Chapter 2
EXTRACELLULAR INJURY

In this type of degeneration the metabolic disorders are present in the connective tissue, particularly in the stroma of the organs and in the blood vessel walls (the basal membrane of the blood vessels consists of fundamental substance and reticuline fibers). They manifest themselves by the storing of some quantitative and qualitative modified metabolic products in the intercellular substance.

1. Fibrinoid degeneration (fibrinoid intumescence).
This is an irreversible process of disorganization of the connective tissue. It is manifest by the destruction of the fundamental substance and of collagen fibers. There is a considerable increase of vaso-tissular permeability, which leads to fibrinoid formation. Fibrinoid is a complex substance, consisting of proteins and polysacharides, which come from collagen and fundamental substance degradation, from plasma, as a result of an increased permeability of the blood vessels, and from cellular nucleoproteins. The obligatory component of the fibrinoid is fibrin. As a consequence, fibrinoid has tinctorial qualities to fibrin; that is where its name comes from.

Macroscopically, there are no characteristic changes. The function of the affected organs is severely altered.

Two kinds of fibrinoid degeneration can be distinguished: of the connective tissue and of the blood vessels.

Electromicroscopy “Fibrinoid intumescence of the connective tissue” (fig. 33).
The collagen fibers are tumefacted, homogenized, without transversal striation, and have fibrin deposits between them.

The progress of the fibrinoid changes leads to fibrinoid necrosis of the connective tissue.

Microspecimen “Fibrinoid necrosis of the connective tissue in rheumatism” (fig. 34).
A site of complete destruction of the connective tissue is found in this specimen. The collagen fibers are tumefacted, dissociated, in some places disintegrated, and transformed into a homogeneous mass with cosin tinctoriality.

Macrophagic and lymphocytic infiltration is observed around this focus. As a consequence, in the places where the fibrinoid modifications take place, sclerotic processes and hyalinosis appear. In this case the function of the affected organ is severely disturbed. It is seen in some allergic and autoimmune diseases (rheumatic diseases, glomerulonephritis), angioneurotical diseases (hypertensive disease), plasmorrhagic diseases (atherosclerosis), infecto-allergic diseases, etc.
2. Extracellular hyaline degeneration

Hyaline describes a non-specific, homogeneous glassy, pink appearance due to dystrophic alterations in the extracellular space.

**Macrospecimen “Hyalinosis of the heart valves”**.

The cusps of the mitral valve (fig. 35) are thickened, deformed, and fused with a hard white non-transparent substance. The chorda tendineae are thickened and shortened; the left atrio-ventricular opening is reduced, stenosed. The function of the valve is severely affected, and the cardiac valvulopathy develops. There is stenosis or mitral insufficiency, or, more frequently, mitral valve disease with predominance of stenosis or valvular insufficiency. The complications are cardiac insufficiency, pulmonary edema, bronchopneumonia, intracardiac thrombosis, thromboembolia, infarct, etc. It is more frequently in rheumatism.

**Macrospecimen “Hyalinosis of the spleen capsule”**.

The capsule of the spleen is thickened (fig. 36), with a chondroid (like the hyalin cartilage) consistency, whitish color, and shiny and translucent appearance (hence its name “glazed spleen”). It is a local process which develops as a result of chronic inflammation and local sclerosis. Metabolic disorders from the connective tissue, for example, ascites-peritonitis in patients with hepatic cirrhosis cause the condition. An analog mechanism is observed in hyalinosis of large, old scars, especially of those caused by burns (so called keloid scars).

The hyalinosis of the vessels appears especially in the small caliber arteries and arterioles, preceded by the increase of the vascular permeability and plasmatic imbibition (plasmmorrhage) of the vessels wall. Vascular hyalin consists of plasmatic precursors, especially of plasma proteins; the fibrillar elements of the vascular walls are successively destroyed, undergoing imbibition with fibrin and with other plasmatic compounds.

