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Who is to be blamed for the fact that enzymatic drugs are not always effective enough: the doctor, the patient or the pancreas?

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Doctor has always to foreseen the results of drug effect or another kind of therapy for the nearest period of time or future. This prediction relates not only positive effect, but also probable absence of result and moreover negative, as it is called «side effect».

Key words: enzymatic drugs, adequate doses, minimicrospheres, duration of intake, causes of inefficiency

Although widely used in the exocrine pancreatic insufficiency (EPI) minimicrospherical enzyme preparations (EP) enteric-coated, fat hydrolysis normalization does not occur in about half of patients. In the literature, there are a number of studies that prove the effectiveness of AF is not always dependent on the dose and release forms. Perhaps the presence of steatorrhea, while maintaining the external secretion of the pancreas (pancreatic) more than 10% of normal, and, on the contrary, the absence of steatorrhea with a decrease in production of lipase is below 10% of normal. It appears that this effect can be explained as non-pancreatic lipases (mucous produced first, stomach) and prostate specific reserve different patients. Thus, we have shown that in the absence of pancreatic lipase activity can be absorbed more than half fat from food, without enzyme replacement therapy. This is due to the fact that the lipase EPI outpankreatic give about 90% of the lipolytic activity duodenojejunal transition, whereas in healthy - about 7%. That is, to pancreatic insufficiency develops a kind of compensation, which is not always sufficient. Yet the proportion of patients after pancreatectomy not require replacement therapy. Interesting results were received by J. P. Neoptolemos et al. (1996), proved patients after pancreatic resection stool frequency, stool volume and fat content in feces does not depend on the dose of pancreatin. The authors believe that the advantage of modern drugs with a high content of lipase is only a convenience for the patient, because ensures that the prescribed treatment. A. R. Jr. Opekun et al. (1997) came to a similar conclusion when found no relationship between the dose of EP and fat in the feces. Only half of patients with a higher dose of EP contributed to the loss of fat less than 10% of the adopted with

food. There may be a phase transition threshold of efficacy, above which dose the increase does not contribute to decrease of steatorrhoea. It appears that at the high dose OP inactivated lipase contained in the same preparation by proteases is not possible since the increase in lipase isolated AF without increasing doses of other pancreatic enzymes.

Indeed, far from clear in the theoretical foundations and practical applications of AF. Let's deal with this problem. It has three main person involved: the patient, the doctor and RV.

Let's start with the patient. And not because we want to reduce the guilt of a doctor - he, too, will get. Because, really, the main reason for the lack of effectiveness of EP - a violation of Compliance Department.

We conducted our clinic anonymous survey of 200 patients with chronic pancreatitis (CP) with EPI. The results were stunning (Fig.1).

