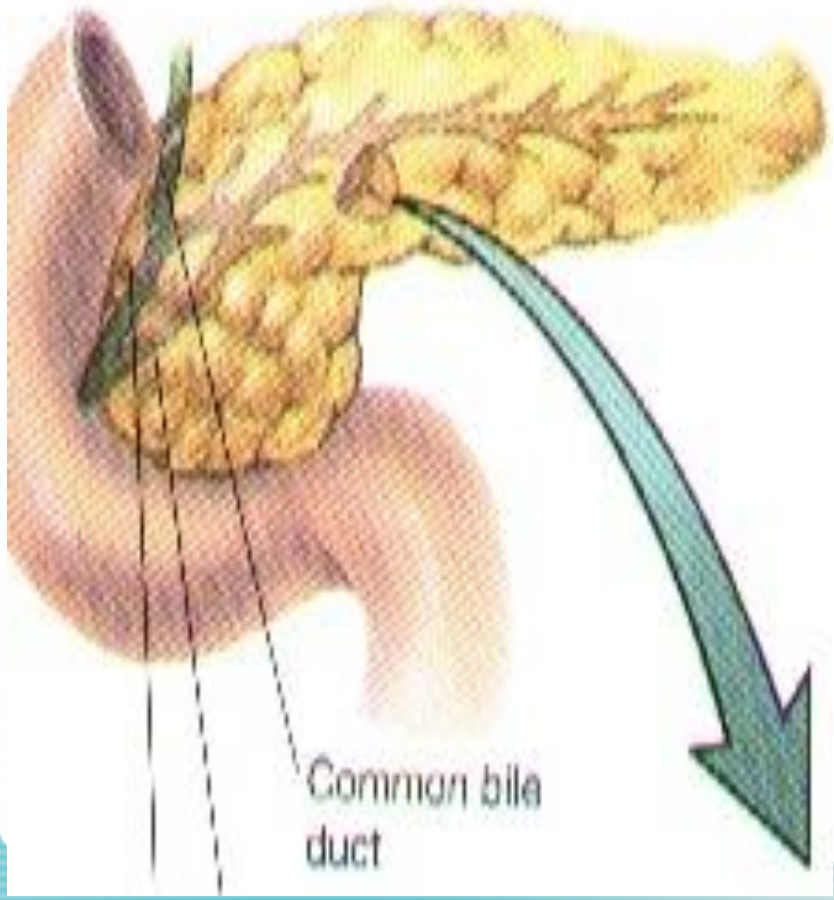
Federal state budgetary educational institution of higher education "Volgograd state medical University" of the Ministry of health of the Russian Federation

