ences among scientists: evidence for accumulative advantage. Am Soc Rev. 1974;39:596–606.
37. Beard GM. Legal Responsibility in Old Age, Russell, New York, 1874.
38. Cole S. Age and Scientific Performance. Am J Soc. 1979;84:958–977.
39. Dennis W. Age and productivity among scientists. Science. 1956;123:724–725.
40. Dietrich A, Srinivasan N. The optimal age to start a revolution. J Creative Behav. 2007;41:339-351.
41. Feist GJ. The psychology of science and the origins of the scientific mind. New Haven: Yale University Press; 2006. p. 316.
42. Gieryn TF. The aging of a science and its exploitation of innovation: Lessons from X-ray and radio astronomy. Scientometrics. 1981;3:325–334.
43. Gingras Y., Larivie're V., Macaluso B. et al. The effects of aging on researchers' publication and citation patterns. PLoS One. 2008;3(1): e4048.
44. Horner KL, Rushton JP, Vernon PA. Relation between aging and research productivity of academic psychologists. Psychology and Aging. 1986;1:319–324.
45. Kyvik S, Olsen TB. Does the aging of tenured academic staff affect the research performance of universities? Scientometrics. 2008;76:439–455.
46. Lehmann N.C. Age and achievement. Princeton, New Jersey, 1953.
47. Lehmann N.C. The creative production rates of present versus past generations of scientists - in: Middle age and aging. Reader in Social Psychology. Ed. by B.L. Neugarten. Chicago, 1968.
48. Merton RK. The sociology of science: Theoretical and empirical investivations. Chicago: University of Chicago Press; 1973. p. 605.
49. Over R. Does scholarly impact decline with age? Scientometrics. 1988;13:215–223.
50. Stephan P, Levin S. Age and the Nobel prize revisited. Scientometrics. 1993;28(3):387-399.
51. Stern S. Age and achievement in mathematics: a case-study in the sociology of science. Soc Stud Sci. 1978;8:127–140.
52. Wray KB. An examination of the contributions of young scientists in new fields. Scientometrics. 2004;61:117–128.
53. Wray KB. Is science really a young man's game? Soc Stud Sci. 2003;33:137–149.
54. Zuckerman H, Merton RK. Age, aging and age structure in science. In: Merton RK, editor. The Sociology of Science. Chicago: Chicago University Press; 1973. pp. 493–560.

T.V.Polivanova, V.A.Vshivkov

FEATURES OF CLINICAL MANIFESTATIONS AND CYTOKINE REGULATION IN GASTRITIS IN SCHOOLCHILDREN WITH FAMILIAL PREDISPOSITION TO THE PEPTIC ULCER DISEASE

DOI 10.25789/YMJ.2021.73.33

Aim: To study the features of clinical manifestations and indicators of circulating cytokines in gastritis in schoolchildren with a family predisposition to peptic ulcer disease.

Material and Methods: 3343 schoolchildren of 7-17 years old were examined in Siberia (Tyva, Evenkia, Aginsky Buryat National District, Krasnoyarsk). 463 children with gastrointestinal complaints underwent esophagogastroduodenoscopy with biopsy of the gastric mucosa. In accordance with the Sydney classification, the morphological diagnosis of gastritis and the presence of Helicobacter pylori was carried out. Blood serum was also taken to determine the level of cytokines (IL-2, IL-4, IL-8, IL-18, IL-1β, IFN-α, TNM-α) by ELISA. The studies were approved by the ethics committee and the consent of the patients and their parents was obtained.

Results: Schoolchildren with family predisposition to peptic ulcer disease with gastritis more often have dyspeptic manifestations. It was found that in children with a familial predisposition, gastritis proceeds with the involvement of the systemic level of cytokine regulation (expression of IL-4, IFN-α). Moreover, in children with H. pylori infection, the cytokine regulation of the inflammatory process is specific (TNM-α expression).

