
# Development of increased epithelial permeability syndrome in rheumatological patients.

**Kh.M. Marufkhanov** **DSc, associate professor** Department of propedeutics of Internal diseases No.2. Tashkent Medical Academy Tashkent city, Uzbekistan.
Email: mullokulov33@gmal.com

**M.V. Sibirkina** **Cand. Sc., associate professor** Department of propedeutics of Internal diseases No.2. Tashkent Medical Academy Tashkent city, Uzbekistan.
Email: mullokulov33@gmal.com

**Kh.T. Nurmetov** **Cand. Sc. associate professor** Department of propedeutics of Internal diseases No.2. Tashkent Medical Academy Tashkent city, Uzbekistan.
Email: mullokulov33@gmal.com

**A.R. Gimadutdinova** **Assistant lecterur** Department of propedeutics of Internal diseases No.2. Tashkent Medical Academy Tashkent city, Uzbekistan.
Email: mullokulov33@gmal.com

**J.J. Mullokulov** **Junior research assistant**
Department of propedeutics of Internal diseases No.2. Tashkent Medical Academy Tashkent city, Uzbekistan.
Email: mullokulov33@gmal.com

ABSTRACT

Currently, the role of the syndrome of increased epithelial permeability of the gastrointestinal mucosa as the main pathogenetic mechanism for the development of inflammatory diseases not only of the intestine, but also of other organs and systems, including rheumatological diseases, is being discussed.The integrity of the intestinal barrier was assessed using morphological examination of mucosal biopsies (M) of various gastrointestinal tract sections, followed by staining with hematoxylin and eosin.Electron microscopy can be used to visualize the distances between epithelial cells and the width of intercellular spaces.The analysis of the conducted studies revealed significant morphological shifts in all the studied departments of the digestive tract in rheumatological diseases, which are expressed in the treatment of infiltration of the stroma of intestinal villi by lymphocytes and plasma cells, expansion of microvessels, an increase in the number of interepithelial lymphocytes, an increase in intercellular gaps, loss of communication with the basement membrane by enterocytes, which indicates the development of SIEP in this category of patients.

**Keywords:** epithelial permeability, rheumatological

Currently, the scientific community pays special attention to the study of the syndrome of increased epithelial permeability (SIEP) of the mucous membrane of the gastrointestinal tract

(gastrointestinal tract), primarily the intestine, as the main pathogenetic mechanism of inflammatory diseases not only of the intestine, but also type 1 diabetes mellitus (DM), rheumatoid arthritis, immunodeficiency states, multiple sclerosis [1-3].

The mucous membrane of the gastrointestinal tract has a global surface area of more than 200 m2, being an obstacle to the penetration of foreign pathogens and preventing their harmful effects, i.e. it becomes the first barrier to protect internal organs from external factors.Factors determining the state of the intestinal barrier are: the epithelial layer of the mucous membrane with interepithelial contacts and cells of the immune system, the layer of wall mucus, the microbiota, as well as the vascular barrier [1,4,5].

Epithelial cells form a physical barrier that prevents the contents of the intestinal lumen from moving into internal tissues, and are connected by intercellular contacts: tight contacts, adhesive contacts and desmosomes. Dense contacts consist of a series of transmembrane proteins, including occludin, claudins, bonding adhesion molecules, tricellulin, which are bound to actin and myosin filaments by cytoplasmic proteins ZO 1,2 and 3 (zonula occludens) [6,7]

The gut microbiota participates in almost all processes of food metabolism, participates in vitamin synthesis, cholesterol catabolism, forms numerous immune responses associated with innate and adaptive immunity, and modulates human relationships with pathogenic microorganisms [8,9]. When the syndrome of increased permeability is formed, a large number of antigens enter the systemic bloodstream, which leads to the launch of the protective mechanisms of the immune system.

