

**“Vitamax-E”**

**BIOLOGICALLY ACTIVE DIETARY  
SUPPLEMENT**

**”NARINE”**

**Collection of research papers and recommendations**

**“Vitamax-E”**

**Yerevan - 2003**

**“NARINE” CDB is lyophilized biomass of live cultures Lactobacillus acidophilus Strain INMIA 9602 (Er 317/402).**

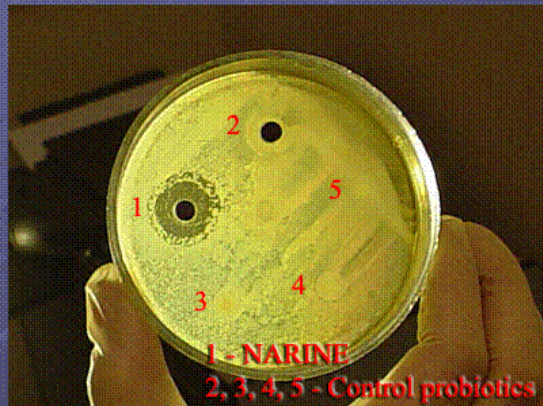
**Advantages of “Narine” strain**

What is the difference of this strain from those previously known?

1. Possesses clearly expressed adhesive properties, possesses high adaptability and stays long in the intestine (two weeks)
2. Possesses high bile- and acid-resistance (PH=2,0)
3. Possesses high antibiotic resistance
4. Possesses high antibacterial, antibiotic and antimycotic activities
5. Zones of brightening on test cultures (zones of growth suppression) are strongly pronounced (e.g. towards Staphylococcus aureus, Proteus, Escherichia coli)

**Antimicrobial properties of “Narine” and other probiotics**

## Антимикробные свойства «Наринэ» и других пробиотиков



*Proteus*

Производитель ООО «ВИТАМАКС-Е»

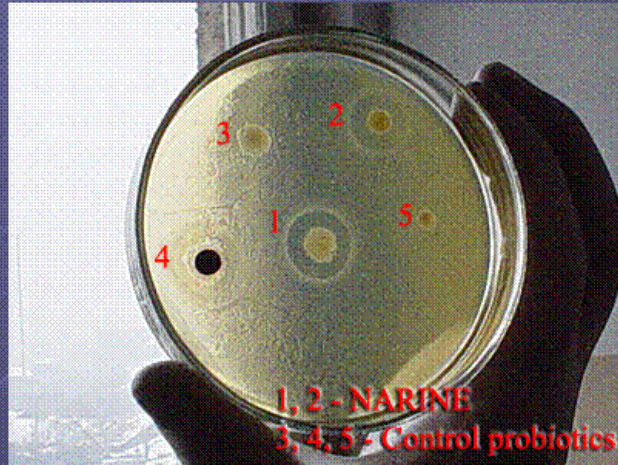
## Антимикробные свойства «Наринэ» и других пробиотиков



*E. coli*

Производитель ООО «ВИТАМАКС-Е»

## Антимикробные свойства «Наринэ» и других пробиотиков



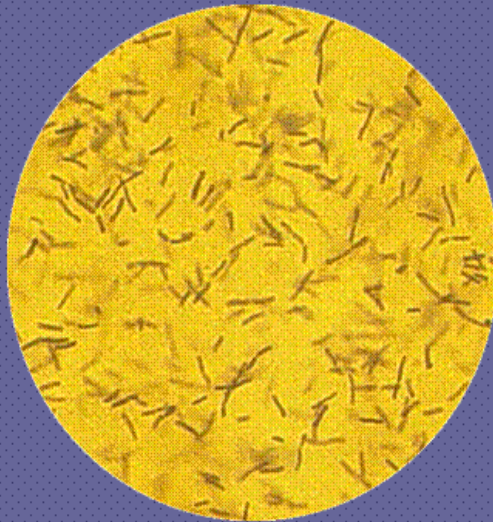
*Staphylococcus aureus*

Производитель ООО «ВИТАМАКС-Е»

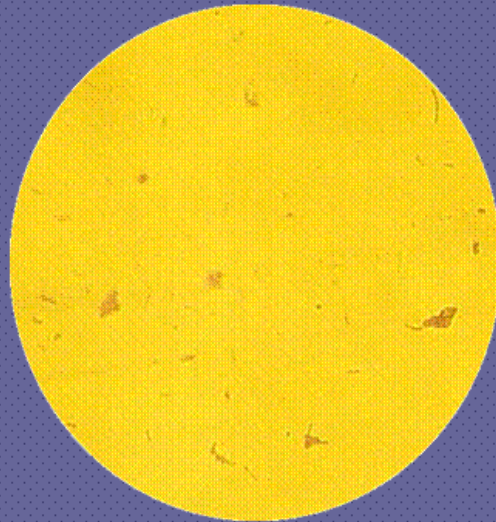
6. In microbiologic examination at PH=3,0 growth of “Narine” bacteria is very active in comparison with other probiotics.

Comparative photographs of “Narine” bacteria growth and that of another probiotic at pH=3,0

Сравнительные фотоснимки роста бактерий  
«НАРИНЭ» и другого пробиотика при  
рН=3.0



*НАРИНЭ*



*Пробиотик*

Производитель ООО «ВИТАМАКС-Е»

“Narine”

**1. Is regulator of the intestine microbial biocenosis**

“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.

**2. Possesses high antibacterial, antibiotic, and antimycotic activities**

Owing to the ability to form lactic acid in the process of fermentation, as well as to produce lectoline, lactocidine, acidophiline, 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 marcescens, 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.

**3. Is immunomodulator**

Research of the past years showed the ability of the “NARINE” drug to stimulate produce of  $\alpha$ - and  $\gamma$ -interferon and increase the activity of natural killers. Interferon produce under the action of “NARINE” was proven *in vitro*. “NARINE” was added onto blood and lymphatic cultures and direct inducing of interferon under the action of “NARINE” was revealed.

**4. Stimulates synthesis of vitamins and lactic acid in the organism**

**5. Ensures assimilation of calcium, phosphorus, vitamins, proteins, carbohydrates**

**6. Neutralizes toxic products of metabolism**

Acido-lactic bacteria and products of their vital activity neutralize toxic products of metabolism (indole, skatole) and quickly eliminate them from the organism.

**7. 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 30g to 45g of milk fat with a certain amount of lecithin possessing bactericidal characteristics, from 27g to 37g 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.

**8. 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.**

**Indications for use:**

“NARINE” CDB and prepared on its basis fermented dairy product “NARINE” are recommended:

- to infants beginning from 6 months in a liquid form as a supplement nutrition;
- in the intestinal infections (colibacteriosis, salmonellosis, dysentery, klebsiellosis, yersiniosis, staphylococcal 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.

**Side effects**

No side effects have been registered while administration of “NARINE” probiotic.

**Contra-indications**

There are no absolute contra-indications.

**Forms of “NARINE”**

Usually “NARINE” is used in a liquid form that leads to considerable inconveniences (short term of storage, non-transportability, special regime of preparation). Dry form of “NARINE” is of significant practical interest.

“NARINE” CDB has a number of advantages over existing forms:

1. the term of storage of the drug is 2 years;
2. high degree of transportability;
3. stability and exclusion of the product spoilage;
4. large concentration of acido-lactic bacteria in a volume unit while microbiological examination, and correspondingly comparatively high treatment and prophylactic effect.
5. “Narine” powder, dissolved in sterile water or sodium chloride solution, or prepared ointments can be used for treatment of local injuries of dermal integuments and mucous membranes (burns, purulent wounds, diseases of nasopharynx and oral cavity mucous membranes, vaginitis, colpitis, mastitis, etc.). Upon external application “NARINE” CDB acts as a natural antibiotic.

**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.

Their main summary characteristics are as follows:

1) “NARINE” is given to a newborn as a breast milk substitute, it is also used in feeding of premature infants. Matsun and Kefir do not fulfill these functions.

2) “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.

Matsun and Kefir do not possess such properties.

3) “NARINE” bacteria get adapted in the human intestine for a long time while Matsun and Kefir do not stay long in the intestine. This explains prolonged curative effect of “NARINE”.

4) “NARINE” bacteria are not destroyed under the influence of antibiotics and chemodrugs that is why “NARINE” can be used in combination with them.

5) 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.

**Table 1**

	“NARINE”	Matsun	Kefir	Fermented milk, West Europe
Complex bacteria	A	B	C	D
Aggregation time (hour)	3-6	5-7	6-10	48
Bacteria concentration (%)	1-1,5	5	3-5	3-5
Cultivation number	6,0-7,0	3,0	2,0-3,0	-
Vitamin contents in %				
Folic acid	60-66	10-12	None	27 decrease
Thiamine	50-72	15-30		11 decrease
Riboflavin (%)	11-32	13		16 decrease
Phenol tolerance (%)	0.4-0.5	0.3	0.2-0.3	0.3
Antibiotic resistance (%)	0.003	0.0001	0.0001	-
Sulfamine resistance (%)	0.8-1.0	0.4-0.5	0.4-0.5	0.4
Acid maximum output in Terner degrees	350-400	250-300	200-250	250-300
Vegetable protein contents (%)	32	15-17	-	11-15
Fixation in the small intestine	Fixed	Not fixed	Not fixed	Fixed for a short time
Bactericidal activity to population of : (mm)				
- Staphylococcus aureus	33-25	15-23		
- Escherichia aureus	23-25	15-18		
- Salmonella typhous	22-25	15-16		
- Klebsiella	23-25	16-18		

## 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, eufloora 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 eufloora 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.

## **Dysbacteriosis of the intestine (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 eufloora 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 gasroenteric 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.

### **Clinically proven spheres of “NARINE” 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; 3<sup>rd</sup> and 8<sup>th</sup> 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 treatment and prevention of a number of diseases.

### **"NARINE" and dysbacteriosis of the intestine (symptom of "bare intestine")**

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 diseases (1,2).

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 5<sup>th</sup> day, in 65% - on the 10<sup>th</sup>, in 25% - on the 15<sup>th</sup> 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 atonic 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 severity (12). 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 recommendations (4). The degree of dysbacterial change manifestations (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>) was evaluated by scheme (2). 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, 15<sup>th</sup> days. In the control group analyses were carried out on the 10<sup>th</sup> and 20<sup>th</sup> 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<sup>-8</sup> in 1g 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, *Klebsiella*, staphylococci (Refer to Table 2).

**Table 2*****Intestinal microflora composition before and after treatment with “Narine” (in %)***

Examination term	Bifidobacteria in feces 10 <sup>-8</sup>	Lactosedefective and hemolytic Escherichia coli	Proteus	Other conditionally pathogenic enterobacteria
Before treatment	6.9	31	24.1	34.4
After treatment	91.4	6.9	6.9	5.1

In the first group in 32 patients of the main group prior to treatment dysbacteriosis D<sub>1</sub>, in 19 patients – D<sub>2</sub> and in 7 patients – D<sub>3</sub> were observed. In the control group 6 patients had D<sub>1</sub> and 10 patients had D<sub>2</sub>. 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 D<sub>3</sub> transformed to D<sub>1</sub>). 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 D<sub>3</sub>, who had Proteus in high concentration on the 15<sup>th</sup> 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 5<sup>th</sup> day, in 39 patients – on the 10<sup>th</sup>, and in 11 – on the 15<sup>th</sup> day of treatment. After correction of dysbacteriosis the patients continued to get “Narine” up to their discharge. Easy forms of dysbacteriosis (D<sub>1</sub>) yielded better to correction – on the average in 5-10 days, D<sub>2</sub> in 10-15 days, the most severe forms of dysbacteriosis (D<sub>3</sub>) in 3 patients were liquidated correspondingly on the 10, 15 and 25<sup>th</sup> days, in 3 cases D<sub>3</sub> transformed to D<sub>1</sub> 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 D<sub>1</sub> dysbacteriosis group have demonstrated positive dynamics on the 15<sup>th</sup> day, and 5 patients from D<sub>1</sub> group and 2 patients from D group – on the 20<sup>th</sup> 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 (5,6).

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 1ml 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 staphylococci 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, colicy 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 acido-lactic bacteria per os and per rectum.

### **Treatment of dysbacteriosis in the Gastroenterological Department of the Scientific-Research Institute of Spa Treatment and Physical Medicine under the Ministry of Health and Social Security of Armenia**

Effect of "Narine" on the clinical course of intestinal dysbacteriosis has been studied in 30 patients of both sexes (14). 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 100g 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*, *Klebsielli*, *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 lactobacterin, as well as bactisubtil and chilak-forte as an alternative choice.

### **Clinical hospital No. 83**

Pursuant to the Agreement on the basis of the Gastroenterological Department of Clinical Hospital No.83, Moscow during 2 months of 1998 clinical testing of the “Narine” drug has been carried out aimed at correction of the intestine dysbacteriosis in patients with organic and functional diseases of gastroenteric tract organs. The group of patients included 16 persons at the age of 22 to 70. The main diagnosis was stoneless cholecystitis. Biliary dyskinesia, chronic hepatitis, peptic ulcer were presented by a less number of patients. The course of treatment made up 15 days, doses were selected individually.

Summarizing the results of clinical trials it is necessary to mention that all patients displayed positive results, painful syndrome was stopped in all patients, according to laboratory data the drug exerted favorable effect on pathogenic and conditionally pathogenic intestinal flora (disappearance of *Staphylococcus aureus*, fungi of candidi species, klebsiellas). At the same time recovery of the normal intestinal microflora was revealed only in 8 patients that poses a question on the necessity to prolong the drug taking.

Thus “Narine” is an efficient corrector of the intestinal microflora when the latter is disturbed in patients with various pathologies of the gastro-intestinal tract. Two-week course of treatment enables to eliminate pathogenic microflora and achieve partial recovery of the normal microflora.

### **Treatment of the intestinal dysbacterioses with “Narine” drug in pediatry**

Intestinal dysbiosis in children is the most urgent problem as it is a primary syndrome in diseases of gastroenteric system, allergic diseases, appears in prolonged use of antibiotics and chemotherapeutic drugs. In newborns and infants dysbiosis can be consequence of prematurity or the result of early artificial feeding. Extent to which intestinal dysbiosis disorders in children under 3 years have spread makes up 30-50% in different authors (7).

*The aim* is evaluation of efficiency of “Narine” probiotic as compared with bifidumbacterin, lactobacterin, linex.

*Methods of research* – on our part on the basis of the Republican Children’s Clinical Hospital, Yerevan, 122 children under 3 were examined. They were divided into 4 groups:

First group (46 children) - took “Narine”

Second group (28 children) – took linex

Third group (23 children) – took lactobacterin

Fourth group (25 children) – took bifidumbacterin

The research program included anamnestic data, laboratory examinations (general and biochemical blood count, analysis of the urine, coprological and bacteriological feces analyses).

Treatment efficiency was evaluated based on clinical symptomatology and results of laboratory examinations.

*Results of examinations and their discussion* – before treatment all sick children exhibited clinical symptomatology – anxiety, meteorism, dyspeptic stools, sometimes with the tendency to constipation. By the method of bacteriological analysis in all patients dysbiosis with disturbance of II-III degrees was revealed, which manifested itself by decrease of the number of bifidobacteria, lactobacteria and Escherichia coli, increase in the amount of lactosenegative and hemolytic Escherichia coli, Streptococcus, and in severe cases by the presence of a great number of Proteus, Clostridium, staphylococci aureus, and Klebsiella.

Children were admitted to the hospital with the following diseases (Table 3):

**Table 3**

*Main diseases by nosologies*

Nosology \ Age	Acute respiratory viral infection, bronchitis, obstructive syndrome	Pneumonia	Sepsis
0-1 year	51	23	4
1-3 years	31	11	2
Total	82	34	6

At the same time the majority of children had bad premorbid background.

**Table 4**

*Premorbid background*

Age \ Premorbid background	0-1 year	1-3 years	Total
Exudative catarrhal diathesis	42	21	63
Rachitis	32	22	54
Hypotrophy	34	-	34
Thymomegalgia	18	41	59

Artificial feeding	49	20	69
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Furthermore, analysis of the examination results showed that the majority of children with the aim of treatment of various infectious-inflammatory pathologies and diseases of the respiratory system before admittance to the hospital as well as afterwards took groundlessly antibacterial and antimicrobial treatment (Table 5).

