Chapter 6

IMMUNOPATHOLOGIC PROCESSES

Immunopathologic processes occur because of functional disorder of the immunocompetent (lymphoid) tissue. During these processes, the immune reactions, which normally have the defense function of the body against various foreign antigen substances, can cause the alteration of the self tissues. The immune reactions, in these conditions, act more harmfully upon the tissues than the antigens themselves.

The immune response can be of cellular or humoral types, and are morphologically manifest by cellular proliferation and differentiation in the central and peripheral organs of the lymphoid system. The character of the immune reaction depends especially on: antigen peculiarities, its quantity, the way of access into the body, and previous contacts with the respective immunogenic antigen. When various soluble antigenic substances, for example microbial toxins or extracellular pathogenic agents (bacteria) penetrate into the body, a humoral type immune reaction is unleashed. Its essence consists in the destruction of the antigen by the specific antibody, produced by plasmocytes, whose predecessors are the B lymphocytes. The antigen-antibody complex is phagocitized and eliminated from the body by macrophages — immune phagocytosis (fig.151). Thus, the effector cell in the humoral immune reaction is the plasmocyte.

In cases when cellular (tissular) antigens penetrate into the body, for example foreign cells or some pathogenic agents which parasitize intracellularly (especially viruses and fungi) cellular type immune reaction is stimulated. The essence of it is in the destruction of the antigen by the sensitized T (killer) lymphocytes, with the help of macrophages, without the participation of antibodies the immune cytolysis (cytolytic ant cytopathic action of the lymphocytes). The effector cells from the cellular immune reaction are the T - killer lymphocytes and the macrophages (fig.152).

Each type of immune reaction includes 3 consecutive stages: afferent stage — information transmission from specific reactive cells, central stage — cellular proliferation and differentiation from the lymphoid system (blastic transformation of B or T lymphocytes, the appearance of plasmocytes, the sensitizing of T lymphocytes) and the efferent stage — the reaction of specific antibody and sensitized T lymphocytes with the antigen.

The morphologic manifestations of the immunopathologic processes can be divided into 2 groups: immunogenesis disorders and local immune reactions (allergic or hypersensitivity reactions).
Immunopathologic processes

Immunological disorders

Immunological disorders are seen in cases of massive (long time) antigenic stimulation, in immunodeficiency states (immunodeficient syndromes) and autoimmune diseases. They are manifest by characteristic lesions of the central lymphoid organs (thymus) and peripheral lymphoid organs (lymphatic ganglions, spleen, lymphoid formations of the digestive tract: tonsils, Peyer's patches, vermiform appendix, solitary follicles of the large intestine).

The lesions of thymus, which can be observed in immune disturbances are represented in table 25. These lesions are the result of, and in some cases, the cause of immunologic homeostasis disturbances. Thymus disease can lead to a number of immunodifferent syndromes, autoimmune diseases and endocrine disturbances.

### The modifications of thymus in immunological disturbances

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Morphologic characteristic</th>
<th>Causes</th>
<th>Consequences, functional importance</th>
</tr>
</thead>
</table>
| Accidental involution           | Macrocopically - the rapid decrease of thymus weight and volume (8-10 times); microscopically - the progressive destruction of lymphocytes, collapse of the reticuloepithelium, dystrophy of the Hassall corpuscles; the characteristic sign - reversal of the thymic lobule layers | Severe infectious diseases, malignant tumors with metastasis, leukemia    | a) Thymus regeneration  
b) Thymus atrophy                          |
| Atrophy                         | The decrease in weight and volume of the thymus                              | It is a consequence of accidental involution                           | Acquired immunodeficiency                                                |
| Thymomegaly                     | Thymus has an increased weight and volume, the histologic structure is normal | Can be a congenital or acquired malformation (in chronic insufficiency of the adrenal glands) | Functional insufficiency of the thymus, immune deficiency of cell - mediated reactions |
| Thymus hyperplasia with lymphoid follicles | Thymus is increased in size, is infiltrated with B lymphocytes and plasmocytes; the thymic lobules contain lymphoid follicles with germinative centers, which are not normally present | Immuno competent system functional disorders                            | The appearance of autoimmune processes                                   |
| Agenesis (aplasia)              | Thymus is either absent or persists as a embryonic rudiment                  | Congenital malformations                                               | Congenital cellular or mixed immunodeficiency                            |
| Hypoplasia                      | The incomplete development of the thymus                                     |                                                                        |                                                                          |
| Dysplasia                       | The structure of the thymus is altered, the number of lymphocytes is reduced |                                                                        |                                                                          |
Microspecimen “Accidental involution of the thymus”.

