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ABSTRACT

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GENERAL CHARACTERISTICS OF LYMPHOID TISSUE ASSOCIATED WITH THE MUCOUS MEMBRANES OF THE DIGESTIVE SYSTEM

Introduction. Lymphoid tissue associated with the mucous membranes of the digestive system plays an important role in the functioning of the immune system, acting as the body's first line of defense against external pathogens. Considering that the digestive system is one of the main routes of entry into the body of both beneficial and pathogenic microorganisms, the mechanisms of immune protection in this region should be as effective and adapted as possible. It is the presence of a branched structure of mucosa-associated lymphoid tissue (MALT), which includes tonsils, solitary and aggregate lymphoid nodules, in particular Peyer's patches, that ensures timely immune control and tolerance to obligate microflora. The study of the structure, functions, and interactions of lymphoepithelial formations with pathogens and commensals is important for understanding the pathophysiology of many diseases associated with immunodeficiency or immune aggression, as well as for the development of new approaches for the treatment and prevention of infectious and autoimmune diseases of the digestive system.

Methods. An analytical review was carried out on the basis of own research and peer-reviewed articles, monographs, textbooks. A literature search on the anatomical and functional characteristics of lymphoid tissue associated with the mucous membrane of the digestive system was carried out using the electronic databases PubMed, Google Scholar and the scientific library of the Poltava State Medical University.

Results. Studies have shown that the structured lymphoid formations of the mucous membranes of the digestive system are important components of barrier protection, which is formed during ontogenesis and is activated after birth. Lymphoepithelial formations of the intestines have a high concentration in the caudal direction, which coincides with

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the growth of the concentration of microflora that adapts in this environment. It was found that single lymphoid nodules and Peyer's patches were located in critical areas of the intestine where there was close contact with commensal and pathogenic microorganisms. Lymphoid nodules did not have a connective tissue capsule, but the cells of lymphoid tissue were grouped according to the type of reticular tissue, which allowed rapid activation of immune mechanisms. An important component was also the presence of follicle-associated epithelium, which provided a protective function and served as a barrier for pathogens.

Conclusion. Thus, the lymphoid tissue of the digestive system, integrated into the epithelial structures, forms a complex immune barrier, which is an important part of the mucosa-associated lymphoid tissue. Lymphoepithelial formations, as the data show, are adapted to control the microflora and ensure tolerance to commensals, which indicates their evolutionary significance. The results of the study confirm that the structured lymphoid formations of the mucous membranes of the digestive system are important not only for the physiology of digestion, but also for the maintenance of immune homeostasis, and also open the prospects for further research in order to develop new therapeutic strategies for the treatment of immune disorders of the digestive tract.

Keywords: immune system, mucous membrane, lymphocytes, Mucosa Associated Lymphoid Tissue (MALT), Gastro Associated Lymphoid Tissue (GALT), small intestine, colon, lymphoid nodule, Peyer's patches, intestinal crypts.

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РЕЗЮМЕ

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ЗАГАЛЬНА ХАРАКТЕРИСТИКА ЛІМФОЇДНОЇ ТКАНИНИ, АСОЦІЙОВАНОЇ ЗІ СЛИЗОВИМИ ОБОЛОНКАМИ ТРАВНОГО ТРАКТУ

Вступ. Лімфоїдна тканина, асоційована зі слизовими оболонками травного тракту, відіграє критично важливу роль у функціонуванні імунної системи, виступаючи першою лінією захисту організму від зовнішніх патогенів. Враховуючи, що травний тракт є одним із головних шляхів потрапляння до організму як корисних, так і патогенних мікроорганізмів, механізми імунного захисту в цьому регіоні мають бути максимально ефективними та адаптованими. Саме наявність розгалуженої структури мукозоасоційованої лімфоїдної тканини (МАЛТ), яка включає мигдалики, солітарні та агрегатні лімфоїдні вузлики, зокрема пейєрові бляшки, забезпечує своєчасний імунний контроль та толерантність щодо облігатної мікрофлори. Дослідження структури, функцій та взаємодій лімфоепітеліальних утворень з патогенами і коменсалами має важливе значення для розуміння патофізіології багатьох захворювань, пов'язаних з імунодефіцитом або імунною агресією, а також для розробки нових підходів до лікування та профілактики інфекційних та аутоімунних хвороб травної системи.