Department of clinical laboratory diagnostics

# LECTURE №3

# Diabetes Mellitus

# The pancreas

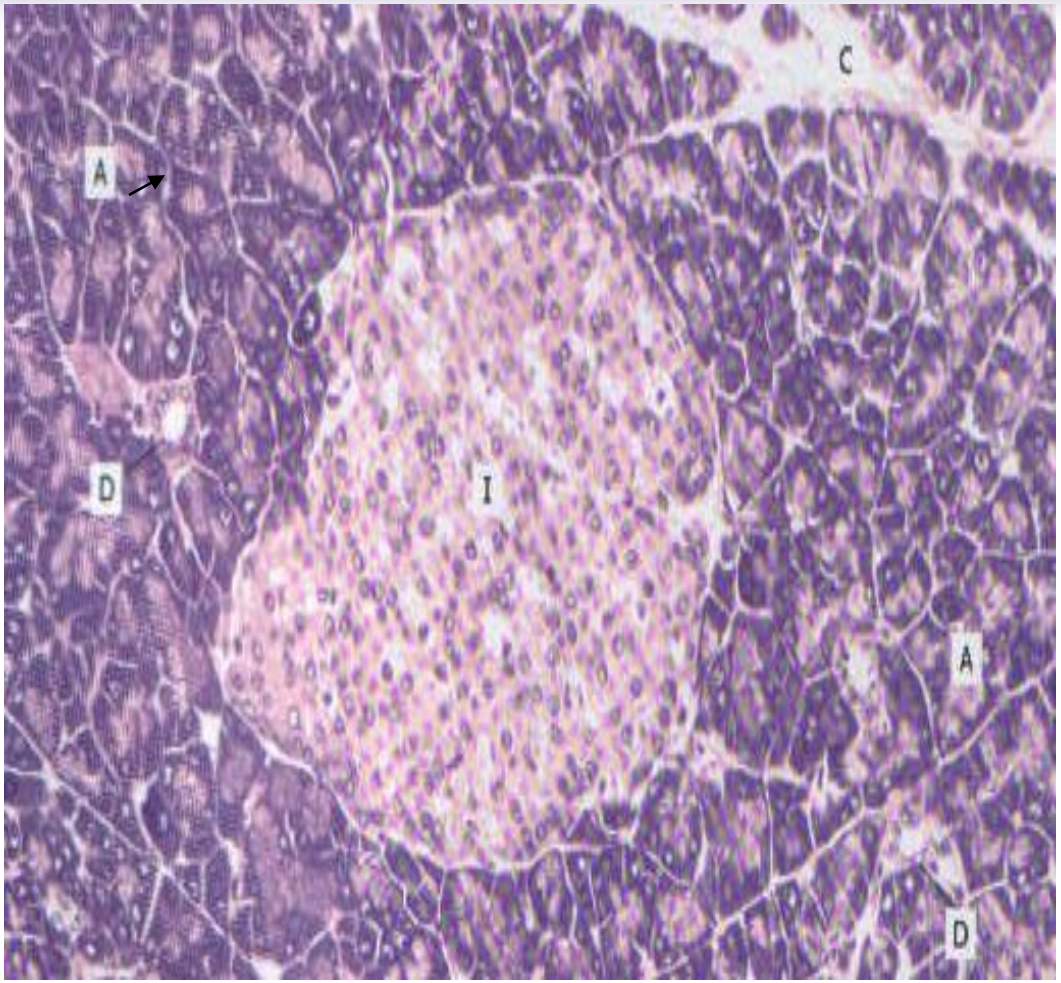



The pancreas is an elongated organ located in the abdomen. It plays an essential role in converting the food that we eat into fuel for the body's cells.

The pancreas has two main functions: an exocrine function that helps in digestion and an endocrine function that regulates blood sugar level.

The pancreas is located behind the stomach and is surrounded by other organs including the small intestine, liver, and spleen. It is about fifteen cm long and is shaped like a flat pear. The wide part, called the head of the pancreas, is positioned toward the center of the abdomen; the middle section is called the neck and the body of the pancreas; the thin end is called the tail and extends to the left side.

