

DEGENERATION

Degeneration (dystrophy) is a pathological process due to disturbance of either cellular or tissue metabolism which causes changes in the structure of cells, tissues, etc.

Cellular or tissue metabolism is called trophism. **Trophism** is the entity of mechanisms responsible for nourishing of the definite structure and determining its metabolism.

Trophism mechanisms are cellular and extracellular:

- 1) cellular: autoregulation within a cell (enzymes);
- 2) extracellular: transportation systems (blood, lymph); endocrine regulation; nervous regulation.

There are several **morphogenetic mechanisms** of degenerations:

- 1) infiltration: abundant invasion of metabolic products from the transportation system to the cell followed by their accumulation;
- 2) decomposition: this is destruction of cellular ultrastructure (lipoprotein complex from cellular membranes) with accumulation within a cell;
- 3) disturbed synthesis: intracellular synthesis of the substances which are not produced normally (e.g. amyloid, glycogen in renal tubular epithelium in diabetes);
- 4) transformation: formation of products of one type of metabolism from the common primary products, e.g. increased polymerization of glycogen from glucose.

Organ dependence has been found according to different morphogenetic mechanisms. Infiltration is more characteristic for the renal epithelium; but decomposition for the heart, transformation and disturbed synthesis are more characteristic for the liver.

Classification of degenerations

1. According to the localization:
 - a) parenchymatous,
 - b) mesenchymatous,

c) mixed type.

2. According to the type of metabolism disturbance:

- a) albuminous (protein),
- b) fatty (adipose), (lipidoses),
- c) carbohydrate,
- d) mineral.

3. According to the origin:

- a) acquired,
- b) inherited.

4. According to propagation:

- a) general,
- b) local.

If manifestations of cellular metabolism disturbance are present it is parenchymatous degeneration. If manifestations of the connective tissue and extracellular area are observed it is mesenchymatous degeneration. In mixed degeneration morphological manifestations of the disturbed metabolism are observed both in the cells and in the connective tissue (stroma), as well as in the vascular walls.

Parenchymatous degenerations.

Parenchymatous albuminous degenerations

Parenchymatous albuminous degenerations (dysproteinoses) are manifestations of cellular metabolism disturbance.

Several years ago we used the following classification of parenchymatous albuminous degenerations: 1) granular, 2) hyalin-drop, 3) hydropic, 4) horny (development defect).

In the modern literature the following classification of parenchymatous albuminous degenerations can be found: 1) hyalin-drop, 2) hydropic.

Granular and horny degenerations are disputable problems. Since the time of Virchow parenchymatous albuminous degenerations have been regarded as granular dystrophy. The new methods of investigation (electron microscopy, immune techniques) have demonstrated that the "grains" are not accumulations of protein but cellular ultrastructure hyperplasia i.e. manifestation of maximal functional strain of the organ in response to different irritants. For example, we can see some grains in the cell cytoplasm of the liver, thyroid gland, myocardium. But if these grains appear as a result of pathological affect, we will call this pathological process - granular degeneration.

Nowadays horny degeneration is often explained as a result of development defect, that's why this pathological process may be inherited.

According to the causes we distinguish denaturation and coagulation or hydration and colliquation in the intracellular proteins. If there are denaturation and coagulation, hyalin-drop degenerations will develop with resultant coagulative necrosis. If there are hydration and colliquation, hydropic degeneration followed by colliquative necrosis will develop.

Hyaline-drop degenerations can transform to hydropic degeneration.

Hyalin drop degeneration occurs when hyalin-like protein drops filling the entire cytoplasm are formed. We usually observe this degeneration in the kidneys, liver, myocardium. Macroscopic study does not reveal any changes.

The outcome is unfavorable because of coagulative necrosis.

Hydropic degeneration (edematous, balloon). In this degeneration vacuoles of cytoplasmic fluid appear in the cytoplasm. Hydropic degeneration develops in the kidneys, skin, liver, muscles, nerves. Macroscopic study does not reveal any changes. Microscopic findings are as follows: the nucleus is displaced to the peripheral areas and there are vacuoles in the cytoplasm. Hydropic degeneration is often caused by viral herpes and cachexia.

The outcome of this degeneration is unfavorable because of colliquation necrosis.

Horny degeneration manifests itself by abundant formation of horny substance in keratinized epithelium in hyperkeratosis and ichthyosis and its appearance in the places where it is not found under normal conditions (leukoplakia).

Parenchymatous fatty degenerations

It is known that cellular cytoplasm is mainly formed of lipids, which, together with proteins form lipoprotein complexes (cellular membranes). Besides, there is neutral fat, it is localized in the fat depots, i.e. subcutaneous fat, mesentery, subepicardial fat etc.

For identification of different kind of fats we usually use special reactions (staining): Sudan 111 - stains fat red, Sudan 1Y - black, Nile blau sulfat - stains fatty acids blue and neutral fats red.

Disturbance of fat metabolism may manifest as:

- appearance in the place where it does not appear under normal conditions (e.g. in the myocardium),
- appearance of fat of unusual composition;
- increase of fat amount in the places where it is present under normal conditions (e.g. in the fat depots).