Conclusion: The features of the course of gastritis in children with a familial predisposition to peptic ulcer disease have been established, and they can be considered markers of the unfavorable course of the pathology.

Keywords: children; gastritis; peptic ulcer; hereditary predisposition; cytokines; DS; GERD.

The problem of diseases of the stomach and duodenum in childhood does not lose its relevance [7], which is largely due to the lack of dynamics to reduce their prevalence and weighting the course. The age of formation of the pathology of the gastroduodenal zone in the majority falls on the school and preschool periods of life, which is represented mainly by gastritis [2, 5, 7], which is, with further progression, the morphological basis of diseases such as peptic ulcer (PUD). YaB belongs to the category of multifactorial. The most unfavorable stage in children, characterized by the growth of the disease, is the period of schooling [1]. Familial predisposition to pathology also has a pronounced negative effect on the formation of ulcer [14]. Predisposition to ulcer, as shown by numerous studies, is based on the features of neurohumoral regulation and morpho-functional characteristics of the stomach, which have a genetic basis. As such, an increase in the formation of pepsinogen-1, an increase in the mass of parietal cells and their hypersensitivity to gastrin, congenital deficiency of mucus fukomucoproteins, and a number of others are considered [3]. In recent years, the features of the cytokine profile in persons with peptic ulcer disease have been shown [10, 11]. The participation of cytokines in the inflammatory process is multifaceted: it is also the regulation of intercellular and intersystem interactions that determine the differentiation and survival of cells, the functional activity of proliferation and apoptosis [4]. There are features of the course of the inflammatory process in the gastric mucosa (GM), initiated by Helicobacter pylori (H. pylori) infection, which induces the production of a number of cytokines. It is known that IL-1β, IL-6, tumor necrosis factor (TNF) -α, TGF-β1, IL-17, IL-18, IL-21 and IL-22 are actively involved in this pathological process [19].

In persons with a family predisposition to peptic ulcer disease, morpho-function-

POLIVANOVA Tamara Vladimirovna – Doctor of Medicine, Chief Researcher of Clinical Department of the Pathology of Digestion System in Adults and Children of Scientific Research Institute for Medical Problems of the North of Federal Research Centre «Krasnoyarsk Scientific Centre» of Siberian Division of Russian Academy of Sciences; e-mail: tamara-polivanova@yandex.ru; **VSHIVKOV Vitaliy Alekseevich** - PhD (Medicine), Senior Researcher of Clinical Department of the Pathology of Digestion System in Adults and Children of Scientific Research Institute for Medical Problems of the North of Federal Research Centre «Krasnoyarsk Scientific Centre» of Siberian Division of Russian Academy of Sciences; e-mail: vitali1983@mail.ru

al features of the stomach and features of regulatory mechanisms are created, which create the prerequisites for a decrease in the level of the body's resistance to the effects of adverse environmental factors [9]. In such individuals, the disease progresses faster to atrophy and metaplasia [15]. In addition, they have a higher risk of developing diseases for which they have a predisposition. In this regard, deviations in the course of the disease in persons with a predisposition should be considered as prognostic markers [6].

Aim: To study the features of clinical manifestations and indicators of circulating cytokines in gastritis in schoolchildren with a familial predisposition to peptic ulcer disease.

Material and methods. The research was carried out in different regions of Siberia in two stages. At the first stage, a cross-sectional screening examination was carried out with the collection of gastrointestinal complaints and anamnestic data on the presence of peptic ulcer disease in relatives of 1 and 2 degrees of relationship in 3343 schoolchildren aged 7-17 years (1502 boys and 1841 girls; junior schoolchildren 7-11 years old - 1602; senior schoolchildren 12-17 years old - 1741). Examined in Tyva (Turan, Saryg-Sep village) - 1535 children; in Evenkia (Baykit village) - 842 children; in the Aginsky Buryat National Okrug (Aginskoe settlement) - 790 children. In addition, similar data were obtained from 176 schoolchildren in Krasnoyarsk who are being examined and treated at the clinic of the Research Institute of Medical Problems of the North for problems with the gastrointestinal tract.