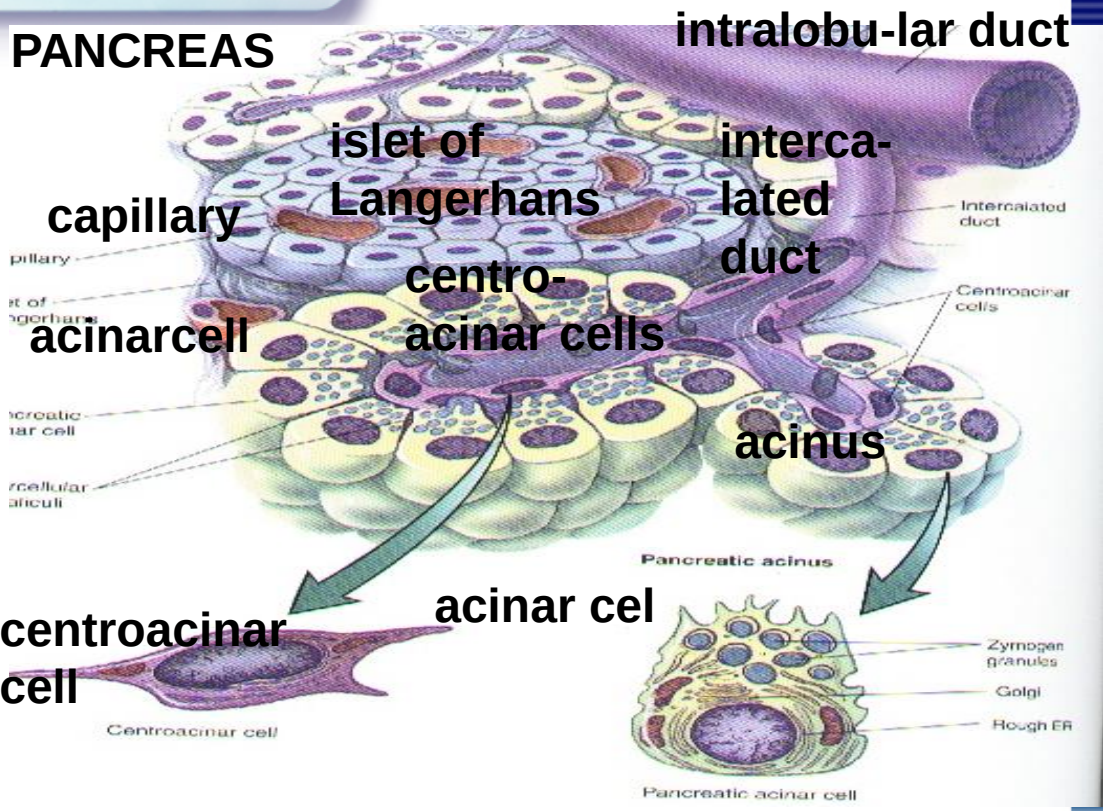
# The pancreas, H & E




The pancreas is both an exocrine gland that produces digestive juices and an endocrine gland that manufactures hormones. Its flimsy connective tissue capsule forms septa which subdivide that gland into lobules. The vascular and nerve supply as well as its system of ducts, travels in the connective tissue compartments

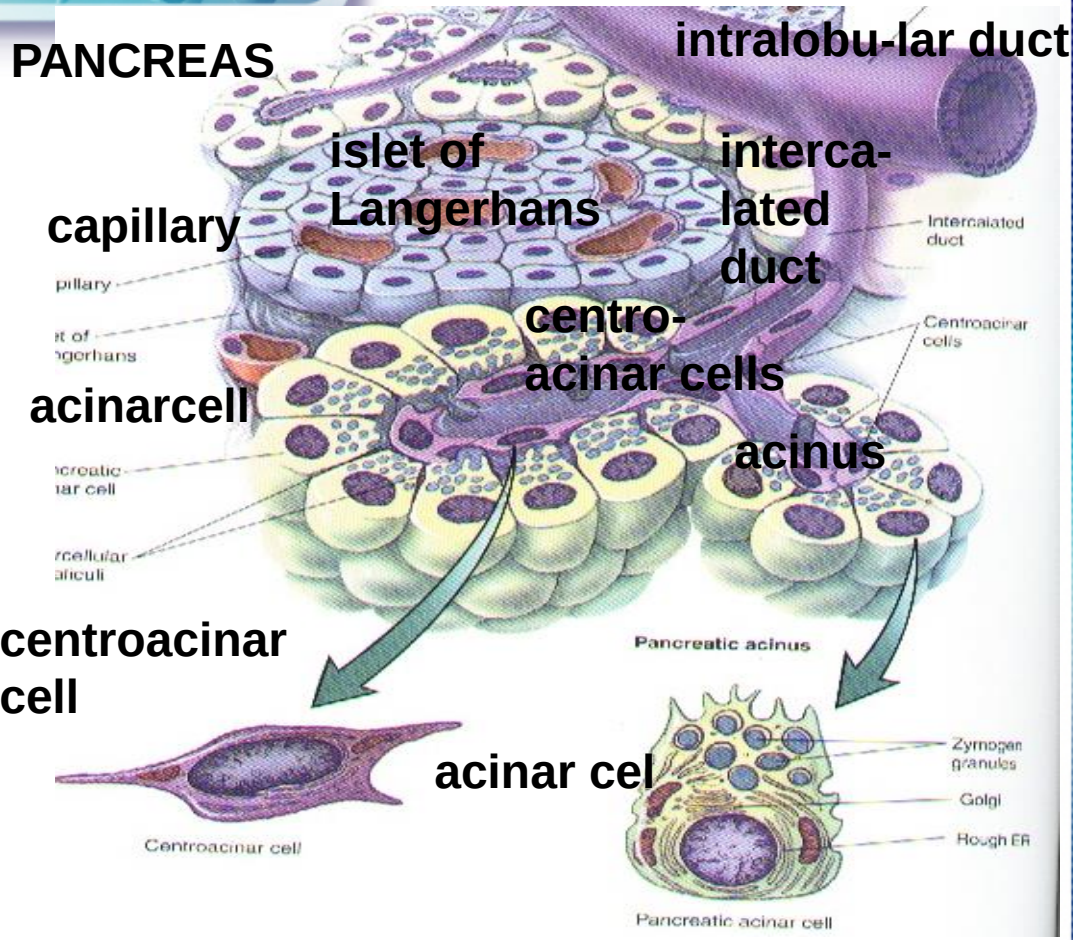
# The pancreas

The endocrine component of the pancreas, islets of Langerhans, are scattered among the exocrine secretory units. The exocrine pancreas is a compound tubuloacinar compound gland that produces daily about 1200 ml of a bicarbonate-rich fluid containing digestive proenzymes. The islets are composed of five types of cells, which can be differentiated from each other only with special stains.