**Table 5**

*Use of antibiotics according to nosologies*

Treatment \ Nosology	Acute respiratory viral infection, bronchitis, obstructive syndrome	Pneumonia	Sepsis
1 antibiotic	70	14	-
2 antibiotics	12	14	2
3 and more antibiotics	-	6	4

Treatment of dysbiosis disorders with “Narine” probiotic in comparison with other drugs has a number of advantages. Acido-lactic bacteria of “Narine” probiotic are the most acid- and bile-resistant, stay longer in the intestine and faster recover the disturbed microflora as compared with other lyophilized drugs, more stable to the action of antibiotics, contain other metabolites that normalize the intestinal microflora. Administration of “Narine” enables faster recovery of clinical symptomatology and intestinal biocenosis.

**Table 6**

*Efficiency of treatment*

Drug \ Terms of recovery	5-10 days	10-15 days	More than 15 days
Narine	41	5	-
Linex	19	7	2
Lactobacterin	15	5	3
Bifidumbacterin	17	6	2

As it is seen from Table 6 the majority of patients in the first 5-10 days while taking “Narine” showed improvement of the clinical picture in comparison with other drugs that improve the state in later terms.

Thus use of “Narine” probiotic against a background of antimicrobial treatment of infectious-inflammatory diseases promotes treatment and prevents intestinal dysbiosis.

### **Clinico-laboratory effectiveness of dysbacteriosis treatment (in children of early age ill with salmonellosis)**

In children of early age, mainly, of the first year, the most spread intestinal infection is salmonellosis. In Armenia, and in all parts of the former Soviet Union the prevailing etiologic factor of salmonellosis is *S.typhimurium*. Frequency of severe forms and duration of the disease flow in little children predetermines the necessity of wide and repeated administration of antibacterials drugs that inevitably leads to development of intestinal dysbacteriosis and aggravates severity of salmonellosis. Along with this, as is known, increase of microbe resistance, formation of polyresistant strains of *S.typhimurium* are observed. This, in its turn, changes the ecology of pathogene, makes it more stable to various factors of the environment, forms particular virulence of hospital *Salmonella* strains and enables growth of intrahospital salmonellosis. On the basis of literary data and personal clinical observations it is established that etiotropic treatment of salmonellosis in children of early age with the available antibacterial drugs is not sufficiently effective. It is, evidently, connected both with wide spread of antibioticresistant *Salmonella* strains and frequent generalization of infection that impedes creation of sufficient concentration of the drug in foci of microbe reproduction.

Clinicians and microbiologists’ attention as usual is focused on search of novel efficient antibacterial agents.

Under experiment conditions on calves (Scientific-Research Institute of Microbiology, National Academy of Sciences, Armenia), as well as on *Shigella* and *Salmonella* in vitro (Laboratory of Nutrition Hygiene under the Scientific-Research Institute of General Hygiene and Professional Diseases under the Ministry of Health, Armenia) antibacterial properties of “Narine” proposed by Doctor in Biology L.A.Yerzinkyan (Scientific-Research Institute of Microbiology, National Academy of Sciences, Armenia) were revealed. Authors of the recommendation for the first time have established clinical efficiency of “Narine” administered in complex treatment of salmonellosis in children. Parallel with this, in latter dynamics of microflora formation under the action of “Narine” was studied. The basis for these investigations served observations proving that the reason for a great number of acute and chronically proceeding diseases appeared disturbance of the intestinal microflora composition. So far no research in determining effectiveness of this mixture in intestinal infections has been carried out whatsoever.

Producing lactic acid “Narine” creates acidic medium in the intestine thus suppressing putrefactive and pathogenic microflora, i.e. fulfills an antagonistic function. Acidic medium enables absorption of calcium, vitamin D, ferrum. Moreover, it contains vitamins, mineral salts, including vitally important amino acids, required microelements, antibiotic substances. Nutritious value and antibiotic properties of “Narine” served an additional basis for its approbation as a curative product.

Quantitative and qualitative contents of the intestinal microflora were determined in dynamics (13). The control group included 30 patients with salmonellosis who took kefir or kefir and breast milk instead of “Narine” in complex treatment. All examined children were of the first year of life, 73,6% of them - of the first half-year.

All children were diagnosed salmonellosis based on positive copro or urinculture with dissemination of *S.Typhimurium* in all cases (Table 7).



The research of many native and foreign authors established that in healthy children anaerobic Garm-positive bacillus *B. bifidum* comprises 98% of the whole intestine microflora. Infant's health, especially in the first years of its life depends greatly on the amount of bifidobacteria in the intestine.

Bifidoflora increases infant's resistance to diseases, participates in the enteral synthesis of vitamins, regulates intestinal peristalsis. During transition to artificial feeding composition of the intestinal normal microflora changes, frequent revealing of *Proteus* takes place. Here bifidoflora is no longer dominating and the total quantity of aerobic bacteria (*Escherichia coli* and *Enterococcus*) increases, colicinogenic activity of coli-flora decreases (N.N. Liz'ko, et al., 1978).

Estimating manifestation of the intestinal dysfunction in the patients under supervision it can be noted that frequency of stools in the course of the disease was different from 1-2 times to 7-10 times, sometimes even more frequent, as much as 15-20 times a day. By its nature stools was liquid, yellowish, or green, marsh slime-like, with mucus, in 23% of cases with appearance of hemocolitis in the kind of veins or significant enough admixture of blood in stools in combination with tenesmus in two children.

Terms of stools normalization depended on duration of "Narine" administration (Table 8).

**Table 8**

*Terms of stools normalization in children ill with salmonellosis*

Groups	Children quantity	Stools normalization by days							P	M ± m	T	
		2-3	4-6	7	8	14	15-19	21-29				More than a month
Main		8	15	2	2	-	-	-	-	0.98	4.5±0.775	2.480
Control		-	-	-	-	2	8	12	8	0.98	23.2±4.07	2.467

**Table 7**

*Clinical diagnosis in children*

N	Z	Groups	Children total	Salmono llous	Salmono	Salmono llousis,	Flow severity		Accompanying diseases						
							Se ver	Me	Ni cro	Otitis	Uri	No	Rachitis	Hypotrophy	Ex and

									Catarrhal	Purulent			I	II	I	II	III		
1	Main children group taking "Narine"	27	20	6	1	26	1	14	4	-	2	1	6	1	6	6	4	4	1
2	Control children group (kefir and breast milk)	30	19	10	1	29	1	15	6	1	2	-	6	2	3	13	-	7	-

According to clinical and bacteriological studies it was established that when taking "Narine" recovery of the intestinal dysfunction occurs as early as from the 3<sup>rd</sup> day, and stable normalization of stools without aggravation of the intestinal process takes place on the 4<sup>th</sup> day. At the same time normalization of stools in the control group was observed in the 3<sup>rd</sup> week and later, on the average in 23 days, and not always stable. The difference is statistically authentic. Due to the mentioned shortened terms of the intestinal dysfunction normalization the terms of antibacterial therapy with "Narine" administration were sharply reduced as compared with the control group. Aggravation of the intestinal process in one child of the main group was connected with joining of pneumonia and transition to kefir feeding. In the control group aggravation was noted in three children, in one of them stools shaping did not come whatsoever. It is necessary to point that fast rates of stools normalization when "Narine" administration depended on the age.

When a child due to the lack of appetite, vomiting ate the mixture in the less volume (100-200ml a day) stools shaping delayed.

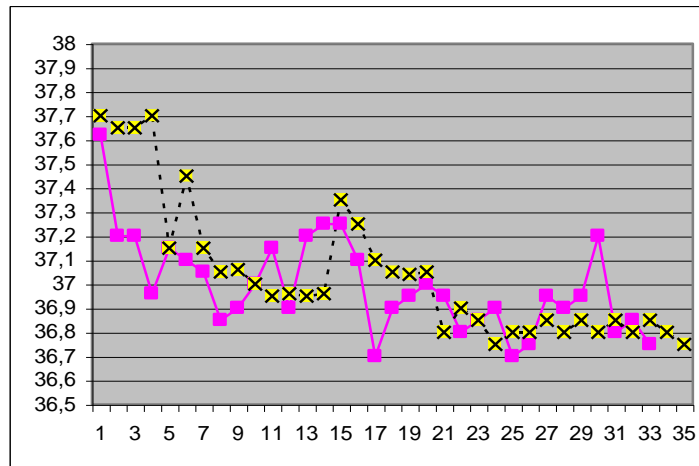
The height and duration of the temperature reaction are given in Figures 1 and 2 in the form of curves that reflect severity of the infectious process and prove the less manifested and shorter temperature cycle in patients who took "Narine" in comparison with children of the control group.

Distinct differences are obtained on comparing such indices as putting on weight and duration of stay in the hospital in children of the main and control groups with non-aggravated flow of the

disease. Thus, children who took “Narine” put on 288,0g in 21 days or 13,6g per day, while in the control group they put on 266,6g in 38,6 days or 8g per day.

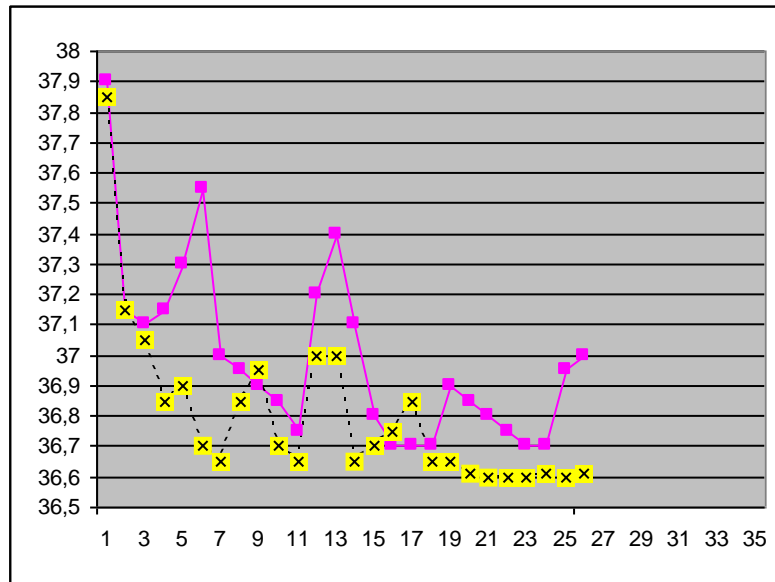
All observed patients without exception got from 4 to 7 various antibacterial drugs included into complex therapy during approximately 17,4 days in the main group and 21,2 in the control one. Duration of treatment in the control group is associated with persistence of intestine dysfunction in patients. It is necessary to note that in the process of the performed research not always “Narine” was included into complex therapy from the very first day. Sometimes “Narine” was given to patients with the delay of 4 days, on the average. Inclusion of “Narine” into complex treatment from the first day of stay in the hospital even more intensified the curative effect and shortened duration of the disease and terms of treatment.

**Fig. 1**



Thus, introduction of “Narine” into complex treatment promoted more effectiveness of the latter, resulted in duration reduction of etiologic agent administration, smoother flow of the disease in children of the main group as compared with the control one.

**Fig. 2**



Dynamics of the intestine microflora formation under the action of the fermented milk product “Narine” in children suffering from salmonellosis has also been studied before and after its taking. The basis of the research is (92).

The state of dysbacteriosis in the examined children before taking “Narine” was characterized by decrease of the total amount of microbes, Escherichia coli, Enterococcus (aerobes), bifidobacteria, Lactobacillus (anaerobes), and appearance of yeast fungi in a greater number than in the norm. Results of the research are presented in Table 9.

**Table 9**

*Quantitative indices of various groups of microorganisms in the intestine of children ill with salmonellosis as compared with the normal microflora of those healthy*

Microorganisms	The norm	In children ill with salmonellosis	
		Before taking “Narine”	After taking “Narine”
Total number of microbes in 1g of feces	9,3 ± 0,4	7,595 ± 0,13	8,746 ± 0,184
Escherichia coli	8,6 ± 0,5	7,107 ± 0,214	8,359 ± 0,221
Lactose-	0	6,554 ± 0,247	4,699 ± 0,497
Lactose+	7,6 ± 0,5	6,969 ± 0,265	8,366 ± 0,210
Enterococcus	8,3 ± 1,2	6,383 ± 0,291	8,063 ± 0,281
Bifidobacterin	8,9 ± 0,4	6,626 ± 0,265	8,384 ± 0,340

Lactobacillus	7,3 ± 0,1	5,044 ± 0,368	7,127 ± 0,422
Yeast fungi	0	6,136 ± 0,082	6,700 ± 0,731

I quantity of microbes in 1g of defecation                      M ± m                      t = 2,262

The data obtained give the basis to think that in salmonellosis patients taking “Narine” recovery of the total amount of microbes proceeds more intensively at the beginning and upon reaching the norm the intensity slows down. With accompanying diseases recovery of the total number of microbes proceeds limply.

Thus laboratory effectiveness of “Narine” became apparent in normalization of the total number of microbes, both of anaerobic and aerobic floras, as well as of typical associations. The amount of lactic acid bifidobacteria and Enterococcus rose to the norm at permissible probability of 0,95 to 2,262. Evidently, not only the volume of the received “Narine” (500-1000 ml in conformity with the age) is of importance, but also the treatment duration. Its average duration made up 13,5 days. This term is enough for recovery of the total amount of microbes in patients’ intestine as much as 80-90%. Increase of the latter resulted in normalization of aerobic and anaerobic microfloras and the nature of their association. In that way, increase of the total amount of microbes in case of dysbacteriosis to the norm appears good indicator of the health state recovery.

The norms of “Narine” taking in healthy children of the first year of life are given in Table 10 and they are drawn up with due regard for the available norms of infants’ feeding, as well as recommendations of L.A. Yerzinkyan (93).

**Table 10**

***Recommended norms of “Narine” administration in healthy children of the first year of life***

Infant’s age	“Narine” quantity in grams at each feeding	Number of feedings
1-5 days	20-30	
Up to 1 month	Gradual increase of the dose up to 80-120	7 times (in 3 hours)
1-3 months	120-160	7-6 times (in 3-3,5 hours)
4-6 months	160-200	6-5 times (in 3,5 hours)
6-12 months	200 and more	5 times (in 4 hours)

“Narine” may be given to sick children beginning from their birth. “Narine” is included into complex therapy from the very first day of treatment and it is recommended not to discontinue its administration after termination of the course of antibacterial therapy. The volume of the received feeding and number of feedings depend on severity of the state and sick infant’s age.

If in children of early age the intestinal disease proceeds in light or mid-serious form, in the acute period of the disease it is advisable to decrease nourishment to 1/3 - 1/2 of the day volume. The number of feedings increases in comparison with the period of health, the dose of “Narine” becomes less for each feeding. In patients suffering from salmonellosis with the clinical picture of the intestinal toxicosis after 10-12-hour water-tea pause “Narine” is prescribed fractionally, starting from 10,0-20,0 in every 2 hours (10 times a day with 4-hour night interval). Every day the twenty-four-hours’ amount of the mixture may be increased by 100,0-150,0g with the baby’s state improvement, decrease of the intoxication symptoms, cessation of vomiting.

With increase of the amount of “Narine” up to 70-80 ml intervals between feedings make up 2,5 hours. When a patient gets up to 90-140 ml interval between takings increases to 3 hours. By the 7-8th days the baby is transferred to the usual rhythm of feeding (94).

The best results of treatment of the children being on artificial feeding are observed in full transition to “Narine”.

While treatment with acido-lactic product “Narine” the first two days of treatment, in some cases depending on the nature of the disease, clinical severity and patient’s state, stools can be a bit more frequent, however, in 1-2 days it normalizes.

### **Izmailovskaya Children’s clinical hospital**

The research involved 30 sick children suffering from various diseases. Out of them 18 children had gastritis or gastroduodenitis, esophagitis was determined in 12 children, asthmatic bronchitis in 4, diseases of the blood system (thrombocytopenia, hemovasculitis) in 2 children, 1 child suffered from pyelonephritis, 9 children developed signs of proctitis and proctosigmoiditis, 1 child had duodenal ulcer, 1 – vulvovaginitis. At the same time all of them had disorders of the gastroenteric tract functions of different etiology with painful abdominal syndrome and manifestation of dysbiosis of the 1<sup>st</sup> and 2<sup>nd</sup> degrees. The research included 16 boys and 14 girls at the age of 5 to 14 years (the average age was 9,3 years).

