Review

Therapeutic Effects of *Lactobacillus acidophilus* Er–2 Strain 317/402, “NARINE”

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Abstract

“NARINE” is lyophilized biomass of live cultures *Lactobacillus acidophilus* Er–2 Strain 317/402 and “Narine” strain has the difference of advantages from those previously known as follows; it possesses clearly expressed adhesive properties, possesses high adaptability and stays long in the intestine (two weeks), possesses high bile- and acid-resistance (PH = 3.0), possesses high antibiotic resistance, and possesses high antibacterial, antibiotic and antymycotic activities. Therefore “NARINE” has many useful characters for human as fellows; it is regulator of the intestine microbial biocenosis, it is immunomodulator it stimulates synthesis of vitamins and lactic acid in the organism, it ensures assimilation of calcium, phosphorus, vitamins, proteins, carbohydrates, it neutralizes toxic products of metabolism, it is breast milk substitute, and acido-lactic bacteria are characterized by their resistance to the action of antibiotics and other chemotherapeutic drugs, as well as by high adaptability in the gastroenteric tract.

Effects of “Narine” on the clinical course of many fields such that dysbacteriosis of the intestine, the oncologic practice, antibiotic therapy, postnatal mastitis, prophylaxis of infectious diseases of *streptococcic* etiology, obstetrics, gynecology, radiation-thermal injury, hypercholesterolemia, Periodic disease, gastroesophageal reflux, chronic pancreatitis, treatment of *Helicobacter pylori*-associated pathologies, cosmetology, parodontosis has been studied during more than 40 years in Armenia and Russian. We report several parts of their academic achievements by review.

Key words: “NARINE”, *Lactobacillus acidophilus* Er–2 Strain 317/402, Therapeutic Effects

Introduction

Yerzinkyan L. A., ph.D discovered “NARINE” strain in 1953 from separation of 163 numbers bacteria in stool of new-born. Since, “NARINE” strain was studies by many researchers in Armenia and Russia. Microbial characteristics of “Narine” strain reported the optimum temperature for the cultivation is from 36°C to 40°C, the heat-resistant is until 40°C and it is difficult to live over body temperature, it is slightly aerobic bacteria and it possesses clearly expressed adhesive properties, possesses high adaptability and stays long in the intestine (two weeks), possesses high bile- and acid-resistance (PH = 3.0), possesses high antibiotic resistance, possesses high antibacterial, antibiotic and antymycotic activities, and no side effects have been registered while administration for 40 years.

“Narine” strain satisfies probiotics requirements that it is alive, it has high bile-and acid-resistance, it is one of bacteria of the intestine, it is useful for human and possesses high adaptability in the intestine, it has large concentration of acido-lactic bacteria in a food volume unit while microbiological examination, it is safety for foods.

“NARINE” normalizes microbial biocenosis in the intestine, in shortened time regenerates anaerobic flora (bifidumbacteria and lactobacteria), suppresses growth of conditionally pathogenic flora, increases activity of normal *Escherichia coli*. Owing to the ability to form lactic acid in the process of fermentation, as well as to produce lectoline, lactocidine, acidophile, lactobacteria “Narine” possess high antibacterial activity. Thus, the experiment proved their ability to
suppress growth of putrefactive and pus-producing microorganisms: Pseudomonas, E. coli, Kl. Pneumonia, Proteus Mirabilis, S. enteridis, S. gallinarum, S. Cholerae suis, S. Typhimurium, Shigella Serrata marcences, staphylococci, streptococci of L-form, Candida albicans. Having weakly pronounced antigenic properties, lactobacilli are able to get into close contact with the intestine mucous and prevent it from possible permeability of the pathogenic flora.

Research of the past years showed the ability of the “NARINE” drug to stimulate produce of α- and γ-interferon and increase the activity of natural killers. Interferon produce under the action of “NARINE” was added onto blood and lymphatic cultures and direct inducing of interferon under the action of “NARINE” was revealed. “NARINE” stimulates synthesis of vitamins and lactic acid in the organism. “NARINE” ensures assimilation of calcium, phosphorus, vitamins, proteins, carbohydrates. “NARINE” neutralizes toxic products of metabolism. “NARINE” is breast milk substitute. From dry powder “Narine” it is possible to obtain “Narine” fermented milk mixture, which can be used as breast milk substitute since it is an easily assimilable product, contains a great amount of vitamins, minerals, proteins, fats and carbohydrates.

One liter of fermented milk mixture “NARINE” prepared from whole milk contains from 30 g to 45 g of milk fat with a certain amount of lecithin possessing bactericidal characteristics, from 27 g to 37 g of various proteins (casein, albumin, globulin). Protein matters of milk are rich in vitally important amino acids including lysine and methionine. The valuable physiological significance of methionine is its ability to favour detoxication and elimination of pyridine and other cyclic compounds from the organism. “NARINE” is rich in vitamins of B group, aromatic matters, thanks to which it is a biologically valuable nutritious product for children and adults.

There is no history of traditional use of “NARINE” strain as fermented milk products. But researchers in Armenia studied comparative characteristics of “NARINE” and other forms of fermented milk. Similar to “NARINE” there are several forms of fermented milk, such as Matsun, Kefir, and some others in the Caucasus, the region famous in the former USSR for its long-living persons. “NARINE” is given to a newborn as a breast milk substitutes, it is also used in feeding of premature infants. Matsun and Kefir do not fulfill these functions. “NARINE” has high ability to stimulate synthesis of vitamins and lactic acid in the organism, and as a result is their rapid assimilability from the intestine. “NARINE” bacteria get adapted in the human intestine for a long time while Matsun and Kefir do not stay long in the intestine. “NARINE” bacteria are not destroyed under the influence of antibiotics and chemodrugs that is why “NARINE” can be used in combination with them. Bactericidal effect of “NARINE” is 1.5–2 times longer than that of Matsun and Kefir. Therefore, “NARINE” is used in therapy of many diseases in contrast to Matsun and Kefir.

Here is the history of the name of “NARINE”. “NARINE” is female’s name in Armenia that named to granddaughter of Yerzinkyan L. A., ph.D. She “NARINE” caused inflammation of her intestines since she was born, but it was no effect to take medicine for her. When Dr. Yerzinkyan gave her “NARINE” strain that he had been researching, she had recovered excellently. So, he named the lactic-acido bacteria for his granddaughter “NARINE”.

“NARINE” strain and prepared on its basis fermented dairy product “NARINE” are recommended by indications for use of medical purposes as fellow: to infants beginning from 6 months in a liquid form as a supplement nutrition; in the intestinal infections (colibacteriosis, salmonollosis, dysentery, klebsielliosis, yersiniosis, staphilococcic infections, etc.); in various forms of dysbacteriosis; while and especially after taking antibiotics; for clearance of the organism from poisons and residues; in premature aging and general discomfort after prolonged stress situations; for normalization of the intestine functioning (constipations, diarrheas, etc.); as an immunostimulator in virus and somatic (bodily) diseases; in treatment of after-effects of radiation injuries, poisoning with heavy metals and industrial poisons; in Helicobacter pylori-associated pathologies (chronic gastritis of B-type, peptic ulcer); in liver pathologies; in chronic pancreatitis; in gastroesophageal reflux; in allergies; in treatment of
gynecologic diseases; for prophylaxis of nipple cracks and omphalitis; in cleansing of nasal cavity in newborns.

“NARINE” strain has been studied during more than 40 years in Armenia and Russian. But their academic achievements wasn’t made public to Western countries for 40 years. For the reasons, it wasn’t necessary to advertise “NARINE” strain in the former USSR in those days. And for example, one of their academic achievements of “NARINE” strain that had been given to the cosmonauts who placed in an extreme stress situation was military secrets, it couldn’t be made public. This time, our purpose of this review is to report several parts of their academic achievements to Japan and Western countries, and we believe that thi review are significant for Japanese researchers of lactic-acido bacteria.

I. Dysbacteriosis of the intestine (DI)

1) Normal microflora

If somebody asks you to enumerate organs of digestive system many of you will probably forget to include in the list of organs normal microflora of gastroenteric tract (GET), which is currently considered by many scientists an indispensable part of digestive system, its the so-called, extracorporeal organ. During many thousands of years, thanks to the evolution of species, between a man and animal macroorganisms and a friendly symbiotic microflora mutually advantageous relations have been formed enabling their normal co-existence.

Microbes are spread all over gastroenteric tract, beginning with the oral cavity and ending in rectum. The widespread existing opinion of upper section of gastroenteric tract (gastroduodenal section) sterility is far from being correct, though concentration of microorganisms in this section is much lower than in more distal sections, however, even this concentration is sufficient for carrying out their functions. The intestine microflora is divided into two types: obligatory bacteria constantly comprising the normal flora composition (among them is Lactobacillus acidophilus. Lactobacilli are Gram-positive, unsporulating, immovable, obligatory anaerobes of Lactobacillus genus, Lactobacillaceae family) playing an important role in metabolic processes, host organism protection from infection, and optional microorganisms often observed in healthy people, but of conditionally pathogenic nature, i.e. able to cause disease development in case of the organism resistance reduction. Against a background of such abundance of microbes naturally the question arises whether we really need microflora. The answer is simple: undoubtedly yes, as it helps us to manage better quite a number of problems, make up for the lacks and defects. Functions of normal microflora of the intestine are extremely diverse, however, one of the most important functions, in our opinion, is microbial antagonism: the normal microflora fights against pathogenic and conditionally pathogenic microbes so as to maintain our organism in a normal state. In addition to this, euflora is an important immuno stimulator and immuno modulator, i.e. it “teaches” our organism how to fight against infection: stimulates lymphoid and endocrine systems, synthesis of immunoglobulins, interferon, sex and anti-inflammatory hormones, increases macrophage activity, level of complement, lysozyme, in other words, exerts neuro-endocrine-immunomodulating effect. All this hinders excessive reproduction of conditionally pathogenic microflora in gastroenteric tract.

The other important, in our opinion, function of the normal microflora of the digestive tract, which is rather to be called beneficial help, is its powerful synthetic potential. Microflora of the intestine synthesizes for our organism quite a number of the most important matters: vitamins (K, those of group B, folic and nicotinic acids; furthers absorption of vitamin D, calcium, phosphorus, essential amino acids), biologically active compounds, etc.

Besides these “global” functions euflora of gastroenteric tract performs also a great deal of “local” functions.

Normal microflora:

- participates in choline, bile and fatty acid metabolism, biliary pigment exchange, metabolism of uric acid
- enhances protein hydrolysis, ferments carbohydrates, saponifies fats, dissolves vegetable cellulose
- regulates motility of the gastroenteric tract
- the large intestine microflora secretes a series
of compounds necessary for the proper regeneration of the intestine mucous.

2) Clinical pathology of DI (symptom of “bare intestine”)

Dysbacteriosis of the intestine (DI) is a state characterized by the disturbance of mobile equilibrium of the intestinal microflora, rise of qualitative and quantitative changes in the “microbial landscape of the intestine”. DI is an actual problem in modern gastroenterology. DI can appear both as an independent disease, and join other ones complicating the course of plenty of infectious and uninfected gastroenterological pathologies. DI is accompanied both with decrease of favourable influence of euflora and enhancement of pathogenic microbe influence on macroorganism.