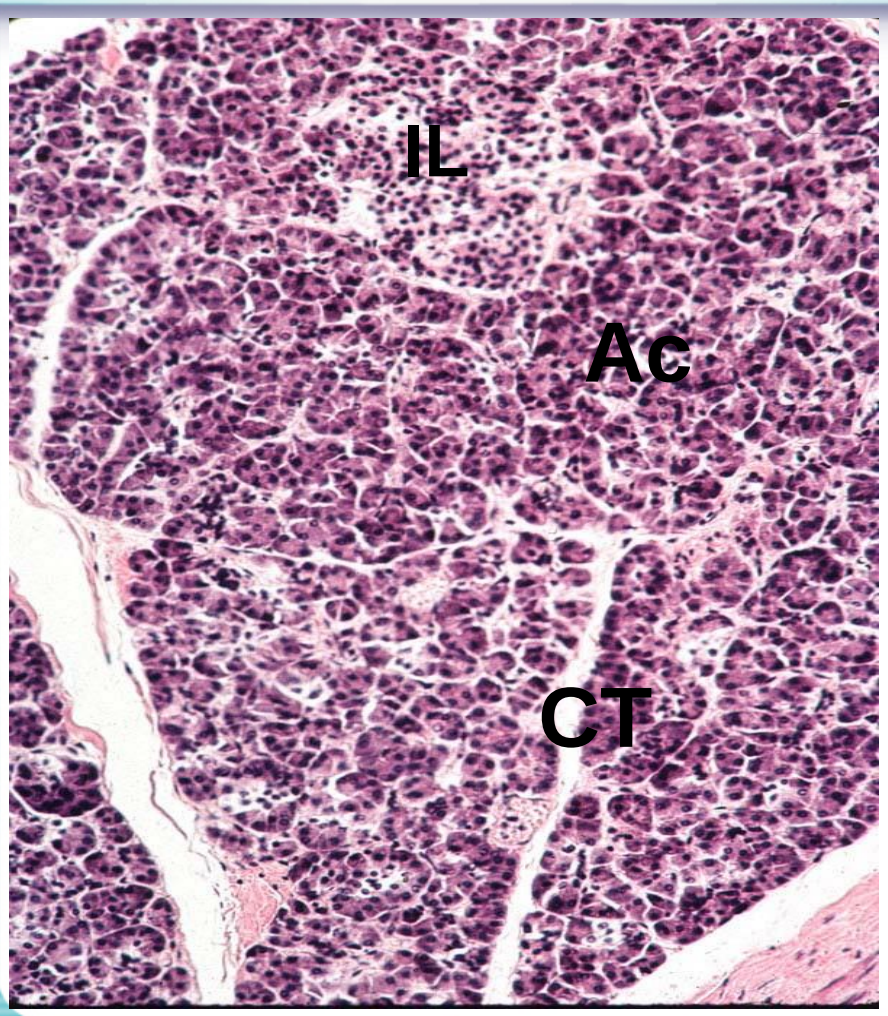


# The pancreas

**The duct system of pancreas begins within the center of the acinus (A) with the terminus of the intercalated ducts (D), composed of pale, low cuboidal centroacinar cells. Centroacinar cells and intercalated ducts both have receptors on their basal plasmalemma for secretin and acetylcholine.**