All children underwent the objective clinical examination, endoscopic examination (endogastro examination and rectoscopy), functional and laboratory methods of examination. 12 children were subjected to immune status examinations together with examination of leukocyte activity so as to determine immunomodulating function of “Narine”. In the comparison group 5 children who took decaris were included at random.

Among children included in the examination 18 persons had gastroduodenitis. While carrying out rectoscopy all children displayed signs of inflammation of the large intestine mucous membrane in the form of the vascular picture reinforcement, edema, and folds enlargement, mixed character and mucosal hyperemia, availability of thick mucus in the intestine lumen (Patients’ clinical characteristic is presented in Table 7).

Children with congenital heart diseases, marked hepatic and renal insufficiency, acute intestinal infection were not included into the research.

From accompanying diseases 12 children developed vegetovascular dystonia of sympathicotonic type, 4 - bronchial asthma (asthmatic bronchitis), 2- diseases of the blood system.

“Narine” was prescribed as monotherapy according to the firm recommendations, that is 1 capsule (150mg) 3 times a day 20 minutes before a meal, within 10 days.

Estimation of the therapy efficiency was carried out every day on the basis of the main clinical symptoms dynamics: painful, dyspeptic, nausea, vomiting, diarrhea, as well as change of the endoscopic picture of the mucous membrane before and after completion of the therapy, estimation of the large intestine microbiocenosis (estimation was carried out on 20 parameters of microflora). Gradation of efficiency of “Narine” use included four classes:

Excellent effect: total disappearance of clinical manifestations.

Good effect: Disappearance of pains, majority of clinical symptoms, or decrease in their manifestations.

Satisfactory effect: insignificant positive dynamics, preservation of morbidity, dyspepsia.

Poor effect: absence of clinical symptoms positive dynamics.

“Narine” tolerance was estimated by the development of side effects during treatment.

### ***Research results***

Dynamics of clinical symptoms against a background of “Narine” treatment is given in Table 8. Prior to treatment all children complained of pains in the abdomen. Pains were every day, of short duration, often appeared after physical load, sharp movements. Pain intensity was very strong (1 child), strong (9 persons), moderate (14 children), or weak (6 children). Against a background of “Narine” treatment pains disappeared in all children, the disappearance was registered on 3-6 days of treatment, in 3 children the pains retained up to 8 days (on the average pains ceased on the 4-7 days). In case of taking decaris no positive dynamics was registered.

18 children (52%) had diarrhea with an average stools frequency 1-2 times within 24 hours. Complete or partial normalization of stools was noted in all children on the 2-4 days. Children against a background of taking “Narine” showed normalization of stools, even if before treatment retention of stools for a day or two was observed (9 children).

Analysis of the chosen dosage compliance with the obtained clinical effect revealed that “Narine” prescription of 150mg thrice a day before a meal is optimal.

Analysis of clinical effect manifestation showed that in 11 cases (36%) the effect was excellent; in 13 patients (56%) the effect was good, in 1 patient (6%) – satisfactory (Table 9). All patients with chronic diarrhea exhibited excellent effect. Thus, “Narine” is a highly effective drug normalizing the gastroenteric activity.

Microbiological feces analysis in all children before treatment revealed dysbacteriosis of the 2<sup>nd</sup> degree of activity. After taking “Narine” 23 children showed normalization of the intestine microflora. Children in whose feces analysis microorganisms of the Candida type were available in plenty after conducted treatment with “Narine” displayed for certain either decrease of their number, or the same amount, without changes. In case of taking decaris no positive changes of the microbiocenosis picture under its influence was registered in the control group.

### **Side effects and tolerance**

While studying immunomodulating function of “Narine” moderate increase in the activity of cell-helpers was observed comparable to decaris action. However, due to a short period of observation it is impossible to draw remote conclusions.

### **Conclusion**

1. “Narine” is an effective drug to be used as a substitution therapy in dysbacterioses of 1-2 degrees accompanying various diseases.

2. “Narine” exerts fast clinical effect on patients suffering from dyskinesia of the gastro-intestinal tract upper and lower parts with painful syndrome, as well as with “small” and “large” diarrhea.
3. The optimal efficient dosage of “Narine” equals 150mg 3 times a day in 24 hours, 20 minutes before a meal, within 10 days.
4. “Narine” has immunomodulating effect.
5. “Narine” in the dosage used does not cause side effects in children and is well tolerated.
6. “Narine” is recommended for registration and clinical use in the Russian Federation.

**Table 11**

*Clinical characteristic of patients*

Diagnosis	Age and sex									Total
	5-7 years			8-11 years			12-14 years			
	girls	boys	%	g	b	%	g	b	%	
Gastroduodenitis	8	1	30	1	4	23	1	3	16	18
Vegetovascular dystonia				4	3	42	3	2	44,4	12
Total	8	1		5	7		4	5		30

**Table 12**

*Dynamics of clinical symptoms against a background of “Narine” treatment  
(with indication of days)*

Symptoms	Dynamics of clinical manifestations  Number of children, date of disappearance
Pains in the abdomen (25 children)	22 children, on the 6 <sup>th</sup> day (90%) 3 children, on the 8 <sup>th</sup> day (10%)
Eructation (11 children)	11 children, on the 3 <sup>rd</sup> day (100%)
Meteorism (19 children)	14 children, on the 5 <sup>th</sup> day (73,7%)



	3 children, on the 8 <sup>th</sup> day (15,8%) 2 children, did not disappear (10,5%)
Nausea (9 children)	9 children, on the 2 <sup>nd</sup> , 3 <sup>rd</sup> days (100%)
Vomiting (2 children)	2 children, on the 3 <sup>rd</sup> day (100%)
Diarrhea (18 children)	18 children, on the 2 <sup>nd</sup> -4 <sup>th</sup> days (100%)

**Table 13**

*Clinical efficiency of “Narine”*

<b>Effectiveness</b>	<b>Patients’ number</b>
Excellent	11 children (36%)
Good	13 children (56%)
Satisfactory	1 child (6%)
Bad	None

“NARINE” CDB has been studied in children’s clinical practice at the Department of Resuscitation and Intensive Therapy of the Republican Clinical Hospital, Yerevan.

From November 1997 to April 1998 “NARINE” capsules were given to 63 sick children in complex treatment of diseases proceeded with the intestinal toxicosis against a background of dysbacteriosis developed as a result of a basic disease and use of antibiotic therapy.

Effect of “NARINE” capsules was compared with a control group of 16 persons who in their complex treatment took bactisubtil capsules instead of “NARINE”.

“NARINE” capsules were prescribed immediately from the very first days of a disease in complex treatment in one or two courses over 10 to 20 days. Capsules were given according to the following scheme: 1:1, 20 minutes before a meal.

The results were evaluated both clinically (cupping of the temperature reaction, toxicosis, improvement of the appetite, decrease of abdominal distention, normalization of stools) and according to laboratory data (feces for dysbacteriosis, feces bacteriological analysis). As a result of the analysis carried out it was revealed that in children who received “NARINE” capsules in their complex treatment compared with the control group the temperature reaction cupped 2-3 days earlier, toxicosis symptoms disappeared 1-2 days earlier, the appetite improved quicker, stool was normalized 2-3 days earlier. As to laboratory results, symptoms of dysbacteriosis disappeared 5-7 days earlier; there was not a single case with signs of bacteria carriage whereas in the control group such a case was observed.

In the Semipalatinsk State Medical Academy and Pavlodar Center of Clinical Immunology and Reproduction (Republic of Kazakhstan) the program of recovery of mucous and small intestine by the “Narine” drug and oats decoction has been proposed (89). After sanitation measurements as well as in patients who took many antibiotics it is necessary to restore surfactant of mucous and normal microflora. 50% of nourishing matters for the small intestine and more than 80% for the large intestine enter from their lumens. Within a week of starvation the large intestine mucous is atrophied (95).

At the same time potentially pathogenic microbes become active. If nourishment consists of simple carbohydrates, peptides, amino acids, fatty acids, the larger part of it is absorbed in the upper sections of the gastroenteric tract. This also results in mucous atrophy, but not so fast as in starvation. Prescription of complex fibres and proteins predetermines the state of low sections of the gastroenteric tract. Normal microflora of the large intestine ferments them with output of the necessary nutritive substances, for example, amino acids (arginine, glutamine). As a substrate for fermentation, oats suits

most of all because it contains membrane lipoids 100 times as much as any other food. Membrane lipoids comprise the base of surfactant – a protective layer covering mucous membrane of the gastroenteric tract.

Lactobacteria used simultaneously with oats suppress potentially pathogenic flora and further development of normal microflora of the gastroenteric tract. Normal flora improves fermentation, formation of surfactant and enables better protection of the intestine mucous. Results of the research are confirmed by numerous experimental models and clinical trials.

Grains of oats contain fat (6-9%), starch (44-60%), proteins (13-16%), ferments, vitamins of groups B, PP, E, A, glutamine, choline, tyrosine, ethereal oil, mineral salts – phosphorous, calcium, etc. Amino acid composition of oatmeal appears to be the closest to muscle protein that makes it especially valuable product. Oats promotes removing of cholesterol excess from the organism.

The mixture of oats and curative product “Narine” is advisable in gastroenteric diseases, emaciation, drop in appetite, thyrotoxicosis, kidney diseases, obesity, atherosclerosis, diabetes mellitus, chronic hepatitis and pancreatitis, after infectious disease, influenza, colds. The remedy is useful for those recovering after serious diseases, people suffering from hypotonia, in amenorrhea, and dysmenorrhea. As additional treatment it is recommended in neurasthenia and insomnia, in intensive mental work.

Since “Narine” was able to lyse pathogenic bacteria and fungi, stimulating normal microflora development, it became possible to prescribe it blindly without labor-consuming preliminary examination.

The newborns feeding on “Narine” are guaranteed to gain their weight against the initial one by the end of the first month of their lives in comparison with those only nursed.

As compared with cow milk in “Narine” contents of vitamins increases: of folic acid - by 66%, thiamin (vitamin B1) – by 45-72%, riboflavin (vitamin B6) – by 11-32%, free acids - 2-4 times as much.

“Narine” is employed for children’s feeding, for treatment and prevention of various gastroenteric diseases, such as dysbacteriosis, dyspepsia, salmonellosis, typhoid, dysentery, dysentery, staphylococcosis infection, irritated large intestine syndrome, spastic and atonic constipation, functional diarrhea, acute and chronic colitis, non-specific ulcerative colitis, etc. Even in case of cow milk intolerance fermented milk product “Narine” may be administered as a substitute of breast milk, as well as additional nourishment for infants and elder age groups, including pre-mature children, weakened, with low contents of hemoglobin in blood, having hypotrophy, rachitis, those born from mothers with negative Rhesus factor. As far as “Narine” treats dysbacteriosis, which occurs in 85% of population its usage is necessary practically to everyone taking also into account other positive properties of the product. “Narine” more effectively and faster than other similar drugs normalizes microbial biocenosis of the intestine, recovers in shortened terms anaerobic flora (bifidobacteria and lactobacteria), suppresses growth of pathogenic and conditionally pathogenic flora (Salmonella, Shigella, staphylococci, enteropathogenic Escherichia, citrobacter, Klebsiella, enterobacter, citrobacter, proteus, fungi, Lactosedefective and hemolytic forms of Escherichia coli), increases activity of normal Escherichia coli, possesses high antagonistic activity with respect to Gram-positive and Gram-negative microorganisms. “Narine” is highly resistant towards antibiotics, therefore it is not only withdraws side-effects of antibiotic therapy, but also reinforces the curative action of antibiotics.

While taking “Narine” the general condition improves, normalization of the gastroenteric tract function is observed, in children distinct gaining of weight and height is marked. Prescription of “Narine” milk reduces the terms of antibiotic therapy, as well as the terms of treatment. Besides, “Narine” increases assimilation of ferrum, calcium, stimulates vitamin synthesizing function of the intestinal microflora.

“Narine” ensures decrease in frequency of postoperative pyo-inflammatory complications (suppuration of laparotomic wound, anastomosis insufficiency, localized peritonitis, paracolostomic abscesses, perineal wound suppuration, etc.).

Currently the fermented milk product “Narine” has found wide application in treatment of various purulent and inflammatory diseases in children and adults: staphylococcosis, furunculosis, mastitis, gynecologic and urologic diseases.

“Narine” provides normal antigenic stimulation of the intestine lymphatic system that is required for normal differentiation of immunocompetent cells, treatment and prophylaxis of immunologic insufficiency, allergy and immunopathology. Taking of “Narine” ensures timely vaccinations, increases their efficiency and reduces probability of vaccinal prevention complications. Positive effect was observed in patients suffering from allergy, in particular, in case of antibiotic intolerance, in patients with bronchial asthma. Positive results have been achieved in treatment of various inflammatory diseases of different localizations: of gastroenteric tract, oral cavity, respiratory organs, genital sphere, etc.

“Narine” exerts immunostimulating, immunocorrective and antiinflammatory action, possesses radioprotective properties, suppresses putrefactive processes in the intestine, normalizes cytotoxic activity of natural killers responsible for antineoplastic protection.

Effect of the treatment is demonstrated in patients on the 5-15 days of “Narine” administration, rarely on the 25<sup>th</sup> day and later. Dysbacteriosis correction coincides with the positive dynamics of clinical and laboratory data, results of endoscopic examination. Product “Narine” has presented itself in a good light as a mass general tonic preventive agent for adults at the enterprises with harmful labor conditions. Beverage “Narine” may also be applied in wide consumer net. For example, kefir as compared with fermented milk product “Narine” has low curative-preventive properties being, in essence, only the nutrition product. Yeast fungi, streptococci, contained in spread fermented milk products cannot promote recovery of patients with chronic streptococcosis (chronic tonsillitis, relapsing erysipelas, streptoderma, rheumatism, etc.), and in patients suffering from eczema, exudative catarrhal diathesis their consumption can cause aggravation of condition, itch intensification if these diseases are connected with allergy towards streptococci. Patient does not tolerate streptococcus in the fermented milk product rather than the product itself. “Narine” consumption does not cause allergic reaction.

“Narine” is used both as an independent curative and prophylactic agent, and in combination with other antibiotic and chemotherapeutic drugs. In the latter case “Narine” hinders colonization of the intestine by conditionally pathogenic microflora, thus preventing side effects of antibiotic- and chemotherapy. In the majority of cases prescription of “Narine” helps to avoid inevitable (as one would think) use of antibiotics in those frequently and lingeringly ill.

The product is taken in. The course of treatment is 10-25 days, but more prolonged administration is also possible. In chronic forms of gastroenteric diseases the course of treatment should be repeated 2-3 times. With simultaneous administration of antibiotics or chemo drugs “Narine” is given 2 hours before or after antibacterial remedies taking. “Narine” is prescribed to children under 1 year – 5-7 times at a daily dose of 0.3-1 liter, to children from 1 to 5 years – 5-6 times at a daily dose of 1-1,2 liter, over 5 years – 4-6 times at a daily dose of 1-1,5 liter, to adults - 4-6 times at a daily dose of 1-1.5 liter. In severe cases when a patient is not able to take large doses of the product at a time, it is recommended to give a daily dose of “Narine” more frequently and in small portions. After recovery “Narine” can be taken as a preventive remedy with intervals and without them at doses of 0,2-1 liter.

In correction of dysbacteriosis in the first 2-4 days it is expedient not to take any food other than fermented milk product “Narine” (infants feeding on breast milk may comprise an exclusion), and the following days the daily norm of “Narine” milk may be gradually decreased with inclusion of other products in the food. The aforementioned doses are taken the first days, later on doses may be decreased with gradual transition to “Narine” at the doses similar to other fermented milk products. Once a week it is advisable to arrange “kefir” (“yoghurt”) days taking only “Narine”. Other time it is

also expedient not to lump “Narine” with other products, taking it in the intervals between eatings, on an empty stomach in the morning, before sleep, since the drug dilution decreases its efficacy. “Narine” in the ratio of 1:2 is still able to lyse staphylococcus.

