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# ВОПРОСЫ И ОТВЕТЫ К ЛЕКЦИЯМ ПО ОБЩЕЙ ПАТОЛОГИИ

Учебно-методическое пособие по судебной медицине для студентов
3 курса факультета по подготовке специалистов
для зарубежных стран медицинских вузов

# QUESTIONS AND ANSWERS TO THE LECTURES ON GENERAL PATHOLOGY

Teaching workbook on forensic medicine for 3rd year students
of the Faculty on preparation of experts for foreign countres
of medical highes educational institutions

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# INTRODUCTION

***What is pathology?***

Pathology is the science that studies the causes, mechanisms and effects of the diseases. Anatomic pathology is the study of tissues and organs which are morphologically modified in the course of a disease.

***How can we define the pathologist and what does he do?***

The pathologist (anatomo-pathologist) is the physician specialized in the study of diseases, and deals with:

— Macroscopic and microscopic analysis of tissues and organs originating from deceased patients (postmortem autopsy/necropsy).

— Macroscopic and microscopic analysis of tissues and organs obtained from living patients in order to diagnose their diseases (biopsy).

***Which are the analyzing methods in pathology?***

The methods used in pathology are:

— Visual examination (macroscopy of the diseased organ), which explores the macroscopic appearance of the diseased organs and helps to select representative tissue samples for further microscopic examination.

— Microscopic examination (microscopy of the diseased tissues or histopathology), which explores the microscopic details of the histological structure of the diseased organs under the light microscope.

— Electronic microscopy which offers a more detailed description exploring the intracellular structures and organelles and the intercellular compartment.

— Immunohistochemistry which investigates some specific structures and features of the cells and tissues using antibodies targeted against specific antigens.

— Molecular biology using molecular, genetic end even chromosomal analysis.

— Cytopathology or isolated cells examination, cells obtained through brushings or by fine needle aspiration (extraction) from different tissues.

***Which are the basic concepts for understanding a pathological process?***

In order to understand a pathological process, one has to know:

— the etiology (the cause of a disease);

— the pathogenesis (the mechanism of a disease);

— the morphology (macroscopic and microscopic pattern of diseased organs);

— the evolution (towards healing or towards death following different complications).

***How is organized the study of pathology?***

The study of pathology is traditionally divided in two parts: general pathology and systemic pathology:

— general pathology is focused on the main pathological processes, their mechanisms and evolution without giving any further details about the specific modifications occurring in different organs;

— systemic pathology is focused on the mechanisms of the pathological processes in particular systems and organs.

**Which are the pathological processes studied in General pathology?**

General Pathology has four main chapters:

— disorders of the blood and the interstitial liquid flow;

— disorders of the metabolism;

— inflammations;

— neoplasia.

***What does the Systemic Pathology study?***

Systemic pathology studies the pathology of different organ systems from the body:

— respiratory system;

— cardiovascular system;

— digestive system;

— urinary system;

— genital system;

— endocrine system;

— nervous system;

— osteoarticular system;

— hematopoetic and lymphatic system.

# CHAPTER 1
# GENERAL PATHOLOGY

## METABOLIC DISORDERS

**Which are THE CELLULAR ADAPTATIONS?**

***Definition:*** cellular adaptations are modifications that the tissue cells undertake under the influence of aggressive agents of mean intensity, modifications which do not cause cellular death but instead allow the cells to adjust to the new conditions.

Agents that generate cellular aggressions:

— hypoxia;
— acquired genetic changes;
— physical factors;
— chemical agents;
— immunological factors;
— endocrine agents;
— nutritional agents;
— infectious agents.

**What is THE METABOLIC ADAPTATION?**

***Definition:*** metabolic adaptations are adjustments of the cellular processes at biochemical and molecular levels, without producing morphologic cellular changes visible at light microscopy.

**What is THE STRUCTURAL ADAPTATION?**

***Definition:*** structural adaptations are modifications of the cells visible microscopically; these modifications can be one of the next: the growth, the reduction or the transformation of the cells as a result of the cellular aggression.

**What is ATROPHY?**

***Definition:*** atrophy is the reduction in size and function of the cells, which produce an overall reduction in size and function of a tissue or organ. ***Differential diagnosis must be made with:***

— *Hypoplasia* — which is a congenital condition — the organ is smaller than normal at birth.

— *Aplasia or agenesia* — which is a congenital condition — the organ is missing at birth due to defective embryogenesis.

***Pathogenesis:*** organ atrophy may be due to:

— inactivity;
— inanition;
— ischemia;
— compression;
— neurogenic causes;
— endocrine factors;
— autoimmune processes.

### *Types of atrophy according to etiology*

**1. Atrophy by inactivity:** occurs when an organ ceases its function for a longer period of time or its function is not at full capacity

*Examples:*

— The limbs will display signs of muscular atrophy after prolonged immobilization (i.e. after bone fractures with long immobilization).

— In cases of mitral stenosis, the left ventricle receives a lesser quantity of blood from the left atrium through the narrowed atrioventricular valve, causing in time a ventricular atrophy.

**2. Atrophy by inanition:** appears when the tissues and cells do not receive their basic energetic, that is their normal nutritional requirements.

*Examples:*

— Food deprivation (starvation) with lack of the minimal nutritional intake.

— The lack of nutritional absorption (diseases of enterocyte, such as the microvillus inclusion disease).

— Inadequate nutrient absorption due to accelerated loss of the digestive tract contents (vomit, diarrhoea, etc.).

Other terms used for this type of atrophy by inanition are cachexia, tissue-wasting, athrepsia (extreme weight loss in infants)

**3. Atrophy by ischemia:** appears in cases of slow and partial ischemia, particularly caused by atherosclerosis; the consequence of the atherosclerotic arterial obstruction is the process called sclerous atrophy (the cells from the vicinity of the partially obliterated blood vessel become smaller = atrophy, the cells most distant from the blood vessel suffer a process of apoptosis and are slowly replaced by connective tissue = sclerosis; the global process is described as scleroatrophy).

*Examples:*

— In organs as kidneys, myocardium etc.

— At the level of the lower limbs.

**4. Atrophy by compression** is a variant of atrophy by ischemia, being produced directly on the cells and also by the external compression of the blood vessels which penetrates the tissue.

*Example:*

— On the surface of the brain, a subdural haematoma or a meningioma may generate the atrophy of the adjacent neural parenchyma by slow compression on the brain and on the vessels from the region.

— At the level of the brain, atrophy may also occur secondary to the excessive accumulation of cerebrospinal fluid in the lateral ventricles (hydrocephalus), case in which the accumulated liquid generates a slow compression of the brain (and his blood vessels) against the skull.

— In the kidney, atrophy of the renal parenchyma appears in the case of a periureteral obstruction, with stagnation and accumulation of the urine in the renal pelvis (hydronephrosis), with gradual compression of the renal parenchyma and vessels.

**5. Neurogenic atrophy:** appears in cases of nerve signalling suppression to the muscles, when the denervated muscle suffers a process of atrophy.

*Examples:*

— In cases of poliomyelitis, the polyoma virus destroys the motor neurons from the anterior medullary horns, inducing paralysis in which the denervated motor units of the muscles will suffer a severe atrophy.

**6. Endocrine atrophy (hormonal):** in cases of hormonal insufficiency, atrophy appears in the organs depending on these hormones.

*Examples:*

— In cases of hypopituitarism (deficiency of one or several hormones from the anterior pituitary gland) the other dependent endocrine organs are also affected; atrophy affects the thyroid (following reductions in TSH), the adrenal gland (by the reduction of the ACTH), the ovaries (by the reduction of FSH); in cases of complete hypopituitarism as Sheehan or Simonds syndrome, the patients may also present cachexia.

— Atrophy of the endometrial glands appears in insufficient synthesis of ovarian hormones.

— Adrenal gland atrophy appears in cases of adrenal insufficiency following long term administration of synthetic cortisone, in which the adrenal gland is no longer endogenously stimulated by ACTH with reduced production of endogenous cortisol.

— The atrophy of the gonads (testicle and ovaries) which appears in andropause or menopause.

**7. Autoimmune atrophy:** in immune responses reacting with self-antigens (targeting the individuals' own tissues or molecular structures), in which the targeted organs suffer atrophy.

*Examples:*

— Autoimmune gastritis in pernicious anemia.

— Autoimmune Hashimoto thyroditis.

— Autoimmune adrenalitis presenting with Addison's disease.

**The macroscopy of atrophy:**

— The atrophic organ is reduced in size.

— The shape of the organ is preserved.

— In the tubular organs the folders of the mucosa often disappear.

— On the parenchymatous organs the capsule became wrinkled.

— Pale or brown colour (due to intracellular accumulation of lipofuscin).

— Increased consistency (because of the fibrosis).

*Differential diagnosis* must be made with *pseudohypertrophy (the parenchyma of the organ is atrophied but at the same time the organ displays enlargement of his overall size due to an increased quantity of adipose tissue) and with *sclerosis (the atrophic organs are deformed because of the retractile connective tissue).

**The microscopy of atrophy:**

— the reduction of the size of the cells (and of the cellular organelles);

— the number of the cells decreases;

— a relative (due to the reduced number of parenchymal cells) or a real expansion of the connective intercellular tissue;

— the accumulation of lipofuscin in the cells (lipofuscin, also called aging pigment, is the result of the incorporation of cytoplasmic organelles in autophagic vacuoles, where, reacting with the enzymes, will form residual corpuscles; these corpuscle will appear at light microscopy in HE stain as yellow or brownish intracytoplasmic granules).

*The evolution of atrophy:*

— The organs scleroatrophy lead to functional insufficiency of the organs.

**What is INVOLUTION?**

*Definition:* involution is the physiological type or normal atrophy, which occurs in the same way at all individuals.

*Examples of involution:*

1. During embryonic life, atrophy occurs in different sites:

— The branchial arcs — undergo a complex process of remodelling by involution — ultimately forming different structures of the neck (larynx, pharynx).

— The thyroglossal duct — when involution does NOT appear, it may rest as cyst on the midline of the neck, sited anywhere from the base of the tongue to the thyroid gland.

2. Teenagers display partial atrophy of the haematopoietic marrow in the long bones, of the thymus or of other lymphoid structures.

3. Women may experience atrophy of the mammary glands after lactation.

4. Atrophy of the genital organs in andro/menopause.

5. In advanced age the whole organism undergoes a global atrophy (senescence):

— weight loss;

— the muscles, skin, nails are modified;

— the skeleton is weakened due to demineralisation (osteoporosis), the hormonal changes having their role;

— some organs (the liver, the heart, etc) became brownish (brown atrophy);

— aging is not always associated with senescence; tissue aging may appear early in life as the result of a genetic disease progeria, in which the patient displays all the modifications seen in elderly at very early age.

**What is HYPERTROPHY?**

*Definition:* hypertrophy is the growth in size and function of an organ; this growth implies the increase in size and function of each constituent cell. The cells become bigger, with a larger nucleus and with more structural components as mitochondria, endoplasmic reticulum, etc.

*Types of cells in an organism:*

1. Labile: normally they multiply during the person's life (the cells of the epidermis, the cells of the digestive tract, etc.)

2. Stable: they multiply only in certain pathological conditions (hepatocytes, epithelia of the renal tubules, etc.)

3. Permanent: they usually don't multiply after birth (neurons, muscles) *Hypertrophy appears in permanent cells,* particularly in muscular cells, but it can also appear in stable cells.

***Types of hypertrophy:***

**1. Physiologic hypertrophy:**

— During pregnancy, the uterine muscular fibres increase in size (in length and width) under the influence of gestational hormones.

**2. Adaptive hypertrophy:**

*a) Effort hypertrophy:*

— The skeletal (striated) muscles — after prolonged, repeated efforts (e. g. training, body-building).

— The myocardium — e. g. concentric hypertrophy of the left ventricle appearing in patients with long-standing arterial hypertension.

— The muscles of the digestive tract — hypertrophy is encountered in the segment anterior to an obstacle (e.g. pyloric stenosis will induce hypertrophy of the gastric muscular layer, in an attempt to increase the propulsive force of the stomach).

— The muscles of urinary bladder — hypertrophy of the detrussor muscle of the bladder appearing in cases of prostate enlargements with urethral obstruction.

*b. Compensatory:*

— In the case of paired organs — when one organ is removed, the remaining organ shows a compensatory hypertrophy (kidneys, suprarenal gland).

*c. Hormonal:*

— Excess of STH (can produce hypertrophy and hyperplasia) - if it appears before puberty it produces gigantism (very tall persons) and if it appears after puberty it produces acromegaly (the growth of extremities: the short bones, the mandible, the nose, etc.).

— The administration of androgenic hormones at body-builders (anabolic steroids), can lead to excessive growth of the muscles (but with many side effects — hepatic tumors, myocardial infarction, etc.).

**What is HYPERPLASIA?**

*Definition:* hyperplasia is the increase in size and function of an organ by the increase of the number of its constituent cells. Affects the labile cells, but can also appear in stable cells. It may simultaneously appear with hypertrophy.

Hyperplasia and hypertrophy should be differentiated from hypergenesia, which involves the congenital overdevelopment of an organ.

*a) Hormonal overproduction:*

— STH increase: gigantism and acromegaly.

— TSH increase: goitre.

— Corticoid hormone increase: Cushing syndrome (obesity, «full moon» face, hirsutism, arterial hypertension).

— Increase in androgenic hormones: adrenogenital syndrome.

*b) Hormone-directed hyperplasia in hormonally dependent organs:*

— The mammary gland undergoes physiologic hyperplasia in women at puberty or during pregnancy (the prolactin effect); the pathologic form is represented by gynecomastia, which is the increase of the breasts in men (hyperplasia of the ductal epithelia) due to the action of increased estrogens.

— The endometrial glands and stroma undergo hyperplasia under the influence of estrogens.

*c) Lymphoid organs:*

— During infections the lymph nodes and spleen present transient hyperplasia.

Hyperplasia is a self-limited process, but some imbalances in its regulation may result in tumoral proliferation. It is well established that many benign tumors and some malignant tumors have hyperplasic precursors with superposed genetic defects.

**What is METAPLASIA?**

*Definition:* metaplasia is the replacement of a tissue with other type of tissue. The metaplastic tissue is histologically normal, but its location is abnormal. The young cells of a tissue proliferate changing also their type of differentiation. It does not occur in adult, mature or «differentiated» cells. Metaplasia is often reversible.

**Types of metaplasia:**

— Epithelial metaplasia:
  a) squamous epithelium;
  b) glandular epithelium.
— Mesenchymal metaplasia.
— Mesothelial metaplasia.
— Tumoral metaplasia.

**A. Epithelial metaplasia *Squamous metaplasia:***

1. In the bronchi (airways): the ciliated cylindrical pseudo-stratified epithelium (with cilli and mucus which clean, heat and moist the air flow) is replaced with squamous epithelium. This process can be triggered by cigarette smoke, chronic bronchitis etc; the new type of epithelium has greater resistance to the aggressive agents, but it is the first step which makes possible the development of bronchial squamous carcinoma.

2. In certain circumstances, the endocervical cylindrical epithelium of the uterus is replaced with squamous epithelium; it is the first step which makes possible the development of cervical squamous carcinoma.

3. In organs with cavities (urinary bladder, gallbladder) and in some ducts (pancreatic, salivary excretory ducts) the normal epithelia are frequently replaced with squamous epithelia due to lithyasis (by mechanical chronic aggression).

***Glandular metaplasia:***

1) The oesophageal squamous epithelium may be replaced with glandular epithelium of gastric or intestinal type in the gastro-oesophageal reflux; the

metaplastic tissue is more resistant to the intermittent return of the acidic content of the stomach in the oesophage; this metaplasia appears in the lower third of the oesophage = Barrett oesophagus; it is the first step which makes possible the occurrence of oesophageal adenocarcinoma.

2) In the stomach, the gastric type mucosa can be replaced with intestinal type mucosa in cases of chronic gastritis. It favours the development of gastric adenocarcinoma.

**B. Mesenchymal metaplasia:**

1. The stem cells circulating in the bloodstream may undergo metaplasia into fibroblasts, endothelial cells etc.

2. The yellow bone marrow of the adults (previously red haematopoietic bone marrow in childhood) may undergo metaplasia and hyperplasia due to chronic anemia, returning in red, haematopoietic bone marrow.

3. Different pathologic structures (atheromas, damaged endocardial valves, tuberculous nodules, large haematomas, myositis ossificans) may be organized in fibrous scars (replaced with fibrous connective tissue) with calcium deposition and finally with foci of osseous metaplasia (transformation into bone).

4. During the healing of a fracture the clot initially formed between the two bone fragments gradually undergoes connective organization, (fibrous callus), calcification and finally bone metaplasia (osseous callus).

**C. Mesothelial metaplasia:**

— Squamous or glandular metaplasia can occur at the level of the pleura, peritoneum etc.

**D. Tumoral metaplasia:**

— Foci of squamous metaplasia in adenocarcinoma = adenoachantoma.

**What are THE CELLULAR LESIONS?**

*Definition:* The cellular lesions are the pathologic modifications of the structure of the cells due to aggressive agents of higher intensity than those producing adaptive changes.

*Pathogenesis:*

— Hypoxia.

— Chemical injuries (toxic substances).

*Evolution:* lesions are reversible or irreversible depending on the intensity or the duration of the aggressive factor.

**What are THE REVERSIBLE LESIONS?**

*Definition:* reversible lesions are cellular modifications that can disappear when the aggressive factors cease their action and consequently the cells return to their normal structure.

**Types of reversible lesions:**

1. The hydropic swelling.

2. Fatty change or steatosis.

**What is THE HYDROPIC SWELLING?**

*Definition:* the hydropic swelling is the loading and intoxication of cells with water, secondary to hypoxia or exposure to various toxic substances (chemicals, bacterial or viral toxins).

*Pathogenesis:* during hypoxia the cell metabolism is perturbed with dysfunction of the Na/K ATP-ase (the sodium/potassium pump), increased Na influx into the cell and passive intracellular water influx (and subsequent cellular swelling).

*Macroscopic features:*

— Large, pale organ with slightly increased consistency (resembling boiled meat).

— The organs most frequently affected are the liver, the kidney, the heart.

*Microscopic features:*

— Granular dystrophy: swollen cells with amorphous, small, homogenous eosynophil granules — that are at electron microscopy (EM) enlarged, swollen mitochondria due to the accumulated water.

— Vacuolar dystrophy: swollen cells with small clear vacuoles (at EM, the mitochondria's and the endoplasmic reticulum are swollen).

— Ballooning dystrophy: large cells, with a homogenous, pale, clear cytoplasm (at EM: overhydration of the entire cytoplasm).

*Evolution:*

— The cells can return to their normal state once the cause has disappeared.

— The cells can evolve directly onto cellular necrosis.

**What is FATTY DYSTROPHY?**

*Definition:* fatty dystrophy or steatosis is the accumulation of triglycerides in parenchymatous cells.

*Etiology:* hypoxia, various toxic chemicals (i. e. alcohol, carbon tetrachloride).

*Macroscopic features:*

— Larger, yellow, softer organ.

— Most frequently affects the liver («filled goose liver») but also the heart («tiger-striped myocardium»), the kidneys.

*Microscopic features:*

a) In the hematoxylin and losin stain (HE stain), clear intracellular, well-delimited vacuoles appear (the fat will dissolve during tissue processing and staining). The differential diagnosis with other dystrophies is necessary when white vacuoles in the cytoplasm appear in HE stain: hydropic dystrophy (there is no existing stain for the water) glycogenic dystrophy (in glycogen dystrophies, the tissue stained with Carmin Best reveals red vacuoles).

b) In fatty dystrophy these can be accurately diagnosed using special stains or histochemical methods for fat; the stains are performed on frozen sections to avoid dissolving the fat during processing.

The special stains commonly used for fats are:

— Scharlach red: stains the fat in red.

— Sudan III: stains the fat in yellow.

*Evolution:*

— The cells can return to normal as long the nucleus is not irreversibly affected.

— The evolution of the cells tends towards necrosis when the quantity of fat accumulated in the cell compresses the nucleus.

**The steatosis of the main organs:**

**1. Hepatic Steatosis (the fatty liver).**

*Definition and etiology:* hepatic steatosis is the accumulation of triglycerides in the cytoplasm of the hepatocytes following the exposure or the use of toxic substances, alcohol, drugs or in the course of some diseases (i. e., diabetes mellitus, obesity).

*Macroscopic features:*

— Liver increased in size (3 to 6 kg).

— Yellow, soft.

— The anterior border rounded *Microscopic features:*

*a) Macrovesicular steatosis (alcoholic):*

— Small clear globules (liposomes).

— Clear vacuoles.

— Large accumulations, which move the nucleus to the periphery of the cell.

— Large accumulations compressing the nucleus to the cell membrane.

— Fatty cysts.

— Disrupted fatty cysts: the fat reaches the interstitium: lipogranuloma.

*b) Microvesicular steatosis (the **Reye Syndrome).***

**The Reye Syndrome:**

— Affects especially children (3–10 years old) and pregnant women.

— It usually occurs in the course of a respiratory or digestive viral disease, when the child is treated with aspirin.

— Clinical signs: vomiting, changes in the mental and neurologic state, and coma, that may quickly progress to death.

— At necropsy: macroscopically a massive cerebral oedema and hepatomegaly; the microscopic examination reveals microvesicular hepatic steatosis (sometimes also encountered at the level of the renal tubular epithelial cells).

— Survivors end up with neuromuscular sequelae and motor deficit.

**2. Cardiac steatosis.**

*Definition:* cardiac steatosis is the accumulation of triglycerides in the myocardial fibres.

**Types of myocardial fatty dystrophy:**

*1. Partial dystrophy ("tiger striped heart").*

*Etiolgy:* moderate and prolonged hypoxia.

*Macro-features:* the myocardium has yellowish coloured fibres (with fatty dystrophy) among its normal red-brownish fibres.

*Micro-features:* vacuoles coloured in red with the special Scharlach red stain can be found in the cytoplasm of the dystrophic fibres.

*2. Total dystrophy*

*Etiology:* significant hypoxia, diphtheria.

*Macro features:* yellow, flaccid myocardium.

*Micro features:* all the fibres contain triglycerides deposits accumulated in the cells.

**3. Renal steatosis:**

*Definition:* renal steatosis is the accumulation of triglycerides in the epithelia of the urinary tubs.

*Etiology:* nephrotic syndromes (with proteinuria).

*Maro-features:* swollen, yellowish kidneys.

*Micro-features:* vacuoles with fat in the epithelial cells of the proximal convoluted tubes.

**What are THE IRREVERSIBLE CELLULAR LESIONS?**

*Definition:* irreversible lesions lead to the irreversible loss of the structure and of the vital functions of the cell (cellular death).

**Types of cellular death:**

— Autolysis: is the death of the cells in a dead organism.

— Apoptosis: is the genetically programmed, physiologic or pathologic death of a cell in a living organism without any inflammatory reaction.

— Necrosis: is the accidental cellular death in a living organism due to agents or factors that exceed the capacity of the cell to withstand aggression and which determines an inflammatory reaction.

**What is APOPTOSIS?**

*Definition:* apoptosis is the genetically programmed, physiologic or pathologic death of a cell in a living organism that does not induce a reaction in the neighbouring cells and is not followed by inflammation (as in the case of necrosis). By the physiologic standpoint, it represents the reverse of mitosis or proliferation in the process of maintaining the normal number of functioning cells in a living organism.

*The main stages of apoptosis and their morphologic features:*

— A pericellular halo — the cell separates from the neighbouring cells (the tight intracellular junctions are released).

— The cytoplasm dehydrates and the cell contracts, but the cytoplasmic organelles stay normal.

— The chromatin condensates peripherally, under the nuclear membrane and is cleaved into nucleosomes (nuclear fragments with DNA) by endonucleases.

— The cellular membrane splits and reverse dividing the cell into apoptotic bodies, any apoptotic body containing a fragment of cytoplasm with cytoplasmic organelles and nucleosomes.

— The apoptotic bodies disappear by phagocytosis by the neighbouring cells (if they are deep) or by exfoliation (if they are on a surface).

— The apoptotic body does not influence the neighbouring cells and does not cause any inflammatory reaction.

Apoptosis appears during:

— Organogenesis: the lumen occurrence in various ducts and tubular organs, the disappearance of the interdigital membrane, etc.

— The renewal of the normal adult tissues that normally regenerate life long needs initially the apoptosis of the senescent cells, the normal state representing a balance between mitosis and apoptosis.

— Hormonal: the decrease of a hormone level in the blood lead to the reduction of size and function of the dependent organ, obtained by atrophy combined with apoptosis (i. e. endometrium in menopause).

— Immunology: the clonal selection and deletion of lymphocytes during the immune system development and in immune responses; perturbations in these processes may result in autoimmune diseases.

— Viruses: in acute hepatitis, hepatocytes die by apoptosis (Councilman corpuscle = apoptotic bodies).

— Neurodegenerative diseases: the Alzheimer disease.

— The spontaneous apoptotic death of some malignant tumor cells or following radiotherapy and chemotherapy.

**What is NECROSIS?**

*Definition:* necrosis is the cellular death in a living organism, which determines an inflammatory reaction.

*Etio-pathogenesis* varies according to the type of necrosis:

— There are two main types of necrosis: the coagulative necrosis (through proteic denaturation) and the liquefactive necrosis (through enzymatic digestion).

*The macroscopy* is different according to the type of necrosis.

*Microscopy:*

— The nucleus becomes smaller, and turns hyperchromatic (pyknosis), and then the nucleus is destroyed through random, erratic fragmentation (karyorexis) or through enzymatic lyses (karyolysis).

— The cell membrane becomes hyperpermeable and the water enters in the cell and the organelles swell (the mitochondria, the endoplasmic reticulum, the lysosomes).

— The lysosomes break and release enzymes that ultimately lead to the autolysis of the cell.

— Following multiple structural alterations, the cellular membrane disappears.

**Types of necrosis:**

**1. The Coagulative necrosis**

*Pathogenesis:*

— Ischemia (white infarction), some bacterial toxins or chemical substances (acids) can produce coagulative necrosis.

— Mechanism: the modification of structural and enzymatic proteins by blocking the cellular proteolysis.

— It is also called «dry necrosis»; its pattern derives from the proteic coagulation and the local loss of water.

*Macroscopic features:*

— The area with necrosis is opaque, pale, well-defined.

— Example: the white infarction in the spleen, kidney, heart.

*Microscopic features:*

— The cellular nucleus becomes pyknotic and then disappears.

— The cytoplasm becomes markedly eosynophilic, homogenous.

— The cellular membrane persists for variable periods of time (it maintains its structure), then it disappears.

— The area becomes amorphous (without structure), acellular (without cells), and acidophil (eosynophilic, red).

*Evolution:*

— Cellular fragmentation, disappearance and death.

— Monocytes/macrophages, and neutrophils migrate in the area and initiate the endocytosis of the cellular debris, concomitantly with new capillary formation and deposition of extracellular matrix by fibroblasts (creating a granulation tissue), generating a scar connective tissue.

**2. The Liquefactive necrosis**

*Pathogenesis:*

— Appears in cerebral infarctions, in abscesses.

— The hydrolases contained by the necrotic neurons and glial cells digest and soften the necrotic area, the disintegrated myelin retaining water.

— Infection with pyogenic bacteria of a region leads to liquefactive necrosis due to liquefactive enzymes (abscess).

*Macro-features:*

— The necrotic tissue is pale and softened.

*Micro-features:*

— Cellular debris dispersed in a pale, eosynophilic background.

**3. Fatty necrosis (steatonecrosis)**

*Pathogenesis:* fatty necrosis (the necrosis of the fatty cells) may have different causes, the most frequent being:

*1) The enzymatic necrosis of the fat:*

— It appears in cases of acute necrotic-hemorrhagic pancreatitis.

— The necrosis of the fat is due to the release of the pancreatic lipase which induces the lyses of the adipose cells, that finally results in the extracellular release of the triglycerides; these are in turn degraded to fatty acids and glycerine, the resulting fatty acids reacting with the calcium to form calcium soaps.

*Macroscopic features:*

— Whitish or yellow areas (spots), similar to wax drops.

*Microscopic features:*

— The necrotic fatty cells initially appear as eosynophilic cellular shadows without nuclei; after the disappearance of the cellular membrane the area becomes homogenous and basophilic due to the calcium deposition which stains blue in HE stain.

*2) Traumatic fatty necrosis:*

— It appears especially in the traumatized breast.

— Clinically: firm area, vaguely delimitated.

*Macroscopic features:*

— Yellowish, consistent nodule or cyst that contains necrotic fat.

*Microscopic features:*

— Degraded fatty cells and haemorrhage. Then in the necrotic area appear siderophages (macrophages with intracytoplasmic ferric brown pigment), cholesterol crystals, hystiocytes, lymphocytes, and plasmocytes; finally, the area heals with fibrosis.

*Evolution:*

— Fibrosis which is retractile and calcified — careful differential diagnosis with a breast carcinoma is needed.

**4. Fibrinoid Necrosis**

— Fibrinoid necrosis is a type of necrosis that is only microscopically observed, the area involved being intensely eosynophilic.

— The term «fibrinoid» indicates a resemblance to the fibrin (pink, homogenous area), but actually it is not formed by fibrin.

— The area of fibrinoid necrosis is mostly composed by degraded collagen fibres and may get different patterns during the various pathological processes.

Fibrinoid necrosis is encountered in cases as:

— Peptic gastric or duodenal ulcer (induced by the hydrochloric acid secreted by the gastric mucosa which pass over on the mucus bicarbonate barrier and digest the gastric or duodenal mucosa).

— Malignant arterial hypertension (extremely high arterial pressure which destroys the arteriolar walls).

— Rheumatic fever (the Aschoff nodule).

— Rheumatoid arthritis (the centre of a rheumatoid nodule — autoimmune reaction against self antigens).

— Collagenosis and vasculitis: systemic lupus erythematosus, nodular polyarteritis, etc. (autoimmune diseases in which immune complexes are deposited in the vessel walls).

**5. The Caseous Necrosis**

— Occurs in tuberculosis.

— *Macro:* white-grey nodules, which have a soft consistency (caseum, lat.=cheese).

— *Micro:* total eosynophilic necrosis.

**6. The Gummatous necrosis**

— Occurs in syphilis.

— *Macro:* syphilitic gums.

— *Micro:* eosynophilic necrosis.

**7. The Gangrene:** a particular type of necrosis and subsequent degradation of a tissue through an ischemic mechanism sometimes associated with a

superposed bacterial infection. Most frequently it occurs at the level of the limbs and in some internal organs Gangrene Types:

*1. Dry gangrene*

*Definition:* coagulation necrosis through an ischemic mechanism of tissues exposed directly to the air, mostly at the level of the lower limbs, but also affecting hands, ears, nose other extremities.

*Causes:* slowly installed ischemia through, slow, incomplete but progressive arterial obstruction, as in arteriosclerosis (superposed on atherosclerosis), obliterating thrombangeitis, prolonged and intermittent arterial spasms (the Raynaud disease).

*Clinical signs:* the necrosis starts at a very distal site from the obliterated vessel which is the less perfused (e.g. the first finger of the leg, the obliteration being at the level of the femoral artery) with slow development onto the higher levels until the region were the tissues are well nourished by the blood, the limit between the perfused and the ischemic tissues being very clear (line of self amputation); the skin is initially pale, cold, dry, with hair loss, then turns black (the iron pyrites resulted by myoglobin degradation and air oxidation), mummified.

*Evolution:* towards self-amputation of a clearly delimitated area or towards infection (transforming the dry into wet gangrene).

*2. Wet gangrene*

*Definition:* infarcted tissues or tissues with dry gangrene secondarily infected (streptococci, staphylococci etc.)

*Location:* inferior limbs, intestine, appendix, gall bladder, lungs etc. *Clinical signs:* starts randomly (not at the most distal sites from the obliterated vessel), the area is grey-black, swollen, with a bad smell, imprecisely delimitated and rapidly extending to the neighbouring tissues.

*3. Gas gangrene*

*Etiology:* Clostridium perfringens or other anaerobic germs, which have enzymes, that produce necrosis but also fermentation releasing gases that dissect and disrupt the tissues and cause subcutaneous or internal vesicles (blister) formation It may appear in open fractures, extensive traumas, large crushed wounds, al contaminated by dirt or other infected foreign bodies.

*Clinically:* a dark swollen area, with a fetid fluid discharge, putrid smell, and cracks sensation at tissue palpation (due to the presence of gas bubbles in the tissue) and severely altered, rapidly deteriorating clinical status; in the absence of an urgent surgical treatment with the disruption of the anaerobic conditions the disease has a lethal outcome.

**VIII. Pressure or decubitus ulcer**

— Occurs in bed-ridden patients, with limited mobilization (paralysed patients, cardiopulmonary or cancer terminally ill patients, athretic children).

— Pressure or decubitus ulcer is a type of ischemic necrosis; the vessels (mostly capillaries) and tissues are compressed between the bed and the bones of the patients.

— It may vary from superficial skin lesions to full thickness skin loss, extensive subcutaneous tissue necrosis and muscles onto the bone.

— In supine position are affected the occipital region, the shoulders, the sacral region, the buttocks, the ankles, the elbows.

— In lateral decubitus: the ear, the shoulder, the hip, the knee, malleoli.

— The lesion is a wound that resembles initially to the dry gangrene, and then becomes humid/wet; it becomes ulcerated and smells badly; it cannot be cured by drug therapy.

# CHAPTER 2
# THE INTERSTITIAL PATHOLOGY

*Definition:* The interstitial pathology comprises the disorders of the structural elements found between cells (the extracellular matrix).

The main components of the extracellular matrix are:

— The matriceal or fundamental substance (proteoglycans).

— The fibres (collagen and elastin).

**What is THE PATHOLOGY OF THE FUNDAMENTAL SUBSTANCE?**

*Definition:* the fundamental substance contains proteoglycans: glycosaminoglycans (GAG), glycoproteins, etc.

***The myxoid dystrophy*** is the excessive accumulation of proteoglycans (myxoid = it resembles to the myxomatous tissue or Wharton's gelatine).