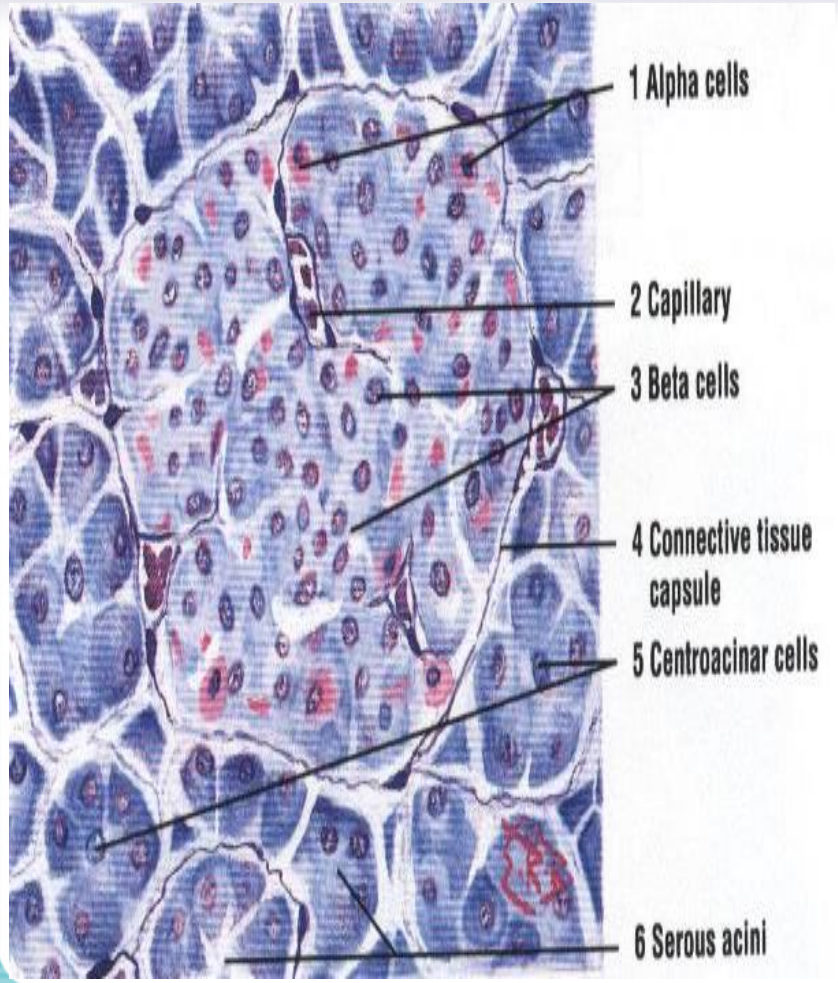
# The pancreas




Each of the islets contains approximately 3,000 cells. The approximately 1 million islets distributed throughout the human pancreas constitute the endocrine pancreas. A somewhat greater number of islets are present in the tail than in the remaining regions.

Each islet is surrounded by reticlar fibers which also enter the substance of the islet to encircle the network of capillaries that pervade it. The cell types in the islet of Langerhans may not be differentiated from one another by routine histological examination.

# The pancreas




**Five types of cells compose the parenchyma of each islet of Langerhans: beta-cells, alpha-cells, delta-cells, PP cells and G cells. These cells may not be differentiated from one another by routine histological examination, but immunohistochemical methods allow them to be recognized.**

**EM also display features that distinguish various cells types, especially the size and electron density of the granules**

# CELLS AND HORMONES OF PANCREATIC ISLETS

| cell | % of total | location | fine structure of granules | hormone and mo-leular weight | function |
|---|---|---|---|---|---|
| beta cell | 70% | scattered throughtout the islet but concentrated at the center | 300 nm diameter, dense core granule surrounded by a wide electron-lucent halo | insulin, 6000 Da | decreases blood glucose levels |
| alpha cell | 20% | islet periphery | 250 nm in diameter, dense core granule surrounded by a narrow electron-lucent halo | gluca-gon, 3500 De | increases blood glucose levels |
| delta cell | 5% | scattered throughtout the islet | 300 nm diameter, electron-lucent homogenous granules | somato-statin, 1640 Da | paracrine: inhibits hormone release by alpha & beta cells; endocrine: reduces contractions of GIT and gall-bladder smooth muscles |

# CELLS AND HORMONES OF PANCREATIC ISLETS

| cell | % of total | location | fine structure of granules | hormone and molecular weight | function |
|---|---|---|---|---|---|
| G cell | 1% | scattered throughtout the islet | 300 nm in diameter | gastrin, 2000 Da | stimulates production of hydrochloric acid by parietal cells of stomach, gastric motility and emptying, and the rate of cell division in gastric regenerative cells |
| PP cell | 1% | scattered throughtout the islet | 180 nm in diameter | pancreatic polypeptide 4200 Da | inhibits exocrine pancreatic secretion |

# Diabetes mellitus

**Diabetes mellitus is a chronic metabolic syndrome commonly accompanied by hyperglycemia, glycosuria and ensuing metabolism disturbances. This condition develops because of absolute or relative failure of insulin hormone and results in disorders of carbohydrate, fat and protein exchange.**

**The main symptom determining pathogenesis and clinical presentations of DM is hyperglycemia. In OK content glucose fasting varies in within 3,8-5,8 mmol / l in adults.**

# Classification of Diabetes Mellitus

**Etiologic classification sugar diabetes (WHO, 1999)**

**I. Sugar diabetes 1st type (Destruction beta cells, absolute Insulin failure)**

**Autoimmune**

**Idiopathic**

**II. diabetes mellitus type 2 (Mainly peripheral resistance to insulin with relative insulin failure)**

# Classification of Diabetes Mellitus

**III. Others specific types of diabetes mellitus**
**A. Genetic defects of beta-cell function**
**B. Genetic defects in insulin functioning**
**C. Diseases exocrine of Pancreatic Cancer**
**D. Endocrinopathy**
**E. diabetes mellitus induced by chemicals and drugs**
**F. Infections (congenital rubella, cytomegalovirus)**
**G. Unusual form of immune-mediated diabetes**
**N. Other genetic syndromes sometimes combined with diabetes (Down syndrome, syndrome Klinefelter, Turner's syndrome etc.)**
**IV. Diabetes of the pregnant**