Infants from 3-10 days of lives with each feeding should be given 20-30 ml of “Narine” with gradual increase in the dosage. At the age of 1 month the infant can be given as much as 120-150 ml of fermented milk product “Narine” with each feeding in case breast is not given. The product is prescribed several times a day being alternated either with any other children’s nutrition, or given to finish feeding. When using “Narine” sugar, syrup, sugar substitutes (slastiline, sladosten, sorbite, etc.) may be added as well as 1/10 part of boiled and cooled rice-water. Before infant’s feeding “Narine” should be warmed up to the breast milk temperature, but not lower than 30°C. If a nursing mother has mastitis or subclinical form of mastitis (significantly infected breast milk) nursing should be temporarily ceased, infant should be given “Narine”, and mother sanitized.

To avoid children’s diarrhea and dysentery it is expedient to feed infants under 1 year and elder on “Narine” milk, especially in summer time.

“Narine” is good for any frequently and lingeringly ill. In Iova syndrome (skin affection) or Bakli syndrome (internal organs and skin affection) stipulated by allergy towards Staphylococcus aureus, streptococcus, or Candida fungi and manifested in the form of exudative catarrhal diathesis, neurodermite, bronchial asthma, etc., “Narine” is one of the most cardinal curative drugs. For example, if a nursing baby is ill with exudative catarrhal diathesis it is necessary not only to give fermented product “Narine” for drinking (intestinal dysbacteriosis treatment), but also to drop the filtered off beverage into baby’s nose (sanitation of rhinopharynx from pathogenes), cleanse with fermented milk product “Narine” baby’s dermal integuments, as well as nipples of the breast before and after feeding (prevention of mammary gland from being infected, effective prophylaxis of mastitis, treatment and prevention of mammary gland nipple cracks).

Fermented milk product “Narine” is excellently tolerated and in essence does not have contra-indications, except cases of intolerance of acido-lactic products. While treatment with “Narine” in particular cases aggravation of a patient’s state with reinforcement of abdominal pains is possible on the first two days of treatment. Stools can become a bit more frequent and be accompanied with plentiful mucus discharge. In rare cases patients can develop short-time constipations. However, in such cases it is necessary to continue “Narine” taking and in 1-2 days stools will be gradually normalized. In patients with gastroenteric diseases bentonitic clay taking one teaspoon in a glass of water up to 1-3 times within 2-3 days removes quickly the stated manifestations or prevents them. Later on “Narine” is taken separately.

For those who do not tolerate fermented milk products or cannot by some reasons ferment milk (being in a hospital, lack of milk, inability or unwillingness to perform constant, from day to day, milk fermentation) one of two procedures of “Narine” product taking, given below, might be recommended.

“Narine” can be used in a dry form (in case of milk products intolerance) at the dose of 250-500 mg (bottle contents) a day no less than 10 days. In colitis, dysbacteriosis microclysters after cleansing enema can be prescribed: per 5ml in 5 days (temperature 37°C). Microclyster application hastens recovery, particularly, in hyperacidity of gastric juice, because in such cases part of lactobacteria perish in stomach, and their introduction immediately per rectum promotes faster recovery. Microclysters should not be prescribed to patients with non-specific ulcerative colitis since rectum mucous is strongly erosive. At the same time, taking of “Narine” peroral by patients with non-specific ulcerative colitis exerts, inevitably, favorable action.

In bacterial conjunctivitis and eye mucous inflammation provoked by fungi, mucous can be cleansed with newly fermented product “Narine” several times a day, not forgetting of taking it per os.

On the clinical basis of the Department of Pediatrics No.2 of the Yerevan Medical Institute n.a. M.Heratsi, in Children’s Clinical Hospital No.3, Yerevan, the product of Lactobacteria metabolism, strain 317/402 “Narine” in the form of lyophilized drug obtained by collaborators of the laboratory of

fermentative microorganisms under the Institute of Microbiology NAS Armenia, was used aimed at prevention and treatment of intestinal dysbacteriosis in newborns and children of early age (96).

163 children at the age from 2 days to 1 year were under observation, out of them 68 newborns (35 mature and 33 premature) and 95 infants (from 1 month to 1 year). By sex: 89 girls and 74 boys. They were divided into 3 groups:

I group - 35 mature newborns at the age of 2 to 15 days.

II group – 33 premature newborns at the age of 5 to 23 days (out of them of the I degree – 13, II- 15, III – 5).

III group – 95 infants at the age of 1 to 12 months, out of them 36 infants at the age of 1-3 months, 21 infants at the age of 3-6 months, and 38 infants at the age of 6-12 months.

Based on clinico-laboratory, instrumental and roentgenologic data 74 (45%) were diagnosed acute respiratory viral infection, 38 (23%) - pneumonia, 15 (9%) – sepsis, and 36 (23%) had other diagnoses (localized purulent-septic infection, ante- and postnatal hypoxia, conjugated hepatitis, hemolytic disease of newborn, hypoxic encephalopathy, etc.).

The control group included 135 infants of the corresponding age in all indices comparable with the main group, getting the similar etiopathogenetic therapy with other probiotics.

Newborns and infants, especially with a heightened pre-morbid background (exudative diathesis, anemia, rachitis, hypotrophy) are the most vulnerable to dysbacteriosis, however, intestinal dysfunctions in patients under examination, as well as stools frequency in the course of disease varied from 1-2 days to 7-10 days depending on duration peculiarities of the main disease in children of different age groups. By its nature stools was liquid, yellowish-green with mucus. Terms of stools normalization depended on clinics and course of the disease, as well as duration of the drug administration.

The dry drug was prescribed against a background of complex (etiotropic and pathogenic) therapy of the main disease from the very first day of hospital admittance. The drug is taken per os at the individual dosage depending on the purpose (preventive or curative) 3 capsules a day in preventive purposes and 5 capsules in curative. The drug is taken 15-20 minutes before meals within 5-14 days. While taking the drug side effects, complications, intestinal syndrome aggravation have not been observed.

The drug efficiency was determined clinically and by qualitative-quantitative study of the intestine microbial landscape. As compared with the control group children who took “Narine” displayed fast improvement of the general condition, short terms of stools normalization, distinct weight gain, reduction in the terms of antibiotic therapy and stay in the hospital.

Irrespective of the established diagnosis changes in the intestinal microflora manifested themselves by revealing of conditionally pathogenic microbes, and sometimes even associations of 1-2 types at one time (staphylococcus, *Pseudomonas aeruginosa*, yeast-like fungi of the *Candida* type, lactose-negative bacteria of the intestinal family – proteus, *Klebsiella*, enterobacteria, etc.), in a number of cases reduction in the quantitative contents of normal *Escherichia coli* was observed, as well as pronounced inhibition of obligatory anaerobic microbes, both lactobacteria and bifidobacteria in more than 50% of children (of the main and control groups) as early as on the first days of stay in the hospital.

Favorable action of the drug has been proved by progress in the intestinal microflora after the carried out treatment. In the group of ill children who took the course of treatment with “Narine” drug dysbacteriosis was revealed in 32% of children, and in the control group in 52% that is probably connected with the intensive antibacterial therapy. The number of children with the normal microflora became twice as much after treatment with “Narine” drug.

Thus, the research carried out showed that inclusion of “Narine” drug into complex treatment of various diseases aimed at prevention and treatment of the intestinal dysbacteriosis in newborns and nursing children furthers more rapid recovery and improves the intestinal microflora. Simplicity and

accessibility of the elaborated procedure of the dry drug preparation allow to recommend it for broad implementation in health practice.

### **“Narine” in the 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 (37).

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 acido-lactic 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 dysbacterioses 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 drugs (S.D. Kim and coauthors, 1984; F.A. Tumanov and coauthors, 1985).

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. Disbacteriosis of the 1<sup>st</sup> degree (D<sub>1</sub>) being revealed in 68 (46.6%) of patients, dysbacteriosis of the 2<sup>nd</sup> degree (D<sub>2</sub>) – in 59 (39.6%), and dysbacteriosis of the 3<sup>rd</sup> degree (D<sub>3</sub>) – 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 80-100T and was easily taken by patients. The 2<sup>nd</sup> 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 in patients who took fermented milk mixture “NARINE” peroral it was revealed that intestinal dysbacteriosis observed in 54 (80.6%) patients in the group was completely corrected in 40 (74.1%) patients. D<sub>1</sub> observed in 24 (44.4%) patients was completely corrected in all of them in 6-8 days on the average. Out of 23 (42.6%) patients with D<sub>2</sub> microflora was utterly normalized on the average in 8-10 days in 16 patients; in the rest of cases D<sub>2</sub> transformed into D<sub>1</sub>. Dysbacteriosis of the 3<sup>rd</sup> degree observed in 7 (13%) patients failed to be completely corrected in anyone, 3 of them being ill with a serious form of diabetes mellitus as an accompanying disease.

Upon bacteriological examination of the patients' first stools on the 3,4<sup>th</sup> 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, 9<sup>th</sup> 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 pathogens of pyo-inflammatory complications after operations on the large intestine. Use of "NARINE" has decreased a number 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 (51). 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 (97). This provision is confirmed by the data about the fact that among 180 chemical agents (unconditional, possible, and probable carcinogenes for man) more than 90% are able to injure DNA of cells (Bartsch, Malaveille, 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 antimutagens, which are able to reduce the induced by various medium factors level of mutational changes (Gebhart, Arytyunyan, 1990. Talalay, 1996. Wattenberg, 1996). One of the main requirements to the compounds used for cancer chemoprophylaxis is availability of antimutagenous 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 fungous 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 (52, 53). 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 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 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  $-23,3 \pm 1,8$ ; positive control (intestinal cells + carcinogen)  $-117,3 \pm 6,5$ ; lactobacilli + MNNG  $-58,8 \pm 2,7$ . Lactobacilli reduced for sure the genotoxic effect of carcinogen on rats’ cells by 50% as compared with positive control. This proves that the lactobacilli are able to connect metabolites of carcinogens. The other possible mechanism of anticlastogenic action of “Narine” lactobacilli is their interferonogenic activity (Kita et al., 1986), as interferon inductors have antimutagenous activity (Zolotareva, et al., 1993).

The research of antitumor action of “Narine” lactobacilli was carried out on rats with re-inoculated tumors – carcinosarcoma Walker (CSW), Peis’s lymphosarcoma (PLS) and ovary cancer cells (OYa) (54). The results of experiments carried out on 80 rats of Vester line showed that introduction of 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 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 lactobacilli in later terms, as well as introduction of killed lactobacilli did no exert antitumor effect.



The combined action of “Narine” lactobacilli and chemodrugs on mean life span of rats with re-inoculated tumors CSW, PLS and OYa was studied (55). Lactobacilli were introduced to rats intragastric on the 2<sup>nd</sup>, 3<sup>rd</sup> 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 25mg/kg three times a day; natulan – 10mg/kg 4 times a day; thioTEF – 1mg/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 lactobacilli and chemodrugs (10 animals) for certain exceeded mean life span of animals that got only chemodrugs. Lactobacilli decreased tumor mass by 32.4%, natulan - by 44,6%, both factors together – by 67,6%. Combination of antibiotics with lactobacilli increased IT as much as 57,3%.

Thus the results of experiments carried out on 210 rats demonstrated that 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” lactobacilli protected DNA cells of rats from genotoxic effect of carcinogens, were able to strengthen antitumor effect of chemodrugs widely used in clinical oncology (cyclophosphanum, 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 vaginorrhaphy 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 extragenital 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-inflammatory effect [87, 88]. Besides, acido-lactic Lactobacilli acidophilus by their morphological and biochemical properties are identical with vaginal Bacillus Doderlein, and favorably affecting the bacterial flora, physiologically recover the natural microbiocenosis of the vagina [86].

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-K” drug after extensive onco- genital operations.

With a view to study the effect of “Narine-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 general characteristic of clinical material is presented in Table 14.

**Table 14**

General characteristic of sick	Number
Age	
Under 40	29
40-60 years	55
60 and more	16
Diagnosis	
Cancer of the body of the uterus	40
Atypical hyperplasia of endometrium	40
Cancer of the cervix of the uterus	20
Accompanying gynecologic pathology	
Uterus myoma	35
Endometriosis	20
Ovarian cyst	15
Accompanying extragenital pathology	
Available	43
Not available	57

The examined patients' contingent was divided into two clinical groups. In the first group (n = 50) beginning from the third day after operation "Narine'K" drug was introduced to the vagina within 25 days, every day in the amount of 5ml, 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 [85].

Clinical characteristic of the vaginal stump healing process in both groups is given in Table 15.

**Table 15**

Criteria of the wound process course	1 <sup>st</sup> group (n=50) n, %	2 <sup>nd</sup> group (n=50) n, %
Time of perifocal inflammatory reaction cupping		

Up to 5 days	37 (74%)	16 (32%)
5-7 days	13 (26%)	21 (42%)
8-9 days	-	13 (26%)
<b>Characteristic of the wound discharge</b>		
Suppurative	7 (14%)	29 (50%)
Serous	43 (86%)	21 (42%)
<b>Time of granulation appearance</b>		
Up to 10 days	35 (70%)	11 (22%)
10-14 days	15 (30%)	17 (34%)
<b>Complete wound healing</b>		
Up to 25 days	33 (66%)	3 (6%)
25-35 days	11 (22%)	11 (22%)
35-45 days	6 (12%)	20 (40%)

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<sup>th</sup> days after operation, whereas in women who got “Narine-K” the given index made up 8-11 days.

Dynamics of cytograms from the wound of the vagina stump presented in Figure 3 obviously demonstrates positive effect of the drug on the course of the wound process.

### **Cytogram type**

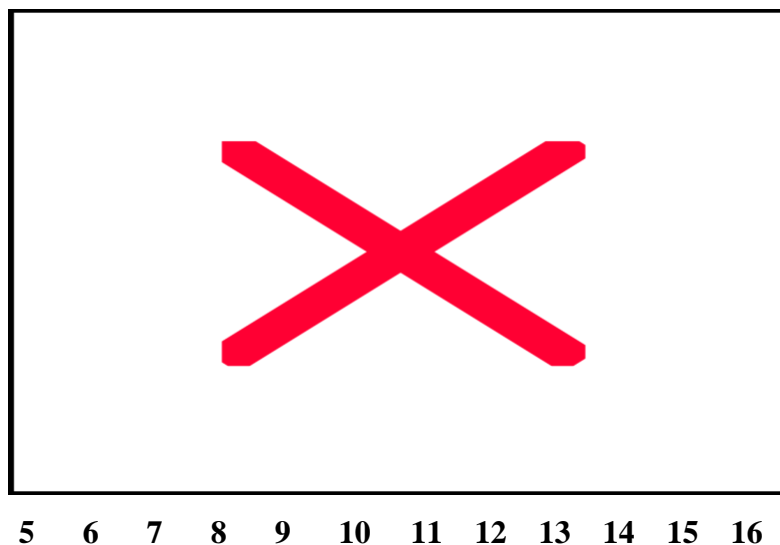
**Degenerative**

**Regenerative-Inflammatory**

**Inflammatory-Regenerative**

**Regenerative**

**Days after operation**



**Fig.3. Cytogram dynamics from the wound of the vagina stump**

Thus regenerative-inflammatory type of the cytogram signifying favorable course of the wound process in patients of the 1<sup>st</sup> 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<sup>st</sup> group complete wound healing on the 25<sup>th</sup> 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.

### **Use of “Narine” in antibiotic therapy**

Dysbacteriosis prophylaxis is much more expedient and easier than its treatment.

That is why in all potentially dangerous cases it is recommended 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 intestinal microflora (31). 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 euflorescence 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 (1989).

I degree: increase of the number of conditionally pathogenic microorganisms against high level of bifido-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<sup>st</sup> 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<sup>nd</sup> 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<sup>nd</sup> group and in 10 patients of the 1<sup>st</sup> group (Ia subgroup) DI was not revealed, the rest 9 patients of the 1<sup>st</sup> group (Ib subgroup) had DI of the 1<sup>st</sup> degree.

#### *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<sup>nd</sup> group 8 developed DI of the 1<sup>st</sup> degree, and one – DI of the 2<sup>nd</sup> 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 antimycotic drugs (in particular, Nystatin) fails not only to prevent decrease of the amount of normal microflora, but also rise of conditionally pathogenic fungus-free microflora in antibacterial therapy.