There are a lot of reasons for dysbacteriosis development. Herein we will enumerate the main reasons of disturbance of the gastroenteric tract microflora:

1. medicamental therapy (first of all, antimicrobial drugs, cytostatics, immunosuppressors, hormonal drugs, including contraceptives, radiotherapy)
2. many diseases of digestion organs (chronic gastritis, peptic ulcer, pancreatitis, liver and gallbladder pathologies, chronic colitis, and enteritis, diarrhea, constipations, etc)
3. immunodepression
4. atherosclerosis
5. malignant tumors
6. disturbance of the diet (use of one and the same food, overeating, vitamin, protein deficiency in food, improper water, etc.)
7. frequent chronic stress
8. infectious diseases
9. ionizing radiation

The main disorders arising from dysbacteriosis development in the digestive tract are:

1. first of all, control over activity of conditionally pathogenic and pathogenic microbes (Proteus, lactosonegative Escherichia, klebsiellas, candidi, etc.) is disturbed
2. activation of pathogenic and conditionally pathogenic microflora leads to reinforcement of fermentative and putrefactive processes in the intestine that in its turn results in increase of toxic metabolite formation (indole, skatole, ammonia).
3. active microbial reproduction leads to lesion of the intestine epithelium with affection of mucous membrane integrity, which is also provoked by decrease of trophic function of normal microflora. Such a process results in excessive toxin absorption.
4. reproduction of pathogenic and conditionally pathogenic microflora is accompanied with spreading of microorganisms into the upper sections of the intestine (small intestine and duodenum).
5. proteolytic enzymes isolated in a large amount by these microorganisms destroy digestive enzymes. The process is accompanied with digestion disorders. Nutritive matters are used by microbes in an excessive amount, which leads to development of nutritious product deficiency against a background of their normal consumption. Besides, vitamin deficiency develops due to reduction of their synthesis on the part of normal microflora.
6. infringement of the “microbial landscape” leads to disturbance of both local and general immunity.

3) Clinically proven spheres of administration

Proceeding from the afore-stated mechanisms of biological action of acidophilic lactobacteria, physicians and scientists collaborating with the “Vitamax-E” Corporation (Yerevan city) in various clinics and scientific-research centers of Yerevan, Ukraine, and Moscow (State Research Center of Preventive Medicine, Ministry of Health, Russian Federation; Moscow Medical University; “Armenia” Republican Medical Center under the Ministry of Health, Armenia; University Medical Clinic under the Yerevan State Medical University after M.Heratsi; “Erebuni” Research Medical Center; 3rd and 8th city clinical hospitals, Yerevan; “Emergency” Research Medical Center; Children’s Allergological Center, Ministry of Health, Armenia; Republican Children’s Clinical Hospital; Republican Medical Center of Mother and Child’s Health Protection, Ministry of Health, Armenia; Institute of Medical Radiology, Ministry of Health, Armenia, etc.) have carried out numerous multi-profile clinicolaboratory examinations the results of which confirmed efficiency of the “Narine” drug in treat-
ment and prevention of a number of diseases.

4) Clinical effects for DI

Intestine dysbacteriosis in its pure form, i.e. when there is lack of primary pathology of gastroenteric tract organs, is a widely spread pathology, especially against a background of uncontrolled use of various medicated drugs, in the first place antibacterial drugs. Disbacterial disturbances of the intestine microflora accompany many functional and inflammatory diseases of the large intestine. Appearing as sign of a disease later on dysbacteriosis aggravates its course. In dysbacteriosis development increase of the amount of conditionally pathogenic microflora in the large intestine occurs against a background of drop in the amount of anaerobic flora, in particular, microbes of acido-lactic fermentation (bifido bacteria and lactobacilli). This process is given a leading role in pathogenesis of the large intestine diseases1,2.

As the researches showed in a majority of cases (80%) dysbacteriosis correction with the help of “NARINE” was achieved within 10 to 15 days. Thus, in 10% of patients positive effect was already observed on the 5th day, in 65%—on the 10th, in 25%—on the 15th day of treatment. Positive changes in the intestinal microflora and dysbacteriosis correction coincided with the positive dynamics of clinical data, results of endoscopic examination, patients’ general condition and mental attitude.

The effect of “Narine” on the intestinal microflora was studied in 30 patients with functional diseases (syndrome of “irritated” intestine, spastic and tonic constipation, functional diarrhea) and 28 patients with inflammatory diseases of the large intestine: 21 patients suffered from catarrhal colitis, and 7—from nonspecific ulcerative colitis (NUC). The group of comparison comprised 16 patients with functional and inflammatory diseases of the large intestine accompanied with dysbacteriosis of various degrees of severity3. The patients took “Narine” orally 2 capsules a day within 20 days and as microclysters, per 30 ml at 37 °C in 5 days. NUC patients did not get microclysters. In the group of comparison the patients took bificol 10 doses each and colibacterin, 15 doses each in 20 days. Specific and quantitative microflora composition was studied pursuant to the methodical recommendations4]. The degree of dysbacterial change manifestations (D1, D2, D3) was evaluated by scheme2). Studies of the intestinal microflora of the patients who took “NARINE” as treatment were carried out in the process of dysbacteriosis correction on the 5, 10, 15th days. In the control group analyses were carried out on the 10th and 20th days. Preliminary investigations showed that before this term no changes occurred in the intestinal microflora composition while bificol or colibacterin treatment.

Lack of dysbacteriosis was ascertained by the repeated negative feces analyses for dysbacteriosis.

In patients examined before treatment the following changes in the intestinal microflora were detected: reduction in the amount of anaerobic bifidoflora (less than $10^{-8}$ in 1 g of feces) or its absence (in 93% of cases); increase of conditionally pathogenic aerobic flora: in 30.4% of cases lactosedefective hemolytic forms of Escherichia coli were inoculated, in 23.4% of cases—Proteus, in 33.9%—other representatives of conditionally pathogenic flora were inoculated: enterobacter, citrobacter, Klebsielli, staphylococci.

In the first group in 32 patients of the main group prior to treatment dysbacteriosis D1, in 19 patients —D2 and in 7 patients—D3 were observed. In the control group 6 patients had D1 and 10 patients had D2. In the group of patients having taken “NARINE” by the end of treatment in 96.6% of cases either total normalization (in 53 patients), or significant positive changes of the intestinal microflora composition were observed (in 3 patients D2 transformed to D1). Almost in all cases there were observed regeneration of bifidoflora, disappearance or decrease of concentration of conditionally pathogenic flora; hemolytic and lactosedefective forms of Escherichia coli yielded their places to valuable Escherichia. Only 2 patients with NUC and D3, who had Proteus in high concentration on the 15th day of treatment did not show considerable changes in the intestinal microflora composition.

As investigations have shown in an overwhelming majority of cases (75.8%) dysbacteriosis correction by means of “NARINE” was achieved in
10–15 days. Thus, in 6 patients positive effect has already been achieved on the 5th day, in 39 patients —on the 10th, and in 11 —on the 15th day of treatment. After correction of dysbacteriosis the patients continued to get “Narine” up to their discharge. Easy forms of dysbacteriosis (D₁) yielded better to correction —on the average in 5–10 days, D₂ in 10–15 days, the most severe forms of dysbacteriosis (D₃) in 3 patients were liquidated correspondingly on the 10, 15 and 25th days, in 3 cases D₃ transformed to D₁ within 15 days in 2 patients and within 10 days in 1 patient.

Positive changes in the intestinal microflora and correction of dysbacteriosis coincided with positive dynamics of clinical data, results of endoscopic examination, the way the patient felt physically and mentally.

As to the control group of patients having taken bificol, 7 patients from D₁ dysbacteriosis group have demonstrated positive dynamics on the 15th day, and 5 patients from D₂ group and 2 patients from D group —on the 20th day. In the group having taken colibacterin within the period mentioned, only 6 patients showed positive dynamics.

Thus, the investigations carried out showed that correction of dysbacteriosis with the help of “Narine” is more productive than that with bificol which is thought to be the most effective remedy in correction of this state.

Proceeding from the fact that while taking “NARINE” part of acido-lactic bacteria (and products of their metabolism) perish in their way through the gastroenteric tract under the influence of gastric juice and intestinal enzymes, collaborators of the Department of Infectious Diseases, collaborators of the Department of General Surgery of the Yerevan Medical Institute decided to introduce the culture of acido-lactic bacteria, strain 317/402 per rectum immediately into the distal section of the intestine by means of a rubber catheter once a day after cleansing enema in the amount of 5 ml in 5 days. The amount of 5 ml is chosen because larger amount would cause defecation tenesmus. The total amount of the culture gathered in the 10 ml syringe is 7 ml for the catheter volume (2 ml). Proceeding from the fact that 1 ml of milk fermented by culture 317/402 contains 200 mln of cells of lactic acid bacteria, 1 billion of the latter was introduced into the distal section at a time.

The following movements are known to be observed in the large intestine (besides peristalsis): small pendulum-like, large pendulum-like, large movements of the large intestine, and at last, antiperistaltic movements that are observed periodically in 4–5 minutes. The mentioned movements promote both mixing of the large intestine contents, and its movement in the oral direction. Consequently, culture 317/402 introduced to the sigmoid section of the large intestine is spread all over the large intestine. Moreover, the stated procedure is useful for surgical patients due to the fact that the large intestine possesses an expressed ability to absorb liquids. Antibiotic substances of acido-lactic bacteria introduced together with microbes are spread hematogenically all over the organism, which is also prophylaxis of wound infection.

Intestinal dysbacteriosis was observed in 29.6% of patients who applied to the hospital with surgical pathology. Microbiological examination of these patients’ feces revealed dissemination with *staphylococi aureus*, *Proteus*, *harny*; *Sch. Flexneri carriers* were also encountered.

Clinical manifestations were observed in 37% of patients with the revealed bacteriological dysbacteriosis. Patients suffered from diarrheas, rarely from constipations, heavy discharges of mucous, mucous-purulent and sometimes purulent-bloody nature, tenesmus, colicky pains in belly. Patients with pronounced clinical picture exhibited weakness, headaches.

Control examinations were carried out in a week after the treatment course was over. By bacteriological examination only in one case gaphnia was revealed in insignificant amount. In other cases neither pathogenic, nor conditionally pathogenic microorganisms were revealed. Patients with the afore-mentioned disease symptoms along with microbiological recovery in an overwhelming majority of cases also exhibited clinical recovery.

Analyzing results of the investigations carried out one can draw a conclusion that treatment of the intestine dysbacteriosis by means of introduction of the acido-lactic bacteria culture of strain 317/402 “Narine” to the distal section of the large intestine is one of the rational methods of these microorganisms and their antibiotic substances
employment. Moreover, these microorganisms are known to be well adapted in the human intestine. It goes without doubt that it is possible to achieve more effect in combined administration of acidolactic bacteria per os and per rectum.

Effect of “Narine” on the clinical course of intestinal dysbacteriosis has been studied in 30 patients of both sexes. The age range varied from 20 to 60 years. Bacteriological coprological examinations were carried out in dynamics—before and after treatment. Against a background of the prescribed diet patients took 100 g of “Narine” product per day, divided into 2 doses. The minimum course of treatment comprised 15 days, in more severe cases 20–25 days.