# The main symptoms

***Polyuria,*** **that is, increased urine output, which is caused by increasing its osmotic pressure due to the presence of dissolved urine glucose (normal glucose in urine should not be present). Fairly frequent urination during the day and at night is noted.**

***Polydipsia,*** **which is unquenchable thirst due to substantial loss of water in the urine, as well as an increase in the osmotic pressure of blood. Patients drink 3-5 liters of fluid and more a day.**

***Polyphagia,*** **which is constant insatiable hunger. This symptom is caused by metabolic disorders accompanying diabetes, the inability of cells to absorb and process glucose without insulin.**

# Complications of diabetes

**Acute complications of diabetes**

**(often resulting from inadequate therapy)**

- **ketoacidic coma**
- **hyperosmolar coma**
- **lactic acidosis coma**
- **hypoglycemic coma**

**Late complications of diabetes**

- **Microangiopathy (retinopathy, nephropathy)**
- **Macrovascular disease (myocardial infarction, stroke, gangrene of the feet)**
- **Neuropathy**
- **Other organs and systems - enteropathy, hepatopathy, cataracts, osteoarthropathy, dermopathy, etc.**

# Impact Insulin on metabolism

In almost all tissues of the body insulin affects the metabolism of carbohydrates, fats, proteins and electrolytes, increasing the transport of glucose, proteins and other substances through the cell membrane.

The main action of insulin is to increase glucose transport across the cell membrane. Glucose in the blood serum reflects the ever-changing state of the two processes under permanent control of insulin: glucose utilization and release of glucose into the bloodstream.

Its biological effect on the cellular level is exercised through the appropriate insulin receptor in tissues. Stimulation of insulin increases the rate of glucose transport in cells 20-40 times.

# Absolute and relative insulin deficiency

**The basis of the disease is *absolute* and *relative* insulin deficiency.**

**Absolute failure develops due to a decrease in insulin B-cells of Langerhans islets of the pancreas as a result of degenerative changes or necrosis under the influence of damaging factors or impaired insulin synthesis, resulting in incretion hormone with reduced biological activity.**

**Absolute insulin deficiency contributes to autoimmunity (disturbed immunogenesis system causing development of auto-immune aggression with selective lesion of B-cells), viral infection, inflammatory disease, fibrosis or calcification of the pancreas, circulatory changes (atherosclerosis), cancer**

.

# Absolute and relative insulin deficiency

**Absolute insulin deficiency is the cause of diabetes in only 10% of patients. In most cases, development of the disease occurs in normal or even high concentrations of endogenous insulin in the blood.**

**The cause of metabolic disorders in these cases is *relative insulin deficiency,* which is based on reduced sensitivity of insulin-dependent tissues to the action of endogenous insulin: tissue insulin resistance.**

# Glucose in whole blood and plasma

**Normal fasting glucose values range between 3.3-5.5 mmol / l in children under 14, and 3.8-5.8 mmol / l in adults.**

**In whole blood glucose concentrations are lower than in plasma. The cause of this discrepancy is the lesser water content in the whole blood.**

# Hyperglycemia

**Hyperglycemia is a clinical symptom indicating high blood sugar (glucose) in the blood serum.**

**There are several conventional degrees of severity of symptoms:**

**- slight hyperglycemia (blood sugar is 6 - 10 mmol / L);**

**- moderate hyperglycemia (10 -16 mmol / L);**

**- severe hyperglycemia (over 16 mmol / L);**

**In people with diabetes mellitus, there are two types of *hyperglycemia:***

**- Fasting hyperglycemia (if the person was not eating for about 8 hours, the level of blood sugar rises above 7.2 mmol / L);**

**- Postprandial hyperglycemia (after meals blood sugar rises above 10 mmol / L).**

# Glucosuria

**Glucosuria means identification of glucose in the urine. In the urine of healthy humans glucose is contained in a very low concentration (0.06-0.083 mmol / L).**

**With normally functioning kidneys glucosuria develops when the level of glucose in the blood exceeds 8.8-9.9 mmol / L, the so-called "renal threshold" or glomerular glucose clearance.**

