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SIMULATION OF PHYSIOLOGICAL SYSTEMS IN ORDER TO EVALUATE AND PREDICT THE HUMAN CONDITION IN A SPACE FLIGHT

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16. Abstract

The article discusses various simulation and mathematical modeling related in general to space medicine and biology. It concludes with the observation that simulation modeling in space biology has a broad outlook.

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SIMULATION OF PHYSIOLOGICAL SYSTEMS IN ORDER TO EVALUATE AND PREDICT THE HUMAN CONDITION IN A SPACE FLIGHT

by

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The development of manned space flights has evolved on the /1* path of an increase in their duration, complexity and autonomy, which makes ever more significant the problem of predicting the state of health and performance capacity of the crew members both during the actual flight and in their subsequent re-adaptation to normal terrestrial conditions. In addition to the heuristic prediction mainly based on erudition and the intuitive capabilities of the experts, methods of prediction must play a considerable and gradually increasing role, methods that use the simulation models that permit an estimate of the reactions of the main physiological systems to the significant effects under conditions of space flight and the occurrence of the adaptation process of these systems to the complex effect of the flight factors. The problem of the basic applicability of the simulation for these purposes has been discussed many times during the preceding meetings of the Soviet-American working group [1-5]. We are prone to completely share that opinion of the U.S. specialists stated in 1978 [6] that this method "is a unique means for

*Numbers in margin indicate pagination in original foreign text.

interpreting experimental data." On our part we would consider it to be proper and possible to add that man's penetration into space has initiated the emergence of a number of theoretical problems of space biology and medicine for which the simulation models can serve as an adequate weapon to study them. Their introduction into the practice of space biology and medicine will to a certain measure promote the progress of biology and medicine as a whole, for the rapid development of physics and related sciences that was started in the 17th-18th centuries in no small degree was governed by the use of the mathematical formalization of the studied problems, and in the final analysis, the construction and study of the models of processes and phenomena.

In accordance with the discussion of the problem the past conferences have acknowledged that it is expedient to conduct experimental simulation during the joint Soviet-American experiment on hypokinesia carried out simultaneously in the USSR and the United States in the summer of this year. Simulation was a part of the mathematical computer analysis of this experiment. This report discusses only the questions of simulation associated with this.

The possibilities for using simulation in the given situation were determined by the specific nature of the experiment: its brevity and comparatively good degree of previous study of those /2 physiological mechanisms which determine the dynamics of the developing processes. Therefore it was acknowledged that it is expedient to focus primary attention on the simulation of physiological tests in the background and restorative period in order to pinpoint the quantitative characteristics of the extant biological ideas on the effect of antiorthostatic hypokinesia, as well as additional approval and verification of the models.

Since the leading effect during antiorthostatic hypokinesia is redistribution of fluid masses, resulting through shifts in the neuro-humoral regulation to changes in the water-saline exchange, a decision was made to simulate the effect of a 2% water load. According to the program of the experiment this functional test was conducted both in the background and in the restoration period. For the simulation a model was used of the water-saline exchange that was reported at the eighth meeting of the Soviet-American working group [7]. A block diagram of the model is presented in figure 1. Preliminary approval of the model according to previous results of functional tests yielded applicable results (figure 2).

Initially during simulation of the functional tests with water load the task was advanced of verifying the following hypothesis: can the differences in the reaction to load be explained only by the difference in the conditions of hormonal concentration (ADH and aldosterone). The tests, in accordance with the cyclogram of the experiment, were made in the background period and on the second days of the restoration period. The effect of the initial ADH and aldosterone concentrations was evaluated also by computation. In particular, the value of diuresis is a function of the amount of glomerular filtering, of the relative ADH level, a certain coefficient linked to the ratio of maximum diuresis to the background and to a certain "normal" value of diuresis rate, which from the results of past experiments [15] were estimated at 1 ml/min. By knowing the maximum amount of filtering and the diuresis rate at this moment when the relative ADH level is close to zero, one can estimate VM which makes it possible with a "normal" value of filtering to compute ANM--the relative intensity of the ADH effect. In a similar manner an estimate was made with the help of the amount of sodium excretion of the intensity of the effect of aldosterone AM that is the relative as compared to the norm.