*Macroscopic features:*

— The tissue gets soft and gelatinous aspect.

*Microscopic features:*

— Numerous star-like shaped fibroblasts; they are dispersed in a fine, discrete basophilic matrix.

*Examples of myxoid dystrophy:*

— Pretibial and retroocular myxoedema (in hyperthyroidism — Basedow-Graves disease).

— Generalized myxoedema (in hypothyroidism), with rounded "full moon" face, macroglosia (enlargement of the tongue), dermal and visceral oedema.

— The sinovial pseudocysts.

— The pseudocysts of the media layer of the aorta (fragmentation of the elastic lamellas and accumulation of mucopolysaccharides in the aortic media of the patients with Marfan Syndrome, or in patients with chronic arterial hypertension).

— The prolapse of the mitral valve; clinically manifests with fatigue, thoracic pain, dyspnoea; at echocardiography one can notice that during the systole the cusps recoil (prolabate) into the left atrium; microscopically, a sponge-like aspect appears at the level of the fibrous tissue of the cusps, with mucopolysaccharides accumulated in these spaces.

— Connective tissue tumors, neural tumors, etc.

**What is THE FIBER PATHOLOGY?**

Types of fibres existent in the extracellular matrix:

I. Collagen fibres.

II. Elastic fibres.

**I. The pathology of collagen fibres**

1. Degenerative lesions:

— Collagen related diseases (collagen depolymerisation, collagenosis).

— Atrophy of the collagen at older ages or following prolonged administration of cortisone.

2. Productive lesions:

— Fibrosis (a microscopic term), represented by the proliferation of the fibrous connective tissue at microscopic level (proliferation of fibroblasts which secrete the fibres).

— Sclerosis (the term derives from the macroscopic pattern), used to describe a proliferation of connective tissue in larger quantities, macroscopically visible; it appears as white-grey, firm areas, which at the level of the entire organ induces size reduction and an irregular surface (retractile tissue) and harder consistency than normal.

***Types of fibrosis:***

1. According to its main, predominating elements:

— Collagenous fibrosis: many collagen fibres.

— Fibroblast-collagen: made of cells (fibroblasts) and collagen fibres.

— Vascular fibrosis: made by cells, fibres and numerous blood vessels.

2. According to its etiology:

— Post-inflammatory (ex: chronic hepatitis).

— Dystrophic (ex: necrosis: granulation tissue: connective tissue).

— Tumoral (ex: nodular fasciitis, fibromatoses, the connective stroma of a carcinoma).

3. According to its topography (location within the organ and relation with his main structure):

— *Systematic fibrosis* — does not modify the overall structure of the organ (ex: pulmonary fibrosis).

— *Encapsulating fibrosis* — is the formation of a connective tissue capsule around a pathological process (around an abscess, haematoma, etc.).

— *Dissecting fibrosis* — the fibrosis appears randomly, severely distorting the organ and modifying its architecture (ex: liver cirrhosis, myocardial infarction).

4. According to its quantity and to his retractile characteristics:

— *"Atrophic" fibrosis* — causes the retraction of the affected area (ex: hepatic cirrhosis, renal scleroatrophy, etc)

— *"Hypertrophic" fibrosis* — the connective tissue proliferates excessively without retraction (hypertrophic scars or *keloids* which appear as excessive, white, glassy, hardened areas).

5. According to its evolution:

— *Stable* — it does not evolve in time (the capsule of a haematoma, the scar of a myocardial infarction).

— *Evolving* — fibrosis extends at the same time with the pathological process (ex: chronic hepatitis, hepatic cirrhosis).

**II. The pathology of the elastic fibres.**

***A. Degenerative lesions.***

***1. Hereditary degenerative elastopathies:***

*a) The Marfan syndrome* (AD): patients presenting the following signs:

— They are very tall.

— They have long and slender limbs.

— Long and slender fingers (arachnodactily).

— Muscular hypotonia.

— Hyperlaxity of the joints and tendons.

— Crystalline dislocation.

— The arteries containing elastic structures (the aorta, the pulmonary artery and the cerebral arteries) present multiple lesions similar to the medial necrosis of the aorta due to the fragmentation of the elastic fibres of the aortic media. Cystic cavities with a mucoid or myxoid content occur, weakening the arterial wall and allowing incomplete ruptures (of the intima and partially of the media) the blood entering into the media. From here, the blood advances dissecting longitudinally the media, resulting a *dissecting haematoma of the aorta* or a *dissecting aneurysm of the aorta.*

*b) The Ehler-Danlos syndrome* (AD) — consists in the degeneration of the elastic fibres and the atrophy of the collagen fibres; patients present:

— Vascular dilatation (telangiectasia).

— Cutaneous hyperlaxity.

— Cutaneous fragility, slow healing lesions, insufficient scars.

*c) The elastic pseudoxantoma* (AR); patients present:

— Small, yellow, laterocervical tumefactions.

— Swollen, broken elastic fibres (elastorrhexis).

— Calcium deposits.

— The arteries of the digestive system are usually affected and severe digestive haemorrhages may occur.

***2. Acquireddegenerative elastopathies***

*a) Stretching scars* are tegument lines located especially on the lower abdominal wall, upper areas of the buttocks or thighs, and around knees and breasts. Stretching scars affect mostly the dermal elastic fibres. Initially the stretching scar lines are violet, and then they turn white-nacreous. These scars occur in people who gain and lose weight suddenly, during growth spurts in teenagers, in pregnant women or at people with Cushing Syndrome, etc.

*b) Senile elastosis (actinic)* are white spots, which appear at older persons, by elastic fibres degeneration induced by the sun on the uncovered skin.

*c) Post-radiotherapy elastosis.*

*d) Elastosis* resulting secondarily to some dermatological diseases.

***3. Productive elastopathies***

*1. The fibroelastosis of the endocardium:*

— It usually occurs in neonate children (rarely in adults).

— Macroscopically, the parietal endocardium, especially that of the left atrium and left ventricle is swollen, porcelain-like, white, hard; it surrounds the trabecular muscles.

— Microscopically, the endocardium is covered with excessive intermingled layers of elastic and collagen fibres.

— The evolution: the myocardium cannot contract ^ cardiac failure ^ death.

*2. Elastic hyperplasia of the vascular intima*

— Macroscopically: arteries with narrowed lumen due to the thickness of the intima; when sectioned, the intima is white, tough.

— Microscopically: the proliferation of the elastic fibres.

— Evolution: towards ischemic phenomena.

**What are METABOLICAL DISORDERS?**

*Definition:* metabolic disorders are heterogeneous complex diseases, which may be classified according to their biochemical substratum at the cell or tissue level. Consequently, they may be classified as:

— disorders of the protein metabolism;

— disorders of the lipid metabolism;

— disorders of the glucose metabolism;

— disorders of the metabolism of pigment substances;

— disorders of the metabolism of the mineral substances.

**What are THE DISORDERS OF THE PROTEIN METABOLISM?**

*Definition:* protein metabolic disorders mean the dystrophic changes of the protein structures or of their components of a living cell, which are pathologically significant The pathology of the protein metabolism:

1. The keratinous dystrophy.
2. The mucous dystrophy.
3. Amyloidosis.
4. Hyalinosis.

**What is KERATINOUS DYSTROPHY?**

*Definition:* keratinous dystrophy is a metabolic disorder that affects the production of keratin in the squamous epithelia (normal squamous epithelia or squamous metaplasia).

**A. The keratinous squamous epithelium (of the skin)**

a) A basal layer that may display:

— The hyperplasia of the basal layer: the number of basal cells increases.

b) A stratum corneum that may display:

— Acanthosis: the hyperplasia of the stratum corneum.

— Acantholyses: the dissociation, separation of the corneal cells because of the destruction of the intercellular desmosomes.

— Atrophy: decrease in the thickness of the stratum corneum.

— Ballooning degeneration: the cytoplasmic vacuolisation of the corneal cells.

— Spongiosis: intercellular oedema, blisters, dissociation of the cells.

b) A granular layer that may show:

— Hyperplasia.

c) A clear stratum.

d) A keratinous stratum that may display:

— *Hyperkeratosis.*

— With *ortokeratosis* — the thickening of the normal, enucleated, homogeneous, eosynophilic keratinous layers.

— With *parakeratosis:* nuclear debris can be found between the thickened keratin layers (meaning accelerated cellular turnover and keratinisation).

— *Dyskeratosis:* the presence of keratin in other places than normal, which occurs because of a premature keratinisation of the cells, already in the stratum corneum or in the basal cells layer.

— Benign: it appears in *Molluscum contagiosum.*

— Malignant: it appears in squamous carcinomas "in situ" or invasive.

**B. Non-keratinised squamous epithelium** (squamous mucosa of the digestive system, respiratory tract, genital tract etc., which normally are humid, being covered by mucus) may present:

— Keratosis: the occurrence of keratin at the surface of squamous epithelia of the mucosa (e.g. in the mouth, larynx etc); it may appear macroscopically as a white spot, named leucoplakia.

— Leucoplakia or leucoplasia: the occurrence of macroscopically white spots on the squamous mucosa.

Macroscopically, leucoplasia may be:

— Flat: less important, being reversible if the cause disappear.

— Verucous: it can progress to a carcinoma.

— Hairy: it is in relation with the Epstein-Barr virus infection and HIV.

Microscopically, leucoplasia may hide:

— Hyperkeratosis, parakeratosis and benign or malignant dyskeratosis (sometimes one can see the progression towards an "in situ" carcinoma, then to an invasive carcinoma).

**What is MUCOUS DYSTROPHY?**

*Definition:* mucous dystrophy means the excessive production of mucus by the mucus secreting epithelia; the mucus is produced by specialized epithelial cells, either organized in glands (salivary glands) or dispersed between other cells in various surface epithelia (respiratory or gastro-intestinal mucosa, etc).

The macroscopy of the mucus:

— White, transparent, filamentous fluid.

The microscopy of the mucus:

— Mucus appears pale, slightly basophilic (blue) in HE stain.

— Mucus appears red in PAS stain and mucicarmin.

— Mucus appears blue in Alcian blue stain.

Circumstances evolving with excessive secretion of mucus:

1. Intracellular accumulations:

— The mucus-producing cells increase in size, their cytoplasm turns pale and the nucleus is pushed to the cell membrane (the cell look like a "signet ring").

— These changes may occur in chronic bronchitis (catarrhal mucus secreting inflammations), "signet-ring" cell adenocarcinomas.

2. Interstitial accumulations:

— Mucigen carcinomas (mucus accumulations in the tumor, originating from hypersecretory, broken tumoral glands).

3. Accumulations in cavitary organs:

— Resulting mucocele of the appendix, gallbladder.

4. The accumulation of mucus in the peritoneal cavity (pseudomyxoma of the peritoneum), which may occur by the rupture in the peritoneum of a large mucocele or of an ovarian mucus secreting cystic tumor.

**What is AMYLOIDOSIS?**

*Definition:* the amyloidosis is a disorder of some protein metabolism that leads to the extracellular deposition of abnormal proteins as inert fibrils.

Macroscopically, the deposited substance resembles the amydone (a glucose polymer existent in starch), hence its name: amyloid (amylos = starch, oid = resembling). The EM (electron microscopy) structure of amyloid:

a) The fibrils, variables, derived from proteic components, appear as tightly packed bundles of fibres.

b) The non-fibrillary part is a constant globular "P" component, identical with a normal circulating seric glycoprotein produced by the liver. This component has a pentagonal structure.

**Characteristics of the amyloid:**

— it has a very resistant structure;

— it cannot be fragmented by enzymes;

— it is not endocytosed by macrophages;

— it does not have antigenic properties;

— it cannot be removed by any known therapeutic methods.

**Types of amyloidosis:**

**1. AA** (reactive or secondary) amyloidosis:

— It appears in chronic aseptic inflammations (rheumatoid arthritis), chronic microbial infections (chronic osteomyelitis, tuberculosis, suppurated bronchiectasia), malignant tumors (renal, pulmonary carcinoma, Hodgkin lymphoma).

— An AA amyloid protein is deposited; the protein is derived from a circulating seric precursor (SAA), which is a high density lipoprotein (HDL) as apolipoprotein.

— It is localized in the heart, the digestive tract, the spleen, the kidneys.

— Clinically: enlarged organs (organomegaly) with functional failure.

**2. AL** (immunoglobuline defects or primary) amyloidosis:

— It appears in B lymphocyte dyscrasia: multiple myeloma, Waldenstrom macroglobulinemia.

— An immunoglobuline derived protein is deposited; this protein is either the κ or X light chains of immunoglobuline or the entire immunoglobuline molecule.

— It is localized in the mesenchymal tissues.

— Clinically: peripheral or autonomous neuropathy, carpal tunnel compression syndrome with the compression of the carpal nerve, macroglossia, restrictive cardiomiopathy, artropathy of the large joints, visceral lesions.

**3. Hereditary systemic amyloidosis**

— Familial amyloid polineuropathies — AD disease, in which the amyloid is the transthyretin (a prealbumin that caries thyroxin and retinol).

— The Mediterranean familial fever — AR disease in which the amyloid is of AA type fibril protein.

**4. Senile amyloidosis**

— Cardiac: in men over 70, without specific symptoms, transthyretin is deposited in the ventricular wall and the atrial natriuretric peptide in the atrial walls.

— Cerebral: Alzheimer disease in which a beta-amyloid is deposited in the cerebral parenchyma and in the brain blood vessels.

**5. Amyloidosis associated with dialysis**

— Beta 2-microglobulin that is not filtered through the membranes used for dialysis and accumulates in the body.

— It is found in joints, tendon sheaths (the carpal tunnel syndrome).

**6. Localized amyloidosis**

— It affects single organs (the skin, the bladder, etc) and it appears as pseudo-tumoral nodules.

**7. Endocrine amyloidosis**

— In the thyroid in medullary carcinoma, when pre-pro-calcitonin fragments are deposited; it originates from the C cells of the thyroid which produce calcitonin.

— In the pancreas: tumors secreting insulin (insulinoma).

**The macroscopic aspect of the amyloidosis:**

— The organs are enlarged, white, hardened.

— The parenchyma undergoes atrophic changes because the amyloid deposited in the blood vessels gradually narrows their lumens inducing partial ischemia.

— Applying a iodine solution (potassium iodine or Lugol) on the cut surface of the organs with amyloidosis their colour turns brown; the further application of a diluted solution of sulphuric acid will change this colour in blue-green.

**The microscopic aspect of amyloidosis:**

— The amyloid appears red in HE stain; it is also homogenous, amorphous, looking very much alike the hyaline.

— The specific stain for amyloid is *Congo Red* which makes the amyloid to turn red-orange; if the slide is viewed with polarized light becomes shiny green (green birefringence).

— Other stains for amyloid are the violet crystal, thioflavine.

— The fibril structure of the amyloid is seen in EM.

**Organs with amyloid:**

*1. The amyloidosis of the spleen*

Macroscopic features:

— Mild splenomegaly with a diffuse whitish colour (the lardaceous spleen) or with little white nodules (the Sago spleen).

Microscopic features:

— In the lardaceous spleen, the amyloid is accumulated in the red sinusoidal pulp.

— In the sago-like spleen, the amyloid is deposited in the walls of the penicillated arterioles of the white pulp.

*2. Renal amyloidosis.*

Macroscopic characteristics:

— The kidneys are swollen, pale, with increased consistency.

Microscopic features:

— Glomerulus: deposits in the mesangium and in the glomerular basement membrane.

— Urinary tubes: deposits in the tubular basal membrane.

— Blood vessels: deposits in the arteries and arteriolar walls which leads to the narrowing of their lumens.

*3. Hepatic amyloidosis*

Macroscopic characteristics:

— Slightly enlarged, paler, heavier and hard organ.

Microscopic features:

— Deposits in the Disse space (between the hepatocytes and the sinusoids) — leads to the atrophy of the hepatocytes and narrowing of the sinusoids.

*4. Cardiac amyloidosis*

Macroscopic characteristics:

— Swollen, pale heart Microscopic featuresAmyloid is deposited in the myocardial fibres, on the valves, in the wall of the coronary arteries.

*5. Digestive amyloidosis*

Macroscopic features:

— It is deposited at any level of the gastro-intestinal tract.

Microscopic features:

— First it is deposited in the blood vessels, then it affects other structures.

Other localizations:

— Endocrine glands.

— Respiratory tract.

— Peripheral nerves.

**What is HYALINOSIS?**

*Definition:* hyaline is a structure that microscopically in HE stain is homogenous, glasslike, and intensely pink. Hyaline does not represent a certain substance, but is a descriptive term used for this particular pattern, found in many instances in different intracellular or extracellular sites.

***A. Intracellular hyaline***

1. The *Mallory corpuscles* ("alcoholic hyaline") are round, red structures found in the cytoplasm of many hepatocytes of alcoholics; these corpuscles are located around the nucleus and represent condensations of the cytokeratines.

2. The *Councilman corpuscles* appear during a viral hepatitis as a result of hepatocytic apoptosis.

3. In $\alpha$ *1- antitrypsin deficiency,* in the cytoplasm of the periportal hepatocytes appear red droplets represented by the accumulated $\alpha$ 1 -antitrypsin

4. The *Russell corpuscles* are eosynophilic inclusions in the cytoplasm of the plasmocytes in chronic inflammations (rhinoscleroma). Their substratum is the excessively synthesized immunoglobulines.

5. The *Dutcher corpuscles* appear in plasmocytes in lymphomas.

6. The *Lewy corpuscles* occur in the cytoplasm of the neurons in the Parkinson disease.

7. Hyaline globules occur in the K cells in the Kaposi sarcoma 8. In the cytoplasm of the proximal tubular epithelial cells, in cases of proteinuria

***B. Extracellular hyaline***

*1. Connective hyaline*

— Thickening of the different organs capsules (the spleen capsule, the hepatic Glisson capsule).

— Hyperplastic scars (keloids).

— Old lesions in tuberculous infection.

— Nodules of silicosis.

*2. Vascular hyaline:*

— In arterial hypertension, at the level of the coronary arteries, retinal arteries (the Sallus sign, in which the retinal arterioles appears similar to the copper wires), renal arteries (arterial hyalinosis).

— In diabetes, especially in the kidneys.

3. Haematogenous hyaline: in DIC.

4. The hyaline membranes disease:

— It appears in premature newborn infants, in children of diabetic mothers or in children born by caesarean section.

— It manifests through increasingly severe dyspnoeic crises and finally, death with respiratory insufficiency. Survivors may develop pulmonary bronchodysplasia (the "honey-hive shaped" lung).

The cause of the disease is the insufficiency of the surfactant, which leads to the collapse of the alveolar walls. The surfactant and other proteins coagulate and coat totally or partially the alveoli as hyaline membranes.

**What is THE DISORDER OF THE CARBOHYDRATE POLYMERS METABOLISM?**

1. Glycogenic dystrophy means the increasing quantity of normal or abnormal glycogen in the cells.

2. Glycogenoses are hereditary diseases, with glycogen storage following various enzymatic disorders.

3. Mucopolysaccharidoses are autosomal recessive (AR) diseases. Mucopolysaccharides are deposited in different organs.

**I. Glycogenic dystrophy**

Macroscopic features:

— Swollen, hardened, pale organs.

Microscopic features:

— Clear vacuoles appear in the haematoxylin-eosin stain (similar pattern as in hydropic or fatty dystrophy).

— It is coloured in red in PAS stain.

— It turns red in Carmin-Best stain (specific stain).

Glycogen deposits may be:

a) Localized: in tumors (the renal cancer named clear cell carcinoma, lung cancer, seminoma).

b) Generalized (pluri-organic) in:

— Prolonged hyperglycaemia (diabetes mellitus), when glycogen is stored in the hepatocytes, in the cells of the proximal convoluted tubes, in the myocardium, in the в cells of the Langerhans islets.

— In prolonged corticoid therapy, glycogen is deposited in hepatocytes and in the striated muscles (increased glycogenesis induced by the cortisone).

**II. Glycogenoses** are genetically transmitted diseases (AR), characterised by disorders in the synthesis or in the catabolism of the glycogen.

*1. Von Gierke disease* (glycogenoses Type I):

— Pathogenesis: Glucose-6-phosphatase deficiency.

— Clinical features: cutaneous xanthomas (hyperlipidemia), gout (hyperuricemia), convulsions (hyperglycaemia), hepatomegaly (hepatic adenoma and hepatocarcinoma may also appear).

— Macroscopic features: enlarged, hardened, pale organs.

— Microscopic pattern: glycogen deposits in cells.

*2. Pompe disease* (glycogenoses Type II):

— Pathogenesis: deficit of alpha-glycosidase, with subsequent lysosomal depositing of the non-degraded glycogen.

— Clinically: it affects the myocardium, the striated muscles, the liver; patients usually die with cardiac failure.

— Macroscopic features: cardiomegaly.

— Microscopic features: glycogen vacuoles accumulation predominantly in the muscular fibres (cardiac and skeletal).

**III. Mucopolysaccharidoses**

— These are syndromes characterized by a genetic deficit of the lysosomal enzymes involved in the degradation of the mucopolysaccharides.

— Result in lysosomal deposits of: keratane-sulphate (normally in bone matrices), dermatane-sulphate (bones and viscera), heparane-sulphate (the central nervous system).

*1. The Hurler syndrome:*

— Skeletal malformations, dwarfism.

— Gargoylism (gross facial deformities).

— Mental retardation.

— Hepatosplenomegaly.

— Mucopolysaccharides accumulate in the liver, myocardium, fibrocytes, condrocytes, osteocytes as well as in lymphocytes and PMN neutrophils (Adler anomaly).

— Microscopically, balloon-like cells, with clear cytoplasm or small vacuoles, PAS+.

**What are DISORDERS OF THE LIPID METHABOLISM?**

*Definition:* The disorders of lipid metabolism are characterised by accumulation of various lipid substances. These may be grouped as:

I. Accumulation of triglycerides.

II. Accumulation of lipoids.

III. Lipoidoses.

**What is TRIGLYCERIDE ACCUMULATION?**

*Definition:* triglycerides accumulations can occur inside a parenchymal cell (intracellular steatosis — as it was already discussed) or in the interstitium as adipose tissue. The second form may be:

1. Local.

2. Regional.

3. General.

1. Localized interstitial accumulations (lipomatosis):

— Subcutaneous.

— Epicardial.

— Peripancreatic.

— Perirenal.

2. Regional interstitial accumulations:

— In Cushing disease, fat deposits on the face and trunk.

— Male hypogonadism: lipid deposits on the hips and the upper part of the body.

— Hyperfolliculinemia: on thighs ("riding breeches").

— Medelung disease: occurs in alcoholic men, symmetric deposits on the nape, the neck, axilla/arm pit.

— Dercum disease: occurs in postmenopausal women as painful swellings, that is poorly delimited fat deposits.

3. Generalized accumulation (obesity):

*Definition:* generalized accumulation of triglycerides (subcutaneous, perivisceral, mediastinal, in the omentum).

*Pathogenesis:*

— Genetic factors: genetic obesity.

— Environmental factors: sedentary life, inactivity, eating disorders, irregular meals.

— Neurological and psychiatric factors: stress, emotional disorders.

— Factors disturbing the energetic balance: neurologic disorders (nuclei in the hypothalamus), endocrine disorders (insulin, glucocorticoids, colecystokinines), enzymatic disorders.

*Potential association with other diseases (co-morbidities):*

— Atherosclerosis.

— Diabetes mellitus.

— Arterial hypertension.

— Polyglobulinaemia.

— Cholesterol calculi.

Obesity can also be associated with the development of tumoral processes (endometrial, mammary and colon carcinomas), osteoarthritis, and hypercholesterolemia.

**What is LIPOID ACCUMULATION?**

*Definition:* lipoids are complex lipids (of which the most important is the cholesterol) that may accumulate in intracellular or extracellular position.

*a. Intracellular deposits:* in macrophages, that gradually increase in size and display clear vacuoles (dissolved cholesterol), giving the cytoplasm a pale foamy pattern; these "foamy cells" may be of two types:

— Xanthomatous cells, with a small and central nucleus.

— Touton cells, a multinucleate macrophage.

*b. Extracellular deposits* (cholesterol deposits) in interstitium as acicular crystals, which rest as clear spaces (dissolved cholesterol) in HE stain that may trigger a foreign-body type inflammatory reaction.

According to the fashion and the tissue where the cholesterol accumulates, one can distinguish:

*1. Localized deposits:*

a. In non inflamed but "dystrophic" tissues:

— Haematoma.

— Cerebral infarction.

— Cholesterolosis (in the gallbladder).

— Xanthelasma (yellow deposits at the internal angle of the eye).

— Tumours: renal cells carcinomas, benign fibrous histiocytoma.

b. in inflamed tissues:

— Xanthomatous cholecystitis.

— Xanthomatous pyelonefritis.

— Xanthomatous salpingitis.

*2. Generalized:*

a) Atherosclerosis: cholesterol deposits in the subendothelial intima of the arteries.

b) Xanthomas: occur in hyperlipidemia as nodular, pseudotumoral, yellow nodules; the light microscopy reveals xanthomatous cells; xanthomas may be classified as:

— Eruptive xanthomas: small nodules on the posterior wall of the trunk, on the back side of the hips, elbows or knees.

— Tuberous xanthomas: periarticular, tendinous.

— Flat xanthomas: in the palm or on the sole of the foot.

**Atheromatosis**

*Definition:* Atheromatosis is the formation of atheromas (atheromatous plaques) on the internal walls of the arteries, by cholesterol deposition. Atherosclerosis is the fibrosis of the atheromatous plaques.

*Pathogenesis* (favouring factors):

— Hyperlipidemia.

— HTA.

— Diabetes.

— Smoking habits.

— Obesity.

— Stress.

*Macroscopic features:*

— Simple lesions: spots, striations, patches, plaques (with a cholesterolic core).

— Complex lesions: plaques ulcerations, suprathrombosis, intra atheromatous haematomas, connective tissue organisation, calcification and ossification of the plaques, atrophy of the media.

*Microscopic features:*

— Subintimal accumulation of cholesterol crystals, xanthomatous cells, cellular debris.

— Inflammatory cells in the intima surrounding the cholesterol, connective tissue reorganisation at the periphery of the plaques.

***The effects of atherosclerosis:***

*a) Localized:*

— Towards the lumen: stenosis, fissures followed by haemorrhage in the plaques with narrowing of the lumen, thrombosis.

— Towards the wall: rupture (haemorrhage), aneurysms.

*b) Regional:*

— Embolism (cholesterol or plaques fragments released from the lesion or from the associated thrombi).

— Partial ischemia (scleroatrophy) or total ischemia (infarction).

***Co-morbidities:***

— Atherosclerosis.

— Arterial hypertension.

— Obesity.

— Diabetes mellitus.

— Polyglobulinaemia.

— Cholesterol calculi.

— Xanthelasma.

**What is LIPOIDOSIS?**

*Definition:* Lipoidoses are congenital diseases, with lack of specific enzymes and subsequent deposition of their excessive substrates, which rest not metabolised in the monocytic-macrophagic system and in the central nervous system Lipoids are complex lipids, some of them found cellular membrane component and in the myelin.

Lipoidoses can be associated with mucopolysaccharidoses and rarely with glycogenoses.

*Macroscopically,* the affected organs appear enlarged (spleen, liver, lymph nodes).

*Microscopically:* liposomal deposits may be observed.

*Examples of lipoidoses:*

**1. Gaucher disease,** AR

— Congenital deficiency of glucocerebrosidase, with consequent accumulation of its substrate, the glucocerebroside.

*Macroscopic feature:*

— Liver and spleen enlargement.

*Microscopic feature:*

— The "Gaucher cell" which is a large, characteristic macrophage, with pale cytoplasm and fine striations: the Gaucher cells block the hepatic sinusoids, causing portal hypertension; it also compress the hepatocytes, leading to their atrophy and finally to hepatic fibrosis.

*Clinical features:*

— Hepatic fibrosis.

— Anemia, thrombocytopenia and neutropenia by hypersplenism with increased destruction of the blood cells.

— Bone pain and spontaneous fractures (Gaucher cells accumulate in the bone marrows).

— Neuropathies (Gaucher cells accumulate in the brain, in the Virchow-Robin space and in the nervous parenchyma).

**2. The Nieman-Pick disease,** AR

— It affects the sphingomyelin which may be absent (type A) or significantly reduced (type B).

— The characteristic cells are large macrophages with fine cytoplasmic vacuoles (with sphingomyelin and cholesterol).

*Clinically:*

— Splenomegaly.

— Hepatomegaly (Kuppfer cell deposits or in hepatocytes).

— Lymph nodes enlargement.

— Expansion of the bone marrow.

— Severe brain atrophy, oedema and destructions of the neurons and demyelinisation of the nervous system.

*Types of diseases:*

— Type A: in children, with progressive hepatosplenomegaly and death in the first 3 years of life.

— Type B: hepatosplenomegaly, neuronal lesions; patients survive to adulthood.

**3. Gangliosidoses**

— Two types: GM1 and GM2.

— GM2 is more frequent than Tay-Sachs disease (GM1), AR.

— Due to the lack of hexaminidase A; gangliosides accumulate intracellulary, particularly in the brain and in the retina where large, rounded cells appear.

*Clinical features:*

— Psychomotor retardation, megaloencephaly (abnormal enlargement of the brain), spasticity, convulsions, visual impairment.

*Evolution:*

— Death within 4 years after birth.

**What are DISORDERS OF THE PIGMENTARY SUBSTANCES?**

*Definition:* pigments are naturally occurring, coloured substances whose excess or lack may cause pathological processes.

The pigments whose disorders may generate disease are:

I. Haemosiderin.

II. Bilirubine.

III. Melanin.

**What is HEMOSIDERIN PATHOLOGY?**

*Definition:* haemosiderin is a degradation product originating from haemoglobin; the compound is rich in iron, a fact that can be identified macroscopically and microscopically.

Iron is absorbed mostly in the duodenum, then bound and transported in the plasma by transferrine, an enzyme that ultimately delivers the iron to the cells.

*Macroscopic feature:*

— Macroscopically, the haemosiderin deposits appear brown.

*Microscopic aspect:*

— Haemosiderin appears as brown granules in HE stain.

— In the Perls stain (Prussian blue or Berlin blue) haemosiderin appears coloured in blue-green; this special histochemical stain for haemosiderin is obtained following the reaction of nitroprussiate with the iron in its composition.

The haemosiderin accumulations may be local or regional.

**I. Local deposits appear in:**

— The chronic pulmonary stasis ("the cardiac cells").

— In haematomas (macrophages loaded with haemosiderin, called siderophages).

— In red infarctions.

***— Pulmonary essential haemosiderosis:***

a) A disease which appears in children and young people.

b) Clinically manifests with cough, haemoptysis, anemia.

c) Unknown pathogenesis.

*d) Macroscopically:* red-brown areas of hardened pulmonary tissue.

*e) Microscopically:* congestion of the septal capillaries, alveolar haemorrhages.

*f) Evolution:* pulmonary fibrosis, pulmonary hypertension, pulmonary heart insufficiency or cardio-respiratory failure, death.

**II. Generalized deposits**

***Generalised haemosiderosis or secondary haemochromatosis***

*Etiology:*

— Repeated transfusions (intravenous iron overloading).

— Increased absorption of iron during chronic hepatopathies (alcoholic hepatitis, cirrhosis).

— Increased nutritional supplement (the Bantu tribe siderosis).

— Haemolytic anemia.

*Pathology:* Iron depositions in the mononuclear phagocytes, then in the parenchymatous cells; the iron accumulates affecting the function of the organs in various ways.

***Primary haemochromatosis:***

— Hereditary disease, AR, clinically more frequent in men (women lose iron in their menstruation period).

— Primary defects in the absorption of the dietary iron (the iron is absorbed completely).

*Clinically:*

— Cirrhosis, diabetes mellitus, cutaneous hyperpigmentation ("suntanned diabetics").

*Liver:*

— Enlarged organ, rust-brown, micronodular hepatic cirrhosis.

— Iron depositions in the hepatocytes and in the Kupffer cells.

— It can progress towards hepatocarcinoma.

*Pancreas:*

— Swollen, firm, rust brown, shrunken due to fibrosis.

— Both the endocrine and exocrine pancreas will be affected with the destruction of the Langerhans islets and of the glands, diabetes mellitus and enzymatic insufficiency.

*Endocrine glands:*

— It affects the pituitary gland, the thyroid, parathyroid and the adrenal glands.

— ACTH and MSH increase, melanic hyperpigmentation of the teguments.

*Heart:*

— Swollen, brown, fibrosis.

— The iron is deposited in the myocytes.

*Clinically:* arrhythmias, restrictive cardiomiopathy, and cardiac insufficiency, death.

**What is the BILIRUBINE PATHOLOGY?**

*Definition:* The alterations of the normal bilirubine metabolism due to various causes, which initiate a series of pathologic processes, specific for this pigment; the non-conjugated bilirubine, produced by haemolysis (indirect bilirubine) is conjugated in the hepatocytes resulting the direct, conjugated bilirubine; it is then excreted in the gallbladder, forming the bile, and next in the duodenum, where is partly reabsorbed, returning into the liver (the hepato-entero-hepatic circuit). Bilirubine metabolism in the liver comprises a series of steps:

— Delivery and incorporation into the hepatocytes.

— Transportation through the cytosol with the help of.

— Conjugation with the glucuronic acid under the action of glucuronil-transferases.

— The excretion from hepatocytes into the billiary tract.

According to the bilirubine concentration in the blood and its clinical manifestations, the main entities of bilirubine pathology are:

1. Hyperbilirubinemia: over 1mg/dl of bilirubine in the blood.

2. Icterus (jaundice): yellow teguments, mucosa and tissues because of the increase over 2–2,5 mg/dl of the circulating bilirubine.

3. Cholestasis: billiary pigment deposits in the hepatocytes, associated with bile "clots" in the billiary canaliculi.

**Icterus (jaundice)** classification:

I. Pre-hepatic (haemolytic).

II. Hepatocellular (hepatic).

III. Post-hepatic (obstructive).

***I. Pre-hepatic icterus (haemolytic)***

*Definition:* increased production of the bilirubine due to an excessive destruction of the erythrocytes (haemolysis).