Методи. Проведено аналітичний огляд на основі власних досліджень та рецензованих статей, монографій, навчальних

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посібників. Літературний пошук з анатомо-функціональної характеристики лімфоїдної тканини, асоційованої зі слизовою оболонкою травного тракту, здійснено за допомогою електронних баз PubMed, Google Scholar та наукової бібліотеки Полтавського державного медичного університету.

Результати та їх обговорення. Дослідження показали, що структуровані лімфоїдні утворення слизових оболонок травного тракту є важливими компонентами бар'єрного захисту, що формується ще в онтогенезі та активується після народження. Лімфоепітеліальні утвори кишечника мають високу концентрацію в каудальному напрямку, що збігається зі зростанням концентрації мікрофлори, яка адаптується в цьому середовищі. Виявлено, що поодинокі лімфоїдні вузлики та пейєрові бляшки розташовані в критично важливих зонах кишківника, де відбувається тісний контакт з коменсальними та патогенними мікроорганізмами. Лімфоїдні вузлики не мають сполучнотканинної капсули, але клітини лімфоїдної тканини згруповані за типом ретикулярної тканини, що дозволяє швидко активувати імунні механізми. Важливою складовою є також наявність фолікуло-асоційованого епітелію, що забезпечує захисну функцію та слугує бар'єром для патогенів.

Висновок. Таким чином, лімфоїдна тканина травного тракту, інтегрована в епітеліальні структури, утворює комплексний імунний бар'єр, який є важливою частиною мукозоасоційованої лімфоїдної тканини. Лімфоепітеліальні утворення, як показують дані, адаптовані для контролю над мікрофлорою і забезпечення толерантності до коменсалів, що свідчить про їх еволюційне значення. Результати дослідження підтверджують, що структуровані лімфоїдні утворення слизових оболонок травного тракту є важливими не тільки для фізіології травлення, але й для підтримки імунної гомеостазу, а також відкривають перспективи подальших досліджень з метою розробки нових терапевтичних стратегій для лікування імунних порушень травного тракту.

Ключові слова: імунна система, слизова оболонка, лімфоцити, мукозо-асоційована лімфоїдна тканина, лімфоїдна тканина травного тракту, тонка кишка, товста кишка, лімфоїдний вузлик, пейєрові бляшки, кишкові крипти.

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INTRODUCTION

The total area of contact of the mucous membranes of an adult with antigens of external origin significantly exceeds the area of the skin, amounting to about 300–400 m^2 [1].

The largest proportion of this area is accounted for by the mucous membranes of the digestive system, including the mouth, pharynx, esophagus, stomach, small and large intestine [2].

The second largest portion of the body belongs to the respiratory system, which includes the nasal cavity, larynx, trachea, and bronchi. The rest belongs to the mucous membranes of the ducts of the genitourinary system, which include the ureters, bladder and urethra, and in women, additionally, the fallopian tubes, uterus and vagina. Of course, each of these parts, along with the general principles of immune protection of the mucous membranes, has its own specific features that must be taken into account in each case. However, despite the anatomical division of many of them and morphofunctional differences, they are united by a systemic similarity in the implementation of immune

reactions, which is called "immune solidarity of mucous membranes" [3–6].

It should be understood that the immune response is not limited to the mucosal surface of a separate system, but extends to all other mucous membranes, i.e. immunization through one area leads to the production of antibodies to a given pathogen in all mucous membranes.

The unicellular layer of the intestinal mucosa epithelium is formed by enterocytes, goblet cells, Paneth cells, crypts, enteroendocrine cells, M cells and intraepithelial lymphocytes. Dendritic and mast cells, macrophages, and lymphocytes are found in the mucosal lamina propria [7, 8].

Lymphocytes in the mucous membranes form Mucosa Associated Lymphoid Tissue (MALT), which initiates an immune response to specific antigens found on all surfaces of the mucosa [9, 10].

Organized lymphoid tissue associated with the mucous membrane of the digestive tract (GALT – Gastro Associated Lymphoid Tissue), first described by Bienenstock, is represented by single and group lymphoid nodules (Peyer's patches) of the small intestine, lymphoid nodules of the colon, lymphoid tissue of the cecum, as well as regional mesenteric lymph nodes [11–15].