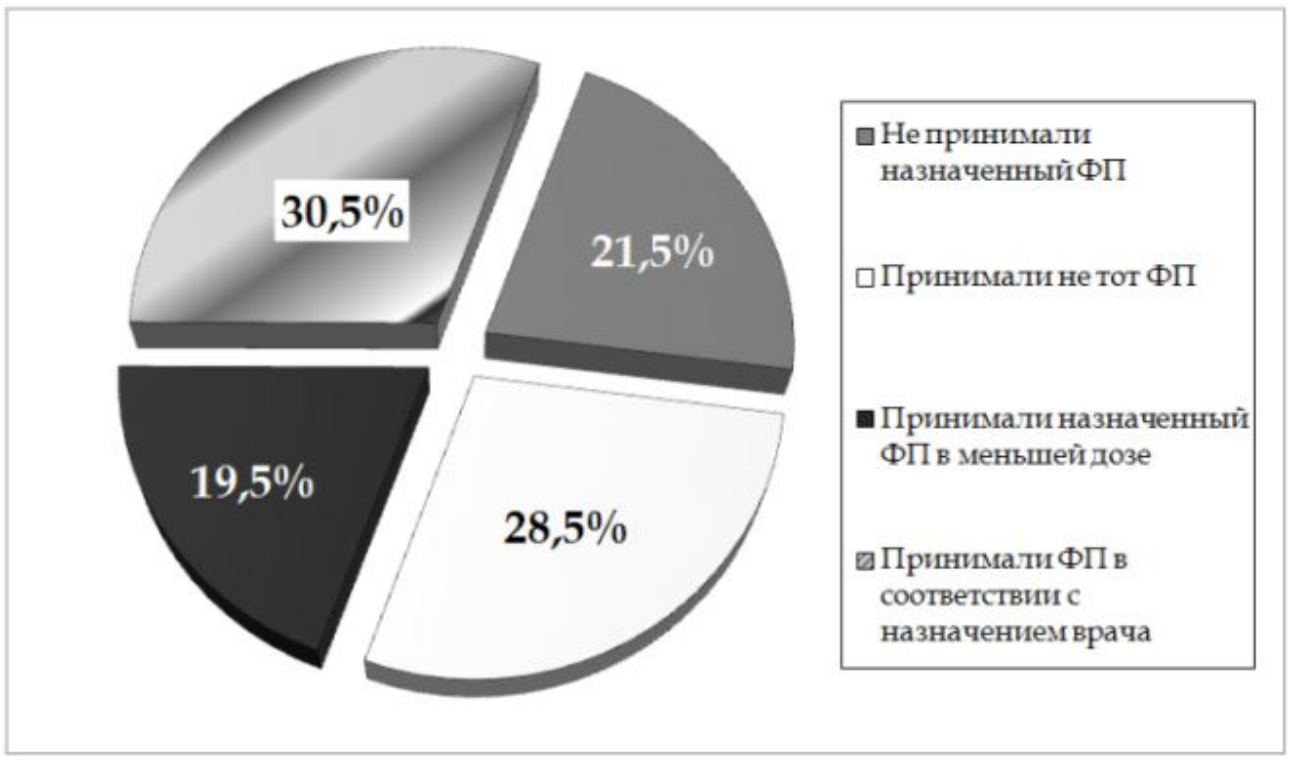

Fig. 1. Frequency of violation of compliance by patients with CP and EPI with respect to EP intake.

(21,5%) patients do not have to take prescribed AF, 57 (28.5%) patients were taking the wrong OP, who was appointed (of course, we assign the "gold standard" PC - Creon), 39 (19.5%) patients received the assigned EP but at a lower dose, and only 61 (30.5%) patients received EP in accordance with the recommendation of a physician.

What treatment success EPI we can talk? The reasons for these results: the lack of trust to the doctor (should take account of its low social status), lack of education of the patients (to be honest, illiteracy in the medical sense), but for some reason everyone in Ukraine consider

themselves well-versed in medicine, and, of course, low income population that can not get the necessary cheap, but quality medicines.

Undoubtedly, we should agree with Academician I.A. Kassirskiy: "The problem of the treatment of complex, primarily because it requires prolonged and persistent system of discipline and treatment. The patient should understand it deeply, then he can hope for success»

Now for the second "person responsible" lack of effectiveness of AF in some cases - to the doctor. That he should know the physiological basis of enzyme replacement therapy and administer it in accordance with them. Again, Academician I.A. Kassirsky: "The first and foremost task physician should be limited to the knowledge of the theory of action of drugs on the diseased organism." First of all, the physician should assign adequate dose of AF.

The secretion of pancreatic enzymes rapidly increases approximately 6 times after ingestion compared with interdigestive level and reaches a maximum after 20-60 minutes. Then enzyme products returned to a level which is 3-4 times higher than the basal. Such pancreatic secretion is maintained for 3-4 hours. This means that the maximum production of lipase after ingestion of 3-6 million IU. FIP / min and the average production of the enzyme in healthy people after ingestion - 2-4 million IU. FIP / min. Enzyme replacement therapy should mimic a similar profile production of enzymes in patients with EPI. None of the available AF can not ensure the delivery of a duodenal lumen of more than 360 thousand units. FIP active lipase, which is secreted by the pancreas under physiological conditions. Despite this, most of the patients involved in the hydrolysis EPI fat gastric lipase and residual pancreatic lipase production capability can effectively improve the hydrolysis and absorption of fat until their normalization. To eliminate steatorrhea in these patients it is important to ensure the delivery of EP in the duodenum (duodenal), together with the chyme at least 30 thousand units. FIP active lipase.

Thus, the first step in ensuring the effectiveness of treatment EPI - Compliance Department is to provide for the admission of AF. Secondly, the dose of AF should be sufficiently high that the means assigning at least 40-50 thousand units. FIP lipase with the main meal and 20-25 thousand units. FIP lipase in between meals.

It is not only dose, but also the duration of the assignment PT.

There are three basic strategies destination AF (Fig. 2):

- permanent (life) taking of EP;
- reception OP to create a "functional rest" the pancreas, in the period of acute HP and for some time afterwards (10-14 days);
- taking OP "on demand" - for the relief of indigestion after overeating.

Fig. 2. Strategies of EP prescription.

1st strategy should be chosen for patients with a reduction in the functional tests, especially the fecal elastase-1. That is, in the presence of reducing the exocrine pancreas due to its fibrosis, atrophy, cystic degeneration - due to organic causes (for HP, cystic fibrosis, etc.) - can hardly hope for a spontaneous or even under the influence of self-restoration treatment of pancreatic secretion. On the contrary, you need time to assign adequate doses of Creon for continuous use. This is also true for some patients with mild but steady EPI. This approach allows us not only to eliminate, but also to prevent disease manifestations trophological.

