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# Comparative Immunomorphological Characteristics of the Thymus in Humans and Laboratory Animals: Review of Literature

**Igamova O. K.[1], Nuraliev N. A.[2]**

[1]Urgench State University, Urgench, Uzbekistan
[2]Bukhara State Medical Institute, Bukhara, Uzbekistan

**Abstract** The article provides a literary review of clinical and experimental studies on the study of immunological and morphological aspects of the thymus of humans and laboratory animals, similarities and species differences between them are given, and age-related features of thymic involution are described. Modern research methods were used, which made it possible to describe at the cellular level some immunomorphological aspects of the study of the thymus.

**Keywords** Human and laboratory animal thymus, Thymic hormones, Morphology and morphometry of the thymus, Thymic involution

## 1. Introduction

Thymus translated from Greek means "vital force," as this organ ensures rejuvenation of the entire body. It is known that the thymus not only differentiates lymphocytes, but also produces thymic hormones, which activate the immune system, improve skin regeneration, and promote rapid cell recovery [1].

The thymus gland (thymus) has attracted the attention of researchers for four or more centuries; only in the 20th century was the attitude of scientists towards this organ determined as a generator and regulator of immune reactions, a participant in the production of many populations of immunocompetent cells of the immune system [12,18,23,31].

The thymus is still considered as a derivative of the body's immune system and as its central organ. Infectious diseases, systemic autoimmune and oncological diseases, the problem of tissue incompatibility determine human life expectancy and therefore scientific interest in the topic of studying the functions of the immune system and its central organ, the thymus, is understandable [19,27,32].

Over a long period, the ontogenesis of immunity experiences a number of critical stages that must be taken into account when assessing the state of the body's natural defenses. The difficulty of studying lies in the huge number of integral connections of the thymus with other components of the immune system, nervous, endocrine, hematopoietic and connective tissue, organs and cells that provide barrier function [10,25].

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The thymus, as the primary organ of the immune system, plays a vital role in the embryonic period and immediately after birth. In humans, it has a maximum mass at the age of 1 year, after which age-related involution begins, and about 3% of active thymic tissue is lost annually [12,19].

The microenvironment of the thymus ensures the formation of clonal diversity of T-lymphocytes through the processes of positive and negative selection of clones with the formation of tolerance to "self" and functional heterogeneity of T-cells. At the developmental stage, the T lymphocyte acquires an antigen recognition receptor (TCR-T- cell receptor), associated with the CD3 complex, which, after binding to the antigen, ensures transmission of the signal into the cell [29,33,35].

The main functions of the thymus (lymphatic, immunoregulatory and endocrine) are carried out due to the secretion of polypeptide hormones by epithelial cells - thymosin, thymopoietin, thymulin. The amount of thymulin in the blood serum is an important parameter for assessing - the hormonal function of the thymus [1,29,34].

The main functions of the thymus are to ensure the maturation and differentiation of thymocytes, integrating various populations of thymocytes and macrophages to implement immune responses. The morphofunctional state of the thymus determines the activity of peripheral structures of immunogenesis and the severity of the body's defense reactions [11,18]. An age-related decrease in the level of thymic hormones, removal of the thymus, as well as the effect of unfavorable environmental factors and a number of congenital and acquired diseases lead to a weakening of the function of T-lymphocytes. This may serve as the basis for the development of secondary immunodeficiency states [30,34].

In all mammals, the thymus is located in the mediastinum; in humans, it is located in the anterior part of the superior mediastinum. Adjacent to its ventral surface are the body of the sternum, the sternohyoid and sternothyroid muscles, the parietal pleura, and to the dorsal surface are the pericardium, trachea, aortic arch, internal jugular and brachiocephalic veins, and the recurrent laryngeal nerve [9,12,27].

The rat thymus is located in the chest cavity, in the cranial mediastinum, at the level of the cranial parts of the lungs, but to one degree or another penetrates into the neck area. In situ, the rat thymus resembles an onion or cone. The thymus is adjacent to the trachea and the main bronchi, the aortic arch and its branches, the ascending aorta and pulmonary trunk, the vena cava (thoracic part), the base of the “cone” to the atria and the roots of the lungs [16,17,26].

The number of lobes in the human thymus varies from one to five, which was confirmed in the 20th century, but the main structural variant of the human thymus is its two-lobe organization. In rats, the thymus consisting of two lobes is also most often found, while in adult rats a thymus consisting of three lobes was found in 4.3% of cases, and in newborn rats this variant of the organ structure was found in 21.8% of cases [11,20,21].