**Microspecimen “Hyalinosis of the splenic arteries”** (fig. 37).

The lumen of the central arteries of the follicles are narrowed, and the walls are thickened because of the hyalin accumulation under the endothelium. The hyalin masses move to the exterior and destroy the elastic membrane. The media (muscular fibers) undergoes atrophy. Gradually, the arteriole transforms into a hyalin tube (like a glass tube) with a thickened wall and a narrow, sometimes even completely obstructed lumen. These modifications lead to the ischemia and hypoxia of the organ, the atrophy of the parenchyma, and the perivascular proliferation of the connective tissue. The hyalinosis of the splenic arteries is a physiological process determined by the morphofunctional peculiarities of the spleen as a blood depositing organ. Generalized hyalinosis of the arteries is characteristic in hypertensive disease, secondary hypertension, and diabetes mellitus. First of all are affected the arteries of the brain, heart, kidneys, endocrine glands, etc.

Hyalinosis is, usually, an irreversible process which can lead to functional disorders and severe complications (for example arteriolosclerotic nephrosclerosis with the shrivelling of the kidneys in the hypertensive disease, rheumatic cardiac valvulopathies, intercapillary glomerulosclerosis and diabetic retinopathy, etc).

3. Amyloidosis

**A. Definition:** Accumulation of abnormal proteinaceous substance between cells in various tissues and organs of the body. The predominant morphogenic mechanism of amyloidosis is the pathological synthesis. Amyloid is a glycoprotein in which the fibrillar proteins are conjugated
with polysaccharides. It consists of two main components: the **fibrillar (F)** component, which is a fibrillar protein and the **plasmatic (P)** component - plasma proteins and polysaccharides. The proteopolysaccharidic components are tightly bound both with each other and with the elements of the tissue depositing the amyloid, especially with the chondroitinsulfats of the fundamental substance of the connective tissue. The proteins make up to 96-98%, while polysaccharides make up 2-4% of the whole mass of the amyloid.

**B. Appearance:**

1. **Gross:**
   Organs may be enlarged in weight and volume, nodular or diffuse pale gray, somewhat firm, with a translucent waxy or lardy appearance.

2. **Light microscopic:**
   Pink, amorphous to fibrillar material in hematoxylin-eosin stain.

**Macrospecimem “Nodular and diffuse amyloidosis of the spleen”**.

In both specimens the spleen is enlarged and hardened. In the nodular type (initial stage) of amyloidosis, multiple whitish, translucent nodules disseminated in the white pulp can be observed in cross section (fig. 38). This gives the spleen a spotted appearance. The explanation of this is that amyloid accumulates in the walls of the centrofollicular arteries, extending after this into the entire follicle. The lymphatic follicles become larger, semitransparent, and have a glassy shine like sago beans. That is why such a spleen is also called “sago spleen” (Virchow).

In the diffuse type (second stage), the amyloid uniformly deposits in all the parenchyma along the reticular fibers. The spleen is much larger, its weight can reach up to 1000g (fig. 39), it is of hard consistency, and has a translucent red-brown appearance, like smoked meat (spleen with smoked or lard meat appearance).

**Macrospecimen “Amyloid dystrophy of the kidney” (fig. 40).**

The kidney is larger in volume, of hard consistency and a whitish-pale translucent (lardy) appearance in cross section, especially in the cortical region (“big lardy kidney”).

Using customary microscopic stain (hematoxyline and eosin, picrofuxine) the amyloid substance appears unstructured and homogeneous. For elective identification of amyloid, a series of histochemical methods are used (table 3).

### Table 3

<table>
<thead>
<tr>
<th>Staining methods</th>
<th>Characteristics</th>
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<td>1) Macroscopic Virchow reaction</td>
<td>At successive application, of Lugol solution and sulphuric acid (10%), the amyloid will be violet-blue or a dark shade of green on the cross section surface</td>
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<tr>
<td>2) With Congo red</td>
<td>Amyloid is stained a dark shade of red, while the rest of the tissue yellowish-pink</td>
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<tr>
<td>3) With methyl-violat or with gentian violet</td>
<td>Amyloid is stained red, while the rest of the tissular elements are stained violet (metachromatic staining)</td>
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<tr>
<td>4) With thioflavin-S or -T</td>
<td>At the luminescent microscope (ultraviolet light), amyloid appears to be of a yellowish-green color</td>
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Macroscopically the amyloid can be identified with the specific Virchow reaction: the amyloid depositions are stained with iodine (Lugol solution) in red-brown. This color changes into violet-blue or almost dark green after the application of sulphuric acid (10%) (fig. 41).