Bacteriological examination of feces before treatment revealed dysbacteriosis of various degrees. As a rule, decrease in the amount of bifidobacteria and Escherichia was observed, the amount of Streptococcus faecalis, hemolytic Escherichia coli increased; in a number of cases fungi of the Candida type were revealed, and in more pronounced pathological process Staphylococcus aureus, Klebsiella, Proteus and Clostridium appeared.

After the course of “Narine” product taking 28 patients out of 30 exhibited pronounced improvement of macro- and microcoprological picture: color and consistence of feces improved, mucus admixture and fetid smell of stools disappeared; bacteriological examination revealed disappearance or sharp drop in pathogenic and conditionally pathogenic microorganisms, rise in the amount of bifidobacteria and Escherichia coli. In 22 patients the indices under examination practically reached the norm, in 5 there was a distinct tendency towards improvement of the intestine biocenosis. Parallel with the improvement of coprological indices the clinical picture of the disease also distinctly improved: appetite appeared, pains, distention and sensation of discomfort in the intestine disappeared, frequency of stools dropped.

In dysbacteriosis of III–IV degrees treatment with “Narine” drug should be continued up to 25–30 days.

Thus, clinical trials demonstrated that “Narine” drug was highly effective in treatment of intestinal dysbacteriosis. In especially severe or neglected cases more prolonged course of treatment should be recommended with additional inclusion of bacterial drugs, such as coli-, bifidum-, and lactobacte- rin, as well as bactisubtil and chilak-forte as an alternative choice.

II. Oncologic practice

In the Oncologic Research Center of the Ministry of Health of the Republic of Armenia purposeful investigations are being carried out aimed at prophylaxis of oncologic diseases.

According to the data of some authors (A. V. Kuznetsov et al., 1983; E. I. Abolmasov, et al., 1987) more than 80% of patients suffering from the large intestine cancer have intestine dysbacteriosis of different degrees of manifestation.

Moreover, against a background of decrease in the asporogenic anaerobic flora, in particular, of acidolactic fermentation microbes (bifidobacteria and lactobacteria), or its absence, increase in the number of hemolytic and lactose-defect forms of the Escherichia coli, sporulating anaerobes, conditionally pathogenic enterobacter, Proteus, Pseudomonas aeruginosa has been observed. Disorders of the intestine microbiocenosis, in their turn, aggravate the course of the basic disease, worsen its prognosis, and in a number of cases being developed for the second time, intestinal dyubacterioses become determinative in formation of macroorganism’s pathological state. Therefore the intestinal dysbacteriosis should be also given proper attention in the surgical practice, especially in treatment of postoperative infectious complications in patients suffering from rectum and colon cancer.

As an original trend in treatment and prophylaxis of diseases accompanied by biocenosis, or resulting in disturbance of microorganisms’ normal biocenosis appears application of biological remedies, drugs prepared from living microbes, obligatory for the intestinal microflora of a healthy man. However, biological bacterial drugs produced by medical industry (dry bifidumbacterin, bificol, etc.) did not find wide application in practice due to a number of reasons. They include the necessity of prolonged use (2 to 4 weeks and more) for gaining effect, the possibility of prescription only after the course of antibacterial therapy, rather high price of
proceeding from the afore-stated we found it expedient to use acido-lactic bacteria “NARINE” for recovery of the normal intestinal cenosis in patients with the large intestine cancer during preparing for the operation and in postoperative period.

Complex examination of 181 patients at the age of 18 to 79 years with the large intestine cancer of various localization was carried out. In 149 (82.7 %) patients while studying the intestinal microflora intestinal dysbacteriosis of this or that degree of manifestation was revealed. Dysbacteriosis of the 1st degree (D1) being revealed in 68 (46.6 %) of patients, dysbacteriosis of the 2nd degree (D2)—in 59 (39.6%), and dysbacteriosis of the 3rd degree (D3)—in 22 (14.8%) of patients.

All patients were divided into 3 groups. The first group included 67 patients, who in the course of preoperative preparing took fermented milk mixture “NARINE” peroral 1 liter a day. The mixture had acidity 80–100 T and was easily taken by patients. The 2nd group—46 patients took “NARINE” by means of retrograde introduction into the large intestine with the help of Bobrov’s apparatus. The group of comparison comprised 68 patients who did not get “NARINE” in the preoperative period.

Analyzing dynamics of the intestinal microflora changes in the process of preoperative preparing took fermented milk mixture “NARINE” peroral 1 liter a day. The mixture had acidity 80–100 T and was easily taken by patients. The 2nd group—46 patients took “NARINE” by means of retrograde introduction into the large intestine with the help of Bobrov’s apparatus. The group of comparison comprised 68 patients who did not get “NARINE” in the preoperative period.

Upon bacteriological examination of the patients’ first stools on the 3, 4th days after an operation it was revealed that on the whole, the intestinal microflora regenerated before the operation did not suffer essential changes. However, in spite of stable correction of the intestinal microflora it is expedient to continue introduction of acido-lactic bacteria in the postoperative period, taking into account influence of the operative trauma, postoperative antibiotic therapy on the microbial cenosis. In the postoperative period patients got “NARINE” 200 to 300 ml (equivalent analog is 1/5 of a capsule) within the first 4–5 days with gradual increase of the mixture amount as much as 1 liter by the 7, 9th days after the operation.

Upon examination of the intestinal microflora before discharge from the hospital dysbiotic changes were basically revealed in patients having taken prolonged antibiotic therapy on occasion of emerged postoperative pyo-inflammatory complications.

For the purpose of immediate influence on the large intestine microflora all along its length, the method of retrograde introduction of “NARINE” with the help of Bobrov’s infusion apparatus was used in 46 patients. Fermented milk mixture with a small amount (40 ml) of radiopaque water-soluble drug was introduced at 37°C in the amount of 300 to 500 ml, which was enough for filling the whole large intestine; the latter was confirmed roentgenologically. The way of retrograde introduction permits to use mixture with higher acidity (140–160° T).

Changes in the intestinal microflora composition in the comparable patients’ groups prior to dysbacteriosis correction were similar. Use of the “NARINE” retrograde infusion method by means of Bobrov’s apparatus permitted to achieve full correction of the intestinal microflora in 86.9% of patients having reduced the time of microbial cenosis regeneration for 1–2 days.

Thus, studies carried out demonstrated that “NARINE” was an effective remedy allowing patients with large intestine cancer in the reduced time of preoperative preparing to gain regeneration of normal intestine microbiocenosis. Use of “NARINE” enabled also to suppress in the intestine pathogenic and conditionally pathogenic bacteria that are potential pathogenes of pyo-inflammatory complications after operations on the large intestine. Use of “NARINE” has decreased a num-
ber of postoperative enteroparesis to 19.8% of cases.

Proceeding from the afore-said “NARINE” acido-lactic bacteria may be recommended for use in a complex of preoperative preparation and postoperative treatment of patients with the large intestine cancer.

In the Oncologic Research Center n.a. V. A. Fanardjian work has been carried out on “Modification of mutagenesis and carcinogenesis by the “Narine” strain". Actuality of work is as follows:

Many chemical, biological and physical agents possess mutagenous effect. Mutations in sex cells result in increase of the genetic load of populations, mutation in somatic cells of the organism i.e. to appearance of malignant neoplasms (DeMarini, 1985). Investigations in the field of molecular biology prove that the normal cell transforms to a malignant one as the result of mutations that activate oncogenes, inactivate antioncogenes or genes responsible for DNA reparation\(^{[10]}\). This provision is confirmed by the data about the fact that among 180 chemical agents (unconditional, possible, and probable carcinogens for man) more than 90% are able to injure DNA of cells (Bartsch, Malaville, 1990). Therefore, one of the most important problems of modern biology and medicine is protection of the unique genetic information of man’s cells from the injuring action of carcinogenic and mutagenic factors. As one of the approaches to solve this problem appears employment of antimitagens, which are able to reduce the induced by various medium factors level of mutational timutagens, which are able to reduce the induced by the compounds used for cancer chemoprophylaxis. One of the main requirements to the compounds used for cancer chemoprophylaxis is availability of antimitagenous activity.

One of the most significant problems of clinical oncology is search for the possibility of reducing side effect of chemo- and radiotherapy (mutagenicity, carcinogenicity, toxicity) (Shlyankevich, et al., 1993). With this purpose application of strains of microbes and polysaccharides of microbial and fungal origin is prospective (Kupin, 1992, 1993, Nio et al., 1996). Epidemiological research has shown that usage of dairy products containing lactobacilli leads to decrease of morbidity with mammary gland and intestine cancer (Adachi, 1992. Van t Veer, et al., 1989). Experimental research showed that some strains of lactobacilli possess antimutagenous activity (Pool-Zabel, et al., 1994, 1995). Microbial immunomodulators were revealed to be able to inhibit activity of oncogene produce (Umezawa, 1995. Reddy, 1996).

It was shown for the first time that “Narine” lactobacilli possessed anticlastogenic activity, weak antitumor action and can strengthen antitumor effect of chemodrugs.

Many lactobacilli strains are known to reduce output of enzymes (nitroreductase, glucosidase, glucuronidase, azoreductase) by the intestine microflora in the organism. These enzymes metabolize carcinogens (Reddy, 1986, 1996). Epidemiological research has shown that lactobacilli used in food reduce risk of mammary gland and intestine cancer development in man (Adachi, 1992. Van t Veer, et al., 1989). As the mechanism of anticarcinogenic and antitumor action of lactobacilli appears inactivation of exogenous carcinogens in the gastrointestinal tract, inhibition of endogenous produce of carcinogens and increase of immunoreactivity of the organism (produce of INF, interferon and interleukin) (Kanbe, 1992).

On 15 rats of the Vistar line the trial on availability of clastogenic activity of these lactobacilli was carried out. The latter were introduced to rodents intragastric during a month, every day, at the dosage used by man with re-computation for rats\(^{[11,12]}\). As control 5 rats were used who got sodium chloride solution intragastric within a month. Results of the experiments have demonstrated complete lack of clastogenic properties in two strains of lactobacilli. In the next series of experiments “Narine” was introduced to 50 rats in 15 days at the doses used by man. As mutagens CPh, thioTEF and adriblastin were used at the doses inducing appearance of 20% of aberrant cells in rats’ bone marrow. 5 rats got Pasteurized milk with killed lactobacilli. It was shown that “Narine” lactobacilli decreased clastogenic effect of CPh by 60.9%, thioTEF by 44.7%, and adriblastin by 58.8%. Killed bacilli did not affect clastogenic activity of CPh.

Thus it was shown for the first time that lactobacilli “Narine” had anticlastogenic activity.
Study of influence of \textit{lactobacilli} “Narine” on the genotoxic activity of carcinogen and mutagen of direct action N–methyl–N–nitro–N–nitrosoguanidine was carried out in the Institute of Nutrition Physiology (Karlsruhe, Germany) under the guidance of Prof. Dr. B. Pool-Zobel. The research was carried out on the intestinal cells of CD-line rats, which were incubated with carcinogen and \textit{lactobacilli} in 30 minutes. After incubation cells were subjected to microgelelectrophoresis (“comet assay”).

The basic criterion of genotoxic effect is DNA migration length. This index expressed in special units (image units) was equal to: intact control — 23.3 ± 1.8; positive control (intestinal cells + carcinogen) — 117.3 ± 6.5; \textit{lactobacilli} + MNNG — 58.8 ± 2.7. \textit{Lactobacilli} reduced for sure the genotoxic effect of carcinogen on rats’ cells by 50% as compared with positive control. This proves that the \textit{lactobacilli} are able to connect metabolites of carcinogens. The other possible mechanism of anticlastogenic action of “Narine” \textit{lactobacilli} is their interferonogenic activity (Kita et al., 1986), as interferon inductors have antmutagenous activity (Zolotareva, et al., 1993).