OBJECTIVE. To summarize the available data on the structure and functions of single and group lymphoid nodules of the small intestine and appendix, to evaluate modern approaches to their study, to analyze the results of research, hypotheses and theories related to their anatomical and physiological features, and to justify the prospects for further applying of the knowledge obtained for the deepen understanding of immunological processes.

MATERIALS AND METHODS. This analytical review is based on the results of our own research and published peer-reviewed articles, books, textbooks, and monographs. For the purposes of this systematic review, the literature search (concerning the study of the anatomical and functional characteristics of lymphoid tissue associated with the mucous membrane of the digestive tract) was carried out on the World Wide Web, domestic and foreign sources of literature (PubMed and Google Scholar), scientific and electronic library of Poltava State Medical University using the following keywords "lymphoid tissue", "immune system", "mucous membrane", "small intestine", "colon", "lymphoid nodule", "Peyer's patches", "intestinal crypts". The search period covered the period from 2011 to 2023, but the review includes some valuable data from earlier years, as these literature sources are of significant scientific value.

The following inclusion and exclusion criteria were used:

- inclusion criteria: original articles published in journals and conference proceedings, books, textbooks, monographs; language of publication: Ukrainian, English;

- exclusion criteria: reviews, thematic studies, editorials, letters, etc., not peer-reviewed; language of publication: other.

RESULTS AND DISCUSSION. From an evolutionary viewpoint, the immune system of the mucous membranes of the digestive tract was formed much earlier than other organs of the immune system. In addition, in ontogeny, the organs of the respiratory system develop from the anterior part of the primary intestine, which leads to the formation of a common entrance gate for both systems in the form of the mouth and nose. This contributes to the fact that during the first inhalation of the newborn, the mucous membranes of the digestive tract and tracheobronchial tree are simultaneously colonized by microflora, which contains beneficial and pathogenic bacteria that actively interact with the epithelial membrane of the respective mucous membranes. As a result, the body's immune system develops tolerance to normal (obligate) microflora, while a complex barrier is ontogenetically provided for in the mucous membranes against pathogens. The first component is a polarized epithelial layer, the apical surface of which is covered with a layer of mucus, which is a product of the secretion of countless small glands located in the thickness of the mucous membranes [16, 17].

Obviously, in this case, we are talking about a well-known nonspecific morphophysiological barrier, which in mucous membranes is supplemented by structured lymphoid formations that are formed during ontogeny under the direct influence of pathogenic microflora [18–20]. In this regard, it is interesting to note that in animals raised under sterile conditions (gnotobionts), these formations, the rudiments of which appear in embryogenesis, do not develop further.

At present, these structured lymphoid formations: single and group lymphoid nodules are considered together with tissue elements of the morphophysiological barrier called "mucosa-associated lymphoid tissue" (MALT) [21].

Nevertheless, in our opinion, they should be distinguished separately under the name of lymphoepithelial associations, because they represent a close relationship between lymphoid tissue with epithelial structures in a pronounced form.

The largest number of them is in the digestive tract, due to its physiological characteristics, which consist in the fact that massive amounts of food substances (the vast majority of which are genetically alien to the body) are constantly passed through it, along with

microorganisms. Therefore, the digestive system primarily provides natural mechanisms by which all food substances bearing pronounced signs of foreign genetic information (proteins, polysaccharides, fats, their various compounds, and nucleic acids) are deprived of their antigenic properties by enzymatic breakdown into component molecules (nutrients) that become acceptable for absorption into the internal environment of the body, where they are used to build their own corresponding macromolecular compounds [22].

Microorganisms that enter the human body are immunocontrolled by the above-mentioned lymphoepithelial formations, which include tonsils, single (solitary) and group (aggregate) lymphoid nodules (Peyer's patches), and appendix [22–24]. Although they have different anatomical shapes and are located in different parts of the digestive tract, they are united by similarities in structural organization.

