EDITORIAL

From the Flight of Yu.A. Gagarin to the Contemporary Piloted Space Flights and Exploration Missions

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On the 50th Anniversary of the First Human Space Flight

Abstract—The first human flight to space performed by Yu.A. Gagarin on April 12, 1961 was a crucial event in the history of cosmonautics that had a tremendous effect on the further progress of human civilization. Gagarin's flight had been preceded by targeted biomedical research with the use of diverse biological objects on board rockets and artificial satellites. This research led to the conclusion on the fundamental possibility for humans to fly in space. After a series of early flights and improvements in the medical support system, space missions to the *Salyut* and *Mir* stations were gradually extended to record durations. The foundations of this extension were laid by systemic research in the fields of space biomedicine and related sciences. The current ISS system of the crew's medical care has been successful in maintaining the health and performance of cosmonauts, as well as in providing the conditions for research in various fields related to space flights. The ISS abounds in opportunities for the preparation for piloted interplanetary missions. At the same time, the ground-based simulation of a mission to Mars is a venue for carrying out scientific and technological experiments in space biomedicine.

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Fifty years have passed since the flight into space of Yuri Alekseevich Gagarin, an outstanding event in the history of cosmonautics and modern civilization.

The flight of Gagarin, which lasted for 108 min, capped long-term preliminary studies in the sphere of aviation medicine, biology, and physiology performed in close collaboration with designers of rocket-space systems and specialized medical and telemetric devices.

In the 1950s and 1960s, biological experiments were conducted in flights of altitude rockets and orbital flights on satellites and orbital spaceships to study the effect on various biological objects of extreme factors inherent to space flights (SFs).

From 1951 to 1958, 29 launchings of rockets with dogs aboard were performed. It was shown that animals normally endured exposure to short-term microgravity and acceleration.

The next important stage was the performance of biological studies in space. In November 1957, the second artificial Earth satellite with the Earth's first living being aboard, the dog Laika, was put into orbit [6]. The experiment demonstrated that animals can tolerate G-loads and conditions of microgravity; this result was supported in subsequent flights of other dogs.

In 1960–1963, in four flights of satellite spaceships, physiological, biological, and radiobiological studies were performed using dogs, rodents, and other biolog-

ical objects (plants, algal (chlorella) cultures, microorganisms, cultures of cells and tissues).

Postflight examinations of animals revealed no significant changes in their general state or behavior [39].

The main goal of the studies was to provide scientific justification of human flights to space.

This task was successfully solved based on the analysis of a large number of experimental studies performed mainly by the staff of the Research Institute of Aviation Medicine, and the fundamental possibility and safety of the flight of living organisms into space were justified.

The results of the performed studies were summed up by Academician N.M. Sisakyan et al. who wrote that a series of remarkable biological experiments on board the second, third, fourth, and fifth orbital spaceships made it possible to solve many important problems. The main starting data were obtained for an extremely important conclusion as to whether a human flight along the circular orbit located knowingly below the radiation belts will be safe for human health and life, from the biological and medical viewpoints [38].

PREPARATION FOR THE FIRST HUMAN FLIGHT TO SPACE

Along with experiments on animals, multi-sided studies of the effect of extreme factors of SF on the human body were performed.

These studies formed the basis for the creation of biomedical support of SF, elaboration of methodology, devices and methods of physiological studies, and creation of a system of life support and means of rescue.

In correspondence with the governmental decree of January 5, 1959 "On the Intensification of Research Works in the Sphere of Biomedical Support of Space Flights," the Research Institute of Aviation Medicine was transformed into the State Research Experimental Institute of Aviation and Space Medicine. A new scientific line began to be developed at the institute, directed by V.I. Yazdovskii, to solve issues of medical support of SF, study the effect of SF factors, as well as to select and train crews.

The Department of Space Physiology was formed. It was headed by O.G. Gzenko, who, in this period of his scientific activity, together with his colleagues, made a big contribution to the performance of biological and physiological studies conducted on animals in SF, to the analysis of the obtained results, and vision of perspectives of subsequent studies [7, 8].

By 1959, the main approaches for the preparation of cosmonauts were established, and the first group of candidates was selected.

With the participation of specialists of the State Research Experimental Institute of Aviation and Space Medicine, a program for the preparation of cosmonauts for the first SF was elaborated that included a system of training and tests and undertaking a course of studies on biomedical disciplines, familiarization with rocket technique, flight dynamics, construction, systems, and equipment of the orbital spaceship *Vostok*, as well as the means of spaceship control.

During preparation of the first human flight to space, a large amount of work on its technical support was performed. On board orbital spaceships, the pressure suit, and means of life support and landing were tested. Devices for controlling the most important indices of the state of health of cosmonauts and the operation of the systems ensuring the safety of flights were created.