The research of antitumor action of “Narine” \textit{lactobacilli} was carried out on rats with re-inoculated tumors—carcinosarcoma Walker (CSW), Peis’s lymphosarcoma (PLS) and ovary cancer cells (OYa)\textsuperscript{13}. The results of experiments carried out on 80 rats of Vester line showed that introduction of \textit{lactobacilli} 5 days before the tumor re-inoculation and then every day, authentically lengthened rats’ mean life span by 31–35% in considerable tumors, and by 22% in OYa. Introduction of \textit{lactobacilli} on the day of re-inoculation of tumors and then every day unauthentically lengthened rats’ mean life span by 21–27% (CSW and PLS) and by 18% (OYa). Effect of \textit{lactobacilli} in later terms, as well as introduction of killed \textit{lactobacilli} did no exert antitumor effect.

The combined action of “Narine” \textit{lactobacilli} and chemodrugs on mean life span of rats with re-inoculated tumors CSW, PLS and OYa was studied\textsuperscript{13}. \textit{Lactobacilli} were introduced to rats intragastric on the 2\textsuperscript{nd}, 3\textsuperscript{rd} days after re-inoculation when the tumors could be touched (CSW, PLS) or in a day after introduction of OYa cells. Treatment with chemodrugs also started in the same terms and introduced them intraperitoneal every other day (CPh at the dose of 25 mg/kg three times a day; natulan—10 mg/kg 4 times a day; thioTEF—1 mg/kg 4 times a day). 154 rats were used in all.

The results of experiments showed that in all cases mean life span of rats having got \textit{lactobacilli} and chemodrugs (10 animals) for certain exceeded mean life span of animals that got only chemodrugs. \textit{Lactobacilli} decreased tumor mass by 32.4%, natulan—by 44.6%, both factors together—by 67.6%. Combination of antibiotics with \textit{lactobacilli} increased IT as much as 57.3%.

Thus the results of experiments carried out on 210 rats demonstrated that \textit{lactobacilli} could strengthen antitumor effect of chemodrugs.

Conclusions: “Narine” drug has been found to possess anticlastogenic, antitoxic and antitumor activity. By the method of microgelelectrophoresis it was shown that “Narine” \textit{lactobacilli} protected DNA cells of rats from genotoxic effect of carcinogens, were able to strengthen antitumor effect of chemodrugs widely used in clinical oncology (cyclophosphamum, adriblastin, thioTEF and natulan).

In operations on the occasion of oncopathology of body and cervix of the uterus (simple and enlarged uterus extirpation) the so-called “open method” of vaginarraphy has found wide application. In this method, lumen of the vagina stump is left open for drainage of the retroperitoneal space without tampons. The given method proves its value most of all in patients weakened with extra-genital diseases in the presence of the infected tumors with decomposition. However, with all obvious advantages of this method, healing of the open wound of the vagina stump proceeds by second intention and under conditions of infection.

Thus the question of fast healing of the vagina stump wound in oncologic patients is very urgent. Numerous drugs available today allow to struggle with wound infection rather successfully. One of these remedies is ecologically pure, biologically active liquid bacterial concentrate “Narine–K” obtained in Armenia.

Metabolites of acido-lactic bacteria are known to possess high antibacterial activity with respect to pyogenic microflora and pronounced anti-inflam-
flammatory effect\textsuperscript{15,16}. Besides, acido-lactic \textit{Lactobacilli} acidophilus by their morphological and biochemical properties are identical with vaginal \textit{Bacillus} Doderlein, and favorably affecting the bacterial flora, physiologically recover the natural microbiocenosis of the vagina\textsuperscript{17}.

This fact is especially important in patients suffering from cancer and precancer diseases of body and cervix of the uterus when presence of long bloody discharge or infection of decomposing tumor results in serious disorders of the natural bacterial vaginal medium.

In the surgical and gynecologic practice cases of using acido-lactic bacteria drugs are known aimed at treatment of purulent wounds and inflammatory processes of the vagina. We were the first to attempt to employ the "Narine\textsuperscript{K}" drug after extensive onco-genital operations.

With a view to study the effect of "Narine\textsuperscript{K}" drug on the processes of healing of the vagina stump wound, data on 100 women operated in the Oncologic Department of the Oncologic Research Center (under the Ministry of Health, RA) on the occasion of cancer and precancer diseases of body and cervix of the uterus were examined.

The examined patients' contingent was divided into two clinical groups. In the first group \((n = 50)\) beginning from the third day after operation "Narine\textsuperscript{K}" drug was introduced to the vagina within 25 days, every day in the amount of 5 ml, warmed up to the room temperature. From the fifth day after operation the procedure was performed after preliminary sanitation of the vagina with a weak solution of potassium permanganate. Patients of the second group \((n = 50)\) got only vagina sanitation. In both groups the vaginal stump was sutured by the open method. The course of the wound process was managed clinically on the basis of a number of criteria, such as the nature of wound discharge, time of perifocal inflammatory reaction cupping, appearance of granulation islands, epithelization and period of the wound healing. As an objective criterion, dynamic cytological examination of smears—imprints from the wound by the methods of Pokrovsky and Makarova was employed\textsuperscript{18}.

According to the data obtained, the average time of perifocal inflammatory reaction cupping in the first group made up 5.5 days versus 7.2 days in the control group. Suppurative discharge from the wound, characterizing its second infection, in the group of patients who took "Narine–K" was encountered almost 1.5 times less. Beginning of the second phase of the wound process, characterized by appearance of granulation islands, in the control group came on the average on the 15–17\textsuperscript{th} days after operation, whereas in women who got "Narine–K" the given index made up 8–11 days.

Thus regenerative-inflammatory type of the cytogram signifying favorable course of the wound process in patients of the 1\textsuperscript{st} group was revealed on the average a week earlier whereas, in the control group proliferative phase of the wound process proceeded rather limp, granulations had a dim look, coarse-crumbled structure with the grayish tint and mucous consistence. In 36 patients of this group (72\%) in 40 and more days after the operation developed granulation polyps in the vagina stump.

In the 1\textsuperscript{st} group complete wound healing on the 25\textsuperscript{th} day after the operation was noted in 66\%. It should be underlined that the course of proliferative phase of the wound process proceeded rather favorably with formation of small-crumbled granulations.

Thus analysis of the obtained results permits to conclude: local application of "Narine–K" drug in the postoperative period in oncologic patients after simple and enlarged uterus extirpation promotes fast clearance of the vaginal stump wound from the pyogenic microflora stimulating the regeneration processes and positively affecting both phases of the wound process, permits considerably to reduce the time of the wound healing.

\textbf{III. Antibiotic therapy}

Dysbacteriosis prophylaxis is much more expedient and easier than its treatment. That is why in all potentially dangerous cases it is recommend to carry out dysbacteriosis prophylaxis. One of the most dangerous and spread cases of dysbacteriosis occurrence is connected with antibacterial therapy, which provokes dysbacteriosis. Use of "NARINE" in complex with antibacterial drugs will enable efficiently to prevent disorders of the in-
intestinal microflora\textsuperscript{19}. Antibacterial therapy is one of the main reasons of developing dysbacteriosis of the intestine (DI). Suppression of the intestinal microflora is practically an inevitable consequence of modern antibacterial therapy. Development of DI in antibacterial therapy is, first of all, connected with suppression of euflora progress by antibacterial means, and then against this background, reinforcement of conditionally pathogenic microflora progress. A certain role plays weakening of protective forces of the organism emerging while antibacterial therapy.

The purpose of the research is to reveal the efficiency of “NARINE” drug in prophylaxis of DI in antibiotic therapy and to carry out comparative characteristic of effectiveness of “NARINE” and Nystatin.

Clinical observations have been performed on 34 patients of 18–75 years of both sexes who received treatment with antibiotics of aminoglycoside, cephalosporin, and tetracycline series for a period of 10 to 14 days. All patients before and after antibiotic therapy have undergone feces microbiological analysis for DI. To evaluate DI, classification by Znamenskiy and Degtyar was employed\textsuperscript{(1989)}.

I degree: increase of the number of conditionally pathogenic microorganisms against high level of bi\-fido-bacteria ($10^9$). Dysbacteriosis, as a rule, is compensated.

II degree: bifidobacteria are determined at the low limit of the norm ($10^8$) and increase in conditionally pathogenic microorganisms’ association is registered. In some cases dysfunction of the intestine can take place.

III degree: drop in the amount of bifidobacteria (less than $10^7$) in combination with pronounced changes in aerobic microflora. Decompensated dysbacteriosis.

Patients were divided into 2 groups: the 1\textsuperscript{st} group included 19 patients. During antibiotic therapy they got a capsulated form of the “NARINE” drug at a daily dosage of 3 capsules, the 2\textsuperscript{nd} group consisted of 15 patients who took “NARINE” at a daily dosage of 1.5 mln ME.

Before and after the course of antibiotic therapy in all patients of the 2\textsuperscript{nd} group and in 10 patients of the 1\textsuperscript{st} group (Ia subgroup) DI was not revealed, the rest 9 patients of the 1\textsuperscript{st} group (Ib subgroup) had DI of the 1\textsuperscript{st} degree.

\textbf{Results and discussion.}

After the course of antibiotic therapy not a single patient of subgroup Ia developed DI, and in patients of Ib subgroup DI did not aggravate. At the same time, only in 6 patients of group II after the course of antibiotic therapy microflora of the intestine remained normal. From the other 9 individuals of the 2\textsuperscript{nd} group 8 developed DI of the 1\textsuperscript{st} degree, and one—DI of the 2\textsuperscript{nd} degree.

Thus, there was revealed high clinical efficiency of a capsulated form of “NARINE” in prophylaxis of DI development in antibiotic therapy. Application of this method is pathogenetically grounded thanks to high antagonistic activity of “NARINE” drug in relation to conditionally pathogenic microflora of the intestine. Besides, the ability of the “NARINE” drug to strengthen nonspecific and specific immunologic resistance of the organism has been exhibited.

At the same time accepted in practice use of antymycotic drugs (in particular, Nystatin) fails not only to prevent decrease of the amount of normal microflora, but also rise of conditionally pathogenic fungous-free microflora in antibacterial therapy.

\section*{IV. Postnatal mastitis. Prophylaxis of infectious diseases of \textit{staphylococcic} etiology}

In many clinics healthy carriage of hospital strains of \textit{staphylococcic} aureus by medical personnel of curative institutions, hospitals, puerperas, and newborns is widely spread. This is one of the main reasons of wound infectioning, development of postnatal mastitis, and many infectious diseases of \textit{staphylococcic} etiology in newborns\textsuperscript{20}. Practice has shown that newborns are especially vulneravle to \textit{staphylococcic} infection, that can be manifested both in the form of carriage, and disease itself. One of the main methods of struggle against \textit{staphylococcic} aureus carriage is sanitation of the main bio- tope of anterior sections of nasal cavity. Currently to sanitize carriers antibiotics, \textit{staphylococcic} bacteriophage, hexachlorophene, nitrofurazone (furacin), boric acid, and other drugs are used. However, the known ways of carrier sanitation are not sufficiently effective, and often they do not
result even in temporary elimination of carriage. Due to use of antibiotics, various chemodrugs and antiseptics often allergical reactions arise, immunologic reactivity of the organism is suppressed, resistant forms of microorganisms are formed, the consequence of which are superinfections and dysbacteriosis.