The thymic lobules (fig.153) are smaller in size, the cortical layer is thinner and poor in lymphocytes as a result of progressive destruction and phagocytosis by macrophages. The medullary layer gets equal or even richer in lymphocytes than the cortical layer (the reversing of thymic lobule layers). The thymic corpuscles are also of smaller dimensions, and present as homogeneous eosinophilic masses. Some of the corpuscles undergo fusion and cystic formation. Dystrophic calcification sites (of an intensified eosinophilic color) also occur; the reticuloeipithelium is collapsed, the interlobular connective tissue septa are thickened.

Macroscopically, the dimensions and weight of the thymus decrease rapidly (by about 8-10 times).

Involution is seen in many childhood diseases with intoxication, especially in severe infectious diseases, trauma, overcooling or overheating, malignant tumors, leukemia, etc.

The degree of thymus involution depends on the duration and severity of the respective disease. If the disease evolution has a short course, the thymus can be rehabilitated. The main cause of thymus involution in these cases is the hypersecretion of glucocorticoid hormones in stress conditions, as well as long time massive antigenic stimulation.

The accidental involution of the thymus can be reversible, due to the high regenerative capacity. In cases of severe infectious diseases, (bacterial or viral) infections with purulent processes or malignant tumors with metastasis, acquired atrophy of the thymus may result.

The clinic-functional importance of thymic accidental involution depends on the degree of decrease of cellular and humoral immunity, due to the diminished thymic hormonal secretion.

Macrospecimen “Thymomegaly”.

The thymus has considerably increased in size (fig.154), leading to the compression of the neighboring organs, especially the trachea, causing respiratory disorders. It is usually seen in children, and represents a congenital condition. The histologic structure of the thymus is unchanged. As a rule, it is associated with developmental disturbances of the cardiovascular system (aorta and major arteries), dysfunction of adrenal and sexual glands. In the same patients, despite thymomegaly, thymic dysfunction with its hormonal secretion and cellular immunity disorders is observed. These patients are very sensitive to antigenic stimulation (to immunization, in infectious and infectoalergic diseases, surgery, narcosis, drugs). Sudden death frequently occurs at the action of various stress factors (for example, during surgical interventions). The sudden death is caused not only by thymus dysfunction, but also by adrenocortical functional insufficiency. It is also seen in adults in cases of chronic adrenal insufficiency (the thymus is a effector organ of the adrenal glands). The causes of death are usually infectious and infectoalergic diseases, whose evolution is aggravated by the disorders of the immune system.

Microspecimen “Thymic hypoplasia in the mixed immunodeficient syndrome”.

The thymic lobules (fig.155) are smaller in size, the number of lymphocytes is considerably reduced, the cortical layer is atrophic, the medullary layer contains an insignificant number of small Hassall corpuscles, which can be totally absent in some regions. The interlobular connective tissue septa are thickened.

Thymic hypoplasia is a congenital development disturbance. Macroscopically, the thymus is incompletely developed, the thymic hormonal secretion is decreased or completely
abolished. It is associated with hypoplasia of the lymphoid tissue from the lymph nodes and spleen, the atrophy affects mainly the thymodependent zones. It is clinically manifest by the body inability to unleash cellular and humoral reactions. Children are predisposed to infectious diseases, which have a relapsing course with severe complications (pneumonia, septicemia). Thymic hypoplasia is frequently associated with other congenital anomalies and malignant mesenchymal tumors.

The modifications which occur in the lymphatic ganglions and in the spleen as a result of antigenic stimulation are unspecific and stereotypical. Macroscopically, these organs have an increased volume, are affected by edema and hyperemia. Microscopically, hyperplasia of the immunocompetent cells, especially the transformation of small lymphocytes into blastic cells is observed.