Then, by the method of random selection, groups of schoolchildren with gastroenterological complaints were formed, who underwent endoscopic examination of the upper gastrointestinal tract with sampling of biopsies from the mucous membrane of the antrum and the body of the stomach for subsequent morphological examination. All children in Krasnoyarsk also underwent endoscopic and morphological examination of GM. In total, instrumental examination with morphological confirmation of the diagnosis of gastritis was carried out in 463 schoolchildren. The criteria for excluding children from the study were: 1. the age of the child under 7 and over 17; 2. the presence of acute inflammatory diseases during the last month; 3. the presence of chronic diseases of other organs in the acute stage; 4. functional failure of organs and body systems. 5. the presence of allergic diseases. 6) the absence of morphological signs of gastritis.

The diagnosis of dyspepsia syndrome was carried out in accordance with the definition of the Committee on Functional Diseases of the World Congress of Gastroenterologists (Rome IV), which is a complex of disorders including pain or discomfort in the epigastrium, a feeling of fullness in the epigastric region after eating, and early satiety. Clinically, two variants of its course were distinguished: 1) epigastric pain syndrome; 2) postprandial distress syndrome [13].

The diagnosis of gastroesophageal reflux disease (GERD) in children was made in accordance with the child's consensus on pathology [8]. At screening, the presence of weekly heartburn in the subjects was taken as a diagnostic criterion for GERD. Heartburn was understood as a burning sensation in the retrosternal region.

Endoscopic and morphological diagnostics of gastritis was performed in accordance with the modified Sydney classification [12, 17]. Morphological evaluation of the presence and severity of the inflammatory process in the gastric mucosa included light microscopy of biopsy sections after staining with hematoxylin-eosin. The degree of gastritis activity was assessed by the intensity of neutrophilic infiltration of the epithelium and / or the lamina propria of the gastric mucosa. Morphological diagnosis of Helicobacter pylori (H. pylori) infection was carried out after staining biopsy sections according to Giemsa.

For the procedure of enzyme immunoassay (ELISA), a 5 ml blood sample was taken from the subjects. The blood sample was centrifuged, the serum was separated and stored at -20 ° C. The concentration of cytokines in blood serum (IL-2, IL-4, IL-8, IL-18, IL-1β, IFN-α, TNM-α) was determined using the standard test systems "Vector-Best" (Novosibirsk).

In accordance with Article 24 of the Constitution of the Russian Federation and the Helsinki Declaration of the World Medical Association (1964), all examined children and their parents were familiarized with the goals, methods and possible complications during the research with the signing of informed consent to participate before their inclusion in the study.

Statistical processing of the results was carried out using the SPSS version 23.0 software (IBM, Inc). The analysis of the statistical significance of differences in qualitative features was carried out using the - test with Yates' correction in the presence of a feature in the group of less than 10, and less than 5 - two-sided Fisher's exact test. The significance of differences in quantitative traits was analyzed using the Mann-Whitney test. The results of the study are presented for samples that do not obey the normal distribution law, median (Me) and interquartile range (C25-C75). The statistical significance of the differences in signs was assessed at $p<0.05$.

Research results and discussion. Undoubtedly, clinical manifestations are one of the most important indicators of the course of the disease. The study of this issue showed that in schoolchildren with a family predisposition for peptic ulcer disease, there was an increase in the frequency of complaints characterized as dyspepsia syndrome (Table 1). Schoolchildren with a family predisposition to peptic ulcer disease noted dyspeptic complaints in 55.5% and 39.2% ($p <0.001$) without predisposition. At the same time, there was no predominance of a specific clinical variant of the course of dyspepsia. They had epigastric pain in 28.0% compared to 18.3% in children without family burden ($p <0.001$). As for the postprandial variant of the clinical course of dyspepsia, it was also more often present in the complaints of children with a familial predisposition to ulcer: in 27.6% and in 20.9% in children without it ($p = 0.001$). The formation of this variant of dyspepsia is largely associated with motor disorders of the gastrointestinal tract. It should be assumed that several leading links of pathogenesis involved in the formation of the disease (acid, changes in visceral sensitivity and motor disorders) increase in children with a family predisposition to ulcer. A definite confirmation of this is the increase in the prevalence of GERD among schoolchildren with a familial predisposition, in the formation and progression of which similar pathogenetic mechanisms are considered. The frequency of GERD was 13.4% among schoolchildren with familial burden of ulcer and 7.7% in the absence of it ($p = 0.001$).