# Glucosuria

**Detection of glucose in the urine indicates pathology.**

**<u>Glucosuria depends on three factors:</u>**

**- concentration of glucose in the blood,**

**- renal glomerular filtrate in 1 minute,**

**-reabsorption of glucose in the tubules in 1 ml.**

**Glycosuria often precedes hyperglycemia. After filtration in the renal glomeruli glucose is reabsorbed in the proximal tubule.**

# Glucose tolerance

**Glucose intolerance is a condition which precedes diabetes.**

**In this condition, the patient's blood glucose level is higher than normal but lower than that justifying the diagnosis of diabetes.**

**Diagnostic importance of this condition is that at this stage it is already possible to identify the risk of type 2 diabetes and to prevent it just in time.**

# Glucose tolerance

**Disturbed glucose tolerance is determined with glucose test as well. To do this, after determining the level of fasting blood glucose, the patient is given a drink of 75 g of glucose dissolved in 250-500 ml of water for 5 minutes (for the kids - 1.75 g per 1 kg of body weight).**

**In a healthy person after taking the glucose there is a rapid rise in blood sugar for 20-60 minutes (slightly different rates in venous and capillary blood) due to the absorption of glucose in the intestine. After this comes its decline due to the reaction of the regulatory system (insulin), down to the original level between 1.5 - 2 hours after glucose intake.**
**In patients with impaired glucose tolerance, fasting blood sugar is somewhat higher and in two hours it does not fall to the initial value (Table 1).**

**Table 1 Diagnostic criteria for assessing glucose tolerance test (WHO Expert Committee on Diabetes Mellitus, 1999)**

| Evaluation results (mg%) | Capillary blood glucose, mmol / L | |
|---|---|---|
| | Fasting | In 2 h |
| Strong | <5.5 | < 7.8 |
| Impaired glucose tolerance | <5.5 < 6.1 | > 7.8 <11.1 |
| Diabetes mellitus | > 6.1 | > 11.1 |

# Methods for determination of glucose

Determination of the concentration of glucose in the blood is one of the most frequently performed biochemical studies in the clinical diagnostic laboratory. Diabetics have to check the level of glucose at home. This is needed so as to adjust the diet and exercise and to monitor the administration of insulin and other glucose-lowering drugs.

Nowadays mainly enzymatic methods are used to determine glucose.

# Oxidase method

**Glucose oxidase catalyzes the transfer of two hydrogen atoms to the first carbon atom of glucose on the oxygen dissolved in liquid reagent. In the course of reaction hydrogen peroxide is formed in equimolar amounts. That is, the concentration of hydrogen peroxide formed correlates determined with glucose concentration. There are several ways of determining hydrogen peroxide that are widely used today in the laboratory.**

**Measurement of the concentration of glucose in the whole blood is conveniently performed with the aid of instruments, based on the amperometric measuring principle, with special enzyme sensors. This method is linear, usually up to 20-30 mmol / l glucose.**

# Hexokinase method

**Hexokinase method consists of two consecutive reactions:**

**Registration is carried out at a wavelength of 340 nm absorption by NADH. This method is highly specific and does not react with other components of blood serum. Hexokinase method is considered the reference for determination of glucose. As a rule, it is linear up to 50 mmol / L, which allowed its widely recommended use for clinics with departments of endocrine disease.**

# Early diagnosis of diabetes mellitus: identification of antibodies to β-cells of the pancreas, proinsulin, C-peptide

***Antibodies to beta-cells of the pancreas (anti-islet cells)*** **serve as a marker of autoimmune destruction of beta cells in the pancreas producing insulin. The main indications for its administration are: diagnosis of diabetes type 1, assessment of risk of diabetes type 1 in individuals with family history of diabetes.**

**The test, in fact, refers to the process of destruction of islet cells. These antibodies appear in patients before clinical manifestations of diabetes develop after infectious diseases caused by Coxsackie B4 virus, mumps and other viruses.**

## Early diagnosis of diabetes mellitus: identification of antibodies to β-cells of the pancreas, proinsulin, C-peptide

***C-peptide*** **is an indicator of insulin synthesis and carbohydrate metabolism. The main indications for its use are: Diabetes type I and II, insulinoma, assessment of insulin secretion in liver diseases, assessment of insulin.**

**C-peptide is a protein fraction of proinsulin, which is formed during the synthesis of insulin. In response to increasing glucose proinsulin is split to form insulin and C-peptide is secreted in equimolar amounts in the blood.**