Quite often, giving lectures to doctors, I get the question of whether or not to suppress long-term use of adequate doses of EP's own pancreas function.I reply as follows. Prolonged intake of AF is shown, as mentioned above, patients with moderate to severe EPI. In these patients, there is practically no hope of restoring his own pancreatic secretion. If you do not provide a complete replacement therapy, then these patients will develop and will progress trophological failure to form a plurality of reaction to the various organs and tissues: hypoproteinemia, hypovitaminosis, osteoporosis, etc Should I condemn the patient to the development of trophological failure recovery capabilities for unreal own secretion of the pancreas? Even the possibility of residual cancer, which

are still preserved in patients with moderate to severe EPI, it is not sufficient to ensure the normal hydrolysis of nutrients and nutritional status. Let's make an analogy with type I diabetes. Pathology for the same body (RV), but its endocrine portion. With a lack of its own insulin to be entered from the outside. Why, in this case we do not come up with the idea of maintaining their own insulin production? Because we understand the unreality of it. We assign these doses of insulin, which provide a decent quality of life of patients. Moreover, the appointment is usually for life. A very similar situation exists in EPI. To give credibility findings H. Friess et al. (1998). The authors conducted a prospective, randomized, placebo-controlled, double-blind study, which included 12 healthy volunteers. They were divided into 2 groups of 6 each. 6 volunteers received one of the groups on day 18 OP capsules containing 20 th Ed. FIP lipase in each capsule, for four weeks. Daily intake of lipase was 360 thousand units. FIP. Volunteers of the second group received a placebo. Before and 2 weeks after administration of placebo or EP studied foreign and pancreatic endocrine function, perform sonography. There was a statistically significant difference between the indices of the functional state of the pancreas before and after the phase transition in each group and between groups, that is, the dynamics of indicators were similar in both groups, and a significant reduction in exocrine pancreas, even when taking high doses lipase has not occurred. There were no changes in the size and structure of the pancreas. Thus, the suppression is not to be feared own pancreatic secretion even when receiving an adequate dose. Much higher priority is to maintain a normal nutritional status and quality of life of patients.

2nd strategy - the use of EP for the relief of pain and dyspepsia during acute HP and after it (it should be noted that at present the EP appointment for the relief of pain is not recommended, although still in some patients it can relieve abdominal pain). However, it is known that acute pancreatitis (CP), and expressed aggravation with HP hyperenzymemia - contraindications to OP, which is self-explanatory. In these cases it is possible aggravation hyperenzymemia, intoxication and painThe fact that the enzymes are absorbed in the small intestine. A healthy person has arisen short hyperenzymemia eliminated increased catabolic enzymes, renal and extrarenal elimination from the body. With this self-regulation is disrupted pancreatitis [9]. In addition,when malabsorption nutrients have reached the terminal segment of the ileum to inhibit stimulated secretion of pancreatic. When you receive a powerful AF these inhibitory effects can be reduced, ie, the mechanism of suppression hyperenzymemia will be eliminated. If HP is not accompanied by worsening hyperenzymemia, the appointment OP appropriate and showed.

As for the OP, it is definitely at the height hyperenzymemia, which is absolutely necessary for this disease, OP contraindicated. But it is important to monitor the performance of pancreatic enzymes in the blood after OP. These patients, in some cases develops CP and pancreatic insufficiency. It is important that after the normalization of the activity of pancreatic enzymes in the

blood of the OP and the beginning of enteral nutrition appointment Creon is both possible and feasible (for tube feeding should be removed from the capsule and minimicrospheres administered with food through a tube).

But even the appointment of sufficient doses of Creon does not always solve the problem of achieving the desired effect of treatment EPI. The three main dangers meet lipase on its way to the KDP (Fig. 3a):

- lipase largely inactivated acid at pH 4 and below, however, without OP acid-shell is not effective in removing steatorrhea;
- evacuation of stomach OP should take place in parallel with the evacuation of the chyme to ensure maximum mixing of enzymes contained in the OP with the chyme in the duodenal lumen. Tableted OP slowly evacuated from the stomach, behind the passage of chyme (asynchronism), which is the cause of their inefficiency;
- pancreatic lipase is inactivated by proteolytic enzymes, particularly chymotrypsin, in the lumen of the small intestine. This, together with the inactivation of lipase in stomach acid, explains why only 8% of lipase received from the OP without acid-resistant shell per os, remains active in the duodenum. Requires taking high doses of lipase (about 1 million units. FIP) per os with food to ensure the delivery of 90 thousand units. FIP lipase activity in the duodenum.

Modern minimikrospherical OP enteric coated (Creon) prevent the inactivation of acid lipase and rapid evacuation of pancreatic enzymes from the stomach along with nutrients. Importantly, these preparations contain a low activity of chymotrypsin to minimize inactivation of lipase (Fig.3б). On this basis, it can be argued that the use of tablet AF without acid-shell currently has no justification for treating EPI. Their use is only possible in patients with achlorhydria due to chronic atrophic gastritis or resection of the stomach (gastrectomy).

Despite the use of modern minimikrospherical OP, certain factors can still interfere with the complete elimination of steatorrhea (Fig. 4).

Low pH in the duodenal lumen leads to inactivation of endogenous and exogenous lipases, if the patient is taken in the AF nonenveloped. Also, acidification duodenal lumen prevents the release of lipase from the enteric coated OP in the proximal small intestine, leading to the precipitation of bile acids, their premature microbial deconjugation and absorption. This reduces the bile acid pool is involved in emulsifying fats. Reduced pH in the lumen of the small intestine also leads to inactivation enterokinase, which also contributes to the formation of maldigestion.

