News of the world pancreatology (according to the materials of the Joint Meeting of the International Association of Pancreatology and Pancreatic Cancer Committee of Chinese Anti-Cancer Association, China, Shanghai, August 27–29, 2015)

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Key words: pancreatology, pancreatitis, pancreatic cancer, exocrine pancreatic insufficiency, treatment

In August, 2015 Shanghai held a joint meeting of the International Association of Pancreatology and Pancreatic Cancer Committee of Chinese Anti-Cancer Association, which presented the latest advances in the diagnostics and treatment of the pancreatic diseases [5].

Our attention was drawn to the results of studies set out below.

M. Lipinski et al. (Poland) studied the possibility of determining the level of serum soluble urokinase plasminogen activator receptor as an early predictor of severity and mortality in acute pancreatitis. The authors examined 108 patients: 22 — severe, 35 — moderate, 51 — with mild acute pancreatitis. It was found that the liminal level of studied indicator for forecasting the acute pancreatitis — 4.7 ng/ml, for the death — 7.0 ng/ml (Fig. 1). The conclusion is made about the prospects of practical application of serum soluble urokinase plasminogen activator receptor.

S. M. Park et al. (South Korea) evaluated the diagnostic capabilities of endoscopic retrograde cholangiopancreatography (ERCP) and endosonography in the absence of choledocholithiasis upon computed tomography in acute biliary pancreatitis and came to the conclusion that the conduction of endosonography can reduce the need for ERCP at 43.9%. There were examined 41 patients with acute biliary pancreatitis and the advantages of endosonography were shown. For example, biliary sludge was detected in 7 patients in the endosonography, and only 3 of these 7 patients it was diagnosed during ERCP. Choledocholithiasis was

detected respectively in 13 and 11 patients. That is, at a much lower risk of complications endosonography seems more informative.

Lecture by Prof. M. Lerch (Germany) has been devoted to etiology and pathogenesis of pancreatitis. Risk factors for acute and chronic pancreatitis (based on 51 population-based study):

- ✓ smoking (RR 1,87)
- ✓ obesity (RR 1,48)
- ✓ alcohol (RR 1,37).

Smoking and alcohol increase the risk of pancreatitis much more than the risk of cancer of the pancreas.

Protecting factors:

- ✓ eating vegetables (RR 0,71)
- ✓ eating fruits (RR 0,73).

Basic mechanisms of pancreatitis:

- ✓ premature activation of proteases
- ✓ inflammatory infiltration
- ✓ violation of the outflow of pancreatic secretion.

With respect to the first mechanism, currently much attention is paid to autoactivation of trypsin at different mutations (Fig. 2). In recent years, more cases of idiopathic pancreatitis have been attributed to heredity, because patients with idiopathic pancreatitis had various mutations with a higher frequency than in the general population (Fig. 3).

Regarding the prospects for the treatment of chronic pancreatitis, Prof. M. Lerch talked about research EUROPAC-2, which is currently underway. This double-blind randomized controlled trial (Phase III) “Treatment of patients with idiopathic and hereditary chronic pancreatitis”. The patients were divided into 3 groups receiving the antioxidants, magnesium drug or placebo. The duration of treatment is 12 months. The preparation of magnesium is selected due to the fact that magnesium competes with calcium and theoretically can inhibit the activation

of proteases in acinar cells and pancreatic secretion as such. Research has not been completed and it is too early results to speak of the results.

Prof. J. Wilson (Australia) gave a lecture about the pathophysiology of alcoholic pancreatitis. Paradox of alcoholic pancreatitis is that its possibility increases with a larger dose of alcohol, but not all the alcoholics have pancreatitis. Among alcoholics, acute pancreatitis develops in 5%, and chronic pancreatitis in 10% of cases. In 10%of the cases the latent chronic pancreatitis is reveled at autopsy. Acute alcoholic pancreatitis is characterized by vacuolization, necrosis of acinar cells; edema and infiltration of the parenchyma; bleeding into the tissue of the pancreas. For chronic alcoholic pancreatitis are typical acinar cells atrophy and fibrosis.

In the pathogenesis of alcoholic pancreatitis two aspects have a value: toxic effect of ethanol on the pancreas and individual predisposition.

Factors influencing the likelihood of developing alcoholic pancreatitis: regime of alcohol intake, type of alcohol, nutrition (limit/excess fats, proteins) smoking, hypertriglyceridemia, micronutrient/antioxidant status, obesity, genetic predisposition. The lecturer stressed the role of endotoxin of gram-negative intestinal flora (specific lipopolysaccharide) in the pathogenesis of alcoholic pancreatitis. Attention is drawn to the following facts: alcoholics had increased permeability of the gut; upon translocation of Gram-negative bacteria lipopolysaccharide penetrates in the blood flow; alcoholics have level of lipopolysaccharide in the blood increased; liver and pancreas damage by lipopolysaccharide is proven. Morphological evidence of more severe pancreatitis, more rapid progression of atrophy of the parenchyma and fibrosis of the pancreas was presented in experimental animals in combination of alcohol and re-injection of lipopolysaccharide (Fig. 4). There were shown the results of experimental studies showing that smoking exacerbates the loss of pancreas caused by alcohol in combination with lipopolysaccharide (Fig. 5). Thus, under the influence of all three factors in pancreatic parenchyma of experimental animals was observed the formation of large vesicles, presence of immature zymogen granules, a sharp

expansion of the endoplasmic reticulum of acinar cells. These changes were more severe than under the influence of alcohol and lipopolysaccharide without smoking.

M. Sahin-Toth (USA) gave a lecture about the genetic risk factors for chronic pancreatitis. He recalled cases of the disease in which genetic factors are important: hereditary (HP), family, early-onset idiopathic, late-onset idiopathic and alcoholic one. It is interesting that the number of identified mutations in individual patients increased from HP to alcoholic pancreatitis, and their etiologic and pathogenetic role, on the contrary, decreased from the beginning to the end of the above list. Classical concepts of pathogenesis of HP are shown in Fig. 6. Let us recall details pathogenesis of HP associated with mutations R122H and N291. Trypsin molecule composed of two subunits joined by polypeptide chain. In this circuit position 117 is arginine. Between the two subunits of trypsin is an active center which is capable of recognizing arginine and lysine and implement in place of the amino compound lysis polypeptide chain. Thus trypsin, mezotripsin and enzyme Y inactivate and 80% of intrapancreatic trypsinogen and trypsin. The remaining 20% of inactivation of intrapancreatic protease is provided by Casal inhibitor (SPINK1). This inhibitor is a specific substrate for trypsin. SPINK1 irreversibly binds serine trypsin lysine its active center. It is important that SPINK1 is synthesized in an amount 20 times smaller than trypsinogen, produced by the pancreas. Therefore SPINK1 can completely inhibit trypsin in the organ's tissue only when the level of trypsin activity is low. In these cases SPINK1 prevents subsequent autoactivation trypsinogen and blocks the cascade activation of pancreatic enzymes and autolysis of the pancreas. With intensive activation of trypsinogen SPINK 1 is unable to inactivate it. In this case, trypsin and other trypsin enzymes as mentioned above, lyse polypeptide chain uniting two trypsin subunits at position 117, i.e. at the junction of arginine and lysine. Upon mutation of cationic trypsinogen R122H, arginine is replaced by histidine, trypsin therefore is not able to lyse trypsinogen and trypsin molecules. Power of SPINK1 in these cases is not enough to block trypsinogen autoactivation, continuing cascade of activation of pancreatic enzymes and autolysis of the pancreas. Upon mutation of

SPINK1 (N291), the degree of inactivation of trypsin decreases, and under the influence of the powerful provoking factor (alcohol) HP is also developing (Fig. 6) [1].

M. Sahin-Toth presented the scheme of possible progression of chronic to acute pancreatitis and pancreatic cancer with an indication of the incidence and progression of the stages of pathology of the pancreas, which is important when genetic predisposition (Fig. 7).