The estimates demonstrated that the change in ADH before the

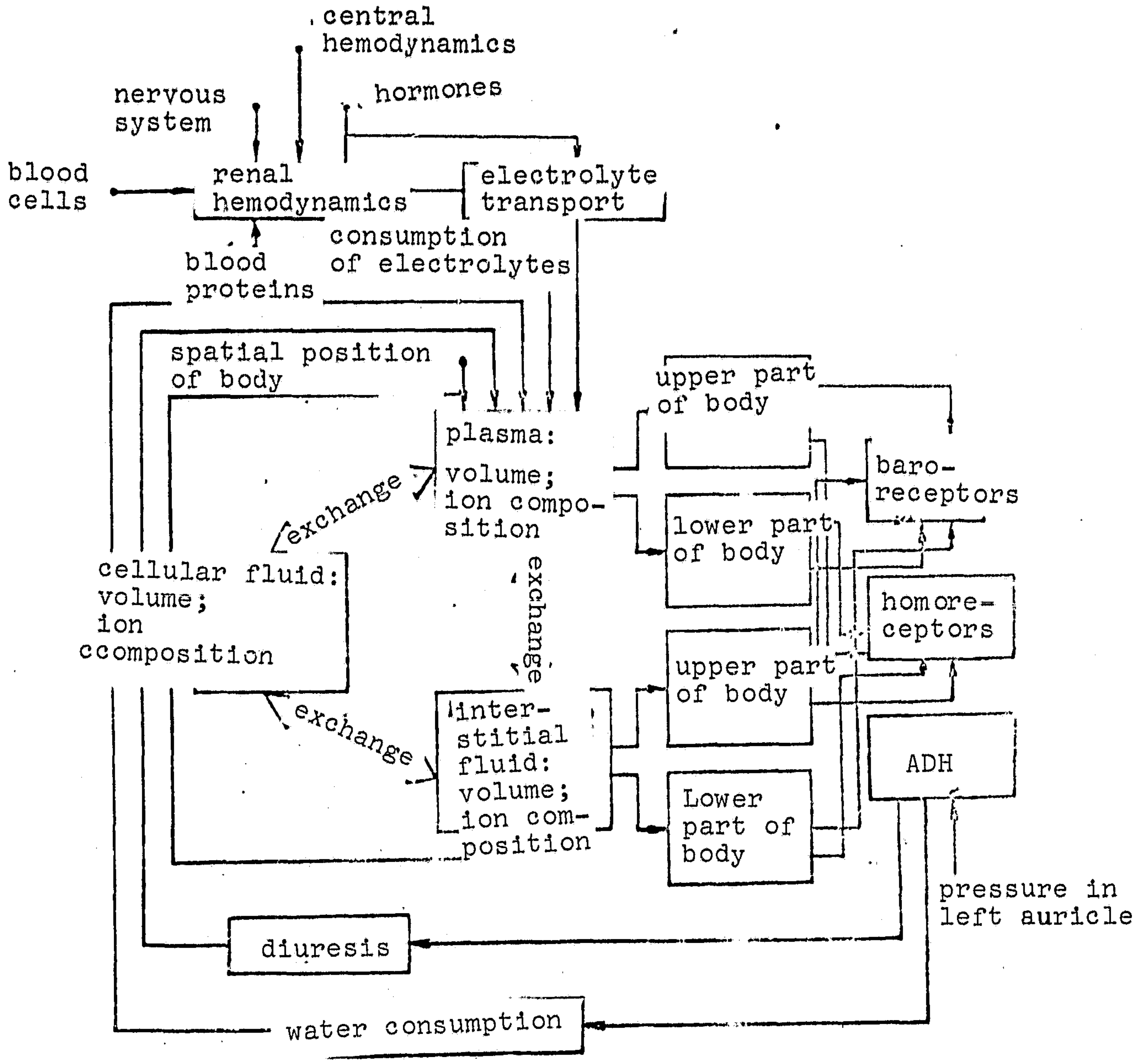


Figure 1. Regulation of Volumes and Ion Composition of Fluid Compartments of Organism (explanation in text)

test in restoration as compared to the background period in both experimental groups had a different-direction which, apparently /3 reflected the individual nature of the reactions of the testers. For this reason it was acknowledged to be expedient to separate in the diuresis simulation the entire set of testers into four subgroups in acccordance with the enclosed plan:

TABLE 1

CHANGE IN ADH LEVEL (MODEL EVALUATION)

Position of testers	↓	↑
Antiorthostasis	[1] 1,5,7	[3] 3,9
	[2] 4,6,10	[4] 2,8

The numbers in the squares represent the conditional number of the group, the remaining numbers identify the testers.

Further the work was conducted as follows: by varying the different coefficients that figure in the model, we strived as accurately as possible to reproduce the real curves of diuresis for the isolated groups and individual testers. The attempt to explain the variability in the reactions to the water load only by variations in the initial hormonal background proved to be unsuccessful. All the differences in the curves that could be associated with these changes have an effect only in the limits of roughly one hour after the start of the test and could not be, for example, the cause of the shift in the diuresis maximum and a number of other significant changes in the shape of the curve. We note that even the variation in these amounts in the limits a fortiori broader than were in the experiment did not yield the desired results. However, very constructive results were yielded by consideration for the variations in the model coefficient VM linked to the ratio of the maximum (with ADH level close to the condition) diuresis to the normal. The VM values estimated with the help of the model equations are presented in table 2 jointly with the estimates obtained by the same method of the ratios to the norm of volumes of extracellular water (VEC), concentration of ADH in the blood (ANM) and aldosterone (AM) according to groups.

TABLE 2 /4

Group	VM		VEC		AHM		AM	
	Ф	Б	Ф	В	Ф	В	Ф	В
I	I5,5	I7	0,96	I	2	I,6	I,4	I,6I
2	I6,5	I7	0,98	I	I,96	I,45	0,85	I
3	I5,5	I6,5	0,96	0,98	I,27	I,5	0,84	I,25
4	I6	I6	0,98	0,97	I,3	I,5I	0,96	I,2

That fact deserves to be noted that the more significant VM changes were noted in the groups in an antiorthostatic pattern. This makes is possible to hypothesize that the summary effect of the experimental factors resulted in a change for these groups in the limit value of rate of water readsorption.

However, consideration for the changes in the VM coefficient was insufficient. In our opinion, a satisfactory approximation of the experimental curves (figures 3,4,5,6) was possible only with a variation in the values of the starting volumes of extracellular fluid. Table 3* shows the VEC values in which the maximum correspondence was attained of the experimental and model curves of diuresis, excretion of sodium and potassium. Apparently, the greatest difference between the background and the restorative period is observed in the "antiorthostatic" groups 1 and 3, although the changes in these groups are of different directions. Since at the moment of simulation we did not possess real data of

*Translator's note: Table 3 missing from original foreign text.

measurements of the body volumes, but only preliminary information on the balance of water and electrolytes, the following explanation of these differences was proposed. The conditions in the background period were governed by intensified water consumption, which due to the individual peculiarities of the testers was most pronounced in groups 1 and 3. Due to this part of the testers could, despite the increase in diuresis in the period of hypokinesia, increase the volume of intracellular fluid. Apparently, the same occurred in group 1, where in one of the testers the water consumption surpassed the diuresis even during hypokinesia. In group 3 the restoration of fluid exchange was lower. This was indirectly indicated by the decrease in weight during the experi- /5
ment, comprising 1% of the body weight in group 1 , and 2% in group 3. In groups 2 and 4 the changes in weight were, respectively +0.1% and -1.4%. This can to a certain degree explain the differences in the estimate of the ADH level, if one assumes that a considerable part of the weight loss occurred due to the release of water. The general conclusion that can be made in an analysis of the work on simulating the diuresis curve consists of the fact that the antiorthostatic pattern revealed in more relief the difference in the dependence of diuresis rate on time, which was poorly distinguishable with the zero angle of body position.

Figure 7 presents the relationships of excretion of sodium and potassium during the water test with the adopted estimates of the volume of extracellular fluid, coefficient of maximum diuresis, activity of ADH and aldosterone and other coefficients adopted in simulation of the diuresis curves. Coincidence of the model curves and experimental data is fairly satisfactory. In the group with the antiorthostatic pattern the trend towards suppression of sodium in the test is noticeable to a greater degree in the restorative period as compared to the background period. The removal of potassium during the tests differed little both in different groups and in different periods of conducting of the tests.

The materials of the Soviet-American experiment on hypokinesia were suggested for use further to approve and study other simulation models of the physiological systems

We planned to conduct work on the development of models by studying individual situations and verifying the hypothesis, counting in the future on turning the set of simulation models into one of the routine resources for estimating and forecasting the state of man in a prolonged space flight.

In accordance with the established tradition we consider it useful in this report also to briefly inform our colleagues of certain basic directions in our current work on simulation modeling.

In addition to the model already discussed in previous reports of the cardiovascular system similar to that described in [4,9] and mainly oriented on simulating the reactions of the system to physiological tests of the orthostatic effect type, physical load, etc., it was acknowledged to be useful to formulate a model that is adapted to a greater degree for analysis of the adaptation-compensatory changes in the circulatory system /6
and that permits the possibility of analyzing the adaptation features of different types of circulatory regulation and the mechanisms of their formation. The main blocks in the model are the block of central regulation, block of hemodynamic parameters of the heart, and the capacity vessels of the large circle, and block of hemodynamic parameters of the resistive vessels of the large circle,the block of hemodynamic parameters of the small circle. Through the block of central regulation the signals locked from the receptor zones of the cardiovascular system: the baroreceptor zones of high pressure of nonmyelinized vagus receptors in the left ventricle and tissue receptors of the skeletal musculature. The sensitivity of the adrenoreceptors of the myocardium and the vessels is modelled. The block of

the left ventricle and the capacity vessels of the large circle also simulate such parameters as the frequency of cardiac contractions, finite-diastolic beat and per-minute volume of the left ventricle, mean, diastolic and mean-systolic pressure in the aorta. At the basis is an idea about the ventricle as a source of the mean isometric stress that has internal active resistance. The block of the resistive vessels of the large circle of circulation isolates three groups of vessels: vessels of the skeletal musculature, internal organs and renal vessels regulating the blood supply level of the kidneys. The model takes into account the biophysical characteristics of the vascular walls and their ability to structurally adapt. The hemodynamics of the small circle is described by an individual block which in the description of a number of situations can be significantly reduced. This "truncated" variant of the model is shown in figure 8.