To prevent formation of carriage of *staphylococi aureus* hospital strains American researchers have applied the principle of “Bacterial Interference”. In an hour after the child’s birth daily broth culture of a nonpathogenic strain—antagonist 502A was put on a child’s mucus of a nose. Staphylococcus strain 502A should have hindered colonization of mucous membranes of a nose by epidemic staphylococcus strains. But this method did not find wide application in practice, as out of 50 newborns populated with a strain-antagonist, 17 were reported to fall ill with pyo-inflammatory diseases caused by virulent mutants of blocking strain 502A(83).

And in case of using strain of acido-lactic bacteria 317/402 “NARINE” as a blocking microbe the effect was evident(42).

For the first time study of the antagonistic activity of acido-lactic bacteria, strain 317/402 “Narine” towards hospital polyresistant strains of *staphylococi aureus* has been carried out. By means of electron microscopy the changes occurring in the cells of *staphylococi aureus* under the action of acido-lactic bacteria “Narine” have been revealed.

For the first time physiological sanitation procedure of carriers of *staphylococi aureus* hospital strains in the nasal cavity by means of the stated strain of acido-lactic bacteria has been elaborated for which Certificate of Rationalization Proposal No. 127 has been granted.

For the first time the method of preventive population of newborns’ nasal cavity with acido-lactic bacteria “Narine” aimed at prevention of colonization of the main biotope by hospital strains of *staphylococi aureus* while newborns’ stay in the Maternity Hospital has been elaborated.

For the first time the procedure of prophylaxis and treatment of puerperas’ mammary glands nipple cracks based on antagonistic activity and vitamin-synthesizing ability of acido-lactic bacteria “Narine” has been worked out, for which Certificate of Rationalization Proposal No. 128 has been granted.

It has been revealed that among permanent and residential carriers out of the number of medical staff of Maternity Hospital No. 3, Yerevan *staphylococi aureus* lysed by phage 83A (83.3%) (by which 59.63% of newborns are also colonized) prevail.

To determine the level of carriage of *staphylococi aureus* hospital strains and reveal permanent and residential carriers in the main biotope, namely, anterior sections of nasal cavity, we have examined 747 people 2–3 times within two months. Dynamics of colonization of 493 newborns’ nasal cavity with *staphylococi aureus* hospital strains during their stay in the Maternity Hospital has been examined. By the “Narine” drug nasal cavity of 169 permanent and residential carriers of hospital strains of *staphylococi aureus*, 168 newborns, mammary glands of 164 puerperas have been treated.

Identification of the isolated *staphylococi* strains has been carried out according to the generally accepted procedure described in Order No. 720 of the USSR Ministry of Health dated 1978. For *staphylococi* differentiation the following tests of pathogenicity have been employed: of lecithovital and plasmocoagulant activities, mannita fermentation under anaerobic conditions, phagotyping, determination of antibiotic sensitivity.

Antagonistic activity of acido-lactic bacteria “Narine” was checked with respect to 147 hospital strains of *staphylococi aureus*. 968 analyses in vitro have been carried out.

As the result of the research of antagonism between “Narine” acido-lactic bacteria and *staphylococi aureus* by the cup method we have found out that growth of the latter stopped by 8–10 mm around the hole with acido-lactic bacteria on the cups kept in the refrigerator for 18–20 hours. In the cups incubated in thermostat, zones of *staphylococi* growth retardation on the average made up: on the cups incubated for 18–20 hours – 13.5 mm, on the cups incubated for two days – 22.2 mm, three days – 32.2 mm, and on the cups incubated for four days the clean zone of growth retardation all over the radius was observed.

Cells of the control, intact culture of *staphylococi*
*aureus* had the structure typical of normal cells. After influence of the “Narine” culture the following ultra structural changes occurred in *staphylococci* cells. Withdrawal of electron dense, homogeneous material of cell wall from cytoplasmic membrane took place. In some cases break of integrity of the cell wall was detected. Similar structural disorganization of *staphylococci* cells was also observed on the septa sites of separating individuals. Structural changes of cytoplasm in the form of formation of electron-transparent sites in a granular component were also seen. Proceeding from the afore-said it can be concluded that ultra structural changes of *staphylococci aureus* cells under the action of acido-lactic bacteria “Narine” relating mainly to the cell wall result in *staphylococci* growth retardation.

From the 2nd day of their lives children’s nasal cavity began to be populated by acido-lactic bacteria. The drug (1 capsule per 1 teaspoon of boiled water) is sterilly bottled, shaken for several times to get homogenous mass; bottles are warmed up in a clenched fist to the body temperature. Then the drug (1 to 2 drops) is infused by individual eye pipette into a newborn’s each nasal passage. The described procedure is repeated thrice a day at 9 a.m., 4 p.m., and 10 p.m. for 5 days. By the mentioned method population of the nasal cavity by acido-lactic bacteria was carried out in 158 newborns in the 3rd Maternity Hospital of Yerevan and in 10 children in one of the Maternity Hospitals of Moscow (in Moscow the procedure was carried out by collaborators of the laboratory of intrahospital infections of the Epidemiological Department of the Research Institute of Epidemiology after N.Ph. Gamalei under the Academy of Medical Sciences, USSR).

Investigations demonstrated that on the 7th day of their lives 45.83% of infants were free of carriage, whereas in the control group all newborns were carriers of *staphylococci* (p 0.001). In the control group among carriers with solitary growth no children with *staphylococci aureus* were noted; Epidermal *staphylococci aureus* carriers comprised 2.78%. In the experimental group the number of children with solitary growth increased: carriers of aureus-type comprised 22.91% (p 0.001) and that of epidermal – 6.25%. The number of newborns with poor growth of *staphylococci* also increased. In the control group only carriers of aureus-type (2.78%) were revealed, and in the experimental one, carriers of epidermal *staphylococci* comprised 2.08% and those of aureus – 8.33% (p 0.1). In the experimental group in children with abundant growth epidermal *staphylococci* carriers comprised 2.08% and aureus carriers – 8.33% (p 0.1). Among children with abundant growth in the experimental group epidermal *staphylococci* carriers comprised 2.08% against 2.78% in the control group, and aureus carriers – 8.33% against 19.44% (p 0.1). And, at last, carriers with merged growth of *staphylococci aureus* in the experimental group comprised 4.17% against 72.22% in the control one. Thus, in the experimental group on the 7th day of their lives a considerable amount of children appeared completely free of *staphylococci* hospital strain carriage. Increase of a number of children with solitary poor growth of *staphylococci* may be also evaluated as a positive result.

As it is seen from the above-mentioned data, use of acido-lactic bacteria “NARINE” for population of newborns’ oral cavity permitted considerably to limit their epidemiological significance and greatly decrease dissemination of hospital strains of *staphylococci aureus* outside the maternity hospital.

So as to clarify what was the advantage of newborns’ population with acido-lactic bacteria, examination was carried out among mothers of the experimental group. Epidemiological studies showed that from 158 puerteras 3 (1.9%) fell ill with mastitis. The number of women fallen ill with postnatal mastitis in the control group 5.4 times (p 0.001) exceeded the number of those in the experimental group.

The results obtained, as well as the properties of acido-lactic bacteria “NARINE” (high antagonistic activity towards hospital strains of *staphylococci aureus* and high vitamin-synthesizing ability) suggested an idea to use them for cleaning of puerteras’ mammary glands. According to the majority of scientists’ opinion, invasion of staphylococcosis deep into mammary glands is carried out by 3 routes – lactogenous, lymphogenous and hematogenous. A number of researchers consider puerteras’ nipple cracks of mammary glands to be the main predisposed reasons for development of postnatal lactation mastitis. From the presented...
data it is obvious that preventive population of nipples and mammary glands (that represent the leading etiologic factor) with hospital strains of 

\textit{staphylococci} is the basic problem in mastitis prophylaxis. Proceeding from the fact that the main source of mother’s mammary gland infection is a newborn, and as the entrance gates (infection atrium) serve cracks, the problem was posed to create temporary artificial biocenosis on the skin of nipples and peripapillary region of mammary glands by means of acido-lactic bacteria of strain 317/402 “Narine” within the whole period of nursing.

Before and after each nursing the skin of nipples and peripapillary areas were plentifully dubbed by “NARINE” drug with the help of sterile gauze tampons. Nipple treatment before nursing was aimed at breaking the ways of \textit{staphylacocci} transference and at the same time intensive population of the oral cavity and gastroenteric tract of newborns with acido-lactic bacteria, that is important for prophylaxis of \textit{staphylococci} and other enteritis. Nipple treatment after nursing was aimed at destruction of \textit{staphylococci} having penetrated with nursing and at increase of local insusceptibility of tissues.

Four groups of puerperas were examined:
1. control group—nipple treatment with 1% brilliant green
2. nipple treatment with the culture of acido-lactic bacteria
3. nipple treatment with the culture of acido-lactic bacteria on ointment basis
4. treatment of formed cracks

Observations were carried out in dynamics from the first to the seventh day after birth. Analysis of the results of smear microbiological research taken from the nipple surface of the control group showed that on the 5–7\textsuperscript{th} days of stay in the maternity hospital almost total dissemination of nipples took place (98%). Inoculation made up: of \textit{staphylococci aureus}—25.7\%, of \textit{staphylococci epidermidis}—37\%, of \textit{staphylococci saprophytic}—34.3\%. With the use of the culture of acido-lactic bacteria inoculation of microflora from nipple surface considerably reduced. Thus in 22.4\% of cases no microflora was isolated while inoculation, in 26.5\%—\textit{staphylococci epidermidis} was isolated, in 47\%—\textit{staphylococci saprophytic}, and only in 4.1\%—\textit{staphylococci aureus}. Epidemiological and microbiological investigations have shown that out of 164 women who underwent while their stay in the maternity hospital treatment of mammary glands by acido-lactic bacteria but not by brilliant green only 2 showed nipple cracks, which is 1.3\% (against 40.5\% in the control group). The data just cited certify that in the group of mothers whose mammary glands were treated by “NARINE” drug, frequency of nipple cracks were 31.2 times (p 0.001) less than in the similar group where glands were treated with brilliant green. Dissemination of mammary glands with staphylacocci was also 11 times less. Clinical observations showed that upon nipple treatment by acido-lactic bacteria clinical manifestations in the form of reddening, edema, painfulness, nipple maceration were less pronounced. Considerable decrease in crack depth, appearance of light-pink granulations, sharp drop in painfulness when nursing took place, and crack healing was observed on the 4–5\textsuperscript{th} days.

Proceeding from the afore-said one can come to a conclusion that use of “NARINE” culture for nipple cleansing with the purpose of prophylaxis and treatment to the utmost prevents appearance of nipple cracks, that is, as a matter of fact, prophylaxis of postnatal mastitis development. The described method of mammary glands treatment is also attractive by the reason that the drug used has an easy and not requiring large expenses preparative procedure that makes it possible to use it in home conditions after discharge from a maternity hospital.