*Causes:*

a) Intravascular haemolysis:

— Hereditary erythrocyte defects (thalasemia, spherocytosis).

— Immune haemolysis (blood type incompatibility).

b) Extravascular haemolysis:

— Significant haemorrhages.

— Large haematomas.

— Hemorrhagic infarctions.

*Clinically:*

— The increase of indirect bilirubine (the non-conjugated form).

— In newborns with "Rhesus" or Rh incompatibility between the newborn and the mother (between Rh+ child and Rh- mother), the plasmatic bilirubine significantly increases (over 15 mg/dl) especially around the 5 to the 9$^{th}$ postnatal days, when the bilirubine is so high that may accumulate in the basal nuclei of the brain (nuclear icterus); result neuromotory disorders with a possible lethal outcome.

***II. Hepatocellular icterus (hepatic).***

*Causes:*

1. Where cellular incorporation of the haemoglobin is impaired:

— Hepatocellular lesions (inflammations).

— Various toxicities.

2. Cases where the hepatic bilirubine conjugation is impaired:

— Syndromes with non-conjugated hyperbilirubinemia.

a) The Criegler-Najjar syndrome:

— Type AR: the glucuronil-transferase is missing; resulting in canalicular cholestasis, nuclear icterus, death.

— AD Type: partial lack of glucuronil-transferase with hepatomegaly, cerebral lesions, but the patient survives.

b) The Gilbert syndrome (AR):

— Low glucuronil-transferase activity.

— Indirect bilirubine is not well conjugated.

— Laboratory: moderate non-conjugated hyperbilirubinemia.

— The patients survive.

3. Cases where the intra-hepatocytic transportation of BR is affected:

— Hepatocellular lesions (infections, toxic substances).

— Genetic disorders: Dubin-Johnson and Rotor syndromes; the patients have problems with the hepatic transportation of the conjugated bilirubine onto the billiary canaliculi. In the Dubin-Johnson syndrome, the liver appears macroscopically as dark grey. Microscopically it is brown at the billiary pole of the hepatocytes; in the Rotor syndrome, the liver looks morphologically normal.

***III. Post-hepatic icterus (obstructive):***

— The specific modifications is the cholestasis *Cholestasis:* the stasis of the bile in the billiary tract.

1. Extra-hepatic cholestasis: obstructions of the common billiary duct by:

— Calculi.

— Post inflammatory strictures.

— Tumors: tumors of the main bile duct, tumors in the pancreatic head.

— External compressions on the duct: tumors, lymph nodes.

2. Intra-hepatic cholestasis: bile stasis at the level of the billiary canaliculi, billiary ducts in the portal space, interlobular billiary ducts:

— Hepatocytic diseases.

— Extrahepatic billiary obstructions.

— Intrahepatic billiary atresia.

— Inflammations of the billiary tracts (cholangitis).

— Primary billiary cirrhosis.

— Cholangiocarcinoma.

Morphologic features in cholestasis:

a) Bile depositions in the dilated billiary canaliculi (between the hepatocytes) initially near the central lobular vein (lobular area 3), next in the middle lobular area (area 2) and then near the portal space (area 1), and in time, in the portal space billiary ducts associated with periportal fibrosis and ductal proliferation.

b) In hepatocytes appear:

— Deposits of billiary pigment.

— Hepatocyte degeneration, as the cells swell by intracellular water accumulation (vacuolar dystrophy).

— Isolated necrosis of the hepatocytes.

— Focal necrosis of some hepatocytes ("billiary infarcts").

— Bile deposits in the spaces released by the necrosed hepatocytes ("billiary lakes").

— Unless the cause is removed, cholestasis progresses towards billiary cirrhosis.

**What is the MELANIN PATHOLOGY?**

*Definition:* melanin pathology is the quantitative and site modification of the melanic pigment.

*General notions:*

— Melanocytes originate from the neural ridge; they contain melanosomes in which the tyrosinase transforms the tyrosine into dopamine (DOPA); following oxidation, the dopamine is transformed into melanin, and transferred into the keratinocytes or endocytosed by macrophages (melanophages).

The pathology of melanin may be classified into:

I. Lesions with melanin excess (hypermelanosis).

II. Lesions with melanin deficit (hypomelanosis).

**I. Hypermelanosis**

***1. Generalised***

*1. Addison disease:*

— In chronic adrenal failure, due to tuberculosis, autoimmune adrenal inflammation, etc.

— It causes a hyper production of ACTH and MSH (the two hormones have the same precursor, the pro-opio-melanocortine) with generalized hyperpigmentation of the skin.

2. Arsenic, silver poisonings (argyria).

3. Haemochromatosis.

4. Cutaneous porphyria tarda.

***2. Localized:***

*1. Cloasma* or the pregnancy mask that appears physiologically in the pregnant women or *melasma* that is the same mask due to the contraceptive drugs. It consists

in the hyperpigmentation of the forehead and cheeks, the hyperpigmentation of the breast areoles, the abdominal wall midline and the external genitalia.

*2. Ephelides or freckles:* brown, small spots, which occur or intensify after sun exposure.

*3. Solar lentigines* (actinic lentigo): various brown spots on the sun exposed skin; they usually occur at elderly people, and are called senile lentigo.

*4. Post-inflammatory hyper pigmentations:* systemic lupus erythematosus, flat lichen, etc.

*5. Nevi:* the benign tumors of melanocytes.

*6. Malignant melanomas:* the malignant tumors of the melanocytes.

**II. Hypomelanosis**

***1. General:***

*1) Albinism* (AR):

— Tyrosinase deficits.

— Clinically: white skin, white hair, red pupils (the retinal melanin is missing and the choroidal blood vessels become visible).

— In the evolution of the disease actinic keratosis may appear on the skin, then basal cell or squamous cell carcinomas may arise due to the absence of the protective melanin (against UV radiation).

***2. Localized:***

*1) Vitiligo:*

— It has autoimmune causes, because of anti-melanocytic antibodies that destroy the melanocytes.

— Frequently associated with other autoimmune diseases: Hashimoto thyroiditis, Addison disease, etc.

— Clinical features: well delimited, white areas, irregular in shape and with a hyperaemic or hyperpigmented rim; usually are localized around the mouth or the eyes, on the chest, dorsal side of the hand, on the genitalia.

2) On the site of old inflammations, traumas, burns (the Koebner phenomena).

*3) Piebaldism* (AD):

— Absence of melanocytes or impairment of melanocytic migration.

— Lesions are present at birth and do not further progress during the life.

— Lesions: small, white spots on the forehead, neck, chest, abdomen.

— Associated with some white hair on the scalp.

— Other manifestations: dwarfism, mental retardation.

*4) Hypomelanosis during cutaneous inflammations:*

— Leprosy.

— Sarcoidosis.

*5) Hypomelanosis of dermatological diseases:*

— White pithyriasis.

— Psoriasis.

*6) Chemical (or toxic) hypomelanosis:*

— Following excessive exposure to retinoic acid, bensoyl peroxid.

**What are THE DISORDERS OF THE MINERAL METABOLISM?**

*Definition:* mineral ions (sodium, potassium, calcium, etc) have essential roles in the normal physiology of the body and their alteration may cause significant metabolic impairments. The most frequent disorders of the mineral metabolism are:

I. Calcium dystrophies.

II. Lithyasis.

**What are the CALCIUM DYSTROPHIES?**

*Definition:* the calcium dystrophies may be classified according to his excess or lack in the organisms, which may lead to certain clinical manifestations.

Calcinosis is the calcium excess that favours calcium depositions mainly in the soft tissues.

*Macroscopic feature:* The calcium is white, hard, and his deposition may be found in several locations:

— Nodular (as stones): in the nodular goitre.

— Small granules (sand): psamomatous corpuscle from the meningioma, or the simpexions in the prostate.

— Large calcified lesions (as plaques): pachypleuritis, constrictive pericarditis.

*Microscopic feature:*

— Calcium appears blue (basophilic) in the Haematoxylin-Eosin stain.

— Calcium appears black in the von Kossa stain.

**I. Dystrophies due to Calcium excess (calcinosis).**

**II. Dystrophies due to Calcium deficiency.**

**III. Dystrophies due to Calcium excess (calcinoses).**

a) Dystrophic calcinosis.

b) Metastatic calcinosis.

***a) Dystrophic calcinosis:*** the calcium salts depositions in necrotic or degenerated tissues, occurring in normal calcemic state (dead tissues uptake the calcium from blood transforming him into salts).

1. In necrotic tissues:

— Fatty necrosis (cyto-steatonecrosis).

— Caseous necrosis (from tuberculosis).

— Large haematomas (Ferro calcite nodules).

— Intrauterine retention of a dead foetus (lithopedion).

2. Scar connective tissue:

— Venous thrombi (phlebolites).

— Atherosclerosis.

— Injured cardiac valves.

3. Tumors:

— Thyroid carcinoma.

— Mammary carcinoma.
— Ovarian carcinoma.
— Uterine leiomyoma.
— Meningioma.
— Oligodendroglioma.

***b) Metastatic calcinosis:*** the calcium deposits in normal tissues in hypercalcaemic states (when calcium is mobilized from bones in different pathological conditions resulting in increased calcium levels in the blood).

*Causes of hypercalcaemia:*

— Primary hyperparathyroidism.
— Increased calcium absorption in the intestine.
— Hyperthyroidism.
— Addison disease.
— Destructive bone lesions (tumoral metastases in the bone).

*Calcium accumulates predominantly in:*

— Kidneys (nephrocalcinosis): calcium is deposited in the interstitium, tubular basal membrane and the lumen of the urinary tubes.
— Lung: calcium deposits in the alveolar septae.
— Blood vessels (coronary).
— Myocardium.
— Gastric mucosa.

**II. Dystrophies caused by calcium deficiency**

1. Rachitism (rickets): in children, due to the lack of the provitamin D.
2. Osteomalacia: in adults with lack of provitamin D.
3. Osteoporosis: in elderly, who present hypocalcaemia.

*Rickets:*

— Lack of provitamin D that may occur in children from regions with less sun exposure (ultraviolet light is needed for the conversion of the provitamin D into its active form, which occurs in the skin).

Macroscopic:

1. Skull: narrow and moist parietal and occipital bones (craniotabes of the occipital area), the fontanels close later, square-shaped mandible, the teeth occur later with enamel and dentine problems.
2. Spine: abnormal rearward curvature (kyphosis), abnormal forward curvature (lordosis), or abnormal double lateral curvature (scoliosis).
3. Sternum: Pectus Carinatum (pigeon chest, carina = keel shaped), increased ribs articulations (rib beads).
4. Narrow, deformed pelvis.
5. Distorted, malformed long bones: inner or outer curvature of the legs, arms with thickened articulations (rachitic arms) and long and thick fingers (arachnodactily).

Microscopic:

— The blood circulation is inadequate and the cartilages are partly resorbed; as the bone mass is deficient in the resorbtion areas, normal, ossified zones alternate with un-ossified areas (mosaic aspect).

**What is LITHYASIS?**

*Definition:* lithyasis is the pathological occurrence of stones or calculi (solid, proteico-mineral bodies) in various excretory ducts of the body.

*Pathogenesis:*

— Increased mineral content in various fluids (e. g. increased salts content in the urine, bilirubine in the bile).

— The presence of a precipitation nucleus (i. e.: desquamated cells, microbes, foreign bodies or organisms).

— The flow stagnates, favouring the concentration and precipitation of the salts and the super-infection.

*Localization:*

— Gallbladder and the billiary ducts.

— Kidneys, ureters, urinary bladder.

— Pancreatic excretory ducts.

— Salivary glands.

*Lung Size:*

— Large, medium, small (gravel).

— Very small, mixed with the normal secretion (billiary mud)/

*Shape:*

— Round, faceted, coralliform, branched.

*Number:*

— Unique or multiple Colour and consistency:

— Carbonates: white, friable.

— Oxalates: grey, hard.

— Cholesterol: yellow, friable.

— Billiary salts: green, friable.

Complications:

— Obstructions.

— Colicative pain: excruciating, severe pain.

— Ulcerous epithelium with haemorrhages.

— Malignant transformation of the surrounding epithelia, due to the prolonged, sustained inflammation.

**I. Billiary lithyasis**

1. Cholesterol calculi are:

— The most frequent (over 75 %).

— Radio-transparent.

— Yellowish, round or oval, and up to several centimetres.

— Granular, hard.

2. Pigment calculi are:

a) Black (in chronic haemolysis):

— Multiple, shinny black stones, irregular form (in the gallbladder), small (0,2–0,5 cm).

b) Brown (in bacterial cholangitis):
— Especially in the ducts.
— High content of calcium and bilirubine.
Consequences of the billiary calculi:
c) Infections:
— Cholangitis, cholecystitis.
— Pancreatitis.
— Hepatic abscess.
d) Obstructions:
— Hydrops, vesicular mucocele.
— Vesicular empyema (gallbladder with puss).
— Billiary colic, icterus.
e) The perforation of the gallbladder:
— Billiary peritonitis.
— Cholecysto-duodenal fistula and billiary ileus.
f) Possible gradual development of a malignant process in the gallbladder wall (carcinoma of the gallbladder).

**II. Urinary lithyasis**

1. Localization: urinary bladder, ureteral tracts, renal pelvis.
2. Composition:
a) Uric acid calculi.
b) Phosphate calculi.
c) Ca oxalates calculi.
3. Lithogenic (pro-lithyasis) effects:
— Hydronephrosis.
— Pyelonephritis.
— Hematuria.
— Colicas.

**III. Pancreatic lithyasis** in alcoholics, associated with chronic pancreatitis.

**IV. Salivary lithyasis** (sialo-lithyasis):
— Phosphate and calcium carbonate sialolithes.

**V. Pulmonary lithyasis** (broncho-lithyasis):
— Broncholithes.

**What is REGENERATION AND REPARATION?**

***Definitions:***

*Regeneration:* the replacement of injured, altered cells and tissues with others of the same type; it may appear in tissues with both type of cells, labile or stabile cells.

*Repair:* the replacement of the injured tissue with a scarr fibrosis; it appears in tissues with permanent cells.

*Healing:* the rebuilding through regeneration or reparation of the tissues destroyed after an aggression.

Agents that may influence the healing process:

1. The destryed cell type (labile, stabile, permanent):

a) Labile cells can be divided during entire life, replacing the destroyed cells continuously: surface epithelia, haematopoetic cells, lymphoid cells.

b) Stabile cells can replicate under the influence of certain stimuli, reconstructing the original structure if the stromal support is maintained: epithelial cells (from the kidneys, the liver, the pancreas) and mesenchymal cells (fibroblasts, smooth muscle cells, osteoblasts, chondroblasts, endothelial cells).

c) Permanent cells which exceptionally multiply after birth: striate muscular fibres, myocardial fibres.

2. Systemic factors:

a) Proteic deficit.

b) Vitamin A and C deficit.

c) Deficit in trace elements: Zn.

d) Systemic diseases: diabetes.

e) Drugs: steroids, cytostatic drugs.

2. Local factors:

a) Local infections in the wound.

b) Foreign bodies and necroses at the level of the wound.

c) Ionizing radiations.

**How does the REGENERATION OCCUR?**

**I. The regeneration of the epithelia**

1. Cylindrical single-layer epithelium:

— When the basal membrane of the epithelium is not affected, the epithelium is regenerated through the replication of the cells from the normal epithelium bordering the lesion.

2. Stratified epithelium (squamous):

— When the spinous cells are affected, the epithelium is rebuilt from the level of the basal cells, which multiply and differentiate replacing the superficial affected cells.

— When the basal cells are also affected, the basal layer is first reconstructed and then proliferate rebuilding the differentiated layers upwards (the stratum spinosum) onto the surface of the epithelium.

3. The epithelium of various viscera.

a) The liver:

— When the hepatocytes are affected and their basal membrane stay intact, the hepatocytes divide on the basal membrane, rebuilding the liver, structurally and functionally normal.

— When the basal membrane is also affected, the hepatocytes regenerate in a disorderly pattern, resulting an abnormal nodular architecture, functionally impaired (ex. cirrhotic nodules).

a) The kidney :

— When the cells of the urinary tubules are affected but without the involvement of the basal membrane, the epithelial cells recover migrating along the basal membranes, restoring the kidney completely.

— When the tubular basal membrane is affected, the epithelial cells multiply erratically without restoring the original renal structure and function.

b) The lung:

— The pneumocytes may regenerate functionally when the alveolar BM is intact.

— If the alveolar BM is affected, pulmonary fibrosis appears.

**II. The regeneration of peripheral nerves**

— If the nerve is cutted, but the two ends and the Schwann sheath are still in close proximity (few millimeters) the neural cytoplasm (neuroplasm) of the proximal segment proliferates, penetrates into the old sheath and regenerates the nerve morphologically and functionally.

— When the ends of the nerve are too distant (over several millimeters), the neuroplasm proliferates but does not reach the distal segment; instead, a nodule might be formed, called amputation neuroma, which is often very painful.

**How does the REPARATION PROCESS OCCUR?**

The lesions of tissues that cannot usually multiply are repaired by the formation of a scar fibrous connective tissue (fibrosis).

The affected area: granulation tissue: scar connective fibrous tissue.

Granulation tissue:

1. Vascular proliferation (neo-angiogenesis) with the formation of new capillaries from the preexisting blood vessels:

— The basal membrane of the blood vessel near the affected area suffers a process of proteolysis allowing the migration of the endothelial cells towards the lesion.

2. The migration and the proliferation of the fibroblasts, which become active secretory fibroblasts (secrete mostly collagen).

3. The maturation and the organization of the scar fibrous tissue.

4. The CNS reparation:

— In neuronal destructions, the neurons do not regenerate.

— The glial cells phagocytize the neurons the myelin remaining.

— The astrocytes suffer hypertrophy and hyperplasia (reactive gliosis).

5. The reparation of the myocardium:

— The necrosed myocardial fibres are replaced by scarred connective tissue (cardiosclerosis).

— Extensive necrosed areas (the myocardial infarction) become scarred connective fibrous areas.

**How does the HEALING PROCESS OCCUR?**

**I. The healing of the wounds**

1. The healing of *"per primam intentionem":*

— In small, aseptic surgical wounds with regular and close margins.

— The lesion affects the epidermis and the dermis.

*The healing stages:*

— Hemorrhage with the formation of a clot that fills the defect, with a crust formed on the surface (by dehydration).

— The basal cells of the squamous epithelium proliferate from the margin of the wound, beneath the crust, rebuilding the basal stratum from which in time the spinous layers and keratinocytes will be differentiated.

— PMN and Mf invade the clot, changing it in a granulation tissue.

— Collagen is produced from the periphery of the wound in high quantity in order to tie the margins of the wound.

— The lesion is transformed into a scar (fibrous connective tissue).

2. The healing by "per secundam intentionem":

— Between the borders of the wound there may be infectious agents, foreign bodies, cellular debris.

— In the first stage the surgical cleaning of the wound is necessary and clean and straight margins are needed to stick together.

— In the second stage the actual healing begins as in the previous case.

**II. The healing of fractures**

1. The fibrinous callus:

— Between the fractured bones there is a hematoma (it contains fibrin).

2. The fibrous callus:

— A granulation tissue forms in the hematoma, which is organized in fibrous tissue.

3. The bony callus:

— Is a tough area with reparatory tissue that contains connective tissue, cartilage, bone.

— The temporary callus (incipient) will be remodeled; the osteoclasts reabsorb the excessive bone, and the osteoblasts form soft trabecular bone interiorly and cortical bone exteriorly, so the bone receiving a normal shape; it will have a medullary space and a firm cortical bone.

Defective healing: pseudarthrosis when the bone is mobile at the place of the fracture, it does not ossify resting as fibrous callus with hyper-mobility.

# CHAPTER 3

## DISORDERS OF THE BLOOD AND INTERSTITIAL FLUID FLOW

**Which are THE MAIN FLUIDS OF THE BODY?**

The most important fluids of the body are the blood, the lymph and the interstitial fluid. These fluids intermediate the gas and electrolyte exchanges as well the transports of nutrients and other vital substances back and forth to different cells and tissues:

— The blood circulates in a closed cardiovascular system: from the heart, through arteries which become smaller and smaller, to capillaries, and than comes back to the heart through the veins.

— Lymph circulates in an opened system, which connects the extracellular tissue compartment to the intravascular space by absorbing the interstitial liquid remaining in excess and transferring it into the veins.

— The interstitial fluid rests in the extracellular tissue compartment of the entire body and helps the different substances changes between the blood and the extravascular compartment (at the level of capillaries) and between the extravascular space and the cells (by the cellular membrane).

**Which are THE DISORDERS OF THE BODY FLUIDS?**

1. Disorders of the blood circulation.
2. Disorders of the lymph circulation.
3. Disorders of the interstitial fluid circulation.

**Which are THE BLOOD FLOW DISORDERS?**

— The blood flow disorders are: Hyperemia Ischemia Hemorrhage Embolism Thrombosis.

— Disseminated intravascular coagulation (DIC).

— Infarct.

— Shock.

**What is HYPEREMIA?**

***Definition***

Hyperemia is the increase of the volume of the blood in a region of the body (an excessive blood filling of the vessels compared to the normal physiologic state).

***Pathogenesis***

Hyperemia occurs by two mechanisms:

a) Active, arterial mechanism, when more blood is entering in the organ — when hyperemia is called congestion.

b) Passive, venous mechanism, when the blood is hampered to leave the organ — when hyperemia is called stasis.

***Morphology***

*Macroscopically:* the organ is larger, rounded and heavier:

a) In congestion: the organ is red as the arterial blood and warmer than the peripheral blood (as the central, cardiac blood).

b) In stasis: the organ is purplish-blue (cyanotic) and colder than normal.

*Microscopically:* enlarged capillaries, filled with blood.

***Evolution:***

a) In short-standing hyperemia, the normal appearance of the organ is restored if the causative factors disappeared.

b) In long-standing hyperemia, edema and micro hemorrhages may occur.

**What is the CONGESTION?**

***Definition:***

Congestion is the hyperemia which occurs through an arterial, active mechanism.

***Pathogenesis:***

— The physiologic congestion: occurs through the dilatation of arteries in different normal circumstances (e.g. during intense physical exercises).

— The pathologic congestion: dilatation of arteries which occurs in conditions as the acute inflammation.

***Morphology***

*Macroscopically:* compared to the normal the organ is:

— Larger.

— Heavier.

— Blood-red.

— Warmer.

— Pulsatile.

— Painful.

*Microscopically:*

— Enlarged, dilated capillaries, filled with blood.

***Evolution:***

— The pattern may return to normal when the causative factors disappear.

— Complications that may occur: edema and micro hemorrhages.

**What is the STASIS?**

***Definition:***

Stasis is the hyperemia produced by a venous, passive mechanism.

***Pathogenesis:***

— The presence of an obstacle in the lumen of a vein: thrombus, embolus.

— The narrowing of the lumen secondary to a venous wall thickening: inflammation (phlebitis).

— Compression on a vein: neoplasia.

***Morphology:***

*Macroscopically:* the organ is:

— Larger.

— Heavier.

— Colder.

— Cyanotic (purplish-blue).

*Microscopically:* enlarged, dilated veins, filled with blood.

***Types of stasis:***

— Local stasis.

— Regional stasis.

— Generalized stasis.

***Local stasis:*** stasis occurring in an organ with an obstacle at the level of its main draining venous system. It may be acute described above or chronic. Organs that may present more frequently a chronic stasis are:

— The liver.

— The lung.

— The spleen.

***The chronic stasis of the liver***

*Definition:* long-standing stagnation of the venous blood in the liver.

*Pathogenesis:* accumulation of blood in the liver by an incomplete/insufficient evacuation secondary to:

— an obstacle on the suprahepatic veins;

— right heart failure.

*Macroscopically:*

— Increased volume and weight of the liver.

— The anterior edge of the liver became round.

— Spotty pattern on the sectioned surface, with purple, yellow and red-brown circle areas.

*Microscopically:*

— The central lobular veins and the sinusoid capillaries from the inner third of each hepatic lobule are extremely enlarged and filled with blood.

— In the mid-lobular areas, the hepatocytes have a vacuolated, fatty pattern, being charged with triglycerides, due to the metabolic changes caused by the hypoxic conditions generated by the stasis.

— In the external third of the lobule, the hepatocytes have a normal appearance being better supplied with arterial blood, which comes from the hepatic artery of the portal space.

*Evolution:*

— In the chronic liver stasis due to the right heart failure, fibrosis may develop in the centre of the hepatic lobules, replacing the dead hepatocytes and causing the so-called "cardiac cirrhosis" (liver cirrhosis of cardiac cause).

***Chronic stasis of the lung***

*Definition:* the prolonged stasis of the blood in the lung.

*Pathogenesis:*

— An obstacle in the left heart (e. g.: mitral stenosis: blood stagnates in the left atrium:in the pulmonary veins — in the lung).

*Macroscopically:*

— The lung becomes fibrotic because of the chronic stasis and brown because of the deposition of hemosiderin (microhemorrhages), condition known as "brown induration".

*Microscopically:*

— The capillaries of the alveolar septae and pulmonary veins are heavily enlarged.

— Microhemorrhages appear in the septae and in the alveolar spaces — next the degradation of hemoglobin in bilirubin and hemosiderin formation; the latter is endocytosed into the macrophages which become siderophages — brown macroscopically but also in hematoxillin eosin stain — this gives the overall brownish color of the organ at both, the macroscopic and microscopic level.

— Meantime, the fibrosis developed in the septae gives to the lung a harder, increased consistency.

*Evolution:* The lung fibrosis leads to respiratory failure (impaired ventilation and alveolo-capillarie exchange), and also to a "chronic pulmonary heart disease" consecutively (resistance against the blood flow through the lung which result in cardiac insufficiency).

***The chronic stasis of the spleen (fibrocongestive spleen)***

*Definition:* the prolonged stasis of the blood in the spleen.

*Pathogenesis:*

— An obstacle on the splenic vein.

— Liver cirrhosis.

*Macroscopically:*

— Increased volume and weight of the spleen

— Purplish organ.

*Microscopically:*

— Enlarged sinusoids, filled with blood.

*Evolution:*

— In time, the small areas of necrosis due to hypoxia are replaced with connective tissue with secondary calcium and iron deposition on it, which forms characteristic small nodules (Gamna - Ghandi nodules).

**Regional stasis**

*Definition:* stasis caused by a large venous stem vessel which drains several organs or an entire region of the body.

*Pathogenesis:*

— An obstacle in a venous lumen: embolus, thrombus.

— The thickening of the venous wall: phlebitis.

— Compression: tumors, lymphadenopathies.

*Examples of regional stasis:*

— Stasis on the superior cava vein.

— Stasis on the portal vein.

***The stasis in the region drained by the superior cava vein (SCV)***

*Etiology:*

— Tumor emboli (particularly in cases of lung carcinoma).

— Pressure on SCV by tumor lymphadenopathies, lung or mediastinal tumors.

*Evolution:*

— Edema, micro hemorrhages and cyanosis of the head, neck, shoulders and the upper part of the thorax.

***The stasis on the portal vein (PV)***

*Etiology:*

— Pilethrombosis (PV thrombosis).

— Pilephlebitis (PV inflammation).

— Compression on the PV because of tumors or enlarged lymph nodes.

— Liver cirrhosis: during the disease, fibrosis and regeneration nodules are formed in the liver which disturb the normal blood flow in the organ (the most frequent cause of PV stasis).

— Suprahepatic obstacles.

*Evolution:* in all the mentioned situations the portal vein stasis resulted is so important that it cause secondarily a constellation of lesions which all together form the "syndrome of portal hypertension":

— Splenomegaly — leading in time to fibrocongestive spleen.

— Ascites — the deceleration of blood circulation in the portal vein and his branches lead to the accumulation of serous liquid into the abdominal cavity.

— Collateral circulation — because the blood drained usually by the portal vein, now interrupted, must return in the main circulatory system, that is in the inferior cava vein — it will use other vessels, which connect during embryogenesis the portal system and the inferior cava vein (opened during embryogenesis, closed after the birth), forcing their reopening — vessels named porto-systemic anastomoses — clinically manifested with:

— Esophageal varicosities: the dilatation of submucosal veins of the distal third of the esophagus; their rupture, that often occurs during the evolution of the disease, may result in significant bleeding and even in the patient death.

— Hemorrhoids: the dilatation of the veins of the ano-rectal junction.

— "Caput medusae": reopening of the umbilical veins and dilatation of the superficial epigastric veins which runs normally on the anterior abdominal wall — they become visible through the periombilical skin and have a pattern resembling the head of the mythological Medusa, depicted with curly serpents instead of hair.

**Generalized stasis**

*Definition:* the stasis extended or generalized to all the organs of the body.

*Pathogenesis:*

— Failure of the right heart (RHF) secondary to a lung fibrosis or to a chronic lung stasis or a primary decrease in the contractile activity of the right ventricle, which result in an inadequate drainage of the peripheral venous blood and blood stagnation in the entire body.

— Failure of the left heart (LHF), due to a gradual decrease in the contractile force of the left ventricle, or an obstacle in the blood flow (as mitral

stenosis) — in which not all the blood from the left heart (which came from the lung) is evacuated (pumped) into the body; consequently, the pressure of the stagnating blood in the left ventricle or atrium gradually increase, leading to a retrograde chronic lung stasis; the lung stasis generates right heart failure or global heart failure (chronic pulmonary heart disease) manifested with generalized stasis.

*Evolution:*

— Increased pressure in the superior and inferior cava veins, with venous stasis in all the internal organs drained into them.

— Increased pressure in the capillaries of the skin leading to cutaneous edema.

— Increased pressure in the capillaries of the internal organs covered by a serous membrane will lead also to liquids accumulation in the body cavities (hydrothorax, hydropericardium and hydroperitoneum — ascites).

*Evolution:*

— The organs with chronic stasis become harder (due to fibrosis) and brownish (because of the microhemorrhages which result in hemosiderin deposition), as well the skin, particularly on the lower legs, which present trophic changes (due to chronic hypoxia).

**Hypostasis**

*Definition:* blood stagnation in the lower parts of the body because of the gravitational forces during certain pathological conditions.

*Occurs in:*

— The lower and posterior segments of the lung at persons with heart failure (frequently in semi-sitting position).

— In the lower parts of the body (regarded from the horizontal plane of the supine position) such as the paravertebral and sacrate area, in bed-ridden patients with prolonged illnesses or limited mobility.

*Complications:*

— Bronchopneumonia — appears often because of the lung hypostasis, in persons with heart diseases.

**What is ISCHEMIA?**

*Definition:* the decrease of the arterial blood flow into a tissue or organ
*Pathogenesis:* arterial obstruction due to:

— Causes related to the arterial lumen.

— Thrombi.

— Emboli.

— Causes related to the arterial wall.

— Arteritis (inflammation of the arterial wall and narrowing of the lumen).

— Atherosclerosis (inflammatory and metabolic disease with subendothelial deposition of lipids and inflammatory cells resulting in atheromas).

— Accumulation of different substances (calcium, hyaline, amyloid, etc.).

— Spastic contractions (under the action of various vasoconstrictive factors).

— Causes related to external compressions:

— Enlarged lymph nodes (lymphadenopathy).

— Tumors.

— Medical procedures: external ligature/compression.

*Macroscopy:*

— Initially the organ is pale, then progressively develop one of the two possibilities: necrosis and sclerous atrophy.

*Microscopy:*

— Diminution or disappearance of the arterial lumen.

*Evolution* — the evolution depends on:

— The type of ischemia (total or partial) and the way of its installation (sudden or progressive).

— Total and sudden ischemia leads to infarction (necrosis of the tissue caused by a lack of oxygen that is anoxic conditions).

— Partial and slow ischemia leads to sclerous atrophy (sclerosis = hardening of the tissues due to the replacement of the parenchyma with fibrous tissue; atrophy = the decrease in the size of an organ).

— The resistance of the tissues to hypoxia:

— The nervous tissue in the Central Nervous System (CNS, the neurons) resists 3–5 minutes.

— The myocardial fibers resist 20–30 minutes.

— The kidney resists for about 1 hour.

— The skeletal muscles resist 8–10 hours.

The type of vascularization:

— An existing double or collateral circulation (e. g. double circuit in the liver and lung, rich anastomotic network in the intestinal wall) reduces the consequences of the ischemia.

— A terminal-type circulation (heart, kidneys, spleen and brain) has a very poor ability to compensate ischemia and the consequences are severe.

The speed with which the hypoxia is installed:

— Slowly — allows adaptation by opening or developing collateral branches.

— Rapidly — interrupts suddenly the oxygen and energy supply to the tissue, without enough time to compensate the loss.

**What is HEMORRHAGE?**

*Definition:* the exit of blood outside the blood vessels in a living organism.

*Pathogenesis:* three basic mechanisms:

— Breakage.

— Erosion.

— Erytrodiapedesis.

The breaches in the vessels walls or in the heart can be produced by:

— Traumas: wounds produced by cutting, bone fractures, etc.

— Preexistent diseases: arterial hypertension, atherosclerosis, congenital aneurysms on arteries, aneurysms of the heart wall, etc.

The erosion of the vessels may be:

— Chemical: gastric ulcer caused by the action of excessive chlorhydric acid.

— Traumatic: supplementary ribs which may erode the aorta.

— Inflammatory: infectious endocarditis may generate "mycotic" aneurysms (caused by the action of bacteria distantly, directly on a vessel wall) which may easily break, tuberculosis which destroys the vascular walls as well as the parenchymal tissues.

— Neoplasic: the tumor progression destroys the parenchyma and also the vessels.

Erythrodiapedesis — represents the crossover of the red cells outside the vascular wall and is produced:

— At the capillaries level.

— In a passive way.

— Due to subtle vascular wall lesions causing hyperpermeability.

In cases like:

— Prolonged hyperemia.

— Scorbutic — vitamin C.

— Microbial toxins.

— Some drugs.

— Disseminated intravascular coagulation (DIC).