## 2. Materials and Methods

The thymus is covered with a connective tissue capsule; septa extending from it reach the border between the cortex and medulla and divide the parenchyma into lobules of different sizes. In the thymus lobule there are 2 parts: the cortex is dark, with a dense arrangement of lymphoid cells or thymocytes, and the medulla is lighter, in which there are fewer thymocytes, but reticular epithelial cells are well defined, thymic bodies are also detected here, 90% of the cellular composition of the thymus is represented thymocytes [1,6].

Some authors distinguish 4 zones within the lobule - the outer subcapsular zone, the internal cortical zone, the medulla, perivascular connective tissue, while other researchers describe 3 zones - the cortical, the corticocerebral and the medulla. However, in later studies, 5 zones began to be distinguished in the thymus lobule - 3 in the cortex (subcapsular, central zone of the cortex and bordering the medulla) and 2 in the medulla - zone bordering the cortex and central [1,9,21].

The subcapsular zone of the cortex is formed by a network of epithelial reticulocytes. The cells of this network contain prethymocytes, lymphoblasts and a small number of macrophages. In this section, under the conditions of a specific microenvironment, proliferation occurs and the initial stages of maturation of prethymocytes, which have immigrated here from the bone marrow, take place. In the inner cortical zone, antigen-independent differentiation of thymocytes ends, selection and elimination of auto-aggressive ones are carried out thymocytes, and mature autotolerant cells migrate into the medulla or leave the thymus in the region of the corticomedullary zone. Thymocytes of the inner cortical zone make up up to 80% of all thymic lymphocytes [25,27,32].

Antigen-dependent maturation of thymocytes occurs in the thymic medulla. Thymocytes in this zone have the morphology of medium and small lymphocytes, have a high degree of differentiation, the ability to undergo a blast transformation reaction, and they have the antigenic characteristics of helpers, killers, and suppressors. From here they enter the bloodstream and the thymus-dependent areas of the immune system. At the initial stage of development, the epithelial primordium of the thymus in the cervical part it has a lumen - thymopharyngeal duct that undergoes obliteration [4].

It is known that the immune system functions in close relationship with the neuroendocrine system. In intersystem interactions, the adrenal cortex plays an important role in regulating the functional state of the thymus and bone marrow, as well as in the development of adaptive reactions of the body; with age, rhythmic fluctuations in the level of glucocorticoids in the blood change [6,28].

Petrenko V.M. [22] emphasizes that the thymus can be classified as a neuroendocrine system, since the epithelial cells of the gland produce substances. This organ produces up to 40 types of biologically active substances, divided into cytokines (interferon gamma (INF -γ), tumor necrosis factor ( TNF ), granulocyte colony stimulating factor), which act as thymic hormones - thymosin, thymulin, thymostimulin. Identical results were obtained by Yan F. et al. [36].

Data are presented on the interaction of the neuroendocrine system and the thymus, carried out through the neuroendocrine -immune adaptive systems of the body. The presence of adrenergic and peptidergic nerves in the thymus creates conditions for the action of the neuropeptides they produce. The latter activate receptors on thymic cells, influencing basic processes in the thymus, including the maturation of T lymphocytes, the production of cytokines, hormones and peptides. Thymus-produced peptides and/or cytokines controlled by them enter the brain, influencing neuronal function, which provides the basis for behavioral changes and the maintenance of homeostasis in response to infection. With the aging of the body, as well as a number of diseases, disturbances in the interactions of processes in the thymus and the central nervous system are shown [28].

Using morphological, immunohistochemical, and morphometric methods, it was established that age-related transformations of the tissue structure of the thymus are characterized by the development of fibrous connective and adipose tissue in the cortical septa, which leads to fragmentation of the cortical substance, and then to the separation of fragments of the cortical and medulla [5,15].

The greatest progression of involution processes in the thymus is observed during the second mature age period (36-60 years). In elderly and senile people, islands of parenchyma remain without differentiation into the cortex and medulla, surrounded by adipose tissue. During the process of age-related involution, the content of lymphocytes decreases, their mitotic activity decreases, and the proportion of cells capable of proliferation in the cortex and medulla decreases. This is due to both the lack of influx of bone marrow precursors into the thymus and a decrease in the number of epithelial reticular cells that create the microenvironment for T lymphocytes. Age-related changes are accompanied by a decrease in the number of thymic corpuscles, among which the proportion of mature forms increases; thymic corpuscles are not found in the thymus of elderly people. The rate of age-related involution of this organ is individual in nature and varies widely, which is consistent with the life expectancy of people [9].