The development of SIEP is closely interrelated with inflammation, which is part of the pathogenesis of most rheumatological diseases. One of the mechanisms of SPEP is associated with the activation of intracellular kinases and the reduction of actin-myosin intracellular structures under the action of proinflammatory cytokines: tumor necrosis factor [TNF- α], interleukin-1 (IL-1ß), which leads to the rapid opening of tight contacts (tight joints, TJ) between enterocytes by moving ZO-1 and occludin inside the cell
[10, 11].

Many proinflammatory cytokines [TNF-α, IL-ß, IL-6, IL-12, etc.] can cause oxidative stress in the cell, reduce the expression of ZO-1, occludin and other components of T], which leads to the permeability of dense compounds [12]. The third mechanism of SIEP is the action of matrix metalloproteinases {MMP} on the components of TJ- occludin, claudins, ZO proteins, which also causes disorganization of TJ [13]. It is known that MMP and oxidative stress enhance each other's formation and their levels correlate with each other. For a long course of the inflammatory process, it is possible to rearrange dense compounds by increasing the expression and appearance of claudin 2 in their composition. The role of zonulin, a protein capable of reversibly increasing the permeability of the intestinal wall by changing the structure of tight junctions (tight junction TJ) of the lateral surfaces of intestinal epithelial cells, is insufficient in inflammation.

A balanced gut microbiota stimulates resident macrophages to release a large amount of interleukin [IL] 10 and transforming growth factor beta, thereby preventing an increase in the number of proinflammatory T helper 17 [Th17] cells, and as a consequence prevents the development of SIEP.

In this regard, maintaining the integrity of the intestinal barrier can be of great importance in the development and prevention of autoimmune rheumatological diseases.

**Materials and methods of research**

Assessment of the integrity of the intestinal barrier using morphological examination of biopsies of the mucous membrane (CO) of various parts of the gastrointestinal tract with subsequent staining with hematoxylin and eosin, which allows to identify ulcerative defects, erosion of CO, to assess the density of cellular infiltrate and its composition, as well as the degree of atrophy, which can serve as indirect signs of altered permeability [14]. To visualize the distances between epithelial cells and the width of intercellular croscopy.

For light microscopy, biopsies of the gastric mucosa, duodenum and colon were fixed in 10-12% formalin solution on a phosphate buffer according to Lilly. Paraffin sections were stained with hematoxylin-eosin.

For transmission electron microscopy [TEM], tissue samples were fixed with a 2.5% solution of glutaraldehyde on a phosphate or cacodilate buffer, after dehydration in alcohol - acetone, they were filled with an epono-araldite mixture. Ultrathin sections obtained on the ultratome "ULTRACUT" were contrasted in the Hitachi H-600 electron microscope

For scanning electron microscopy [SEM], the preparations after the above fixation were subjected to dehydration and alcohol-acetone, then dried by the critical point method in the HCP-2 apparatus and sprayed with gold in the IB-2 apparatus. Examined in the Hitachi S405A electron microscope

Photographing was carried out on a color film Kodak Professional Pro Foto 100 or Fuji color superia 100. Micrographs were scanned on a scanner Scan Prisa 640P (Acer) and subjected to computer processing on a computer Computek Pentium III Windows 2000

Semi-thin epoxy sections stained with methylene blue fuchsin were also examined light-optically

Light-optical micrographs were obtained using an Axioscope (Zeizz) microscope with a Sony digital camera

Computer processing of microphotographs was carried out on a Pentium-III computer using Microsoft's "Exel-Office"-"Windows-Professional" application programs.

Research results and their discussion

The analysis of the conducted studies revealed significant morphological shifts in all the studied sections of the digestive tract in rheumatological diseases (RH)

During the study, rheumatological patients revealed significant changes in the mucous membrane of the duodenum, which are expressed in an increase in infiltration of the stroma of intestinal villi by lymphocytes and plasma cells, expansion of microvessels, an increase in the number of interepithelial lymphocytes, the location of epithelial cell nuclei at different levels, which creates the impression of a false multi-row [Fig.1,2]. The brush border is preserved, as well as the integrity of the epithelial lining of the villi. Most of the goblet cells are emptied. In the interstitial spaces, the contents of various types are determined, among which microorganisms can also be distinguished [Fig.1].