Thus, it can be summarized as follows:
1. High antagonistic activity of acido-lactic bacteria of “NARINE” strain 317/402 against hospital strains of \textit{staphylococci aureus} has been established in vitro. As bacteriostatic concentration of milk, soured by means of the mentioned acido-lactic bacteria, appears dilution 1 : 2 containing 5 mln of “NARINE” cells against 7 billion of \textit{staphylococci aureus} cells.
2. Ultrastructural aspect of the “Narine” drug mechanism of action on \textit{staphylococci aureus} has been established, which is revealed by break of integrity of the bacterial cell wall.
3. The level of carriage among puerperas was...
established to reach 75%, and among newborns—91.7–94.4% by the day of discharge.

4. Studies of skin microflora of puerperas’ mammary glands showed massive dissemination with *Staphylococcus aureus* in 73.68% of cases, 40.5% of women being discharged from a maternity hospital with nipple cracks (infection atrium) and 25% of them later on develop mastitis (10.2% against the total amount of puerperas).

5. It has been revealed that among coagulase positive *Staphylococci* isolated from the nasal cavity of medical staff, newborns and puerperas’ mammary glands the following phagotypes prevailed: 83A, 85, 52, 80, 3A, 81.

6. The elaborated method of sanitation of permanent and residential carriers of hospital strains of *Staphylococcus aureus* by means of “NARINE” drug promoted reduction of their epidemiological significance by 82.0%.

7. The proposed method of newborns’ nasal cavity population with acido-lactic bacteria “NARINE” permitted to reduce the level of carriage of *Staphylococcus aureus* hospital strains 7.3 times by the moment of discharge (against the control group), that in its turn resulted in reduction of mastitis morbidity in puerperas 5.4 times.

8. Preventive use of the “NARINE” drug for puerperas’ mammary glands treatment led to decrease in frequency of nipple cracks occurrence 31.2 times as compared with the control group where brilliant green was used.

V. Application in obstetrics and gynecology

Application of acido-lactic bacteria culture in obstetrics and gynecology is physiologically expedient and biologically purposeful and therefore is of certain interest, in our opinion. Acido-lactic bacteria by their morphological and biochemical properties are identical with the vaginal Doderlein bacillus. Use of “Narine” in the form of vaginal globules and rods demonstrated early disappearance of pathogenic and conditionally pathogenic microflora and stable recovery of the natural vaginal medium.

Acido-lactic Bacillus acidophilus by its morphological and biochemical properties is identical with the vaginal Doderlein bacillus.

Treatment underwent 186 girls, 165 gynecologic patients, 64 women in labor and puerperas; and 157 in pregnancy were subjected to sanitation aimed at prenatal training.

Every day within the period of 8 to 15 days the culture of acido-lactic bacteria in the amount of 10–20 ml was introduced. In children’s gynecology the course was repeated in a month. Control over the treatment efficiency was exercised in dynamics with a set of clinicolaboratory methods, visual observations, colposcopy, bacterioscopic, and bacteriological examinations.

172 samples from vagina and 84 from cervical canal were subjected to bacteriological examination.

Bacteriological examination of vaginal contents in gynecologic patients has revealed both pathogenic and conditionally pathogenic microflora, as well as candidi fungi in 91.7% of cases. In a majority of cases microbes were inoculated in association.

The course of colpitis in pregnant women often proceeds asymptotically. Attention should be paid to the fact that pathogenic microflora and availability of colpitis were revealed without complaints, only upon hospitalization on the occasion of some other obstetrical pathology.

Thus, in 2/3 cases of pregnant women 4th degree of vaginal flora purity and association of more than 2–3 species of microbes were revealed.

Every third of the examined women (39.5%) had combination of conditionally pathogenic microflora (pathogenic *Staphylococcus*, *Proteus*, some serotypes of *Escherichia coli*, fungi of candidi species).

Analysis of the results of gynecologic patients and those in pregnancy showed that just after the 1st course all of them without exception exhibited considerable improvement of clinical manifestations of inflammation, the number of leukocytes significantly diminished, fungi disappeared completely. Bacteriological examination of gynecologic patients revealed sharp decrease (83.4%) in inoculation of conditionally pathogenic and pathogenic microflora with preferential predominance of bacilliforms of bacteria. Bacterioscopic examination of smears revealed change of vaginal flora purity with transition from the 4th to the 2nd degree. In pregnant women reduction of inoculation made up 75.8
Use of vaginal suppositoria (globules) and rods demonstrated significantly early disappearance of pathogenic and conditionally pathogenic microflora and steady regeneration of natural vaginal medium as compared with dropping of “NARINE” culture.

Thus, the advantage of using Lactobacillus acidophilus “NARINE” for sanitation in pregnancy, labor, gynecologic patients (girls and women) is in its simplicity and availability, in the opportunity to affect the area of inflammatory process localization. Particularly important is the fact that use of fermented mixture “NARINE” consisting of bacteria pure culture of increased biological activity beneficially influences the vaginal bacterial flora, promotes disappearance of pathogenic microflora, eliminates dysbacteriosis, physologically regenerates vaginal natural medium with normalization of vaginal biocenosis.

VI. Radiation-thermal injury

It has been established that changes of the intestinal microflora took place upon various unfavorable influences on the organism reducing tension of natural immunity. A vivid example is dysbacteriosis developed upon influence of ionizing radiation the characteristic peculiarities of which is decrease in bifidobacteria and lactobacteria with simultaneous increase of representatives of conditionally pathogenic microorganisms55.

The intestine microflora presents a high-sensitive indicator system, which is closely connected with macroorganism. Particular place occupy changes in the intestinal microflora under the action of ionizing radiation. The range of doses, at which changes on the part of various representatives of the intestinal automicrolora—coliform bacteria, Proteus, staphylococci—occur is rather significant: from small $1.7 \times 10^{-4}$ cells/kg (enterococcus) to $2.34 \times 10^{-4}$ cells/kg at which signs of dysbacteriosis develop, yeast-like flora activates (Shubik V. M., 1987). According to Varlamov E. V. (1964) examination of the intestinal microflora of X-ray-radiologic room workers has revealed reduction of antagonistic activity of the intestinal microflora towards conditionally pathogenic microorganisms.

Changes of the intestinal microflora composition under the influence of ionizing radiation are of second character. However development of the intestinal dysbacteriosis significantly influences the course of the main disease, recovery of microbial biocenosis in the intestine; it is of an important moment in complex treatment of persons subjected to the influence of ionizing radiation.

With the purpose of normalizing the intestinal microflora, bacterial drugs containing live microorganisms, which are typical representatives of the intestinal normal microflora, are widely used. In Austria it is Normoflora, in Switzerland—Euglan, in Germany—Colilora, Smolflora, and Simbiodora. In France—Tetralactine, in Czechoslovakia—Lacton, Relacton, Lactobacillin, in the former USSR—Lactobacterin, Bifidumbacterin, Colibacterin, Bificol.

New approaches to the intestinal microflora recovery by means of autostrains of indigenous bacteria (Korshunov V. M., et al., 1985) and immunoglobulin (Klomnarskaya N. N., et al., 1987; Shal’nova G. A., et al., 1989) are of interest.

For correction of the intestinal dysbacteriosis in the persons subjected to the influence of small doses of ionizing radiation for the first time the culture Lactobacillus acidophilus n.v., group Er−2, strain 317/402 isolated by Prof. L. A. Yerzinkyan (Author’s Certificate No. 163573 of April 27, 1964) in the form of lyophilized drug was used.

Under examination were 74 men at the age of 28–50 years with the intestine dysbacteriosis who participated in liquidation of consequences of Chernobyl Atomic Electric Power Station accident, permanently residing in the territory of the Republic of Armenia. They were divided into three groups. I group comprised 44 “liquidators” with dysbacteriosis of the I and II degrees who had taken as treatment fermented milk mixture “Narine” per 1.0–1.5 liter a day in 4–6 steps.

II group included 10 “liquidators” with dysbacteriosis of the I and II degrees who had taken dry drug “Lactobacterin” (produced by Gorkovskii Scientific–Research Institute of Epidemiology under the Ministry of Health, Russian Federation) 15–20 doses a day during 30 days.

III group included 20 “liquidators” with dysbacteriosis of the I and II degrees who had taken as treatment dry lyophilized microbial mass of live
antagonistically active acido-lactic bacteria of strain 317/402. To the bottle with dry mass a glass of boiled cooled water is added and well stirred. The drug is taken peroral 4 times a day at the dose of 5.0 g a day within 15–20 days and more upon physician’s prescription. The patients’ intestinal microflora is studied before and after treatment on the 15th and 20th days. While studying a visual and quantitative composition of the intestinal microflora, methodical recommendations “Bacteriological diagnostics of the intestinal dysbacteriosis” (Epshtein-Litvak R. V., V'il'shanovskaya F. L., 1977) were taken into account.

The examined patients before treatment displayed anaerobic microflora of bifidobacteria and lactobacteria (less than 10⁶ in 1 g of feces) in 100% of cases, decrease in Escherichia coli to 10⁶–10⁷ in 39 patients (52.7%), rise in conditionally pathogenic microflora, in particular, of enterobacteria in 30 patients (40.5%), pathogenic staphylococcus in 32 patients (43.2%). Out of enterobacteria — enterobacter, Klebsielli, lactosenegative Escherichia and hemolytic Escherichia were inoculated.

The group of patients (44 persons) who had taken fermented milk mixture “Narine” for correction, by the end of treatment demonstrated in 70.45% (31 persons) of cases normalization of microflora composition. In 16 patients (36.4%) D₂ transformed to D₁, moreover, decrease in concentration of conditionally pathogenic microflora was observed (Klebsielli, enterobacter, lactosenegative Escherichia, hemolytic Escherichia) to 10²–10³ and increase in concentration of valuable Escherichia coli. Recovery of the number of bifidobacteria and lactobacteria was not observed. As experiments showed in an overwhelming majority of cases, dysbacteriosis correction with the help of fermented dairy mixture “Narine” was achieved in 15–20 days. Thus, in 23 patients (52.2%) with D₁, positive effect was reached on the 15–20th days, and in 16 patients (36.3%) with D₂ — on the 25–30th days. It should be marked, that in an overwhelming majority of patients positive changes in the state of the intestinal microflora and correction of dysbacteriosis coincided with positive dynamics of clinical data. In 5 patients (11.3%) with D₁, dysbacteriosis degree did not change in the process of treatment.

In the comparison group where “Lactobacterin” was prescribed, from 10 patients 7 (70%) revealed D₁, and 3 (30%) — D₂. Positive dynamics in patients of this group was detected on the 30th day in 3 patients (30%) with D₁ and in one patient (10%) with D₂. In the rest 6 patients (60%) correction was not observed.

Thus, the research carried out by us has shown that fermented milk mixture “Narine” has a number of advantages over “Lactobacterin”, namely, it recovers anaerobic protective flora (bifido- and lactobacteria) in shortened terms, suppresses growth of enterobacteria and pathogenic staphylococcus, increases activity of normal Escherichia coli.