The main cause of fatty degeneration is hypoxia which may be due to:

- a) disturbances in transportation systems (e.g. in patient with chronic cardiovascular and chronic pulmonary insufficiency);
- b) chronic intoxications (e.g. alcoholism);
- c) cachexia, avitaminosis;
- d) infections (e.g. diphtheria, tuberculosis).

The heart, liver, kidneys are damaged most frequently.

Its manifestations in the myocardium are impressive. It is called "tiger's heart". Microscopically in "tiger's heart" we can see dust-like or small-capsule adiposity on the cardiomyocytes. It is observed in the papillary muscles and trabecules of the

ventricles in the form of bands (surrounding the veins), because of hypoxia, which is more express surrounding the veins (when compared with the arteries). Macroscopically the heart is enlarged, the chambers are stretched, flabby.

The liver also has impressive appearance. It is called "goose's liver". Macroscopically the liver is enlarged, flabby. Fat drops are seen on incision. The colour is ochre yellow. Microscopically dust-like, small- and large drops in the liver's cells are observed.

The kidneys look like "large white kidney". They are enlarged, flabby. The cortical substance is gray with yellow drops.

The outcome of parenchymatous fatty degenerations depends on the stage. It is seldom reversible. Necrosis and sclerosis usually develop.

Parenchymatous carbohydrate degenerations

Carbohydrates are divided into 3 groups:

- 1) polysaccharides (glycogen);
- 2) mucopolysaccharides;
- 3) glycoproteides (mucin, mucoid).

There are several special reactions for identification of these carbohydrates, PAS or SHIK reaction and carmine according to Best are used for identification polysaccharides (glycogen) and mucopolysaccharides. Polysaccharides and mucopolysaccharides are stained dark pink or red.

Staining according to Haile - for identification glycoproteides. Glycoproteides are stained blue.

Glycogen metabolism disturbance is significant in the human pathology. It is known that glucose which enters the organism with the food polymerizes to glycogen which accumulates in the liver and muscles and is called labile glycogen. Glycogen in the nervous cells, endothelium, connective tissue, cartilages and other cells is called stable glycogen.

Disturbance of glycogen amount manifests with:

- increase or reduction in the amount in the tissues where it is present under normal conditions,
- its appearance in the areas where it is not present under normal conditions.

Glycogen metabolism disturbance occurs in diabetes mellitus. (See *Endocrine pathology*). In this disease insulin insufficiency causes glucosuria and hyperglycemia. Glycogen amount in the tissues reduces sharply (e.g. in the liver) which causes its fat infiltration (fatty liver degeneration). Glucosuria causes changes in the kidneys. Glycogen infiltration of the tubular epithelium develops (we observe glycogen in the cells and lumens). In the glomeruli, microangiopathy develops due to their increased permeability for sugar and protein. It's called intercapillary (diabetic) glomerulonecrosis.

Glycoproteid metabolism disturbance. Mucins and mucoids accumulate in the cells (mucous degeneration). Mucous degenerations are observed in epithelial tumors (gastric cancer), colloid goiter, mucoviscidosis.

Storage diseases

There are a lot of diseases which are due to hereditary factors and connected with metabolism disturbance. Those diseases are called storage diseases or enzymopathy.

A few general comments can be made about all storage diseases:

1. All the storage diseases occur as a result of autosomal recessive, or sex-(X-) linked recessive genetic transmission.
2. Most of the storage diseases are lysosomal storage diseases. Out of the glycogen storage diseases, only type II (Pompe's disease) is due to lysosomal enzyme deficiency.

According to the type of metabolism disturbance storage diseases have been classified into proteinoses, lipidoses and glucogenoses. The type of proteinoses, lipidoses and glucogenoses depends on the defect in the enzyme.

The most frequent of them are described in the above diagrams.

Proteinoses

Disease	Enzyme	Organs in which pathologic proteins accumulate
Cystinosis	-	Liver, kidney, spleen, eyes, skin
Tyrosinosis	Tyrosine-aminotransferase	Liver, kidney, bones
Phenylpyruvic oligophrenia	Phenylalanine-4-hydroxylase	Central nervous system, muscles, skin, blood, urine

LIPIDOSES

Disease	Enzyme	Organs in which pathologic proteins accumulate
Gaucher disease – cerebrosid-lipidosis	Glycrocerebrosidase	Liver, spleen, bone marrow, central nervous system
Niemann-Pick disease (sphingomyelinlipidosis)	Sphingomyelinase	Liver, spleen, bone marrow, central nervous system
Tay-Sachs disease (amaurotic idiopathy)	Hexosaminidase	Central nervous system, retina, spleen, liver
Normann-Landing disease (generalized gangliosidosis)	β -galactosidase	Central nervous system, nervous bands, liver, spleen, bone marrow, kidneys

Some important forms of lipidoses are described below:

Gaucher's Disease

This is an autosomal recessive disorder in which there is deficiency of lysosomal enzyme, glucocerebrosidase, which normally cleaves glucose from ceramide. This results in lysosomal accumulation of glucocerebroside (ceramide-glucose) in phagocytes of the body and sometimes in the neurons. The main sources of glucocerebroside in phagocytes are the membrane glycolipids of old leukocytes and erythrocytes, while the deposits in the neurons consist of gangliosides.