The methodology of medical selection of cosmonauts was elaborated. The main requirements for the candidates in becoming cosmonauts were excellent physical and mental health, the ability to tolerate the effect of extreme factors (G-loads, hypoxia, isolation, heat stress, short-term microgravity, low barometric pressure), high level of physical and intellectual performance, and mental stability.

The physical training of candidates for cosmonauts and the preparation for control of the spaceship systems, and the use of systems of life support and medical control were performed.

THE FIRST HUMAN FLIGHT TO SPACE

On April 12, 1961, the historic flight of Gagarin took place, which opened to humanity the path to

space. This flight had to answer /the main question of whether humans can live and work in space.

It was also important to assess the accuracy of the forecasts based on the knowledge obtained in biological studies on board rockets, satellites, and in ground-based investigations.

Physicians and physiologists were, above all, interested in the state of the cardiovascular system, respiration, and mentality of a cosmonaut, as well as their responses to the effect of SF factors, primarily of microgravity and G-loads.

When taking the spaceship into orbit and under conditions of microgravity, Gagarin felt well and endured the descent and landing successfully [5].

For the medical control of the state of health of a cosmonaut before flight, during flight, and after its termination, the ECG in two pectoral deviations, pneumogram, and the heart rate were recorded and transferred to Earth using telemetry.

During the descent to Earth, the physiological data were recorded using an onboard autonomic system, and after the blast-off of the parachute, with the help of an autonomic recorder fixed on the cosmonaut's body.

In the preflight period and in the start position, the heart rate was 60–76 bpm; 5 min before the start, it increased to 110–133 bpm; and after the flight, it returned to the initial values; the blood pressure before and after flight did not exceed 125/75 mm Hg [5]. After the flight, no significant changes in ECG were recorded in Gagarin; the extent of the tolerance of the functional test with a physical load and the data of the oscillogram of the lower legs' veins indicated that his cardiovascular system was in good shape [5].

Postflight examination did not reveal any pathological or stable functional changes in the nervous system or higher nervous activity, material deviations in the state of sense organs, shifts in the peripheral blood, or changes in the indices of metabolism [5].

Radio communication of Gagarin with the Flight Control Center showed his psychological state was normal and his working capacity was high. The detailed description of subjective sensations related to microgravity and the G-loads presented in Gagarin's report on the flight were important. He wrote that the feeling of microgravity was slightly unusual and that one got a sensation as if one was suspended in a horizontal position on straps. It was slightly unusual, but then one got accustomed to it, adapted, and there were no unpleasant sensations.

Regarding G-loads at the stage of descent, Gagarin wrote that the G-loads, according to his sensations, were beyond 10 g. There was a moment, for approximately two to three seconds when the devices began to become blurred. Then, the G-loads declined. The G-loads decreased smoothly, but more rapidly than they increased.

The successful flight of Gagarin marked the start of space medicine as a new sphere of space sciences on life and led to numerous studies related to human space exploration.

SHORT-TERM PILOTED FLIGHTS

In the first decade of piloted SFs, their duration increased from 108 min to 18 days. Biomedical studies performed in this period proved the possibility of a short-term human stay under the conditions of SF. Typical responses of cosmonauts in short-term SFs were characterized by the development of space movement disorder, changes in some indices of cardiac activity, and the short-term disturbance of movement coordination.

The most significant changes were observed after the flights.

They manifested themselves in general fatigue and moderate detraining of the cardiovascular system to the physical load and orthostatic impacts, the disturbance of the coordination of movements and regulation of vertical posture, and the relative dehydration of the body. The recorded manifestations in some cases were clinically significant [10].

For the subsequent increase in SF duration without damaging the health of cosmonauts, the necessity arose to create efficient prophylactic drugs and methods of medical care.

LONG-TERM SPACE FLIGHTS

The creation of efficient prophylactic drugs became possible after SFs on board orbital space stations began. In the 1970s, these were space stations of the *Salyut* series, on which devices for physical trainings (running road and other prophylactic means) were installed.

A significant contribution to the elaboration of the system of prophylaxis for long-term space flights was made by Academician O.G. Gazenko, professors A.M. Genin, L.I. Kakurin, I.D. Pestov, A.S. Berer, and director A.V. Eremin, who, together with the research team of the State Research Experimental Institute of Aviation and Space Medicine, Institute of Biomedical Problems, Rocket Space Corporation Energia, and Zvezda plant, were awarded the State Prize for this work in 1978.

The improved biomedical care, whose most important component was the system of prevention, enabled cosmonauts P.I. Klimuk and E.I. Sevastyanov in 1975 to successfully perform a 63-day flight on board the *Salyut-4* station.