Depending on the type of the immune reaction, the hyperplastic processes take place in different zones of the peripheral lymphoid organs. The repartition of thymodependent and bursodependent zones is given in table 26.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Bursodependent zones</th>
<th>Thymodependent zones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic ganglions</td>
<td>Cortical layer</td>
<td>Paracortical layer</td>
</tr>
<tr>
<td></td>
<td>Medullar layer</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>The peripheral zones of the lymphatic follicles</td>
<td>Paraarterial zone (around the centrofollicular artery)</td>
</tr>
<tr>
<td>Tonsils</td>
<td>Tonsillar follicles</td>
<td>Interfollicular subepithelial lymphoid zones</td>
</tr>
<tr>
<td>Intestinal lymphoid tissue</td>
<td>Intestinal follicles</td>
<td>Interfollicular subepithelial lymphoid zones</td>
</tr>
</tbody>
</table>

When the humoral immune reaction is stimulated in the bursodependent zones, B lymphocytic, lymphoblastic hyperplasia, plasmoblastic and plasmocytic transformation of the B lymphocytes and the proliferation of macrophages occur. During cellular type immune reaction in thymodependent zones, T lymphocytic activation and sensitizing and macrophagic hyperplasia occur. These hyperplastic processes are more evident in the regional lymph nodes in immediate proximity of the site of antigen entrance into the body. The induction of antibody elaboration during the humoral immune reaction is associated with the appearance of germinative centers in the follicles of the lymph nodes and spleen, the so called secondary follicles (follicles with germinative centers). The proliferation of lymphoblasts takes place in the germinative centers. These follicles are formed around the macrophages which contain the antigen. During the cellular type immune reaction the blastic transformation takes place not in the germinative centers of the follicles but in the paracortical zones of the lymph nodes and in the periarterial zones of the splenic follicles.

**Microspecimen** "Hyperplasia of the lymph node follicles as a result of antigenic stimulation".

The lymph node (fig. 156) contains multiple secondary follicles with clear germinative centers, in which the proliferation of lymphoblasts takes place. The appearance of secondary follicles and its increased development reflects the degree of the immune reaction intensity
and of the plasmocyte antibody secretion. These hyperplastic processes are more intense in
the lymph nodes which are located near the place of antigen entrance into the body.

**Microspecimen “Hyperplasia and the plasmatisation of the lienal follicles in antigenic
stimulation”**.

In the lymph nodes (fig. 157) hyperplasia of the lymphoid follicles and the appearance
of germinative centers can be observed. The T lymphocytes of the periarterial zone (of an
intense basophilic color) move toward the periphery, while at the periphery of the follicles
there can be observed the proliferation of plasmoblasts and plasmocytes. This shows the
intensity of humoral type immune reaction. Macroscopically, the spleen is larger in size,
has a variegated appearance. There are multiple whitish foci, which represent hyperplastic
lymphatic follicles with germinative centers.

In case of hereditary humoral immunodeficiency, the spleen suffers follicle decrease,
and absence of germinative centers and of plasmocytes. In the lymph nodes the lymph
follicles and the cortical layer (bursodependent zones) are absent, while the paracortical
layer (thymodependent zones) persists. In cellular immunodeficiency syndromes, hypoplasia
of paraarterial zones of the lienal follicles and also hypoplasia of paracortical layers of
the lymph nodes is observed. In mixed immunodeficiency there is total hypoplasia of the
peripheral lymphoid tissue.

**The local allergic reactions or the hypersensitivity reactions**

These reactions appear in a sensitized body and are characterized by the local alteration
of tissues.

The main etiologic factors that encourage these reactions are: a) prolonged (repeated)
action of the allergen; b) allergenic overtaxation (big doses); c) general hyperreactivity of the
body; d) hereditary predisposition for allergy.

The hypersensitivity reactions can be: a) immediate type; b) late or delayed type; c)
transplantation immune manifestations (graft rejection reaction).

The general characteristics of the hypersensitivity reactions are summarized in table 27.
The mechanisms of achievement (effector mechanisms) of the allergic processes are:

a) inactivation or neutralization reaction; b) immediate anaphylactic reaction; c)
cytotoxic and cytolytic reaction; d) toxic immune complexes reaction; e) cellular type
sensitization (delayed hypersensitivity); f) granulomatus reaction.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Immediate type</th>
<th>Delayed type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term of appearance</td>
<td>15-20 min after the contact of the specific allergen with the sensitized tissues</td>
<td>24-72 hours after the introduction of the allergen unleashing dose</td>
</tr>
<tr>
<td>Which type of immune reaction it is linked with</td>
<td>With humoral immune reaction</td>
<td>With cellular immune reaction</td>
</tr>
<tr>
<td>Factors that alter the tissues</td>
<td>Complement, circulating immune complexes, circulating antibodies</td>
<td>Sensitized T (killer) lymphocytes and macrophages</td>
</tr>
</tbody>
</table>
The characteristic of these immunopathologic mechanisms is given in table 28 and in fig.158-163.