### **“Narine” in treatment of insulin-dependent diabetes mellitus**

On the clinical basis of the Department of Endocrinology of Children’s Specialized Clinical Hospital No. 14, Kiev, the research of acido-lactic bacteria 317/402 “Narine” in treatment of children with severe forms of insulin-dependent diabetes mellitus has been carried out (38).

16 children were under examination and divided into two groups: I group involved 8 children at the age of 5-10 years with diabetes mellitus revealed for the first time. This group got only the course of insulin treatment.

II group, the control group, included 8 children at the age of 5-10 years diagnosed diabetes mellitus for the first time. Patients of this group took the course of insulin treatment. Simultaneously they got lyophilized drug “Narine” 3 times a day 20-30 minutes before a meal. The total daily dosage made up 5g of the drug per a child.

The course of treatment with “Narine” drug comprised 15 days. During this period of time patients of both groups underwent every day examination for determination of acetone bodies and the level of glycemia in the blood and urine. The patients’ general state was also registered.

In the examined patients of both groups before the course of treatment the level of glycemia was revealed to be 12-20 mm/l, glucosuria – 4-7. The beginning of laboratory compensation in children of the control group was observed on 3-4 days of the treatment course, in those of group I – on 5-7 days. The negative reaction to ketone bodies in patients taking “Narine” drug was revealed 2-3 days earlier than that in the I<sup>st</sup> group.

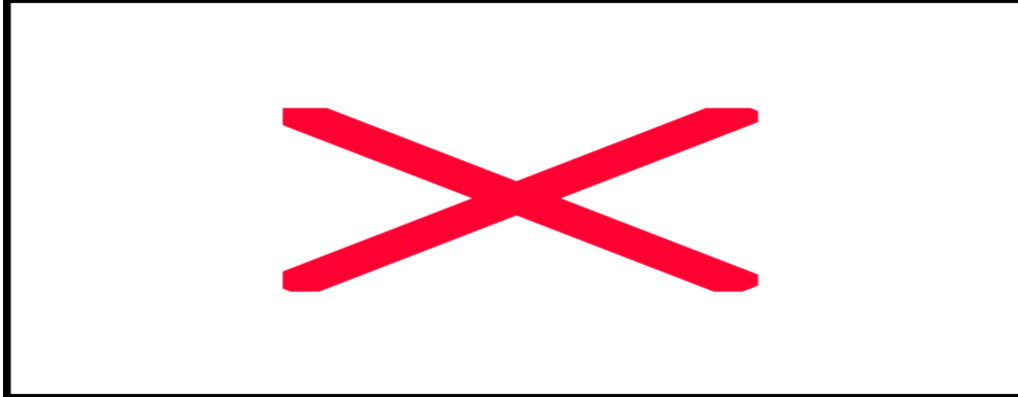
Stable clinico-laboratory diagnosed compensation appeared in patients of group I on the 14-15 days of treatment. In the II group who got the treatment course with “Narine” drug parallel with insulin, on the 10-12 days the level of glucose in the blood equaled 6-8 mm/l, glucosuria less than 15 that proved that clinico-laboratory compensation began in this group of children 2-3 days earlier, the time of ketoacidosis removal was also 1-2 days speeded up.

Use of “Narine” drug favorably affected the general condition of patients. No complaints or side effects were observed. While “Narine” administration in case of diabetes aggravated by allergy stable compensation was achieved 2-3 days earlier than in usual diabetes.

Thus, the research carried out showed that administration of the lyophilized drug “Narine” in complex with other methods of treatment favorably affected the general state of patients and allowed to speed up beginning of clinico-laboratory compensation in cases of diabetes revealed for the first time and diabetes aggravated by allergy towards insulin (38).

### **“Narine” and allergy**

Allergic diseases, in many scientists’ opinion will become one of the most spread and almost insoluble pathologies in the XXI century. Recent researches have finally confirmed the fact of brain



allergy, which is associated with depression, forgetfulness, and memory deficiency, sharp groundless changes of the mood and sudden behavioral reactions. Pay attention that all cited pathologies are widely spread in modern society and present almost insolvable problem for medicine.

The reason of allergy development is, on the one hand, disturbance of the organism reactivity and, on the other hand, is an excessive entering of allergen into an organism. Often as the source of allergen penetration into an organism appears the gastroenteric tract. Excessive formation of toxic products in the intestine during dysbacteriosis and rise of the intestine wall permeability results in abundant absorption of these products into blood and allergization of the organism. It is necessary to mention the fact of disturbance of immune reactivity in the intestinal dysbacteriosis. In patients with various forms of allergic diseases disturbance of the intestinal microflora is frequently revealed. Use of “Narine” for dysbacteriosis correction led in a number of cases to disappearance or significant drop in allergy manifestations.

The properties of acidophilic lactobacterium to decrease formation of histamine from food histidine, reduce permeability of the intestinal wall for toxic and allergic products, increase detoxicational function of the liver, exert immunocorrective action on the organism, together with frequent revealing of dysbacteriosis in persons with allergic diseases, served the basis for using the “Narine” drug by those with atopic skin diseases and bronchial asthma. The obtained results showed that the “Narine” drug favored disappearance or significant softening of allergic symptoms in persons with this pathology. Similar results, namely, stable remission or lessening of attacks have been obtained in treatment of patients suffering from periodic disease.

Studies have been carried out at the Yerevan Republican Children’s Clinical Hospital: children under 3 took 1 capsule once a day 20 minutes before a meal; children over 3 took a daily dose of 2 capsules. All in all 369 children were examined, 185 out of them took “NARINE” and the rest 184 children in the control group did not get “Narine”. In two groups the allergic manifestations were the following: in the form of dermal manifestations of exudative diathesis in 53.6%, infantile eczema – in 4.2%, hives and Quincke’s edema – in 42.2% of children. Upon introduction of “NARINE” positive results were achieved in 52.8% of cases, satisfactory – in 30% of cases, and unsatisfactory – in 17.1% of cases, whereas in the control group good and excellent results were in 40.6% of cases, satisfactory in 35.3%, and unsatisfactory – in 24.1% of cases. Upon “NARINE” introduction no side effects have been registered. The data obtained prove high clinical effect of “NARINE”.

## **“Narine” and immunology**

### **Interferon output**

It has already been known that the ability to produce interferon in cancer patients is significantly reduced as compared with a normal organism. If a healthy person produces interferon in the amount of 5000 units, in a patient with carcinoma of the stomach, liver, lungs, tongue, large intestine or esophagus, as well as in case of leukemia the amount of interferon produced is only 1/5 of the norm.

- 1 – lymphoma, leukemia
- 2 – tongue cancer
- 3 - large intestine cancer
- 4 – stomach cancer
- 5 – hepatoma
- 6 – cancer of another location
- 7 – norm (control)

Studies of interferon produce in healthy people showed that it varied in different people: high in ones, and low in others. After the age of 40 interferon produce significantly decreases (cancer age).

**Table 16**

*$\alpha$ -interferon produce in healthy subjects*

Age	$\alpha$ - interferon				
	<2000(%)	2000-2999(%)	3000-6999(%)	7000-8999(%)	9000(%)
10-19	0/35 (0,0)	0/35 (0,0)	34/35 (97,1)	1/35 (2,9)	0/35 (0,0)
20-29	0/43 (0,0)	1/43 (2,3)	36/43 (2,3)	5/43 (11,6)	1/43 (2,3)
30-39	0/42 (0,0)	2/42 (4,8)	33/42 (78,6)	5/42 (11,9)	2/42 (4,8)
40-49	3/76 (3,9)	5/76 (6,6)	56/76 (73,7)	9/76 (11,8)	3/78 (3,9)
50-59	5/115 (4,3)	18/115 (15,7)	77/115 (67,0)	13/115 (11,3)	2/115 (1,7)
60-69	5/116 (4,7)	16/106 (15,1)	64/106 (60,4)	13/106 (12,3)	8/108 (7,5)
70-79	4/91 (4,4)	5/91 (5,5)	71/91 (78,0)	9/91 (9,9)	2/91 (2,2)
80-89	0/23 (0,0)	2/23 (8,6)	18/23 (78,3)	2/23 (8,7)	1/23 (4,3)
Total	17/531 (3,2)	19/531 (9,2)	389/531 (73,3)	57/531 (10,7)	19/531 (3,6)

**Table 17**

*$\gamma$ - interferon produce in healthy subjects*

Age	$\gamma$ - interferon				
	10(%)	10-19(%)	20-69(%)	70-89(%)	90(%)

<b>10-19</b>	<b>0/23 (0,0)</b>	<b>0/23 (0,0)</b>	<b>20/23 (87,0)</b>	<b>3/23 (13,0)</b>	<b>0/23 (0,0)</b>
<b>20-29</b>	<b>0/31 (0,0)</b>	<b>3/31 (9,7)</b>	<b>24/31 (77,4)</b>	<b>1/31 (3,2)</b>	<b>3/31 (9,7)</b>
<b>30-39</b>	<b>0/59 (0,0)</b>	<b>11/59 (18,6)</b>	<b>32/59 (54,2)</b>	<b>12/59 (20,3)</b>	<b>4/59 (6,8)</b>
<b>40-49</b>	<b>1/108 (0,9)</b>	<b>9/108 (8,7)</b>	<b>76/108 (70,4)</b>	<b>14/108 (13,0)</b>	<b>8/108 (7,4)</b>
<b>50-59</b>	<b>7/93 (7,5)</b>	<b>19/93 (9,7)</b>	<b>68/93 (73,1)</b>	<b>5/93 (5,4)</b>	<b>4/93 (4,3)</b>
<b>60-69</b>	<b>6/23 (26,1)</b>	<b>4/23 (17,4)</b>	<b>11/23 (47,8)</b>	<b>2/23 (8,7)</b>	<b>0/23 (0,0)</b>
<b>70-79</b>	<b>3/14 (21,4)</b>	<b>3/14 (21,4)</b>	<b>8/14 (57,1)</b>	<b>0/14 (0,0)</b>	<b>0/14 (0,0)</b>
<b>Total</b>	<b>17/351 (4,8)</b>	<b>39/351 (11,1)</b>	<b>239/351 (68,1)</b>	<b>37/351 (10,5)</b>	<b>19/351 (5,4)</b>

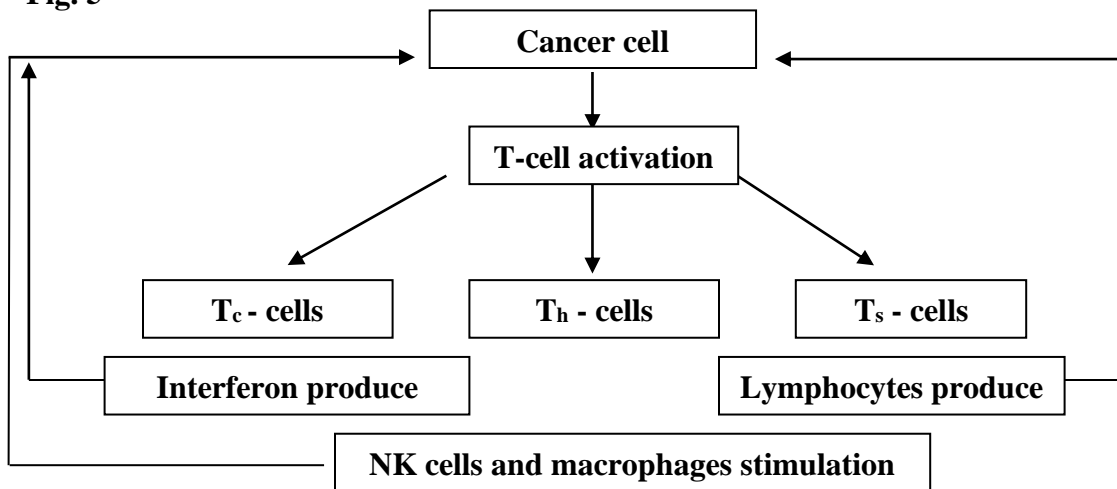
The connection between reduction of interferon output and carcinogenesis is as follows:

- 1) Experiments carried out on animals for a year showed that interferon deficiency promoted cancer formation and its metastatic spreading.
- 2) Interferon produce is decreased in cancer patients.
- 3) Cases of drop of interferon produce increase with the age.

These conclusions point to the connection between interferon produce and carcinogenesis. Teramatsu's group working on the project "Strategy of struggle with cancer" established under the Ministry of Social Maintenance to solve the problem of carcinomatous degeneration and methods of prophylaxis has noted drop in produce of interferon in cancer patients.

When carcinogenesis the human immune system is subjected to an attack on the part of malignant cells, as shown below:

**Fig. 5**



The system participating in interferon synthesis and activated by NK cells is called interferon NK-system.

In 3 years 1000 patients with chronic diseases of the respiratory tract have been examined on the subject of interferon produce. Out of 1000 cases 16 cases of cancer were revealed. 5 from 16 exhibited very low level of interferon produce, lower than 2000 units, in 4 patients the level was as low as 2000-2999 units, and in 6 patients the level of interferon was abnormal. Thus, low or abnormal level of interferon was revealed in 15 out of 16 cancer cases – i.e. in 94%.



Table 18

*Decrease of interferon produce in carcinogenesis*

	Titer of $\alpha$ - interferon					Total
	<2000	3000	6999	8999	Norm	
<b>Sample No</b>	<b>5</b>	<b>4</b>	<b>1</b>	<b>0</b>	<b>6</b>	<b>16</b>
<b>%</b>	<b>(31,1)</b>	<b>(25,0)</b>	<b>(6,3)</b>	<b>(0,0)</b>	<b>(37,5)</b>	<b>(100,0)</b>
<b>Tongue cancer</b>	<b>4</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>5</b>	<b>11</b>
<b>Stomach cancer</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>3</b>
<b>Esophagus cancer</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2</b>

Decrease in interferon produce was noted not only in cancer patients but also in patients with various chronic diseases whose resistance (resistivity) was diminished (in patients with liver diseases, diabetes mellitus, and chronic renal insufficiency).

Japanese scientists (16,17,18,19,20) have carried out experiments on stimulation of interferon produce by fermented dairy product "NARINE", capsules "NARINE" and Kikurage polysaccharide, which is decoction of Kikurage (Kikurage – is a species of fungus that for a long time has been used in China and Japan as a product of health or as a Chinese medicinal herb).

### 1. Induction of interferon *in vitro* by means of "Narine" bacteria

Interferon produce was noted after addition of "Narine" bacteria *in vitro* immediately into the blood or lymphocyte culture. Thus "Narine" bacteria were found to act as interferon inductor.

Table 19

*IFN produce under the influence of "NARINE" in vitro*

Concentration (mg/ml)	IFN – titer in blood	IFN – titer in lymph
<b>2000</b>	<b>184</b>	<b>&lt;10</b>
<b>200</b>	<b>242</b>	<b>343</b>
<b>20</b>	<b>&lt;10</b>	<b>306</b>
<b>2</b>	<b>&lt;10</b>	<b>136</b>
<b>0.2</b>	<b>&lt;10</b>	<b>&lt;10</b>

<b>0.02</b>	<b>&lt;10</b>	<b>&lt;10</b>
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### 1. Change of interferon produce after taking fermented milk “NARINE”.

Three volunteers were given “NARINE” per 20g a day after each dinner within 2 weeks in succession and the change of interferon was checked. Rapid increase of  $\alpha$ -interferon was detected, while  $\gamma$ -interferon increased significantly and the effect appeared to stay longer.

### 2. Change of NK activity after taking fermented milk “NARINE”.

Three volunteers were given “NARINE” per 20g a day after each dinner within 2 weeks in succession and the change of NK activity was checked. Though NK activity in different individuals varied the change of NK activity displayed the tendency towards increase in all cases.

1. “NARINE” capsules – is functional food increasing produce of interferon. “NARINE” capsules were studied on volunteers’ groups.