After this, an increase in the duration of SFs became a leading trend of piloted cosmonautics. This is exemplified by the duration of flights on board *Salyut-7* OS that successively lasted for 96, 140, 175, 185, 211, and 237 days.

The goal of the prophylactic system of SF was the prevention or decrease of unfavorable effects of microgravity. For its solution, experiments on simulation of microgravity using clinical and antiorthostatic hypokinesia, experiments on hypokinesia on laboratory animals, studies using biosatellites, and experiments with a prolonged isolation were used. The duration of the experiments with hypokinesia reached 50, 100, and more days. The most important of them was a 365-day experiment with an antiorthostatic hypokinesia (1986–1987). Recommendations on prophylactic measures obtained in the given experiment were used in the one-year-long SF by cosmonauts V.G. Titov and M.Kh. Manarov.

The possibility of performing long and superlong-term SFs became convincing evidence of the achievements of modern space biology and medicine.

The cosmonaut and physician V.V. Polyakov in 1994–1995 performed a record 438-day flight that opened the way for other cosmonauts for long-term work in space and approached the possibility of future interplanetary missions. On board the *Mir* OS, and then the international space station (ISS), missions with durations of six months and more became common. The number of cosmonauts who stayed in space for more than 600 days in several flights increased (S.K. Krikalev, A.Yu. Kaleri, S.V. Avdeev, V.V. Polyakov, and A.Ya. Solov'ev).

STUDIES ON SPACE PHYSIOLOGY

Throughout the history of space medicine, from its birth to our days, its development was based on profound scientific studies that made it possible to determine the consistent patterns of human body adaptation to the set of factors of SF, the body systems most sensitive to the SF factors, and the main mechanisms of the adaptation of the body and its systems under these conditions, as well as to elaborate the means for health control in SF.

Below, some main aspects of the modern state of space medicine and its prospects are considered.

In studies on space physiology, the main attention is focused on the assessment of the state of the cardiovascular system, skeletal muscles, skeletal system, sensory systems, motor control, and changes in metabolism.

The studies demonstrated that the main factor in circumterrestrial flights is microgravity, whose action causes maximum changes in gravitation-dependent systems, which, under the conditions of earth gravity, perform the work against the gravitational force (the cardiovascular and muscular systems, support apparatus) or are constantly oriented in their activity at the gravitational vector (the vestibular system) [15].

Cardiovascular System

Under the conditions of microgravity, in the cardiovascular system, there may arise unfavorable changes in the electrical properties of myocardium, including sinus arrhythmia and extrasystoles (especially during extravehicular activity and high physical loads), increase in the rate and decrease in the force of heartbeat, decrease in stroke volume and cardiac output, rearrangement of the phase structure of the heart cycle (shortening of isometric contraction and relaxation), decrease in the period of expulsion and the phase of rapid filling of the left ventricle of heart, and decrease in the ECG T-wave amplitude [15, 21].

Changes were recorded in systemic circulation that manifested themselves in a decrease in specific peripheral resistance and diastolic pressure, decrease in the jugular veins contractility, and increase in the blood filling of the jugular veins; signs of venous congestion in the inner organs, disturbance of the regulation of vascular tone, and a decrease in microcirculation were detected [15]. The aforementioned changes lead to orthostatic and physical detraining [26].

Sensory Systems and Vestibular Apparatus

It has been established that the initial period of microgravity causes a significant facilitation of vestibular responses determined by the attenuation of the inhibitory effects of proprioception on the neurons of the vestibular nuclei [24, 50].

This is followed by the phase of inhibition (caused by signals from the cerebellum), which indicates the exclusion of the vestibular canal from the system of sensory support of the movement of the eyes, head, and posture [24, 36].

When the results of flights of cosmonauts were summarized, the phenomenology was systematized, classification of perceptive and sensorimotor disturbances during change of gravitation was elaborated, characteristics and periods of adaptive processes in sensory systems were determined, and examination in cosmonauts of the vestibular function and interacting with it sensory system was developed and implemented into practice [35, 49].

Motor Control

The long-term effect of microgravity and its simulating conditions leads to profound and prolonged shifts in the reflex sphere and pronounced coordination disorders [51].

Microgravity exerts a significant effect on the sensory support of the system of movement control. The cause of this is a decrease in the level of afferent impulses from the otoliths, muscular receptors, and dermal receptors of the foot, as well as the disturbance of vestibulo-oculomotor coordination [24].

As a result, there arises a disturbance of the processes of sensory synthesis, coordination of movements, orientation, control of arbitrary movements and a compensatory increase in the role in the movement control of the visual analyzer, which takes up the function of assessing the body's position in space, which is normally performed by the vestibular apparatus [36].

Based on the data obtained in SFs and ground-based studies, the concept of a hypogravity motor syndrome was confirmed [52].