The suppression of gastric acid secretion with increasing intragastric pH reduces revenues acid in the duodenum. Thus antisecretory drugs may increase the effectiveness of enzyme replacement therapy. The combination of the pancreatin as enteric coated microspheres with H2

receptor antagonists of histamine or proton pump inhibitors improves results replacement therapy in cystic fibrosis. Later it was shown that the addition of OP minimikrospherical proton pump inhibitor significantly enhances and even leads to normalization of the hydrolysis of fat in patients with an inadequate response and EPI replacement therapy. But the at patients with the adequate answer to the monotherapy with OP there is no need to complement it with antisecretory means.

It is shown that if a patient large doses of antisecretory assigned resources for other reasons (gastroesophageal reflux disease, etc.), the dose may be reduced OP.

Combining PC with antisecretory drugs is considered a must not only for gastric hyperacidity and decrease pancreatic bicarbonate production, but also in patients with rapid transit through the small intestine It should be noted that the rapid transit through the digestive tract is typical for patients who underwent resection of the stomach, and for some patients with diabetes.

About the feasibility of combining a PC with preparations containing bile acids, the data are inconsistent. P. G. Lankisch (1987) believes that this combination is impractical, because the bile acids can cause diarrhea and increase hologennuyu thus diarrhea caused EPI. The exceptions are the cases of cystic fibrosis, in which the broken cholepoiesis.

The reason for the lack of effectiveness of AF may be an excessive amount of fat in the diet. The initial approach to the diet of patients with EPI was a significant restriction of fat to reduce steatorrhea. Patients were diet containing less than 20 g fat per day. But keep in mind that such a drastic restriction of fat will result in insufficient absorption of fat-soluble vitamins that are already broken in EPI. Important is the fact that the half-life of pancreatic enzymes (endo-and exogenic) for passage through the small intestine is increased in the presence of their substrates, ie, for example, increased half-life of lipase in the presence of fat. This means that to maintain the activity of lipase in the presence of intestinal transit need of dietary triglycerides. This was demonstrated in an experimental model EPI (dogs). Hydrolysis and absorption of fat was higher when pancreatic enzymes are taken together with food containing a large amount of fat compared to food with low fat content. In this regard, a significant restriction of fat in the diet of patients with EPI currently not recommended. With adequate replacement therapy, the patient must choose the amount of fat in the diet that will not cause diarrhea and steatorrhea, ie, need not be completely excluded from the diet of fats. However, we can not agree with the recommendation that patients with EPI do not need to restrict fat in the diet, which is formulated in the recommendations of the Australian Pancreatic Club treatment EPI.

It is now believed that a special "pancreatic" diet does not exist. Important abstinence from alcohol. It is advisable to advise patients frequent meals in small portions, avoid those foods and forms of cooking, which is not always properly absorbed by healthy people, such as roughage (sinewy meat), very cold foods and beverages, which cause flatulence (beans) and so on. It is now

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Medium-chain triglycerides which are directly absorbed in the small intestine without pancreatic lipase can be recommended patients with significant weight loss, since these triglycerides provide additional calories preparation. They are also appropriate to prescribe patients with steatorrhea and inadequate response to the OP. However, the question of the appropriateness of medium chain triglycerides also remains debatable.

It is important to remember that patients with EPI may need supplemental fat-soluble vitamins, especially patients with alcoholic CP and steatorrhea.

To implement the optimal effect OP need them correctly correlate with eating. Given that exogenous pancreatic enzymes must be involved in the hydrolysis of ingested food, and evacuation of the stomach OP should take place in parallel with the chyme to optimize the hydrolysis and absorption of nutrients is generally accepted that the phase transition should be appointed along with basic and intermediate meals. The value of the phase transition at the reception time EPI has been studied in a prospective, randomized, open comparative cross-sectional study, which included 24 patients with CP and fat maldigestion. The patients were divided into three parallel groups. The effectiveness of AF was higher in their nomination during a meal or immediately after a meal compared with the reception OP directly to food.

One of the major factors hindering the achievement of the effect of enzyme replacement therapy, is a syndrome of bacterial overgrowth in the small intestine (ARIS). In the pathogenesis of ARIS for EPI matter several mechanisms. Patients changing gastrointestinal motility and secretion in biliopancreatic interdigestive period. In patients with CP violation of the parallelism between interdigestive motility and pancreatic secretion. Given that this secretion is reduced, such violations may contribute to the development of ARIS.

When EPI uns nutrients entering the small intestine are rot and fermentation medium for producing bacteria in the form of insufficiently hydrolyzed components chyme. Against the background of these processes due to accumulation of gas in the duodenum of bacterial products formed duodenal hypertension, slowing the evacuation of the chyme. All this is happening against the background of violations of local immunity and the production of secretory IgA. ARIS contributes to the stimulation of local immune serum Ig penetration into the intestinal lumen to

ensure contact between antigens and antibodies in their pervation. The increased permeability of the intestinal wall contributes to inadequate absorption of digested macromolecules. This is the background for the formation of immediate hypersensitivity to food allergens. In addition, lipopolysaccharide (endotoxin) - a component of the outer membrane of most gram-negative bacteria.