B. Lindkvist (Sweden) spoke about the nutritional value of the diagnostic indicators. He clearly defined the diagnostic capabilities of different functional tests in the evaluation of the various stages of digestive disorders involving the pancreas enzymes (Fig. 8). It is now known that in chronic pancreatitis with exocrine pancreatic insufficiency (EPI) there is a fail of trophological status following parameters: levels of apolipoproteins, cholesterol, fat-soluble vitamins, retinol-binding protein, prealbumin (transferrin), calcium, zinc, magnesium, selenium serum. C. M. Sikkens et al. (2013) studied 40 patients with CP, 28 of which according to the fecal elastase test have EPI. It is shown that in patients with EPI blood levels of fat-soluble vitamins significantly reduced [9].

The clinic of Prof. J. E. Dominguez-Munoz examined 114 patients with CP. They determined hemoglobin, mean corpuscular volume, lymphocytes, prothrombin time, total protein, albumin, prealbumin, retinol-binding protein, cholesterol, triglycerides, amylase, folic acid, vitamin $B_{12,}$ glycosylated hemoglobin, transferrin, ferritin, magnesium and zinc. In 38 (33%) patients were found EPI via triglyceride breath test. With EPI associated low levels of magnesium, hemoglobin, albumin, prealbumin, retinol-binding protein, elevated levels of glycosylated hemoglobin. By reducing the hemoglobin index relative risk of having a patient EPI increased 4.8 times, albumin — 13.9 times, magnesium — 14.3 times. The more trophological indicators change, the higher is the probability of EPI (Fig. 9).

The speaker touched on the question “Do we really prescribe insufficient doses of enzyme preparations?” B. Lindkvist resulted in findings of Prof. J. E. J. E.

Dominguez-Munoz, who examined 29 patients with alcoholic CP with steatorrhea. Patients were given 40,000 FIP lipase units at the main meal for 2 weeks. Only 2/3 of patients were able to achieve normalization coefficient of fat absorption, indicating the insufficient dose of enzyme preparations. The best results for a given clinical picture were achieved by assigning higher doses minimicrosphere enzyme enteric-coated preparations (Creon). For instance, D. C. Whitcomb et al. (2010) administered patients with CP and severe EPI 72000 FIP lipase units for the main meal, and V. Thorat et al. (2012) — 80000 FIP lipase units for the main meal, thus reaching the significant increase in the coefficient of fat absorption [7, 11].

C. M. Sikkens et al. (2012) in the survey of 161 patients with CP have found that on average those patients took 6 capsules Creon 25,000 a day, 25% — 3 and less 25,000 Creon capsules daily, only 25% consulted a nutritionist. They also examined 91 patients who underwent resection of the pancreas. They also took an average of 6 capsules Creon 25,000 a day, 25% — 3 and less 25,000 Creon capsules daily, only 36% consulted a nutritionist. In the overwhelming majority of cases in both groups remained steatorrhea, weight loss; many patients had to restrict the fat in the diet (Fig. 10) [8]. This once again confirms that patients received an insufficient dose of Creon. It is advisable when selecting the dose of the enzyme preparation using algorithms developed by Prof. J. E. Dominguez-Munoz (Fig. 11). This approach to therapy EPI is due to the fact that the current goal of treatment is considered not only to address the symptoms, but trophological disorders. In addition, usage for enzyme replacement therapy of exactly minimicrosphere enteric-coated enzyme preparations, unlike minitablets and minisspheres, can increase by 25% the efficiency of digestive enzymes that may ultimately contribute to the achieving of improvements in trophological status.

Lecture by Prof. J. Kleef (Germany) has been devoted to surgical treatment of chronic pancreatitis. The lecturer pointed out the most rational operating methods in various pathologies of the pancreas, especially in chronic pancreatitis. Thus, when HP, suspected malignancy, obstruction of the common bile duct, it is feasible to conduct partial duodenopancreatectomy or total pancreatectomy with

islets autotransplantation; with an increase in pancreatic head ("inflammatory mass") to 4 cm — duodenum-preserving resection of the head; upon painful chronic pancreatitis with diameter of the main duct ≤2 cm — a longitudinal V-shaped excision (Izbicki operation) or total pancreatectomy with islets autotransplantation; at painful chronic pancreatitis with the expansion of the diameter of the main duct — draining operation (Partington-Rochelle, Frey).

Prof. M. L. Freeman (USA) proceeded from traditional surgical approaches in chronic pancreatitis (Fig. 12) to pancreatectomy followed by autotransplantation of islets. He demonstrated a significant increase in the number of operations at the Center of pancreatic surgery in Minnesota (USA) (Fig. 13). It is important that the quality of life after such a procedure stays satisfactory (Fig. 14). Further, the lecturer presented data on perioperative mortality, rate of endocrine pancreatic insufficiency, the need for narcotic analgesics after pancreatectomy followed by islets autotransplantation (Fig. 15). Further standard approaches to chronic pancreatitis have been demonstrated (Fig. 16) compared with the approaches of Minnesota (USA) (Fig. 17).

Particular attention was paid at the congress to autoimmune pancreatitis (AIP). On this subject detailed lecture was read by Prof. T. Shimosegawa (Japan).

AIP is a special form of pancreatitis, pathogenesis of which involves the autoimmune mechanisms, hypergammaglobulinemia, elevated levels of IgG, IgG4 serum occur, autoantibodies are present, distinct positive response to treatment with corticosteroids is registered. There are 2 types of the disease: I type — lymphoplasmocytic sclerosing pancreatitis (LPSP), II type — idiopathic ductal-concentric pancreatitis with granulocyte epithelial lesions (IDCP).

Type I — LPSP:

- ✓ patients older than 50 years
- ✓ predominantly male
- ✓ uniform frequency of worldwide distribution
- ✓ elevated levels of IgG, IgG4
- ✓ detected autoantibodies

- ✓ retained ductal epithelium
- ✓ extrapancreatic manifestations: rarely ulcerative colitis, often sclerosing cholangitis, sialadenitis, retroperitoneal fibrosis.

Frequency of extrapancreatic manifestations, according to the Japan Association of Pancreatologists, is following: sclerosing cholangitis — 60%, sclerosing sialadenitis — 13%, retroperitoneal fibrosis — 9%, interstitial nephritis — 9%, lymphadenopathy — 9%, thyroiditis — 7%, interstitial pneumonia — 7 %, pseudotumor — 2%.

In addition, certain characteristic histological changes are typical for LPSP: pancreatic parenchyma infiltration by lymphocytes, IgG4-positive pamaquines, moiré-form fibrosis, obliterative phlebitis.

IDCP has some peculiarities as compared to LPSP:

- ✓ younger patients
- ✓ more common in women
- ✓ mostly found in Europe and the US
- ✓ mostly normal IgG and IgG4
- ✓ autoantibodies are not detected
- ✓ granulocytic destruction of ductal epithelium
- ✓ often ulcerative colitis, possible association with Evans syndrome and Hashimoto’s thyroiditis
- ✓ positive response to corticosteroid therapy
- ✓ characterized by periductal lymphoplasmocytic phlebitis and infiltration, but it is less evident than in type I
- ✓ typical infiltration of the walls of the ducts by neutrophilic granulocytes.

Differences and common characteristics of LPSP and IDCP:

I. Principal differences — no.

II. Less evident in type I:

- ✓ diffuse tumor-like changes
- ✓ stenosis of the common bile duct

✓ stenosis of the pancreatic duct

✓ involving of the head of the pancreas as compared with the tail.

III. Common for both types:

✓ stenosis of the common bile duct.

Fig. 18 represents the ratio of the frequencies of two types of AIP. The number of patients in Japan has been steadily increasing, most probably due to improved diagnosis of AIP (Fig. 19). The distribution of AIP patients by the age is shown in Fig. 20. Typical of AIP is increased and narrowed main pancreatic duct (Fig. 21).

For the treatment of AIP the following groups of products are used:

✓ corticosteroids — for initial treatment and maintenance therapy, or per os in the form of mini-pulse therapy

✓ immunosuppressants (rarely) — azathioprine/6-mercaptopurine, mycophenolate mofetil

✓ rituksimab.

The main treatment for AIP is done by corticosteroids, and two concepts of therapy are applied (Fig. 22). However, despite the effectiveness of corticosteroids, relapses are possible (Fig. 23).