It was established that the main factor determining profound changes in the organization of motor control and movements in microgravity is the disturbance of activity of the main orientation and proprioceptive systems.

Skeletal Muscles

Conditions of microgravity determining a decrease in the load on skeletal muscles cause disturbances in all components of the neuromuscular apparatus, including intracellular signaling systems [43].

Studies on rats after flights on board biosatellites have demonstrated that the most pronounced changes arise in antigravity muscles bearing a force load during support of the posture and locomotion. Signs of atrophy and decrease in muscular force, increase in fatigue, acceleration of contractions, and transformation of the part of slow fibers into fast-type fibers were revealed [49, 55].

The study of human skeletal muscles after SFs and under the conditions of ground-based simulation of the effects of microgravity revealed a decrease in the strength indices of muscles, most pronounced in the extensor muscles. The changes develop against the background of a significant decrease in the tone and the greater involvement in the activity of fast motor units [19].

Based on the studies performed, the concept of the trigger role of support afferentation in the organization of posture activity and in the development of structural-functional changes in muscles in microgravity was elaborated [53].

Skeletal System

Considerable scientific material was obtained during the study of the state of the skeletal system in SFs and in simulation experiments. Studies of the bone tissue of rats that flew on board biosatellites revealed the inhibition of the growth of bones, retardation of periosteal osteogenesis, development of osteopenia, and a decrease in the mechanical strength of bones [22].

Studies on monkeys after flights on board biosatellites demonstrated a decrease in the volume of bone tissue in spongy structures of the iliac bone and a decrease in the rate of mineralization of trabecular bone tissue [59].

Studies of the bone tissue of cosmonauts by the methods of two-photon absorptiometry and quantitative tomography showed that, after SFs of various durations, the most pronounced and fast changes mainly develop in bones bearing the force load, especially in their spongy structures [32].

In long-term SFs, changes in bone tissue are assessed as a potential risk factor, since the decrease in the bone mineral density due to the loss of calcium and phosphorus increases the possibility of bone fractures and the formation of nephroliths [22].

We note that the processes of postflight recovery of bone tissue require considerable time.

Metabolism and Regulation of Internal Environment

The examination of cosmonauts and experiments with animals on board biosatellites have demonstrated that microgravity exerts a significant effect on protein, carbohydrate, lipid, and energy metabolisms. The development of urgent and long-term adaptive responses that led to the establishment of a new type of homeostasis was found. Shifts in a significant number of metabolic indices of the inner environment, structural rearrangement in some tissues, intensification of processes of catabolism, decrease in the level of energy processes, and formation of a new level of metabolism inherent to microgravity were found [13, 57].

It was shown that an important role in these shifts belongs to changes in the endocrine system, in particular, those caused by a decrease in the somatotrophic and thyrotrophic functions of the pituitary [35]. The cause of these changes may be the development, in a long-term flight, of the hyponoradrenergic syndrome [12]. Analysis of the data obtained made it possible to advance a hypothesis of the minimization of metabolism in microgravity [13]. Studies performed after the return to Earth revealed an acute gravitational stress developing upon transition from microgravity to the Earth's gravitational force [35].

Water–Salt Metabolism

It was shown that the pattern of changes in the state of the cardiovascular system, neurohormonal regulation, and metabolism during an SF determines regular shifts of water–salt metabolism [9, 54].

It was revealed that the change in blood volume regulation in the initial period of microgravity is a consequence of the blood redistribution and shifts in central and renal hemodynamics leading to change in the production of volume-regulating hormones (vasopressin, renin, angiotensin II), as well as aldosterone, and to the formation of a specific water–salt homeostasis with a negative balance of sodium, calcium, and phosphorus.

In the early period of adaptation to microgravity, a negative water–salt balance has been recorded [9]; at later stages of SF, sodium excretion decreases, excre-

tion by kidneys of ADH increases, and the renin–angiotensin–aldosterone system is activated [12]. It has been found that changes in the water–salt metabolism can lead to disturbances of the activity of the cardiovascular system, support–motor apparatus, and blood coagulation system; increase the risk of urolithiasis; and lead to the demineralization of bones and calcification of soft tissues [29].

At the Institute of Biomedical Problems, functional tests for the assessment of the state of the water–salt homeostasis, as well as the means for stopping its unfavorable changes in the initial period of an SF, were developed [9].

PSYCHOLOGICAL SUPPORT OF CREWS IN SPACE FLIGHTS

The tasks of the psychological support of crews in SFs are psychological selection and staffing of the crew, ensuring a high level of professional reliability of the crew, psychosocial support, and performance of rehabilitation measures after the flight.