Regarding their site, the hemorrhages may be classified in:

***1. External.***

***2. Exteriorized.***

***3. Internal.***

1. The ***external hemorrhages,*** regarding the type of the affected vessels at the outer surface of the body may be:

— Arterial, with a rapid, pulsatile flow of a bright red blood.

— Venous, with a slow, continuous flow of a dark red blood.

— Capillary, with a dotted pattern or as a diffuse, whole organ bleeding.

— Cardiac, with a strong spurt of the blood from the heart.

2. The ***exteriorized hemorrhages*** are produced in organs with cavities and exteriorized through natural channels, their origins giving their specific names:

— Epistaxis (from the nasal cavities).

— Otorrhagia (auditory channel).

— Gingivorrhagia (from the gums).

— Stomatorrhagia (from the oral mucosa).

— Hemoptysis (from the lung through the mouth — blood is mixed with saliva).

— Hematemesis (exteriorized by vomiting, from the stomach, with black, "coffee ground" appearance of the blood, because of its partial digestion in the stomach.

— Melena (blood from the stomach, digested, eliminated through the rectum — dark, black stool) and hematochezia (stool mixed with red blood, if the hemorrhage is massive).

— Rectorhagia (red, fresh blood on the stool, the bleeding source being the distal colon or rectum).

— Hematuria (red urine, eliminated through the urethra, with blood from anywhere from the urinary tract).

— Menorrhagia (increased and/or prolonged menstruation).

— Metrorrhagia (uterine bleeding between menstruations).

**3.** The ***internal hemorrhages*** are produced inside the body, the blood remaining at the site of hemorrhage:

— In serous cavities:

— Hemothorax (in pleural cavities).

— Hemopericard (in the pericardium cavity).

— Hemoperitoneum (in the abdominal cavity).

— Hematocele (in the testicular vaginal region).

— Hemarthrosis (in the joint cavity).

— In tissues, meaning in extravascular spaces:

— On surfaces (skin, serous membranes) as purpura (small red spots of 1–2 mm), petechiae (red spots of 2–3 mm) or ecchymose (bruises) of different sizes — a "permanent" red spot can be differentiated from a simple congestion by compression with a thin glass.

— In various tissues or organs as **hematomas.**

A **hematoma** is a well delineated collection of blood, which appears in different organs (e. g. frequently in the brain, skeletal muscle, but also in other organs).

*Macroscopically:*

— Nodular or oval.

— Space occupying, pushing the normal tissue.

— With a slow change in color (gradually, from red to purple, than green and yellow, following the bilirubin normal disintegration) until his disappearance.

*Microscopically:*

— Erythrocytes extravasate into the interstitium and release the hemoglobin; under the action of inflammatory proteases, the hemoglobin is gradually transformed into hemosiderin (brown color), than incorporated in macrophages resulting in siderophages, which together with the lymph remove the hematom.

*Evolution of hematoma:*

— Complete resorption, in the case of small hematomas.

— Enclosure, in the case of large hematomas; large hematomas cannot be totally resorbed but may be slowly surrounded and encased in connective tissue; a yellowish serous component remains usually in the center and hemosiderin and calcium may finally precipitate in the connective tissue which surrounds the old hematomas.

— Infection of the hematoma, if an infection develops in the proximity of the hematoma.

— Fibrosis of the entire hematoma — resulting in a small scar which, in some cases it may involve depositions of hemosiderin and calcium.

*Evolution and complications of hemorrhages*

Evolution of hemorrhages depending on the amount of the loss of the blood:

— Small and unique hemorrhages (under 500 ml) are not followed by significant consequences.

— Small and repeated hemorrhages cause usually chronic post-hemorrhagic anemia.

— Larger, unique hemorrhages can produce acute post-hemorrhagic anemia.

— Massive hemorrhages (involving more than 20 % of the entire blood volume) and produced suddenly, can cause hemorrhagic shock and death.

Evolution of hemorrhages depending on their particular locations:

— Brain: intracerebral hematomas may cause an intracranial hypertension sometimes with a rapid lethal outcome.

— Heart: a hemopericard (due to a ruptured myocardial infarct), which overtake rapidly 500–600 ml of blood, will stop the heart by hampering its diastolic expansion (cardiac tamponade).

**What is EMBOLISM?**

*Definition:* embolism is the mobilization and migration through the bloodstream of a structure named embolus, structure other than blood or aqueous solutions/hydrosoluble fluids.

***Types of embolism*** — by the direction of the circulation of the embolus in the bloodstream.

*Direct embolism:*

— The embolus has the same direction as the blood flow.

— It may circulate through:

• Arteries, where it is capable to pass through larger arteries and their branches without complications but stops and occludes arteries equal in size with the embolus — the consequences depend on the size of the artery occluded (size and site of the embolus), as well as the type of blood circulation (rich collateral network or "end type circulation"): the arterial emboli may cause infarctions.

• Veins, where it can originate and circulate through larger and larger veins and then trough the vena cava to the right side of the heart; next, an embolus ejection through the pulmonary artery will obstruct the two branch of this artery, or if it is smaller, will stop in the lung causing pulmonary infarction (venous emboli lead to pulmonary embolism).

*Indirect embolism (retrograde):*

— The embolus circulates in the blood in the opposite direction as the normal blood flow.

— A classic example would be the embolus circulating in the inferior vena cava which may be pushed back into the renal vein due to sudden movements which result in the reversal of blood flow and subsequently of the embolus (a sneeze, a cough or the Valsalva maneuver).

*Paradoxical embolism:*

— The embolus passes into the venous circulation from the arterial circulation (or the other way around); this situation may occur in certain circumstances such as:

• A defect in the atrial septum (DAS).

• A defect in the ventricular septum (DVS).

• The persistency of the inter-arterial channel (between the left branch of the pulmonary artery and the aorta).

• Congenital arterio-venous communications.

• Arterio-venous communications — which may appear during the postnatal life (e.g. arteriovenous fistulae for dialysis).

***Types of emboli according to their nature***

*Thrombembolus and thrombembolism:* a thrombus or a fragment of it detached and mobilized into the bloodstream. Its types:

*Arterial thrombembolism* — thrombi, usually larges, which originate in the heart or in the large arteries; they end in different organs, resulting in infarctions (e.g. heart — myocardial infarction, brain — stroke, kidneys — renal infarcts) or in the limbs, causing a gangrene.

*Venous thrombembolism* — arise mainly in the deep veins of the lower limbs or in the pelvic region and may cause pulmonary embolism:

• Massive pulmonary embolism, due to a large thrombus — usually causes sudden cardiac death (acute insufficiency of the right ventricle — the blood flow through the lungs and left heart is significantly diminished or stopped, resulting in cardiac shock; the thrombi leads also to a vagal reflex and a coronary spasm which precipitates the death of the patient).

• Pulmonary embolism with mean sized thrombi cause usually pulmonary infarction — this is sometimes prevented by a good arterial circulation (through the bronchial artery).

• Pulmonary embolism with small thrombi — may cause the obstruction of terminal pulmonary arterioles, but without pulmonary infarct; however, the multiple and repeated small emboli rested in the lung will be transformed in a conjunctive fashion, in little scars which will block the pulmonary circulation, cause pulmonary hypertension and lastly a chronic pulmonary heart disease.

*Infectious emboli* — small fragments containing bacteria, mobilized into the bloodstream from the sites of a primary infection, anytime during the course of a septic disease; besides spreading the infection they may cause septic infarctions and abscesses in different distant organs.

*Tumor emboli* are malignant tumor cells detached from a primary tumor that may end in different distant organs, where they may rebuild the tumor, generating secondary independent tumors called metastases.

*Atheromatous emboli* are fragments of broken atheromatous plaques, mobilized into the bloodstream: they may be encountered from large and mean sized arteries and may cause infarctions in different organs.

*Fat emboli* are made up by lipids; these lipids may be released from the fatty tissues most frequently after traumas as fractures of the head of the femur (containing adipose tissue in the bone marrow) or on the subcutaneous fat or on the fatty liver; the fatty embolism may be usually seen in the lungs or brain, using special techniques, that is freezing the tissues and special stains, for not solving the fats as in the standard paraffin embedding technique (were instead the fat rest a clear vacuole).

*Air embolism* is caused by the presence of air in the cardiovascular system, were the air act similarly to a solid structure:

— If the volume of the air is small, the air embolism may have any consequences, but if the volume of the intravascular air exceeds 100 ml, it may cause death.

— It may appear during surgeries (through the opened veins of the head and neck), traumas, unattended intravenous continuous infusions, during delivery or during abortive maneuvers, etc.

— The patient death is caused usually by the obstruction of the pulmonary artery (if the air enters the venous system) or of the arteries of the brain (if the air is present in the arterial system).

— During the necropsies, where an air embolism is suspected as the cause of a death, the examination must include an underwater opening of the heart and lungs to reveal a foamy aspect of the blood.

*Nitrogen gas embolism* is usually seen in the case of the decompression illness, which occurs usually in deep water divers. The nitrogen contained in the compressed air the divers inhale is dissolved into the blood at the high pressures existent at low underwater depths. This nitrogen turns back into gas when the divers get to the surface too fast, gas which may result in small intravascular bubbles that may be transformed into cerebral microemboli, causing the loss of consciousness and even the death of the divers.

*Amniotic fluid embolism* may occur when the viscous amniotic fluid enters the mother's blood through. This may happened through the opened placental vessels (ruptured) during or immediately after delivery. It may lead to the death of the mother because of severe pulmonary embolism and shock.

*Oil embolus* may be sometimes seen when intravenous injections of oily substances are performed.

*Emboli represented by small, foreign bodies* reaching the bloodstream accidentally (e.g. small fragments of a catheter tip).

***Major consequences of embolism:***

— Arterial — emboli may cause ischemia and infarctions in different organs.

— Infectious emboli — can spread infections.

— Tumor emboli — can disseminate the tumor leading to metastasis.

— Venous emboli — can cause pulmonary thrombembolism, which still represents a frequent cause of death.

**What is THROMBOSIS?**

*Definition:* thrombosis is the coagulation of the blood inside the blood vessels and heart during the life of an organism. During thrombosis, a solid structure called thrombus is formed inside the vessels, composed by platelets, fibrin and various other cellular components of the blood.

Thrombosis is a complex process, made up by several sequential events, the most important of which being:

— Platelet adhesion to endothelium or to subendothelial structures.

— Platelet aggregation and amalgamation inside a fibrin network.

— The release of some vasoactive mediators secreted by the platelets.

— The thrombin further converts the fibrinogen into the fibrin.

— The platelet and fibrin mass further adheres to the vessel wall, as new, successive layers which appear as parallel lines (the lines of Zahn).

— Leucocytes and erythrocytes may also be retained into the fibrin network (in correlation to the proportion of each the macroscopic color of the thrombus is established).

*Favoring factors for the formation of a thrombus (the Virchow triad):*

— Quality of the vessel wall (endothelial lesions).

— Nature of the blood flow (disorders of the circulation as stasis or turbulent flow).

— The composition of blood (factors causing hyper-coagulation).

The lesions of the vascular wall may have a crucial role in the thrombus formation and may particularly appear in the following circumstances:

— In the arteries: atherosclerosis, arterial hypertension, arteritis, action of chemical factors (nicotine).

— In the veins: sclerosing substances, hypoxia, neoplasic invasion.

— In the capillaries: extreme temperatures (cold, warm).

— In the endocardium: infarction, myocarditis, infectious endocarditis, rheumatic diseases, cardiac and vascular surgeries (vascular implants).

Disorders of the circulation:

— Stasis (decrease in the speed of the bloodstream).

— Appears in heart failure, bed-ridden patients, phenomena of local stasis (varices).

— The reductions in blood flow velocity prolong the contact between platelets and endothelial cells; the local accumulation of activated factors of coagulation, normally produced by endothelial cells and rapidly dispersed by the rapid bloodstream; the stasis-induced hypoxia and its effects on the endothelial cells.

— The flow turbulences make the blood elements to impact against the vascular wall and together with the shear stress on the vessel wall it may cause endothelial lesions.

— Aneurysms, hydrostatic varices.

— At the site of vessel branching.

— Preexisting lesions that traumatize the venous wall (atheromas, mural thrombi) vegetations or valvular verrucae.

Blood hyper coagulation can occur in some genetic diseases or under the action of some factors acquired during lifetime.

***The macroscopy of a thrombus:***

*Differences between thrombi and postmortem clots.*

The thrombus is:

— Adherent.

— Friable.

— Strong.

— Undeformable Dull.

The clot is:

— Non-adherent.

— Elastic.

— Deformable.

— Glossy.

*The location of thrombi*

In the veins:

— In the deep veins of the legs, where phlebothrombosis (thrombosis without an inflammation of the vein) or thrombophlebitis (thrombosis combined with an inflammation of the venous wall) may appear.

— In the veins of the pelvis (the venous plexuses around the uterus and prostate).

— In the longitudinal venous sinus of the meningeal dura mater (non-infectious thrombosis, infectious thrombosis in infants with severe dehydration, from the original veins with thrombophlebitis).

— The portal vein (pilethrombosis) and its branches.

In the arteries:

— Mural thrombi usually arise in the aorta and in other large arteries (on fissured atheromatous plaques, arteritis and aneurysms).

— Occlusive thrombi usually appear in medium-sized arteries (cerebral, coronary and mesenteric).

In the heart:

— On the endocardium of the left atrium (mitral stenosis, atrial fibrillation) or in the left ventricle (myocardial infarction, dilating cardiomiopathy).

— On the valvular endocardium, as small "tumors" or vegetations (particularly in endocarditis).

*Classification of thromb:*

According to their relationship with the vessel lumen and wall:

— Occlusive thrombus.

— Mural thrombus.

According to their color:

— White thrombi:

• Occur in zones with a faster blood flow (arteries, cardiac valves).

• Are whitish, strongly adherents and have a slow growth.

— Red thrombi:

• Appear in zones with stasis, in compressed veins and inside the chambers of the heart.

• Are red, flattened, elastic, gelatinous.

— Combined thrombi:

• Most frequently form in veins.

• Are made up of three elements: a white thrombus head (adherent to the vein), a fragmented body (a mixture of white and red thrombi) and a red tail (floating free in the venous lumen).

According to the form:

— Cylindrical (in the veins), sometimes with branches.

— Rounded (inside the heart chambers).

— Vegetative (on the cardiac valves).

***Microscopy of the thrombus:***

— The thrombi are made up by fibrin and platelets (the active necessary components) and also blood cells (facultative components, not necessary).

— White thrombi are made of fibrin and platelets (extremely adherent, in conditions which do not permit the other blood cells to be retained — cardiac valves).

— Red thrombi are made up by fibrin, platelets, leucocytes and erythrocytes (in condition of stasis).

— Combined thrombi are platelets mostly made up by fibrin, platelets and leucocytes in the white part and fibrin, and erythrocytes in the red part.

***Evolution of the thrombus***

Autolysis (of small thrombi):

— The activation of fibrinolysis.

The organization in connective tissue (of larger thrombi) (thrombus: granulation tissue: connective tissue scar).

Initially:

— Neutrophils penetrate into the thrombus and slowly remove the fibrin by hydrolytic enzymes.

— Macrophages phagocyte the remaining fibrin and blood cells.

— Myofibroblasts enter from the basis of the thrombus and multiply in the interior of the thrombus.

— From vasa vasorum, the endothelial cells multiply and enter the thrombus forming small capillaries, initially without basement membrane (is formed later).

— The mixture of myofibroblasts, macrophages, neutrophils, other inflammatory cells and the many new formed capillaries form **the granulation tissue —** the first step in connective tissue scarring.

Next:

— Myofibroblasts produce fibers of collagen that have contractile properties (the contraction of the thrombus).

— The capillaries loose their lumen and slowly disappear.

— Finally, the thrombus transforms itself in a connective tissue scar.

— Advantage: it fixes the thrombus to the wall (stops the thrombembolism).

— Disadvantage: stays attached permanently, like a mass that deforms and obstruct the vessel.

The recanalization of the thrombus — reestablishing partially the blood flow:

— Partial lyses of the thrombus.

— The contraction of the myofibroblasts inside the thrombus generates a space between the thrombus and the vascular wall.

— The newly formed capillaries in the thrombus (neoangiogenesis) grow along the vascular axis, crossing over the thrombus.

The noninfectious (sterile) degeneration of the thrombus:

— In large thrombi, that have a small connection with the walls of the veins, neutrophils enter and, with the help of their enzymes, melt the thrombus, liquefying its central core.

The infective degeneration of the thrombus:

— Is encountered in thrombi colonized by bacteria, derived from an infectious source.

— Infected thrombi can generate emboli, further spreading the infection.

The mobilization of thrombus:

— By partial disintegration of the thrombus and his dislodging, the fragments may enter the bloodstream.

The calcification of the thrombus:

— Calcium deposits may form inside venous thrombi (phlebolites) or on the endocardial vegetations.

***Consequences of the thrombosis:***

— Thrombembolism.

— Infarction: hypoxic necrosis following the sudden, complete obstruction of an artery.

— Infarctisation: hypoxic necrosis following the sudden obstruction of a vein.

— Post-thrombotic syndrome: lower limbs having thrombosed varicous veins may display evidence of chronic tissue hypoxia, that gradually leads to dystrophic local changes; the skin becomes thinner, glossy, without normal hair, with brown spots (hemosiderin) then with ulcerations, which have a slow evolution and are particularly difficult to treat.

**What is DISSEMINATED INTRAVASCULAR COAGULATION (DIC)?**

*Definition:* a complex disorder of blood coagulation that manifest simultaneously as a thrombotic and also hemorrhagic state, that is evident synchronously in different, multiple organs.

May be acute, subacute or chronic.

It means a secondary complication of other severe diseases.

*Etiopathology:*

1. Causes:

— Obstetrical: dead fetus retained in the uterus (releases thromboplastine which favorises DIC), infected abortions (complicated with postnatal fever and DIC), amniotic embolism, eclampsy, premature breakage of the water.

— Extensive surgery, particularly on the lung, prostate or uterus.

— Multiple trauma, extended burns.

— Infections, particularly with Gram negative bacteria, viremia.

— Neoplasia: carcinoma (pulmonary, prostate, breast, gastric, pancreatic), leukemia.

— Vascular diseases: intravascular hemolysis (incompatible blood transfusions), aortic aneurysms, vasculitis, vascular prosthesis.

— Shock.

2. Mechanisms:

— *Hypercoagulation state of the blood* with the formation of microthrombi in the capillaries of the entire body.

— *The consumption of coagulation factors* (fibrinogen, platelets, coagulation factors V, VII, X which are retained in the thrombus) with the occurrence of micro-hemorrhages (consumption coagulopathy).

— *Secondary fibrinolysis* (the dissolution of the thrombi in the capillaries and the restart of the hemorrhages).

*Macroscopy:*

— Skin: bleeding at the site of injections, necrotic lesions.

— Stomach: vomiting of digested blood ("coffee dregs").

— Kidneys: bilateral necrosis of the renal cortex.

— Pituitary gland: postnatal pituitary necrosis (the Sheehan syndrome) with complete endocrine or hormonal insufficiency.

— Hemorrhages in different organs: brain, lungs, heart, gut, kidneys or adrenal gland (the Waterhouse-Friedericksen syndrome — medulo-adrenal bilateral hemorrhages in meningococcal meningitis).

*Microscopy:*

— Microthrombi (hyalin fibrinous thrombi which at light microscopy appear as pink, homogenous, intracapillary masses).

— Microhemorrhages.

— Micronecrosis (the small territories corresponding to the microthrombi).

*Evolution:*

— Towards remission and healing, when the syndrome is detected and treated in its initial phases (needs the removal of the cause followed by large transfusions of fresh blood).

— The syndrome may become chronic when the hypercoagulation and microhemorrhagic episodes reappears leading towards death.

**What is INFARCT?**

*Definition:* necrosis of a limited area of tissue through an ischemic mechanism (necrosis — the death of cells in a living organism).

*Pathogenesis:* the same causes as ischemia (thrombosis, embolism, atherosclerosis, compression, external pressure).

*Macroscopy:*

*1. The form:*

— The area subjected to infarction is precisely delineated (only the territory dependent to the obstructed artery) and surrounded by a hyperemic border.

*2. The color of the infarct:*

— White (anemic) infarctions, in organs which have a terminal type circulation: the heart, the kidneys, and the spleen.

— Red (hemorrhagic) infarctions, owing the red color to the oozing or diffuse spreading of the blood (erythrocytes) into the dead area and seen mostly in organs which have a rich collateral circulation, such as the lung and the bowel.

*3. The shape of the infarct:*

— Triangular (the top pointed towards the obstructed artery) appears in the kidneys, spleen and lungs.

— Segmental, occurs in the intestine, and if the adjacent mesentery is also affected, the shape of the infarcted area is triangular.

— Rounded, in the brain.

— Irregular areas (the form of a "geographic map") appears in the heart; a hyperemic rim appears in the region where two coronary artery areas get in contact.

*4. The consistency of the infarct:*

— Hard, solid, in most cases.

— In the brain is softer than in the surrounding normal tissue (jelly-like) (is also called cerebral liquefaction).

*Microscopy:*

— The white infarct has an amorphous, acellular, acidophilic, well-delimited pattern, and at the border one can see many congested capillaries (which assure the leucocytes spreading in the affected area).

— The red infarct has a necrotic (acellular) pattern, but many erythrocytes are present in the affected area.

*Evolution:*

— Death, if the infarct occurs in a vital area for the organism (the brain stem, the Hiss fascicle of the heart) or if the infarct is very extensive.

— If the organism survives the infarct, a process of organization in connective scar tissue of the infracted area occurs — the necrotic zone becomes white, pearly and firm (connective fibrous tissue).

— The infection of the affected area.

***Venous infarctization:*** necrosis through venous stasis mechanism *Cause:* total and rapid obstruction of a vein.

*Macroscopicaly:* red cyanotic zone, edematous, slightly delimitated.

*Microscopicaly:* the structure of the organ disappears; the zone is filled with erythrocytes.

*Evolution:* depends on the significance of the affected zone.

**What is SHOCK?**

*Definition:* a severe pathological condition caused by a dramatic decrease of blood perfusion allover the body, especially at capillary level, with subsequent cellular hypoxia and cellular injuries.

*Pathogenesis:*

— Sudden decrease in the volume of circulating blood through massive hemorrhages or severe dehydration (vomiting, diarrhea, extended burn).

— Decreased and inhomogeneous pressure of perfusion due to vasodilatation and changes in vascular permeability.

— Decrease in the cardiac output by acute myocardial infarction, pulmonary thromboembolism, arrhythmias.

*Classification of shock:*

— Hypovolemic.

— Cardiogenic.

— Infectious (septic) (the endotoxin of the Gram negative bacteria in the blood).

— Neurogenic (painful trauma).

— Toxic.

— Endocrine.

*The macroscopy of shock:* necrosis and hemorrhages in different organs: lung, heart, liver, pancreas, digestive system, brain, renal, pituitary gland, etc.

The *microscopy of shock:*

— Microthrombi.

— Areas of micronecrosis.

— Microhemorrhages.

*Evolution:*

— Reversible in the initial phases, then it progresses to the patient death.

**WHAT ARE THE LYMPHATIC FLUIDS DISORDERS?**

The disorders of lymphatic circulation are:

— Lymphorrhea.

— Lymphatic thrombosis.

— Lymphatic stasis.

**What is LYMPHORRHEA?**

Definition: a flow of lymph from cut or ruptured lymph vessels, occurring in a living organism.

*Etiology:*

— Traumas.

— Inflammations.

— Tumors.

*Macroscopic:* a collection of lymph, clear or yellowish fluid, light-rose color (from the presence of erythrocytes) or opalescent (from lipid particles) outside the lymphatic vessels, usually in serous cavities:

— Chylothorax (in the pleural cavities from the thorax lymphatic channel).

— Chyloperitoneum (in the abdominal cavity, from the cistern chyli / Pequet).

**What is LYMPHATIC THROMBOSIS?**

*Definition:* lymph coagulation into the lymphatic veins in a living organism.

*Etiology:*

— Inflammations.

— Tumors.

*Macroscopy:* white thrombi in the lymphatic veins.

*Microscopy:* fibrin and lymphocytes

**What is LYMPHATIC STASIS?**

*Definition:* absence of the lymph drainage in a tissue or organ with subsequent lymph accumulation, in a living organism.

*Etiology:*

— Malformations of the lymphatic vessels.

— Traumas.

— Thrombosis.

— Parasitic diseases: filariasis (heartworms).

— Surgery: the Halstedt surgery (the extirpation of the breast and of his draining axillary's lymph nodes for breast cancer); in time, an angiosarcoma (a malignant vascular tumor) can appear in the upper limb, due to the chronic lymph stasis.

**WHICH ARE THE MAIN INTERSTITIAL FLUID DISORDERS?**

The interstitial fluid disorders are:

— Dehydration (the lack of liquid).

— Edema (the excess of liquid).

**What is DEHYDRATION?**

*Definition:* the decrease in the volume of the interstitial liquid.

*Etiology:*

— Insufficient liquid intake.

— Massive liquid loss: vomiting, sweating, diarrhea.

*Macroscopy:*

— Adult: dry teguments and mucosa

— Children: dry mucosa, fontanel depression.

*Evolution:*

— Hemoconcentration, increased viscosity of the blood, thrombosis, DIC, shock.

**b.What is EDEMA?**

*Definition:* the increase of fluids in the interstitial compartment.

*Pathogenesis:*

— Increase of the hydrostatic pressure: hyperemia.

— Decrease of the colloid-osmotic pressure: hypoproteinemia.

— The holding of Na ions.

— Disorders of lymphatic circulation: lymhedema.

*Classification of the edema*

Localized edema:

— Venous edema (with transudates, > 4 g, % of total proteins) with the presence of the "pitting sign" — when pressed by the fingertips, the affected area indents and holds the indentation several moments.

— Inflammatory edema (in exudates, < 3 g, % total proteins) with the presence of the signs of Celsius.

— Lymphatic edema (lymphedema), a firm edema, without the "pitting sign".

Generalized edema:

— Cardiac edema.

— Renal edema.

— Hepatic edema.

Fluid accumulation in the various body cavities:

— Hydrothorax (pleural effusions).

— Hydroperitoneum (ascites).

— Hydropericardium.

— Hydarthrosis.

— Hydrocele.

— Anasarca = generalized edema + fluids in the body cavities.

Edema of various organs (lung, brain, glottis).

*1. Pulmonary edema*

*Definition:* accumulation of a quantity of liquid in the pulmonary septal interstitium and in the alveolar space.

*Pathogenesis:* the acute failure of the left ventricle (myocardial infarction) increases the pressure of the blood in the pulmonary veins and capillaries until the level in which the interstitial tissue pressure is exceeded by the blood hydrostatic pressure and a fluid (water, some electrolytes and proteins in small quantities) extravasates into the interstitium (interstitial edema) and in the alveoli (alveolar edema).

*Macroscopy:* enlarged lungs out of which leaks a pink, foamy fluid during the cutting of the lung, and which sometimes exteriorize through the bronchi, and trachea.

*Microscopy:*

— The interstitium is expanded and contains dilated capillaries, filled with blood.

— In the alveoli it is present a thin, proteinaceous pink material (water mixed with proteins) and air bubbles.

*Evolution:* cough combined with foamy and pink spitting, intense dyspnea, and lethal evolution in the absence of a treatment.

*2. Cerebral edema*

*Definition:* increased fluid in the cerebral tissue, due to different causes.

*Pathogenesis:*

— Vasogenic edema in: encephalitis, trauma, cerebral abscess, tumors, cerebral hemorrhage.

— Cytotoxic edema in: ischemia, hypoxia, toxic substances.

— "Interstitial" edema: hydrocephalus.

*Macroscopy:*

— Increased volume and weight of the brain.

— Flattened circumvolutions (gyri) and faded sulci.

— When sectioning the brain the white matter appears glossy.

*Microscopy:*

— The existence of a clear pericellular halo.

*Evolution:*

— Clinically: headaches, convulsions, coma, photophobia, vomiting.

*Complications:* the increase in intracerebral pressure forces the pressure equilibration through the only existing, venting hole" — the occipital hole (foramen magnum); the herniation of the cerebellar tonsilae through it compresses the brain stem and causes ischemia of the bulbar and pontine centers for respiration causing death.

*3. Glotic edema:*

*Definition:* the accumulation of liquid in the glotic mucosa.

*Etiopathology:*

— Acute respiratory infections.

— Immune reactions: angioedema (the Quincke edema).

*Evolution:* death caused by suffocation if a thraheostomy in emergency is not performed.

# CHAPTER 4

## INFLAMMATIONS

**What is INFLAMMATION?**

*Definition:*

An inflammation is an unspecific defense reaction of a living organism in response to an injury.

Terminology used in inflammation:

— Inflamed organ = the suffix "itis" is attached to the name of the organ.

— Inflammation may be:

• Acute: short duration (up to a few days).

• Chronic: long duration (over six months).

The clinical signs of the acute inflammation were recognized and described by Celsius already in antiquity (Celsian signs):

• *Rubor:* redness of the area because of a local congestion.

• *Tumor:* the swelling of the area due to local inflammatory edema.

• *Calor:* the inflamed area becomes warmer due to the vasodilatation and increased influx of arterial warm blood.

• *Dolor:* pain in the inflamed area, due to the action of numerous chemical mediators released locally and due to compression (edema) on the local nerves.

• *Functio laesa* (Gallenus added this feature in the 2$^{nd}$ century AD): the decrease of the functional capacity of the inflamed area because of the pain and local edema.

**What is the ETIOLOGY OF THE INFLAMMATION?**

The factors or agents that may cause inflammation are:

1. Physical factors: heat, cold, radiations (UV, x-rays).

2. Mechanical agents: trauma, friction, stings, cuts, hits, foreign bodies.

3. Chemical and corrosive agents: exogenous (acids, bases, salts, drugs, toxins) or endogenous (uremia, pancreatic enzymes, necrotic tissues).

4. Biological agents: bacteria, viruses, fungi, parasites and the bio-molecules synthesized in response to infection (i.e. cytokines, chemokines).

5. Immunological causes: the immune complex depositions cause fibrinoid necrosis which may promote/maintain inflammatory reaction.

*Pathogenesis:* the inflammatory factors induce the release of numerous biological mediators, which induce arteriolar vasodilatation (congestion) and increased blood flow in the capillaries and tissues (warmth, redness) with the rising of the hydrostatic pressure which together with an increased vascular permeability contribute to plasma extravasation from the vessels into the tissue (extravascular space) generating the exudation and edema.

**What are the PATHOLOGICAL FEATURES OF INFLAMMATIONS?**

The anatomo-pathological main characteristic features of inflammations are:

1. Alteration.

2. Exudation.

3. Proliferation.

During the acute inflammation, all these components exist simultaneously, with the predominance of one of them.

**1. Alteration:** the dystrophic changes of cells and tissues in inflammation that cause changes in their normal morphology are the hydropic dystrophy, fatty dystrophy or necrosis; these are more frequently seen in the parenchymatous organs (the heart, the liver, the kidneys) and more important in acute inflammation.

*Pathogenesis:*

— Direct action of the inflammatory agent on the cells as toxins (toxic chemicals, microbial toxins), viruses, necrotic tissues etc.

— Hypoxia produced by vascular modifications (causing infarcts).

**2. Exudation:** vascular modifications and extravasation of different inflammatory blood cells.

*Vascular modifications*

I. Vessel size (diameter) and blood flow modifications.

a) The arterio-venous constriction phase is the first and brief and appears under the combined action of the neurogenic factors and chemical mediators.

b) The arterio-venous dilatation phase: the pre-capillary sphincter dilation and opening of new capillary beds; these means active hyperemia (congestion)

c) The phase of venous stasis (passive hyperemia): appears after a few hours and lasts a few hours.

II. The increase of vascular permeability

— Between the endothelial vascular cells there are normally tight intercellular junctions, impermeable or with very limited permeability (for only few, very small molecules).

— Increased permeability of the capillaries and venules appears in acute inflammations following alterations of the intercellular junctions and changes in the endothelial membrane permeability, which altogether lead to significant hyper-permeability.

III. Inflammatory exudation (inflammatory edema):

— A large quantity of extravasate fluid shifts from the blood into the interstitial extracellular compartment due to hyperemia and increased vascular permeability.

— The composition of the exudate is similar to that of the plasma containing many proteins as immunoglobulines, complement and fibrinogen (the extravasated fibrinogen is converted into fibrin due to the influence of the tissue coagulation factors, as thromboplastin).

— Unlike the exudate, a transudate has low protein content being the liquid that leave the intravascular compartment secondary to hydrostatic pressure increase on normal vascular permeability.

*A. Cellular response*

1. Types of cells involved in inflammation:

— Neutrophils (polimorphonuclear cells, PMN) dominate the first phase (24 hours) and persist in the inflammatory process for several days.

— After 24–48 hours the macrophages, the lymphocytes and the plasma cells may appear.

2. The neutrophils margination:

— Normally, the blood cells circulate axially and in the center of the blood stream, at a certain distance from the vessel wall and its endothelium.

— During the hyperemia of an acute inflammation, appear many changes in the blood circulation, some of them due to the inflammatory systemic and local mediators: the neutrophils move closer to the endothelium, where transient tethering and rolling increasingly occurs, some of the leucocytes ultimately attaching themselves firmly to the endothelium (adherence).

3. The migration of the neutrophils:

— The attached neutrophils actively pass through the intercellular junctions, then through the basal membrane and thereafter into the interstitial space; the transmigration through the capillary wall takes place rapidly (2–10 minutes).

4. Chemotactic agents:

— In the interstitium, the neutrophils move actively migrate towards the site of inflammation under the influence of numerous chemotactic agents released locally (chemokines) that stimulate the leucocytes and attract the inflammatory cells into the injured area.

5. Phagocytosis:

— Phagocytosis is a biological process during which several types of leukocyte recognize, internalize and digest the non-self structures of the body (foreign bodies, cellular debris, bacteria, etc.).