As characteristics of the progressive course of gastritis to the state of atrophy, its activity is considered. This is especially true for children. An analysis of the question of the association of hereditary susceptibility to ulcer with gastritis activity in the surveyed contingent of Siberian schoolchildren showed the absence of such (Table 2). So high (2-3 degrees) activity of antral gastritis had 48.4% of children with a family predisposition for peptic ulcer disease and 54.6% in its absence ($p = 0.235$). There was no increase in the activity of gastritis in the body of the stomach: in schoolchildren with a family

Table 1

The frequency of clinical syndromes in the examined children, depending on the presence of a family predisposition to peptic ulcer disease

Syndrome		Predisposition to peptic ulcer				p-level (significance of feature differences)
		+ (n=479)		– (n=2864)		
		n	%	n	%	
DS		266	55.5	1123	39.2	0.001
Clinical variants of DS	Epigastric pain	134	28.0	525	18.3	0.001
	Postprandial Distress Syndrome	132	27.6	598	20.9	0.001
GERD (weekly heartburn)		64	13.4	220	7.7	0.001

Note: GERD - gastroesophageal reflux disease; DS - dyspepsia syndrome.

Table 2

The activity of gastritis in the examined children, depending on the presence of a family predisposition to peptic ulcer disease

Gastritis activity		Predisposition to peptic ulcer				p-level
		+ (n=126)		– (n=337)		
		n	%	n	%	
Antral department	1. 1st degree	65	51.6	153	45.4	0.235
	2. 2-3 degree	61	48.4	184	54.6	0.235
Body	3. 1st degree	44	72.1	186	71.0	0.859
	4. 2-3 degree	17	27.9	76	29.0	0.859
p-level (significance of feature differences)	1-2	0.614		0.017		
	3-4	0.001		0.001		

predisposition of 2-3, the degree of activity was determined in 27.9% and 29.0% in its absence (p = 0.859).

It is known that familial predisposition to ulcer affects various regulatory mechanisms of the inflammatory process, including the immune response. Cytokines are largely involved in this. The study of indicators of the cytokine profile in gastritis in schoolchildren with a familial predisposition to ulcer showed certain features. For example, they showed IL-4 expression (p = 0.020) (Table 3). The functional parameters of the participation of IL-4 in the inflammatory process are diverse: suppression of macrophage activity, the production of a number of cytokines (in particular TNF (tumor necrosis factor), IL-6). It is known about the regulatory effect of IL-4 on proliferative processes [4]. In people with peptic ulcer disease, as well as with a predisposition to the disease, there is an imbalance in the protective and aggressive factors of the stomach (local level). And an increase in circulating IL-4, obviously, should be regarded as the activation of a cascade of metabolic, immune events in the body, aimed at ensuring the optimization of proliferative processes in GM. In addition, an increase in IFN-α was noted in children with a familial predisposition to peptic ulcer disease (p = 0.001). It is a cytokine that functionally triggers the body's immune responses to damage [20]. IFN-α has not only antiviral, but also immunomodulatory effect due to the effect on the expression of receptors of the major histocompatibility complex (MHC). In recent years, it has been shown that IFN-α also has an antibacterial effect, which is based on the ability of IFN-α to induce in the affected cell the activity of a number of enzymes with antibacterial activity: in particular, indolamine-2,3- and NO-synthetase [18]. Schoolchildren with a history of ulcer disease showed a tendency to transition to the systemic level of cytokine regulation.