The stay in an isolated, artificial environment, the monotony of the situation and activity, the limited circle of communication, and separation from family and habitual society may exert a negative effect on the mental state of cosmonauts.

An additional psychological load during flights of orbital stations (OSs) is posed by the interaction of crews of mixed cultural and gender compositions.

In long-term SFs, asthenia, sleep disturbance, emotional disorders, and other changes in the psychoemotional state may develop, which can lead to a decrease in the working capacity, quality of operator activity, and deterioration of the psychological climate in the crew [30].

The main criteria during selection of cosmonauts are the state of mental health, professionally important personality qualities, specific features of behavior and activity in a small group, and individual stability to extreme conditions of environment and activity. In the process of preparation for flight, cosmonauts get acquainted with specific features of interpersonal relations and are taught the habits of the formation of optimal interpersonal and intergroup relations.

During selection of cosmonauts, in recent years, parallel to traditional criteria, genetic criteria began to be used that are correlated to tolerance to the effect of extreme factors [3].

During the flight, psychological monitoring and diagnosis of psychophysiological and emotional states are performed, and professional habits of operators are supported using instrumental automated methods [38].

Important components of psychological support in flights are methods of psychoprophylaxis and psychocorrection, including ground-based and onboard methods and means of psychosocial support [23].

The requirements for optimization of the regimens of labor and rest during organization of human life in space, to which Professor B.S. Alyakrinskii paid special attention, remain urgent as before [1].

An important role in psychological support of cosmonauts and in the support of their professional longevity is played by the postflight rehabilitation of cosmonauts.

RADIATION SAFETY OF SPACE FLIGHTS

The main lines of studies for ensuring human health safety in SFs is the study of radiobiological consequences of exposure to space radiations, dosimetry in space, and standardization of radiation exposures of cosmonauts [37].

The main achievements in this area are given below:

- creation of the SF radiation safety system;
- determination of the pattern of formation of radiation fields in the orbit and in the body of cosmonauts [37];
- development of methods for predicting the radiation situation in space [28];
- development and implementation, under SF conditions, of methods and means of dosimetric control [48];
- justification of allowable doses for cosmonauts in long-term SFs, development of norms of radiation safety [18, 33];
- long-term constant monitoring of radiation situation during OS missions (Institute of Biomedical Problems together with the State Research Institute of Nuclear Physics of Moscow State University) [34].

In combination with flight and ground-based radiation, physical and radiobiological studies, including experiments with heavily charged particles on cyclotron at the Joint Institute of Nuclear Studies (Dubna), the following important results were obtained [33, 34, 42, 56]:

- the consistent patterns of the formation of the dose of space rays in biological tissue (experiments with a Phantom device for assessment of dose loads on critical organs of cosmonauts) and in protective material were found;
- coefficients of the relative biological efficiency of space radiation were determined;
- principles of optimal protection from radiation, including active electromagnetic, electrostatic, and dielectric protection, were elaborated (Institute of Biomedical Problems together with Research Institute of Nuclear Physics of Moscow State University);
- acute and delayed consequences of radiation of biological objects with heavy charged particles were determined.

Because of the high penetrating capacity of heavily charged particles, particular attention will be paid to the study of their harmful effect on the central nervous

system, visual function, retina, lens, and formation of mutations and search for the means of protection.

Studies of the combined effect of radiation and microgravity will be also continued [41].

STUDIES OF LIFE-SUPPORT SYSTEMS AND PROBLEMS OF HABITABILITY

Considerable progress was made in the creation and operation of physicochemical life-support systems (LSSs) of orbital space stations:

- standards, methods, and means of monitoring of environmental parameters were developed;
- systems for producing oxygen based on water electrolysis and based on solid substances were engineered;
- regenerative systems of carbon dioxide removal were developed;
- technologies of water regeneration from water-containing products of human life activity and biotechnical systems were implemented [27].

Great attention is paid to elaboration of biological components of LSSs that can become part of promising combined LSSs and increase closed substance cycles in piloted space apparatuses. At the Institute of Biomedical Problems, a large series of ground-based model studies of biological LSSs based on photosynthesis of unicellular algae and higher plants with complete oxygen and water regeneration was performed [44]. In experiments performed on board the *Salyut* and *Mir* OSs and biosatellites, normal development of unicellular algae in an ecologically closed system was shown [40].

In 1979, in an experiment on board the *Kosmos-1129* biosatellite and in the 1990s on board the *Mir* OS, studies were performed that showed the possibility of exercising embryogenesis of birds (Japanese quail) under the conditions of microgravity [20].

Of great importance are studies on the problem of habitability, based on which the system of antiepidemic measures, means of personal hygiene, systems of chemical and microbiological monitoring, and means of the protection of the interior, systems, and equipment from the destructive effect of microorganisms were put into the practice of cosmonautics [27].