Intestinal lymphoepithelial structures

For the general order and systematization of the data, let us briefly describe the structure of this part of the digestive system. As you know, the human intestine, which is approximately 6 m long, starts from the pyloric part of the stomach and ends with the anus. It is clearly divided into two unequal lengths – the small intestine and the large intestine. The small intestine is divided into three parts: duodenum, jejunum, and ileum, which is connected to the colon by the ileocecal valve. In the colon, which is much shorter than the small intestine, there are: 1 – the shortest part, which is located below the level of the ileocecal valve – the cecum; 2 – the longest part – the colon; 3 – the rectum, which is short in length. It should be noted that the cecum has appendix, that is one of the peripheral organs of the immune system [25, 26].

From a physiological viewpoint, the intestine can be divided into the following parts: 1 – the part of the cavity digestion, which consists in continuation of the enzymatic hydrolysis of complex polymeric food substances in the alkaline environment of the duodenum (started in the stomach); 2 – the part of parietal digestion and absorption of nutrients, which includes the mesenteric part of the small intestine; 3 – the part of bacterial digestion – the cecum, while the colon is the part intended mainly for the formation of feces, as a result of which the digestive tract is deprived of ballast substances.

Despite the significant difference in shape and physiological properties, all parts of the intestine have a universal principle of their wall structure, consisting mainly of three layers: the inner mucosa, the middle muscular membrane and the outer serosa or adventitious membrane [27, 28].

In those parts of the digestive tract where the mucous membrane forms folds, there is a well-defined layer of loose fibrous tissue between it and the muscular membrane, called the submucosa.

Of these three layers, the mucous membrane is of paramount importance to us, and first of all, the small intestine, since it contains the bulk of lymphoepithelial formations. Like any mucous membrane, it consists of a connective tissue base – its lamina propria, which is consolidated by the basal membrane with the epithelial layer, which is a polarized epithelial monolayer consisting of enterocytes of different specialization, with the prevalence of fringed (absorptive) cells among them. In conventional histological terminology, this single-layer cylindrical (or prismatic) epithelium is covered with a layer of mucus on the apical surface, which is associated with the parietal intestinal microflora. However, this coating is uneven along the surface of the mucous membrane, because it forms a continuous field of closely spaced elevations called intestinal villi, the maximum height of which reaches 1 mm in some places, and the total number of them is estimated in millions, due to which the surface of contact of the epithelial layer of the mucous membrane with the intestinal contents increases 30–40 times [29, 30].

The intestinal epithelium grows in the form of short microscopic tubes into the underlying connective tissue of the lamina propria, which blindly terminate at their lower parts near the thinnest muscularis lamina, which is part of the mucosa. Thus, the length of these epithelial growths, called libercus glands or intestinal crypts, is equal to the thickness of the mucosal lamina propria. It should be noted that their orifices (the holes through which they open into the intestinal lumen) are hidden between intestinal villi. Importantly, while the size and number of intestinal villi steadily decreases in the caudal direction, disappearing in the ileocecal region, the concentration of intestinal crypts gradually increases in the same direction, reaching a maximum in the cecum. It is interesting that the increase in the concentration of intestinal crypts in the caudal direction coincides with the literature data on the same vector of increase in the concentration of microorganisms in the intestine [31–33].

And only after birth, under the influence of the microbiota colonizing the mucous membranes of the digestive tract, they further develop structured lymphoid tissue, performed in embryogenesis, which is closely associated with the epithelium.

In the intestinal mucosa of an adult, it is represented by lymphoid nodules, some of which are singly scattered (solitary lymphoid nodules), others are collected in separate groups – Peyer's patches [23]. It is important that in the direction of the cecum, their concentration gradually increases, reaching a maximum in the appendix. It is quite obvious that such an increasing concentration of structured lymphoid tissue in the caudal

direction of the intestine directly correlates with the gradient of quantitative increase in the obligate and facultative microbiota, which reaches its maximum in the cecum. In other words, the concentration of intestinal crypts and structured lymphoid tissue directly depends on the strength of the antigenic load experienced by the intestinal mucosa.

According to the literature, solitary lymphoid nodules, which vary in number individually in a wide range, approximately from 200 to 9000, are mainly distributed in the mucous membrane of the ileum and colon, while Peyer's patches (in the amount of 20 to 30) are mainly located in the ileum and appendix [6, 23, 24].