Products bacterial digestion of food in the intestine may lead to changes in its organic mucosa (dystrophy, inflammation), which may result in end-products deteriorate the absorption of nutrients cleavage by the enzymes of the small intestine and pancreas, ie, maldigestion joins malabsorption. This also contribute produced in excess during initial bacterial colonization of the small intestine dekonyugirovannye bile acids, which have a damaging effect on the endometrium.

We conducted a study to determine the frequency of ARIS in patients with CP with EPI. To confirm the presence of pancreatic insufficiency performed fecal elastase test (kits «Schebo» (Germany), enzyme immunoassay analyzer «Sanofi» (France)). For the diagnosis of ARIS in the small intestine before and after treatment were hydrogen breath test (Micro H2 analyzer, Micro Medical Ltd, UK). The study included 64 patients with CP. ARIS frequency was 87.1%

In addition, we have carried out, and another study, which included 33 patients with CP with EPI, confirmed also by the results of fecal elastase test. Patients underwent aspiration of the contents of the initial jejunum. The study included 30 healthy also. For the study of the microbial flora in the secretory jejunal chyme was performed on a number of crop nutrient media (Endo, Saburo, baktagar Ploskireva, salt and blood agar), followed by isolation of pure cultures for identification and the recalculation of the number of microbial cells in 1 ml of secretory chyme.

The level of IgG, A, M was investigated by automated method for biochemical analyzer KONE, Finland [22]. The level of secretory IgA in the duodenal contents was studied using antisera Biomed (Russia) by radial immunodiffusion Patients KP microbial flora in the jejunal contents detected significantly ($p < 0{,}001$) higher (to 67,7 ± 8,2%), than in healthy people (13,3 ± 6,2%). Average of the number of microorganisms in the secretory jejunal chyme of the tested patients were also statistically significant ($p < 0{,}001$) increased to 162,6 × 103 ± 32,1 × 103/ml (in healthy figure was 160,0 ± 21,0 / ml). The number of microbial species jejunal contents different ($p < 0{,}05$) from control group. Thus, when the number of species of bacteria HP reached 1,03 ± 0,17, and the healthy - 0,14 ± 0,09. In addition, it is important that healthy small bowel contents were detected in only one species of micro-organisms - enterococci and in patients with CP is one kind of micro-organisms were detected only in 45,5 ± 8,6% of cases. With a frequency of 9,1 ± 5,0% determined by the form 2, and with a frequency of 12,1 ± 5,7% - 3 kinds of microorganisms. We analyzed the frequency of occurrence of various types of bacteria in CP. In 39,4 ± 8,5% - E. coli in 21,2 ± 7,1% - staphylococci, including a 6,1 ± 4,1% - hemolyzing staphylococci, in 15,2 ± 6 2% of enterococci

were detected in 3,0 ± 2,9% - B. faecalis alcaligenes, to 3,0 ± 2,9% - parakishechnye sticks. In 18,2 ± 6,7% of cases in the small bowel contents were revealed yeast and yeast-like fungi.

CP patients had significantly elevated levels of IgG (0,42 ± 0,04 g / l), IgA (0,25 ± 0,04 g / l) in the intestinal contents in comparison with healthy, where these figures were 0, 19 ± 0,06 g / l and 0,07 ± 0,01 g / l. No significant differences in the content of the secretory IgA in the intestinal contents in patients and normal CP is not revealed (or 0,86 ± 0,04 g / l and 0,68 ± 0,08 g / l; p <0,95).

In the same study, through the analysis of histological changes in jejunal mucosa (aspiration biopsy), we have shown that CP patients develop secondary enteritis, which is accompanied by a mild degenerative changes in the mucosa, thinning of the brush border, reduced the mitotic index of Paneth cells in the crypts. This enteritis accompanied by changes in enzymatic processes in the area of the membrane cavity and digestion, reduced absorptive function of the small intestine, increased epithelial desquamation, reduced local immunity and the development of ARIS. These processes, of course, reduce the effectiveness of enzyme replacement therapy.

Consequently, the lack of effectiveness AF diagnostic search should be carried out in respect of ARIS and identifying its conduct decontamination of the intestine

Physicians should also pay attention to possible errors in diagnosis when the patient holds syndrome malassimiliation nutrients due not EPI, and other diseases (see Table 1, 2). More often necessary to carry out differential diagnosis of celiac disease and giardiasis.