— It occurs in three stages: 1: the recognition of the particle 2: the internalization of the particle (the cells send cytoplasmic extensions that enclose the particle forming a phagosome). 3: the phagosomes then fuse with the lysosomes forming a phagolysosome, the lytic enzymes of the latter contributing to the destruction of the particle.

6. Proliferation:

— The inflammatory cell accumulation at the site of inflammation.

— It can be diffuse (in the whole affected organ) or localized (granulomatous inflammations).

— It is more characteristic for chronic inflammations.

In the inflamed area, the following types of inflammatory cells may accumulate:

a) Cells of the myeloid line:

— PMN (are characteristic for acute bacterial inflammations).

— Monocytes, macrophage, other specialized macrophage cells such as: epithelioid cells, Langhans giant cells, foreign body giant cells, etc. (characteristic for some chronic inflammations).

— B-lymphocytes, immunoblasts, plasmocytes and the T-lymphocytes, immunoblasts, sensitized T-lymphocytes (they are characteristic for acute inflammations caused by viruses, bacteria toxins, parasites, and chronic inflammations of any etiology).

b) Local cells: reactive proliferation.

Examples:

— Epithelial squamous cells in acuminate condylomas (due to Papilloma virus).

— Epithelial secretory cells in chronic gastritis.

**INFLAMMATIONS WITH PREDOMINANTLY ALTERATIVE COMPONENT**

*Definition:* The predominantly alterative inflammation is characterized by the simultaneous presence of the exudative elements (edema and congestion) and proliferative components (cellular inflammations), but the alterative features (hydropic dystrophy, fatty dystrophy and the cellular necrosis in the diseased organ) predominating.

*Examples:*

***1. Alterative myocarditis.***

*Etiology:*

— The diphtheria toxins.

— The typhus bacilli and its toxins.

*Macroscopic feature:*

— "Boiled meat" appearance (due to hydropic dystrophy).

— "Tiger-striped myocardium" (due to fatty dystrophy).

— "Dried leaf" appearance (in necrosis).

*Microscopic features:*

— Hydropic dystrophy of myocytes.

— Myocardial fatty dystrophy.

— Myocardial cell necrosis.

— Edema and interstitial congestion.

— Interstitial infiltration with lymphocytes and plasma cells.

*Evolution:*

— Death due to arrhythmias.

— Healing (cardiosclerosis).

***2. Viral hepatitis.***

***3. Necrotising inflammations:*** tissue necroses predominate due to the products released in some infection.

***4. Gangrenous inflammations:*** the digestion of necrotic tissues by bacteria.

**What are the PREDOMINANTLY EXUDATIVE INFLAMMATIONS?**

*Definition:* in these inflammations, there is an alterative (local cell dystrophies) and proliferative (inflammatory cells) component, but the predominant component is exudative (edema, congestion, and various types of exudates).

Correlations between the characteristics of the exudate and the inflammation type:

I. Serum: serous inflammation.

II. Fibrin: fibrinous inflammation.

III. Pus (PMN): suppurative inflammation.

IV. Red blood cells: hemorrhagic inflammation.

V. Catarrh (abundant, profuse mucus hyper-secretion) catarrhal inflammation.

**What are the SEROUS INFLAMMATIONS?**

*Definition:* the serous inflammation is the acute inflammation manifested with an exudate represented by a serous, pale yellow or citrine fluid formed mainly of water and electrolytes and with a low protein content.

*Etiology:*

— Viral infections, incipient bacterial infections.

— Physical and chemical inflammatory factors.

— Hypersensibility reactions.

*Localization of the serous infection:*

a) On external or internal surfaces (the tegument, mucosal surfaces).

b) At the level of the serosal membranes which coats the various body cavities (pleura, peritoneum, pericardium).

c) In the spongy or compact parenchymatous organs.

**I. On surfaces**

1. *On squamous epithelia* (the tegument and squamous mucosa).

*Etiology:*

— Chemical and physical factors.

— Viruses (varicella-zoster virus, herpes virus).

— Type I hypersensibility reactions (e.g. skin eruptions).

*Macroscopic features:*

— Maculae (flat, non-palpable, well circumscribed area, 1–2 cm in size).

— Papule (small, patchy, red, elevated area).

— Vesicle (an elevated lesion with fluid content, less than 1 cm diameter).

— Bulla (liquid deposit, more than 1 cm diameter).

*Microscopic features:*

— Maculae: capillary congestion in the superficial dermal layers.

— Papule: the liquid extravasates in the epidermis and displaces the cells (intercellular edema) and disrupts the normal histology (this is called also spongiosis).

— Vesicle (blister): intra-epidermal liquid accumulation (epidermal vesicle) or at the dermo-epidermic junction (dermo-epidermic vesicle).

*The evolution of the vesicle (blister):*

— On the skin: the vesicle breaks and leaves behind an ulceration that will be soon covered and sealed by a lymph crust; the epithelium will recover underneath, healing the lesion.

— On the mucosa membranes: the blister breaks, but the ulceration is not covered with the crust but with fibrin (fibrinous pseudo-membrane).

— In deeper ulcerations, lesions are called aphte (aphtous inflammations), and tend to have a slower healing.

*The evolution of the serous inflammations:*

— The serous inflammations may evolve towards regression and healing.

— It may aggravate, evolving towards a sero-fibrinous sero-purulent, sero-hemorrhagic, sero-fibrino-hemorrhagic inflammation.

*2. On mucous membranes (serous catarrh).*

**II. On serous surfaces (in preformed cavities)**

*Localization:* serous pleurisy, serous pericarditis, serous peritonitis, serous meningitis, and serous arthritis.

*Etiology:*

— Various viral infections, tuberculosis.

*Macroscopic features:*

— In cavities: sero-citrine liquid.

— The serosal membranes are congested and may present edema.

*Microscopic features:*

— In the serous membrane one can see degenerated mesothelial cells, congestion, edema, and few inflammatory cells.

*Evolution:* benign, favorable, towards healing.

**III. In parenchymatous organs**

*Etiology:* viral.

*Localization:*

— In subcutaneous tissues it evolves as an inflammatory edema.

— In solid organs (the liver, the myocardium, the brain, the kidneys) it manifests as serous interstitial inflammation.

*Evolution:* favorable, usually towards complete remission.

**What is the FIBRINOUS INFLAMMATION?**

*Definition:* the inflammation in which the exudate is represented by fibrin (resulted from the coagulation of the extravasated fibrinogen).

*Etiology:*

— Biological factors: the diphtheria bacillus, the dysenteric bacillus, the influenza virus, the herpetic virus.

— Endogenous substances: (fibrinous pericarditis in uremia).

*Macroscopically* the fibrin appears white-grayish filamentous substance which resemble the butter.

*Microscopically:* red (eosynophilic), amorphous substance.

Localization of the fibrinous inflammation:

I. On surfaces.

II. In the serosal cavities.

III. In spongy parenchymatous organs (lung).

**I. On surfaces**

*a) The diphteric croup*

*Etiology:* the diphteric bacillus.

*Localization:* at the level of the upper respiratory tract.

*Macroscopically:* thick, white-grayish, adherent pseudo-membranes covering the mucosa of the upper airways (the pharynx, the larynx, the trachea) *Microscopically:* fibrin pseudo-membranes, the subjacent mucosa presenting congestion, edema, and PMN infiltrate.

*Evolution:* the pseudo-membranes may cause laryngeal obstructions (especially at children which have a small glottic space) and may detach causing bronchial obstruction.

*b) Dysentery*

*Etiology:* the dysenteric bacillus.

*Localization:* in the colonic mucosa.

*Macroscopic feature:* the colonic mucosa is hyperemic and covered with thin fibrinous pseudo-membranes.

*Microscopic feature:* the intestinal mucosa has congestion, edema, PMN, fibrin pseudo-membranes.

*Evolution:* the pseudo-membranes may detach and leave superficial hemorrhagic ulcerations.

**II. On the serous surfaces (in preformed cavities)**

*a) Fibrinous pericarditis*

*Etiology:* uremia, myocardial infarction

*Macroscopic feature:* on the surface of the epicardium appears a white hair-like deposit of fibrin (hairy heart); this feature is caused by the heart movements — the fibrin deposit between the epicardium and pericardium is briefly pressed in diastole and pulled apart during the myocardial contraction, when the deposit is stretched.

*Microscopic:* in the epicardium, there is congestion, edema, PMN, and on his surface, fibrin deposits and degenerated mesothelial cells.

*Evolution:*

— When present in small amount, the fibrin is reabsorbed.

— In large quantity the fibrin is replaced by a granulation tissue which transform gradually in a fibrous tissue which leads to adhesions between the epicardium and pericardium; the adhesion may be narrow (bridge) or large (symphyses), with later calcium deposits.

*b) Fibrinous pleurisy*

*Etiology:* lobar pneumonia, tuberculosis.

*Macroscopic features:* on the surface of the pleura appear white filamentary deposits.

*Microscopic feature:* the pleura have edema, congestion, PMN, and on the surface red fibrin filaments with inflammatory cells and desquamated mesothelial cells.

*Evolution:* resorbtion, flanges or symphyses.

**III. In parenchymatous organs**

*Example:* lobar pneumonia.

*Etiology:* bacterial.

*Macroscopic feature:* in two phases of pneumonia called "hepatization", the affected pulmonary lobe presents a condensation because of which resemble to the liver.

*Microscopic:* congestion is found in the septa, whereas in the alveoli are observed fibrin filaments and PMN.

*Evolution:* resorbtion or connective reorganization.

**What are SUPPURATIVE (PYOGENIC) INFLAMMATIONS?**

*Definition:* suppurative inflammation is an acute inflammation in which the exudate is the pus.

*The macroscopic feature* of the pus:

— Yellow, creamy fluid (staphylococcus).

— Whitish or hemorrhagic liquid (streptococcus).

— Grayish, foul smelling (E. coli).

— Bluish (pyocianic).

*The microscopic feature* of the pus:

a) Pathogen agents (microbial colonies, with basophile aspect in H.E.).

b) Cellular detritus (local necrotic cells — liquefactive necrosis).

c) PMN which may have:

— Normal aspect.

— Endocytosed bacteria.

— Necrotic (killed, overwhelmed by the pathogen).

*Etiology:*

— Bacteria: streptococcus, staphylococcus, gonococcus, pneumococcus, E. coli, pseudomonas, proteus sp.

— Chlamydia.

— Chemical substances: terebenthine oil (suppurative aseptic inflammations).

**Types of suppurative inflammations:**

I. On various surfaces.

II. In the serosal surfaces of the preformed cavities.

III. In parenchymatous organs.

***I. On surfaces:***

1. The pustule: vesicles with purulent content.

2. The folliculitis: superficial inflammation of the hair follicle.

3. The furuncle: the inflammation affects several hair follicles and the surrounding tissue.

4. Carbuncle: an agglomeration of furuncles.

5. Suppurative hydradenitis: it affects the deep follicular structures and the sweat glands (located mostly in the armpit).

***II. In the preformed cavities***

Empyema: pus collected in preformed, natural body cavities (i.e., the pleural cavity, cholecyst).

Suppurative pericarditis, suppurative meningitis, suppurative arthritis.

***III. In parenchymatous organs:***

1. ***The abscess:*** circumscribed suppurative inflammation.

*Etiology:* staphylococcus auraeus (the most frequent).

*Localization:* the brain, the lung, the myocardium, the kidneys, and liver.

***a) The recent abscess (acute)***

*Macroscopic feature:*

— The area is well circumscribed; it is rounded, yellow-whitish.

*Microscopic feature:*

— Collection of pus (local agglomeration of normal or degenerated PMN, bacteria and cellular debris).

— At the periphery of the abscess: congestion, xanthomatous: granulation tissue.

*Evolution:*

— The infection is constrained and the area heals (spontaneously or under antibiotic treatment); if the abscess is small the cavity may be obliterated by the connective tissue which expands and fills the cavity.

— If the infectious process is not stopped the abscess becomes chronic.

***b) The old (chronic) abscess***

*Macroscopic feature:*

— Well defined and rounded area.

— In the center of the area is the pus.

— At the periphery there is a fibrous, connective capsule.

*Microscopic feature:*

— The central area: pus made up by various forms of PMN cells, bacteria and local cellular debris result of the liquefactive necrosis.

— The periphery is multi-layered composed by a granulation tissue or a fibrous connective tissue, covered by an inner layer of fibrin which may harbor microbial colonies that may perpetuate indefinitely the infection (the pyogenic membrane).

*Evolution:*

*a) Surgical treatment:* the incision of the abscess cavity and excision of the pyogenic membrane followed by an antibiotic treatment are mandatory.

*b) Spontaneous fistulization:* the infection erodes the surrounding fibrous capsule and the pus migrates along the lines of minimal resistance, finally being evacuated externally; because the pyogenic membrane rest locally, the pus will be reformed.

**2. The phlegmon:** diffuse suppurative inflammation, cellulitis.

*Etiology:* the streptococcus.

*Pathogenesis:* the bacterial enzymes as hyaluronidase and streptolysin liquefy the cellular matrix and allow the diffusion of the process.

*Phlegmon variants*

a) Erysipelas: superficial acute cellulitis of the skin.

Macroscopically: a red area, well defined, with irregular margins, slightly elevated, firm, painful, and rapidly extending.

Microscopically: dermal congestion, edema, and diffuse neutrophilic infiltrate.

b) The phlegmon of the oral cavity (Ludwig angina) is the diffuse inflammation of the mouth floor:

— After dental infections, tonsillitis.

— The infection may extend rapidly along the vessels and muscular fascia into the mediastinal space, compressing the airways, both complications having lethal potential.

c) The phlegmonous infections of the walls of cavitary organs (phlegmonous appendicitis, cholecystitis, gastritis).

**Complications of the suppurative inflammation:**

***1. Bacteriemia:*** the free circulation of bacteria in the blood without any clinical evidence of disease.

***2. Septicemia:*** the circulation and proliferation of the bacteria in the blood, associated with clinical manifestations (positive blood cultures).

***3. Septicopyemia:*** the circulation and the multiplication of bacteria in the blood, with secondary suppurative infections in various organs.

**What are HEMORRHAGIC INFLAMMATIONS?**

*Definition:* a hemorrhagic inflammation is an exudative inflammation simultaneous with an abundant red blood cells extravasation (not a separate entity, but merely a complication of other types of inflammation).

Hemorrhagic exudates cannot coagulate, feature that differentiate it from a hemorrhage that coagulate (e. g. differential diagnosis between hemorrhagic pleurisy and hemothorax).

*Etiology:*

— Bacteria producing powerful toxins: streptococcus hemolytic, meningococcus, anthrax bacillus, pest (plague).

— Viruses, rickets, malaria.

— Aspergillus (it produces vascular lesions).

— Coagulation and platelet disorders.

— Enzymatic hemorrhage (acute necrotico-hemorrhagic pancreatitis).

**What are CATARRHAL INFLAMMATIONS?**

*Definition:* the catarrhal inflammation is an exudative inflammation that appears on the surface of different mucosa. The exudation is called catarrh (it means: to drain on the surface).

*The catarrh can be:*

— Serous.

— Mucous.

— Suppurative.

— Hemorrhagic.

— Mixed (mucous-suppurative, sero-hemorrhagic, etc).

*Etiology:*

— Physical agents (the cold), chemical (alcohol, irritants).

— Viruses, bacteria.

— Allergy agents.

*Acute catarrhal inflammation:*

*Macroscopically:* congested mucosa, sometime presenting ulcerations and hemorrhages, with most often mixed exudate on the surface.

*Microscopically:* congestion, edema, small areas with ulcerations, inflammatory cells, and hyperplasia of the mucous cells, and mucus hypersecretion.

**What is PREDOMINANTLY PROLIFERATIVE INFLAMMATION?**

*Definition:* proliferative inflammations are the inflammations characterized by the accumulation of myeloid cells (leukocytes) in the site of inflammations, sometimes associated with local cells proliferation. This process is more frequent in chronic inflammation.

The myeloid cells involved in the proliferative process are:

— PMN (they appear in the acute inflammatory process).

— Monocytes that become macrophages in the inflamed tissue.

— Modified macrophages: epithelioid cells, giant multinucleated Langhans cells, foreign body giant cells.

— B-lymphocytes: immunoblast: plasma cell (produces antibodies).

— T-Lymphocytes: immunoblast: memory or activated T-lymphocyte.

Local cells proliferating in the inflammatory process (examples):

— In simple squamous epithelia: condylomas, pseudo-carcinomatous hyperplasia.

— In the visceral epithelia: in the kidney (in acute proliferative glomerulonephritis where the podocytes proliferate, or in rapidly progressive glomerulonephritis where the capsular epithelia proliferate as crescents).

— In encephalitis in which the glial cells proliferate (reactive gliosis).

The predominantly proliferative inflammations may be:

a) Diffuse: the inflammatory cells are present diffusely in the organ (i. e., glomerulonephritis, myocarditis, hepatitis, etc.).

b) Local: the inflammatory proliferation has a nodular aspect; the lesions are called granulomas, and the inflammation is called granulomatous inflammation.

Examples of granulomas:

**1. Tuberculoid granuloma**

— It is characteristic for tuberculosis, but it has the same pattern in other diseases as sarcoidosis, syphilis, berylliosis, the cat scratch disease, Crohn disease, granulomatous orchitis, granulomatous prostatitis, and granulomatous thyroiditis.

— Macroscopically: nodular, pseudo-tumoral lesions.

— Microscopically: the central area present an eosynophilic complete necrosis, surrounded by epithelioid cells (long cells, tightly packed to each other as the epithelial cells) and giant Langhans cells (large cells with numerous nuclei located at the periphery of the cells), numerous lymphocytes (the lymphocytic "crown") and finally fibrous tissue at the periphery of the granuloma.

**2. Foreign body granuloma**

— It is formed around exogenous foreign bodies (surgical cat-gut, other foreign materials, parasites, coal, silica, calcium, etc.) or endogenous (cholesterol crystals, urates, cyto-steatonecrosis, haemosiderin, etc).

— The granuloma is composed by PMN-s, macrophages, foreign body giant cells (large cells with numerous nuclei located randomly in the cell), lymphocytes, plasma cells, xanthomatous cells, siderophages.

**3. Aschoff granuloma**

— It appears in the acute rheumatic fever (polyarthritis, etc).

— It contains inflammatory cells and a particular macrophage named Aschoff giant cells.

**4. Giant cell peripheral granuloma**

— It appears on gums, on edentate areas (toothless).

— It contains inflammatory cells and giant multinucleated cells (osteoclastes).

**5. Pyogenic granuloma**

— It frequently appears in the oral cavity, on the gums, etc.

— Macroscopically: it appears as a red, soft, bleeding tumor having a white purulent spot in the center.

— Microscopically: it is composed of granulation tissue with many blood vessels, numerous PMN-s and pyogenic germs (produce pus).

**What are CHRONIC INFLAMMATIONS?**

*Definition:* chronic inflammations are long-standing inflammations of months, years.

**1. The chronic inflammation may appear:**

a) As a consequence of an acute inflammation.

*Examples:*

— Non-suppurative: acute hepatitis -> chronic hepatitis.

— Suppurative: acute osteomyelitis -> chronic osteomyelitis.

b) Discrete inflammation of reduced intensity with slow but continuous evolution.

*Examples:*

— Tuberculosis.

— Silicosis.

— Autoimmune disorders: autoimmune Addison disease, Basedow disease, etc.

**2. The aspect of chronic inflammations:**

— Diffuse.

— Nodular (granulomatous).

**3. The microscopy of the chronic inflammation:**

a) Inflammatory cells:

— The macrophages, originating from the circulating monocytes or from the local, tissue specific macrophages act as simple phagocytic cells or as epithelioid cells/multinucleate giant cells, following their anterior activation.

— B-lymphocytes (B cells): plasmocytes: produce the antibodies.

— T-lymphocytes (T cells): CD4+ helper LT secrete cytokines regulating the function of other cells of the immune system; CD8+ suppressor LT modulate (down regulate) the activity of other immune cells.

— Eosynophilic leukocytes in parasite infections, and in Ig E-mediated immune reactions.

b) Fibrosis which replace the destroyed local cells during the inflammation process.

**4. The evolution of the chronic inflammation**

— Healing (fibrosis, encapsulation).

— Evolutions towards complications and death.

**What is TUBERCULOSIS?**

*Definition:* tuberculosis is the inflammation caused by Mycobacterium tuberculosis.

***I. Etiology:***

a) M. Tuberculosis homini (Koch Bacillus or BK) produces infections through:

— Airborne infection, through the respiratory airways, directly inhaling BK from a sick person, by aerosol droplets (Pflugge droplets) containing microparticles of saliva infected with BK.

— The cutaneous path (through open skin wounds).

— The transplacental path, which result in fetal infection in utero during the pregnancy.

b) M. Tuberculosis bovis (rare) may generate infections through the infected milk from cows suffering from tuberculous mastitis; the patients will present oro-pharyngeal or intestinal lesions.

Risk factors for tuberculosis:

— Patients with immune deficiencies (immune system diseases, AIDS, immunosuppressive treatments).

— Diabetes.

— Pulmonary disease (silicosis).

***II. Pathogenesis:***

1. The first contact with BK induce initially an acute inflammatory reaction where PMN-s predominate but are inefficient.

2. Massive infiltration with macrophages.

3. The macrophages attempt the phagocytosis of the BK but the enzymes of phagolysosome cannot destroy them; thus it occurs the spread and dissemination of the infection first through the lymphatic channels to the neighboring lymph nodes.

4. After 2–3 weeks the cellular mediated immune response begin:

— The mycobacterial antigens released by the macrophages will stimulate and activate the T-cells.

— The CD4+ T cells (CD4) will secrete interferon that will activate other macrophages and NK cells increasing their ability to destroy the infected cells.

— Some macrophages are transformed into epithelioid cells while other macrophages will fuse and form giant multinucleated Langhans cells.

**5. Caseous** necrosis appears in the center of the nodule, mainly because of the macrophage lysosomal enzymes.

***III. The pathology of tuberculosis***

***1. Proliferative lesions***

a) The hard tubercle formed by:

— Epithelioid cells, giant Langhans cells and lymphocytes at the periphery (in the absence of necrosis, there is a challenging differential diagnosis with other tuberculoid granulomas).

b) The soft tubercle composed of:

— A central area of caseous necrosis which, in the early stages may still contain basophilic nuclear debris, later becoming intensely eosynophilic.

— At the periphery of necrosis there are epithelioid cells and giant Langhans cells.

— At the periphery of the tubercle there are numerous T-lymphocytes.

***2. Exudative lesions***

a) In the lungs:

— Tuberculous pneumonia and bronchopneumonia.

— In the alveoli: sero-fibrinous exudate with PMN-s, lymphocytes, macrophages and BK.

— There may occur massive caseous necrosis.

b) On the serous surfaces:

— examples: Tuberculous pleurisy, tuberculous meningitis, etc.

**A. Primary pulmonary tuberculosis**

*Definition:* the disease appears at the first contact to BK, frequently in the early childhood.

*Etiology:*

— M. tuberculosis homini — airborne infection through the respiratory tract.

*Pathology:*

**I. The primary tuberculosis lesion:**

*a) Localization of the disease:*

— Under the pleura.

— In the upper area of the inferior lobe, or in the upper portion of the inferior lobe of the right lung (more frequently).

*b) Macroscopic features:*

— Nodule of 1–1,5 cm, firm, rose-grayish.

— Then it becomes white, softer, friable.

*c) Microscopic feature:*

— Initially there is an unspecific inflammatory reaction as against the other types of bacteria, that means a localized fibrino-neutrophilic pneumonia.

— Because this type of reaction is ineffective, the immune system activated by the B. Koch antigens start the granulomatous type of reaction described above microscopically.

— Initially appear hard granulomatous nodules (without necrosis).

— Later soft granulomatous nodules (with central necrosis).

*d) Evolution*

— The BK circulate free or in the macrophages through the peri-bronchial lymph vessels, generating a tuberculous lymphangitis.

— The BK reaches the hilar lymph nodes producing a tuberculous lymphadenitis.

— The primary lesion + lymphangitis + lymphadenitis, represents the marker of primary tuberculosis, or the triad of the Ghon complex.

***The evolution of the primary tuberculous complex***

*1. Healing* occurs in 98–99 % of the cases by fibrosis in which calcium is frequently deposited (dystrophic calcification) visible at examination with Rx (HC: hilar calcification).

*2. Progressive tuberculosis*

a) *Direct development,* that is a gradual growth of a caseous lesion, that may erode a bronchial wall so that the caseum may be eliminated in the bronchus, or it may erode the pleura and the caseum is released into the pleural cavity; in both cases it leaves behind a caseous cavity (the primary cavity).

*b) Bronchial dissemination* when the liquefied caseous material enters bronchially (from a primary caseous lesion or from an affected lymph node). If several bronchial branches are affected, then a tuberculosis bronchopneumonia may occur (small white peribronchial nodules); if lobar bronchium is affected, tuberculous pneumonia occurs and the entire lobe is transformed into caseum (galloping phthises).

*c) Lymphatic dissemination* in the hilar: mediastinal: laterocervical lymph nodes (they grow getting a pseudo-tumoral aspect).

*d) Hematogenic dissemination* (BK septicemia) leads to the occurrence of small, 2–3 mm, numerous white nodules that may be found in the entire body, nodules that microscopically have either hard or soft granulomatous structure — miliary tuberculosis.

**II. Secondary pulmonary tuberculosis**

*Definition:* the reactivation of the preexisting lesions or a re-infection (very rare).

First lesion: apical Assman lesion:

— The nodule is situated at the top of the lung, in the infraclavicular region (Rx examination).

— *Macroscopically:* 2–3 cm large nodule which does not communicate with the bronchus and may or may not transform into a cavity.

— *Microscopically:* reduced caseification.

— *Evolution:* most frequently with fibroses and calcification (the solitary nodular lesion, large to 5–6 cm with condensed caseous content is called tuberculoma).

**Evolution of secondary tuberculosis**

*1. Healing* with fibro-calcareous scars and pleural retractions.

*2. Progressive pulmonary tuberculosis:*

a) Nodular tuberculosis (caseous): the formation of nodules of different sizes: from micronodules (under 1 cm) to macronodules (1–2 cm), white-grayish, caseous.

b) Cavitary tuberculosis: the erosion of a bronchus allows the elimination of the caseum remaining a cavity with irregular walls, covered by caseum, that is a recent caverna; if the caseum is completely eliminated, the walls of the caverna gets an increased content in connective tissue, become flat and gradually covered with bronchial epithelium or squamous metaplastic epithelium, clear from caseum and cystic, that is an old caverna.

c) Fibrous lesions: through the fibrous connective healing of preexisting tuberculous lesions by encapsulating fibrosis (the disease remain active).

d) Mixed tuberculosis: combined lesions of caseo-cavitary or fibro-caseo-cavitary types.

**Complications of tuberculosis**

***1. Pulmonary complications:***

— Bacterial infection (abscesses).

— Fungal colonization (Aspergilloma).

— Pleural caseous "empyema" with secondary appearance of symphyses or pachypleuritis.

— Squamous metaplasia (particularly inside the cavities) with a tendency for malignant transformation into a squamous cell carcinoma.

— Hemorrhages, sometimes lethal — in a caverna may rest almost intact a broncho-vascular; missing the exterior support, the arterial wall may dilate, creating an aneurysm inside the caverna which may rupture easily (by a cough).

***2. Extrapulmonary complications:***

— The hematogenic dissemination of pulmonary tuberculosis with the appearance of milliary tuberculosis in the entire body.

— The occurrence of digestive tuberculosis, following the ingestion of the infected sputum.

— Secondary amyloidosis.

**Digestive tuberculosis**

***1. Primary digestive tuberculosis***

— It appears on the oral mucosa, the tongue, the gums, the small intestine.

— It is caused by the consumption of infected fresh milk from cows with tuberculous mastitis (not pasteurized).

Macroscopically:

— In the upper digestive tract the primary lesion (initially caseous, then ulcerative), together with the lymphangitis and lymphadenitis of the latero-cervical lymph nodes, forms a primary complex; due to the enlarged lymph nodes, the neck

becomes swollen, and sometimes ulcerations and exterior caseous fistulas may occur; the term "*scrofula"* is also used to describe the condition.

— Caseous transversally oriented ulcers appear in the small intestine (small caseous nodules grow and ulcerate, releasing the caseum into the intestinal lumen — the primary lesion) and together with the lymphangitis and the lymphadenitis of the mesenteric lymph nodes form the mesenteric primary complex.

**2. Secondary digestive tuberculosis**

— From pulmonary tuberculosis, after swallowing the infected sputum or following hematogenous dissemination.

***Evolution of intestinal tuberculosis:***

— In evolution, the ulcerations become fibrotic and may cause narrowing (stenosis) of the intestine with occlusions.

— Apart of intestinal stenosis, evolution may be complicated by the occurrence of perforations and caseous peritonitis.

— In intestinal and peritoneal tuberculosis, peritoneal ascites and caseous nodules may also appear.

**Uro-genital tuberculosis**

**I. Renal tuberculosis** is only secondary and it can appear as ascendant or descendant tuberculosis infection:

a) The ascendant tuberculosis means infection of urinary bladder, next of the ureters, pelvis and finally the kidneys.

b) The descendant infection means the hematogenous route, that is the appearance of small granulomas in the cortical region of the kidneys where ends the blood-vessels.

*Macroscopically:*

— "Large ulcero-caseous tuberculous kidney": the kidneys present many caseous nodules from which the caseum may be eliminated into the pelvis and ureters, caseous nodules and cavities remaining in the kidneys.

— Sometimes the caseum may not be eliminated, the kidney being gradually destroyed, and becoming entirely caseous and retracted because of multiple fibrous scars, that transform the kidney in small, nonfunctioning "mastic-like tuberculous kidneys" (functional auto-nephrectomy).

According to the recommended treatment, renal tuberculosis may be classified into:

— Medical tuberculosis: both kidneys are affected but the renal function may be partially recovered by antibiotic treatment.

— Surgical tuberculosis: the kidney is completely destroyed and must be surgically removed (if possible).

**II. Genital *tuberculosis*,** can be primary (very rare) and secondary

1. In men, the epididymis is mainly affected; caseous nodules, ulcerations, and fibrosis with sterility appear; the testicle and the prostate are seldom affected by caseous nodules.

2. In women, the salpynx is mainly affected; nodules, ulcerations, stenosis with sterility appear; if the salpynx is obstructed, caseum may accumulate inside resulting a cold tuberculous abscess; if the process auto-sterilizes, the salpingeal accumulation will become a clear, watery fluid that means a hydrosalpinx; the endometrium may be also affected, with tuberculous granulomas appearing in this area; the ovary may be affected appearing a tuberculous oophoritis.

**The tuberculosis of the central nervous system** appears only as a secondary form.

• Tuberculous meningitis occurs following hematogenous dissemination on the choroid plexuses. From there, it migrates with the cerebrospinal fluid trough the Lushka and Magendie holes in the subarachnoidian space of the base of the brain. Here results a typical meningeal tuberculous lesion named basilar meningitis. A typical gelatinous greenish deposit appears, at the base of the brain, retained between the piamater and arachnoid lepto-meninges. Along the blood vessels of the Willis polygon very small caseous nodules may also appear. Microscopically, between the piamater and the arachnoid one can see an exudate with macrophages and lymphocytes, and just rarely the typical TB granulomas. The evolution is towards death or healing with fibrosis. The fibrosis induces multiple complications as hydrocephaly due to adherences, which impairs the LCR drainage or cranial nerves paralysis by compression.

• Tuberculous encephalitis, most frequently as single well-circumscribed Tb lesion, that is a tuberculoma, which appears in the adult's brain hemispheres or in the children's cerebellum.

**Osteo-articular TB** is secondary.

I. BK may reach the spine via the blood; it affects the hematogenous marrow of the vertebral bodies where caseous nodules appear. Through the destruction and collapse of the vertebral bodies' the spine change its shape inducing kyphosis, lordosis or scoliosis (gibbous or hunchback). The resulting lesion is called morbus of **Pott.** The caseous necrosis migrates along the para-vertebral muscles and accumulates under the skin where appears as typical cold tumefaction or "cold abscess". Due to the gravitation forces, the caseum also migrates from the lumbar spine to the pelvis and along the fasciae and muscles through the greater sciatic foramen reaches the antero- medial subcutaneous area of the thigh.

II. The tuberculosis of the long bones: the metaphysis of the bones are first affected in BK septicemia.

III. The joints are affected via hematogenous dissemination. Tuberculous granulomas appear in the articular sinovia destroying it and the articular cartilage. Characteristic fragments of cartilage resembling the rice grains (risiforme corpuscles) appear in the joint.

IV. Short bone tuberculosis (phalangeal tuberculosis) — necrosis of the central area occurs while the periosteum is thickened secondarily by reactive bone deposition.

**What is SYPHILIS?**

*Definition:* syphilis is a sexually transmitted disease caused by Treponema pallidum (which is a Spirocheta). There are also cases of congenital syphilis with trans-placentar transmission.

Diagnosis is made by clinical and anatomo-pathological examination and confirmed by several serologic tests (venereal disease research laboratory — VDRL, the Wasserman Bordet reaction test — RBW test).

I. Acquired syphilis

— Infection occurs in the overwhelming majority of cases through sexual contact.

— It has four stages of evolution.

**1. Primary syphilis**

It appears 1–3 weeks after the contaminating contact.

*Manifestations:*

***a) The firm chancre***

— Circumscribed, firm nodule with slightly elevated margins, painless, reddish, 1–2 cm diameter, which centrally ulcerates. At the bottom of the ulcerated sore there is a serous liquid, very abundant in Treponema.

— Localization:

1. Genital (90 %) — in women appear on the vulva, vagina or the uterine cervix, and in men on the gland, prepuce, scrot.

2. Extra genital (10 %), on the lips, breasts, fingers, perineal region.

— *Microscopic aspect:* perivascular lympho-plasmocytic infiltrate, and obliterating endarteritis (swollen, proliferated endothelia).

***b) Inguinal lymphadenitis***

*Macroscopically:* swollen, firm, painless lymph nodes.