The localization of the amyloid deposits in organs and tissues is characteristic:
- in blood or lymph vessel walls (in the intima or adventitia);
- on the basal membranes of the glandular structures (tubules, channels, ducts);
- in the stroma of the organs, along the reticular or collagen fibers;
- in the stroma of the organs, along the reticular or collagen fibers.

Microspecimen “Renal amyloidosis” (fig. 42).

Selective depositions of dark red amyloid masses are observed in the meazgium and in the glomerular capillaries, under the endothelium of the small artery walls, under the basal membrane of the tubules and along the reticular fibers of the stroma. In the epithelial cells of the contort tubes there can be observed dystrophic modifications, while in some lumens there are hyalin cylinders. As the dystrophic process evolves, the glomeruli and the pyramids are completely replaced by amyloid masses. Subsequently the diffuse proliferation of the connective tissue with the amyloid shrivelling of the kidney takes place.

The fibrillar structure of the amyloid substance is clearly observed at electronmicroscopic examination.

Electronmicrography “Amyloidosis of myocardium” (fig. 43).

Filamentous structures with a chaotic arrangement, representing the fibrillar protein – (the main component of the amyloid substance), are observed on the surface of the sarcolemna of cardiomyocytes. It is observed that the amyloid deposits extracellularly. The mitochondria are slightly tumefacted, while the crista are partially destroyed.

Amyloidosis is an irreversible process, which ends with progressive atrophy of the parenchyma and sclerosis of the affected organs. Severe insufficiency or the abolition of organ function results.

The effects of amyloid dystrophy on the parenchyma of the affected organs are clearly observed in the amyloidosis of the liver.

Microspecimen “Hepatic amyloidosis” (fig. 44).

Extensive zones, in the hepatic trabeculae which are atrophied. In some areas they are completely absent and substituted with amyloid masses, homogeneously stained with eosin. The function of the liver is severely altered in amyloidosis. Amyloid shrivelling develops in the liver as a result of parenchyma atrophy and sclerotic processes which take place as a consequence of the increased activity of fibroblasts, in hypoxia conditions.

C. Pathogenesis

Most forms of amyloidosis involve:
1. Induction and accumulation of a proteic excess in tissues.
2. Proteolytic cleavage to form orderly filaments that are arranged in β -pleated sheet configuration.
3. Abnormal accumulation in tissues is associated with abnormal tissue function.
D. Forms of Amyloidosis

1. Primary amyloidosis (immunocyte-associated amyloidosis): amyloid is composed of immunoglobulin light chains: amyloid AL, and is associated with B-cell (lymphocyte/plasma cell) proliferative diseases, such as multiple myeloma and monoclonal gammopathies. May be associated with defective degradation of light chains AL protein. Seen in plasma cells tumors.

2. Secondary amyloidosis (also known as reactive systemic amyloidosis): amyloid is composed of a unique, non-immunoglobulin protein called Amyloid AA (amyloid-associated). It is the most frequent and important form of amyloid in humans. It is also of great clinical importance. This form of amyloidosis develops on the background of other affections such as:
   a) some chronic infections (tuberculosis, syphilis, leprosy, dysentery, bacterial endocarditis, actinomycosis, etc.);
   b) diseases accompanied by chronic purulent processes (suppurative bronchiectasia, abscesses, osteomyelitis, suppurative wounds, empyema, chronic septicemia);
   c) rheumatismal diseases (especially rheumatoid arthritis and systemic lupus erythematous);
   d) malignant tumors (chronic paraproteinemic leucosis, lymphogranulomatosis).

3. Endocrine amyloid in certain endocrine tumors (medullary carcinoma of thyroid, islet tumors of pancreas), in islet of pancreas in patients with type II diabetes mellitus; amyloid derived from hormones - procalcitonin, islet amyloid polypeptide, secreted by β-cells.