The model makes it possible to simulate the following situations: relative calm, dynamic pattern and stress effects not accompanied by physical activity. The level of the physical load is simulated by the assignment of the amount of blood flow adequate to the needs for supplying the skeletal musculature with blood. The controlling signal for auto-regulation of the skeletal musculature vessels is the signal "debt of blood flow." In the situation of stress effect not accompanied by motor activity the indicated signal is blocked, general excitation is not accompanied by dilation of the vessels in the skeletal musculature, and it is not provided with the corresponding venous influx from the muscular pump. The possibility was examined of the emergence of hyperkinetic effects due to the increase in sensitivity of the beta-adrenergic receptors of the myocardium to the controlling effects of the sympatho-adrenal system and as a consequence of the increase in the tonic action of this system. The model was identified as applied to the conventional-normal type of person. Currently study is underway of the possibility of its application /7

2% water load under normal conditions

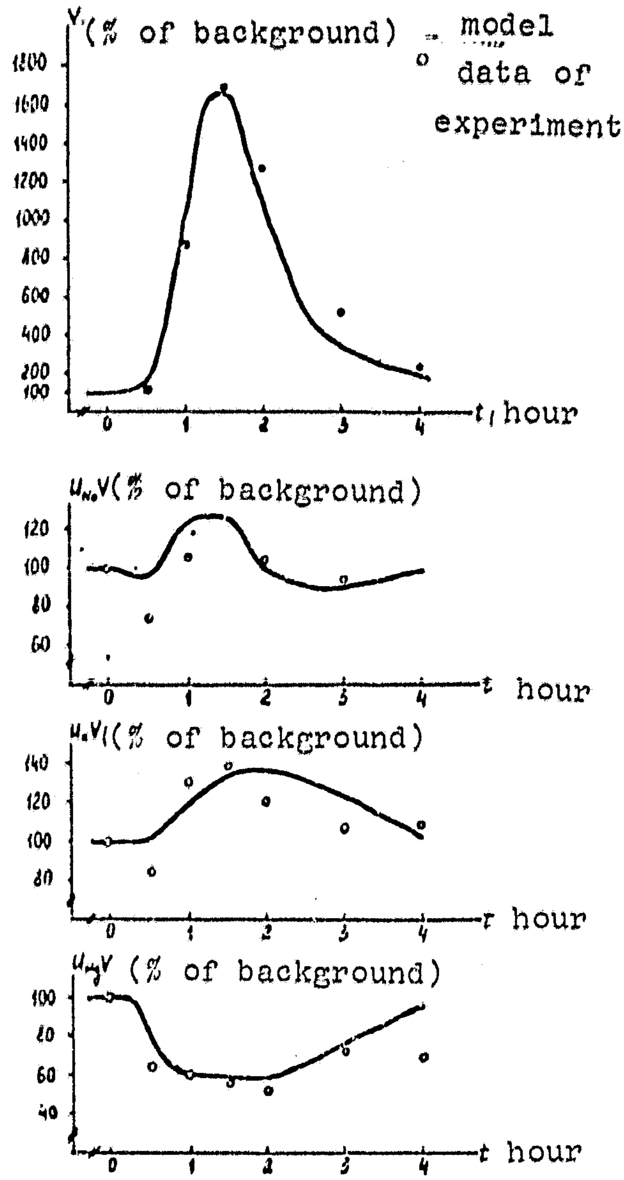
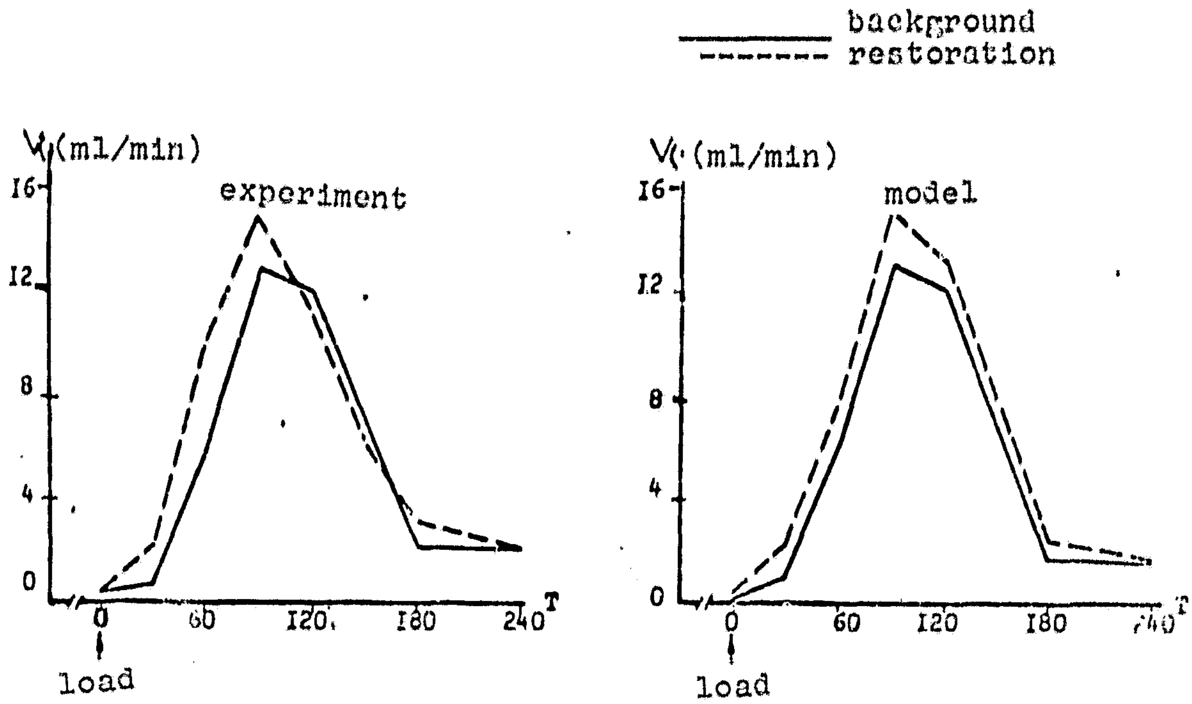


Figure 2. (Explanation in Text)

to analysis of the state of the cardiovascular system of operators experiencing psychophysiological effects.