Clinically, there are 3 types of Gaucher's disease:

Type I or classic form is the adult form of the disease in which there is storage of glycocerebrosides in the phagocytes of the body, principally involving the spleen, liver, bone marrow and lymph nodes. This is the most common type comprising 80% of all cases of Gaucher's disease

Type II is the infantile form in which there is progressive involvement of the central nervous system.

Type III is the juvenile form of the disease having features in between type I and type II, i.e. they have systemic involvement like in type I and progressive involvement of the CNS as in type II.

The clinical features depend upon the clinical subtype of Gaucher's disease. In addition to involvement of different organs and systems (splenomegaly, hepatomegaly, lymphadenopathy, bone marrow and cerebral involvement), a few other features include pancytopenia, or thrombocytopenia secondary to hypersplenism, bone pains and pathologic fractures.

Microscopically large number of characteristically distended and enlarged macrophages called Gaucher cells which are found in the spleen, liver, bone marrow and lymph nodes, and in the case of neuronal involvement, in the Virchow-Robin space. The cytoplasm of these cells is abundant, granular and fibrillar resembling crumpled tissue paper. They have mostly a single nucleus but occasionally may have

two or three nuclei. Gaucher cells are positive with PAS, and Prussian-blue reaction indicating the nature of accumulated material as glycolipids admixed with haemosiderin. These cells often show erythrophagocytosis and are rich in acid phosphatase.

Niemann-Pick Disease

This is also an autosomal recessive disorder characterized by accumulation of sphingomyelin and cholesterol. Majority of the cases (about 80%) have deficiency of sphingomyelinase which is required for cleavage of sphingomyelin, while a few cases probably result from deficiency of an activator protein.

The condition presents in infancy and is characterized by hepatosplenomegaly, lymphadenopathy and physical and mental underdevelopment. About a quarter of patients present with familial amaurotic idiocy with characteristic cherry-red-spots in the macula of the retina.

The storage of sphingomyelin and cholesterol occurs within the lysosomes, particularly in the cells of mononuclear phagocyte system. The cells of Niemann-Pick disease are somewhat smaller than Gaucher cells and their cytoplasm is not wrinkled but is instead foamy and vacuolated which stains positively with fat stains. These cells are widely distributed in the spleen, liver, lymph nodes, bone marrow, lungs, intestine and brain.

GLUCOGENOSSES

Disease	Enzyme	Organs in which pathologic proteins accumulate
Gierke's (type 1)	Glucose-6-phosphatas	Liver, kidneys
Pompe's (type 2)	Acid -L-glucosidase	Muscles
MacArdle's (type 5)	System of muscles's phosphorilas	Muscles
Hers' (type 6)	Liver's phosphorilas	Liver
Forbes-Cori (type 3)	Amylo-1,6-glucosidase	Liver, muscles, heart
Andersen's (type 4)	Amylo-1,4-1,6-trans- glucosidase	Liver, spleen, lymphatic glands

In the type 1, 2, 5, 6 - the structure of glycogen in the tissues is not changed. In the type 3,4 - glycogen structure is changed.

GIERKE'S DISEASE (TYPE I)

This condition is inherited as an autosomal recessive disorder due to deficiency of enzyme, glucose-6-phosphatase. In the absence of glucose-6-phosphatase, excess of normal type of glycogen accumulates in the liver and also results in hypoglycaemia due to reduced formation of free glucose from glycogen. As a result, fat is metabolized for energy requirement leading to hyperlipoproteinemia and ketosis. Other changes due to deranged glucose metabolism are hyperuricaemia and accumulation of pyruvate and lactate.

The disease manifests clinically in infancy with failure to thrive and stunted growth. Most prominent feature is enormous hepatomegaly with intracytoplasmic and intranuclear glycogen. The kidneys are also enlarged and show intracytoplasmic glycogen in tubular epithelial cells. Other features include gout, skin xanthomas and bleeding tendencies due to platelet dysfunction.

POMPE'S DISEASE (TYPE II)

This is also an autosomal recessive disorder due to deficiency of a lysosomal enzyme, acid maltase, and is the only example of lysosomal storage disease amongst the various types of glycogenoses. Acid maltase is normally present in most cell types and is responsible for the degradation of glycogen. Its deficiency, therefore, results in accumulation of glycogen in many tissues, most often in the heart and skeletal muscle, leading to cardiomegaly and hypotonia.

Mc ARDLE'S DISEASE (TYPE V)

The condition occurs due to deficiency of muscle phosphorylase resulting in accumulation of glycogen in the muscle (deficiency of liver phosphorylase results in type VI glycogenoses). The disease is common in 2nd to 4th decades of life and is characterized by painful muscle cramps, especially after exercise, and detection of myoglobinuria in half the cases.

The outcome of storage diseases is unfavorable because of insufficient development of the respective organ.