Stroma infiltration also increases in the colon mucosa, and the number of interepithelial lymphocytes increases.

Scanning electron microscopy (SEM) shows that the microrelief of the surface of the mucous membrane of the pyloric part of the stomach largely loses its regularity. The apical parts of the surface-pit cells are located at different heights.There are intercellular gaps and depressions.On the surface of the cells there is a small layer of various inclusions and overlays.There are also microerosions of the apical parts of epithelial cells [Fig.3].

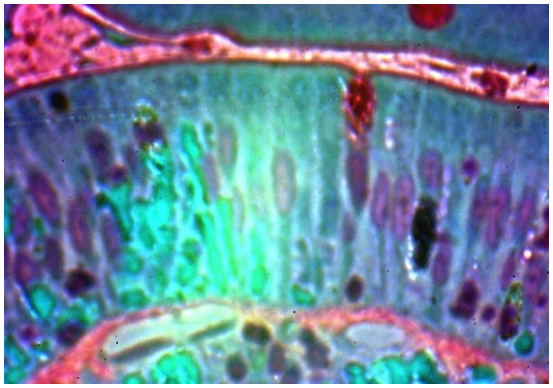

***Fig.1. An increase in the number of interepithelial lymphocytes and false multi-row epithelium of the duodenum in RB. PTS 10 x 40.***

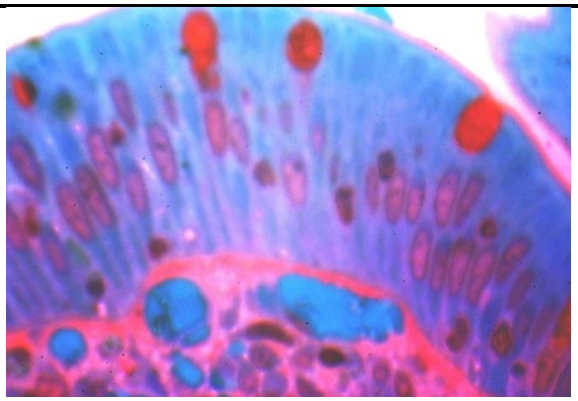

*Fig.2. Polymorphism of the nuclei of the duodenal epithelium in RB. PTS 10 x 40.*

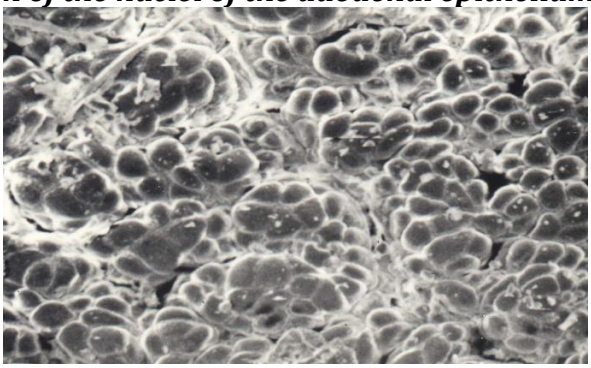

*Fig.3. Uneven microrelief of the surface of the mucous membrane of the pyloric part of the stomach in RB, SEM x 1000.*