Group A was indicated “NARINE” 2 capsules a day, and group B – 6 capsules a day for 4 weeks in succession. Changes of NK activity and interferon produce were controlled.

a) Change in interferon produce was noted in both groups. Average indices of interferon in group A was 3767 units before taking “NARINE” and 5479 units after taking “NARINE”. The difference was considerable. Average interferon indices in group B were 2234 units before, and 4119 after taking “NARINE”. The difference was considerable.

b) Change in NK activity. Considerable change of NK activity was fixed in 4 out of 10 those examined in group A, and in 4 out of 9 from group B. Average indices of NK activity increased from 0.4% before taking “NARINE” tablets to 14.1% after taking “NARINE” in group A, and from 11.7% to 16.0% in group B after taking “NARINE”. Significant difference was detected in the 2<sup>nd</sup> group.

## **Postnatal mastitis. Prophylaxis of infectious diseases of staphylococcic etiology**

In many clinics healthy carriage of hospital strains of staphylococci 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 staphylococcic etiology in newborns (21). Practice has shown that newborns are especially vulneravle to staphylococcic infection, that can be manifested both in the form of carriage, and disease itself. One of the main methods of struggle against staphylococcus aureus carriage is sanitation of the main biotope of anterior sections of nasal cavity. Currently to sanitare carriers antibiotics, 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 staphylococci 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 502 A was put on a child's mucous of a nose. Staphylococcus strain 502 A 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 502 A (22).

And in case of using strain of acido-lactic bacteria 317/402 “NARINE” as a blocking microbe the effect was evident (23).

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

For the first time physiological sanitation procedure of carriers of staphylococci 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 staphylococci 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 staphylococci aureus lysed by phage 83 A (83,3%) (by which 59,63% of newborns are also colonized) prevail.

To determine the level of carriage of staphylococci 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 staphylococci 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 staphylococci aureus, 168 newborns, mammary glands of 164 puerperas have been treated.

Identification of the isolated staphylococci 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 staphylococci 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 staphylococci aureus. 968 analyses in vitro have been carried out.

As the result of the research of antagonism between “Narine” acido-lactic bacteria and staphylococci 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 staphylococci 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 staphylococci 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 2<sup>nd</sup> day of their lives children’s nasal cavity began to be populated by acido-lactic bacteria (24). The drug (1 capsule per 1 teaspoon of boiled water) is sterilely 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 3<sup>rd</sup> 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 7<sup>th</sup> 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 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 7<sup>th</sup> 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 puerperas 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 .

## **Efficiency estimation**

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 cleansing of puerperas’ mammary glands (57). 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 puerperas' 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 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 nipple 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 staphylococci 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 staphylococcal and other enteritis. Nipple treatment after nursing was aimed at destruction of 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<sup>th</sup> days of stay in the maternity hospital almost total dissemination of nipples took place (98%). Inoculation made up: of staphylococci aureus – 25,7%, of staphylococci epidermidis – 37%, of 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% - staphylococci epidermidis was isolated, in 47% - staphylococci saprophytic, and only in 4,1% - 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 (Fig. 8). Dissemination of mammary glands with staphylococci 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<sup>th</sup> 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 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 staphylococci aureus cells.

2. Ultrastructural aspect of the “Narine” drug mechanism of action on 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 staphylococci aureus in 73.68% of cases, 40.5% of women being discharged from a maternity hospital with nipple cracks (infection aetium) 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 staphylococci 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 staphylococci 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.

## **APPLICATION OF ACIDO-LACTIC BACTERIA “NARINE” 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 4<sup>th</sup> 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 1<sup>st</sup> 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 4<sup>th</sup> to the 2<sup>nd</sup> degree. In pregnant women reduction of inoculation made up 75.8%.

Use of vaginal suppositories (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, physiologically regenerates vaginal natural medium with normalization of vaginal biocenosis.

### **Prophylaxis and treatment of postoperative stump inflammations with "Narine" drug in oncogynecologic patients**

In modern oncogynecologic practice surgical intervention as an independent method of treatment is employed very rarely though ranks high. In an overwhelming majority of cases malignant tumor therapy requires complex approach implying parallel or successive application of two or several kinds of influence on the tumoral process [75,76]. In particular, while treating carcinoma of uterine cervix and body the most widely used is the combined method including operation with subsequent radiotherapy carried out on the second stage of treatment.

Radiotherapy is performed by the combined method the component of which is intracavitary gamma-therapy with bringing the source of radiation immediately to the cupula of vaginal stump. Presence of inflammatory processes in the postoperative wound of vaginal stump can lead to delay in the terms of transition to intracavitary gamma-therapy, and in some cases to forced reduction of the total focal dose of radiation that adversely affects the remote results of treatment.

### **Administration of "Narine" in 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 microorganisms (39).

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 automicroflora – coliform bacteria, Proteus, staphylococci - occur is rather significant: from small  $17,3 \times 10^{-4}$  cells/kg (enterococcus) to  $2348 \times 10^{-4}$  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 cenosis 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 – Coliflora, Smoflora, and Simbioflora. 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 indigeneous 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 Chernobil 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 5,0g a day within 15-20 days and more upon physician's prescription. The patients' intestinal microflora is studied before and after treatment on the 15<sup>th</sup> and 20<sup>th</sup> days. While studying a visual and quantitative composition of the intestinal microflora, methodical recommendations "Bacteriological diagnostics of the intestinal dysbacteriosis" (Epshtein-Litvak R.V., Vil'shanovskaya F.L., 1977) were taken into account.

The examined patients before treatment displayed anaerobic microflora of bifidobacteria and lactobacteria (less than  $10^8$  in 1g of feces) in 100% of cases, decrease in *Escherichia coli* to  $10^4 - 10^3$  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, *Klebsiella*, 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%) D<sub>2</sub> transformed to D<sub>1</sub>, moreover, decrease in concentration of conditionally pathogenic microflora was observed (Klebsiella, enterobacter, lactosenegative Escherichia, hemolytic Escherichia) to 10<sup>2</sup> – 10<sup>4</sup> 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 D<sub>1</sub>, positive effect was reached on the 15-20<sup>th</sup> days, and in 16 patients (36,3%) with D<sub>2</sub> - on the 25-30<sup>th</sup> 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 D<sub>1</sub>, dysbacteriosis degree did not change in the process of treatment.

In the comparison group where “Lactobacterin” was prescribed, from 10 patients 7 (70%) revealed D<sub>1</sub>, and 3 (30%) – D<sub>2</sub>. Positive dynamics in patients of this group was detected on the 30<sup>th</sup> day in 3 patients (30%) with D<sub>1</sub> and in one patient (10%) with D<sub>2</sub>. 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 D<sub>2</sub> on the 15<sup>th</sup> day of treatment drop of conditionally pathogenic microflora was observed, in particular, of Proteus mirabilis, enterobacter, Klebsiella to 10<sup>3</sup> – 10<sup>4</sup>, increase of valuable Escherichia coli as much as 10<sup>5</sup> – 10<sup>6</sup>, but no recovery of bifidobacteria or lactobacteria was observed, i.e. D<sub>2</sub> transformed to D<sub>1</sub>. Correction of dysbacteriosis was revealed in these patients on the 20<sup>th</sup> day of research. In 8 patients (40%) with D<sub>1</sub> positive effect was detected on the 15-20<sup>th</sup> days, and in 2 patients (10%) with D<sub>1</sub> 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 lyophilized 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 (49).

### **Joint administration of “Narine” and gentamycin in combined radiation-thermal injury (58)**

One of the main factors determining severity of combined radiation-thermal injury (CRTI) is decrease of the organism resistance to infection. Endogenous infection is one of the factors heightening the course of the combined radiation-thermal injury when combined influence of ionizing radiation at minimum lethal doses with non-lethal burn (59,60,61). It has been established that within the first four

days after CRTI, permeability of the small intestine mucous membrane increased for bacterial endotoxins, activity of mechanisms of “local” colonization resistance decreased, conditions for adhesion, reproduction and translocation of the intestinal Gram-negative microbes to the portal vein and system blood flow were established. By the beginning of the third period of CRTI clinical flow in conditions of sharply pronounced leukopenia, destruction of lymphoid organs and deep immunodepression, and breakdown of pool of functionally active tissue macrophages the organism becomes practically unprotected before invasion of Gram-negative intestinal microbes and increasing microbial load on the part of burn wound (62). Therefore, search for effective remedies of endogenous infection treatment in CRTI and increase of the level of the organism immunological reactivity under these conditions belong to the most urgent problems of radiation medicine.

As prerequisites for carrying out these investigations appeared the data (63) according to which lactobacilli reduce severity of radiation injury through normalizing influence of microbes of acidolactic fermentation on the intestinal microflora of irradiated animals, and gentamycin prevents microbial dissemination of the small intestine.

Experiments were carried out on 310 white mongrel rats with the mass of 160-180g. The animals were subjected to general momentary even irradiation on RUM-17 apparatus at the dose of 4,4g. III B degree burn of 15% of the body surface was inflicted immediately after irradiation by the contact method. Animals were divided into 8 groups. Animals of the I group got fermented milk product, of the II group – gentamycin, III group – gentamycin + fermented milk product, IV group – physiologic salt solution, V group - fermented milk product + CRTI + fermented milk product, VI group - fermented milk product + CRTI + gentamycin, VII group - fermented milk product + CRTI + fermented milk product + gentamycin, VIII group - fermented milk product + CRTI + physiologic salt solution. The therapeutic dose of lactobacteria comprised  $75 \times 10^8$  cells. Efficiency of “Narine” administration was estimated by indices of peripheric blood, contents of complement in the blood serum, phagocytic activity of the peripheric blood neutrophiles, by mass and cellularity of the spleen, investigations of the contents of the small and large intestine for revealing bacteriological signs of dysbacteriosis.

Results of the research showed that in peroral simultaneous use of fermented milk product and gentamycin (III group) increase of mass and cellularity of the spleen was noted. The increase was almost twice as much as compared with the control (I group) In animals with CRTI who got complex treatment the tendency towards increase of phagocytic activity was marked.

Administration of gentamycin in irradiated rats was established to aggravate the disturbed microbial biocenosis characterized by increase of the amount of enterobacteria in the large intestine contents.

While studying microflora in 1g of the intestine contents of animals with CRTI who got complex treatment, increase of *Escherichia coli* in the large intestine up to  $10^7$ , increase of anaerobic microflora up to  $10^8$  and decrease of aerobic conditionally pathogenic microflora was established. In the small intestine *Escherichia coli*  $10^4$  was revealed and the process of dissemination by other bacteria was practically absent.

Standard “Lactobacterin” practically did not affect staphylococci and did not prevent their contamination to the jejunum whereas “Narine” lactobacteria completely suppressed staphylococci growth on the 15<sup>th</sup> day. Positive action of “Narine” also manifested itself on *Clostridium* exerting destructive action on them as early as on the 22<sup>nd</sup> day.

Thus, administration of “Narine” jointly with gentamycin effectively decreases the level of contamination of jejunum with *Enterococcus*, *Clostridium*, *staphylococci aureus* and completely normalizes microflora of the large intestine thus facilitating the course of radiation sickness.

## OMPHALITIS

In the department of infectious diseases of the Yerevan Medical University, Research Institute of Epidemiology after N.Ph. Gamalei under the Academy of Medical Sciences, USSR clinical trials of “NARINE” have been carried out aimed at treatment and prophylaxis of omphalitis. Proceeding from the fact that in an umbilical small wound there are no such preventive barriers as skin and mucous membrane it was decided to use in the 1<sup>st</sup> experimental group for omphalitis prophylaxis metabolic products of the mentioned strain of acido-lactic bacteria, conditionally called “NARINE-f”. This drug was used upon permit given by the Academic Medical Council under the Ministry of Health of Armenia. One of unconventional and efficient methods of omphalitis prophylaxis is also application of home film-forming drug “Liphuzol”, which was used in the 2<sup>nd</sup> experimental group.

Three groups of newborns have been examined: control, first and second experimental. Treatment of newborns’ omphalitic bed in the control group (162 newborns) was carried out by the conventional method, namely, before and after decidualization of funic remnant it was treated with 70°C alcohol and manganese solution.

The 1<sup>st</sup> experimental group included 179 newborns. Omphalic bed treatment included:

- a) treatment with 70° alcohol;
- b) treatment with sterile tampon, medicated with “NARINE-f” . After decidualization of funic remnant “NARINE-f” was dropped into umbilical wound 6 times a day;

The 2<sup>nd</sup> experimental group comprised 149 newborns. Omphalic bed treatment included:

- a) treatment with 70° alcohol
- b) covering of funic remnant with 3 layers of “Liphuzol”. The drug was dispersed from the distance 10-15 cm off the area of treatment in 1-2- seconds, 3 times with the intervals of 30 seconds. The same procedure was repeated after decidualization of funic remnant.

Material for bacteriological examination was taken with sterile cotton wool tampons.

Epidemiological observations of newborns were carried out over 2 months after discharge from a maternity hospital. Statistical processing of the results obtained was performed according to Student.

Analysis of the results of newborns’ omphalic bed microbiological examinations in the control group showed that in an overwhelming majority of cases staphylococci (85.6%) were isolated and in 14.4% of cases other microorganisms (Escherichia coli, streptococci, fungi of Candidi species) were isolated. In staphylococci - aureus species prevailed (64.2%), staphylococci epidermidis were isolated in 16.1% of cases and staphylococci saprophytic in 5.3% of cases.

In the 1<sup>st</sup> experimental group of newborns the total dissemination made up 49.1% (in 50.9% of cases microorganisms’ growth was not revealed).

Staphylococci were isolated in 40.0% of cases (aureus – in 14.1%, epidermal – in 18.4%, and saprophytic in 75.5% of cases). In 9.1% of cases growth of other representatives of conditionally pathogenic microflora was obtained.

In the 2<sup>nd</sup> experimental group dissemination of umbilical bed equaled 54.3%. Staphylococci were isolated in 41.5% of cases (aureus species in 4.9%, epidermal – in 16.8%, and saprophytic – in 19.8%).

Comparison of the presented data demonstrated that in both experimental groups there was observed evident reduction of total dissemination of an umbilical bed in newborns: with “NARINE-f” treatment cases reduced 2 times, and with “Liphuzol” treatment cases reduced 1.8 times. In the 1<sup>st</sup> experimental group inoculation of staphylococci aureus reduced 4.5 times and in the 2<sup>nd</sup> – 13.1 times.

Administration of drugs “NARINE” and “Liphuzol” accelerates decidualization of funic remnants. Upon umbilical wound healing while infants’ stay in a maternity hospital not a single case of inflammatory changes of the umbilical ring skin or signs of umbilical vessels inflammation in both experimental groups have been detected. Rapid reduction of umbilical wounds has been observed. Epidemiological observations after discharge from a maternity hospital showed that in the control

group umbilical wound was skinned over without complications in 46.6% of newborns (dry umbilicus), in the 1<sup>st</sup> experimental group – in 77%, and in the 2<sup>nd</sup> experimental group - in 81.1%. Wet umbilicus was registered correspondingly in 35%, 23%, 18,1% of newborns. Purulent omphalitis was registered in 8.3% of the control group, in 0.8% of the 2<sup>nd</sup> experimental group, and was not observed in the 1<sup>st</sup> experimental group. In both experimental groups no cases of sepsis were revealed, in the control group patients who developed such a disease made up 1,8%.

Thus, the data presented prove high efficiency of two unconventional methods of omphalitis prophylaxis, as compared with generally accepted. They manifested themselves both in decrease of umbilical bed dissemination and in morbidity with omphalitis and umbilical sepsis. Both methods of purulent omphalitis prophylaxis may be widely introduced into the practice of public health.

## **Prophylaxis of postoperative suppurations**

In present-day conditions the urgency of the problem of prevention and treatment of surgical infection is beyond doubt. It is no coincidence that this problem became the subject of special discussion at such representative forums as XXIV Congress of the International Surgeons' Society, XXIX, XXX, XXXI All-Union Surgeons' Congresses, I and II All-Union Conferences on wounds and wound infection.