Table 1

Pathophysiology of maldigestion and malabsorption syndromes with different diseases

(according to P. J. Grigoriev, E. P. Jakovenko (2001))

Pathophysiology	**Illness, syndromes**
The intra-digestion	
Reduced production of pancreatic enzymes	HP, pancreatic cancer, cystic fibrosis
The inactivation of pancreatic enzymes in the gut	Gastrinoma, microbial contamination of the small intestine
Rapid transit of intestinal contents; reduced enzyme concentration by diluting	Postgastroresection syndrome, microbial contamination of the small intestine, postcholecystectomical syndrome, a disease Menetries
Violation of mixing enzymes with food chyme	Duodenal and / or gastric stasis, intestinal pseudo, irritable bowel syndrome

Impaired production of cholecystokinin	Structural damage to the mucosa of the small intestine
Deficiency of bile acids in the small intestine	Biliary obstruction and cholestatic liver diseases, microbial contamination of the small intestine
Membrane digestion	
The deficit disaccharidases	Lactase deficiency (congenital, acquired), Crohn's disease
Atrophy of enterocytes	Crohn's disease, gluten enteropathy (celiac disease). Sarcoidosis. Lymphoma. enteritis
Violation of lymph drainage from the gut	
Obstruction of lymphatic ducts	Lymphoma, tuberculosis, carcinoid lymphangiectasia
Combined	
Diabetes. Giardiasis. Hyperthyroidism. Amyloidosis. HIV infection	

Table 2

Differential diagnostic signs of violations of the level of assimilation of nutrients (according to A. I. Parfenov (2009))

Signs **Functional tests** **Instrumental techniques**	**The level of violation of assimilation of nutrients**			
	cavitary digestion	**membrane digestion**	**absorption**	**lymphatic obstruction**
Diarrhea	May be absent	associated with food intolerance	systematic, abundant, more watery	dominated by pasty frequent stools
Polifekaliya	+++	±	+++	+++
Steatorrhea	+++	±	+++	+++
Food intolerance	–	+++	–	–
Qualitative impairments in the trophic	±	±	+++	±
Enteric protein exudation, edema gipoproteinemic	–	–	++	+++ often resistant to therapy
Osteoporosis, bone pain	–	–	+++	–
Reduced serum iron	–	–	++	–
Reduction of folic acid	–	–	++	–
Decrease of vitamin B12	–	–	++	–
Hypocholesterolemia	–	–	+++	+++
Test D-xylose	norm	norm	reduced	norm
Test withI131-triolein	+++	±	+++	+++
The pH test with lactose	norm	elevated in hypolactasia	Increased	norm
Histology of the mucous membrane of the small intestine	norm	normal	dystrophy or atrophy	lymphostasis
Histochemical studies of enzymes of the small intestine	norm	decreased synthesis of enzymes	decreased synthesis of enzymes	norm

Malassimilation difficulty of treating patients with celiac disease in the fact that this disease is formed duodeno-pancreatic insufficiency and enterogenous In addition, the possible development of HP and primary pancreatic insufficiency. First decline in exocrine pancreas described in celiac disease D. A. Dreiling in 1957. The frequency of pancreatic insufficiency in celiac disease varies according to different authors, depending on their applicable functional tests. Thus, P. T. Regan et al. (1980) found half of pancreatic insufficiency in patients with celiac disease, and in 10% of cases, this deficiency was severe A. Carroccio et al. (1991) found that in celiac 22.7% of trypsin reduced products and / or the results of lipase-tserulein secretin test [34]. Later, the same authors showed decreases in chymotrypsin in stool in 37% of patients with celiac disease.

In addition to the above-described dysregulation of exocrine pancreas, celiac disease in the development of pancreatic insufficiency, and other relevant factors trophological failure, the possibility of development of autoimmune or other option (alcoholic, idiopathic) pancreatitis, an increase in the number of D-cells in the mucosa of the small intestine (somatostatin suppresses external secretion of the pancreas), decreased production of gastrin, pancreatic polypeptide.

Dysregulation of exocrine pancreas in celiac explain two other mechanisms. Given that the atrophy of the mucosa of the small intestine is giperregeneratornoy, characterized by an increase in mitotic activity in the crypts, it suggests not only an increase in the number of enterocytes, but the D-cells. And the somatostatin products increase only in the lining of the small intestine, which changes the paracrine regulation of exocrine pancreas. Somatostatin influences the production of secretin and cholecystokinin-pancreozymin duodenal mucosa. This mechanism, along with a reduction in the production of these hormones due to atrophy of the intestinal mucosa of the KDP is also essential in the development of pancreatic insufficiency in celiac disease. However, increased production of somatostatin has other consequences. Because of the overproduction of the hormone gastrin level is reduced, and this reduction is a functional one, since the number of G-cells in the stomach is not reduced.

In this connection it should be noted that the gastrin and cholecystokinin are the same family of gastrointestinal hormones and have some common determinants and react cholecystokinin receptors and gastrin. Consequently, changes in the level of gastrin in the blood is likely to change pancreatic secretion. Furthermore, holetsistokininovye receptors respond and hydrochloric acid. Generally there are three types of receptors holetsistokinin. CCK-A receptors are involved in stimulating the release of cholecystokinin nutritional ie stimulated chyme fats; CCK-B receptors take part in the secretion of pancreatic enzymes at reflux cavity WPC solution of hydrochloric acid and some amino acids; CCK-G-tropic gastrin receptors. Based on the effect of gastrin on the production of cholecystokinin, it becomes clear that reducing production of gastrin in celiac disease

is reduced holetsistokinin stimulation of the pancreas, which also contributes to the development of pancreatic insufficiency.