In the mucous membrane of the ileum, Peyer's patches are located in the form of a chain along it on the opposite side to the mesentery attachment site. It is still impossible to explain this unilateral, polar arrangement.

Solitary nodules are small (no more than 2 mm in size), pear-shaped whitish lesions, the thickened parts (bases) of which are located in the submucosa, reaching the muscle membrane, and the blunt cone-shaped apices penetrate the mucosa, forming rounded elevations on its surface, covered with a single layer of intestinal epithelium associated with lymphoid tissue. At the same time, these apical sections, freely open to the intestinal cavity, are surrounded by intestinal villi (Fig. 1).

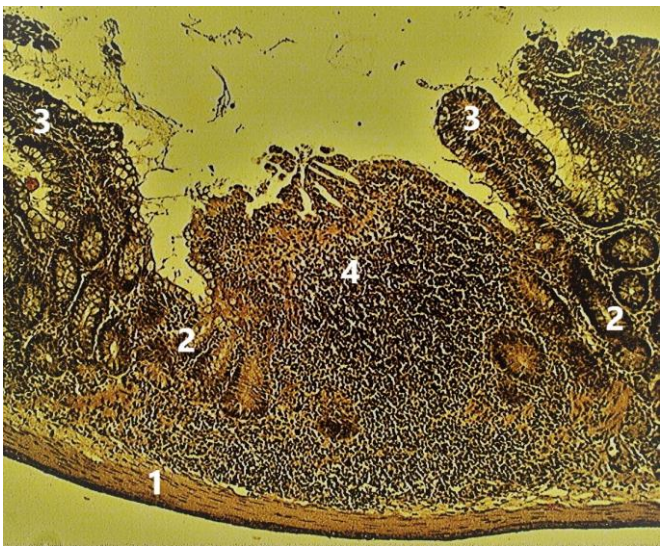

Fig. 1. Microscopic structure of the lymphoid nodule of the small intestine of a white rat (author's preparation): 1 – muscular membrane; 2 – intestinal crypts; 3 – intestinal villi; 4 – lymphoid nodule

In the thickness of the mucous membrane, single lymphoid nodules are closely surrounded by an extensive network of lymphatic capillaries that are connected to the lymphatic drainage pathways from the intestinal villi adjacent to them. It is known that lymph flows from these networks to the mesenteric lymph nodes, which suggests that these "milk" pathways transport not only the products of fat hydrolysis from intestinal villi, but also lymphocytes activated in lymphoid nodules. Thus, lymphoid nodules (not only single nodules but also those that are part of Peyer's patches) are morphologically and functionally connected with regional lymph nodes via lymphatic vessels that extend from them, which is also typical for the structure of tonsils.

Lymphoid nodules (both single and grouped – Peyer's patches) are not limited by a connective tissue capsule, but the immunocompetent cells of which they consist are grouped in cells of a fine network of reticular tissue, similar to the cortical substance of lymph nodes. In addition, as in lymph nodes and tonsils, intestinal lymph nodes contain reactive centers of lymphocyte proliferation (mainly B lymphocytes), which are recognized in histological sections by the presence of light areas in them.

When describing the structure of intestinal lymphoid nodules, the literature usually refers to their group clusters – Peyer's patches. In humans, compared to laboratory animals, they are rather large formations (Fig. 2).

To visualize them, directly during anatomical dissection, it is necessary to dissect the distal part of the ileum along the line of mesenteric attachment and flatten it. Usually, they are located in the direction of the longitudinal axis of the intestine, having an elongated shape, about 1–2 cm wide and 2–10 cm long, with the largest of them being in the most distal part of the ileum. If you look closely, you can see that they consist of a certain number of closely spaced lymphoid nodules corresponding to their size, which do