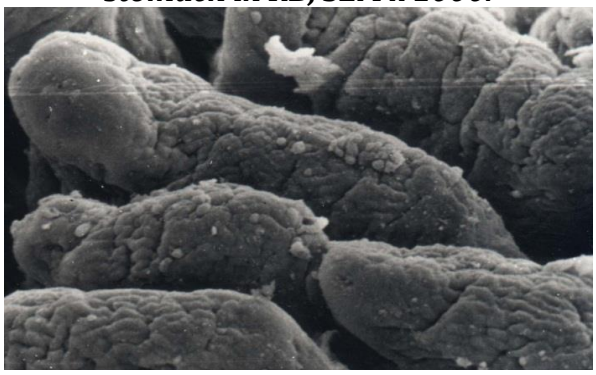

*Fig.4.Duodenal villi with overlays in RB, SAM x 400.*

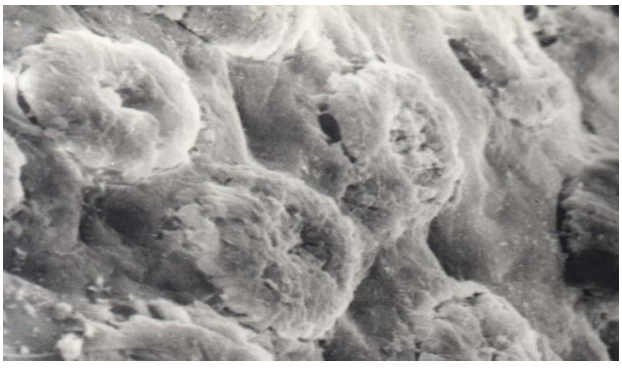

*Fig.5 Microrelief of the colon surface in RB. Mucus and microorganisms. SAM x 800.*

The villi of the duodenum have a fairly regular leaf-shaped shape with a small number of different inclusions on the surface.Among which it is possible to distinguish erythrocytes, lymphocytes and other formations [Fig. 4].

The lumen of the crypts of the colon is filled with mucus, various inclusions, including microorganisms, are located in it [Fig.5]. Smallerosions are detected on the surface of epithelial cells.

The change in the morphology of the gastrointestinal tract aggravates the use of nonsteroidal anti-inflammatory drugs (NSAIDs)

In the stroma of the mucous membrane of the pyloric part of the stomach, the number of plasma and other infiltrate cells increases. Surface-pit epithelial cells are characterized by pronounced polymorphism. This polymorphism is expressed in different cell height and shape and mucoid content.The number of interepithelial lymphocytes increases [fig.6,7]. The intercellular spaces in the basal parts of the epithelial cells expand significantly, which leads to their extrusion.There are significant areas of eroded epithelial cell surfaces [Fig.7,8]

Significant changes are also noted in the mucous membrane of the duodenum.

The number of infiltrate cells increases significantly. At the same time, plasma cells dominate in the stroma of the villi. The basal parts of the enterocytes become enlightened, the intercellular gaps increase. Some enterocytes lose their connection with the basement membrane [Fig. 9]. However, in the duodenum at the debut of NSAID use, there are no violations of the integrity of the epithelial lining and the formation of microerosions.

SEM studies have shown that in the pyloric part of the gastric mucosa, the "debut" of the use of NSAIDs causes significant changes in the microrelief of the surface.The apical parts of the cells become different in shape, size and height [Fig. 10]., which leads to a violation of the rhythm and relative symmetry of the microrelief.

Numerous microerosions are detected on the cell surface.The number of overlays on the cell surface increases, the intercellular spaces expand [Fig. 10].

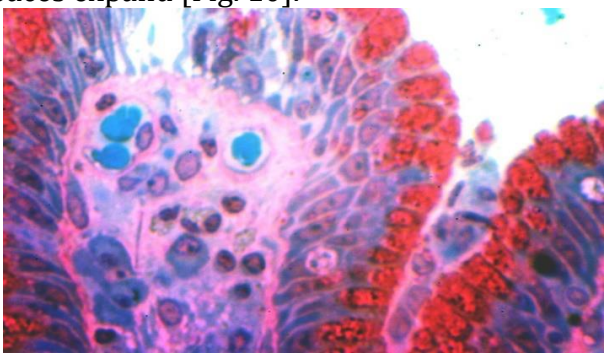

***Fig.6. An increase in the number of interepithelial lymphocytes and false multi-row epithelium of the duodenum in RB. PTS 10 x 40.***