The risk of recurrence is increased in the presence of the following factors of pre-treatment:

✓ involvement of other organs (RR 9.3)

✓ sclerosing cholangitis (RR 3,4)

✓ diffuse/segmental increase in the pancreas (RR 12.5, compared with focal zoom)

✓ uneven stenosis of Wirsung's duct (RR 5,1).

After treatment with corticosteroids increased risk of relapse in the AIP is indicated by constantly elevated levels or raising from the normal level of IgG4 [6].

A distant forecast of AIP is presented on Fig. 24.

Min Keun et al. (South Korea) reported on the informativeness of endosonography with contrast in the differential diagnosis of AIP and pancreatic

adenocarcinoma. The authors examined 27 patients with AIP and 53 patients with adenocarcinoma of the pancreas, and came to the following conclusions:

- ✓ for AIP —high contrast of the arterial phase, with its weakening in the late phase (89% vs. 13% in adenocarcinoma, $p<0.001$), diffuse heterogeneity of formation (78% vs. 17%, $p<0.001$)
- ✓ sensitivity of high contrast for the diagnosis of AIP — 88.9%, specificity — 86.8%
- ✓ sensitivity of diffuse heterogeneity for the diagnosis of AIP — 77.8%, specificity — 83.0%.

Several papers were devoted to the diagnosis of neuroendocrine tumors of the pancreas. Thus, Han Hianlin et al. (China) conducted 50 operations Da Vinci about insulinoma using intraoperative ultrasonography to determine the location of the tumor. In 13 cases insulinoma was located in the pancreatic head, in 21 cases — in the body, in 13 cases — in the tail of the pancreas; including two multiple insulinoma and one ectopic (in peritoneum). The mean operative time was 142 min, with anterior hemorrhage — 165 ml. After 60 min postoperative glucose blood level increased from 1.20±3.73 mmol/l to 6.23±1.78 mmol/l. In all patients the symptoms disappeared after the operation; there were no infectious complications and deaths.

Tiegong Wang et al. (China) analyzed the results of computed tomography of benign and malignant neuroendocrine tumors of the pancreas. Total surveyed 96 patients, including 40 patients the tumor was benign, and 56 — malignant. The authors noted that in the case of malignancy were recorded: the size of the formation of more than 3 cm, heterogeneous structure, destruction of tissue formation, calcification, increased pancreatic and common bile duct.

Y. Liu et al. (China) compared the diagnostic informative value of different imaging techniques in the neuroendocrine tumors of the pancreas and the following information:

- ✓ sensitivity of endosonography — 100% (even in tumors less than 2 cm)

✓ sensitivity of transabdominal sonography — 64.7% (in tumors less than 2 cm — 50.0%)

✓ sensitivity of CT — 93.3% (in tumors less than 2 cm — 77.8%)

✓ sensitivity of magnetic resonance imaging — 64.3% (in tumors less than 2 cm — 33.3%)

✓ sensitivity of positron emission tomography — 78.6% (in tumors less than 2 cm — 50, 0%).

H. Jeong et al. (South Korea) evaluated the results of needle biopsy in the endosonography in patients with solid tumors of the pancreas. The study included 83 patients, of whom only 4 formations proved to be benign (chronic pancreatitis). The sensitivity of the needle biopsy for the diagnosis of adenocarcinoma of the pancreas was 82.9%, for the diagnosis of formations on the background of chronic pancreatitis — 61.5%. Benign formation is pointed by younger age (47 versus 68 years for malignant tumors), lower levels of CA19-9 (24 vs. 60.95 U/ml), abdominal pain without jaundice and weight loss.

Lecture by Prof. S. Chari (USA) has been devoted to the mechanisms of dysfunction of β-cells and diabetes upon cancer of the pancreas. First of all, we highlighted the following points:

- ✓ percentage of diabetes upon cancer of the pancreas is very high — 50–67%
- ✓ 75% of cases of diabetes — new-onset (less than 3 years)
- ✓ firstly arising diabetes disappears after resection of the pancreas, as insulin resistance is eliminated
- ✓ experiment shows that upon cancer of the pancreas dysfunction of β-cells develops.

Then Prof. S. Chari introduced a scheme of pathogenesis of diabetes upon cancer of the pancreas (Fig. 25). Development of β-cells dysfunction in the pancreatic adenocarcinoma is associated with increased production of pluripotent adrenomedullin hormone by tumor cells which inhibits the production of insulin. Tumor increts adrenomedullin in blood, and then it enters in the composition of exosomes in β-cells, causing their dysfunction (hypothesis of "Trojan horse").

Great interest was aroused by a lecture by Prof. M. Buchler (Germany) for the surgical treatment of cancer of the pancreas. He told about the different methods of surgical treatment with excellent results. For example, Fig. 26 shows the survival rate of patients after total pancreatectomy. Prof. M. Buchler answered the question of how to achieve improved results of treatment of pancreatic cancer. The lecturer stressed 3 positions:

1. Surgical techniques must be advanced.
2. Multidisciplinary approach is of great importance.
3. Experience and courage of the surgeon play the crucial role.

We also made a presentation on the differential diagnostics of pancreatitis and macroamylasemia. Candidate of Medicine N. V. Byelyayeva received a grant for scientific research on genetic features of ethanol metabolism in patients with chronic pancreatitis.

Congress was very interesting. It is such a pity that other pancreatologists from Ukraine could not take part in it.

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News of the world pancreatology (according to the materials of the Joint Meeting of the International Association of Pancreatology and Pancreatic Cancer Committee of Chinese Anti-Cancer Association, China, Shanghai, August 27–29, 2015)

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Article presents an overview of the results of the Joint Meeting of the International Association of Pancreatology and Pancreatic Cancer Committee of Chinese Anti-Cancer Association, describes the main achievements in the field of diagnosis and treatment of pancreatitis, pancreatic cancer. Particular attention is paid to the treatment of exocrine pancreatic insufficiency, diagnostics and treatment of autoimmune pancreatitis.

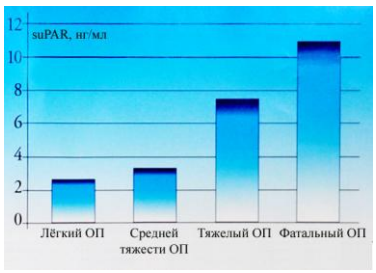

Fig. 1. The level of serum soluble urokinase plasminogen activator receptor (suPAR) in acute pancreatitis of varying severity.

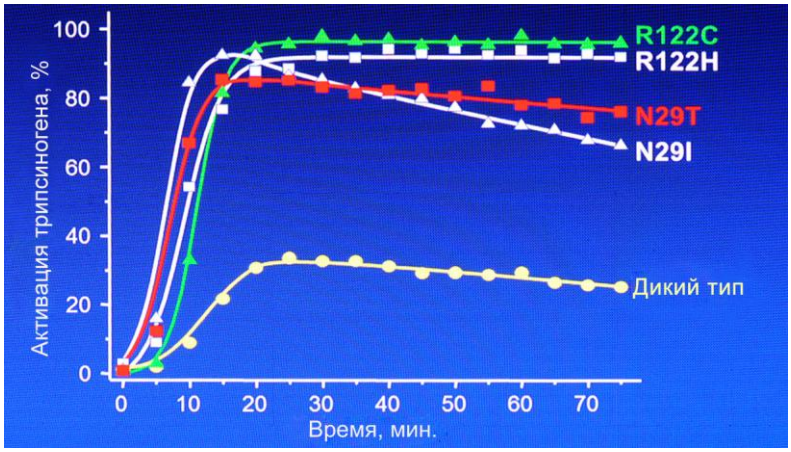

Fig. 2. Tripsinogen activation at different mutations in patients with hereditary pancreatitis in the presence of chymotrypsin C (according to A. Szabo et al., 2012 [13]).