*The evolution* of the firm chancre:

— The healing occurs with or without treatment in 2–3 months after the infection.

**2. Secondary syphilis**

It appears 2–3 months after the infection.

***Cutaneous-mucous lesions***

— Syphilitic maculae or roseoles: well circumscribed, pink, flat or raised, symmetric rash that involves the palms and the soles of the feet; maculae with hypo pigmented borders at the base of the neck (the Venus' collar) or follicular syphilides with areas of alopecia (hair loss).

— White-silvery, glossy, and painless mucosal plaques, seen mostly in the mouth and on the genitals; they may ulcerate, resulting serpiginous (serpent-like) very contagious ulcers.

— Extensive *condyloma lata* on wet muco-cutaneous areas (frequently on the genitalia, perineal region), appearing as flat red-brownish lesions, 2–3 cm large.

c) **Generalized micro-poly-adenopathies** (lymph nodes reactive enlargements).

**3. Tertiary syphilis**

It appears in 1/3 of the non-treated cases, many years after the infection.

***a) Gummatous syphilis***

— Syphilitic gumma = nodular lesion, up to 10–15 cm in diameter, white-gray, with rubbery consistency (gummatous necrosis), which later undergoes central liquefaction (liquefactive necrosis).

— Microscopically: incomplete eosynophil necrosis (it maintains the architecture of the preexisting structures), surrounded by epithelioid cells, Langhans giant cells and at the peripherally with a granulation tissue which contains many lymphocytes and plasma cells around the new formed capillaries.

— It can appear in various organs, deforming them (bones, hard palate, testicles, liver); in the liver, the syphilitic gummas cause organ enlargement with multiple nodules and fibrotic retractions, giving a mixed pseudolobular pattern — the so-called "hepar lobatum").

**b) Diffuse, infiltrative lesions** (mainly cardio-vascular and digestive)

— It is caused by the small and medium sized arterial wall inflammation (endarteritis and periarteritis).

— Aorta: syphilitic aortitis, which is secondary to the arteritis of vasa vasorum (obliterating endarteritis and peri-arteritis of the vasa vasorum) that produces a chronic ischemia of the aortic wall — this result secondarily in the atrophy and fibrosis of the aortic wall (especially of the media), which induce a giant sacciform aneurismal dilatation of the aorta.

— The plastic syphilitic linitis of the stomach and rectum, the walls of these organs becoming rigid, without peristaltism.

**4. Quaternary syphilis**

It is considered (by some authors) to be the disease of the nervous system (neurosyphilis), manifested with:

***a) Syphilitic meningitis***

— Lympho-plasmacytic perivascular infiltrate in the lepto-meninges.

— Evolution: meningeal fibrosis, adherences and hydrocephaly.

***b) Cerebral syphilitic arteritis*** with vascular endothelitis followed by vascular stenosis, cerebral atrophy especially in the frontal lobes and affliction of the cerebral cortex and progressive general paralysis.

***c) Tabes dorsalis:*** degenerative processes of the posterior medullary horns, with sensitivity disorders and lesions on the posterior roots of the spinal nerves (demyelinisation and lympho-plasmocytic infiltrates).

**II. Congenital syphilis**

The treponema passes from the maternal blood into the blood of the fetus, mostly after the 5th month of intra-uterine life (there are no early abortions because of syphilis, but only late abortions, stillborn babies or newborn babies with syphilitic lesions).

**1. Lesions incompatible with life**

Almost half of the fetuses are stillborn, and many of the living newborns will die prematurely due to:

— Syphilis involvement of the placenta.

— "White pneumonia" — the lung is hardened, white-grayish, the lesions revealing microscopically abundant lymph and plasma cell infiltrates and ischemic atrophy and fibrosis.

**2. Lesions compatible with life**

***1. Early***

— Skin rash (erithemato-papulous syphilides), petechiae.

— Syphilitic pemphigus (vesicles and crusts on the palms of the hands and the sole of the feet).

— Syphilitic rhagades (perioral, perivaginal).

— Rhinitis (snuffles).

— Hepatosplenomegaly, lymphadenopathy.

— Anemia.

— Mental retardation, hydrocephaly (frontal bossing).

***2. Late***

— Hutchinson triad: keratitis (inducing blindness), labyrinthitis whith the acoustic nerve (VII) affection (deafness of nerve transmission cause), the Hutchinson teeth: superior central incisors are small, conical, and on their incision surface there is a central notch (scalariforme teeth).

— Gumma of the nose (saddle nose) and on the palate (perforations of the palate).

— Numerous other osteo-articular anomalies (arthritis, osteo-chondritis, periostitis — "scimitar-shaped tibia").

**What is RHINOSCLEROMA?**

*Definition:* rhinoscleroma is a chronic inflammation specific to the upper respiratory tract.

*Etiology:* Klebsiella rhinoscleromatis.

*Clinically:*

— It starts as a nonspecific cattarhal rhinitis, that evolves into purulent, then atrophic forms when the nasal mucous membrane becomes thin and dry.

— In later stages, under the mucous membrane may develop multiple, firm, white-grayish nodules, which grow and extend slowly, creating pseudotumors which produce severe nasal obstruction.

— It can extend also to the paranasal sinuses, the pharynx, the larynx, in the cartilages and bones with their destruction and various degrees of airway obstruction.

*Microscopically:*

— The surface epithelium can present squamous metaplasia and sometimes pseudocarcinomatous hyperplasia.

— There are signs of chronic inflammatory process in the subepithelial area with a granulation tissue that contain PMN, neutrophils, eosynophils,

lymphocytes, plasma cells, specific macrophages (Mikulicz cells). Two features are pathognomonic for rhinoscleroma: the Mikulicz cells, that is macrophages with foamy, vacuolated cytoplasm containing Klebsiella rhinoscleromatis, visible in Gram stain and the Russel bodies (hyalin globules in the plasmocytic cytoplasm containing antibody deposits).

*Evolution:* the nodules slowly increase and may lead to various degrees of respiratory obstruction; it may be attempted a combination of antibiotic treatment against Klebsiella and surgery (removal of the nodules).

**What is ACTINOMYCOSIS?**

*Definition:* actinomycosis is a chronic infection caused by Actinomyces israelli that evolves with the formation of numerous abscesses in a background of chronic fibrotic inflammatory process. Actonomyces israelli is a commensal, normally nonpathogenic, anaerobic bacterium.

*Macroscopic pattern:*

— When penetrate deeply into the tissues (e. g. trauma), the infection triggers an acute suppurative inflammation that turn rapidly in a chronic inflammation. There will remain many abscesses surrounded by granulation of fibrotic scar tissues. This makes the entire area to be swollen, firm, red, with many deep abscesses which may fistulise exteriorly by numerous draining tracts.

— The exteriorized pus appears as small yellow-golden droplets or "sulfur granules" (pus with the microbial colonies).

*Microscopic pattern:*

— Micro-abscesses (made up of PMN neutrophils, cellular debris and centrally bacteria) surrounded by granulation tissue (capillaries, lymphocytes, plasmocytes, macrophages, fibroblasts) and mature fibrotic connective tissue at the periphery of each abscess.

— The bacteria are present as basophilic colonies, with polycyclic contours. On their periphery they have radial filaments ending in small eosynophilic buttons, containing antigen — antibody complexes (Splendore-Hoeppli phenomena).

*Evolution:* healing after antibiotic treatment.

*Anatomo-clinical forms:*

***1. Head and neck actinomycosis***

— It begins at the gums and extends as a firm "phlegmonous" like infection towards the lower jaw with many purulent fistulas.

— Complications: it can spread to the sinuses, and induce osteomyelitis with bone destruction.

***2. Pulmonary actinomycosis***

— The bacteria may reach the lungs through the airways; it infects the inferior pulmonary lobes where it may cause nodules, cavities, and pleural effusions; complications such as pleural empyema or spread into the pericardium may appear.

***3. Abdominal actinomycosis***

— It s due to the swallowing of the bacteria.

— It affects mainly the colon, the caecum (typhilitis), the appendix.

— It may spread to the small intestine causing perforation, fistulae, and peritoneal abscesses. Through the portal vein it can reach the liver where may causes multiple abscesses (the "honey-comb liver").

***4. Pelvic actinomycosis***

— More frequently in women with an intrauterine device.

— It affects mostly the tubes and the ovaries.

**What is CANDIDOSIS?**

*Definition:* candidosis is an infection and inflammation caused by fungi of Candida species.

*Etiology:* most frequently Candida albicans, but other subspecies or associations may occur.

1. In healthy individuals the presence of the fungus in the oral cavity, digestive or respiratory tract, vagina, skin does not cause clinically evident disease (Saprophyte).

2. With serious impairments of the immune system the normal immunologic defense is over passed and invasive disease may develop (Pathogen).

Local favoring factors:

— Trauma, burns, ulcerations, surgical interventions, catheters.

— A moist environment (i. e. impermeable, rubber clothing).

— Prolonged treatments with antibiotics.

Systemic favoring factors:

— Immune deficiencies (AIDS patients, hereditary immune deficiencies).

— Diabetes melitus, malignant tumors, leukemia, anemia, endocrine disorders.

— Pregnancy, contraceptive drugs.

— Treatments with corticoids, cytostatic treatment, transplant recipients with immunosuppressive treatment.

*Types of candidosis:*

**A. Superficial Candidosis**

— It appears in moist, warm, macerated areas.

I. Skin folds:

— In the armpit region (axilla) and in the inguinal folds, under the breast, in the interdigital space or between the buttocks.

— Eczematous and granulomatous lesions, abscesses.

II. On the finger nails:

— onychomycosis of the finger nail and paronychia of the tissues around the nail.

III. On the various mucosa:

— The oral cavity, the tongue, the cheek mucosa, the mouth corners.

— It is a whitish and soft deposit that may be removed by scratching, leaving underneath an irritated, red mucosa; in contrast, the leukoplasia, which is also white cannot be removed by scratching.

— It also appears on the esophagus, the stomach, the intestines (esophageal candidosis usually signals severe immunodepression at is of AIDS).

— The external genitalia and the vaginal mucosa may also be affected.

B. Invasive candidosis

— In the heart: vegetative endocarditis.

— Kidneys, lungs, liver, brain: abscesses.

— It can also cause: meningitis, enteritis, arteritis, osteomyelitis.

*Microscopic features:*

— The yeast cells: small round structures.

— Pseudohyphae.

— Hyphae (mycelia): like bamboo sticks, narrow, septate, without branches.

*Stains*

— H-E: red.

— PAS: red.

— Methenamine sylver: black.

*Evolution:* the antimycotic treatment associated to the causative factor removal of the cause.

**What is ASPERGILLOSIS?**

*Etiology:* Aspergillus fumigatus, frequently an opportunistic pathogen.

— Ubiquitous on soil, plants, animal feces.

*Anatomo-pathological forms:*

a) The allergic broncho-pulmonary aspergillosis:

— Inhalation of the germs.

— Clinically it resembles asthma, with respiratory wheezing and cough.

— Microscopically: lymphocyte and plasma cell infiltrate, eosynophilic infiltrate.

b) The colonizing aspergillosis:

— In preexisting pulmonary cavities (tuberculous caverns, evacuated abscesses, excavated cancers) the colonies of Aspergillus develop in a nodular form as a black-grayish nodule (fungus ball) called Aspergilloma.

c) The invasive aspergillosis:

In immunodeficient hosts:

— Initially in the lungs and then in the blood — hematogenous dissemination may occur in the heart, lungs, brain, and kidney.

**What is TOXOPLASMOSIS?**

*Etiology:* Toxoplasma gondii, a protozoan intracellular parasite

— From the cat intestine (the definitive host), toxoplasma survives in the external environment for months causing the infestation of other animals who consume food contaminated with cat feces or after careless handling of cat litter.

— Swallowed ovocysts (eating infested meat) disseminates in various body tissues, infecting several cells; after ingestion, ovocysts transform into tachyzoites, and then bradyzoites.

*Anatomo-clinical forms:*

*1. Acquired toxoplasmosis.*

a) In immuno-competent individuals

— Cysts with bradyzoites in different organs (brain, striate muscle), are clinically asymptomatic (positive Sabin-Feldman reaction).

— When the cysts break, they produce inflammation, fever, and laterocervical lymphadenopathy (needing differential diagnosis with the Hodgkin disease).

— Microscopically: lymph nodes with paracortical folicular hiperplasia and epithelioid cells.

b) In individuals with immune system depression:

— AIDS, transplant immunosuppression, etc.

— Brain: edema, foci of necrosis and hemorrhage.

— Lungs: interstitial pneumonia.

— Myocardium: interstitial myocarditis, cysts with toxoplasma.

— Eye: toxoplasmic chorioretinitis.

*2. Congenital toxoplasmosis:*

— Placental, at women infested during pregnancy.

It can pass to the fetus:

— Ocular lesions (chorioretinitis) -> blindness.

— Hydrocephaly with periventricular necrosis and calcifications (sanded).

— Intracranial calcifications (granulomatous lesions, with lymphocytes, plasma cells, that calcify dystrophically).

— Necrotic foci in the lungs, myocardium, liver.

**What is PNEUMOCYSTOSIS?**

*Etiology:* the Pneumocystis carinii.

1. The child's pneumocystosis:

— It is most frequently encountered in premature infants, or malnourished infants.

— Clinical manifestations: unspecific, discrete initial phase, growth deficit, cough with exertion, dry (low sputum).

— Macroscopically: condensed and brown lungs covered with a gelatinous secretion.

— Microscopically: in H-E stain, the interstitium is enlarged, with a rich plasma cell infiltrate (plasmocytic interstitial pneumonia), and in the alveoli there is a spongelike exudate.

— Special stains for Pneumocystis: methenamine-silver stain, Giemsa stain which shows the parasite cysts in the alveoli.

2. The pneumocystosis in the immunodepressed adult:

— It appears in: congenital immunodeficiency, after treatments with cortisone, antitumor drugs, transplant immunosuppression, etc.

— AIDS patients often present pneumocystosis.

— The inflammatory response is very mild.

— The disease is often recurrent.

**What are the VIROSES?**

*Definition:* the viroses are infections caused by viruses.

*The virus:* a noncellular structure composed mainly of nucleic acid (DNA or RNA) within a proteic coat/capsule (glyco- or lipoprotein subunits — capsomeres). Viruses are very small (100–2,000 nm) and do not carry out the functions of the living cells (i. e., respiration, growth) but enter in living cells (intra-cellular parasite) and use the host chemical energy and its protein — and nucleic acid - synthesizing ability to replicate themselves.

The characteristics of the virus:

— It acts only inside the cells.

— It does not have: energetic deposits or own enzymes.

The life cycle of the virus:

— During the intracellular replicative phase, the viral components (virions) are formed in the host cell by a self-assembly process, then capsomere subunits assemble into a protein coat around the nucleic core.

The extracellular phase: following the lyses of the host cell or emission from the host cell surface, the viruses become free and may continue to spread and re-take the replication cycle in other cells.

*The mechanism of cell infection:*

1. The fixation of the virus on the cellular membrane through receptors or by merging with a host cell membrane, following by the engulfment of the viral particle.

— After entering the body, HIV attaches to the CD4 receptors of the CD4+ T-lymphocytes and some blood monocytes; the attachment of the viral particle to the receptors on the lymphocyte membrane enables fusion with the cell membrane and the viral RNA moves into the lymphocytic cytoplasm.

— Epstein-Barr virus binds to the CD3 receptors.

— The rabies virus attaches to the acetyl-cholinic receptors.

2. After penetration of the virus into the cell through pinocytosis, the virus leaves its capside totally or partially outside the infected cell.

3. The transcription phase: the viral genome is incorporated into the cell genome and viral products are synthesized following the usual RNA->mRNA sequence or RNA- >DNA (through reverse transcriptase) then in mRNA.

*The pathology of viral infections:*

a) The virus may act directly on the host cell:

— It may remain in the cell without any harm.

— It may transform the cell: e. g. immoralization or malignant transformation.

— It harms or kills the host cell.

b) Viral infection leads to cell biochemical and morphological abnormalities, and/or cell death.

c) The cell expresses viral proteins on its surface, thus triggering an immune response.

I. ***The virus-cell relationship*** (morpho-functional changes of the host cells in the presence of viruses):

1. The absence of cellular modifications:

— The symbiotic relationship, or a steady-state (e. g., HIV uses the monocytes in order to multiply and just marginally and slowly affects the cellular functions; it takes up to 10 years until the infection has such effects).

2. Cellular stimulation:

a) Large cells which present circumscribed, spherical inclusion bodies (viral inclusions):

— Intracytoplasmic inclusions: the viruses of rubella, rabies, and poliomyelitis.

— Intranuclear inclusions: the herpetic virus.

b) Fusions of infected cells leading to the formation of a giant multinucleated cells of syncytial type (the respiratory syncytial virus).

c) Stimulation of cellular proliferation: the Papilloma virus, Molluscum contagiosum.

3. The injury or the destruction of the host cell:

— Ballooning dystrophies that may evolve to necrosis of the cell (the hepatic virus).

— The death of the cell by modifying or arresting the synthetic activity.

— The cell lyses through immune mechanism — the cells expresses on the surface viral proteins from the viral capsule or other foreign membrane epitopes, thus triggering the immune recognition and aggression towards the infected cell.

4. The neoplasic transformation (oncogenic viruses):

— Immortalisation by inhibition/suppression of apoptotic genes.

— Following the incorporation of the viral genome into the host genome, the viruses may activate preexisting oncogenes (responsible of cell proliferation), leading to cancerous transformation of the cell (e. g. Epstein-Barr virus).

II. ***The virus-organism relationship*** (the modifications that appear in the organism during virosis).

1. Hyperthermia: an unspecific defense mechanism, that may accelerate some immunologic processes while simultaneously it may slow the viral replication.

2. Inflammation:

— Predominantly perivascular lymphocyte and plasma cell infiltrate.

— Hemorrhage (in cases of vasculotropic viruses).

— The production of interferon (biomolecules with antiviral activity).

3. The stimulation of humoral immunity:

— Synthesis and release of local IgA and circulating IgM and IgG, preventing the virus attach to the cells, limiting their replication or causing the lyses of the infected cells.

4. The stimulation of cellular immunity:

— The lymphocytes destroy the infected cells, attract monocytes and stimulate the production of interferon.

***The classification of viruses:***

***I. DNA viruses***

1. Poxviruses

— The variola virus (eradicated).

— Molluscum contagiosum: microscopic pattern — the proliferation of the squamous epithelium, eosynophil inclusions in the stratum spinosum and granulosum, represented by viral and keratin particles.

2. The human herpetic viruses (HHV): macroscopically the lesion has vesicular, blistery aspect; microscopically intranuclear inclusions; following the acute eruptive episodes, the viruses may rest latently in the nerve ganglia and may periodically reactivate.

— Virus herpes simplex.

— HSV-1: genital and oral.

— HSV-2: predominantly genital (it may be transmitted to the newborn during labor causing serious lesions in the babies brain, liver, lungs, adrenal glands).

— The varicella — zoster virus (HHV-3): varicella (chickenpox) during childhood; the virus remains latent in the dorsal ganglia and may reactivate as herpes zoster (vesicles on the skins or mucosa corresponding to the affected sensitive nerves).

— The Epstein-Barr virus (HHV4) can produce infectious mononucleosis (fever, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis, the Burkitt lymphoma, the naso-pharyngeal carcinoma, Hodgkin lymphoma, and hairy leukoplasia.

— The cytomegalovirus (HHV5), microscopically, it is a big cell with a large nucleus containing an inclusion surrounded by a clear halo. In the newborn, it may generate trombocytopenia, hepatitis, pneumonia, and in AIDS patients it may cause ulcerative lesions on the digestive tract, pneumonias, encephalitis.

— HHV6, HHV7.

— HHV8 is implicated in the genesis of the Kaposi sarcoma (AIDS).

3. The papovaviruses: the most important is the human papilloma virus (HPV) which has the following characteristics:

— It produces proliferations of the stratified squamous epithelium, presenting some specific cells called koilocytes (large cell, with a small hyperchromatic nucleus, surrounded by a clear halo).

The lesions produced by the papilloma virus:

— Verruca vulgaris: particularly in children, small multiple hyperkeratotic lesions on the fingers.

— Flat verruca: brownish, on the face.

— Acuminate condyloma: sexually transmitted, large, verucous, confluent lesions looking similarly to a cauliflower on the external genitalia, perineal region (ano-rectal).

— Flat condylomas: on the female external genitalia; sexually transmitted; HPV 6 and 11, have reduced clinical significance, but the lesions caused by HPV 16 and 18 may evolve into a carcinoma of the uterine cervix.

***II. RNA viruses***

1. Orthomyxoviruses:

— The influenza virus: it produces tracheitis, bronchitis, interstitial pneumonia and evolves with the destruction of the respiratory ciliate epithelium.

— Initially, viral infection involves the ciliated columnar epithelial cells, but it also may involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages.

2. Paramyxoviruses:

— The measles virus (rubella):

— The measles virus invades the respiratory epithelium and spreads via the bloodstream to the reticulo-endothelial system, from which it infects all types of white blood cells, thereby establishing infection of the skin, respiratory tract, and other organs; it is also affecting the fetus of pregnant woman with important malformative sequelae.

— Interstitial pneumonia with multinucleated giant cells or cells with intracellular inclusions (intracytoplasmic); generalized damage to the respiratory tract, with resultant loss of cilia, which predisposes to secondary bacterial infections such as bacterial pneumonia and otitis media.

— The syncytial respiratory virus: in infants, interstitial pneumonias with multinuclear cells, with a syncytial aspect; severe bronchiolitis or pneumonia, characterized by necrosis of the bronchiolar epithelium and a peri-bronchiolar infiltrate of lymphocytes and mononuclear cells; alveolar septae thickening and filling of the alveolar spaces with fluid may also be found.

3. Retroviruses:

— The Retroviridae family includes three subfamilies: Oncoviridae, with human T-cell lymphotropic virus (HTLV) type I as the most important in humans; Lentiviridae, of which the **human immunodeficiency virus** (HIV) is the most important and Spumaviridae, the "foamy" viruses, named as because of the microscopic pattern of the infected cells.

— Retroviruses contain an RNA-dependent DNA polymerase (a reverse transcriptase), that after the infection of the host cell directs the synthesis of a DNA from the viral genome.

**— HIV causes AIDS (acquired immune deficiency syndrome)**

The disease is characterized by progressive immunodepression or suppression that favors infections with opportunistic germs, malignant tumors, and neurological manifestations.

***The epidemiology of the HIV-infection:***

— The major transmission way is the sexual intercourse (homosexuals, bisexuals, heterosexuals).

— Intravenous drug users.

— Hemophiliacs, patients transfused with contaminated blood.

— Contaminated surgical instruments or maneuvers (i. e., injections).

— Breast feeding.

*Etiology:*

— HIV: a human retrovirus from the family of lentiviruses.

— Two forms genetically related: HIV-1 (associated with AIDS especially in the USA and Europe) and HIV-2 (more frequent in Africa and India).

*Pathogenesis:*

— The high-affinity binding of gp120 protein (via a portion of its V1 region near the N terminus) to its receptor on the host cell surface, the CD4 molecule (a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper or inducer function in the immune system).

— Following binding, fusion with the host cell membrane occurs via the gp 41 molecule, and the HIV genomic RNA is uncoated and internalized into the target cell.

— The reverse transcriptase enzyme contained in the infecting virion catalyzes the reverse transcription of the genomic RNA into double-stranded DNAt.

— The DNA translocates to the nucleus and integrates randomly into the host cell genome (chromosomes) through the action of another virally encoded enzyme, *integrase.*

— This provirus may remain transcriptionally inactive (latent), or it may manifest with varying levels of gene expression, up to active production of the virus.

— HIV infected macrophages (Mf) represent a virus deposit, a transporter of the virus to the organs and an area of viral replication in the late stages of the infection.

*Major anomalies of the immune system functions in AIDS:*

— Lymphopenia: the selective reduction of CD4 T-lymphocytes; when the CD4+ T-cell count falls below a critical level (less than 200 cells/micro liter) the patient becomes highly susceptible for opportunistic diseases (infections, tumors).

— The reduction in the function of the remaining T-lymphocytes => opportunistic.

— The polyclonal activation of B-lymphocytes.

***The natural clinical evolution of the HIV infection:***

1. The acute phase: 50 to 70 % of individuals with HIV infection experience an acute clinical syndrome approximately 3 to 6 weeks after the primary infection.

— An ordinary, usual viral infection, no specific general symptoms.

— High viremia and colonization of the lymphoid tissue.

2. The chronic (middle) phase:

— Up 7–10 years are clinically asymptomatic (clinical latency).

— Intact immune system, but there is a viral replication in the lymphoid tissues.

— Generalized lymphadenopathy (> 1 cm) in two or more extra inguinal sites for more than 3 months without an obvious cause.

— May be associated with other signs (cutaneous eruptions, fever, fatigue), which announces the crisis phase.

— Opportunistic infections.

3. The phase of manifest disease:

— The destruction of the defense mechanism.

— Persisting fever for over a month, fatigue.

— Diarrhea, weight loss.

— Clear manifestations of AIDS: opportunistic infections, secondary tumors, neurological disease.

***Anatomo-pathological modifications in AIDS:***

There are no specific lesions for the diagnosis

— Lymphocyte depletion in the lymphoid organs.

— Generalized follicular hyperplasia (seen early in the disease).

— Lymph node biopsy is not indicated in the lymphadenopathy seen early in disease unless it is associated with rapid enlargement, unusual consistency, or coalescence of the nodes.

— Kaposi's sarcoma may present in a lymphadenopathic form early in the disease.

— Blood: thrombocytopenia, neutropenia (in approximately half of patients with HIV infection), anemia (the most common hematologic abnormality).

— Myocarditis.

— Kaposi sarcoma (in approximately 25 % of the AIDS patients).

— Oral cavity: herpes, candidosis, or other fungal infections, hyperkeratosis, leukoplakia (white lesions on the tongue that it cannot be scratched, presumed to be caused by Epstein-Barr virus) acanthosis, and aphtous ulcers, particularly common during this phase.

— Central nervous system: aseptic meningitis or meningo-encephalitis, seen in late stages of the disease; also called *HIV-associated dementia* or *AIDS dementia complex.*

— Peripheral nervous system: peripheral neuropathies, spinal cord disease (myelopathy).

— Tumors associated with AIDS: Kaposi sarcoma, non-Hodgkin lymphoma with B cells, primary cerebral lymphoma, and invasive carcinoma of the uterine cervix, hepatocarcinoma.

— **Infections:** are late complications of the HIV infection, mostly with opportunistic organisms, such as

— *Pneumocystis carinii, Mycobacterium avium* complex, CMV and other organisms that do not ordinarily cause disease in the absence of a compromised immune system

— Toxoplasmosis (the most common cause of secondary CNS infection in patients with AIDS), invasive fungal infections (Candida infections of the upper respiratory tract — the most common fungal infections in HIV patients, cryptococcosis — leading cause of meningitis in patients with AIDS, histoplasmosis, aspergillosis — a pseudomembranous tracheobronchitis), protozoal diarrhea (Cryptosporidia, microsporidia, and *Isospora belli),* viruses (Herpes simplex, the Varicella-zoster virus, Epstein-Barr virus, Human Papillomavirus, Hepatitis Viruses).

# CHAPTER 5

# NEOPLASIA (TUMORS)

**What is NEOPLASIA (TUMORS)?**

*Definition:*

A neoplasm or a tumor is a newly formed tissue, an overgrowth (lat. tumor) that result from the progressive and uncontrolled proliferation of its component cells.

**The ETIOLOGY OF TUMORS**

Some neoplasias originate in preexisting lesions and other on apparently intact tissues. Some have identified, well defined risk factors whereas the majority have unidentified causes. Most probably, the process of tumorogenesis is due to multi-factorial causes, which combine environmental factors with genetic susceptibility. Some neoplasms are also related to veritable tumorigenic inborn chromosomal/genetic alterations (mutations). However, the great majority of neoplasms are apparently caused by the prolonged action of the causative or risk factors during lifetime.

**I. Genetic factors**

The genes involved in tumorogenesis (formation of tumors):

a) Oncogene: normal genes that assure the normal mitosis of a cell — if these genes are over-expressed in a cell by mutations, they facilitates or initiates tumorogenesis (it triggers uncontrolled proliferation of the cells).

b) Anti-oncogene or tumor suppressor genes: normal suppressive genes that usually inhibit the proliferation of cells and induce apoptosis of the harmed cells and which may be deactivated by mutations that may hinder the development of cancer cells.

The activation of the oncogenes or anti-oncogene may be the consequence of:

a) Point mutations — localized changes in the sequence of a gene (e.g. the *ras* gene mutated in 90 % of pancreatic cancers)/

b) Chromosomal translocations (e. g. in the Burkitt lymphoma, the proto-oncogene C-myc is traslocated).

c) Genetic amplification (e. g.: N-myc in neuroblastoma)/

**II. Environmental cancerogenetic factors:**

**A. Radiations.** Following their action on the nucleic acids, the genome may be harmed and may present mutations that may lead to the loss of some normal features (i. e., the loss of contact inhibition) or the development of new ones (i. e., loss of pro-apoptotic genes, so that the new cell will never die - immortal cell).

a) UV-radiation has low energy and low penetration, therefore its potential harmful effect is limited to the body surface, where it may facilitate the appearance of cutaneous malignant melanoma.

b) Ionizing radiations (Rx) have higher energy (and penetration) and may promote tumorogenesis in deeper organs:

— Leukemia.
— Thyroid cancer.
— Squamous carcinoma.

c) Other types of high energy radiations, like those produced during nuclear catastrophes:

— Hiroshima: initially high incidence of blood malignancies in survivors (leukemia).
— Cernobyl: greatly increased incidence of thyroid cancer.

e) X-rays (Roentgen) in medical personnel working in radiology:

— Skin cancer on the surfaces excessively exposed to radiations (usually the hands).

**B. Chemical substances** (in the initial phase it may cause mutations in the cellular genome, and in the proliferation phase it may stimulate the tumoral proliferation):

— Nitrosamine: gastric and colonic carcinoma.
— Aniline: cancer of the urinary bladder.
— Tar substances in the cigarette smoke: lung cancer.
— Aflatoxin: liver cancer.
— Vinyl chloride, asbestosis: pulmonary cancer.

**C. Viruses**

*1. DNA viruses:*

a) Human papilloma virus (HPV):

— The serotype 6 and11 have a low risk for tumor development.
— The serotype 16 and 18 have high risk cervical cancer.

b) Epstein-Barr virus (EBV):

— Burkitt lymphoma.
— Nasopharyngeal carcinoma.

c) Hepatitis B and C viruses — chronic viral hepatitis greatly increases the risk of hepatocarcinoma.

2. RNA-viruses:

— HTLV (the human T-cell leukemia virus) may cause hairy cell leukemia or cutaneous lymphoma with T-cells.

**PRENEOPLASIA**

*Definition:* pre-neoplasia (pre-malignancy) represent a number of anatomo-clinical lesions with high risk of evolution towards malignancy.

*Examples:*

— Hyperplasia of the endometrium.
— Hyperplasia of the mammary glandular epithelium.
— Squamous metaplasia of the bronchus.
— Glandular metaplasia of the esophagus.
— Dysplasia of the colonic mucosa (in ulcerative colitis).
— Cholangitis during primary sclerosing cholangitis.

## CLASSIFICATION OF THE TUMORS

Classification of the tumors is important in the description of the tumoral features, and from both medical and scientific reasons.

**I. The classification of tumors according to the tissue of origin:**

1. Epithelial tumors.
2. Mesenchymal tumors.
3. Mesothelial tumors.
4. Melanocytic tumors.
5. Tumors of the lymphatic system.
6. Tumors of the nervous system.

**II. The classification of tumors according to their evolution**

***A. Benign tumors***

1. Grow slowly.
2. Compress the neighboring tissues.
3. Are well delimited, usually encapsulated.
4. Are rather mobile.
5. Do not metastasize.
6. After surgical excision have not usually relapses.

***B. Malignant tumors***

1. Grow fast.
2. Extend rapidly, infiltrating the neighboring tissues (invasion by destruction).
3. Have poorly defined borders.
4. Usually have limited or no mobility, due to the invasion/adherence to different neighboring structures.
5. Metastasize (form secondary tumors at distant sites).
6. Tend to recur after surgical removal.

***C. Borderline tumors*** share features of both benign and malignant tumors:

— Some times reappear after surgical removal.
— Rarely metastasize.
— E. g. the borderline tumors of the ovary (borderline cyst-adenoma).

**What are METASTASES?**

*Definition:* a metastasis is a secondary tumor that appears in an organ different from the primary tumor, but bearing similar morphological and functional features with the original tumor.

After various intervals of time, the tumor progression make possible detachments of tumor cells from the primary tumor, with their blood dissemination, spreading them throughout the body; the cells will seeds multiple different tissues/organs (homing process); cell proliferation at these sites lead to the occurrence of secondary tumors called metastases; the process of metastasizing depends on numerous complex biological factors such as the ability of cells to survive in inappropriate environment, such as the extracellular matrix, detached from a solid substrate as the blood; usually sites were normal cells rapidly die but because of some acquired mutations the tumor cells resist.

In the case of epithelial cells, the gaining of a metastatic potential requires an epithelial to mesenchymal phenotype transition that includes the loss of epithelial junction proteins (E-cadherin), the acquirement of new enzymes (matrix metalloproteinases MMP-2, MMP-9), of new cell adhesion molecules (to fibronectin) or growth factor receptors.

*The phases of metastasizing process:*

— Subset of cells separate from the bulk of a primary tumor; these are resistant high proliferating etc. cells (with the loss of contact inhibition, loss of E-cadherin).

— These cells cross the extracellular matrix (by the adherence to fibronectin, MMP-s matriceal lyses).

— The cells adhere to a neighboring basal membrane, breach the basal membrane (by the secretion of proteases) and cross it.

— The penetration of the cells into a vascular lumen (by pushing aside the pericytes, smoth muscle cells and endothelial cells).