Work to develop a model of the respiratory system whose variant was reported at the eighth meeting of the Soviet-American

Simulation of diuresis with 2% water load



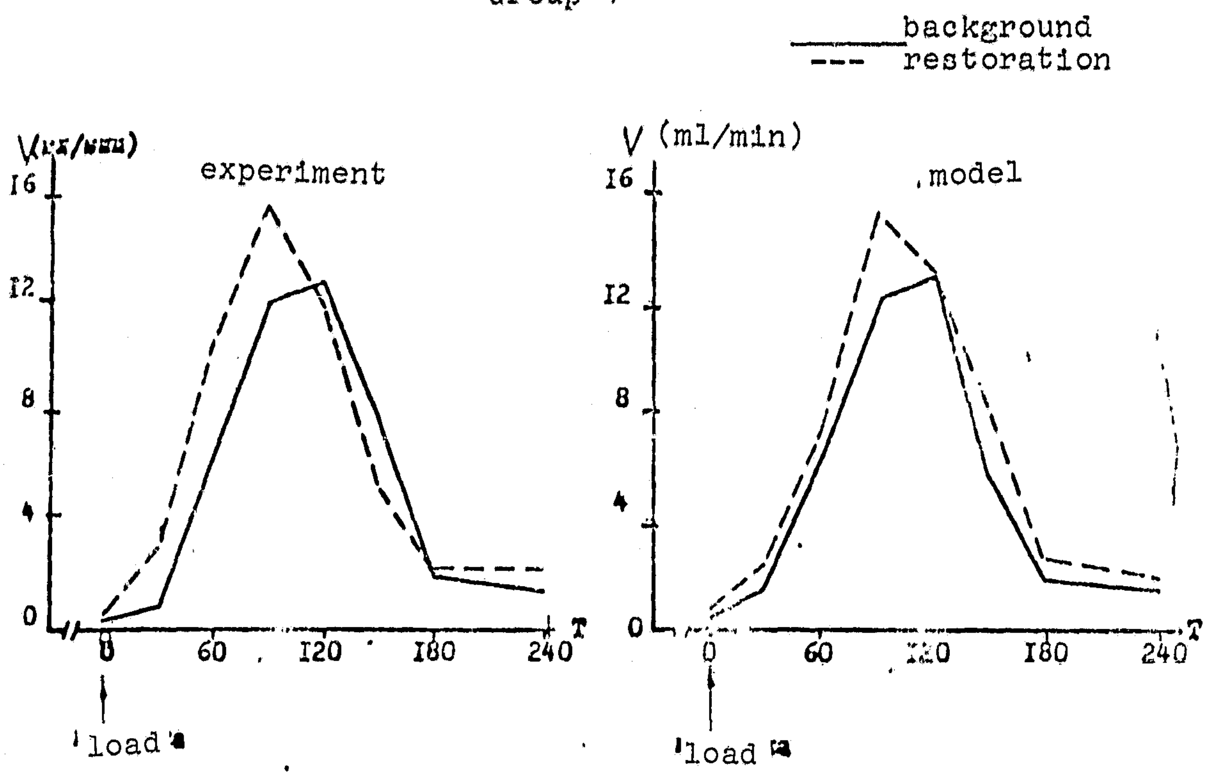
Group 1,4,5,6,7,10

Figure 3. (Explanation in text).

working group [8] was linked, in particular, to the theoretical analysis of the effect of the condition of the small circle of circulation on the distribution of ventilation-perfused relations and gas exchange in the lungs. The results of the experimental studies [10] indicate the significant effect of hemodynamics of the small circle on the degree of functional heterogeneity of the lungs. With the help of the model a study was made of the dependence of arterial-alveolar difference on the pressure in the pulmonary artery. The study results made it possible to evaluate the effect of possible changes in the tone of the pulmonary vessels and the pressure in them as a result of the prolonged effect of weightlessness on the distribution of Va/Q and the gas exchange.

In the model of functionally heterogeneous lungs blocks of

Group 4



Group 0

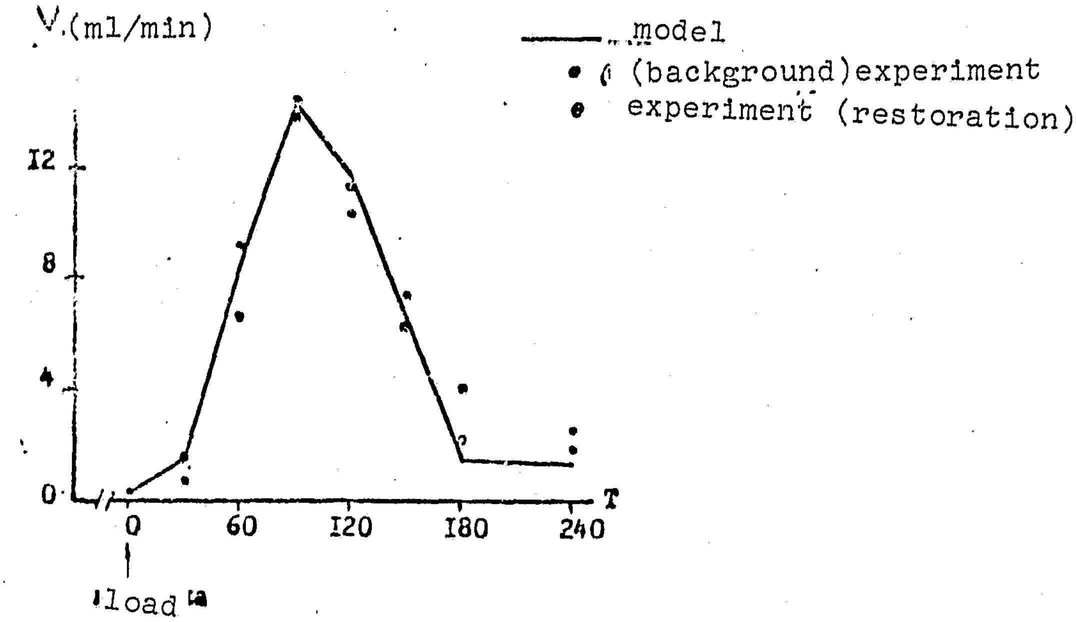


Figure 4. (Explanation in text)

blood flow, ventilation and gas exchange are isolated. In an estimate of the blood flow the stationary flow is estimated in the elastic vascular channel. Seven compartments were isolated of the vascular channel. To compute the distribution of pleural pressure and ventilation a model of pulmonary parenchyma [11] was used. Ten horizontal layers of the lungs were examined with the use of computed values of ventilation and blood flow, and equations describing the stationary gas exchange in each layer of the lungs were numerically solved. A computation was made of the composition of the mixed arterial blood,of the mixed alveolar air and the alveolar-arterial difference in the pressures of the respiratory gases. Figure 9 shows a comparison of the computed and experimental [11] curves for the distribution of the ventilation-perfused ratio according to the height of the lungs. For experimental curves 1 and 2 the pressure in the main pulmonary artery is, respectively, 19.5 and 16.5 mm Hg, pressure in the pulmonary veins 8.2 and 5.2 mm Hg. On the x-axis the distance is plotted from the top of the lungs in cm. Figure 10 shows the effect of pressure in the main pulmonary artery on ΔP_{O_2} and ΔP_{CO_2}. The numbers of the curves correspond to the different amounts of the arterial-venous difference in pressures 11.3, 7.5 and 6 mm Hg.