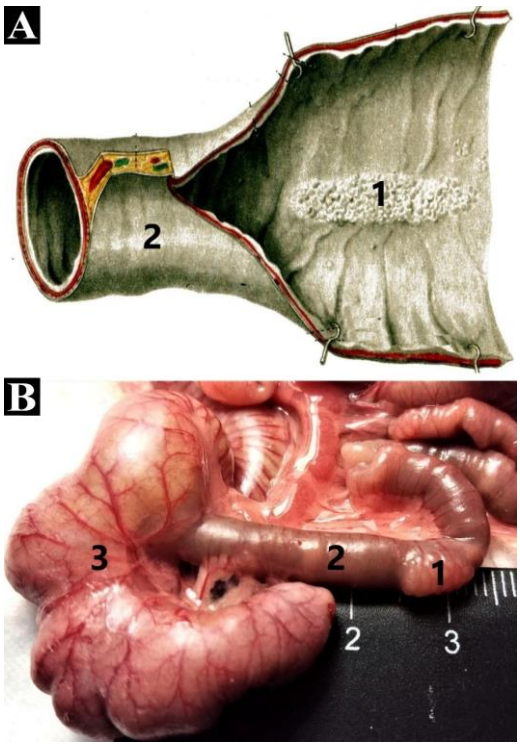

Fig. 2. External view of Peyer's patches in the human small intestine (A) and white rat (B – author's preparation): 1 – Peyer's patches; 2 – small intestine; 3 – cecum

not differ significantly from the solitary nodules [50]. In other words, the size of Peyer's patches directly depends on the number of lymphoid nodules of the same type, but slightly different in size and shape, integrated into them (Fig. 3).

Microscopic examination of Peyer's patches revealed that the lymphoid nodules in them are grouped in such a way that each of them is closely surrounded by a number of intestinal villi, and in addition, intestinal crypts (libercuate glands) are embedded in their thickness (Fig. 1). But nowadays, special attention is focused on the epithelium covering the apical parts of lymphoid nodules, which is called "follicle-associated epithelium". It is the same typical single-layer intestinal epithelium consisting of enterocytes of different specialization, which are closely united by tight intercellular contacts, which serves as an obstacle to the penetration of pathogenic microorganisms into the connective tissue of the mucous membrane located under the epithelium (interstitial compartment of the internal environment of the body). Of course, this general, universal statement is inherent in all mucous membranes without exception. However, it is advisable to consider it here due to the fact that, according to the currently accepted notion, the follicle-associated epithelium contains M cells, which are attributed with

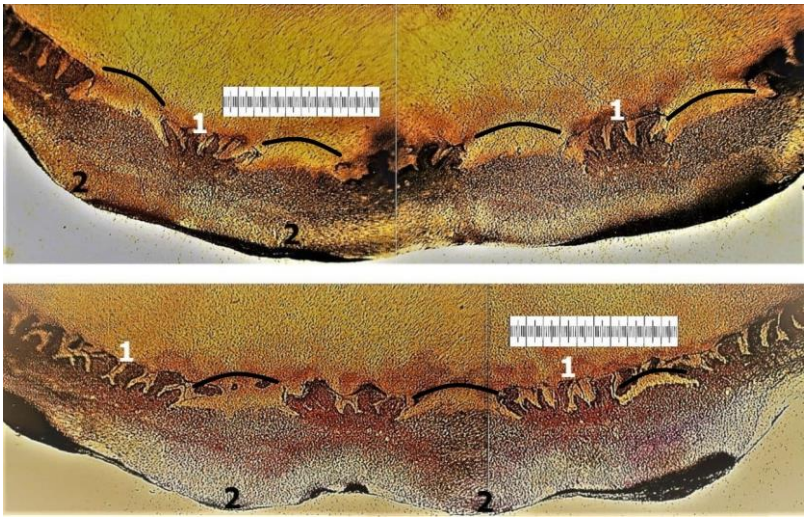

Fig. 3. Microphotographs of Peyer's patches in the small intestine of a white rat (4^{x} objective). Epoxy stain. The length of the scale bar is 1 mm. The arcs indicate the apical sections of lymphoid nodules (author's preparations): 1 – intestinal villi; 2 – lymphoid nodules

not quite usual properties, consisting in their ability to move various pathogens across the epithelial barrier, delivering them unchanged to the basal epithelium, where they are captured by dendritic macrophages, which, after processing a particular pathogen, present it in molecular form to T lymphocytes, thereby initiating an appropriate immune response.

The currently generally accepted concept of follicle-associated epithelium (by the way, it would be more appropriate to call it "lymphoid-associated epithelium" because the word "follicle" used in it is an anachronism) and especially the leading role of M cells in it, which we have presented in a simplified form, is not indisputable [34, 35].