In the recent decades for surgical clinics of all countries world-wide general and significant increase of the number of postoperative pyo-inflammatory complications manifested in the form of operative wound suppurations, pneumonia, thrombophlebitis, inflammatory diseases of the urinary tract, sepsis, etc. is typical (Vishnevskii A.A., Kostyuchenoc B.M., et al., 1974; Kuzin M.I., Kostyuchenoc B.M., 1981; Kurbangaleev S.M., 1985; Gostishev V.K., et al., 1986; Aglietti P. et al., 1974; Condon R.E. et al., 1983). In spite of elaboration and implementation of new methods of antisepsis, administration of many antibiotics, the amount of postoperative infectious complications does not decrease, but on the contrary, has the tendency towards further increase reaching the level of preantibiotic period (Prokhorov V.M., et al., 1976; Komarov B.D., 1977; Shaposhnikov Yu.G. et al., 1979; Struchkov V.I., et al., 1981; Scripnichenko D.F., 1983; Milani U., 1972; Ponkirov S., 1974; Giezhake F.W., 1975; Bernander S. et al., 1978). The quantity of severely proceeding infections, complicated forms of purulent diseases not yielding to treatment has also increased, transition of acute purulent processes to chronic ones has become more frequent (Belyakov V.D., et al., 1976; Kuzin M.I., Kostyuchenoc B.M., 1981; Struchkov V.I., 1983). Wide, unaimed, not well grounded administration of antibiotics with therapeutic, and often with preventive purposes has exerted mighty, selective influence on microflora and led to spreading of extremely stable towards antibacterial therapy highly virulent microbes ("hospital strains") (Akatov A.K., 1966; Marshak A.M., Kolker I.I., 1974; Proskurov V.A., 1974; Baroyan O.V., Porter D.R., 1975; Shelyakhovskii M.V., et al., 1977; Vishnevskii A.A. et al., 1979; Ivashkevich G.A., et al., 1979; Freedman L.R., 1978). Despite administration of a great number of new antibiotics their action in connection with growth of antibiotic-resistant and appearance of antibiotic-dependent form of microbes does not produce the expected results. The main pathogens of purulent diseases became staphylococci. The role of *Escherichia coli*, *Bacillus pynocyaneus*, *Proteus* has also grown (Struchkov V.I., 1972; Surovikin D.M. et al., 1972; Girkhake F.B. et al., 1972; Troyanova K. et al., 1981). It became apparent that change of the pathogenic microflora character, as well as suppression of immunity, sensitization of macroorganism, dysbacterioses, and the like factors led to a noticeable drop in effectiveness of prophylaxis and treatment of infection in surgery (Kuzin M.I., Kostyuchenoc B.M., 1981; Kanshin N.N. et al., 1983; Kurbangaleev S.M., 1985). While development of pyo-inflammatory complications the period of patients' stay in the hospital becomes significantly longer, as well as total expenditures on treatment, resulting in essential economic losses (Baroyan O.V., et al., 1975; Struchkov V.I., 1983; Green J.W., et al., 1977; Loshontsi D., 1978). All

above-said necessitates improvement of old and working out of novel non-traditional agents and methods of prevention and treatment of postoperative pyo-inflammatory complications. Proceeding from the afore-mentioned we attempted to enlarge a store of prophylactic and medical agents for treating wound infection by administering strain of acido-lactic bacteria antagonistically active towards hospital conditionally pathogenic microflora (Hambartsumyan A.Dz., Dekhtsunyan K.M., 1983), as well as by low-frequency ultrasound.

**The aim of the research** is decrease of the level of postoperative purulent wound complications by means of ultrasound sanitation of operative wounds with use of working solution of products of acidolactic bacteria metabolism, as well as study of their influence on the course of the wound process in experiment and in clinics.

On the bases of the Department of Surgery, Epidemiology, Histology of the Yerevan State Medical University methods of operative wound treatment by low-frequency ultrasound with metabolic products of acido-lactic bacteria aimed at prophylaxis of postoperative suppurations have been worked out.

In the experiment (74) antibacterial and anti-inflammatory activities of metabolic products of acidolactic bacteria strain 317/402 (conditionally called by us “Narine-F” were studied together with the course of wound process under the influence of the latter in two species of animals – inbred mice and rats.

Antibacterial activity of “Narine-F” was studied by the method of breeding in relation to a number of representatives of conditionally pathogenic microflora – “hospital” strains of staphylococci aureus, Bacillus pynocyanus, Escherichia coli, and Proteus. In the similar way antibacterial activity of “Narine-F” subjected to sonic treatment with vibration frequency of the waveguide end 26,5 kHz and vibration amplitude 35-40 µm was also studied.

Antiinflammatory activity of “Narine-F” was studied on the models of acute exudative and chronic proliferative inflammation where 107-140g of “Narine-F” was used, correspondingly. Effect of “Narine-F” on the local disturbance of vascular permeability in exudative inflammation was studied in 47 white mongrel mice weighing 20-24g.

The course of the wound process in mice was studied on the model of localized staphylococci purulent infection caused by intradermal introduction of St. aureus-186. The experiments were carried out on 63 inbred mice weighing 16-18g. Experiments on rats were carried out on the model of open (musculocutaneous) purulent wound infected with the culture of polyresistant “hospital” strain of staphylococci aureus. 24 Rats of “Shinshilla” breed weighing 2,5kg were used. For comparison in the parallel experiments similar research was carried out on the animals treated with rivanol and untreated ones.

Clinical study of “Narine-F” efficacy as a remedy of local therapy of purulent wounds was carried out on 112 patients. From this number in 37 patients suppurations of postoperative wounds were observed, in 55 – post-injection abscesses, in 20 – lactational mastitis (intramammarial). 123 patients served as control; their purulent wounds were treated by the generally accepted in clinics agents (administration of 10% sodium chloride solution with abundant bathing by antiseptic solutions (hydrogen peroxide, rivanol, furacin) till complete wound clearance and salve dressings when there are granulating and epithelializing wounds. According to nosologies patients of the control group were distributed in following way: postoperative suppurations were observed in 43 patients, lactation mastitis – in 16 patients, and in the rest 64 patients post-injection abscesses were revealed.

Administration of local therapy remedies in both groups of patients was carried out after preliminary surgical treatment of suppurative focus, dissection of necrotic and lacking vitality tissues with further wound caring by open procedure (under dressings and tampons).

As efficiency criteria of the conducted therapy with “Narine-F” in the experiment and clinics served:

- bacterioscopic and bacteriological research with an allowance for the nature and quantitative contents of microbes per 1g of tissue in dynamics for every 3rd day of treatment by the Baxter C. and coauthors' procedure (1973), Loebel E. and coauthors (1974) in modification of Kuzin M.I., Kodker I.I., Kostyuchenoc B.M., and coauthors (1980);
- investigations of cellular composition of wound prints and scrapes from the wound surface by the procedure of Pokrovskaya M.P. and Makarov M.S. (1942). Kamaev M.F. (1954) with their quantitative estimation according to Steinberg D.M. (1948) for every 3<sup>rd</sup> day of treatment;
- morphological (histological and histochemical) examination of wound biopsy in dynamics for every 4-5<sup>th</sup> day of treatment;
- determination of the wound surface area and the volume of wound cavity in dynamics with further calculation of the rates of granulation and epithelialization;
- clinical estimation of the course of the wound process (macroscopic picture of the wound) with an allowance for the nature and amount of the wound discharge, intensity and terms of the wound clearance, appearance of the first granulations, epithelialization, terms of complete cicatrization of wounds.

For the purpose of revealing the efficiency of ultrasonic sanitation of operative wounds in prophylaxis of postoperative wound infection we have examined 498 patients divided into 4 groups according to the used work solution. One group comprised patients without prophylactic ultrasonic sanitation in the amount of 145 people. In the 2<sup>nd</sup> group of 103 patients ultrasonic wound treatment was carried out in the indifferent physiologic salt solution. In the 3<sup>rd</sup> group, which included 75 patients ultrasonic treatment was carried out in furacin solution (1:5000). In the 4<sup>th</sup> group of 175 patients as work solution for wound sanitation "Narine-F" was administered. Patients of each of the four examined groups were distributed to two subgroups – "clean" and "conditionally clean". Into the subgroup of "clean" operations were included patients operated on for simple forms of acute appendicitis and incarcerated inguinal hernia (without opening the intestinal lumen). To the subgroup of "conditionally clean" operations were included the patients operated on for destructive forms of acute appendicitis with presence of purulent exudates in the abdominal cavity.

For ultrasonic treatment of operative wounds the native medical setting URSK was employed. The treatment was carried out in a resonance mode - vibration frequency of the waveguide end was 26,5 kHz and vibration amplitude 35-40 μm. The time of ultrasonic treatment depended on the size of the wound cavity and varied from 4 to 7 minutes. Aimed at revealing efficiency of the administered methods of operative wound sanitation, strict allowance for postoperative complications (infiltrates and suppurations) was conducted, terms of patients' stay in the hospital, normalization of the temperature curve, indices of hemograms, etc. were compared. Ultrasonic sanitation was carried out under bacteriological control.

Statistical processing of the obtained experimental and clinical research was carried out by Students' method, and in some particular cases also by Litchphield-Wilkinson method.

## **RESULTS OF THE RESEARCH**

**Antibacterial activity of "Narine-F"** was studied simultaneously with such accepted in surgical clinics antiseptics as 3% hydrogen peroxide, furacin (1:5000), 2% boric acid, rivanol (1:1000). Total growth suppression of "hospital" strains of staphylococci aureus (as well as strain 906), Bacillus pynocyanus, Proteus and Escherichia coli was achieved in all cases by dilution of "Narine-F" in ratio 1:2 and 1:4. Similar results have been obtained in studying antibacterial properties of "Narine-F" subjected to ultrasonic sounding. Study of antibacterial activity of hydrogen peroxide, furacin, and boric acid has shown that microorganisms under examination have pronounced resistance towards them

(plentiful growth of microorganisms in all dilutions). Delay in growth in dilution 1:2 was obtained only in inoculations from tubes with rivanol.

**Study of anti-inflammatory activity** has shown that “Narine-F” possesses an expressed anti-inflammatory effect on the development of exudative process.

While studying influence of “Narine-F” on the experimental pleurisy it turned out to suppress the development of exudative inflammation similar to Prednisolone by 44-49% ( $P < 0,001$ ). In studying the local action of “Narine-F” it was established that it suppressed aseptic inflammation by the type of Prednisolone by 57-58% ( $P < 0,001$ ). Since one of the main reasons of the inflammatory edema development in exudative inflammation is local disorder of vascular permeability, effect of “Narine-F” on this process was studied. Results of the experiments revealed suppressing action of “Narine-F” on local disorder of vascular permeability in exudative inflammation (by 63%) ( $P < 0,001$ ).

**Comparative analysis of study results of therapeutic effect of “Narine-F” in local administration on the model of localized staphylococci purulent infection in inbred mice** has shown that in treating with it the cases of infection generalization with animals’ death decreased 1,9 times, wound clearance off pus and necrotic tissues occurred comparatively early, reparative processes in wounds were speeded up resulting in drop of time of healing. Thus, on the 10<sup>th</sup> day of treatment complete wound healing in survived control animals was observed in  $36,4 \pm 14,5\%$  of cases, in treating with rivanol – in  $50,0 \pm 14,4\%$ . In treating with “Narine-F” total wound healing with recovery of epidermal and hairy integument was revealed in  $94,1 \pm 5,7\%$  ( $P < 0,01$ ) of survived animals. Recovery of epidermal integument was accompanied with lack of inflammatory changes in subcutaneous fat. When pathohistologic examination of biopsies of the control (untreated) group animals’ wounds in the same period moderately expressed inflammatory infiltration of the subcutaneous fat by leukocytes, eosinophiles, lymphoplasmacytes, as well as availability of staphylococci were observed.

**Study of the course of the wound process under the influence of “Narine-F” in rabbits of all three groups (untreated and treated with rivanol and “Narine-F”)** revealed (by the main clinical indices) that in treatment with “Narine-F” perifocal inflammatory reaction is cupped off considerably faster; the terms of wound clearance off necrotic tissues and fibropurulent applications are reduced (on the average 2,5 times as compared with control and 2,0 times as compared with the animals treated with rivanol); reparative processes in wounds appear and proceed faster, the time of wound treatment reduces 2,0 times (in comparison with the control animals); wound healing occurs by a soft, elastic scar. Thus, total wound clearance in animals of the untreated group was noted by the 17,5<sup>th</sup> day. The same index in treatment with rivanol and “Narine-F” made up 13,5 and 6,1 days, correspondingly. Complete wound healing in untreated rabbits was observed on the average on the 29<sup>th</sup> day, in animals treated with rivanol – on the 24,7<sup>th</sup> day of treatment. In administering “Narine-F” complete wound healing was noted on the average on 14,6<sup>th</sup> day of treatment.

The afore-mentioned was also confirmed by the results of bacteriological, cytological, histological and histochemical examinations. Thus, in morphological examination of untreated animals’ wound biopsies on the 10<sup>th</sup> day of observation the following picture was detected: inflammatory changes with the presence of abundant microflora was determined in all layers of the wound, necrosis foci and microabscesses in the subcutaneous fat took place. In some spots along the edges of the wound there was noted spreading of a thin layer of basal cells of the growth zone of epiderm deep inside the inflammatory focus with availability of a granulation tissue and tender net of fibrillar structures under epithelium. Newly formed vessels in the regeneration section had vertical or slanting direction. Upon coloring according to Van Gison in the granulating tissue tender collagenation was determined and coloring with toluidine blue revealed a pronounced accumulation of glycosaminoglycans. In cytoplasm of fibroblasts expressed pyroninophilia, granular fuchsinophilia were marked that also were intensively revealed in macrophages and leucocytes.

In biopsies of the animals treated with rivanol, inflammatory changes were comparatively weaker expressed than those in control. Granular fibrinous layer was thinned, dilution of pus in the wound cavity with predominance of serous component was observed. Along the edges and at the bottom of the wound pronounced spreading of the granulation tissue took place, which in deep layers was accompanied with processes of fibrosis. Foci of cellular infiltrations and microabscesses were encountered; at some spots thin epithelial covering along the surface of granulation tissue appeared. Comparative decrease of leucocytes was observed together with appearance of phagocytosing macrophages and cells of lymphomonocytic series.

In the animals treated with “Narine’F” granular-fibrinous layer was absent, the wound bottom and edges were presented by granulation tissue with distinct differentiation of cellular elements and fibrillar structures towards ripening. For a considerable distance the wound surface was laid with epithelial covering with the tendency of thickening and recovering of its superficial layers. In the majority of cases inflammatory changes both in the superficial and deep layers of the wound, and in the tissues surrounding the wound were absent. Moderate metachromasia, pyroninophilia were determined in the superficial layers of granulation tissue against the background of their comparative reduction in cellular structures. In deeper layers the aforestated histochemical reactions on the whole were not observed.

Comparative analysis of cytological examination results in all groups of rabbits in dynamics showed that in treatment with “Narine’F” decrease in inflammatory elements and microflora, appearance of cells of a collagen forming series and of fibrillar structures were detected in comparatively early terms (dynamics of the cytogram main element changes is reflected in Fig.6).

Thus the results obtained by us prove pronounced therapeutic efficiency of “Narine’F” in local administration in the experiment on the models of localized staphylococci infection in inbred mice and open purulent wound in rabbits (results of these examinations are confirmed by the data of bacteriological, cytological and morphological examinations).

The obtained results of experimental examinations permitted to hope for effectiveness of “Narine’F” in clinical use. With permission of the Ministry of Health of Armenia approbation of the metabolic products of acido-lactic bacteria strain 317/402 was carried out in clinics – efficiency of “Narine’F” as a remedy of local therapy of soft tissue purulent processes, as a work solution in preventive ultrasonic sanitation of operative wounds was studied.

**Clinical estimation of “Narine’F” efficiency as a remedy of local therapy of purulent wounds** showed that in patients treated with “Narine’F” by the end of two days significantly decreased signs of perifocal inflammation (edema, infiltration, dermal hyperemia around the wound), and the total cupping of perifocal inflammatory reaction was observed on by the 4-5<sup>th</sup> days of treatment. Usually after I-II dressings with “Narine’F” discharge from the wounds, though abundant, was considerably diluted, odor disappeared, and by the 3-4<sup>th</sup> day of treatment discharge from the sounds dropped sharply, acquired seropurulent character with predominance of a serous component. By these terms (3-4<sup>th</sup> days) wounds comparatively cleared off fibropurulent applications and necrotic tissues. Complete clearance of wounds off necrotic tissues in the patients treated with “Narine’F” was noted on the 5,9<sup>th</sup> day in suppurated operative wounds, on the 7,6<sup>th</sup> day in abscesses and on the 8,3<sup>th</sup> day in mastitis. At the beginning edge epithelialization (on the average by the 10-11<sup>th</sup> days) appeared. The average time of stay in the hospital beginning from the abscess cutting to complete epithelialization of the whole wound surface made up 13,7 days in postoperative suppurations, 19,9 in patients with abscess, and 16,8 in patients with lactational mastitis.

