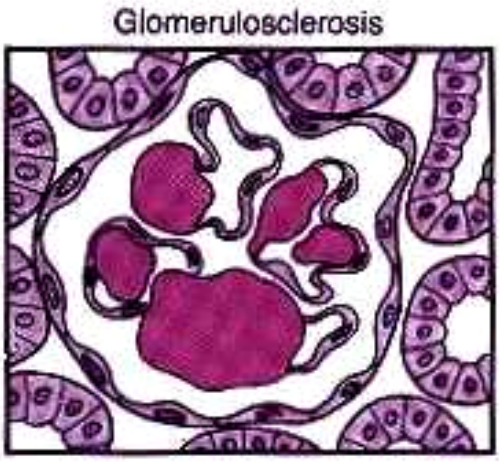
Normal Retina



Diabetic Retinopathy

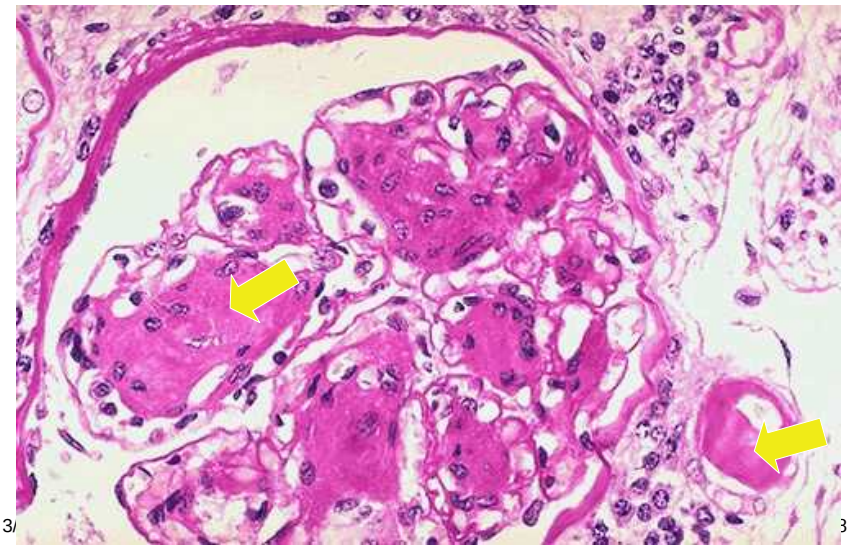


Pathogenesis of Nephropathy



3/4/2005

Diabetic Glomerulosclerosis



Laboratory Diagnosis:

- Urine glucose - dip-stick –Screening
- Random or fasting blood glucose (<11)
- Fasting > 7mmol, Random >11mmol
- If Fasting level is between 7-11 then OGTT

- HbA1c - for follow-up, not for diagnosis
- Fructosamine - for long term maintenance.

Points to remember:

- Type-I - Acute Metabolic complications
  - Ketoacidosis.
- Type-II - Chronic Vascular complications
  - Microangiopathy – Kidney,Retina,Brain, BV.
- Hypoglycemia is more dangerous. Not hyper
- Infections are due to microangiopathy and ischemia, immuno suppression and hyperglycemia. (not just hyperglycemia)

Thank You!