4. Aging associated amyloidosis.

Amyloid is composed of:
   - the normal transthyretin molecule (TTR - protein which transports thyroxine and retinol) in senile systemic and senile cardiac amyloidosis;
   - the mutant form of transthyretin in familial amyloid polyneuropathies;
   - the β-amyloid protein in Alzheimer’s disease cerebral plaques.

5. Amyloidosis related to long-term hemodialysis; amyloid content β2-microglobulin (component of MHC class I molecule).

E. Tissue distribution of amyloid (predominant).

1. Immunocyte-associated amyloidosis: heart, gastrointestinal tract, lung, peripheral nerves, skin, tongue (occasionally the eye and skeletal muscle).

2. Reactive systemic amyloidosis: kidney, liver, spleen, intestine, adrenal glands, lymph nodes, thyroid and others tissues.

3. Organ dysfunction is the result of cells death subsequent to vascular occlusion and/or physical barrier due to progressive amyloid deposition.

4. Organ-specific lesions.

a. Kidney:

   Amyloid accumulates in the glomerulus (capillary basement membranes, mesangium), as well as the peritubular interstitium and blood vessel walls. Glomerular barrier to protein (charge and molecular barrier) is altered to result in protein-loosing nephropathy.

b. Spleen: amyloid accumulations in the splenic follicles (a sago spleen on gross exam). Amyloid in the splenic sinuses form dense sheets (a lardaceous spleen).
c. Liver: amyloid accumulates in the spaces of Disse, squeeze out hepatocytes and obliterates the sinusoids, liver atrophy and failure may result in advanced cases in man.

d. Pancreas: amyloid accumulates in the islets, diabetes mellitus results.

e. Heart: usually in the coronary arteries of old man.

f. Gastrointestinal tract:

Can occur at all levels, and may accumulate in the mucosa, submucosa, or the muscular tunics. It causes defects in absorption of nutrients, interferes with secretion of locally active enzymes, and impairs motility.

g. Lung: nodular masses described in bronchi and trachea.

4. Lipidic extracellular degeneration.

The metabolic disorders of extracellular fats are found in adipose tissue; they are represented by excessive accumulation of fat (obesity), or their decrease (cachexia).

Obesity can be primary, determined by constitutional or hereditary factors (the necessity of a highly caloric alimentation, which is genetically determined) and secondary, which is symptomatic and can be observed in some cerebral, endocrine and hereditary diseases (table 4).

Morphologically, obesity is manifested by the increase of fat in the subcutaneous tissue, large omentum, mediastinum, mesentery, retroperitoneal tissue and in the stroma of some internal organs (heart, pancreas, kidneys, liver). The lipomatosis of the heart is present in all types of obesity.

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<tr>
<th>Type of obesity</th>
<th>The main etiopathogenic factors</th>
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<tr>
<td>a) Alimentary</td>
<td>Excessive nutrition, hypodynamia</td>
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<tr>
<td>b) Cerebral</td>
<td>Cerebral tumors, trauma, neurotropic infections</td>
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<tr>
<td>c) Endocrine</td>
<td>1) Hypercorticism (basophilic adenoma of the anterior lobe of the pituitary gland or hormonally active tumors of the adrenocortical glands; 2) Hypothyroidism; 3) Hypogonadism (inflammatory processes, tumors, castration, climax); 4) Hyperinsulinism (beta-cell adenoma of the pancreatic islets)</td>
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<tr>
<td>d) Hereditary</td>
<td>Genetic defects (including hereditary enzynopathies)</td>
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**Table 4**

Microspecimen “Lipomatosis of the heart” (fig. 45).

The specimen contains groups of adipose cells (adipocytes), which infiltrate the myocardium, dissociating the muscular fibers, most of which are atrophied.

Macrocoscopically (fig. 46) the heart is larger and contains fat accumulations under the epicardium which surround the heart as a muff.

These manifestations are more visible in the area of the right ventricle, which is about 1-2 cm thick (the normal thickness is of 2-3 mm).

The contraction force of the myocardium is decreased, leading to cardiac insufficiency. The rupture of the right ventricular wall is also possible, leading to heart tamponade and sudden death.

It must be mentioned that obesity (including the lipomatosis of the heart) is one of the risk factors of the cardiac ischemic disease (ischemic heart disease).