A very important direction in the development of models to estimate and predict man's condition during a space flight and /8
after its end is the construction of a model that simulates the change in parameters of erythron. It is known that one of the consequences of the effect of space flight factors on the human organism is a change in the quantity of the erythrocytic mass. In past reports we gave information about a model of erythropoiesis [2,12]. The rate of synthesis of erythropoietin and the rate of entrance of the reticulocytes into the blood are assigned by two differential equations. Synthesis of erythropoeitin is stimulated by a reduction in the hematocrit and the

Simulation of diuresis with 2% water load

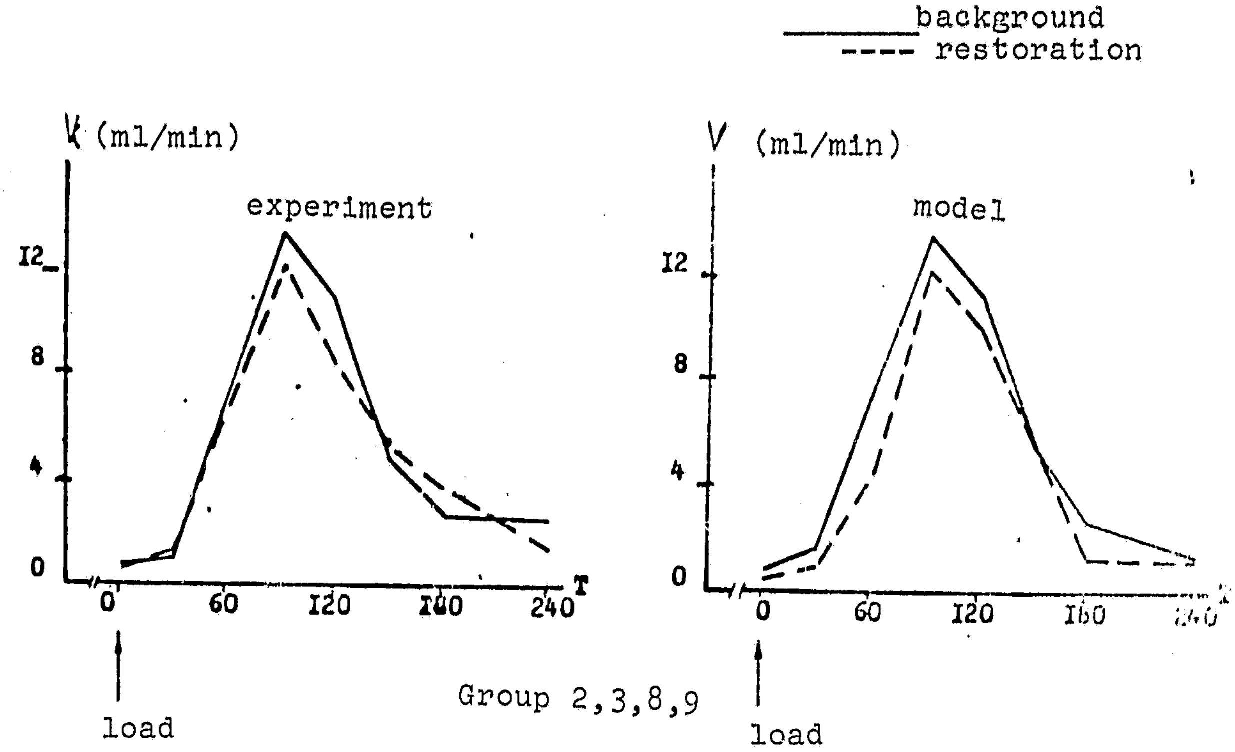


Figure 5. (Explanation in text).

presence of an oxygen debt signal. A measure of the oxygen debt is the difference between the quantity of oxygen necessary for the given level of metabolism and the oxygen capacity of blood. Since the model takes into account age structure of the population, it can take into account the dependence of the oxygen capacity and the level of the natural energy outlays of the erythrocytes on their age. With the assignment of functions that describe the change in the metabolism and the volume of plasma, the model makes it possible to evaluate the number of erythrocytes, hematocrit, oxygen capacity of blood, content in blood of erythropoeitin and a number of other informative parameters.