In order to reduce the possibility of infectious diseases in SFs, systematic studies of microflora comprising microecosphere of OSs and assessment of metabolic, phenotypic, and genotypic-specific features of microorganisms are performed [4].

One of the new lines of microbiological studies on board the ISS is the study of survival of spore forms of microorganisms under conditions of open space (the Biorisk experiment). It has been shown that spores after many months under extreme conditions of space do not lose their viability [31]. Parallel to spores of microorganisms, under these conditions, the survival of resting stages of several organisms (seeds of higher

plants, larvae of mites, eggs of lower crustaceans) are also studied.

The survival of these biological objects is also to be studied in an interplanetary mission of the Fobos-Grunt space apparatus. These studies are important for the problems of exobiology and for the formation of the concept of planetary quarantine.

PILOTED FLIGHTS OF THE ISS

The system of maintenance of the physical and psychological health of cosmonauts in long-term SFs successfully implemented in the OSs *Salyut* and *Mir* became the basis of medical care at the Russian segment of ISS, including the following aspects:

- flight monitoring of the crew members' health;
- a system for the prevention of unfavorable effects of long-term SFs;
- medical support of extravehicular activity;
- the system of rendering medical help;
- the system of life support;
- monitoring the environment;
- radiation control, measures of radiation safety [2].

The medical support of the health of ISS crews is based on the integration of the latest medical knowledge and technologies used in various countries to solve the practical tasks of the provision of medical safety and support of the health of the crews of the ISS. Of great importance is the use of unique international requirements for medical support of SFs and standards of health of cosmonauts and astronauts, as well as the integration of the means of medical care at the ISS, including onboard systems of prophylaxis and providing medical aid, means of monitoring the environment, radiation, personal hygiene, feeding, and the water supply [2].

The system of prophylaxis occupies an important place in the maintenance of the health and working capacity of cosmonauts on board the ISS. It uses training facilities, including a treadmill, a bicycle ergometer, resistance bands, a load suit, the Penguin suit to create dynamic and static loads, and an electromyostimulator, and is aimed to load the musculoskeletal system, activate proprioceptors, and preserve posture and locomotor functions [45]. An important component of the system of prophylaxis is a special training cyclogram and the possibility of diagnosing the motor system using the locomotor test.

In order to maintain the distribution of liquid media at a level close to the Earth, a Chibis device and occlusion suits are used. Means for prevention of loss of water and minerals and the maintenance of orthostatic stability are applied. Means of prophylaxis include a balanced diet, vitamins, and drugs to correct the negative responses of the body during an SF.

At the Russian segment of the ISS, a large-scale research program is underway that includes the study of the state of the cardiovascular system, water—salt

homeostasis and its hormonal regulation, and the immune state of the periodontium. Psychophysiological assessment of an operator's activity and radiation-physical, radiobiological, genetic, biotechnological, and other experiments are also performed.

IMPORTANCE OF THE LATEST TECHNOLOGIES FOR THE DEVELOPMENT OF SPACE BIOLOGY AND MEDICINE

The experience of biomedical support of SFs indicates the exceptional importance of scientific studies for the solution of the most complex problems set by piloted cosmonautics. The assessment of risks for various body systems in SFs, scientific analysis of the obtained information on their state, determination of mechanisms of the observed changes, elaboration of practical measures and means to reduce and prevent unfavorable shifts, and the objective assessment of their efficiency is the necessary sequence of problem solution. Throughout the 50 years that have passed since the first human flight to space, one can trace a pronounced tendency for the perfection of the methodology of biomedical studies and the solution of the set tasks of the achievements of modern biology and medicine and other sciences.

The scientific progress in recent years is rightly called biological revolution. The requirement and need of using these achievements to give a powerful stimulus to the development of biology and medicine are beyond doubt.

In terms of the methodology, it is necessary to use approaches from the standpoint of the molecular genetic system of controlling the body functions and performing experimental studies at the levels of cells, cell structures, and biomolecules.

In this respect, definite steps are being made. This is exemplified by studies performed at the Institute of Biomedical Studies on gravitational cell physiology, space biotechnology, and in the sphere of proteomics.

The data have been accumulated that the changes in the body and its individual systems upon exposure to extreme factors of an SF may be based on changes of cellular and molecular processes.

In particular, under the conditions of microgravity, changes in the migration activity of cells, the reduction in resistance to cytotoxic agents, the change in the expression of molecules, adhesion on the surface of cells, potentiation of the effects of cytokines, and modification of the cytoskeleton have been shown [46, 47].

The following studies in this direction seem promising:

- (1) Determination of genes involved in the perception and processing of the gravitational stimulus.
- (2) Study of the effect of microgravity on intercellular interactions and conductance of intracellular signals.