In the third group of patients (20 persons) dysbacteriosis correction was carried out by means of lyophilized “Narine” drug. In 10 patients (50%) with D₂ on the 15th day of treatment drop of conditionally pathogenic microflora was observed, in particular, of Proteus mirabilis, enterobacter, Klebsielli to 10³–10⁴, increase of valuable Escherichia coli as much as 10⁴–10⁶, but no recovery of bifidobacteria or lactobacteria was observed, i.e. D₂ transformed to D₁. Correction of dysbacteriosis was revealed in these patients on the 20th day of research. In 8 patients (40%) with D₁ positive effect was detected on the 15–20th day, and in 2 patients (10%) with D₁ the degree of dysbacteriosis did not change in the course of treatment. In the majority of patients positive changes in the condition of the intestinal microflora and dysbacteriosis correction coincided with positive dynamics of clinical data.

The obtained data have completely confirmed the results of experimental research earlier revealed by us.

Thus, the research performed in the persons affected by small doses of ionizing radiation revealed equally positive effect on the intestinal microflora of both fermented dairy mixture “Narine” and its lyophilized drug.

While comparative study of acido-lactic bacteria strain 317/402 and “Lactobacterin”, efficiency of the studied by us strain for correction of dysbiotic changes in the intestinal microflora has been established. The time of dysbacteriosis correction by means of acido-lactic bacteria strain 317/402 depended on the degree of dysbiotic change severity.
Based on technical advantages of the lyophilizated drug as well as a possibility to use it under extreme conditions we consider advisable to recommend it for correction of dysbiotic disturbances of the intestinal microflora in persons affected by small doses of ionizing radiation\textsuperscript{26}.

VII. Hypercholesterolemia

Clinicoexperimental investigations of the last years have shown that in the intestine of patients with various forms of hyperlipoproteinemia, like in the experiment on the model of hyperlipoproteinemia in rats, there were observed microecological disorders in the intestine, dysbacteriosis with bifido- and lactobacilli insufficiency. They are accompanied with disturbance of lipid and, in particular, of cholesterol metabolism. On the other hand, study of an active series of strains of lactobacilli in vitro determined their cholesterol degrading ability. This ability directly correlated with the strain activity. Inclusion of “NARINE” in a capsulated form into the complex treatment of patients with hypercholesterolemia permitted to talk about potentiation of “NARINE” action on decrease of cholesterol level.

At the State Center of Preventive Medicine of the Ministry of Health, Russian Federation, influence of fermented milk product “NARINE” on the cholesterol level of blood serum in hypercholesterolemia has been studied.

Recent clinicoexperimental investigations demonstrated that similar to the experiment on the model of hyperlipoproteinemia in rats, in the intestine of a sick person with various forms of hyperlipoproteinemia microecological disorders in the intestine, dysbacteriosis with bifido- and lactobacilli insufficiency that were accompanied by lipid and, in particular, cholesterol metabolism were observed\textsuperscript{27,28}.

On the other side, studies of the active series of lactobacilli strains in vitro have established their cholesterol degrading ability\textsuperscript{29}. This ability directly correlated with the strain activity, exposition duration, and depended on the substrate concentration, medium temperature, and oxygen access.

In administering this strain in a limited contingent of persons positive effect was observed in 60\% of cases. Thus the final opinion of the great significance of microecology of the gastro-intestinal tract in lipid (cholesterol) metabolism was confirmed.

Proceeding from the afore-stated examination of individuals with hypercholesterolemia (HChS) was carried out so as to study the influence of “NARINE” on ChS level of blood serum.

The examination involved practically healthy people of both sexes at the age of 40–60, with HChS who had ChS level $\geq 240$ mg/dl. The average level was 268 $\pm$ 34 mg/dl.

Persons who had pathology on the part of cardiovascular system and gastro-intestinal tract were excluded. The average mass of body equaled 76.39 kg, surplus weight was not basis for exclusion from the research.

All patients were prescribed low-cholesterol (200 mg of nutritional ChS a day), low-fat (to 25\% of the total caloric value) diet. They were recommended to increase consumption of coarse-fibered food. The latter was of particular importance since played an essential role in creation of favorable medium for reproduction of microorganisms introduced into the intestine.

Two groups were formed, comparable by the age and sexual composition. The control group (I) was only on the diet, and the experimental group (II) got additionally “NARINE” 2 capsules a day, 3 times, 20 minutes before a meal within 20–25 days. ChS level of blood serum was determined by a fermentative method on autoanalyzer Centrifichem−600 before and after a preventive course of diet and biologically active nutritious supplement.

Positive dynamics in ChS level of blood serum was revealed, more expressed in the 1\textsuperscript{st} group of individuals as compared to the 2\textsuperscript{nd}. Thus, if in the 1\textsuperscript{st} group the average level decreased statistically trustworthy ($p<0.05$) from 265.7 $\pm$ 24.1 mg/dl to 242.5 $\pm$ 19.3 mg/dl ($-8.7\%$), in the 2\textsuperscript{nd} group decrease occurred statistically untrustworthy. ($p>0.05$) from 271.6 $\pm$ 242.2 mg/dl to 258.9 $\pm$ 17.3 mg/dl ($-4.7\%$).

Let us try to evaluate the discrepancies of relative values between two groups by the method of calculation of consent criterion of ChI quadrate. Thus, in the 1\textsuperscript{st} group positive result (reduction of ChS level) occurred in 11 out of 12 persons, and in
the 2nd—in 6 out of 12 (ChS—quadrate = 5.07, p < 0.05, discrepancies are trustworthy).

Thus, the data obtained point to the potentiation of hypercholesterolemia effect of the diet, which is realized through a multifactor mechanism of “NARINE” influence. Along with the direct cholesterol-degrading ability the following is of high account:

1. positive influence upon metabolic functions of the liver. Thus, use of representatives of the intestinal normal microflora in complex therapy of patients with various diseases parallel with clinical improvement of patients’ state and recovery of the microflora’s ability to degradation of exogenous ChS and nitrate reduction led to a positive trend of biochemical processes\(^{30,27}\); participation of the liver in these processes is evident and does not require proofs;

2. participation in metabolism. Lactobacteria have been recently proved\(^{28}\) to be used in regulation of other kinds of metabolic disorders very frequently attended by disturbance of lipoid metabolism. These bacteria have been proposed to be used in prophylaxis of oxaluria, gout, and urolithiasis;

3. immunomodulating action. Well-known is favorable effect of conditionally pathogenic microflora of man on indices of cellular and humoral immunity;

4. antistress mechanism;

5. participation in synthesis of vitamins of group B, role and significance of which in ChS metabolism was proved long ago;

6. microbial biotransformation with synthesis of bioseleunium, bioiodine, biozinc, and other catalysts of cholesterol-transforming reactions\(^{31}\);

7. rise in antioxidant potential of the organism connected in particular with improvement of the intestinal functional state\(^{32,30}\), and as a result of the latter, absorption of vitamin-antioxidants A, E, C and microelement Se;

8. competitive inhibition of growth of the most currently widespread conditionally pathogenic microflora: Helicobacter pilori actively participating in ChS metabolism in the intestine; chlamydia modifying phosphatides in the gastroenteric tract (GET); viruses affecting smooth myoblast of artery walls, and increasing ChS accumulation in them; of fungi synthesizing cholesterol-oxidase\(^{33}\);

9. improvement of endocrine function of sexual glands. Biologically active supplements, containing acido-lactic bacteria are widely used in treatment of inflammatory diseases of genital sphere having conjugated with the intestine regional blood and lymph circulation (adnexitis in women, prostatitis—in men).

### VIII. Periodic disease (PD)

First reassuring results have been obtained in the course of recovery of patients suffering from such a serious ailment as periodic disease (Mediterranean fever).

Based on a number of gastroenteric tract and intestine immunity examinations of patients with PD it can be stated that dyspeptic complaints of PD patients are connected rather with dysbacteriosis than with secretory and absorption deficiency of GET, in particular it is connected with suppression of symbiotic microflora and rise of conditionally pathogenic microflora with further development of inflammatory processes in GET.

According to the results about 82% of patients suffer from dysbacteriosis of different degrees and 63% have super antigenic infection (yersiniosis, chlamydiosis, toxoplasmosis). Change of the intestinal symbiotic microflora resulting in inflammatory atrophic and erosive changes in the GET is the cause of suppression of the intestinal barrier, endotoxin absorption into blood and break of the organism immunologic network. This accounts for high occurrence of superinfections observed in PD patients. Presence of lactobacteria in the intestine lumen provides normal trophicity of the large intestine epithelium, mucin synthesis and prevents reproduction of conditionally pathogenic microflora.

22 patients with PD not complicated with amyloidosis have been examined. None of them had undergone colchicine therapy, as in 3 patients it was ineffective, and 19 had side effects. In the group under observation there were 15 male and 7 female at the age of 17 to 53 with a disease lingering for 15 to 50 years. 17 Patients suffered from abdominal form of PD, 1—of thoracic, and 4—developed a mixed form, 16 patients had attacks of PD
more than twice a month, 6 patients had 1–2 attacks a month.

After taking “NARINE” almost all patients in the first months of treatment had PD attacks not so often as before and later on remissions occurred lasting from 3 to 8 months.

IX. Gastroesophageal reflux

Normal microflora of the gastroenteric tract plays an important role in regulation of gastroenteric tract organs motility. Gastroesophageal reflux is caused by disturbance of normal motility of the upper section of the gastroenteric tract (malfun-ctioning of sphincter and delay in gastric emptying). Inclusion of “NARINE” into complex treatment of gastroesophageal reflux provided significant decrease in the disease clinical manifestations. Long-term remission of a disease has been detected.

The purpose is to establish the role of dysbacte-riosis of the intestine (DI) in pathogenesis of gas-troesophageal reflux (GER). The problem is to compare efficiency of treatment in patients with GER with regard for DI. Materials and methods of examination—together with generally accepted examination of patients with this particular pathology feces bacteriological analysis was carried out. 25 patients with GER were under examination. All patients have revealed DI of I and II degrees. Patients of the 1st group got generally accepted treatment of GER and those of the 2nd group got additionally bificol and “NARINE” for 30 days. The results—complex treatment with the regard for DI provided a noticeable decrease of the disease clinical manifestations, a significant positive change in paraclinical indices, bacteriological and feces analyses. Prolonged remission of the disease has been detected. Conclusions—DI has a definite meaning in GER pathogenesis. For this purpose so as to increase efficiency of this disease treatment it is advisable to include bificol and “NARINE” into a therapeutic complex.

X. Chronic pancreatitis

Disturbance of the digestion process in chronic pancreatitis (due to insufficiency of digestive enzymes) leads to excessive entering of undigested matters into the large intestine. This results in excessive reproduction of putrefactive and fermentative microflora. Dissemination of microbes in the small intestine speeds up decay of digestive enzymes and still more disturbs the process of digestion. Clinical examinations have shown that introduction of “NARINE” drug into complex therapy of chronic pancreatitis promotes more pronounced and stable improvement of digestion in patients with chronic pancreatitis.

We have studied the state of the intestine microflora in chronic pancreatitis. We meant to find out the extent to which manifestation of malabsorption syndrome is connected with pancreatitis or dysbacteriosis of the intestine.

To evaluate dysbacteriosis the following scheme is proposed:

I degree: accumulation of a number of conditionally pathogenic microorganisms when bifidobacteria are on high level ($10^9$). Dysbacteriosis, as a rule, is compensated.

II degree: bifidobacteria are determined at the low limit of the norm ($10^8$) and accumulation of association of conditionally pathogenic microorganisms is observed.

III degree: reduction of a number of bifidobacteria (less than $10^7$) in combination with pronounced changes in aerobic microflora. Decompensated dysbacteriosis.