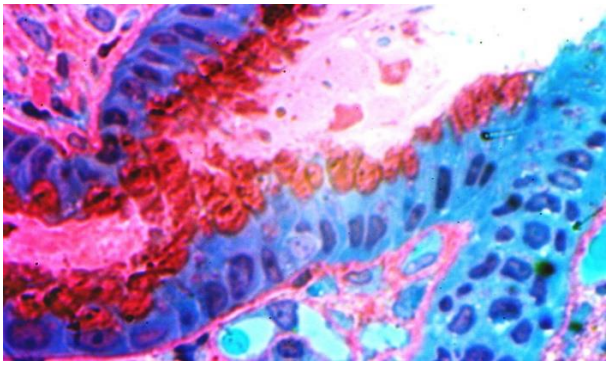

***Fig.7. Polymorphism of epithelial cells, cells in the lumen of the pyloric department at the "debut" of the use of NSAIDs. PTS 10x 40.***

Morphological studies have shown that the very presence of RB causes significant changes in the pyloric part of the stomach of the duodenum and colon.

Before taking NSAIDs, these changes have the character of chronic inflammation, expressed to one degree or another. For the stomach, this picture fits into the framework of chronic gastritis without atrophy. For the duodenum -moderate duodenitis. In the colon, changes occur in the form of moderate colitis.

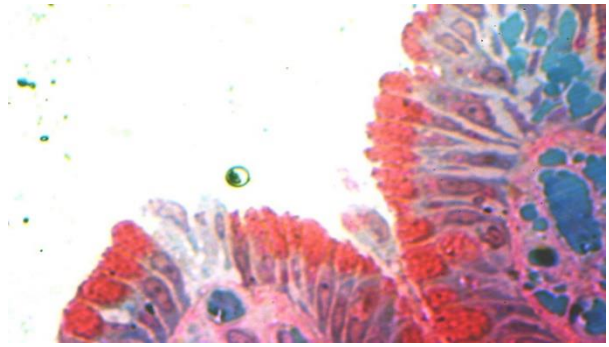

***Fig.8. Polymorphism of the nuclei of the duodenal epithelium in RB. PTS 10 x 40.***

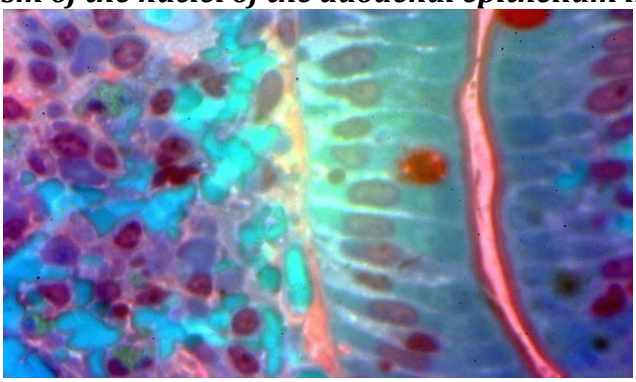

***Fig.9. Expansion of the intercellular spaces of the basal parts of the enterocytes of the duodenum at the "debut" of the use of NSAIDs. PTS 10x 40.***

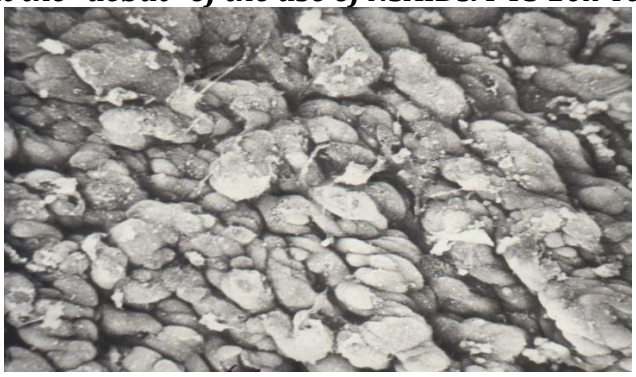

***Fig.10. Uneven microrelief of the surface of the mucous membrane of the pyloric part of the stomach in RB, SEM x 1000.***

The initial use of NSAIDs causes more pronounced changes in the mucous membrane.