## Early diagnosis of diabetes mellitus: identification of antibodies to β-cells of the pancreas, proinsulin, C-peptide

***Proinsulin*** **is an insulin precursor synthesized by beta-cells of Langerhans islets of the pancreas. The main indications for its use are: clinical signs of insulinoma, identifying causes for hyperinsulinism.**

# Criteria for diabetes compensation

**The patient's satisfactory state, a stable course of the disease (daily glycemic values within normal) and normal levels of glycated hemoglobin are considered to be the criteria allowing the physician to regard the diabetes as compensated criteria for compensation of diabetes are now considered: good condition, stable disease.**

**Normally HbAIc content in the blood is 5 - 7% of total hemoglobin.**

# Criteria for diabetes compensation

**A long-term objective indicator of the degree of compensation of diabetes is glycosylated (glycated) hemoglobin (or glycohemoglobin or Hb A1s test, where Hb - hemoglobin, Al c - bound glucose).**

**Hemoglobin and other proteins bind with glucose in a slow non-enzymatic reaction, which depends on the concentration of glucose. The more glucose in the blood, the more glycated hemoglobin accumulates in erythrocytes. Determination of glycosylated hemoglobin test reflects the average blood glucose over the past 2-3 months.**

# Criteria for diabetes compensation

**Fructosamine – a product of protein glycosylation of blood plasma (the compound of glucose and proteins). Albumin gives more than 60% of all proteins that react with glucose. The degree of glycosylation of plasma proteins depends on the concentration of glucose in the blood and the length of the proteins half-life period.**

# Criteria for diabetes compensation

Number of fructosamine in the blood is a good indicator for retrospective monitoring of blood glucose in patients with diabetes and it evaluates the effectiveness of the treatment without laborious daily monitoring of blood glucose.

The half-life of serum proteins is less than the life of red blood cells. Therefore, in contrast to the glycosylated hemoglobin, fructosamine levels reflect the degree of permanent or transient increase in blood glucose for 1–3 weeks before the study.

# Lipid profile in diabetes

## Lipid profile in diabetes

**The lipid spectrum in diabetes type 2 is characterized by the "lipid triad", which includes:**

- **increase in the concentration of triglycerides,**
- **reduction in high density lipoprotein cholesterol (HDL) and**
- **predominance of small dense particles of blood low-density lipoprotein (LDL).**

**This condition is the result of rupture, or regulation and postprandial lipids and can lead to the development of metabolic syndrome.**

- **Complex metabolic, hormonal and clinical disorders, that are risk factors for cardiovascular disease, which are based on insulin resistance and compensatory hyperinsulinemia**

# Metabolic syndrome

**The mechanism of occurrence and development of the metabolic syndrome**

- **When there is insulin resistance, beta cells of the pancreas increase the synthesis and secretion of insulin to compensate for the disturbed insulin sensitivity and maintain normal glucose tolerance, and hyperinsulinemia develops.**
- **Chronic hyperinsulinemia causes paradoxical vasoconstriction and increased cardiac output blood volume, resulting in hypertension.**
- **Insulin regulates the rate of synthesis of VLDL in the liver. When it is a growth enhancing VLDL synthesis.**

**Onizhenie P content of HDL.**

# Metabolic syndrome

**Clinical presentations**

**The main symptoms and signs of the metabolic syndrome:**

- **abdominal visceral obesity**
- **Insulin resistance and hyperinsulinemia**
- **Dyslipidemia**
- **hypertension**
- **impaired glucose tolerance / diabetes type 2**
- **early atherosclerosis / CHD**
- **hemostatic disorders**
- **Microalbuminuria**

**Treatment**

- **weight-reducing diet**
- **Increasing physical activity**
- **Eliminating smoking and alcohol consumption as factors in the development of disease.**

# Hypoglycemic coma

**The increase of blood sugar level is dangerous, but sudden decreasing of glucose concentration is more severe. In concludion, one of the most common acute complications of diabetes is hypoglycemic coma.**

**In the basis of this condition is hypoglycemia, that is, drop in blood sugar. The disease occurs when the blood glucose is between 3 and 3.5 mmol / l or less, although in some situations, such as an active physical work, a number of features can be observed at 4 mmol / l**.

# Hypoglycemic coma

**Hypoglycemia is often a consequence of a breach of reception of tablets sugar-reducing drugs or insulin. Depending on the severity can distinguish mild, moderate and severe hypoglycemia. Most often this condition can occur in diabetes l-type, being just the result of violations of the dosage of insulin, but often can occur in elderly patients with diabetes mellitus type 2.**

**Hypoglycemic coma - is severe manifestations of hypoglycemia.**

# Thank you for your attention!