The fact is that the main role attributed to M cells in the initiation of immune reactions in Peyer's patches cannot be considered sufficiently substantiated, because the lymphoid-associated epithelium contains other enterocytes with phagocytic properties. These epithelial phagocytes are quite capable of absorbing parietal microorganisms and transferring them to immunocompetent cells of lymph nodes, thereby duplicating the function of M cells. Moreover, it is known that the latter are found not only in the lymphoid-associated epithelium of lymphoid nodules but are also constantly found among enterocytes of other parts of the intestinal tract. This implies that the initiation of immune reactions in the intestine can be carried out over the entire surface of its epithelial layer. If this is true, the question arises: what is the true role of structured lymphoid tissue in the form of single and group lymphoid nodules in these processes? In this regard, our attention was drawn to the literature data that M-cells, which are part of the lymphoid-associated epithelium, are considered as a gate for the penetration of bacteria into the mucous membrane. However, it turns out that this interpretation is not new, because in the second half of the last century it was found that the intestinal mucosa epithelium has tubules through which microbial cells penetrate the submucosa and stimulate lymphoid cells. This became the basis for the development of methods for oral immunization of animals and humans with live vaccine. It is indicated that the use of live microbial cells for this purpose is more effective, as they fully induce cellular and humoral immunity.

Solitary lymphoid nodules and their group clusters – Peyer's patches – can undoubtedly be considered outposts of the immune system, which, on the one side, are responsible for local immune responses to a given pathogen, and on the other side, they initiate activation of the immune system, thus causing general sensitization of the mucous membranes. The key role in these processes belongs to dendritic (antigen-presenting) cells, which are usually located in lymphoid nodules, along with tissue macrophages directly under the lymphoid-associated epithelium. There are no clear indications in the literature of a separate role for these and other phagocytic cells. It should be assumed that dendritic cells belong to the inductive links of adaptive (specific) immunity, while free macrophages with the ability to migrate perform purely local nonspecific reactions. An argument in favor of the latter process is the fact that macrophages are constantly present in large numbers in the intestinal contents. This was the reason to believe that the intestine is constantly undergoing a "smoldering" inflammatory process, which should be considered a physiological norm. This becomes clear if we consider that the digestive tract regularly receives a significant mass of various microorganisms with food. At the same time, it is known that Peyer's patches, which control the intestinal microflora, are in some cases the target of infectious disease [36–38].

It is considered to be the next part of the digestive tract after the small intestine, in which the small intestinal chyme undergoes a non-enzymatic method of utilizing the useful nutrients contained in it. These mainly include the structural polysaccharide cellulose, for the splitting of which the human digestive tract lacks the necessary enzyme; therefore, the vital activity of rotting microorganisms belonging to the normal (obligate) intestinal microflora, to which the immune system of the mucous membranes is tolerant, is used for its processing. Although the normal microflora of the cecum is in competitive antagonism with pathogenic bacteria, the virulence of the latter cannot be ruled out. This danger exists constantly, due to the fact that new strains of microorganisms are regularly delivered to the cecum as part of the chemos from the ileum. This explains why the cecum has a special organ of the peripheral immune system, which is the appendix. But it should be remembered that an important role in protecting the intestinal mucosa is played by the intestinal crypts described above, which reach their maximum concentration in the cecum. If they belong to the structures of congenital (nonspecific) immunity, the appendix, in our opinion, is a component of adaptive (specific) immunity, although this division should be considered conditional, because there is a close morphofunctional relationship between them, which is manifested in the structure of the appendix.

According to the literature and the results of our studies, the human appendix becomes a fully formed lymphoid-epithelial organ in infancy, as evidenced by the presence of solitary nodules and Peyer's patches in its mucous membrane (along the entire organ from its base to the apex) [39, 40].

It reaches its maximum development between 10 and 20 years of age, after which its involution occurs, which consists mainly in a decrease in the amount of structured lymphoid tissue in it. But, according to our data, a certain number of lymphoid nodules still remain in it up to old age (Fig. 4).