In the mucous membrane of the pyloric part of the stomach, there are violations of the connections of the integumentary pit cells with the basement membrane, the expansion of intercellular spaces in the basal part of the epithelium, the appearance of microerosions on the apical surfaces of epithelial cells and their pronounced polymorphism. At the same time, there is an increase in inflammatory changes.

Changes in the mucous membrane of the duodenum also indicate an increase in the manifestations of inflammation and a weakening of the strength of the epithelial lining.

In the colon, changes under the influence of NSAIDs are expressed to the least extent.

According to modern concepts, SIEP and microbiota disturbance are considered as a trigger factor or an important element of the etiopathogenesis of RH [15]. Published works in which the effect of correction of increased permeability of the gastrointestinal tract and microbiotic disorders on the development and course of RH was studied. Thus, there are data indicating a decrease in the activity of the disease, the level of proinflammatory cytokines and CRP in RA patients with gingivitis after effective sanitation of the oral cavity [16,17]. A number of works are devoted to the effectiveness of probiotics in RA, AS and SLE [18,19,20]. A significant increase in intestinal permeability was found, not only in patients with AS, but also in their closest relatives, which indicates the genetic nature of intestinal permeability disorders leading to the development of SIEP [21], which requires a comprehensive approach to the treatment of patients with this group of diseases, aimed at reducing the severity of autoimmune lesions of the elements of the musculoskeletal system, and to reduce the severity of SIEP.

**Conclusion:**

Thus, close contacts between epithelial cells and the microbiota play a key role in maintaining the integrity of the intestinal barrier. The pathological permeability of the intestinal barrier leads to the translocation of bacteria and their metabolites into the internal environment of the body, which can cause inflammatory changes in target organs and create a pathophysiological basis for the development of a number of autoimmune diseases, which creates the need for an integrated approach to the diagnosis and therapy of patients with this group of diseases.

**References:**


1. Sturgeon C., Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases.Tissue Barriers.2016; 4: e1251384.
2. Chang J., Leong R.W., Wasinger V.C. et al.Impaired intestinal permeability contributes to ongoing bowel disease and mucosal healing Gastroenterology.2017; 153: 723-31
3. Fukui H. Incresed intestinal permeability and decreased barrier function: does it really influence the risk of inflammation? Inflamm Intest Dis. 2016; 1(3): 135-45 doi:10.1159/000447252
4. Graziani C., Talocco C., De Sire. Et al. Intestinal permeability in physiological and pathological conditions: major determinant and assessment modalities. Eur Rev Med Pharmacol Sci. 2019; 23(2): 795-810.
5. Turner J.R. Intestinal mucosal barrier function in health and disease.Nat Rev Immunol. 2009; 11: 799-809.
6. Luettig J, Rosenthal R, Barmeyer C, Schulzke J.D. Claudin-2 as a mediator of leaky gut barrier during intestinal inflammation Tissue Barriers.2015;(1-2):e977176.
7. Anderson J.M. Van Itallie C.M. Physiology and function of the tight junction.Cold Spring Harb Perspect Biol.2009; 1(2):a002584
8. Pessione E. Lactic acid bacteria contribution to gut microbiota complexity:lights and shadows.Front Cell Infect Microbiol.2012;2:86
9. Kumar M, Nagpal R, Kumar R, et al. Cholesterol lowering probiotics as potential biotherapeutics for metabolic diseases. Exp Diabetes Res.2012:902917.
10. Al-Sadi R, Guo S, Ye D, et al. TNF-a Modulation of Intestinal Tight Junction Permeability Is mediated by NIK/IKK-a Axis Activation of the Canonical NF-Kb Pathway.Am J Pathol.2016;186(5):1151-65.
11. Cunningham KE, Turner J.R. Myosin light chain kinase: pulling the strings of epithelial tight junction function.Annals of the New York Academy of Sciences.2012;1258(1):34-42.
12. Gangwar R, Meena A.S, Shukla P.K, et al.Calcium-mediated oxidative stress: a