Morphologically, the allergic processes are manifest by classic inflammatory reactions (acute or chronic immune inflammation).

### Table 28

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>General characteristic</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Inactivation and neutralization reaction | The elaboration of antibodies against some biologically active substances or cellular surface receptors:  
- inactivation of hormones, enzymes (insulin, thyroglobulin, clotting factors), toxins (in diphtheria, tetanus);  
- cell function alteration due to the antireceptor antibodies (antibodies against insulin, acetylcholine, thyroid stimulating hormone, thyroglobulin receptors, against parietal cells of the gastric mucous membrane);  
the antireceptor antibodies in some cases are bloc-king, in other cases are stimulating the functional activity of the cells | Insulin dependent diabetes mellitus, myasthenia gravis, hypothyroidism, thyreotoxicosis, pernicious anemia, coagulopathies |
| Anaphylactic reaction of immediate type | At first antigen (Ag) penetration, IgE are elaborated, which stick to the surface of mast cells and basophil leukocytes; at repeated administration of the same Ag, the antigen-antibody reaction causes the degranulation of mast cells and the sudden release of mediators (histamine, serotonin, heparin), which cause spasms of the smooth muscles of the bronchi and intestine, edema, mucus hypersecretion, vascular dilatation and hyperemia | Anaphylactic shock (to drugs, insect venom), urticaria, atopic bronchial asthma, allergic rhinitis, hay fever, Quincke edema, alimentary or medicamentous allergy |
| **Cytotoxic (cytolytic) reaction** | The antibodies are elaborated against the super-ficial antigenic components of the heterogeneous cellular membrane (the cells of the transfused or self blood, transplant). There can be two variants:  - the cytotoxicity mediated by the complement (activation of the complement causes the secretion of mediators and the lesion of the target cell);  - the cytotoxicity mediated by antibodies (antibodydependence - Ag-Ab reaction) takes place on the surface of the target cells, which subsequently are destroyed by K (killer) cells or NK (natural killer) cells, or phagocytized by macrophages | The hemolytic disease of the newborn, posttransfusion reactions, autoimmune hemolytic anemia, medicamentous cytopenia (agranulocytosis, thrombocytopenia), vascular purpura, graft (transplant) rejection reactions |
| **The reaction of toxic immune complexes** | The antigen-antibody immune complex leads to the activation of complement components, basophil and neutrophil leukocytes, to the elimination of the inflammatory mediators. The lytic action of the toxic immune complexes can be produced by:  a) excess of antibodies with inflammatory re-action in the site of antigen entrance (Arthus reaction);  b) excess of antigen with generalized reaction and the depositing of the immune complexes in the basal membranes of the capillaries from the kidneys, articulations, skin (serum disease) | Serum sickness disease, glomerulonephritis, rheumatic diseases (disseminated lupus erythematosus, rheumatoid arthritis), allergic dermatitis, farmer’s lungs |
| **Cellular type allergic reaction (cellular sensitizing)** | The immune response appears after 24-72 hours, depending on the T lymphocytes and macrophages, which are responsible for the im-mune cytolysis - the destruction of target cells, which contain antigens; the morphologic substrate - lymphocytic and macrophagic infiltration | Tuberculin type reaction, contact dermatitis, graft rejection, autoimmune diseases, tuberculosis, syphilis, helminthosis, mycosis |
| **Granulomatous reaction** | Appears in case of long time (or unlimited) antigenic persistence; the granulomatous reaction leads to the isolation and delimitation of the pathogenic antigen (allergen). The main cellular components of the granulomas are the epithelioid and giant cells | Tuberculosis, syphilis, rheumatism, sarcoidosis, Crohn disease, berylliosis |