Among other established features of cytokine regulation, there was one more: differences in the expression of interleukin 1β, which was higher in schoolchil-

Table 3

Indicators of cytokines in blood serum in children with gastritis with a family predisposition to peptic ulcer disease

Cytokines	Predisposition to peptic ulcer						P
	+ (n=73)			– (n=106)			
	Me	C_{25}	C_{75}	Me	C_{25}	C_{75}	
1. IL-2	0.1	0.1	0.5	0.1	0.1	0.1	0.108
2. IL-4	1.6	0.9	2.0	1.1	0.4	1.8	0.020
3. IL -8	16.4	0.1	73.9	13.5	0.1	82.8	0.652
4. IL -18	131.2	58.4	186.8	127.8	54.7	212.9	0.859
5. IL-1β	0.1	0.1	0.1	0.2	0.1	0.3	0.024
6. IFN-α	0.7	0.1	1.8	0.1	0.1	1.0	0.001
7. TNM-α	0.1	0.1	0.2	0.1	0.1	0.1	0.203

Table 4

Indicators of cytokines in blood serum in children with gastritis with a familial predisposition to peptic ulcer disease and the presence of *H. pylori*

H.pylori	Cytokines	Predisposition to peptic ulcer						P
		+			–			
		Me	C_{25}	C_{75}	Me	C_{25}	C_{75}	
H.pylori + (nPU+ = 31; nPU– = 60)	1. IL-2	0.1	0.1	0.5	0.1	0.1	0.1	0.234
	2. IL-4	1.5	0.5	2.1	1.0	0.5	1.8	0.208
	3. IL-8	22.6	1.4	86.4	18.6	0.1	91.2	0.487
	4. IL-18	124.6	38.9	194.9	138.1	82.7	227.3	0.445
	5. IL-1β	0.1	0.1	0.1	0.1	0.1	0.4	0.051
	6. IFN-α	0.5	0.1	1.6	0.1	0.1	1.1	0.017
	7. TNM-α	0.2	0.1	0.5	0.1	0.1	0.1	0.048
H.pylori – (nPU+ = 36; nPU– =41)	8. IL-2	0.1	0.1	0.4	0.1	0.1	0.1	0.249
	9. IL-4	1.6	1.0	2.0	1.1	0.4	1.9	0.061
	10. IL-8	8.3	0.3	74.3	7.6	0.1	84.5	0.575
	11. IL-18	117.9	86.7	173.9	117.7	24.1	155.3	0.575
	12. IL-1β	0.1	0.1	0.1	0.1	0.1	0.1	0.133
	13. IFN-α	0.6	0.1	1.8	0.1	0.1	1.1	0.001
	14. TNM-α	0.1	0.1	0.1	0.1	0.1	0.1	0.337
p-level (significance of feature differences)	1-8	0.976			0.929			
	2- 9	0.445			0.807			
	3-10	0.369			0.641			
	4-11	0.927			0.289			
	5-12	0.108			0.240			
	6-13	0.713			0.531			
	7-14	0.125			0.215			

dren without a family history of peptic ulcer disease (p = 0.024). Increased levels of IL-1β are observed in some infectious diseases and inflammatory processes of a non-infectious nature [16]. The pathophysiological meaning of this needs to be studied. Evaluating the results obtained for the state of the cytokine profile and the expression of some of them in gastritis in schoolchildren with a burdened family history of ulcer, a natural question arises that the revealed changes could be the result of different levels of H. pylori infection in children with and without a predisposition to ulcer, which is the primary cause of inflammatory process. Consequently, the existing differences in the expression of cytokines should reflect to a greater extent the characteristics of the inflammatory process in GM of infectious genesis.