With the help of this model the reaction to a decrease in

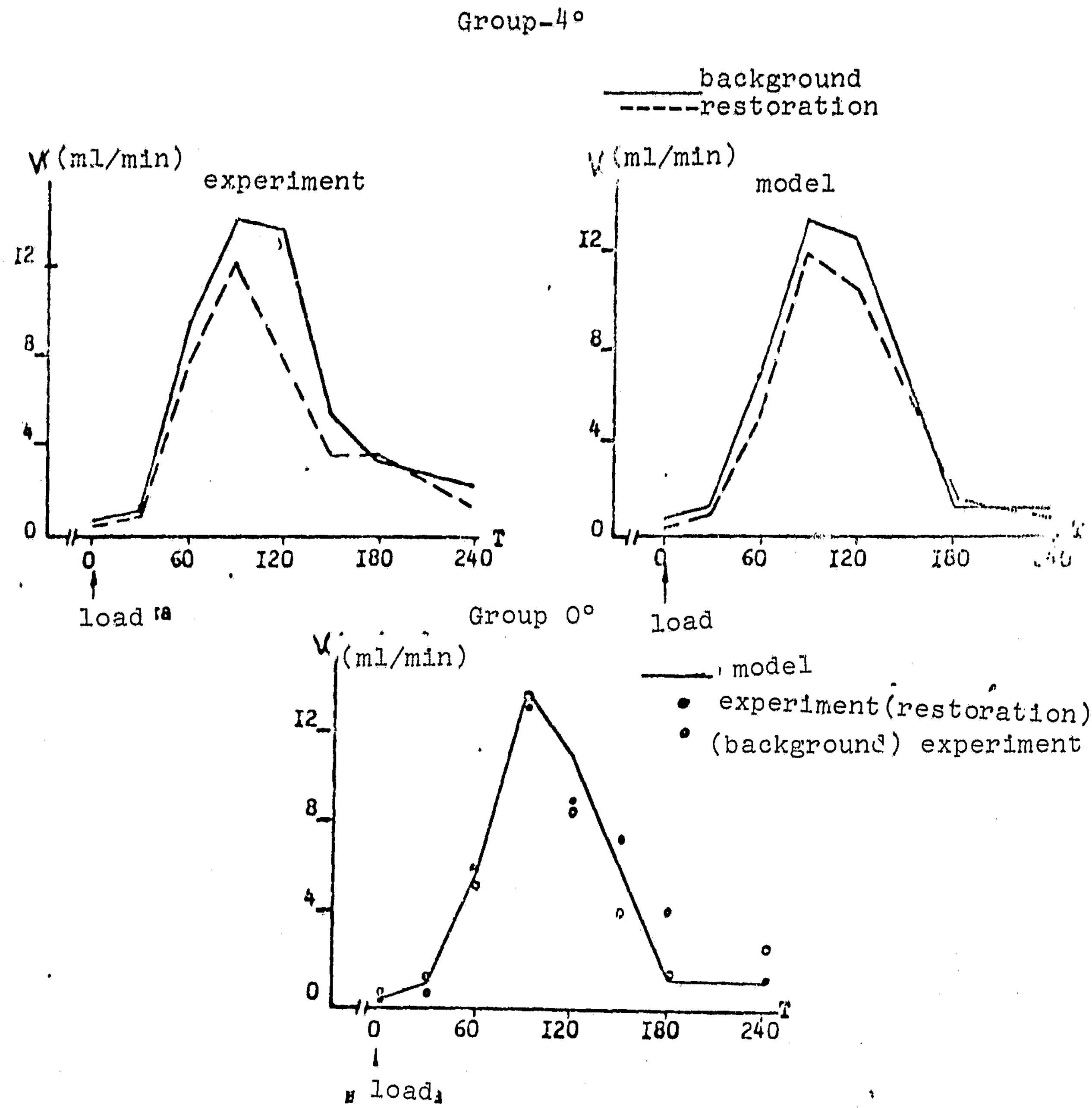


Figure 6. (Explanation in text).

the volume of plasma and intensity of metabolism. Report [2] showed the qualitative good coincidence of the model curve for the course of restoration of the erythrocytic mass after restoration of the plasma volume and intensity of metabolism with real

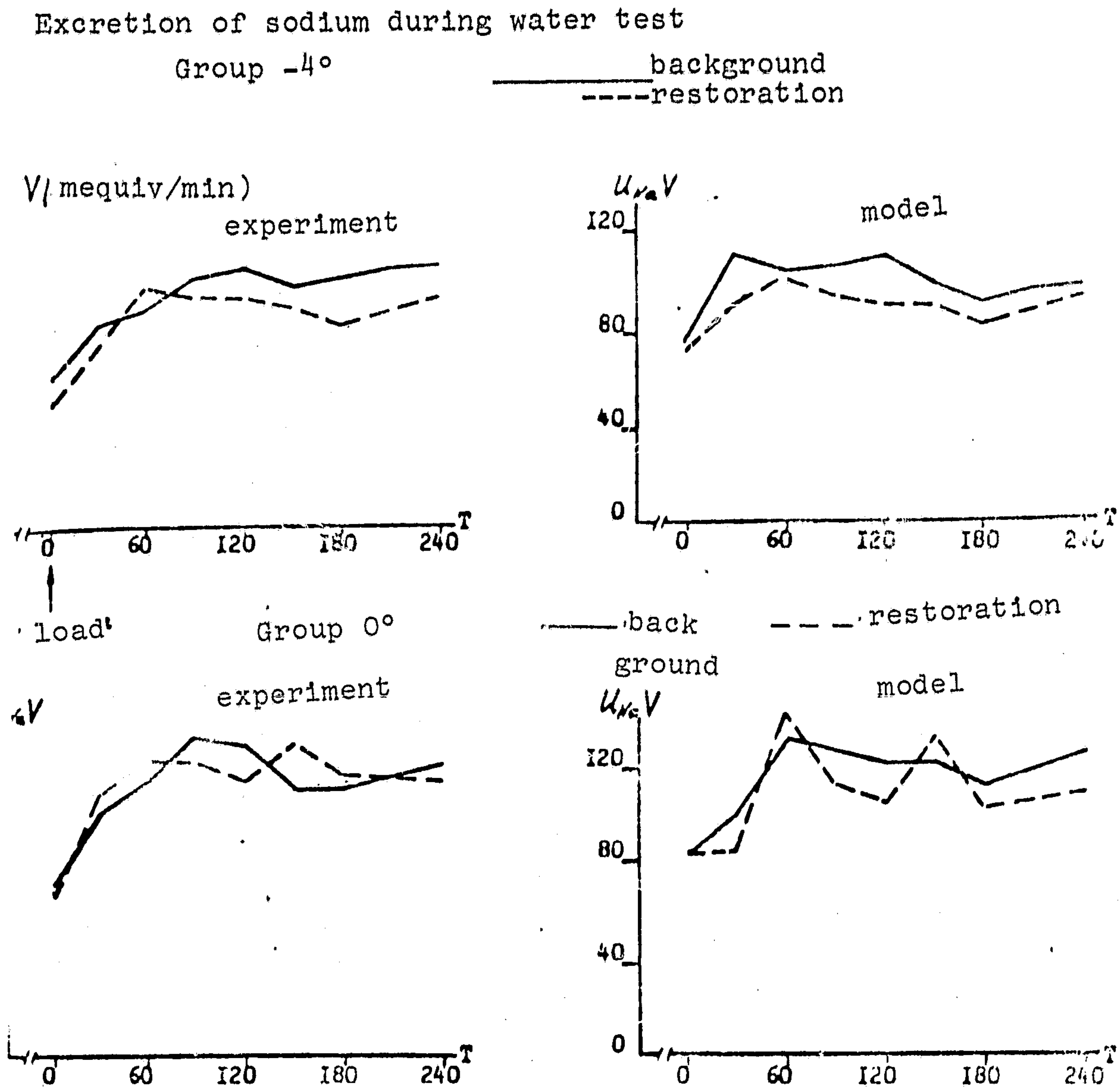


Figure 7. Explanation in text. (continued on next page)

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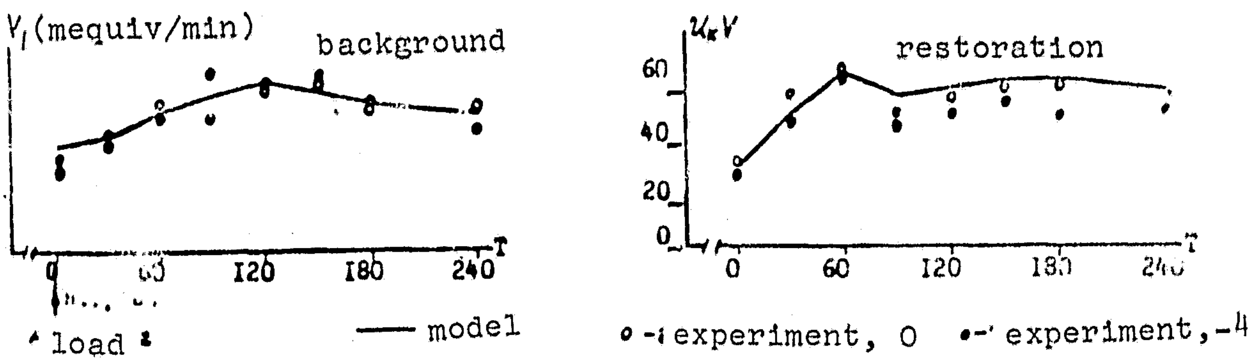
Excretion of potassium during water test



data obtained in experiments on the orbital station "Skylab." A number of complexities in the further verification and practical introduction of the model produces a difficulty in assigning the function D--measure of oxygen debt. In estimating the results of the first expedition on the orbital station "Salyut-6" the following tactics was used: the hypothesis was studied that the curve D experiencing a temporal reduction during the flight is restored by its end with the help of a physical load.