At celiac disease is increased production of vasoactive intestinal peptide, which could lead to violations of the microcirculation in prostate tissue and also to reduce its external secretion.

Trophological failure characteristic of celiac disease is accompanied by impaired function of the digestive glands, including the pancreas, reduced tolerance to the components of chyme, the destabilization of cell membranes (more likely the OP or exacerbation of CP).

The possibility of development of autoimmune pancreatitis in celiac disease is confirmed by U. Volta et al. (1997) [60]. We have found in 26% of patients with celiac antibodies to at least one of the following tissues: thyroid to (21%), parietal cells of the gastric mucosa (11%) to the adrenal cortex (4%), pancreatic islet cells (3%). Furthermore, 21% of patients with celiac disease is combined autoimmune diseases (type I diabetes, thyroiditis, autoimmune hepatitis, etc.). Although HP clinic for celiac disease is masked by similar manifestations of the underlying disease, but 29% of adults and 26% of children with celiac disease, there is a resurgence of amylase and / or lipase blood, 69% - trypsin blood, 19% - leukocyte elastase. The presence of CPs in celiac disease contributes to the development of severe disease trophological inssuficiency.

It should be noted that there may be errors - overdiagnosis of pancreatitis in celiac disease. This may be due to the fact that in some cases of celiac disease in developing makroamilazemiya when also revealed a significant increase in blood amylase Ratios.

Importantly, in the absence of CP pancreatic insufficiency in celiac disease is reversible with effective treatment of the underlying disease (gluten-free diet), which is explained by the improvement of the functional state of the small intestine mucosa and increased production of secretin and cholecystokinin-pancreozymin. A. Carroccio et al. (1997) showed a reduction of fecal chymotrypsin in 36.9% of patients before treatment, a 26.1% - after 30 days from start of treatment and only 4.3% of patients after 60 days from the beginning.

Pancreatic insufficiency is one of the reasons for lack of efficacy of treatment of celiac disease. So, EY Gubskaya (2008) showed that the results of the study of fecal pancreatic elastase-1 in patients with celiac disease is detected enterogenous pancreatic insufficiency, and, in some cases, this failure reaches severe level. The same author has shown that in the treatment of celiac disease is a gluten-free diet is advisable to combine with the appointment of Creon 25000 three times a day.

Results of E.Y. Gubskaya confirmed by other authors. P. T. Regan et al. (1980) also believe that the main reason for lack of effect of a gluten-free diet in celiac disease - pancreatic insufficiency. A. Carroccio et al. (1997) reported that patients with initial low levels of fecal chymotrypsin worse gaining weight on a gluten-free diet. The same authors have shown that the lower the level of the source of fecal chymotrypsin, the less weight gain after the appointment of the

diet 0,56).–(r = The authors concluded that low-chymotrypsin in the stool before the start of a gluten-free diet - a predictor of lack of efficacy of treatment and the need to use Creon [65]. Thus, if the weight gain of celiac disease in 30 days from the start of dieting without prescription Creon was 732 ± 399 g, then when taking Creon - 1131 ± 461 g (p <0,006).

We are also using the fecal elastase test was diagnosed with mild pancreatic insufficiency in 15.6%, moderate - in 3.1%, severe - in 3.1% of patients with celiac disease. In 15.7% of cases, a gluten-free diet was not effective. The result of treatment in these patients has improved significantly in the appointment of Creon in a dose of 90-120 thousand FIP units per day (Fig. 5) [42]. Given that ARIS is present in the vast majority of patients with celiac disease, the positive effect is decontamination with rifaximin KDP. It also helps to improve the results of treatment of Creon. In the lumen of the jejunum in patients with celiac disease, there is a large number of pathogenic, symbiotic microorganisms and fungi. Bacterial colonization causing 69% of patients in the appearance of the proximal small intestine of free bile acids and reduction in the proportion of conjugated bile acids. Premature bacterial deconjugation of bile acids with the formation of free bile acids have detergent properties, also contributes to the violation of the assimilation of fats, sodium and water, exacerbating the diarrhea.

Fig. 5. Results of studying the indices of fecal elastase-1 in patients with celiac disease and the results of a gluten-free diet (according to N. B. Gubergrits (2009) [**Ошибка! Источник ссылки не найден.**]).

Certainly enterogenous pancreatic insufficiency in conjunction with malabsorption develops not only atrophic duodenitis and celiac disease, but a variety of other diseases of the small intestine after major resection. Small bowel resection, the mechanisms described above except enterogenous pancreatic insufficiency matter reducing surface absorption and pancreatic enzymes asynchronism passage of the chyme, bile acids and pancreatic enzymes. When combined enterogenous malabsorption and deficiency characteristic of diseases of the small intestine, many symptoms develop malassimilyatsii nutrients, ie failure trophological.