CONCLUSIONS. Based on the literature data and the results of our own research, we have come to the following conclusions: intestinal crypts are essential basic structures of the mucous membrane of the small and large intestine. They are also the main sources of specialization and replacement (renewal) of all known types of enterocytes. Their bottom sections, where stem cells are concentrated, are considered to be the growth (germinal) zone.

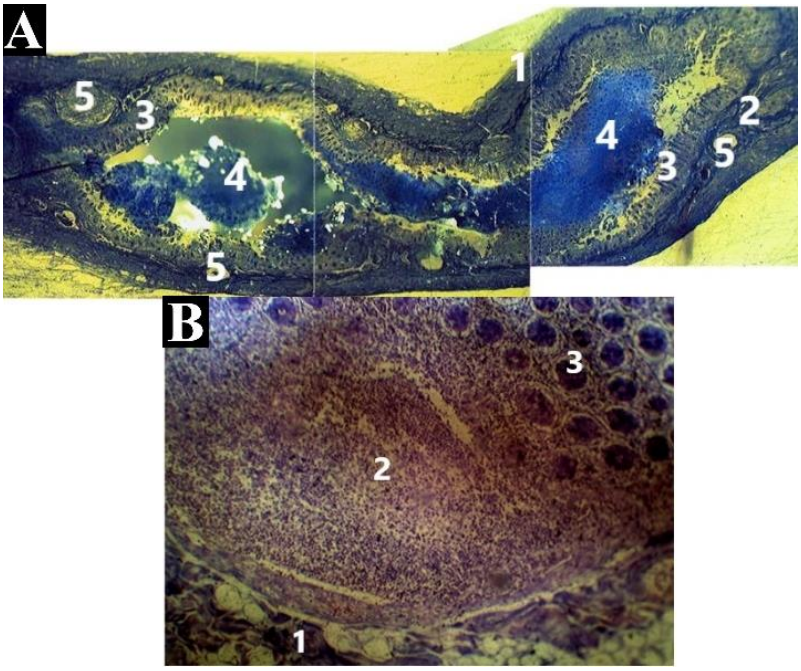

Fig. 4. Microscopic structure of the newborn appendix and adult human (author's preparations).

A - appendix of a newborn human in longitudinal section. Epoxy grinding; methylene blue staining; 7^x objective: 1 – muscular membrane; 2 – submucosal base; 3 – mucous membrane; 4 – contents of the internal lumen; 5 – lymphoid nodules.

B – lymphoid nodule of the appendix of an elderly woman (90 years old). Epoxy grinding; methylene blue staining; 10^x objective: 1 – submucosal base; 2 – lymphoid nodule; 3 – crypts in cross-section

In the same zone, along with stem cells, there are special secretory Paneth cells, which are sources of production of the bactericidal enzyme lysozyme (mureinase), which is known to be one of the active humoral factors of nonspecific immunity. In addition, they secrete substances containing zinc, which, according to recent data, is involved in the activation of local immune responses.

In the embryonic period, the formation of intestinal crypts precedes the beginning of the laying of structured lymphoid tissue. At the same time, they contain an increased concentration of Paneth cells. It follows that in the fetal period and immediately after birth, the protection of the intestinal mucosa is limited only by the mechanisms of nonspecific, innate immunity, the main carriers of which, in our opinion, are intestinal crypts.

Solitary lymphoid nodules and their group clusters – Peyer's patches – can undoubtedly be considered outposts of the immune system, which, on the one side, are responsible for local immune responses to a given pathogen, and on the other, immunocompetent cells that make up their composition initiate activation of the immune system, thus causing general sensitization of the mucous membranes.

The appendix becomes a fully formed lymphoepithelial organ in infancy, because its mucous membrane contains lymphoid nodules individually and in groups throughout the entire length from the base to the apex. However, in some cases, even in senile age, single lymphoid nodules sometimes remain in the mucous membrane of the appendix, in the typical organization of which the association of lymphocytes with the epithelium of the crypts is structurally fixed. However, the functioning of these structures is not so active and functionally complete.

PROSPECTS FOR FUTURE RESEARCH

Prospects for future research is to continue the study of the structural and functional features of the lymphoid tissue of the gastrointestinal tract in normal conditions and during inflammatory processes of the organs of the peritoneal cavity.

AUTHOR CONTRIBUTIONS

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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