Galeeva E.N. [5,6] in their work used sectioned material from 100 human fetuses obtained through artificial termination of pregnancy at the age of 16 to 22 weeks of gestation. To assess the quantitative skeletopy of the thymus, the distance from the center of the vertebral body of the studied level to the edge of the posterior surface of the thymic lobes, the distance from the center of the vertebral body of the studied level to the edge of the anterior surface of the thymic lobes, the distance from the manubrium and body of the sternum to the edge of the posterior surface of the thymic lobes were studied., distance from the manubrium and body of the sternum to the edge of the anterior surface of the thymus lobes, longitudinal size of the cervical and thoracic thymus lobes, transverse size of the thymus lobes, thickness (antero - posterior size) of the thymic lobes, carried out from the level of the lower edge of ThII -III to ThV. Features of skeletotopy of the thymus were noted.

Other sources present the results of a morphological study of the thymic lobes of humans and outbred rats in postnatal ontogenesis using the thymic lobes of 53 humans and 71 rats. It has been established that in postnatal ontogenesis, common features and species differences can be traced in the structure of the thymus of humans and white outbred rats. These differences were manifested in different topography of the lobes: the relative position of the lobes, the position of the lower pole, the contact of the lobes with the sternum. The data obtained can be taken into account when modeling experimental studies on outbred white rats [21].

Evstropov V.M. [8] studied in guinea pigs of different ages (group 1 3-4 weeks, group 2 3 months). thymus cells of some subclasses having immunological significance. The content of thymocytes with receptors for peanut agglutinin (PNA+ cells) in the thymus was studied; E-ROK with rabbit erythrocytes; EAC-ROK in rosette formation with rabbit erythrocytes coated with antibodies and complement; Tμ-thymocytes rosette formation with bovine erythrocytes (EA-RO) loaded with the IgM fraction of specific antibodies, as well as Tγ cells rosette formation with bovine erythrocytes loaded with the IgG fraction of specific antibodies. It has been shown that to characterize age-related differences in the guinea pig thymus, methods for determining in the thymus cells of various subclasses that have immunological significance, in particular Tγ cells and PNA+ cells, can be used.

In representatives of four classes of terrestrial vertebrates (*Amphibia, Reptilia, Aves, Mammalia*, including humans), a number of macro- and micromorphological parameters of the thymus were studied: thymus mass index, corticocerebral index, index of length, width and thickness of thymic lobes, relative area of the bloodstream, the number and size of thymic bodies, the number of thymocytes of the cortex and medulla. The degree of influence of each morphological indicator on the morphological structure of the thymus as a whole has been established. It was revealed that an increase in the capacity of energy metabolism and the development of warm-bloodedness has the most significant impact on the morphology of the thymus of vertebrates and humans. It has been shown that, according to the studied morphological parameters, the human thymus differs from this organ of vertebrates living in a natural ecologically clean environment, which is associated with the influence of extreme anthropogenic conditions on human health [16].

The thymus, as the central organ of immunogenesis, responds to various environmental, stress, balneological and extreme factors by changing structures and cell populations. The severity of the body's protective reactions depends on the condition and activity of the thymus [23,24,34].

Thymus dysfunction leads to disruption of the body's defense mechanisms, but hyperactivation can trigger autoimmune and proliferative processes. Adequate functioning of the thymus in childhood ensures the development of an immune system capable of fighting infections. The size of the thymus varies significantly throughout life, and to date, misinterpretation of its condition has led to unnecessary open biopsies and thymectomies. [12].

It has been established that long-term exposure of rats to elevated ambient temperatures leads to a significant decrease in the organometric parameters of the thymus. The conducted morphometric study indicates to a decrease in the area of the thymus lobules and an increase in the area of the stromal component in comparison with the control. The cortex is characterized rarefaction of the visual field due to a decrease in lymphocytes, a decrease in their mitotic activity, the concentration increases destructive cells and macrophages. The amount in the medulla increases Hassall's corpuscle. These signs indicate functional depletion of the thymus of rats exposed to extreme elevated temperatures. mode [2].