As mentioned above, the syndrome malassimilyatsi nutrients develops and Giardiasis, in which case the OP ineffective since this pathogenesis is not associated with malassimiliation EPI. Giardia parasites mainly in the initial sections of the small intestine at the brush border microvilli, ie, in the region where there are intensive processes of hydrolysis of nutrients and absorption of nutrients (Fig. 6). On 1 cm2 mucosa may parasitize about 1 million lamblia. Giardia parasite in the small intestine accompanied by the following pathological effects:

- damage to the structure of microvil of the small intestine, inflammation of the cytopathic effect of metabolic products of the parasite;
- subatrophy and mucosal atrophy of the small intestine, leading to malabsorption;
- absorption of nutrients giardia in the area of intestinal digestion by the central pair of flagella, which also contributes to a malabsorption syndrome;
- mechanical blocking of the suction surface of the villi of the small intestine→; malabsorption
- irritation of the nerve endings of the intestinal wall, the destruction of the glycocalyx, resulting in disruption of motility of the small intestine;
- violation of binding bile acids is also a consequence of the small bowel dysmotility, itchy skin, dysfunction of the biliary tract, pancreas;
- reduced secretory IgA synthesis leads to chronic inflammatory processes in the gastrointestinal tract and to the formation ARIS;
- endointoxication;
- secondary immunodeficiency;
- allergy.

Yet it should be noted that Giardia can affect prostate and thus may form EPI.

Fig. 6. Giardia on the brush border of the small intestine.

In recent years, proved a distinct pathogenic effects of Giardia in the pancreas. Giardia can have a direct effect pankreotoksicheskoe, penetrating into the parenchyma of cancer and the development of pseudotumor causing pancreatitis. So, J. E. Carter et al. (2007) described a clinical case of pseudotumor of pancreatitis in man 59 years old, who admitted to the hospital with complaints of abdominal pain and weight loss. The examination revealed tumor formation in the pancreatic head. In connection with a suspected malignant tumor fine-needle biopsy was performed under the control of pancreatic endoscopic sonography. Histologically atypical cells were not identified, but found G. lamblia. Perhaps the development of even severe complications of pancreatitis in patients with giardiasis. Published observations of association of giardiasis with pancreatic calcification.

Another interesting observation was published T. Miyahara et al. (1997). The authors diagnosed with giardiasis pancreas in a patient with diabetes. Interestingly, cytology giardia were found only in the prostate tissue, but absent in the gall bladder. Endoscopic retrograde cholangiopancreatography revealed multiple small cysts of the pancreas, and secretin-tserulein test was able to diagnose pancreatic insufficiency. After treatment with metronidazole RV function improved significantly.

Development EPI Giardiasis described in other studies and the results of direct and indirect assessment tests of exocrine pancreatic function. The possibility of a significant reduction in production, proteolysis, and amyloid-lipolytic pancreatic enzymes, and after the treatment of giardiasis external pancreatic secretion to normal. Giardia are able to reduce the activity of trypsin in vitro. n particular, live Giardia incubation with trypsin enzyme activity decreased. While as Giardia inactivated by incubation with trypsin or trichomonas, its inactivation did not occur. Similar results were obtained in respect of that Giardia reduced pancreatic lipase activity. Mechanisms of

the effect of Giardia on pancreatic secretion is not fully understood and require further study. However, it is now clear that giardia can attack the pancreas directly, through the development of biliary and duodenal pathology. They contribute to the reduction of exocrine pancreatic function and reduce the effectiveness of enzyme replacement therapy in CP.

Emphasis is placed on two clinical observations M. Furukawa et al. (2009) and A. Kurita et al. (2009). There have been reports cases of association with prostate cancer giardiasis. These cases raise the question again, so it really is a harmless disease giardiasis. Probably, timely diagnosis and treatment are crucial.

The result of the analysis of the reasons was the lack of effectiveness of AF algorithm enzyme replacement therapy in patients with EPI formulated by prof. J. E. Domínguez-Muñoz (2011) (Fig.7).

Fig. 7. Recommendations for the enzyme replacement therapy in patients with EPI (according to J. E. Domínguez-Muñoz (2011) [**Ошибка! Источник ссылки не найден.**]).

Two other points. In severe diarrhea, loperamide EP addition can reduce steatorrhea.

Early symptoms EPI - flatulence and flatulentsiya that could significantly affect the quality of life. Such patients are shown defoamers, for example, simethicone. They should be used in parallel with AF. It is shown that this combination helps to reduce and subjective and objective symptoms EPI. The fact that the gas mixing with the liquid intestinal contents, forms foam. It

covers the bowel wall and chyme, thereby making access to the enzyme substrate, enzyme and gives absorption at intestinal villi

We have examined the reasons for the lack of effectiveness of AF associated with the patient and the doctor. But what about the third "decoy" - RV? "RV - Queen of digestion" (G.F. Korot'ko), so she did not, and we should listen to her whims and adapt to pathophysiological situations emerging in EPI. Although it was pancreatic disease - the main culprits of its functional failure. But that's a whole other aspect pancreatology.

In conclusion, the present Russian wise idea therapist M.V. Chernorutskii: "On the one mistake out of ignorance are nine errors of inattention." On the basis of the information provided in the article, we can eliminate the error of ignorance. Now up to us to prevent errors from neglect.