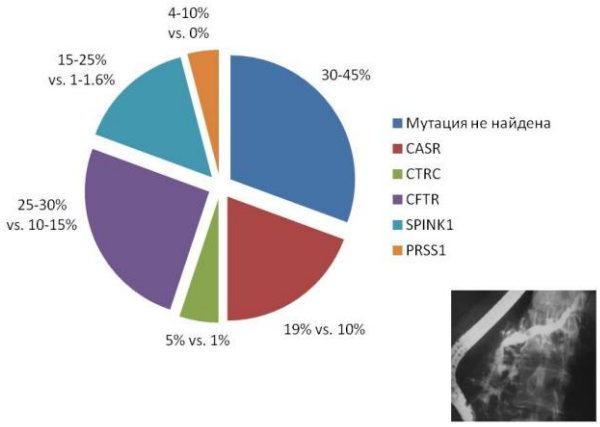

Fig. 3. The frequency of the different mutations in idiopathic pancreatitis (contains the mutation frequency in idiopathic pancreatitis as compared to their frequency in the general population).

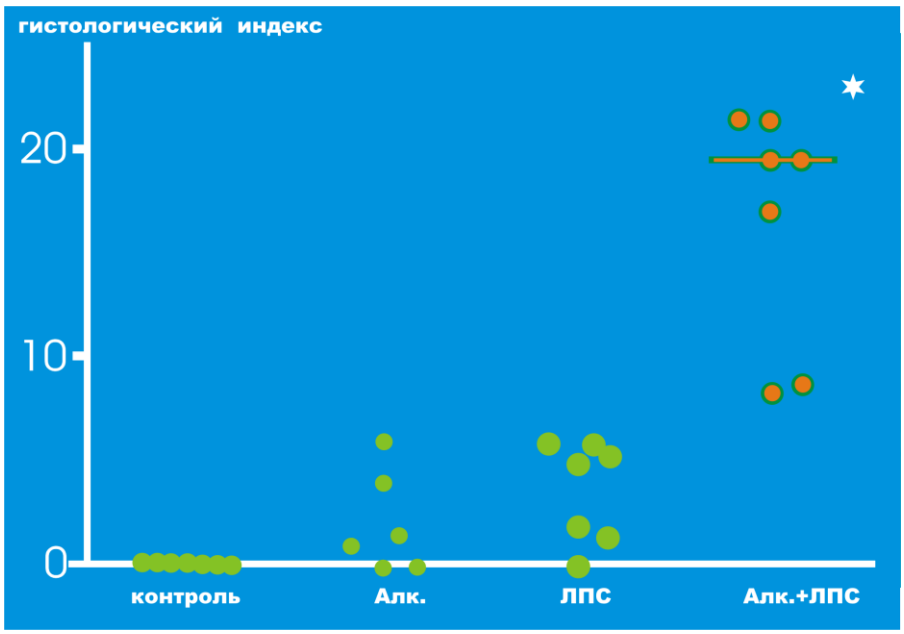

Fig. 4. Increased morphological severe pancreatitis with simultaneous introduction of alcohol and lipopolysaccharide to the experimental animals (repeated injections). LPS — lipopolysaccharide, alc. — alcohol.

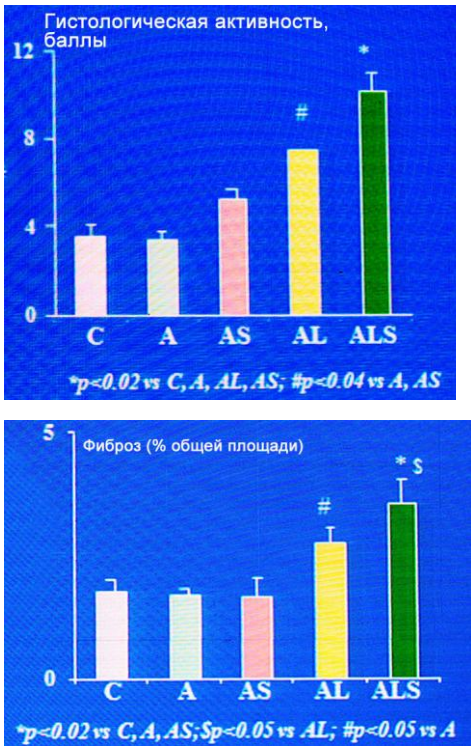

Fig. 5, b. Histological results of experimental studies confirming the worsening influence of smoking on pancreatic lesions caused by alcohol in combination with lipopolysaccharide. C — control, A — alcohol, S — smoking, L — lipopolysaccharide.

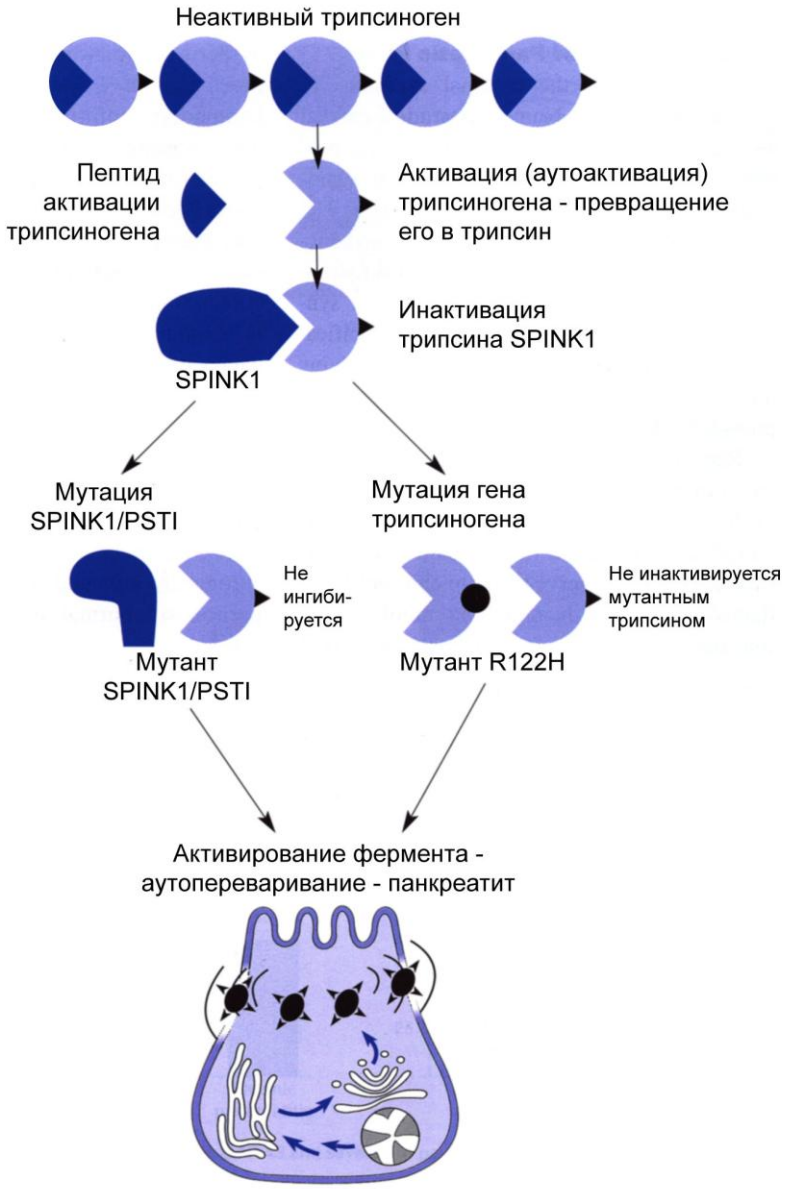

Fig. 6. Intrapancreatic trypsinogen activation and genetically determined anomalies of defense mechanisms from intraorgan excessive activation of the proenzyme (according to M. W. Buchler et al., 2004 [1]).