(3) Assessment of the effect of gravitation on the differentiation of stem and embryonic cells.

(4) Study of the mechanisms of the transformation of the gravitational stimulus in a cell.

High-precision methods of proteomics permit studying hundreds and thousands of human body proteins simultaneously. In this area, studies on the limits of the variability of the protein composition of liquids in the body of cosmonauts (blood, urine) have been initiated. It was found that the qualitative composition of urinary proteins and their levels change after the SF. Variability of some blood proteins in healthy people can be greater than the so-called clinical norm describing the possible range of changes for a group of approximately 150 proteins [58].

Note also that, in piloted studies on board the *Bion-M1* satellite, during the study of the mechanisms of the effect of microgravity on living systems of various levels of phylogenetic development, special attention will be paid to molecular genetic and molecular biological changes upon exposure to SF factors.

BIOMEDICAL ASPECTS OF THE PILOTED MISSION TO MARS

Performance of a piloted mission to Mars is the most important promising task of modern cosmonautics/astronautics.

The uniqueness of the Martian mission is determined by its autonomy, long duration, specific features of the interplanetary environment and stay on Mars (possibility of receiving dangerous doses of ionizing radiation, hypomagnetic environment), alternation of various levels of gravitation (from G-loads to microgravity and 0.38g on Mars), remoteness from Earth and social isolation, large psychological loads (high level of possible risks, high responsibility, problems of communication in the crew), severe climate, danger from meteorites, and the possibility of dust storms. The listed factors set extremely high requirements for the provision of medical safety at all stages of the preparation and performance of the mission, and also after its termination.

The solution of biomedical tasks of the Martian mission will require target studies and efficient developments in a number of fields (the concept of the medical center, telemedical technologies in interplanetary flight, an improved set of prophylactic drugs, creation of autonomic LPS, and support of the activity of cosmonauts in periods of interplanetary flights and on the planet, etc.) [16, 17, 27].

Problems of Crew Selection

It seems expedient to select participants of the mission among persons who have experienced SFs. This will facilitate the task to physicians who, in this case, will have at their disposal medical data on the state of

the health and responses of the body of candidates in previous flights.

Methods of selection should promote revealing latent pathology, particularly, mental disorders, and the reduced level of functional loads.

It is necessary to search for objective criteria for predicting the resistance to stress and osteoporosis, individual radio sensitivity, and other important indices based on methods and the criteria of genetics and molecular medicine [3]. Individual selection should take into consideration professional and personal qualities.

Problems of Medical Support

The autonomy of the Martian mission and its significant duration will require the creation of an on-board medical center and the inclusion in the crew of a highly qualified physician capable of providing diverse medical aid, including surgical and stomatological. The medical center should be equipped to perform medical control, diagnostics, and treatment, as well as have at its disposal telemedical technologies with the possibility of a high-quality connection, transfer of medical video images, and obtaining consultative help. Optimization of the onboard set of drugs will be also needed with the inclusion of efficient clinically tested drugs with an increased period of storage, as well as the development of improved sets of instruments to perform diagnostic manipulations and provide medical aid.

System of Prophylaxis

The creation of a highly efficient system of prophylaxis of gravitational effects at all stages of the flight to Mars will be needed. During its elaboration, the system of prophylaxis existing on board the ISS can be adopted after certain modification. In this respect, the ISS can be regarded as a test ground for the perfection of various medical and medico-technical technologies of future interplanetary flight.

There are grounds to suggest that it is expedient to augment the system of prophylaxis by the artificial gravitational force (AGF) created using a short-radius centrifuge (SRC). A.R. Kotovskaya et al. generalized the results of studies on the application of rotation in centrifuges under the conditions of simulated microgravity [25]. It was shown that AGF increases gravitational stability, reduces unfavorable changes in the functions of the cardiovascular system, external respiration, as well as the state of the water-salt metabolism and the blood coagulation system, etc.

The positive prophylactic effect of AGF was found also under the conditions of microgravity at the *Kosmos-936* satellite. AGF in flight was produced by rotating rats in a centrifuge with an acceleration of 1g.

It has been found that the effect of AGF reduces atrophic changes, prevents metabolic disturbances in

skeletal muscles, and reduces the concentration of calcium, phosphorus, and minerals in tubular bones [22].

For practical implementation of the idea of using AGF in interplanetary missions, it is necessary to solve a number of problems, including determination of the efficiency of controlled interval AGF to ease the unfavorable effects of the simulated microgravity of various durations on various organs, systems, and functions of the human body; and the elaboration of optimal regimes, methods, and cyclograms for the performance of rotations on AGR, the assessment of the negative consequences of rotations on an SRC, determination of a way to reduce them, and elaboration of methods for using AGF in combination with traditional means of prophylaxis.