Bobrysheva I.V., Kashchenko S.A. [3] conducted a morphometric study of the thymus of white outbred rats of 3 age periods: puberty, reproductive and the period of pronounced senile changes, which were administered an immunosuppressant cyclophosphamide. It has been shown that the administration of cyclophosphamide causes unidirectional negative changes in the morphometric parameters of the thymus in rats of all age periods on days 1-30 of observation. In animals of the reproductive period, as well as the period of pronounced senile changes, under the influence of cytostatics on the body, the intensity of involutive processes increases.

## 3. Result and Discussion

The authors studied the effect of experimental cold stress on the morphofunctional state of the rat thymus on different days using morphometric analysis. On the 7th day after exposure to cold, the area of the cortex significantly decreases compared to the control group, the area of the medulla and the number of epithelioreticular cells in the subcapsular zone increases, and the number of lymphocytes decreases. On the 14th day of exposure, the indicators of the areas of the cortical and medulla, the cortical-cerebral index do not differ from the control indicators. It was established that as a result of cold stress on days 7, 21 and 30, a redistribution of volume and cellular composition occurs, indicating a decrease in the functional activity of the thymus, increased death of lymphocytes, a decrease in mitotic activity and the accumulation of macrophages. Morphofunctional data from the 14-day experiment indicate the development of compensatory and adaptive changes in the thymus to cold exposure [7].

By morphological and morphometric studies, the authors established a negative effect of genetically modified products (soybeans) on the state of the thymus gland when fed for 30 days [35].

Loginova N.P. et al. [15] in their work presented the results of an immunohistochemical assessment of the expression of cytokeratins: pancytokeratin, CK 5/14, CK 8/18 in the epithelial cells of the thymic stroma in children 1 year of age with various intrauterine disorders of cardiac development. A relationship has been established between the accumulation of cytokeratins in the epithelial cells of the thymus and the severity of the development of cardiac defects. Immunocytochemically verified the immaturity of thymic epithelial cells, the cells lost contact with each other, and the architecture of the epithelial network was disrupted. As a consequence of this, the disappearance of cytokeratin, CK 8/18, was observed in the cortex in the epithelial cells of the thymus.

Circadian and circannual biorhythms play an important role in the body's adaptation to changes in environmental conditions; they are also characteristic of the immune system. It has been established that during aging, disturbances in the rhythmic functioning of the thymus and bone marrow are associated, and the introduction of bioactive thymic factors restores altered circannual rhythms of some immune parameters in old mice [14].

An analysis of 200 protocols of pathological studies of fetuses and newborns who lived after birth for no more than 48 hours, with different sizes of the thymus, was carried out. It was found that the smallest perinatal losses (20%) were in individuals with an average thymus size, the largest (44.5%) in individuals with a large thymus. It was shown that in children with different sizes of the thymus, a different spectrum of diseases was detected: in children with an average size of the thymus, diseases of infectious etiology were rarely recorded, in children with a small thymus, bacterial infections dominated among the diseases of this group, and in children with a large thymus, diseases were caused by intracellular pathogens [25].

Original data on the size of the thymus of 669 practically healthy children are presented and a comparison of the size of the organ by age with the National Vaccination Calendar is carried out. The fact that the thymus gland increased to very large values, reaching the 95th percentile or more in periods of 4-6 and 13-24 months, which coincides with the timing of the introduction of a particular vaccine and reactions to it, the breaks between their administration coincided with a decrease in the number of children with large thymus [13].

## 4. Conclusions

To assess the functional activity of the thymus, a method was used based on the identification of ring structures of T-lymphocyte DNA in the blood based on the content of T-receptor excision rings (TREC) in them. Studies have shown that in children with a large thymus, against the background of acute respiratory infections, the content of TREC increases and reaches the level of children with a medium-sized thymus. This fact indicates that the organ is working on the edge of the possible, which in certain situations can lead to a "breakdown" of its compensatory capabilities [13].

Thus, an analysis of the scientific literature of domestic and foreign researchers over the past 10-15 years has shown that a large number of clinical and experimental studies have been carried out to study the immunological and morphological aspects of the thymus. Modern research methods were used, which made it possible to describe some immunomorphological aspects of this problem at the cellular level. It has been established that there is not enough research into the immunological and microbiological aspects of the thymus of various bio- and immunocorrectors, and therefore research in this direction remains relevant and in demand.

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