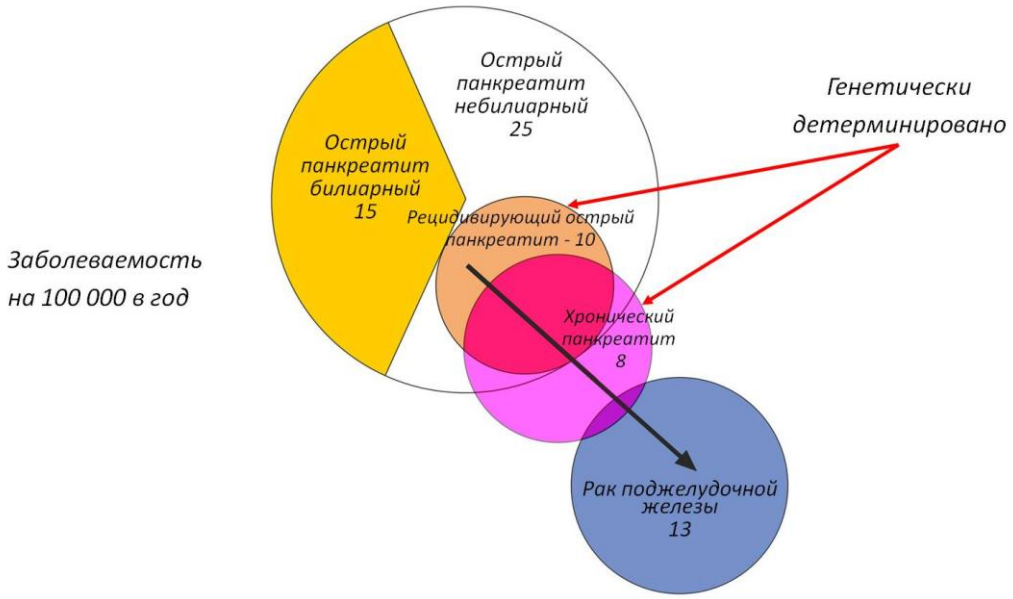

Fig. 7. The progression of acute pancreatitis to chronic one and cancer of the pancreas.

Fig. 8. Chain of pancreatic digestive and functional tests to evaluate separate stages (according to B. Lindkvist et al., 2012 [12]). MRCP — magnetic resonance cholangiopancreatography.

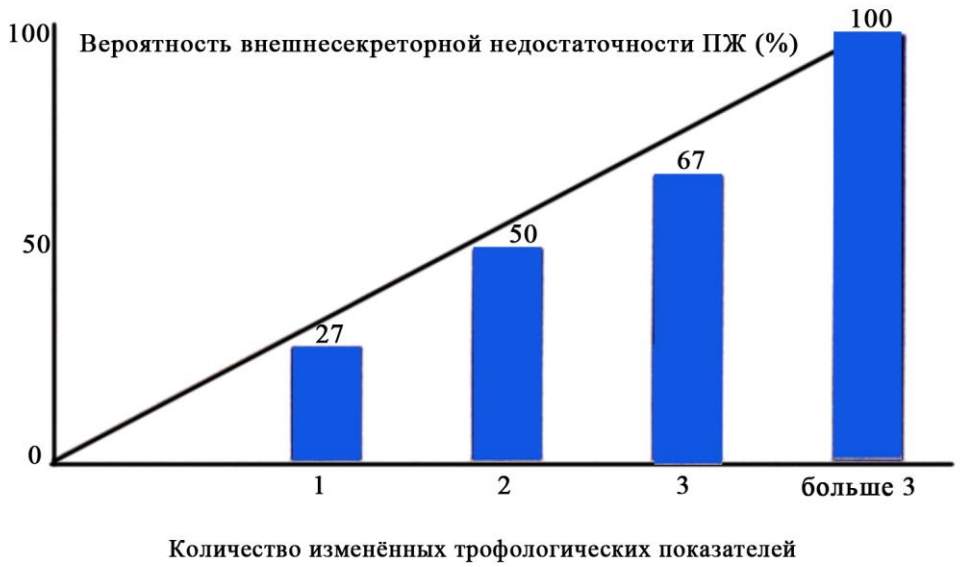

Fig. 9. Correlation between the probability of EPI and amount of changes in indicators of nutritional status (according to B. Lindkvist et al., 2012 [12]).

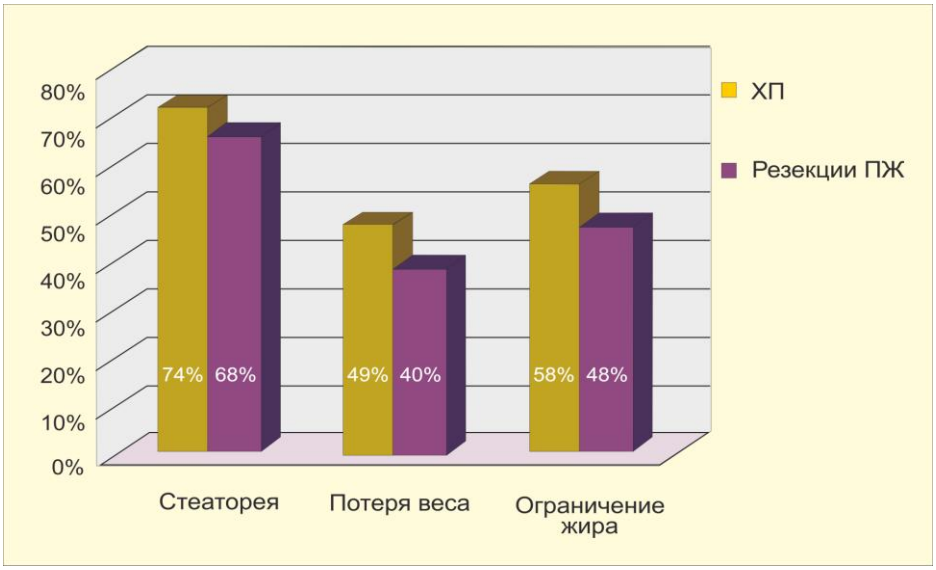

Fig. 10. Preserved EPI symptoms and the need to limit fat in the diet with insufficient dose of Creon (according to C. M. Sikkens et al., 2012 [8]).

Fig. 11. EPI treatment algorithm (according to J. E. Dominguez-Munoz et al., 2011 [2]).

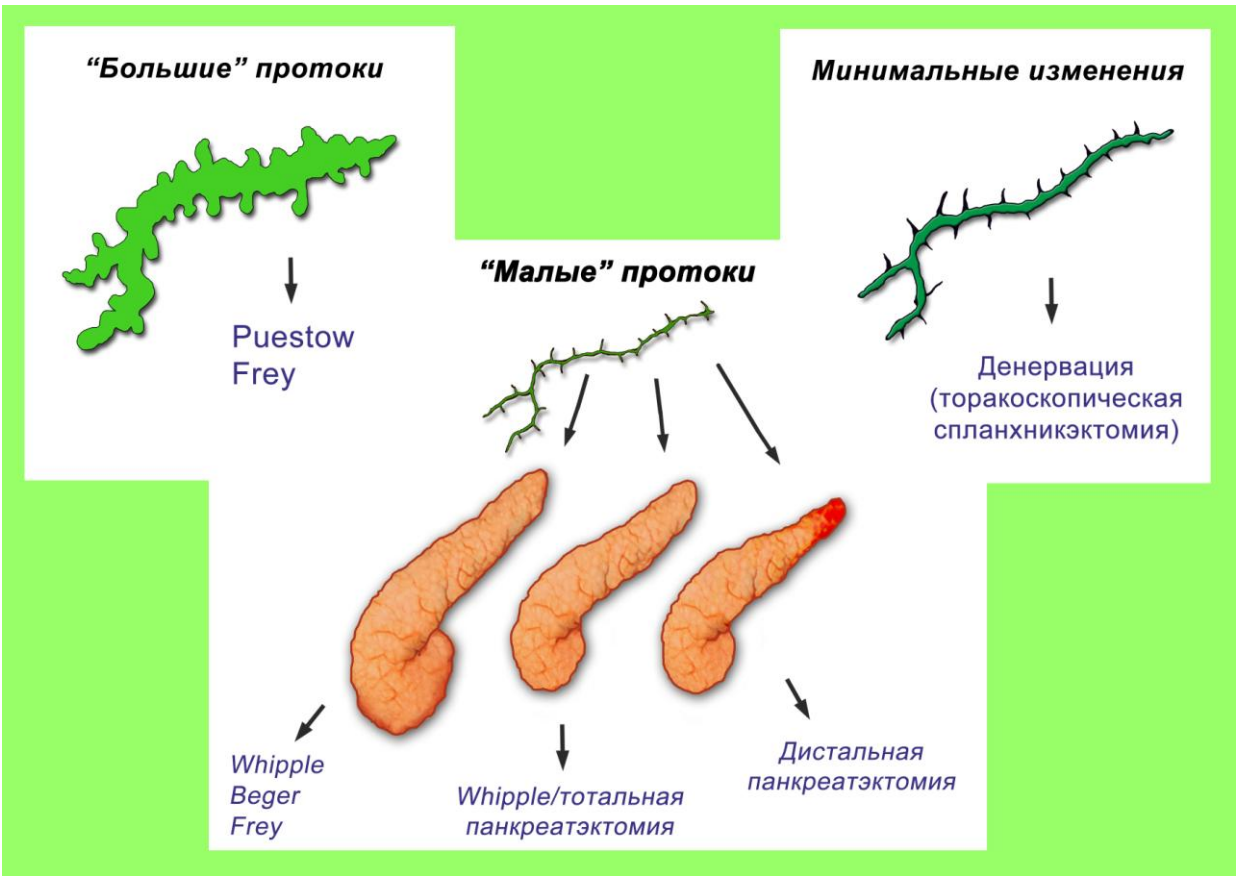

Fig. 12. Traditional approaches to surgical treatment of chronic pancreatitis.