A large amount of preliminary ground-based studies will be needed to reveal the effects of artificial gravitation at various regimes of centrifuge rotation.

Radiation Safety

Radiation safety is the most difficult task during the flight to Mars.

Protons of solar explosions and the heavy nuclei of galactic space rays present a serious danger and require measures for the protection of cosmonauts (radiation shelter, local protection, special pharmacological drugs, radiation monitoring along the flight route, dosimetric control). A serious danger in terms of protection is galactic space rays having a high penetrating capacity.

Psychological Problems

There is a variety of psychological problems on whose solution the maintenance of an adequate level of professional activity and optimal relations of the crew members depends. These include the problem of leader selection, intergroup communication (with regard to multicultural and gender composition of the mission), efficient psychological support, etc. Parallel to it, it is necessary to create tools for monitoring the psychological state and training equipment for supporting habits of hand control and assessment of the psychophysiological cost of activity.

Problems of Life Support and Sanitary and Hygienic Safety

It will be necessary to develop autonomic regenerative systems of life support using physicochemical and biological technologies with an optimized environment.

Problems of life support should be considered in terms of actual biocenosis, taking into account the interaction of biological chains (humans, microorganisms, plants, and a heterogeneous chain of birds, fish, and mollusks). It is necessary to create modified technologies to breed higher plants in onboard greenhouse

devices (decrease in the use of energy, regeneration of soil substrate, etc.)

At the present time, technologies for the creation of systems of transformation of the waste of human life activity that will be an important module of LSS are insufficiently elaborated.

It is also necessary to create onboard devices for the analysis and monitoring of toxic substances in the atmosphere and develop photocatalytic cleaning systems. Safe and quick methods of identification of microorganisms and environment disinfection will be also needed.

The listed set of tasks should be solved in scientific and technological experiments, in long-term circumterrestrial SFs, and in integrated model experiments. An important experiment in this area is being conducted at the Institute of Biomedical Problems.

MARS-500 EXPERIMENT ON GROUND-BASED SIMULATION OF A PILOTED MISSION TO MARS

In 2010, at the Institute of Biomedical Problems, a 520-day international model experiment on the perfection of elements of biomedical support of piloted flight to Mars (director of the project, E.V. Morukov) was initiated.

The tasks of the experiment are give below:

—Testing modified devices and methods for the prophylaxis of the unfavorable effect of microgravity and other factors of SF;

—Further improvement of promising devices and methods of medical control of the state of health of crew members;

—Testing new devices and methods of medical aid in flight, including telemedical.

Considerable attention in the experiment is paid to psychophysiological problems:

—Further improvement of promising devices and methods of checking the activity of operators and their psychophysiological state;

—Optimization of the system of selecting and training crews;

—Assessment and regulation of group interaction in the crew with regard to the culturally specific features of the participants of the experiment.

As for the problem of inhabitability, it is planned to perform modified monitoring and checking of the environment and functioning of the systems of life support, as well as to perfect technologies of biological LSS.

The experiment on inhabitability was performed successfully and ended in November 2011.

Space biology and medicine have accumulated significant scientific material on the state of the main systems of the body and their regulation and checking of the state of health of cosmonauts under the conditions of SF. Theoretically and practically important facts

have been established, and their mechanisms at the body, organ, biochemical, and morphological levels were clarified.

The complication of the pattern of activity of cosmonauts at circumterrestrial orbits and prospects of exploration of distant space set new tasks for space biology and medicine. Their solution will require multi-profile scientific studies and the development of key technologies using the latest achievements of molecular biology, genetics, genomics, biotechnology, and proteomics that will determine the basis for the prospects of developing space biology and medicine.

Celebrating the 50th anniversary of the flight of Gagarin, we should in full measure assess the importance of this event, the greatness of the personality of Earth's first cosmonaut, and his contribution to the formation of cosmonautics. Academician M.V. Keldysh said that the exploit of Gagarin made a large contribution to science; it opened a new epoch in the history of mankind, namely, the beginning of human flight to space and the path to interplanetary communications.

CONCLUSIONS

In conclusion, we point out the highly professional labor during the preparation and performance of programs of piloted space flights of researchers of the State Research Experimental Institute of Space Medicine, Institute of Biomedical Problems of the Russian Academy of Sciences, Gagarin Research Cosmonaut Training Center, Energia Rocket Space Corporation, Central Research Institute of Mechanical Engineering, Research Institute of Chemical Engineering, Zvezda Plant, Research Institute of Nuclear Physics of Moscow State University, Joint Institute of Nuclear Studies (Dubna), specialists of many institutes of the Russian Academy of Sciences and the Russian Academy of Medical Sciences and congratulate all of them on the Day of Cosmonautics.

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