When analyzing the level of cytokine expression in schoolchildren with confirmed H. pylori infection, peculiarities were noted in the presence of familial ulcer problems (Table 4). In particular, the expression of TNM-α (tumor necrosis factor), the main role of which is the induction of the inflammatory process. These are the production of IL-1, IL-6 and TNF itself, stimulation of the processes of adhesion and antibody formation, participation in the redistribution of immunocompetent cells, etc. [4]. It is possible that the systemic level of TNF expression is involved in the redistribution of immunocompetent cells from the peripheral blood to the inflammation focus. In persons with a family predisposition to ulcer, the local level of protection of the gastric mucosa is reduced. Under conditions of H. pylori invasion, systemic defense mechanisms are involved, including through TNF.

In addition, the replication of IFN-α, noted in schoolchildren with a hereditary predisposition, was observed both in the presence of H. pylori infection and in its absence. This emphasizes the dominant role of genetic mechanisms in changes in cytokine regulation. Regardless of the presence of infection in children with a familial predisposition to ulcer, replication of IL-4 persisted, but in the form of a trend that was more pronounced without the presence of H. pylori.

Conclusion. Thus, schoolchildren with a family predisposition to ulcer have features of the clinical and molecular manifestations of gastritis. In such children, the systemic level of cytokine regulation increases, the functional orientation of which is associated with the activation of plastic processes and immune reactions. In H. pylori-associated gastritis, they increase the expression of cytokines associated with the induction of a systemic immune response. Whereas there were no changes in gastritis activity indicators in children with a family predisposition to ulcer.

Литература

1. Бораева Т.Т., Цветкова Л.Н. Распространенность и факторы риска формирования воспалительных заболеваний верхних отделов пищеварительного тракта у детей в Республике Северная Осетия-Алания. Педиатрия. Журнал им. Г.Н. Сперанского. 2010;3:140–143. [Boraeva TT, Tsvetkova LN. Prevalence and risk factors for the formation of inflammatory diseases of the upper digestive tract in children in the Republic of North Ossetia-Alania. *Pediatriya [Pediatrics. Journal of G.N. Speransk]y.* 2010;3:140-143].

2. Воробьева А.В. Особенности течения хронического гастродуоденита у детей. Вестн. нов. мед. технол. Электронное издание. 2016; 1: 229-234. [Vorobiyova AV. The peculiarities of chronic gastroduodenitis in children (literature review). *Vestn. nov. med. tekhnol [Bulletin of new medical nechnologies].* Electronic edtion. 2016;1:229-234].

3. Лопатина В.В. Факторы риска в развитии язвенной болезни. Здоровье населения и среда обитания. 2011;12(225):16-18. [Lopatina VV. Risk factors in the development of ulcer disease. *Zdorov'e naseleniya i sreda obitaniya. [Public Health and Life Environment].* 2011;12(225):16-18].

4. Макарова В.И., Макаров А.И. Роль цитокинов в реализации воспалительной реакции // Экологическая физиология. 2008;5:31-5. [Makarova VI, Makarov AI. The role of cytokines in the implementation of the inflammatory response. Ekologicheskaya fiziologiya [*Ecological physiology].* 2008;5:31].

5. Маланичева Т.Г., Зиатдинова Н.В., Дени-

сова С.Н. Распространенность заболеваний верхних отделов пищеварительного тракта у детей раннего и дошкольного возраста. Эксперим. и клин. гастроэнтерол. 2012;1:55-58. [Malanicheva TG, Ziatdinova NV, Denisova SN. Prevalence of upper gastrointestinal tract diseases in infants and preschool children. *Eksperimentalnaya i klinicheskaya gastroenterologiya*. [Experimental and clinical gastroentherology] 2012;1:55-58].