common mechanism in tight junction disruption by different types of cellular stress.Biochemical Journal.2017;474(5):731-49.
13. Al-Dasooqi N, Wardill H.R, Gibson R.J, Gastrointestinal Mucositis: The Role of MMP-Tight Junction Interactions in Tissue Injury Pathol.Oncol.Res.2014;20:485-91.
14. Wang L, Llorente C, Hartmann P, et al. Methods to determine intestinal permeability and bacterial translocation during liver disease.Journal of Immunological Methods.2015;421:44-53.
15. Konig M. The microbiome in autoimmune rheumatic disease.Best Pract Res Clin Rheumatol.2020;34(1):101473.doi:10.1016/j.berh.2019.101473.
16. Гордеев А.В., Галушко Е.А., Савушкина Н.М., Лила А.М. Пародонтит-предвестник ревматоидного артрита? Научно-практическая ревматология.2018;56(5):613-21.
17. Radwan-Oczko M, Dus-Ilnicka I, Richards P, et al. Rheumatoid artritis patients' oral health and disease activity.IntJ Rheum Dis.2019;22(8):1538-43.
18. Horta-Bass G, Romero-Figueroa MDS, Montiel-Jarquin A.J et al. Intestinal Dysbiosis and Rheumatoid Artritis: A Link between Gut Microbiota and the Pathogenesis of Rheumatoid Arthritis.J Immunol. Res. 2017;2017:4835189.
19. Jenks K, Stebbings S, Burton J, et al. Probiotic therapy for the treatment of spondyloarthritis: a randomized controlled trial. J Rheumatol.2010;37(10):2118-25.
20. de la Visitacion N, Robles-Vera I. Toral M, Duarte J. Protective Effects of Probiotic Consumption in Cardiovascular Disease in Systemic Lupus Erytematosus Nutrients.2019;11(11):2676.
21. Караиаев А.Е., Галушко Е.А. Поражение кишечника у больных спондилоартритами.Научно-практическая ревматология.2015;53(2):190-9
22. Development of increased epithelial permeability syndrome in rheumatological patients.
23. DSc, associate professor, Kh.M. Marufkhanov , Cand. Sc., associate professor, M.V. Sibirkina,
24. Cand. Sc. associate professor Kh.T. Nurmetov, Assistant lecterur A.R. Gimadutdinova,
25. Junior research assistant J.J. Mullokulov
26. Currently, the role of the syndrome of increased epithelial permeability of the gastrointestinal mucosa as the main pathogenetic mechanism for the development of inflammatory diseases not only of the intestine, but also of other organs and systems, including rheumatological diseases, is being discussed.The integrity of the intestinal barrier was assessed using morphological examination of mucosal biopsies (M) of various gastrointestinal tract sections, followed by staining with hematoxylin and eosin. Electron microscopy can be used to visualize the distances between epithelial cells and the width of intercellular spaces.The analysis of the conducted studies revealed significant morphological shifts in all the studied departments of the digestive tract in rheumatological diseases, which are expressed in the treatment of infiltration of the stroma of intestinal villi by lymphocytes and plasma cells, expansion of microvessels, an increase in the number of interepithelial lymphocytes, an increase in intercellular gaps, loss of communication with the basement membrane by enterocytes, which indicates the development of SIEP in this category of patients.