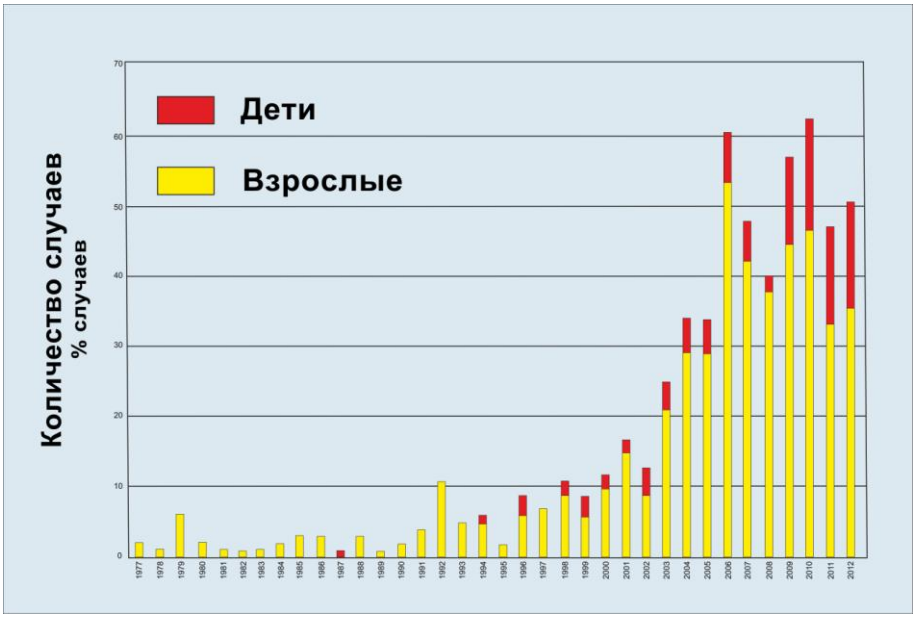

Fig. 13. The frequency of pancreatectomy followed by autotransplantation of Langerhans islets concerning various pancreatic pathologies in a Center of pancreatic surgery in Minnesota (USA).

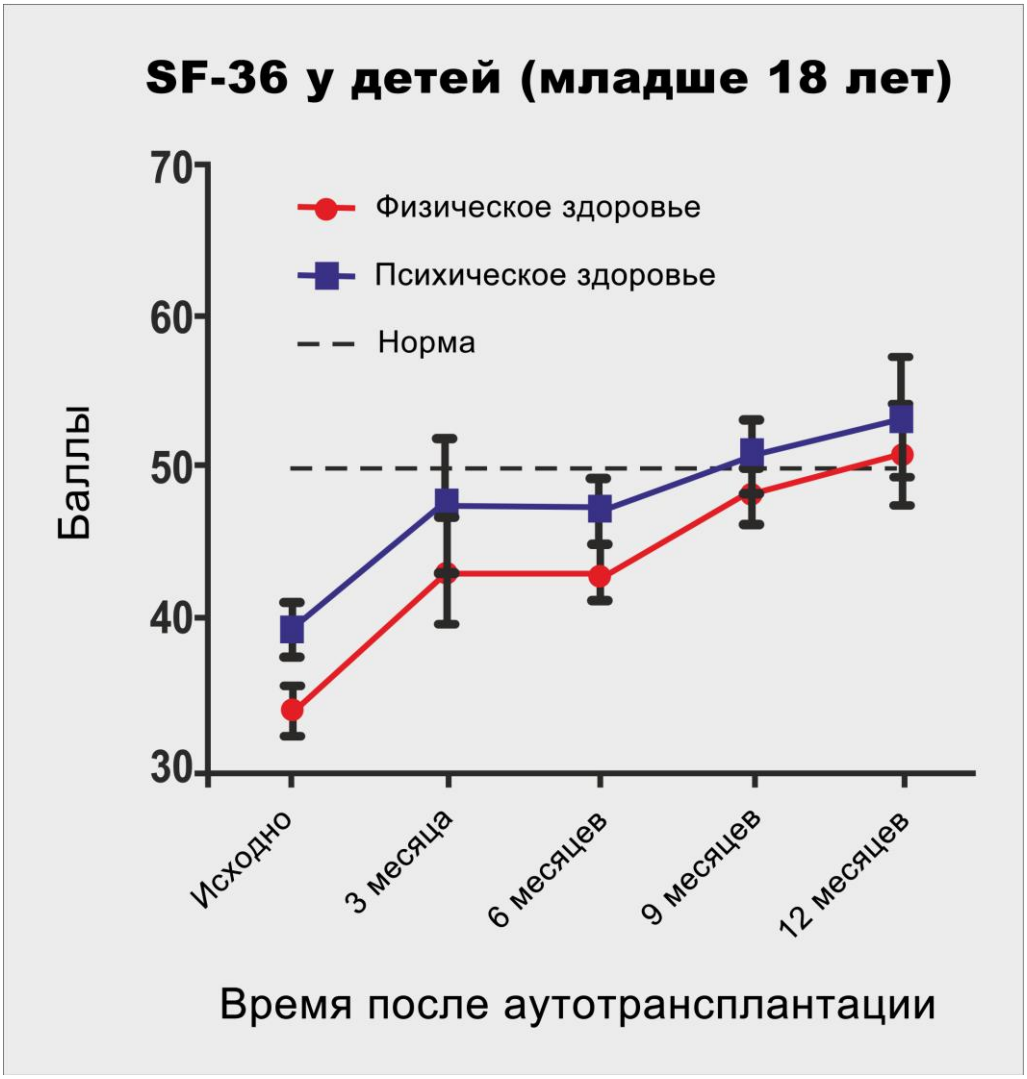

Fig. 14. Quality of life after pancreatectomy followed by autotransplantation of Langerhans islets (according to M. D. Bellin et al., 2010 [10]).