6. Поливанова Т.В., Вшивков В.А. Взаимосвязь семейной предрасположенности к патологии желудка с эрозивно-язвенными поражениями гастродуоденальной зоны и ГЭРБ у школьников Сибири. Якутский медицинский журнал. 2020;2(70):88-92. [Polivanova TV, Vshivkov VA. Relationship of family predisposition for gastric pathology with GERD and erosive-ulcerative lesions of the gastroduodenal zone in schoolchildren in Siberia. *Yakut medical journal*. 2020;70(2):88-92.] DOI: 10.25789/YMJ.2020.70.26

7. Проблемы и перспективы современной детской гастроэнтерологии. А.М. Запруднов, К.И. Григорьев, Л.А. Харитонова [и др.]. Педиатрия. Журнал им. Г.Н. Сперанского. 2016;6:10-18. [Problems and perspectives of modern pediatric gastroenterology. Zaprudnov AM, Grigoriev KI, Haritonova LA. [et al.]. *Pediatria Pediatrics. Journal of G.N. Speransky*. 2016;6:10-18

8. A Global, Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Pediatric Population. PM Sherman, E Hassall, U Fagundes-Neto [et al.]. *Am J Gastroenterol.* 2009;104(5):1278-95. DOI: 10.1038/ajg.2009.129

9. Analysis of risk factors associated with precancerous lesion of gastric cancer in patients from eastern China: A comparative study. M Wei, Y Wu, Y Fan [et al.]. *Journal of Cancer Research and Therapeutics*. 2013;9(2):205-209. DOI:10.4103/0973-1482.113351

10. Association of TNF-α but not IL-1β levels with the presence of Helicobacter pylori infection increased the risk of peptic ulcer development. M Tourani, M Habibzadeh, A Karkhah [et al.]. *Cytokine*. 2018;110:232-236. DOI: 10.1016/j.cyto.2018.01.003

11. Decreased circulating interleukin-33 concentration in Helicobacter pylori-infected patients with peptic ulcer: Evaluation of its association with a cytokine gene polymorphism, gender of patients and bacterial virulence factor CagA. A Bassagh, A Jafarzadeh, N Kazemipour [et al.]. *Microb Pathog.* 2019;136:103708. DOI: 10.1016/j.micpath.2019.103708

12. Dixon MF, Genta RM, Yardley JH. Histological classification of gastritis and Helicobacter pylori infection: an agreement at last? The International Workshop on the Histopathology of Gastritis. *Helicobacter.* 1997;2(1):17–24.

13. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. *Gastroenterology*. 2016;150:1262–1279. DOI: 10.1053/j.gastro.2016.02.032

14. Dunlap JJ, Patterson S. Peptic ulcer disease. *Gastroenterology Nursing*. 2019;42(5):451–454. DOI: 10.1097/SGA.0000000000000478

15. Konturek PC, Konturek SJ, Brzozowski T. Helicobacter pylori infection in gastric cancerogenesis. *J Physiol Pharmacol*. 2009;60(3):3-21.

16. Interleukin-1 Beta-A Friend or Foe in Malignancies? R Bent, L Moll, S Grabbe [et al.]. *Int J Mol Sci.* 2018;19(8):2155. DOI: 10.3390/ijms19082155

17. Kyoto global consensus report on Helicobacter pylori gastritis. K Sugano, J Tack, EJ Kuipers [et al.]. *Gut.* 2015;64(9):1353-1367. DOI: 10.1136/gutjnl-2015-309252

18. STAT3/p53 pathway activation disrupts IFN-β-induced dormancy in tumor-repopulating cells. Y Liu, J Lv, J Liu [et al.]. J *Clin Invest*. 2018;128(3):1057-1073. DOI: 10.1172/JCI96329

19. The biological functions of IL-17 in different clinical expressions of Helicobacter pylori-infection. N Bagheri, F Azadegan-Dehkordi, H Shirzad [et al.]. *Microb Pathog*. 2015;81:33-8. DOI: 10.1016/j.micpath.2015.03.010.

20. Liu X, Diedrichs-Möhring M, Wildner G. The Role of IFN-alpha in Experimental and Clinical Uveitis. *Ocul Immunol Inflamm*. 2019;27(1):23-33. DOI: 10.1080/09273948.2017.1298822