In contrast to this in patients of the control group treated with traditionally in a clinic agents the terms of total necrosis in postoperative suppurations, abscesses, and mastitis made up 12,9; 17,1; 17,6 days, correspondingly. Beginning of the edge epithelialization in patients of this group appeared to be on the 18,2<sup>nd</sup> day in suppurated postoperative wounds, on the 22,2<sup>nd</sup> day in abscesses, and on the 21,4<sup>th</sup>



day in patients with mastitis. The average time of stay in the hospital beginning from the abscess cutting to complete healing of wounds made up 24,5 in postoperative suppurations, 31,7 in abscesses, 26,5 on mastitis.

Bacteriological examination while cutting of a purulent focus revealed staphylococci aureus in 60,9% of cases, Escherichia coli in 21,7%; Proteus and Bacillus pynocyaneus in 2,2% of cases, correspondingly, associations of staphylococci with Escherichia coli in 13,0% of cases. Proceeding from the fact that in dynamics of a purulent process besides qualitative characteristic, of great significance sometimes even decisive, is a quantitative characteristic of the microflora inoculated from the wound, we have studied the amount of microorganisms inoculated in 1g of tissue in the process of treatment.

Upon the first examination (immediately after cutting and surgical treatment of a purulent focus) the amount of inoculated microorganisms in both groups of patients made up from  $1 \times 10^6$  up to  $1 \times 10^9$ . On the third day of treatment patients of the control group (treated by conventionally accepted remedies) revealed insignificant reduction in the amount of inoculated microflora that made up  $5 \times 10^5 \div 5 \times 10^7$ . Essential changes in quantitative characteristic of microflora in the wound from the 3<sup>rd</sup> to 6<sup>th</sup> days were not revealed. By the 9<sup>th</sup> day in 22,2% of patients of the indicated group microorganism growth was not revealed. In the rest 77,8% of patients quantitative index again made up  $5 \times 10^4 \div 5 \times 10^7$ . By the 12<sup>th</sup> day of treatment the number of patients who displayed cessation of microflora inoculation increased up to 33,3%, and in the other 66,7% of cases the number of microorganisms made up  $5 \times 10^3 \div 5 \times 10^7$ . By the 15<sup>th</sup> day of treatment in 55% of patients of the control group inoculation of microorganisms was not observed. In the rest cases (44,5%) the amount of microorganisms made up  $1 \times 10^4 \div 1 \times 10^6$ .

Similar examinations carried out in patients treated with "Narine-F" showed that as early as on the 3<sup>rd</sup> day of treatment in 6,7% of cases growth of pyogenic microflora stopped, and in the rest cases significant decrease (in 93,3% of cases) in the number of the stated microorganisms to  $1 \times 10^5 \div 1 \times 10^6$  was observed. By the 6<sup>th</sup> day of treatment microorganisms were not revealed in 33,3% of patients ( $P < 0,02$ ); and in the rest 66,7% of cases their number was equal or lower than the "critical" level and made up from  $1 \times 10^4$  to  $1 \times 10^5$ . In the next examination by the 9<sup>th</sup> day of treatment the number of patients who failed to inoculate microflora increased sharply (86,7%) ( $P < 0,001$ ). In the rest 13,3% of cases their number was lower than "critical" and made up  $1 \times 10^3 \div 1 \times 10^4$ . Growth of microorganisms stopped in all the remaining patients of this group by the 15<sup>th</sup> day of treatment.

Analyzing data of bacteriological examinations one may conclude that when administering Narine-F" wounds faster "become free" of pyogenic microflora, which in its turn plays a role of no small importance in the course of reparative processes.

Analysis of the cytological examination results also revealed a definite difference in cytograms of patients with purulent wounds treated with "Narine-F" and with traditionally accepted in clinic remedies. In cytograms of the patients treated with "Narine-F" beginning from the 3<sup>rd</sup> day noticeable decrease in the number of destroyed neutrophilic leucocytes, reduction of bacteriological contamination of the wound, appearance of phagocytosing leucocytes were observed. On the 5-6<sup>th</sup> days of treatment neutrophilic leucocytes were determined in large amount, microflora reduced significantly, phagocytosis had a completed character; in some cases appearance of lymphocytes and eosinophiles was noted. Profibroblasts and fibroblasts were encountered in drugs. In a considerable amount were macrophages, polyblasts, histiocytes. On the 9-10<sup>th</sup> days of treatment with "Narine-F" side by side with insignificant amount of neutrophilic leucocytes, lymphocytes, macrophages there were also determined cells of the type of fibroblasts, profibroblasts, fibers of fibrous tissue. In the control group of patients the cytological picture of smears of the 1<sup>st</sup>, 3<sup>rd</sup> and 6<sup>th</sup> days scarcely differed: destroyed neutrophilic leucocytes, polyblasts, histiocytes with vacuolized cytoplasm, plenty of microflora, perverted or uncomplete phagocytosis were determined. Only on the 11-13<sup>rd</sup> days of taking the matter in smears against the background of significant amount of leucocytes, there were determined macrophages,

polyblasts, histiocytes; phagocytosis became complete; separate elements of profibroblasts were revealed. Shifts towards strengthening of regenerating changes in the wound of patients of this group were observed only on the 20-21<sup>st</sup> day of treatment.

Comparative analysis of the results of histological and histochemical examinations of wound biopsies of both groups' patients revealed that when administering "Narine-F" cupping of the inflammatory reaction and necrolysis were observed faster, reparative processes in wounds appeared and proceeded on the average 6-7 days earlier.

Thus, proceeding from analysis of the data obtained by us it follows that the generally accepted in clinic remedies of purulent wound treatment significantly yield to therapy with "Narine-F". Owing to the pronounced antiinflammatory, antibacterial, antiedematous effect of "Narine-F", in local therapy it considerably faster cups off inflammatory processes in wounds, terms of wound clearance from necrotic tissues, fibropurulent applications and wound microflora are reduced that in its turn promotes comparatively early appearance and proceeding of reparative processes, reduction of the time of wound healing (on the average 1,7 times).

Study of prophylaxis effectiveness of postoperative wound infection by ultrasonic sanitation with the use of various work solutions showed that in the 2<sup>nd</sup> group of the examined patients (with ultrasonic sanitation in the indifferent - physiologic salt solution), as compared with the 1<sup>st</sup> group (without ultrasonic sanitation) decrease in the number of cases of postoperative wound infection was observed 1,4 times in "clean" operations, and 1,8 times in "conditionally clean" ones. At the same time comparative analysis of the examination results of the 2<sup>nd</sup>, 3<sup>rd</sup> (sanitation in fucarin) and 4<sup>th</sup> (sanitation in "Narine-F") groups clearly demonstrated that efficiency of ultrasonic treatment depended on the work solution in which tissue sounding was carried out. On the other hand, comparison of the obtained data revealed the expressed effectiveness of prophylactic ultrasonic sanitation in metabolites of acidolactic bacteria ("Narine-F"). Reduction of the total level of postoperative wound infection was noted 3,5 times as compared with the control group; moreover, drop in the amount of complications was observed 3,9 times in "clean" operations ( $P < 0,001$ ) and 3,4 times in "conditionally clean" ( $P < 0,01$ ).

Rare postoperative wound complications after ultrasonic sanitation with "Narine-F" were in the form of small subcutaneous infiltrates, or suppurations that upon the corresponding therapy were significantly faster liquidated in comparison with complications in other groups of patients.

Efficiency of ultrasonic treatment in "Narine-F" is also proved by the results of bacteriological examinations. Inoculation from the operative wound before treatment gave growth of microorganisms (more often of Escherichia coli, staphylococci, or different microbial associations) that convincingly proved contamination of the operative wound in the process of operative intervention. The inoculation taken from the same patients after ultrasonic treatment (in "Narine-F") was practically always sterile.

All the afore-stated clearly prove economic efficiency of the method of ultrasonic sanitation in "Narine-F". Thus, for treatment of 26 patients of the 1<sup>st</sup> group with suppurations and infiltrates of postoperative wounds in the total 17474 roubles 67 copecks were spent. Expenditures for treatment of patients with postoperative wound infection in the 4<sup>th</sup> group made up only 4714 roubles 05 copecks in spite of the fact that in a quantitative relation the total number of patients in the 4<sup>th</sup> group considerably surpassed the 1<sup>st</sup> one.

Based on the above-mentioned it proceeds that the method of ultrasonic sanitation of operative wounds in prophylaxis of postoperative suppurations is highly effective, simple and available. Its efficiency to the certain degree depends on the correct choice of the work solution in which sounding of the wound is carried out. Antiinflammatory and antibiotic activities, harmlessness for tissues, simplicity of obtaining, and other properties of "Narine-F" (see above) in combination with ultrasonic cavitation result in essential decrease in the level of postoperative wound infection.

Thus, the results obtained by us prove effectiveness of the products of metabolism of acidolactic bacteria strain 317/402 in prophylaxis and treatment of wound infection. The suggested methods

lead to significant drop in postoperative wound complications and shortening of treatment time of purulent wounds; these methods are simple and available, inexpensive, easily performed, may be widely implemented into the practice of public health and lead to considerable economic effect.

As a result of the research it may be concluded that:

1. use of the products of metabolism of acido-lactic bacteria strain 317/402 as a work solution in prophylactic ultrasonic treatment of operative wounds promotes decrease in the general level of postoperative wound infection 3,5 times as compared with control;

2. reduction of the number of complications is observed 3,9 times in “clean” operations and 3,4 times in “conditionally clean”.

3. high efficiency of the products of metabolism of acido-lactic bacteria strain 317/402 as a remedy of local thapy of purulent wounds in experiment and in clinics has been revealed. While administering “Narine” in comparison with traditionally accepted in clinics drugs fast cupping of inflammatory processes, clearance off wound detritus and pyogenic microflora, speeding up of reparation processes, shortening of terms of wound healing (1,7 times on the average) has been observed.

4. Cytomorphologic picture of the wound process flow under the action of “Narine” was characterized by strengthening of phagocytic reaction, disappearance in shortened time of edema, purulent infiltration of tissues, appearance and ripening of elements of newly formed connective tissue with further recovery of all layers of epithelial integument and regulated disposition of thin tender collagenous fibers in deep layers of regenerate.

### **Effect of “NARINE” on the level of cholesterol in 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 cholesterindegrading 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 hyperlipoproteinedema in rats, in the intestine of a sick person with various forms of hyperlipoproteinedema microecologic disorders in the intestine, dysbacteriosis with bifido- and lactobacilli insufficiency that were accompanied by lipid and, in particular, cholesterol metabolism were observed (46, 47).

On the other side, studies of the active series of lactobacilli strains *in vitro* have established their cholesteroldegrading ability (44). 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 76,39kg, 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 (II) was only on the diet, and the experimental group (I) 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<sup>st</sup> group of individuals as compared to the 2<sup>nd</sup>. Thus, if in the 1<sup>st</sup> 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<sup>nd</sup> group decrease occurred statistically untrustworthy. ( $p > 0,05$ ) from  $271.6 \pm 24.2$  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<sup>st</sup> group positive result (reduction of ChS level) occurred in 11 out of 12 persons, and in the 2<sup>nd</sup> – 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. Alongst with the direct cholesteroldegrading 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 (45, 46); participation of the liver in these processes is evident and does not require proofs;

2. participation in metabolism. Lactobacteria have been recently proved (47) to be used in regulation of other kinds of metabolic disorders very frequently attended by disturbance of lipid 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 bioselenium, bioiodine, biozinc, and other catalysts of cholesteroltransforming reactions (43);

7. rise in antioxidant potential of the organism connected in particular with improvement of the intestine functional state (41, 45), 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 (48);

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).

## **“NARINE” and chronic liver pathologies**

Intestinal dysbacteriosis very frequently accompanies chronic liver pathologies, especially in acute condition of a disease and often can appear as a provoking factor. Development of the intestinal dysbacteriosis in liver pathologies is connected with malfunctioning of bile metabolism (which is one of regulators of the intestinal microflora composition), disturbance of immunity, and with general deficiency of nutritive matters in the organism.

Due to intestinal dysbacteriosis formation and absorption of toxic products into the system of portal vein increases, which sharply enlarges load on detoxication liver system. Furthermore endotoxins, formation and absorption of which is significantly increased in case of intestinal dysbacteriosis, being mighty stimulators of inflammatory cells activity can all alone provoke or intensify inflammatory process in liver tissue.

Nutritive matter deficiency developed in intestinal dysbacteriosis also furthers worsening of the liver function. Of no less importance is the fact that disturbance of immunity in intestinal dysbacteriosis also negatively influences the course of the liver pathologies, especially of viral.

Use of “NARINE” in complex treatment of chronic liver pathologies allowed to obtain good clinical results and often to avoid aggressive interventions on the organism (use of steroid hormones, cytostatics, interferon, etc.).

## **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.

### **“NARINE” in 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 (malfunctioning 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 dysbacteriosis of the intestine (DI) in pathogenesis of gastroesophageal reflux (GER) (50). 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 1<sup>st</sup> group got generally accepted treatment of GER and those of the 2<sup>nd</sup> group got additionally bifidol 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 bifidol and “NARINE” into a therapeutic complex.

### **“NARINE” and 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 (56).

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 1<sup>st</sup> group included 8 patients with the 1<sup>st</sup> stage of the disease;

The 2<sup>nd</sup> group included 6 patients with the 2<sup>nd</sup> stage of the disease;

The 3<sup>rd</sup> group included 3 patients with the 3<sup>rd</sup> stage of the disease.

In 5 patients of the 1<sup>st</sup> group dysbacteriosis of the 1<sup>st</sup> degree was revealed.

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

Out of 3 patients of the 3<sup>rd</sup> group 2 had dysbacteriosis of the 2<sup>nd</sup> degree and 1 – displayed dysbacteriosis of the 3<sup>rd</sup> degree.

The results of our research have proved that dysbacteriosis of the intestine in chronic recurring pancreatitis is characterized by increase in a number of lactosensitive 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 1<sup>st</sup> group without dysbacteriosis, and became less in 3 patients of the same group with dysbacteriosis of the 1<sup>st</sup> degree. The rest of patients did not show marked improvement of their state. Patients who developed the 1<sup>st</sup> 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 2<sup>nd</sup> 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 3<sup>rd</sup> 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, lectoline, lysine, lactocidine, acidophillin. “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.

### **Use of “NARINE” in 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 1<sup>st</sup> group got omeprazole, amoxicillin, quamatel at a standard dosage; the 2<sup>nd</sup> group got the same complex together with “NARINE” produce containing Lactobacillus acidophilus.

**The results** – in the 2<sup>nd</sup> group positive dynamics after treatment was more pronounced, the picture of the intestinal microbial flora was normalized.

**Conclusions** – “NARINE” promoted cicatrization of ulcera, erosions, suppression of Helicobacter pylori activity and improvement of the intestinal microflora.

## “Narine” in 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 (89). 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.

## Use of “Narine” in 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 is carried out, turundae are introduced into pockets, and gauze napkins wetted with milk “Narine” fermented with acido-lactic bacteria strain 317/402 are applied to the surface. Duration of applications is 30-35 minutes. The course of treatment is 10-15 days.

The invention refers to medicine, may be used for treatment of parodontium diseases.



The aim of the invention is shortening of the time of treatment and extension of the remission period.

The procedure is illustrated by the following clinical examples.

Example 1. Patient A, 48 years, was diagnosed parodontitis generalized upon admission, active stage of the 2<sup>nd</sup>-3<sup>rd</sup> 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, 2<sup>nd</sup>, 3<sup>rd</sup> degrees teeth mobility were revealed. Depth of pockets was up to 7-8mm 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.

## **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 nontoxicogenic strains (12 items) c. Diphtherial. Simultaneously sensitivity of *Corinebacteria* towards traditionally administered antibiotics: penicillin, erythromycin, as well as towards additionally taken drugs: gentamycin, fusidin, cyprophloxacin 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 (91).

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**FOR NOTES**