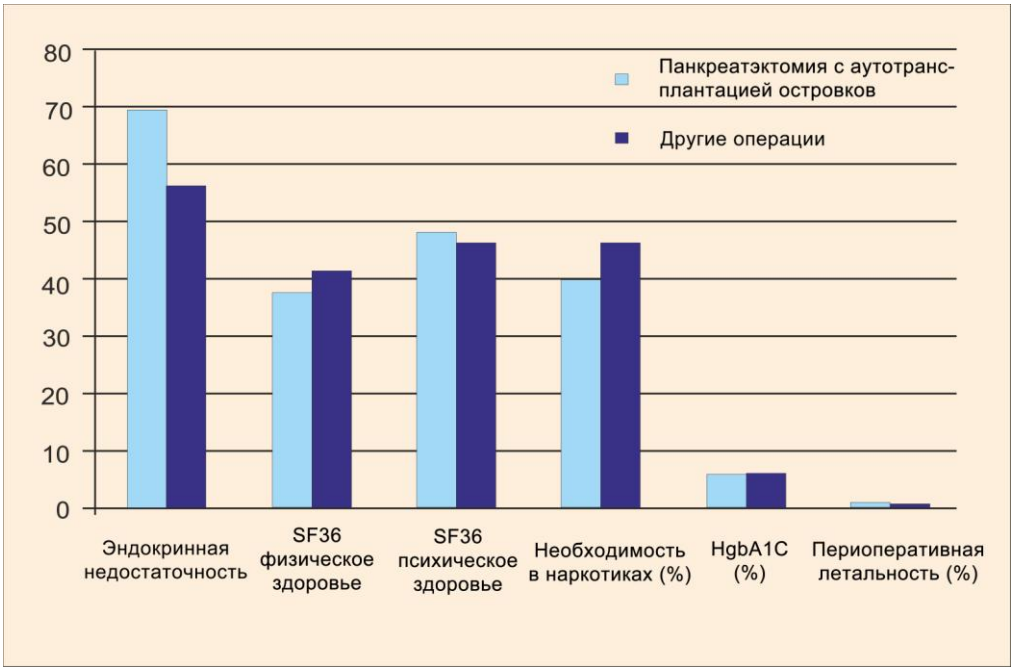

Fig. 15. The results of pancreatectomy followed by autotransplantation of Langerhans islets (according to D. E. Sutherland et al., 2008 [4]).

Fig. 16. The standard approaches to treatment of chronic pancreatitis.

Fig. 17. The approaches to the treatment of chronic pancreatitis in a Center of pancreatic surgery in Minnesota (USA).

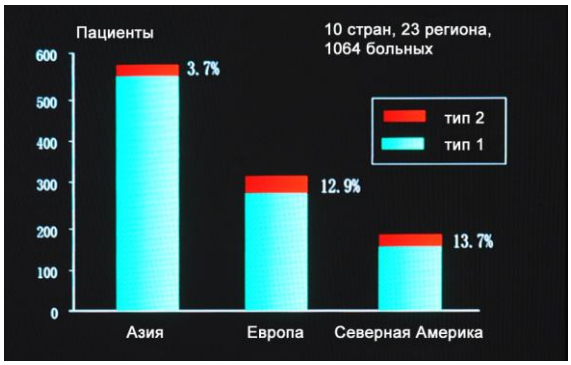

Fig. 18. The ratio of the frequencies of two types of AIP (according to P. A. Hart et al., 2015 [3]).

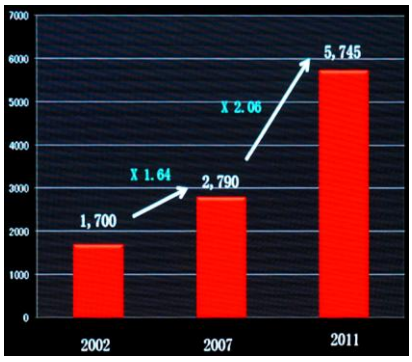

Fig. 19. Increased frequency of AIP in Japan (according to A. Kanno et al., 2015 [6]).

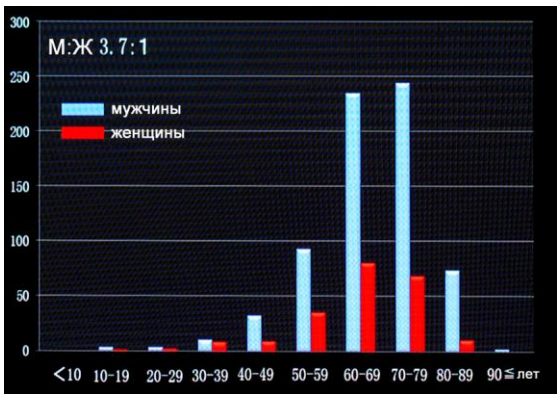

Fig. 20. Distribution of AIP patients by age (according to A. Kanno et al., 2015 [6]).

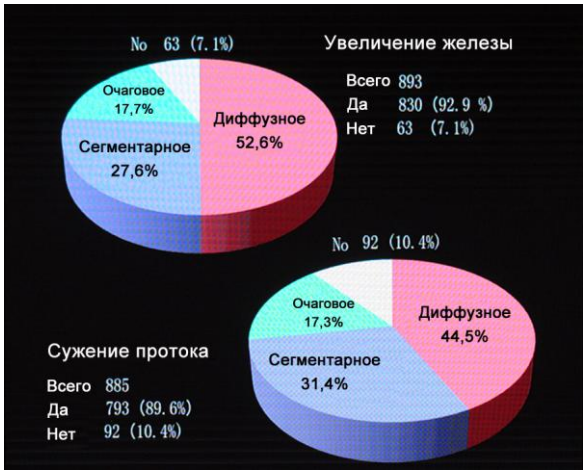

Fig. 21. Changes in the pancreas upon AIP (according to A. Kanno et al., 2015 [6]).

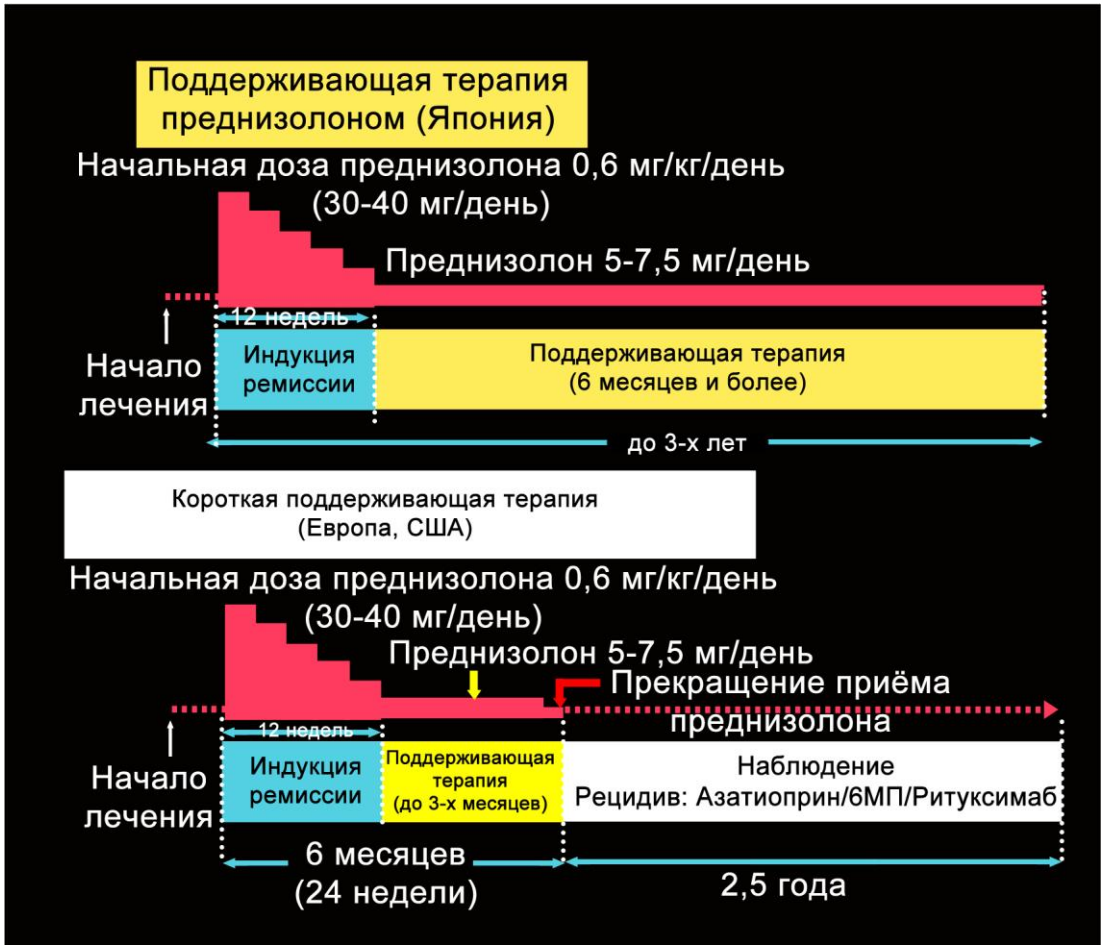

Fig. 22. Current approaches to the treatment of AIP (according to A. Kanno et al., 2015 [6]).