We have examined 17 patients with chronic recurring pancreatitis in the remission stage whom we divided into 3 groups:

The 1st group included 8 patients with the 1st stage of the disease;

The 2nd group included 6 patients with the 2nd stage of the disease;

The 3rd group included 3 patients with the 3rd stage of the disease.

In 5 patients of the 1st group dysbacteriosis of the 1st degree was revealed.

In 4 patients of the 2nd group dysbacteriosis of the 1st degree and in 2 patients dysbacteriosis of the 2nd degree have been revealed.

Out of 3 patients of the 3rd group 2 had dysbacteriosis of the 2nd degree and 1—displayed dysbacteriosis of the 3rd degree.

The results of our research have proved that dys-
bacteriosis of the intestine in chronic recurring pancreatitis is characterized by increase in a number of lactoseneegative forms of Escherichia coli and decrease of a number of lactobacteria and bifidobacteria.

All patients have been treated with fermented drugs at the generally accepted dosage for a long time. As a result of this treatment clinical syndromes of malabsorption disappeared only in 3 patients of the 1st group without dysbacteriosis, and became less in 3 patients of the same group with dysbacteriosis of the 1st degree. The rest of patients did not show marked improvement of their state. Patients who developed the 1st degree of dysbacteriosis we divided into 2 subgroups. Patients of these subgroups (2 patients) were treated with bificol (3-5 doses, 2 times a day) and those of the other (3 patients) with “NARINE” drug (3 capsules a day). All patients after 20–day therapy exhibited marked improvement. We have also examined patients with the 2nd degree of dysbacteriosis, whose treatment was carried out according to the same scheme. Improvement of the state was observed only in those patients who took “NARINE”. Treatment with bificol appeared to be less efficient. Treatment scheme of patients with the 3rd degree of dysbacteriosis was a bit different. The patients got mixed therapy of “NARINE” with an antibiotic, the choice of the latter depended on presence of conditionally pathogenic microflora. Positive effect of treatment was registered in all patients.

The choice of “NARINE” drug was stipulated by the fact that it was a monostrain of lactobacilli.

Antibacterial activity of lactobacteria is related to their ability to form lactic acid in the process of fermentation, as well as to produce lysozyme, antibiotic matters, lactoline, lysine, lactocidine, acidophilin. “NARINE” possesses such properties.

Proceeding from the afore-said it is possible to presume that in chronic pancreatitis clinical manifestations of malabsorption syndrome to a certain extent are stipulated by dysbacteriosis of the intestine. Taking this into consideration, drugs normalizing anaerobic microflora of the intestine should be included into the complex treatment of chronic pancreatitis. Our preliminary results have shown that “NARINE” is the best for this purpose.

**XI. Treatment of Helicobacter pylori-associated pathologies**

Chronic gastritis of B-type, peptic ulcer and carcinoma of distal sections of the stomach relate to the so-called Helicobacter pylori-associated pathologies. Strategy of these pathologies treatment involves eradication of Helicobacter pylori with the help of high dosage of 2 or 3 antibiotics. Investigations of the last years have shown existence of antagonist activity of acido-lactic bacteria against Helicobacter pylori. It being revealed that inhibiting action is also detected long after cessation of acido-lactic bacteria administration. Joint introduction of Helicobacter pylori with the culture of acido-lactic bacteria also prevented adhesion of Helicobacter pylori to the wall of the stomach. The culture of acido-lactic bacteria is a new effective agent in therapy of Helicobacter pylori-associated pathologies. Its inclusion in complex therapy of these pathologies will enable to reduce antibiotic dosage, provide continuous control over activity of Helicobacter pylori, diminish the possibility of re-infectioning by these microorganisms after eradication, as well as prevent development of intestinal dysbacteriosis while attendant use of antibiotics.

Use of “NARINE” in complex therapy of duodenal ulcer provided an opportunity to obtain much better results in effective treatment.

The purpose is to establish antagonistic action of probiotics with respect to Helicobacter pylori.

The problems are to study effectiveness of *Lactobacillus acidophilus* in treatment of duodenal (peptic) ulcer, chronic erosive gastroduodenitis.

The stuff and methods of examination—feces bacteriological analysis and determination of Helicobacter pylori in the stomach and duodenum. Patients were divided into 2 groups. The 1st group got omeprazole, amoksicillin, quamatel at a standard dosage; the 2nd group got the same complex together with “NARINE” produce containing *Lactobacillus acidophilus*.

The results—in the 2nd group positive dynamics after treatment was more pronounced, the picture of the intestinal microbial flora was normalized.

Conclusions—“NARINE” promoted cicatriza-
tion of ulcera, erosions, suppression of Helicobacter pylori activity and improvement of the intestinal microflora.

XII. Cosmetology

Fermented milk product “Narine” may be used as a cosmetic agent in the form of cosmetic masks on skin of the face, neck, as well as on other sites of the skin being exposed to various injuries. In this case pathogenic microorganisms are destroyed; vitamins, nutritious matters penetrate into the skin that favorably affects state of the face, rejuvenate the skin. The mask made of “Narine” is applied for 30–40 minutes up to complete dryness. Skin of the face is washed with soap before application of the mask, after the procedure the mask is washed off with pure water. Before applying “Narine” masks in persons with fatty skin, acneiform eruption, it is advisable to apply to the skin bentonitic clay in a thin layer. This clay decreases fattiness and greasiness of the skin, eruption of acne. In treatment of many skin diseases, such as eczema, exudative catarrhal diathesis, neurodermite “Narine” made a good showing as the main drug in therapy under condition of its general and local application. “Narine” may be used for lavage of conjunctiva in bacterial inflammation and mycosis.

Thus, fermented milk product “Narine” is a fine medical, prophylactic, health-improvement, nutritious, and cosmetic agent.

XIII. Parodontosis

So as to decrease the terms of treatment and prolong the period of remission tooth-gum deposits are removed, curettage and sanitation of the oral cavity are carried out, low-quality fillings are replaced, and rational prosthetics is performed. At the same time treatment of parodontitis launched. With this purpose turundae were introduced into the pockets, and on the surface gauze napkins lavishly wetted with “Narine” milk fermented by acido-lactic bacteria strain 317/402 “Narine” were applied. Duration of applications was 30 minutes. After 7–8 sessions upon external examination the gum color was light-pink, no discharge from pockets. On bacteriological examination before treatment Staphylococcus aureus was inoculated from pocket discharge, after treatment—Gram-positive bacilli. Upon repeated examination in 12 months no signs of parodontitis were revealed.

Example 1. Patient A, 48 years, was diagnosed parodontitis generalized upon admission, active stage of the 2nd–3rd degrees. Tooth-gum deposits are removed, curettage and sanitation of the oral cavity are carried out, low-quality fillings are replaced, and rational prosthetics is performed. At the same time treatment of parodontitis launched. With this purpose turundae were introduced into the pockets, and on the surface gauze napkins lavishly wetted with “Narine” milk fermented by acido-lactic bacteria strain 317/402 “Narine” were applied. Duration of applications was 30 minutes. After 7–8 sessions upon external examination the gum color was light-pink, no discharge from pockets. On bacteriological examination before treatment Staphylococcus aureus was inoculated from pocket discharge, after treatment—Gram-positive bacilli. Upon repeated examination in 12 months no signs of parodontitis were revealed.

Example 2. Patient M., 36 years, was diagnosed parodontitis generalized upon admission, active stage, has been ill during several years. Upon examination hyperemia, myxedema of gingival margin, hemorrhagic diathesis, itch, 2nd, 3rd degrees teeth mobility were revealed. Depth of pockets was up to 7–8 mm with purulent discharge (Staphylococcus epidermidis, Proteus were isolated). Earlier the patient was treated with antibiotics without obvious improvement. The suggested treatment procedure was carried out that included sanitation of the oral cavity, curettage of pockets, removal of tooth-gum deposits and introduction into the pockets of turundae lavishly wetted with “Narine” milk fermented by acido-lactic bacteria strain 317/402. At the same time tampons wetted with this milk were applied on the gums. Duration of this procedure was 30–35 minutes. The course of treatment was 15 days. On treatment completion complete lack of purulent discharge, hemorrhagic diathesis, pathological teeth mobility was observed. Gingival margin tightly adjoined the teeth. Conditionally pathogenic microorganisms were not inoculated. In the remote terms the patient’s state was satisfactory.

The suggested method of treatment permits to shorten the time of treatment from 1.5–2 months to 10–15 days, and prolong the remission period from 3–4 months to 7–12 months.
XIV. Suppressing effect in vitro of ecologically pure fermented milk product “Narine” on Corinebacteria and possibilities of its administration

Antagonistic properties of acido-lactic bacteria towards a series of pathogenic and conditionally pathogenic microorganisms are well-known. The problem was posed to check antagonism of acido-lactic bacteria towards different versions of Corinebacteria of diphtheria—toxicogenic and non-toxicogenic strains (12 items) c. Diphtherial. Simultaneously sensitivity of Corinebacteria towards traditionally administered antibiotics: penicillin, erythromycin, as well as towards additionally taken drugs: gentamycin, fusidin, cyprophloxacillin was determined. Determination of antibiotic sensitivity was carried out by the method of diffusion into agar with the use of disks and cylinders.

The research showed that fermented milk product “Narine” had a zone of growth retention of more than 46 mm as compared both with traditionally administered drugs—penicillin, erythromycin (diameter of growth retention zones is 26–30 mm), and additionally approbated antibiotics (30 mm). Its suppressive action manifested itself both on toxicogenic and nontoxicogenic strains of Corinebacteria of diphtheria.

The obtained results allow to recommend “Narine” administration as a therapeutic and prophylactic agent in diphtheria.

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*Lactobacillus acidophilus Er−2 株317/402
“ナリネ株”の臨床使用における治療効果

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“NARINE”株こと *Lactobacillus acidophilus* Er−2 Strain 317/402は，1953年旧ソビエト連邦アルメニア共和国においてヤンゼルキャン博士により，新生児の胎便中に含まれる163種類の菌分離により発見された。その特長として，培養温度は36℃～40℃で，PH＝3.0の耐酸性により胃酸や胆汁酸に強く，微好気性であり，耐熱性として，人間の体温（40℃）以上では生存しにくく，人由来のため，腸内の定着性は良好であり，毒性においても，40年以上の各種疾患，あらゆる年代の治療経験において副作用の報告はなく，プロバイオティクスの条件を満たし，かつ有用性が認められている。

“NARINE”という名前は，ヤンゼルキャン博士の孫娘の名前だが，彼女が生後まもなく難治性腸炎を患っていたために，当時研究していたこの株を投与したところ，見事に回復したため，これに因んで名づけられた。残念なことに“NARINE”株に関する多くの研究が，西側諸国の学術分野において，半世紀もの間公表されてない。その理由として，当時の共産圏においては普及のための宣伝活動が必要なかったことや，極限ストレス状態にある宇宙飛行士に対する“NARINE”株の使用研究などは，軍事機密として公表できなかったものと推察される。今回我々は，その臨床分野に応用された研究の一部であるが，レビューとして報告する機会をいただいた。この報告が，今後の日本の乳酸菌研究者における“NARINE”株の理解ならびにアルメニア共和国と日本の乳酸菌研究の発展に意義あることとなるよう希望する。