The study on the model demonstrated that in a broad class of curves corresponding to this hypothesis, it is impossible to find the curve that explains the really observed decrease in the erythrocytic mass, if one does not assume the explicitly unreal conditions of decrease in D (up to 50% and less of its background value). Consequently, it is necessary to assume that the level of metabolism is significantly not restored by the end of the flight, i.e., the preventive measures in the executed volume were insufficient. As is known, this is the situation in reality also.

The discussed model is in essence only a certain nucleus /9
of a more pithy system that describes the state of erythron. Among the blocks of this system of models a model is being developed for the metabolism of erythrocytes that takes into

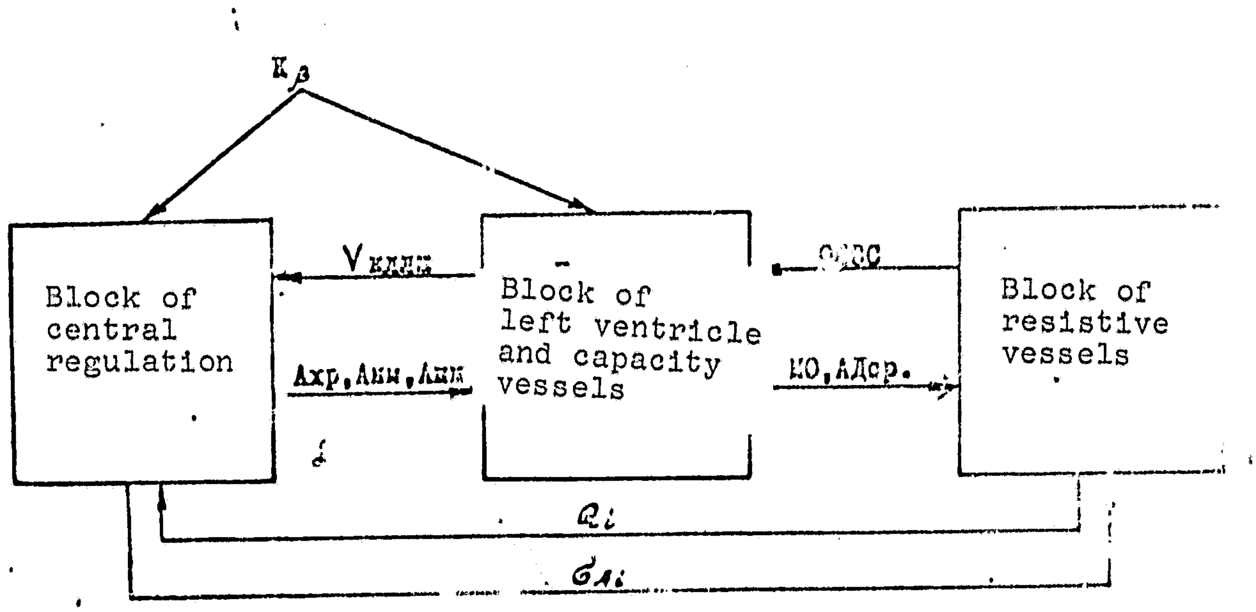


Figure 8. (Explanation in text)

account the dependence of the activities of the main enzymes on such factors of the intracellular and external medium, as pH, osmolarity, partial pressure of O_2 and CO_2, and temperature. At this stage due to the absence of a sufficient amount of experimental data mainly qualitative characteristics of the model are analyzed with the help of the ideas stated in [13] and the literature indicated there. In constructing the model the .hypothesis was used that the activity of each enzyme has a maximum for each of the listed factors. The state of the enzyme systems determines the selection of the path of metabolism in which the glucose consumed by the cell is recovered.The method for recovery of the glucose determines the rates of synthesis of the phosphoglycerine acids and the biological restorers whose content in the cell regulates the relationship of hemoglobin to oxygen and the intensity of the restoration of the enzyme systems and erythrocyte membrane. With the help of the model it was demonstrated that with a continuous change in one of the parameters of the external medium the "engagement" can occur of that path of metabolism for which the current value of the parameter approaches the optimal, or its "disengagement" with a sufficient removal of the distance from the optimum. Thus, a dependence can be obtained of the oxygen capacity of the erythrocytes on the composition and temperature of the blood plasma. Inclusion in the model of the dependence of the rate of membrane restoration on the correlation of metabolic paths makes it possible to describe the change in resistance and permeability of the erythrocytes under the influence of the same external factors. The resistance and oxygen capacity of the erythrocytes can be viewed as inlets for the previously discussed model of population of erythrocytes circulating in the blood. The composition of blood and its temperature can be exits for the models in the systems of external respiration, water-saline exchange, and thermoregulation.

For a more complete description of the state of the system of erythron it is necessary to also simulate the processes of proliferation and differentiation of the hemopoietic precursors of the erythrocytes. The idea is real that the set of maturing blood cells is an active distributed system with diffusion type of communication. Changes in the cellular density is described by equation [14]:

$$\frac{\partial n(\bar{x},t)}{\partial t} = \alpha\, n(\bar{x}, t-\theta) - \beta\, n^2(\bar{x}, t-\theta) + \eta(\bar{x},t) + D\nabla^2 n(\bar{x},t). \qquad /10$$

where the coefficient of diffusion D considers not only the movement of the cells, but also the change in their number due to a variation in the flows of the necessary substrates, while θ--mean time for conversion of stem [illegible] cells into cells determined towards the erythroid direction of differentiation

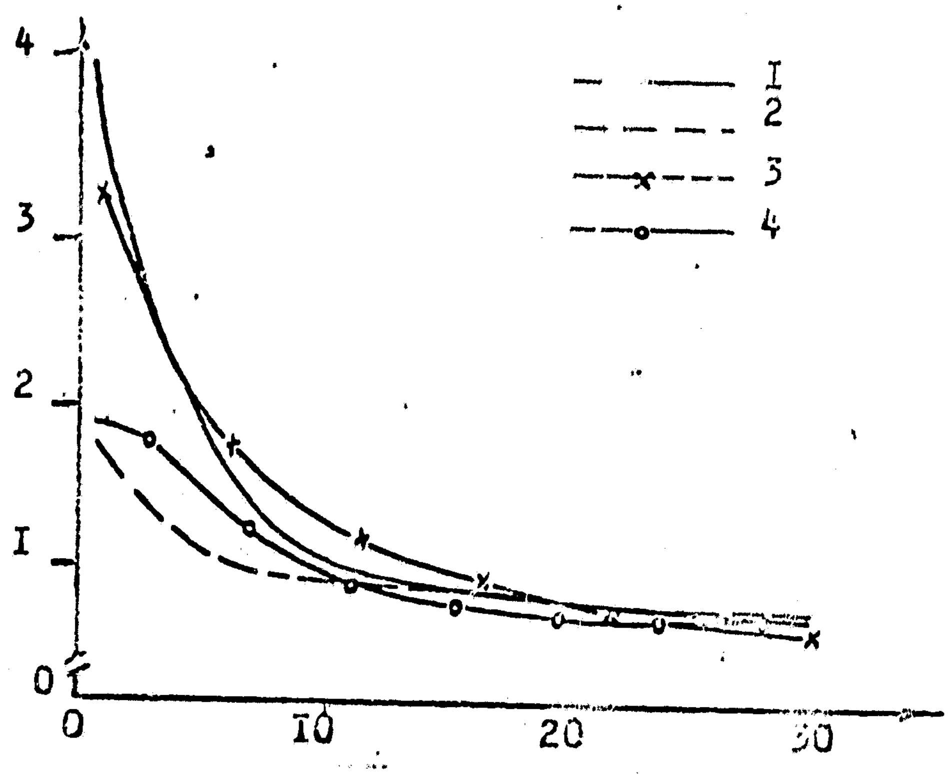


Figure 9. (Explanation in text).