*Microspecimen “Allergic rhinitis”.*

In the specimen (fig.164) there is proliferation of glandular epithelium. The mucous membrane is strongly edematous and hyperemic. An inflammatory infiltrate is located predominantly perivascularly, with a large number of lymphocytes, plasmocytes and eosinophil leukocytes. Clinically, it is manifest by abundant seromucous secretion. It appears as a reaction to allergens of vegetal (pollen) or bacterial origin. It can complicate with the appearance of nasal polyps.
6.1. AUTOIMMUNE DISEASES

The autoimmune diseases represent a group of diseases which are based on the autoantibody and sensitized lymphocytes reaction against the antigens of the self tissues, causing their functional and structural alteration. Among the most frequent etiologic factors of autoimmunization, of a great importance are the chronic viral infections, radiation, and some physical and chemical agents. These act upon the organs of the immunocompetent system as well as target-organs. Three groups of autoimmune diseases may be distinguished depending on autoimmunization development mechanism: I) organ-specific; II) organ-nonspecific; III) affections with secondary autoimmune disorders.

The general characteristic of these groups are represented in table 29.

<table>
<thead>
<tr>
<th>Autoimmune disease group</th>
<th>Mechanisms of producing and the most important causal factors</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ-specific autoimmune diseases (genuine)</td>
<td>Affection of the physiologic isolation of organs and tissues, which are deprived of the immune tolerance, and the alteration of the hemo-vascular barriers; the unmodified antigens of these tissues, which are immunologically isolated (sequestered) cause the elaboration of antibodies and/or T lymphocyte sensitization; the causal factors: chronic viral infection, trauma, radiation, sunstroke</td>
<td>Hashimoto's thyroiditis, encephalomyelitis, disseminated sclerosis, polyneuritis, sympathetic ophthalmia, asperma, idiopathic Addison's disease</td>
</tr>
<tr>
<td>Organ-nonspecific autoimmune diseases (systemic)</td>
<td>Primary functional disorders of the immunocompetent system, the lymphocytes lose the ability to distinguish between self and nonself antigens; the lesions have a generalized (systemic) character; causative factors: mutations, lymphotropic viral infections</td>
<td>Disseminated lupus erythematosus, rheumatoid arthritis, systemic scleroderma, dermatomyositis, thrombocytopenic hemolytic purpura</td>
</tr>
<tr>
<td>Diseases with secondary autoimmune disorders</td>
<td>Secondary autoimmunization, the appearance in the body of some new heterogeneous antigens, which can lead to the suppressing of natural tolerance. Etiopathogenic mechanisms: - protein denaturing in burns, irradiation, cold trauma, chronic inflammation, viral infections; - cross reaction: the appearance of some bacterial antigens, whose structure is identical to the one of some bodily tissues (for example, the cardiac serotype Y of the beta-hemolytic streptococcus has antigenic commonality with cardiomycyte sarcolemma, while the nephritogenic serotype XII - with the basal membranes of the renal glomeruli, klebsiella - with the pulmonary tissue; - the haptenic mechanism; the role of haptens play the necrotic products, drugs, toxins</td>
<td>Glomerulonephritis, rheumatism, myocardial infarction, chronic gastritis, ulcerous colitis, hepatic cirrhosis, medicamentous disease, allergic anemia, etc.</td>
</tr>
</tbody>
</table>
It must be mentioned that the group III affections are not independent autoimmune diseases, the immune conflict is only a complication of the main morbid process. Secondary autoimmune disorders lead to the chronicity and aggravation of the respective disease.

Morphologically, the autoimmune conflict is manifest by the infiltration of the target-organ with immunocompetent cells (lymphocytes, plasmocytes, macrophages), the appearance of lymphoid follicles with germinative centers, dystrophic and necrotic lesions of the parenchyma and the proliferation of connective tissue.

Autoimmune or the Hashimoto’s thyroiditis can serve as an example of a true autoimmune disease. In the microscopic specimen (fig.165 and 166) the stroma of the thyroid gland is diffusely infiltrated with lymphocytes and plasmocytes. Some places contain lymphoid follicles with clear germinative centers. These infiltrates gradually replace the glandular parenchyma. The thyroidian follicles are atrophic, containing weakly stained or vacuolated colloid, some of them without a lumen and with sclerotic foci. Macroscopically, the thyroid gland is larger, harder, with an elastic consistency and without adherences to the neighboring tissues. Clinically, it is accompanied by hypothyroidism and it evolves toward mixedema. It is seen almost exclusively in women 40-50 years of age.