— The formation of tumor emboli (tumor cells coated with platelets, and thus hidden from immune cells).

— The adherence of the embolus to the endothelium, somewhere where the vascular diameter is less than that of the embolus size (e. g., the lung capillary network, the liver sinusoids).

— The extravasations of the tumor cells in the new location and the formation of new colonies of tumor cells (metastases).

Although a tumor is considered in a metastatic stage only in the presence of macroscopically identifiable metastases, small, microscopic colonies of tumor cells (micro-metastases) exist usually in a large number of cases at the time of the initial detection of the primary tumor.

*Paths used in the process of metastasizing:*

**1. Local invasion:** the growth of the tumor occurs by the invasion of the tissues next to the primary tumor.

**2. The extension of the tumor** along the nerves (the perineural spreading).

**3. The transcelomic way** allows the extension of the tumor through the serous cavities:

— Gastric cancer along the peritoneal cavity to the ovaries.

— Ovarian cancer allover the peritoneum.

— Breast cancer pleural dissemination.

**4. The dissemination through the cerebrospinal fluid** of the CNS tumors to the neuro-spinal axis: rarely — glioblastoma multiforme.

**5. Direct implantation:**

— Cancers of the upper lip to the lower lip.

— The insemination of tumoral cells in the abdominal wall during surgery, through the direct contact of the tumor with the wound.

**6. The lymphatic spreading:**

— More frequently the epithelial malignant tumors (carcinomas).

— Sometimes the tumor emboli may obstruct the lymphatic channels leading to the occurrence of a retrograde lymphedema (e. g. on the skin of the breast in breast carcinoma with lymphatic tumor emboli).

— The first seeded thereafter are the regional lymph nodes (e. g. breast carcinoma axillary lymph nodes).

— The tumor emboli may thereafter enter into the blood system (directly through the blood vessels of the lymph nodes or indirectly through the thoracic lymph duct and cava vein).

**7. The hematogenous spreading**

— More often the mesenchymal malignant neoplasms (sarcomas) — with abundant blood perfusion, and the intra tumoral vessels intimately merged with the tumor cells.

— The invasion of the blood vessels usually occurs at the capillary level or at the venous side (thinner blood vessels, slower blood flow).

— Examples: the gastrointestinal tumors follow the splachnic/portal venous drainage and metastasize into the liver, and the tumors of the organs tributary to the vena cava metastasize in the lungs.

*The morphology of the metastases:*

a) Macroscopic features:

— Nodular lesions, well circumscribed, single or more frequently multiple, of various sizes, ranging from microscopic sizes of a few millimeters (micro-metastases) up to several centimeters; the metastases have the same color and consistency as the primary tumor.

b) Microscopic features:

— Have the same histological pattern as the original tumor.

**What are the STAGING SYTEM AND THE GRADING SYSTEM OF THE TUMORS?**

**1. Staging** is the anatomo-clinical term that offers indicators about the size and the extension of the tumor.

The staging of the tumor depends on:

— The location of the primary tumor.

— The characteristics of the local invasion.

— The extension through the lymphatic nodes.

— The presence or absence of secondary tumors (metastases).

**The TNM system** represents a standard schematic method used to stage the tumors, in which:

— T ($T_0$, T i-$T_4$, $T_x$) gives data about the size and local extension of a primary tumor.

— N ($N_0$, $N_1$-$N_4$, $N_x$) gives information about the presence of the metastatic involvement of the lymph nodes.

— M ($M_0$, M 1 $M_x$) gives information about the presence of metastases.

The TNM system is used in every organ and allows the quantification and comparison of tumors of similar type in different patients. On it depends usually

the choice of a treatment and the prognosis of the cancer patient. For example, early local tumors, of stage I (T1N0M0) may safely be treated with more conservative methods (only limited surgical resections or chemo- or radiotherapy alone) whereas the advanced stages (T2-4) sometimes call for more complex, combined therapies (combinations of radical, extended resections, chemotherapy and radiotherapy).

The **grading** system of tumors refers to the histological features of the tumor cells such as differentiation (their resemblance to the tissue of origin) or anaplasia that means the lack of their differentiation. The grading of the tumor gives data about:

— The modifications of the affected tissue architecture.

— The modifications of the cytologic pattern of the tumor cells:

a) The differentiation of tumor cells as compared to the original cells/tissues.

b) The variation in shape and in size of the tumor cells (cellular polymorphism).

c) The number of the mitotic figures as an indicator of the cellular proliferation rate (a higher mitotic index means a more malignant tumor).

The grading system (G) vary from GI to GIV; in GI the tumor is the most differentiated and the least malignant, in GIV the tumor being most undifferentiated that is with the highest degree of malignancy, the GII and GIII representing intermediate forms.

**What are the TUMOR MARKERS?**

Tumor markers are used to diagnose and monitor the evolution of the tumors. Tumor markers may be present in the tumor cells or released into the circulation.

1. **Tissue markers** give information about the type of the tumor and help identify their histologic type; these may be revealed by immunohistochemistry, which use antibody-antigen reaction to identify tissue specific antigens (IHC). The different histologic types of tumors are sensitive in various degrees to chemotherapy or radiotherapy some of them being resistant.

2. **Humoral markers** — some substances secreted and released by the tumors are detected in the blood; these substances may be very useful in the tumors diagnosis and for monitoring the tumor evolution.

— Alphal-fetoprotein (AFP) is an enzyme normally found in small quantities in blood, but greatly increased during the development of certain tumors (liver, colon, testicle); because it also increases in non-tumoral diseases (hemorrhagic recto- colitis, hepatic injuries etc), it has low specificity in the diagnosis, but with great value in monitoring the treatment; thus, a patient with an increased AFP level should de suspected of malignancy and investigated closely; if the AFP heavily decreases after the surgical removal of the tumor mass it means whole tumor removal and good prognosis and if the marker increases again it means relapses or metastases. If the marker remain at raised levels it means metastases or other associated pathology.

— Carcinoembryonic antigen or CEA — increases in intestinal, pancreas, breast and ovarian cancer.

— CA19-9 (increases in gastrointestinal adenocarcinoma).

— PSA (prostate specific antigen) greatly increases in prostatic adenocarcinoma; more modest increases however are seen in benign prostatic hyperplasia or in prostatitis.

**What are the SECONDARY TUMORAL EFFECTS?**

***I. Local effects***

1. Mechanical pressure or obstructions:

— Meningioma — may cause cerebral atrophy through compression or generate intra-cranial hypertension disturbing the cerebrospinal fluid drainage.

— Tumors of the digestive tract may grow and obstruct the gastro-intestinal lumen (acute or sub-acute intestinal obstruction).

2. Tissue destruction:

— Tumors of bones or bone metastases erode the bones and weaken its mechanical resistance, leading to fractures.

3. Hemorrhage:

— Pulmonary carcinoma may erode the vessels and generate hemoptysis.

— Gastric carcinoma may erode the vessels of the stomach and lead to upper digestive bleeding (hematemesis, melena).

4. Inflammations: ischemia with necrosis may appear frequently secondarily infected (especially if there is a communication with the exterior - intestines, lung).

***II. Systemic effects***

1. Weight loss (cachexia):

— Anorexia.

— Mal-absorption.

— Substances secreted by the tumor in the blood which change the normal metabolism of the body: TNF (tumor necrosis factor or cachectin).

2. Hematologic alterations:

— Anemia due to micro-hemorrhages from the tumor and medullar depression by substances released by the tumor.

— Thrombocytopenia due to micro-hemorrhages.

— Hyper-coagulation due to substances secreted by the tumor.

3. Neuro-muscular manifestations:

— Neuropathies.

— Myopathy.

***Paraneoplasic syndromes*** are the indirect effects that appear a time after a tumor appearance or his metastasis and may be caused by the secretion of certain active proteins, polypeptides or hormones, by the tumor cells.

— Migratory thrombo-phlebitis by hyper-coagulation state.

**What are the GENERAL MACROSCOPICAL FEATURES OF TUMORS?**

**I. The shape of the tumors**

1. Nodular:

— In the thickness of the organs: round, oval, lobulated.

— On the surfaces: curved or with an umbilical aspect.

2. Vegetative exophytic overgrowth on a surface

a) Sessile: round, with a large base.

b) Vegetating:

— Pediculated:

•Polyp — a narrow and long stalk, and a nodule at his free, or intra-luminal extremity.

• Papilloma: with a larger base, short and large stalk and a villous surface — Cauliflower-shaped: large, branched with irregular aspect.

3. Ulcerative: loss of tissue from the tumor surface, due to the partial necrosis of the tumor, which will be directly eliminated on the body surface or in a lumina.

4. Infiltrative (scirrhous): the tumor penetrates diffusely into the organ usually hardening and thickening the organ.

5. Cystic or cystic-papillary (the cyst walls covered by tumor cells which overgrowth interiorly as finger-like projections).

**II. The color of tumors**

1. Benign tumors resemble sometimes the tissues of origin:

—Myoma: red.

— Lipoma: yellow.

— Osteoma: white.

2. Malignant tumors have sometimes specific colors:

— Carcinoma: grayish-white.

— Sarcoma: pink, rose.

— Melanoma: blackish-brown.

**III. The consistency of the tumors**

1. Benign tumors have the consistency of the tissue of origin: lipoma — soft, osteoma — hard, etc.

2. Malignant tumors: have specific consistency: carcinoma — firm, sarcoma — soft/rubbery.

**IV. The size of the tumors** varies from a few millimeters (pituitary tumors) up to a few cm (ovary tumors, lipoma etc).

**V. The number of tumors**

— Usually solitary.

— They can also be multiple: polyposis, papillomatosis.

**What are the MICROSCOPIC FEATURES OF THE TUMORS?**

**I. The parenchyma** is the cellular, truly malignant component of the tumor, with various degrees of differentiation or resemblance with the cells of the tissue of origin:

a) Benign tumor cells — are very well differentiated, i.e. they resemble almost perfectly with their source.

b) Malignant tumor cells — present variable degrees of resemblance with the tissue of origin, so they may be well, moderately or weakly differentiated (they resemble slightly to the original tissue) up to undifferentiated tissues (they do not resemble the original cells — that is very anaplastic tumors). The malignant anaplastic tumors present many atypical cellular and architectural features.

The cellular atypicalities are:

a) Cellular polymorphism: variations in shape, size and color of the tumoral cells.

b) Nuclear modifications:

— Large, polymorph, irregular nuclei.

— Positive nuclear/cytoplasm ratio (large nuclei, little cytoplasm).

— Intensely stained nuclei (hyperchromatic).

— Large nucleoli.

— Frequent mitoses, often atypical.

The architectural atypicalities are:

— anaplastic malignant tumors present the lack of the normal histologic architecture, the malignant tumor cells being in groups or diffusely dispersed in the tumor.

**II. The stroma** is the interstitial, vascular and connective component of the tumor, which provides nutritional support and a scaffold for the tumor cells:

— The stromal interstitium contains connective tissue, and various types of inflammatory cells.

— The blood vessels feeding the tumor that vary largely in amount; it depend on the tumor type and the affected region's blood supply: in a tumor may be areas with abundant neo-vascularization with many sprouting capillaries, that are always more abundant at the periphery a from where the new vessels originate and areas with low neoangiogenesis and subsequent ischemic or even necrotic changes; the newly formed capillaries have abnormal structure that is a thin highly permeable basal membrane, that explaining their rupture and intra-tumoral hemorrhage.

— The ability of a tumor to generate neovascularization dictates the rapidity of its growth and the potential of tumor cells hematogenous dissemination.

**III. The stroma-parenchyma relationship** depends mostly on the tumor cells type:

— in the malignant epithelial tumors, the malignant cells are arranged in clusters, with various amounts of stroma between these cell clusters.

— in the mesenchymal malignant tumors, the tumor cells are not clustered, a fine stroma surrounding every separate cell.

**THE CLASSIFICATION OF THE EPITHELIAL TUMORS**

**I. Benign epithelial tumors:**

1. Papilloma.
2. Polyp.
3. Adenoma.

**II. Malignant epithelial tumors: carcinoma**

1. Squamous carcinoma:

— spinocellular (epidermoid).

— basocellular.

2. Adeno-carcinoma.

3. Undifferentiated carcinoma.

**What is PAPILLOMA?**

*Definition:* the papilloma is the benign tumor of the squamous epithelium and urothelium.

*Localization:*

***1. Squamous epithelium***

a) Skin.

b) Mucous membranes:

— Oral cavity, esophagus, anal region.

— Nasopharyngeal region, larynx.

— Vagina, exo-cervix, the foreskin of the penis.

***2. Urothelium:***

— Urinary bladder, urethra.

*Number:*

— Unique: papilloma.

— Multiple: papillomatosis.

*Macroscopic features:*

— Shape: vegetating with a large base and with many digitiform excrescences.

— Grayish-white color.

— Mobile on the subjacent layers.

*Microscopic features:*

— Connective-vascular axes (stroma).

— The squamous epithelium or urothelium arranged on the surface of each connective-vascular axes.

*Complications:*

— Areas of the tumor may become necrotic that induce ulcerations and hemorrhages and favors secondary infection.

**Particular forms of papilloma:**

— Acuminate condyloma (viral) or flat condyloma (syphilis).

— Verruca.

— Laryngeal papillomatosis (multiple papillomas).

— Urinary bladder papilloma.

**Evolution:**

1. Benign.

2. Malignant transformation.

*a) Urinary bladder papilloma (urothelial papilloma):*

— In 95 % cases cured by surgical excision.

— If it is not treated a long period of time — approximately 50 % may transform in urothelial carcinoma.

— the cancerogenesis is produced by the increase of the number of tumor cells layers of the urothelium that covers the fibro-vascular stalk (over 7 layers), disorder in their architecture, atypicalities of the malignant urothelial cells.

*b) Laryngeal papillomatosis (squamous papillomas)* — may produce respiratory obstruction:

— Cancerogenesis by irradiation (irradiation became not recommended in the treatment of laryngeal papillomatosis in spite of his good response).

**THE POLYP**

*Definition:* the polyp is an abnormal tissue overgrowth affecting single-layer epithelial mucous membranes.

Polyp is a macroscopic description of a lesion which affects always single layer epithelia, and looks as a lesion that protrudes into a lumen (may contain histologically different types of lesions).

*Localization:*

— On single-layer columnar epithelia; polyps are commonly found in the colon, stomach, uterus but may occur in the entire body on all covering mucosal membranes (nasal cavity, small intestine).

*Number:*

— The polyp may be isolated (unique) or multiple (polyposis).

*Macroscopic features:*

— Sessile: soft round nodules on the surface of a mucous membrane

— Pedicular: if the polyp has a narrow elongated pedicle, with which attaches to the mucosal surface, and a nodular overgrowth at his free extremity

*Microscopic pattern:*

— Benign tissues formed by a central fibro-vascular stroma covered by a transformed benign mucosa

Types of polyps by the type of the mucous membrane transformation:

— Adenomatous.

— Hyperplasic.

— Fibroepithelial.

— inflammatory.

— Hamartomatous.

— Lymphoid.

— Mesenchymal.

*Evolution:* the polyps may have usually uncomplicated, benign evolution or relatively minor complications (torsion, luminal obstruction, ulceration, hemorrhage); however, the covering epithelium may also undergo malignant transformation (e.g. the adenomatous polyps).

**THE ADENOMA**

*Definition:* adenoma is a benign tumor (neoplasia) of the glandular epithelia.

*Localization:*

a) In parenchymatous organs:

— Endocrine glands: the thyroid, parathyroid, hypophysis, the adrenal gland, endocrine pancreas.

— Exocrine glands: salivary glands, exocrine pancreas, the peribronchial glands.

— Organs as: the liver, kidney, the mammary gland, ovary.

b) On the mucous membranes:

— The digestive tract.

— The uterine mucosa (endometrial).

*Macroscopic features:*

1. In parenchymatous organs:

— Shape:

— nodular, well circumscribed, frequently encapsulated by the stroma of the neighboring atrophic tissue (the stroma being most resistant to compression) that helps to enucleate the tumor.

— Cystic, cystico- papillary.

— Number: unique or multiple.

— Size: variable from few mm (hypophisis) to several centimeters (liver, kidneys).

2. On the mucous membranes:

— It presents as a polyp (adenomatous polyp), with a pedicle, mushroom shaped, or without pedicle as a sessile with a large base insertion cauliflower shaped (villous) overgrowth.

— Flat: a slightly elevated plaque with a central lower area.

*Microscopic features:*

3. In the parenchymatous organs:

— Acinar (glandular), trabecular, follicular, solid, cystic, cystic-papillary, mixed (fibroadenoma).

4. On the mucosal surfaces: example: the polyps of the colon:

— Tubular adenomas (polyps) have a glandular structure (tube-like glands as those of the colonic crypts) and very low risk of malignant transformation.

— Villous adenomas (sessile) with papillary excrescences (outgrowths) with a villous architecture resembling the small intestinal villi (finger-like projections), with a high risk of malignant transformation.

— Tubulo-villous adenoma (the risk of malignancy increases proportionally with the villous component of the tumor).

*The malignant transformation:*

— The epithelium progressive dysplastic features: the cells with large hyperchromatic polymorph nuclei, low mucus secretion, high number of mitosis, mitosis.

— Dysplasia is evaluated according to the cells atypia in to two grades: low degree dysplasia and high degree dysplasia.

**THE CARCINOMA**

*Definition:* carcinomas are malignant tumors arising in squamous, urothelial or glandular epithelia.

*Age:*

— Most frequently, the carcinomas appear in people over 50 years but some may also appear at young adults or in children: hepatocarcinoma, rhino-pharyngeal, thyroid carcinoma.

*Gender:* there are some carcinomas that show a clear gender-dependent distribution (pancreas, pulmonary, laryngeal carcinoma in men, mammary and gallbladder carcinoma in women) but some have equal distribution among genders.

*Macroscopic features:*

Color: most of the carcinomas have a grayish-white color because of the high stromal fibro-vascular tissue content, but there are some exceptions such as hepatocarcinoma (green because of the persistent bile secretion of the malignant hepatocytes), renal cell carcinoma (yellow because of the cytoplasmic high lipid content of cancer cells), choriocarcinoma (red, because of a high vascularization and hemorrhages). Consistency: usually firm because of the fibro-vascular stroma content, but some exceptions exist as the mucinous carcinoma of the stomach which is gelatinous.

*Shape:*

— Carcinomas developed on surfaces: exophytic (vegetative), ulcerative, infiltrative (scirrhus), ulcero-infiltrative.

— In the parenchymatous organs: nodular (irregular borders, with fine or broad infiltrative tumor projections in the neighboring tissues).

*Number:* unique, rarely multiple.

*Dimensions:* variable, from millimeters to several centimeters.

*Secondary changes,* which sometimes help the differential diagnosis with a benign tumor:

— Hemorrhages, necroses, calcifications.

*Microscopic features:*

*Tumor cells:*

— Arranged in clusters, islet or chains (trabecular).

— With atypical sizes, shapes, colors.

— Typical and atypical numerous mitosis.

Stroma:

— Connective-vascular tissues.

*Grading* — based on the tumor cells patterns:

G1: well differentiated G2: moderately differentiated G3: poorly (low) differentiated G4: undifferentiated *6.*

*Extension*

— *Locally:* neighboring tissues invasion — disorderly or along some cleavage structures.

— *Tumor spreading* at distant sites, giving birth to distant metastases (they loose the connection with the primary tumors): especially through the lymphatic pathway into the lymph nodes, but also possible through the blood, or trans-celomically in distant organs (mammary carcinoma to the pleura, ovarian carcinoma in the peritoneum, gastric carcinoma in the ovaries).

**THE BASAL CELL CARCINOMA**

*Definition:* basal cell carcinoma is a carcinoma that originates in the cells of the basal layer of the skin or of the hair follicle (pilo-sebaceous units); it is the most frequent skin cancer.

*Localization:*

— Exclusively on the skin, in the regions exposed to the sun, particularly on the face, ears and scalp.

*Favoring factors:*

— Prolonged overexposure to the sun (farmers).

— Old age.

— Skin type (blonds, with low melaninin protective content in the skin).

*Macroscopically*

a) Nodular-ulcerative basal cell carcinoma: a nodule appears first, that subsequently present central necrosis and gets an ulcerative pattern ("ulcus rodens").

b) Pigmented basal cell carcinoma: brownish (it may arise confusion with melanoma).

c) Sclerosing basal cell carcinoma: hard, poorly defined, yellowish plaque, slightly depressed (confusion with a scar).

d) Superficial basal cell carcinoma: erythematous, desquamative spot, which grows slowly (confusion with eczema); the microscopic extension of the tumor usually overpass the visible macroscopic borders favoring relapses after incomplete excisions.

e) Fibro-epithelial basal cell carcinoma: nodular pediculate shape.

*Microscopically:*

a) Solid basal cell carcinoma (without differentiation):

— Clusters of tumor cells: elongated cylindrical cells, with large, hyperchromatic nuclei and reduced cytoplasm, arranged in palisade at the periphery of each cluster (perpendicular on the border of the cluster and pointing the centre of the cluster) and disposed in a disorderly fashion inside the cluster.

b) Basal cell cc. with atypical differentiation:

— Keratotic — with squamous differentiation and keratin synthesis (probably as the hair follicle keratin synthesis).

— Adenoid — cells arranged around a lumen forming pseudo-glands.

— Pigmented basal cell carcinoma: with melanic pigment.

— Superficial basal cell carcinoma (proliferates in the superficial dermis, next under the epidermis).

— Fibrotic basal cell carcinoma (morphea).

*Evolution*

— Infiltration and destruction of the neighboring tissue (the eye, the orbit, the skull).

— Reappears after incomplete excision.

Does NOT metastasize (exceptionally rare!).

**THE SQUAMOUS CELL CARCINOMA (SPINOCELLULAR, EPIDERMOID)**

*Definition:* the malignant tumor of the squamous epithelia, that is of the epidermis, of the squamous mucosa of many body cavitary/tubular organs, and of the squamous metaplastic epithelia.

*Localization:*

a) On the primary squamous epithelium:

— Skin (mostly on the face, ears, and hands).

— Lips, tongue, esophagus, anal canal.

— Nasal cavity, larynx.

— Vagina, exocervix or penis gland.

b) On the squamous metaplastic epithelia:

— Squamous metaplasia on cylindrical epithelia (bronchia, endocervix).

— Squamous metaplasia on urothelium (urinary bladder).

*Histogenesis:* by dysplasia or squamous intra-epithelial neoplasia as pre-neoplasic lesions:

1) Cytological diagnosis (cellular modifications):

— Hyperchromatic nuclei.

— High nucleo-cytoplasmic ratio.

— Atypical size and shape.

— Abnormal mitosis.

2) Histological diagnosis (structural modifications):

— Losing the polarity of the cells or their normal inter-cellular connections.

— The loss of the normal stratification.

3) The classification of the dysplasia:

— Slight dysplasia: the dysplastic cells occupy one third of the entire thickness of the epithelia that is the inferior layers of the epithelium (grade I dysplasia or low squamous intraepithelial lesion LSIL).

— Moderate dysplasia up to 2/3 of the epithelium (grade II dysplasia).

— Severe dysplasia: more than 2/3 of the epithelium (grade III dysplasia or high squamous intraepithelial lesion HSIL).

— Carcinoma in situ: the dysplastic cells are spread in the entire thickness of the epithelium but do not pass the basal membrane resting in situ (in a normal place) (it is also a high squamous intraepithelial lesion HSIL).

Terms used for the uterine cervix:

— CIN: cervical intra-epithelial neoplasia CIN I, II, III and carcinoma in situ CIS.

— LSIL = CIN I or CIN II, and HSIL = CIN III or CIS).

4) Particular form of dysplastic lesions:

— Bowen disease: macroscopically appears as irregular, erythematous spot on the skin; microscopically there is an in situ carcinoma.

— De Queirat erythroplasia: macroscopically, erythematous lesions on the foreskin of the penis while microscopy reveals an in situ carcinoma.

*Macroscopic pattern of squamous invasive carcinoma:*

— Exophytic (vegetative), ulcerative, infiltrative shape (scirrhus).

*Microscopic pattern of squamous invasive carcinoma:*

— The tumor cells proliferate beyond the basal membrane in the dermis or in the chorion of the squamous mucosa.

— As clusters of squamous cells, with connective-vascular stroma between the clusters.

*Microscopic grading of invasive squamous cell carcinoma:*

• Well differentiated carcinoma (G1): clusters of tumor cells similar to those seen in stratum spinosum, that is large, polygonal cells, with eosinophylic cytoplasm, reduced nuclear atypicalities, relatively rare mitoses; the tumor cells may produce keratin that accumulates in the centre of the cluster as keratin "pearls" (the keratin is dyskeratotic being in other place than normal and also orthokeratotic if is without nuclei or parakeratotic if contains nuclei).

• Medium differentiated squamous cell carcinoma (G2): with more mitoses and atypia and fewer keratin pearls.

• Slightly differentiated squamous cell carcinoma (G3): many mitoses and atypia, rare keratin droplets.

• Undifferentiated squamous cell carcinoma (G4): with lots of mitoses and atypia, no keratin droplets, many isolated tumors cell.

*Specific variants of invasive squamous cell carcinoma:*

— Squamous cell carcinoma with fusiform cells or sarcomatoid carcinoma (it must be differentiated from a sarcoma because of differences in their treatment).

*Evolution:*

— Invasion and local destruction.

— Distant metastasis by lymphatic pathways initially or late hematogenic dissemination.

**THE ADENOCARCINOMA**

*Definition:* adenocarcinoma is the malignant tumor of the glandular, usually columnar, epithelia.

*Localization*

— Salivary glands, pancreas, liver.

— Mammary glands, ovary, prostate.

— Endocrine glands: the thyroid, adrenal gland, pituitary gland.

— The mucosa of the digestive tract: stomach, intestine.

— Respiratory mucous membrane: bronchi.

— Genital mucous membranes: endometrium, endocervix.

*Histogenesis — Premalignant lesions:*

— Premalignancies are lesions with morphological changes of the involved cells, that means cellular atypia (of size, form, color of the cells/nuclei, and their architecture), which reveals chromosomal alterations that may further trigger a malignant transformation.

— These may occur on mucosal surfaces (e. g. gastric dysplasia) or in parenchymatous organs (e.g. atypical endometrial hyperplasia).

*Macroscopic features:*

— In parenchymatous organs, adenocarcinoma may appear nodular, cystic or cystic-papillary.

— On various mucous surfaces, the adenocarcinoma may be: vegetative (polypoid, cauliflower-like), ulcerative or infiltrative (scirrhous).

*Microscopic variants:*

*a) typical adenocarcinoma:* tumoral glands with vascular and connective stroma between them.

*b) variants of adenocarcinoma:*

— Trabecular.

—Acinar.

— Tubular.

— Papillar.

— Cribriform.

— Mucous (with lakes of mucus, mucus secreted initially inside the glands and next exteriorized in the stroma because of the large quantities secreted or with "signet ring" cells, in which the cells contain mucus that compresses the nucleus against the cell membrane).

— Scirrhus (isolated PAS-positive tumoral cells, in a rich connective stroma).

— Adenosquamous (combination of squamous carcinoma and adenocarcinoma).

*Evolution*

— Invasion and local destruction.

— Systemic dissemination (metastasis) via the lymphatic, hematogenic or transcelomic pathway (Krukenberg tumor: bilateral ovarian metastases from a gastric adenocarcinoma).

**THE UNDIFFERENTIATED CARCINOMA**

*Definition:* undifferentiated carcinoma is a malignant type of tumor in which the tumor epithelial cells do not have any histological feature resembling the tissue of origin.

*Variants:*

— With small round cells; it must be differentiated from a malignant lymphoma or an undifferentiated sarcoma.

— With large monstrous cells: it must be differentiated from a malignant melanoma, undifferentiated sarcoma.

*Differentiation dependent tumor markers* — are different cell products (mostly proteins) produced by the different types of epithelial cells, that may

help to detect the original transformed cells or the phenotype of the tumor; these tumor markers may be retained in the tumor cells or released into the systemic circulation; these markers are useful for (1) screening of healthy population or high risk population for the presence of a specific cancer; (2) making a diagnosis of cancer or of a specific type of cancer; (3) determining the prognosis of a patient; (4) monitoring the course of the disease, remissions, relapses, while receiving surgery, radiation, or chemotherapy Several examples of tumor histological markers are given below:

— Cytokeratins — all epithelial cells.

— Muc 1 — marks the mucus secreting cells.

— Vimentin — helps to differentiate the epithelial undifferentiated tumors which are vimentin negative from the mesenchymal vimentin positive undifferentiated tumors.

**What are the MESENCHYMAL TUMORS?**

*Definition:* mesenchymal tumors are also named *soft tissue tumors* (the mesenchymal tissues are conventionally considered the soft tissue of the organisms, in spite of that they include the bones); they are tumors originating in the mesenchymal stem cells that is the primitive, undifferentiated mesenchymal cells having the capacity to transform and further differentiate into several types of mesenchymal tissues.

Mesenchymal tissues:

— Fibrous connective tissue.

— Adipose tissue.

— The skeletal striated muscle, the myocardium, the soft muscles.

— The blood vessels.

— Peripheral nerves.

— Cartilaginous tissue.

— Osseous, etc.

*Mesenchymal tumor terminology*

— the name of the tumor is obtained by adding the suffix "oma" to the name of the tissue in case of benign tumors (e. g., fibroma, lipoma, osteoma) or the suffix "sarcoma" in case of malignant tumors (e. g. fibrosarcoma, liposarcoma, osteosarcoma etc.

**Which are the GENERAL FEATURES OF THE MESENCHYMAL TUMORS?**

*1. The age of occurrence:*

— The benign tumors (B) occur at various ages (some are congenital: hemangioma).

— Malignant tumors (M): mostly in children (ex: rhabdomyosarcoma), teenagers (ex. synovial sarcoma) or in people over 40 years of age (ex. liposarcoma).

*2. Rate of growth:*

— Benign: slow growth, with periods of growth arrest or of rapid growth.

— Malignant: grows rapidly (with rare exceptions).

*3. Localization:*

— Benign: anywhere in the mesenchymal tissue, most often close to the body surface (skin), above the superficial muscular fascia (1 % may exceptionally deep, in the skeletal muscle).

— Malignant: especially in the limbs because is formed mostly by mesenchymal tissue (50–85 %), thoracic or abdominal walls (20 %), retroperitoneal and mediastinal (15 %), head-neck (5–10 %); the majority are situated deeply, under the superficial muscular fascia.

*4. Size:*

— Benign tumors: less than 5 cm (95 %).

— Malignant tumors: over 5 cm (50–90 %).

*5. Delimitation:*

— Benign: well delimitated, encapsulated (exceptions: fibromatosis which may be infiltrating).

— Malignant: infiltrative (some with a microscopically infiltrated capsule).

*6. Shape:*

— Benign: nodular.

— Malignant: nodular.

*7. Color:*

— Benign tumors — maintain the same aspect as the tissue of origin.

— Malignant: pink (as the fresh fish meat).

*8. Secondary modifications:*

— Benign: usually absent, rarely necrosis and hemorrhages when the tumor grows slightly faster (ex. leiomyoma).

— Malignant: frequent necroses, hemorrhages, areas of cystic degeneration, especially in the large tumors.

*9. Microscopic features:*

— Benign tumors — maintain the pattern of the original tissue.

— Malignant tumors display very fine, loose stroma, that surrounds every cell separately, the nutrition of the tumors being supported by an abundant vascular network, sometimes coated directly by the tumor cells.

**What are SARCOMAS?**

*Definition:* sarcomas are the malignant tumors of mesenchymal tissues.

*Incidence:* rare, 1 % of all malignant tumors.

*Etiology:*

— Ionizing radiations: fibrosarcoma.

— Vinyl-chloride: liver angiosarcoma.

— Herpes virus: Kaposi sarcoma in AIDS patients.

— Chronic lymphedema: angiosarcoma.

— Hereditary predisposition: von Reklinghausen neurofibromatosis.

*Macroscopic features:*

— Pinkish or the characteristic color and of the malignant tissue.

*Microscopic feature:*

— The cells can be: fusiform, round, giant, with multi-lobed nuclei or multinuclear, polymorphous.

— The cells can be: differentiated (lyposarcoma, fibrosarcoma, etc) or undifferentiated (round cells, fusiform cells, polymorphic).

— The architecture of the cells can be: fasciculate, palisades forming, storiform, or alveolar.

— The stroma is absent or very fine, present around each cell.

— The nutrition of the tumor is done by vascular slits lined by tumoral cells.

— It can have secondary modifications: hemorrhages, necroses, pseudo-cystic degenerations.

*The diagnosis of sarcomas*

— Most frequently the diagnosis is made at light microscopy.

— Immunohistochemistry for various cell differentiation markers is also used: vimentin (for all types of mesenchymal cells), CD31 (for endothelial cells), desmin and actin (for muscular tissues).

*Sarcomas are graded according to:*

— Cellular density and polymorphism.

— Mitotic activity.

— The areas of necrosis in the tumor.

*The expansion of the tumor is by infiltration along:*

— The fascial planes.

— Nerve tracts and filaments.

— Tendinous sheaths.

*The metastasis occurs by:*

— Blood dissemination (frequently, due to the abundant vascularization of the tumors).

— Lymphatic spread (rare).

*Evolution*

— It remits usually after local excision.

— Metastasis in distant organs occurs especially in the lungs, liver and bones.

**THE TUMORS AND PSEUDOTUMORS OF THE FIBROUS TISSUE**

*Classification:*

**1. Fibrous reactive lesions:**

a) keloid scar;

b) nodular fascitis;

**2. Fibrous locally aggressive lesions:**

a) fibromatoses.

**3. Real fibrous tumors:**

a) fibroma;

b) fibrosarcoma.

**4. Fibrohistiocytic tumors:**

a) benign fibrous histiocytoma;

b) malignant fibrous histiocytoma.

**What are FIBROUS REACTIVE LESIONS?**

*Definition:* fibrous reactive lesions are reactive proliferations of the fibroblasts and myofibroblasts.