in the absence of limiting. In such a system auto-wave processes emerge that intensify the patchiness of cellular distribution in the limits of the given base of blood formation both with respect to density and the intensity of their maturation, and also generate pulsation in the insulae of blood formation. Migration of the hemopoietic precursors functionally unites the spaced foci of blood formation into a unified physiological organ. The fluctuating processes in the population of maturing cells affect the regulation of hemopoiesis on the whole, and in particular, result in the auto-oscillations with period of 25-35 days in the general number of cells of erythroid type and in the intensity of erythropoiesis. Adequate consideration of their dynamic processes is important both for simulation of the

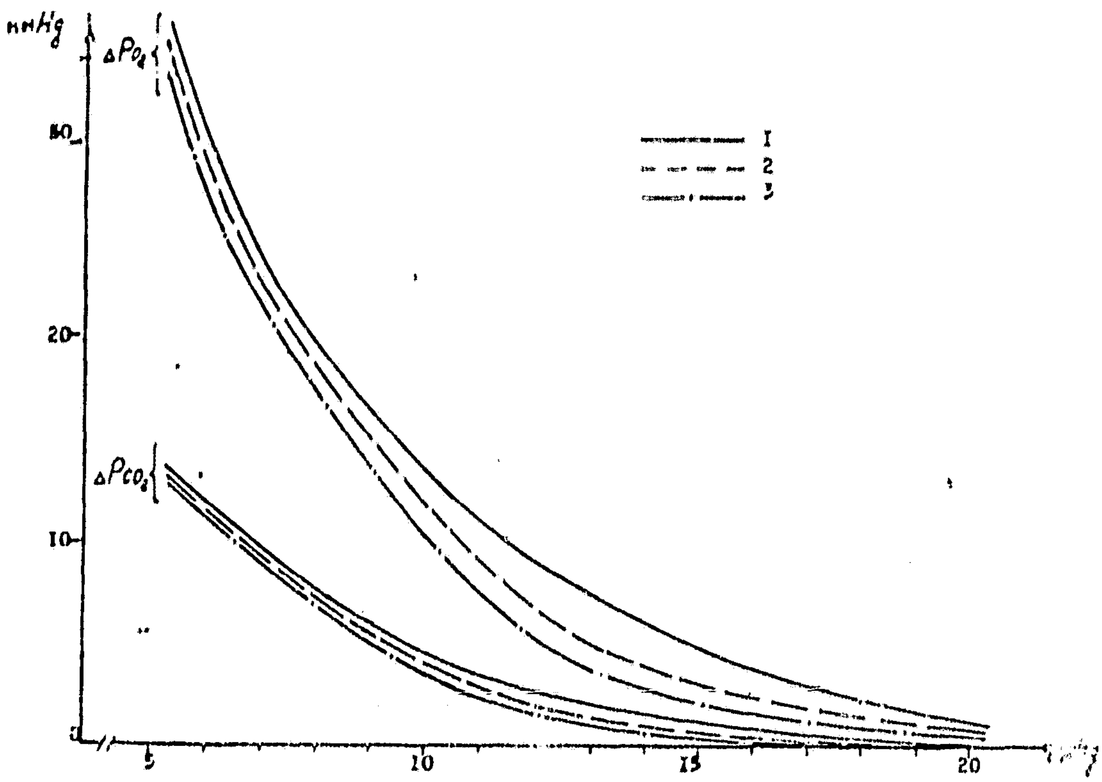


Figure 10. (Explanation in text)

erythron system and for correct interpretation of the data of real measurements in evaluating the state of the system and quantitative prediction of the directivity of its changes.

The great urgency of the study on the vestibular function of man and its modifications and adaptations under conditions of a space flight governed the interest in simulation of the vestibular analyzer. By now mathematical models have been developed that make it possible to described in detail the process of transformation by the vestibular apparatus of the field of accelerations of random form acting on it into an effective value of activities coming from the vestibular receptors into the central nervous system. The data obtained with the help of the model are used to analyze the reactions of the vestibular apparatus on the motor situations of varying type, evaluation of the motions and positions of man that are the optimal in a certain sense in the non-inertial systems of coordinates, comparative analysis of the vestibular apparatus of man and different types of animals for selection of animals adequate for experimenting on the structural interpretation of the results of tests on animals, also for development of methods for testing the vestibular function, methods of acting on the vestibular apparatus, and exercises and training of the vestibular stability.

Work is underway on constructing a model description of the functioning of the vestibular analyzer as an integral formation.

In conclusion we will permit ourselves to make certain notes /11
in relation to the place of simulation and mathematical modeling in general in space medicine and biology as a whole.

Until now we have examined the questions of the use of this method as applied to studies on the state of individual physiological systems and the organism as a whole under the influence of space flight factors. However there also exist other regions of its applications in space biology. One such sphere where methods of mathematical modeling have been used for a very long time and fairly productively is designing of biological systems of life-support. Here the use of mathematical models makes it possible to examine complex theoretical questions of the selection of the structure of the system that guarantees its stability, regulation of the species composition of the trophic level, link of stability to the degree of complexity of the system, etc.

We would like to indicate yet another possible region of application of mathematical modeling in space biology. It is expedient to use it to analyze a number of exobiological problems linked both to the evaluation of the effectiveness of quarantine measures, and to the evaluation of the consequences of bringing terrestrial microorganisms into the atmosphere or on the surface of other planets. The indicated implantation can be conceived as premeditated also, taking into consideration, for example, the plans stated many times for the reconstruction of the atmosphere of Venus by introducing into it photosynthesizing microorganisms. Preliminary estimate of the effectiveness and consequences of such global measures is pertinently made with the help of simulation modeling of the corresponding situation.

Thus, one can conclude with confidence that the use of simulation modeling in space biology and medicine has a broad outlook. Specific results of its application, including the peculiarities for the purpose of estimating and predicting the human condition in space flight depend at the current stage to a considerable degree on the quantity and reliability of the physiological information used in the synthesis of the model, and on the pithiness of the statements of the tasks on simulation.

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