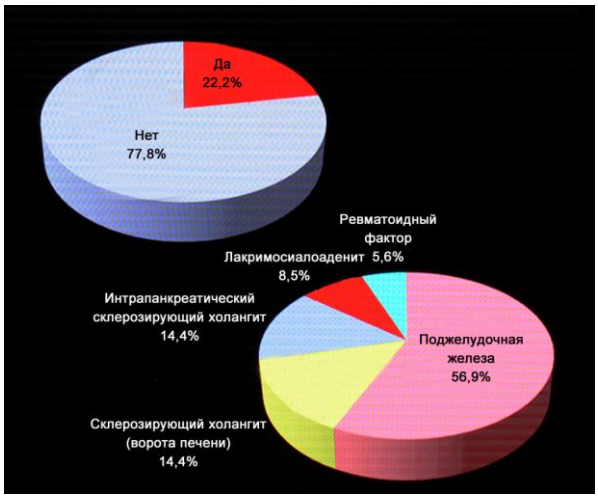

Fig. 23. Relapse of AIP (according to A. Kanno et al., 2015 [6]).

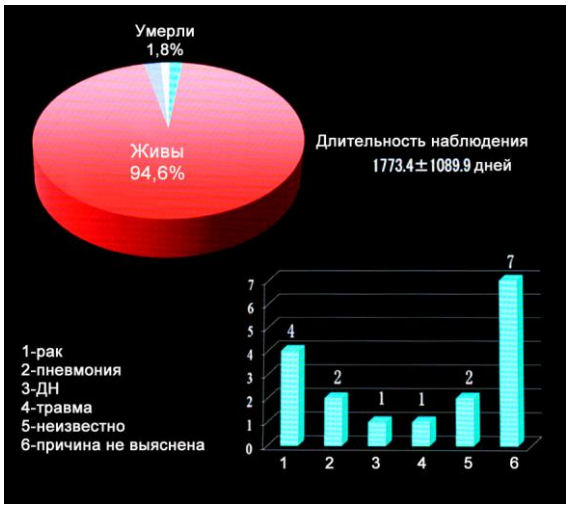

Fig. 24. The long-term prognosis of AIP (according to A. Kanno et al., 2015 [6]). RI — respiratory insufficiency.

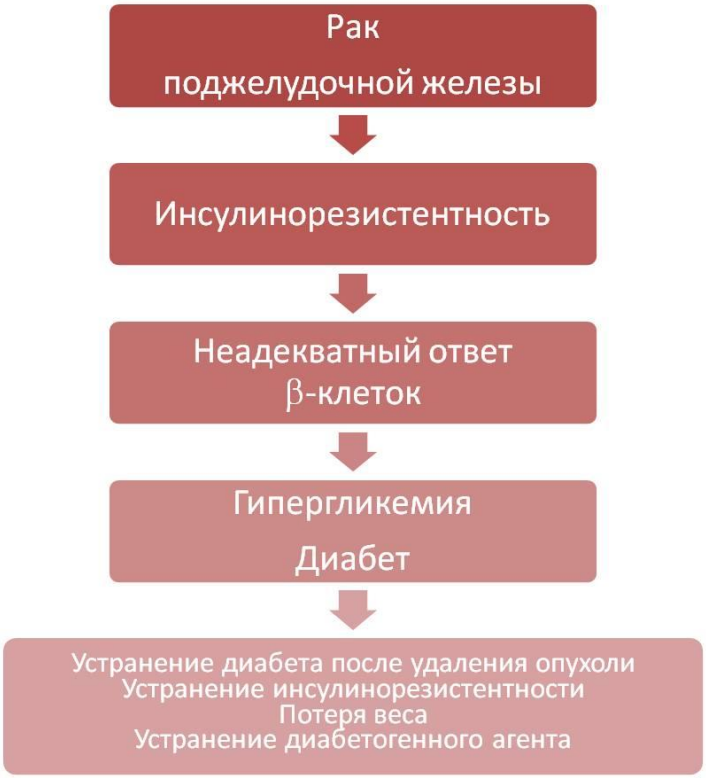

Fig. 25. Pathogenesis of diabetes upon cancer of the pancreas.

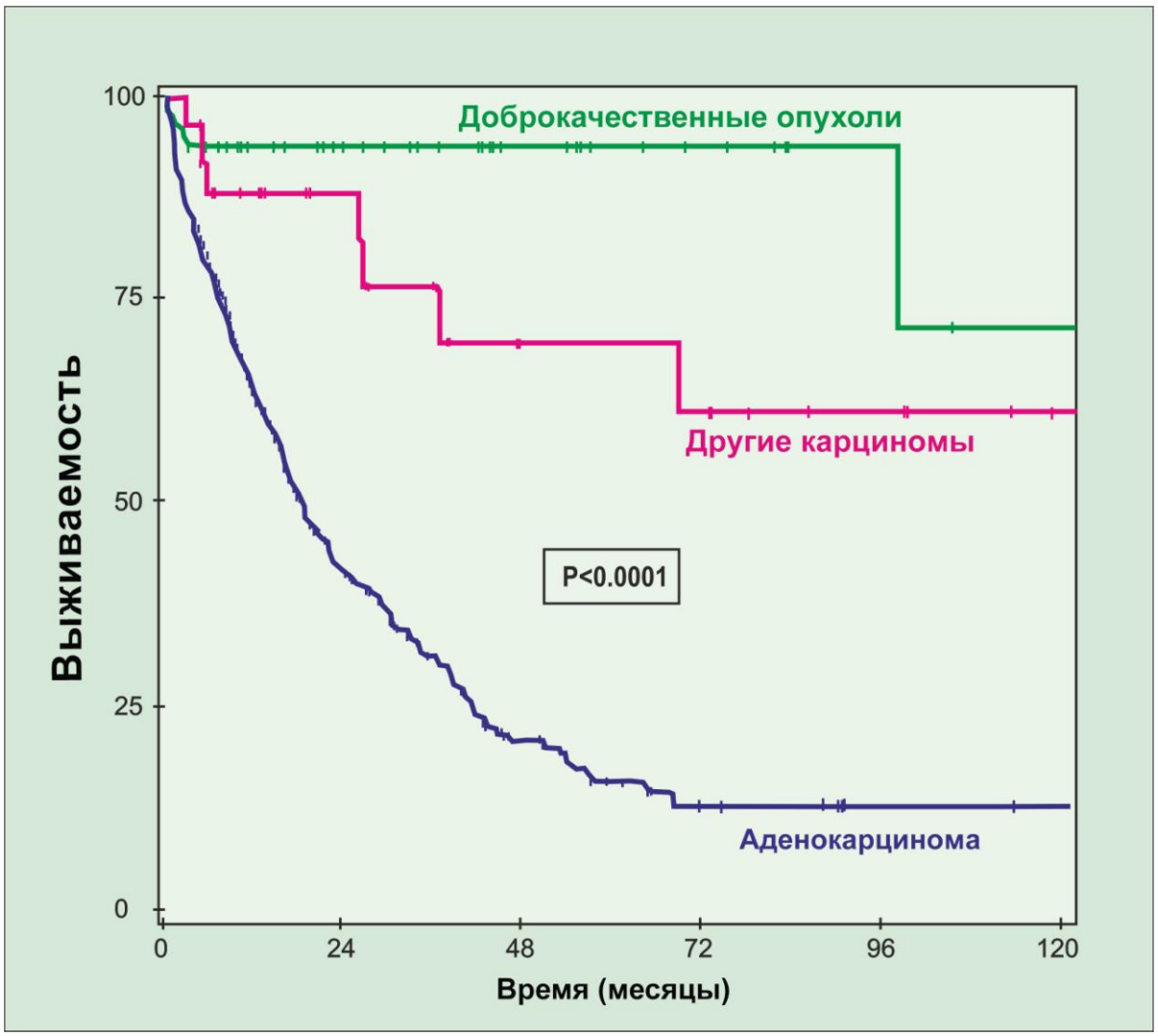

Fig. 26. Survival of patients after total pancreatectomy on adenocarcinoma of the pancreas and other diseases.