**1. The keloid scar**

— It appears in young people at the sites of the healing wounds of the skin, as the result of the excessive collagen deposition in a scar by genetically abnormal fibroblasts (genetic predisposition).

— It extends excessively, the scar passing over the limits of the initial lesion (a simple hypertrophic scar do not extend beyond the original wound).

— Macroscopy: elevated lesion, reddish, firm, rubbery.

— Microscopy: hyaline fibrous tissue.

— Evolution: benign, usually painless; after surgical excision the resultant scar will be also excessive.

**2. Nodular fascitis**

— Clinical signs: in young adults, a small, painful, first rapidly growing nodule (the phase of rapid growth), which at one moment stop his growth (the latent phase); it mostly occurs at the level of the forearm (50 %), chest, head, and neck.

— Macroscopically: 1–3 cm large, subcutaneous, or sometimes deeper nodules.

— Microscopically: in the phase of rapid growth — proliferating fibroblasts and myofibroblasts with numerous mitoses and atypia, embedded in a richly vascularized mixoid stroma, containing lymphocytes. In the "plateau" phase, the lesion evolves towards fibro-hyalinization.

— The evolution is benign but the macroscopic and the microscopic features may generate suspicion, needing differential diagnosis with a sarcoma, the clinical features (age, site, start and way of growth) being very helpful for the diagnosis.

**What is FIBROMATOSIS?**

*Definition:* fibromatosis is a locally aggressive lesion which can infiltrate and recidivate but which never metastasize.

*Clinically:* the growth of the infiltrative lesion is destructive and reappears locally after incomplete surgical excision.

*Microscopically:* well differentiated myofibroblasts without any histological features of malignancy (without atypia or mitoses).

*Variants of fibromatosis:*

***1. Superficial fibromatosis***

*a) Palmar fibromatosis* (Dupuytren's fibromatosis):

— In adult men, often having Nordic ancestry, the frequency increasing with age.

— It begins as a tender lump in the palm; in time, the pain disappears but fibrous bands develop, bending the fingers toward the palm.

— It tends to recur after excision.

*b) Plantar fibromatosis:*

— In children, teenagers – frequently.

— At the level of the sole of the foot.

— It does not produce any contracture.

— It reappears after excision.

*c) Penian fibromatosis* (Peyronie disease):

— It affects the Buck (dorsal) fascia.

— The penis becomes stiffened and curved.

***2. Profound, deep fibromatosis (desmoids)***

— Macroscopy of the desmoids: large nodules, over 5 cm, pale, with whirlpools on the section.

— Microscopy of the desmoid tumors: fibroblasts and myofibroblasts arranged in fascicles, with a fine collagen stroma.

*a) Abdominal fibromatosis:*

— It affects the musculo-aponevrotic structures of the abdominal wall.

— On abdominal muscles, on the scars following caesarian section.

*b) Intra-abdominal fibromatosis:*

— It affects the root of the mesentery or the pelvis wall.

— Frequently is associated with Gardner syndrome.

*c) Extra-abdominal fibromatosis:*

— On the skeletal muscles of the shoulder, the thoracic or abdominal walls, the thigh.

**What are the REAL FIBROUS TUMORS?**

***1. The fibroma:***

— It is the benign tumor of the fibrous tissue.

— Macroscopy: 2–3 cm large nodules, grayish-white.

— Microscopy: mature fibrocytes, fibroblasts, myofibroblasts, collagen fibers.

*Variants of fibroma:*

— Nuchal fibroma mostly occurs in people suffering of diabetes mellitus, subcutaneously on the nape.

— The fibroma of the tendon sheath (the nodule is attached to the finger tendons).

— The solitary fibroma of the pleura, gastric fibroma, ovarian fibroma, osseous fibroma.

— The aponevrotic calcified fibroma occurs mostly in children, in the palms, as small, infiltrative nodules that may reappear after excision but do not metastasize.

— The fibro-lipoma, the fibro- leiomyoma, the fibro-adenoma.

— The elasto-fibroma.

***2. The Fibrosarcoma:***

— It is the malignant tumor originating in fibroblasts (the cells of the connective tissue); therefore, the tumors contain a high amount of collagen fibers; it may occur in different tissues containing fibroblasts such as joints, vessels, bone, muscles.

— Rare, 5–10 % of sarcomas and it appears mostly in adults, sometimes 10–15 years after a radiation therapy.

*Macroscopy:* grayish nodule, lobular, over 10 cm, with necrosis and hemorrhages.

*Microscopy:* the immature fibroblast takes an interlacing, herringbone-like pattern; the grading is done according to the cell density, mitoses.

*Variants:*

— The fibrosarcoma in adults (described above).

— The fibrosarcoma in infants: in children under 2 years old or at birth (congenital), at the distal limbs; the surgical treatment has a favorable prognosis.

— Inflammatory fibrosarcoma (with plasmocyte infiltration) which occurs intra-abdominally in young people and has a poor prognosis.

**What are FIBROUS HISTIOCYTOMAS?**

*Definition:* heterogeneous group of tumors arising from cells resembling fibroblasts (fusiform, elongated cells and nuclei) and histiocytes (macrophage specific for the connective fibrous tissue, with oval, pale cells, with round, pale nuclei); the proportion of the diverse components and the various microscopic patterns led to numerous histopathologic forms.

***1. Benign fibrous histiocytoma*** (dermato-fibroma or sclerosant hemangioma). Occurs in young adults.

*Macroscopy:* the tumor appears as a solitary, brownish-red, firm nodule on the skin of the extremities, millimeters to centimeters in size, which grows slowly.

*Microscopy:*

— Fusiform cells (fibroblasts).

— Histiocytes of various types: xanthomatous (with cholesterol), siderophage (with hemosiderin), Touton giant multinuclear cells.

— Chronic inflammatory cells (lymphocytes), red blood cells.

*Variants:*

— juvenile xanthogranuloma;

— reticulohistiocytoma.

***2. Dermato-fibrosarcoma protuberance (DFSP)***

— Lesions with intermediate malignancy (at the border between benign and malignant tumors).

*Clinically:* this type of tumors appears in young adults, on the skin of the torso, the inguinal area, lower limbs.

*Macroscopically:*

— Small nodules, plates, nodular agglomeration, or large pedicular masses.

*Microscopically:*

— Storiform structure.

— Fascicles of fusiform cells (fibroblasts) which infiltrate the subcutaneous tissues.

*Evolution:*

— It frequently recurs after surgical excision (50 %) but very rarely metastasize (5 %).

*Variants of DFSP:*

— Pigmentary DFSP.

— Giant cellular fibroblastoma.

**Other tumors with limited malignancy:**

— Fibrous angiomatoid histiocytoma.

— Fibro-histiocytic plexiform tumor.

***3. Malignant fibrous histiocytoma (MFH)***

Uncertain histogenesis; it is thought the MFH develops from undifferentiated mesenchymal cells, with fibroblastic and myofibroblastic features.

*Macroscopic:* lobulated mass, large (over 5 cm), with areas of hemorrhage, necrosis, cystic areas.

Location: deep in the thigh or in the retroperitoneal area.

*Microscopically there are more variants:*

1. HFM polymorph-storiform:

— Storiform structure.

— Cellular polymorphism.

— Collagenous stroma with chronic inflammatory cells (lymphocytes), often with foamy macrophages.

2. HFM myxoid (myxofibrosarcoma):

— Lesion with a low malignancy, but it can turn into high malignant tumor (HFM polymorphic).

3. Giant cell MFH.

4. Inflammatory MFH.

5. Angiomatoid MFH.

*Evolution:*

— It frequently reappears.

— It metastasize, particularly in the liver and lungs.

**THE ADIPOSE TISSUE TUMORS**

**I. Lipoma**

*Definition:* benign tumor of the adipose tissue.

*Clinically:*

— It usually occurs in adults, over 30 years old.

— Localization: frequently in the sub cutis of torso, abdomen, and limbs or in the retroperitoneal area.

— Well defined, usually painless, slow growing nodule, usually mobile on the subjacent planes.

*Macroscopically:*

— Soft consistency, yellow.

— Variable sizes (less than 5 cm to 60 cm).

— Often with a thin fibrous capsule at the periphery and fibrous stripes which cross the tumor.

*Microscopically:*

— It resembles the mature adipose tissue.

— Variants: perineural fibrolipoma, fusocellular lipoma, polymorphic lipoma, angiomyolipoma, lipoblastoma (of the fetal fat, it appears in newborns or children up to 3 years old).

*Evolution:*

— It grows autonomously.

— It does not reappear after surgical removal.

**II. Liposarcoma**

*Definition:* the malignant tumor of the adipose tissue.

*Clinically:*

— The most frequent sarcoma in adults (10–25 % of the sarcomas)

— Most frequently occurs in people of 50–70 years of age

— Localization: thigh, torso, the proximal extremities of the limbs, mediastinum, in the retroperitoneal area

*Macroscopically:*

— Large nodule, over 5 cm, yellow-grayish, jelly-like (mucinous), encephaloid or cystic, with necrotic and hemorrhagic areas

*Microscopically:*

— The typical, diagnostic cell is the lipoblast which is a large cell, with clear vacuoles in the cytoplasm, with a central nucleus (these cells exist in all liposarcoma varieties).

*Liposarcoma varieties:*

*a) Well differentiated liposarcoma:*

— 1/2 of the liposarcomas.

— Localized in the intra-abdominal area or in the limbs.

— Microscopically: a blend of normal fat cells and lipoblasts.

— 10 % of liposarcomas evolve in differentiated form.

*b) Differentiated liposarcoma:*

— Rarer occurrence.

— Microscopically: it has areas of well differentiated liposarcoma and sarcomatous area of high malignancy, non-lipogenic (it resembles rhabdomyosarcoma).

*c) Myxoid liposarcoma:*

— A fairly frequent variety of liposarcoma.

— Microscopically: lipoblasts and fusiform cells embedded in a myxoid stroma with numerous capillaries.

*d) Round cell liposarcoma:*

— Microscopically: lipoblasts and small round cells.

— High malignancy.

*e) Polymorphic liposarcoma:*

— High malignancy.

— Microscopically: lipoblasts and cells with heterogeneous aspects (polymorphic).

**What are the MUSCULAR TISSUE TUMORS?**

**A. The tumors of the smooth muscle.**

**I. Benign tumors.**

***Leiomyoma.***

Most frequently found in: uterus, the gastro-intestinal tract, breast, and kidney.

*Macroscopy:* single or multiple nodules, well circumscribed, their size varying broadly between small nodules of several millimeters to giant tumors, over 20–30 cm in diameter; tumor consistency is firm, sometimes rubbery; the sectioned tumor mass reveals a whirled pattern, with alternating white and red bundles and frequent areas of secondary dystrophy (hemorrhages, fibrosis, necroses, calcifications).

*Microscopy:* smooth muscle bundles, with elongated nuclei and abundant eosinophylic cytoplasm, positive for actin and desmin at immunohistochemistry.

***1. Superficial leiomyoma***

**a) Piloleiomyoma:**

On the skin of the head and neck, originating from the erector muscle of the hair and appearing as sensitive, brown-reddish nodules.

**b) Genital leiomyoma:**

In the female external genitalia (labia major), nipple, scrotum 1–2 cm nodular lesions, not painful.

**c) Angioleiomyoma (vascular leiomyoma):**

— Occurs frequently as typical painful nodules, 1–2 cm in diameter, usually subcutaneous or in the deep dermis of the extremities (particularly the lower leg).

— Originates in the smooth muscle cells of arterial or venous walls and contains thick-walled vessels.

***2. Deep leiomyoma:***

In the limbs, torso, retroperitoneal area.

***Uterine leiomyoma:***

— Very frequent, originating in the uterine smooth muscle.

— The tumor may be found close to or inside the uterine cavity, under the endometrium (submucosal), in the thickness of the uterine wall (intramural) or close to the peritoneal side of the uterine wall, protruding on the outer surface of the uterus (subserosal).

**II. Malignant tumors:**

***Leiomyosarcoma (LMS).***

*Localization:* it may be found in the retroperitoneal area, the deep tissue of the extremities, skin, and vascular walls (in the wall of the upper vena cava or in the blood vessels of the lower limbs), genital (uterus and external genitalia).

*Macroscopy:* large nodule, fleshy, with necrotic, hemorrhagic or cystic areas.

*Microscopy:* well differentiated LMS and poorly differentiated LMS, form elongated cellular fascicles, with abundant, eosinophylic cytoplasm, oval nuclei (the number of mitoses is a very important criteria in establishing the tumor type).

**B. The tumors of the striate (skeletal) muscle.**

**I. Benign tumors:**

***1. Rhabdomyoma***

— It has many variants.

**a) Adult rhabdomyoma:**

It appears in adults, especially in men.

*Location:* oral cavity (lips, the base of the tongue, the soft palate), the pharynx, the larynx.

*Macroscopy:* lobular nodule (bosselated surface), encapsulated, 1–5 cm, pink or reddish.

*Microscopy:* large cells, polygonal, eosinophylic, with glycogen vacuoles (cobweb-like) and transversal striations.

**b) Fetal rhabdomyoma**

Appears in children.

*Localization:* subcutaneously in the region of the head and neck (retroauricular area).

*Macroscopy:* circumscribed mass (nodule) of 2–5 cm, pink.

*Microscopy:* rhabdomyoblasts in all stages of differentiation.

**c) Genital rhabdomyoma**

In women, in the fourth-fifth decade of life Polypoid aspect.

**e) Cardiac rhabdomyoma**

In children, it may have an association with tuberous sclerosis It is a hamartoma.

**II. Malignant tumors:**

***Rhabdomyosarcoma***

— 5–15 % of the sarcomas.

— It appears mostly in children and adolescents (50 % of the children's sarcomas) and it is rare in adults.

**1. Embryonary rhabdomyosarcoma.**

**a) The classic type**

In the first years of life.

*Localization:* uro-genital area (bladder, scrotum) head, throat.

*Macroscopy:* grayish, soft tumor.

*Microscopy:* rhabdomyoblasts and small cells, round and fusiform, blue (with little cytoplasm) in a myxoid stroma; positive diagnosis by immunohistochemistry.

**b) Thebotryoid type**

At any age, from infancy to adulthood.

*Localized* under the surface of a mucous membrane of the throat (oropharynx) or of the urogenital tract (bladder, uterine cervix, vagina).

*Macroscopy:* lobulated, polypoid mass, vegetative, towards the cavity, having the shape of a grape cluster.

*Microscopy:* rhabdomyoblasts, round cells and fusiform in a myxoid stroma, arranged in a cambial stratum (cambio = to change) situated under a mucous membrane.

*Evolution:* good prognosis.

**c) The fusocellular type**

*Localization:* paratesticular, prostatic, para-uterine. Good prognosis.

**2. Alveolar rhabdomyosarcoma:**

In adolescents (10–25 years) High malignancy.

*Localization:* the limbs, the head and neck region.

*Microscopy:* the cells are arranged in a pattern resembling the pulmonary alveoli.

*In evolution* it may metastasize to the regional lymph nodes; this variant of rhabdomyosarcoma is very aggressive and has poor prognosis.

**3. Pleomorphic rhabdomyosarcoma:**

Appear in adults, most frequently at the extremities.

Poor prognosis.

**What are the VASCULAR TISSUE TUMORS?**

**A. The blood vessel tumors**

**I. Benign tumors:**

**1. Hemangioma**

— Considered as hamartomas (hamartomas are tumors containing normal tissues which does not normally occur in that structure or region).

— Most frequently it appears in children (rare in adults).

— It can regress and disappear.

*Macroscopy:*

— Superficial: appears like a spot or a plaque on the skin or in the subcutaneous area.

— Deep: red-bluish or purple, rounded nodules of various sizes (millimeters to centimeters), in the liver, brain.

*Microscopy:* Increased amounts of normally structured blood-vessels.

*Variants:*

*a). Capillary hemangioma:*

On the skin.

*Macroscopy:* spots or red-bluish plaques.

*Microscopy:* numerous capillaries grouped in lobules and well delimited from the connective stroma.

*b) Cavernous hemangioma:*

On the skin or deep, in the internal organs (liver).

*Macroscopy:* red-violet, sponge-like.

*Microscopy:* distended capillary network, containing increased amounts of blood, clearly separated in the connective stroma and resembling the cavernous bodies of the penis.

c) *Arterio-venous hemangioma:*

In the head and neck region but also in the limbs.

*Macroscopy:* red-bluish nodules.

*Microscopy:* arterial and venous blood-vessels.

*d) Venous hemangioma*

Retroperitoneal area, skeletal muscle (in adults).

*Macroscopy:* nodular.

*Microscopy:* venous structure which may contain thrombi

*e) Epithelioid hemangioma:*

On the skin.

*Macroscopy:* red or purple plaque.

*Microscopy:* capillaries with swelled, rounded endothelial cells (epithelioid) that may contain eosinophylic and lymphocytic infiltrates.

**II. Tumors with a lower grade of malignancy.**

**1. Kaposi's sarcoma**

*a) The classic type:*

— In old people (of Ashkenazy Jewish descent as well as in people from the Mediterranean area).

— On the skin of the lower limbs.

— Slow evolution, locally invasive.

— May regress, metastasize seldom.

*b) The endemic (African) type:*

— In equatorial Africa.

— In children: generalized lymphadenopathy, ominous prognosis (death).

— In adults: cutaneous lesions with slow evolution on the lower limbs.

*Macroscopy:* the spot phase (red spot brown, superficial) the plaque phase (more profound, reaching the dermis) the nodular phase (intradermic circumscribed mass).

*Microscopy:* in the initial phase (spots) appear blood-vessels and small fusiform cells and blood cells (red blood cells, PMN-s, lymphocytes); in the second (plaque) phase it appears an increased fusocellular proliferation; in the nodular phase, the appearance of numerous fusiform cells with mitoses (similar with fibrosarcoma), with vascular slits between them, with red cells and extra- and intra-cellular hyaline globules.

*c) The type associated with immunosuppression*

— In patients receiving post transplant immunosuppression.

— Slow evolution, with sometimes "spontaneous" regression when the immunosuppressive medication is redrawn.

*d) The epidemic type (associated with AIDS)*

— In young people, particularly homosexuals.

— In relation to HHV-8.

— Lesions: skin, gastro-intestinal tract, lungs, spleen.

*Macroscopy:* first stage as spot, second stage: plaque, third stage: nodule.

*Microscopy:* first stage as telangiectatic blood-vessels, lymphocytic infiltrates; second stage as vascular slits surrounded by fusiform cells (K-cells)

with mitoses and extravasated red cells; third stage as sarcomatous fusocellular proliferation, K cells with hyaline globules (PAS+) and hemosiderin deposits.

*Evolution:* in the early phases it can remit; in the advanced stages has unfavorable prognosis, with multiple metastases and death.

**III. Malignant vascular tumors**

**1. Angiosarcoma**

*Localization:*

— Cutaneous: the head, throat.

— In the limbs with chronic lymphedema (the Stewart-Treves syndrome).

— In the breast: in women 30–50 years old.

— In the soft deep tissues: liver, heart, lungs, the digestive tract, the thyroid gland, the retroperitoneum.

*Macroscopy:*

— Spot, plaque or nodule -> large fleshy tumor with hemorrhage and necrosis areas.

*Microscopy:*

— Vascular areas lined with extruding tumoral cells.

— Grading: from well differentiated (with mitoses, few atypies) resembling a hemangioma to aggressive forms with mitoses and many cellular atypia.

*Evolution:*

— Poor prognosis, survival less than 2 years.

— Highly invasive and early metastasizing (hematogenous spread).

**IV. Other vascular tumors:**

**1. Hemangioendothelioma:** with limited malignancy (borderline).

**2. Hemangiopericytoma:** with limited malignancy (borderline).

3. Glomus tumors

— Localization: the groin, palms, soles of the feet, lungs, stomach.

— Clinically: painful nodule.

— Microscopy: arterio-venous anastomoses.

— Variants: glomangioma and glomangiomyoma.

— Evolution: after tumor excision it usually disappears but in 10 % of cases it may reappear and some may become malignant (very rarely).

**B. Tumors of the lymphatic vessels Lymphangioma**

— In the newborns, children, the young adult.

— May appear as congenital malformation or may be acquired during life.

*Macroscopy:* spot, plaque or "grape cluster" (large vesicles, filled with clear liquid).

*Microscopy:* distended lymphatic vessels, containing lymph and lymphocytes.

*Variants:*

— Cystic lymphangioma (cystic hygroma): in infants, located in the throat or in the retroperitoneum.

— Lymphangiomyoma: hamartoma, composed of muscular cell proliferations within the walls of the lymphatic vessels.

**What are the PERIPHERAL NERVE TUMORS?**

**1. Neurofibroma**

— The benign tumor of the peripheral nerves.

— It occur single or multiple as in the case of von Recklinghausen neurofibromatosis (type I).

— Localization: superficial or inside the body, always in relation with a deep nerve.

*Macroscopy:*

— Soft sometime pediculate nodule occurring on the skin.

— It makes the nerve to thicken diffusely.

— Not encapsulated.

*Microscopy:*

— Fibroblasts, Schwann cells, collagen fibres in a myxoid stroma or collagen.

*Variants:*

a) Diffuse neurofibroma: occurs in children, superficial in the head and neck area and has a diffuse growth.

b) Plexiform neurofibroma: large tumor masses on a nerve tract.

**2. Neurofibromatosis**

*Type I:* von Recklinghausen disease:

— Autosomal dominant (AD).

— Multiple tumors along a peripheral nerve; cutaneous neurofibromas (plexiform neurofibromas) may grow to considerable sizes, leading to grotesque overgrowth of soft tissue and bone in a limb.

— Cutaneous pigmented spots (cafe-au-lait spots).

— Lisch nodules (in the iris).

— 1–5 % becomes malignant.

*Type II:*

— Bilateral acoustic schwannoma.

— It does not turn malignant.

**3. Schawannoma (neurinoma, neurilemoma):**

— Benign tumor of the Schwann cells, forming the nerve sheath.

— In young adults.

*Localization:*

— Head, throat, mediastinum, the retroperitoneal area.

— Intracranial: the acoustic nerve (VIII), trigeminal nerve (V).

*Macroscopy:*

— 1–15 cm nodule, in relation to a nerve tract, sometimes pediculated, well delimitated, encapsulated, whitish, with cystic degenerations.

*Microscopy:*

— Antoni A type areas: cellular areas in which, the diagnostic feature is the Verocay bodies (two parallel rows of nuclei and nervous fibres).

— Antoni B type areas: with a more lax pattern, myxoid.

*Evolution:*

— It does not reappear after radical surgical excision, and does not metastasize.

**4. Malignant schwannoma (neurofibrosarcoma)**

*Macroscopy:* single tumor or multiple tumors.

*Microscopy:* cellular polymorphism.

*Variants:*

— Malignant epithelioid schwannoma.

— Malignant glandular schwannoma.

**What are the CARTILAGE PROLIFERATIVE TUMORS?**

**1. Osteochondroma**

— The most frequent benign tumor of the bone.

— In adolescent, men.

*Localization:* long bones, metaphysis (femur, tibia or humerus).

*Single lesion* (osteochondroma) or multiple lesions (osteo-chondromatosis).

*Clinically:* deformed area on the bone, swelled and painful.

*Macroscopy:* small nodule, under 5 cm, sessile or pedunculated, arising from the bone surface; it has a central osseous area and an outer cartilaginous area.

*Microscopy:* the central area has osseous aspect, while towards the outer layers, the tumor has cartilaginous structure.

*Evolution:* multiple forms may become malignant.

**2. Chondroma**

— Benign cartilaginous tumor, most frequently appearing in teenagers.

*Single* (chondroma) or multiple (chondromatosis).

*Localization:* in the medullar cavity of the small bones of the head and foot (enchondromas).

*Clinically:* a swelled region, sometimes painful, frequently exposed to fractures.

*Macroscopy:* lobular nodule, firm, well delimitated, bluish.

*Microscopy:* lobules of mature hyaline cartilage, with well differentiated cartilaginous cells and vascular axes within the tumor, unlike in the normal cartilage.

*Evolution:* multiple forms can become malignant.

**3. Chondronblastoma**

— It appears in young people.

*Localization:* the epiphysis of the long bones (knees, the higher extremity of the humerus).

*Clinically:* pain at the level of the lesion.

*Macroscopy:* grey-pinkish nodule, with necroses and hemorrhages.

*Microscopy:* small chondroblasts, multinuclear giant cells, cartilaginous matrix.

*Evolution:* it remits.

**4. Chondrosarcoma**

— Malignant cartilaginous tumor.

— It appears at any age but most frequently in adults (40–60 years old).

*Localization:* everywhere in the body but most frequently on the pelvic or shoulder bones (vertebra, scapula, and pelvis).

*Position:* intramedullary or juxtacortical.

*Macroscopy:* lobular tumor, firm, with blended areas of calcification, necrosis, hemorrhage and cysts.

*Microscopy:* grade I with well differentiated cartilages (resembling the chondroma); grade II and III with dense cells, polymorphism, multiple mitoses.

*Evolution:* local recurrence, metastasizes through hematogenic pathway.

**What are the BONE-FORMING TUMORS?**

**1. Osteoma**

— Benign bone tumor.

— Single or multiple (the Gardner's syndrome).

*Localization:* the bones of the face, the cortical bone.

*Macroscopy:* bosselated, round or oval tumor.

*Microscopy:* trabecular structure, similar to the mature bone.

*Evolution:* it grows slowly, it can fill and obstruct the cavities of the sinuses, or they can jut out on the orbit, but they do not become malignant.

**2. The osteoid osteoma or the osteoblastoma**

*Common features:*

— It is benign.

— It appears in young people.

*Macroscopic:* round, with hemorrhagic changes.

*Microscopic:* partially mineralized osteoid trabeculae and lax conjunctive-vascular tissue.

— Radio transparent.

*Specific features:*

*Osteoid osteoma:*

— It appears most often on the upper extremity of the femur and tibia.

— Small, under 1 cm.

— Painful (at night or after alcohol intake); it disappears after non-steroidal anti- inflammatory treatment.

*Microscopy:* the central area variably mineralized (nidus = transparent aspect on the Rx), at the periphery it has an area of dense, sclerotic bone.

*Osteoblastoma:*

— The most common location is in the spine.

— Size — over 1 cm.

— Painless.

*Microscopy:* it does not have a sclerotic bone at the periphery.

**3. Osteosarcoma**

— Malignant tumor characterized by the direct formation of the osteoid or bone by the tumoral cells.

— In young adults.

— Localization: the tumor usually appears at the extremities of the long bones, around the joint (i. e., knee), the humerus or the pelvis.

*Macroscopy:* the tumor can be white, firm (resembling the bone) or pinkish, fleshy, with areas of hemorrhages and necroses.

*Microscopy:* osteoid or bone formation by the tumor cells.

*Histological variants:* osteoblastic, chondroblast, fibroblastic, telangiectatic, with small cells, with giant cells.

*Evolution:* it metastasize early in the evolution, after spreading by the blood into the lungs, the brain, etc.

**What are MELANOCYTIC TUMORS?**

**I. Benign melanocytic tumors Nevi.**

***1. The common (acquired) nevi:***

— The most frequent melanic tumor in humans, their number increases with the age.

— Frequent location: skin of the head, neck, torso, limbs (they can appear everywhere on the body) and rarely squamous mucosa.

— Usually the nevi have small sizes, under 6 mm and variable color (from the skin color up to dark colors, black).

— Shapes: plaque, papule, polyp.

*Variants of the common acquired nevi:*

*a. The junctional nevus:*

— The fist stage of the melanocytic proliferation.

— It can be preceded by lentigo (continual melanocytic proliferation in the basal layer of the squamous epithelium).

*Macroscopically:* spot or small papule, intensely pigmented, without hair.

*Microscopically:* melanocytic proliferation as nests of melanocytic or nevic cells, located at the junction between the epidermis and the dermis which pushes downward the basal membrane.

*Evolution:* towards another types, and may become malignant.

*b) The compound nevus:*

*Macroscopically:* slightly elevated and less pigmented, it may present hair.

*Microscopically:* the basal membrane breaks and nests of nevic cells continue to develop in the dermis; the basal membrane recovers and the nevus remains with two components: junctional and dermal.

*Evolution:* it can become malignant (the junctional component).

*c) The dermal nevus*

*Macroscopically:* plaque or polyp (resembling the compound nevus).

*Microscopically:* the junctional component disappears (it regresses) and only a dermal component remains, containing type A cells (epitheliod), type B cells (lymphoid), and type C cells (neuroid).

*Variant:* halo nevus which presents a white de-pigmented rim.

*Evolution:* it does not become malignant.

***2. The Spitz nevus (fusocellular and epitheliod):***

— In children and young adults.

*Localization:* head, throat, upper limbs.

*Macroscopically:* small nodule, reddish (it can be mistaken with a hemangioma).

*Microscopic:* fusiform and epitheliod cells which present atypical features (they can be mistaken with a malignant melanoma), richly vascularized stroma, few pigment.

*Evolution:* it can become malignant after a very long evolution (> 20 years).

***3. The congenital nevus:***

— 1 % of the newborn.

*Macroscopically:*

— Large lesions (over 20 cm), sometimes giant congenital nevus, intensely pigmented, with thick hairs, may have satellite lesions and carries a high malignancy risk

— Intermediate lesions (1,5–20 cm) with lower malignancy risk

— Small lesions (under 1,5 cm) with an indefinite malignancy risk.

*Microscopically:*

— Compound or dermal type.

— Nevic cells (spindle) which may infiltrate the deeper layers of the dermis and the hypodermis, sometimes infiltrating the sebaceous glands, the erector muscle of the hair, the lymphatic blood-vessels and the nerves.

*Evolution:* some nevi may turn malignant already during the childhood.

***4. The dysplastic nevus:***

— It appears de novo or on a preexisting nevus.

— Macroscopically: single pigmented lesion or multiple lesions, larger than the ordinary nevi (over 6 mm), with irregular shape, variable distribution of the pigment on the surface of the lesion.

— Microscopically: cells with atypical features and mitoses.

— Evolution: high malignancy risk.

— Dysplastic nevus syndrome: transmitted AD, with tens/hundreds of dysplastic nevi with high malignancy risk (one or several nevi).

**II. Malignant melanocytic tumors**

***Malignant melanoma:***

— Rather frequent occurrence at any age but particularly in adults.

— De novo or on melanocytic lesions (acquired nevus, congenital nevus, dysplastic nevus).

**Signs of malignization of a nevus:**

— The asymmetry of the lesion.

— Irregular, random distribution of the pigment (brown, black, blue, red, depigmented areas).

— The lesion has irregular margins.

— Over 6 mm in diameter.

— Red, congested or inflammatory rim.

— Pain and other celsian signs.
— Ulcerations, hemorrhages.
— Satellite nodules (metastasis).

**Factors that favor the malignization:**

— Preexisting melanic lesions.
— Prolonged sun exposure, UV.

**The classification of the melanoma:**

***1. "Insitu" melanoma:*** just above the basal membrane, difficult to diagnose clinically.

***2. The invasive non-metastasizing melanoma***

— Malignant lentigo (lentiginous melanoma).
— Melanoma with superficial extension.
— Acral lentiginous melanoma.

***3. The invasive metastasizing melanoma***

a) The radial or horizontal growing phase (the non-metastasizing phase):

— With limited number of malignant melanocytes in the epidermis ("in situ" melanoma).

— With tumoral melanocytes present in the epidermis and superficial dermis (micro- invasive melanoma).

— This form has a slow evolution (several years) and does not metastasize.

b) The vertical growth phase (the tumor phase):

— The malignant melanic cells form tumoral masses, expanding into the dermis, from one point of the horizontal phase (expansive).

— Cellular clones with metastasizing capacity are selected.

**The stages of the malignant melanoma:**

**1. Clark staging system:** staging according to the depth of invasion into the different skin layers:

Stage I = "in situ" melanoma.

Stage II = the melanoma has begun to penetrate in the papillary dermis (incomplete) Stage III = the melanoma fills the papillary dermis up to the interface with the reticular dermis.

Stage IV = the melanoma has spread into the reticular, deep dermis.

Stage V = the melanoma has penetrated very deeply in the hypodermis (subcutis).

2. **Breslow staging system:** staging according to the thickness of the lesion in mm: Stage I = less than 0,7 mm — with a good prognosis. Stage II–IV = the deeper the lesion, the worse the prognosis.

**The microscopy of the malignant melanoma:**

*1. Cytology:*

— Cells: epithelioid, fusiform, bizarre shaped cells of variable sizes.
— Eosinophylic, spongious, clear cytoplasm.
— Nucleus with large, sometimes eosinophylic nucleoli.
— Melanic pigment.

*2. Structure:*

— Growth: pseudo-granular, pseudo-papillary, or trabecular.

— There may appear areas of fibrosis, cartilaginous or bone metaplasia.

*3. Immunohistochemistry:*

— HMB45 antigen.

— S 100 protein.

**The evolution of the malignant melanoma:**

— Vertical and horizontal growth.

— Intra-epidermic metastasis with the appearance of satellite nodules.

— Metastases through the lymphatic pathway (in the lymph nodes) and hematogenic pathway (allover the body).

**What are MALFORMATIVE TUMORS?**

**Choristoma:** differentiated tissues located at different sites than normal.

*Examples:*

— Pancreatic tissue in the wall of the stomach.

— Adrenal gland in the upper part of the kidney.

**Hamartoma:** well differentiated tissue structures, normal to the specific site, but in abnormal proportion or location:

— Some hemangiomas.

— Some nevi.

— Cardiac rhabdomyoma.

— Pulmonary hamartoma.

**Vestigial embryonic dysplasia** — structures found during the embryonic life that did not adequately regress during organ development (congenital defects).

*Examples:*

— Cranio-pharyngioma.

— Chordoma.

— Cysts of the thyreoglossal duct (on the midline of the neck).

— Branchial cyst.

— Enterocystoma (cysts in the intestinal wall).

— Meckel diverticulum (a remnant of the yolk sack, appearing as an elongated diverticulum of the ileum, located at 40 cm from the ileocecal valve).

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