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PATHOPHYSIOLOGICAL ASPECTS OF THE PROBLEM OF PROLONGED HYPOKINESIA

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16. Abstract

The study of hypokinesia is important for medicine and for the national economy. The changes in man's activity due to modern life with automation and sedentary activities and man's exploration of space in a state of weightlessness have accentuated the importance of hypokinesia. This article discusses the pathogenesis of hypokinesia. Experiments and results made on man and animals are included. The conclusions made are maily hypothetical and require further research.

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PATHOPHYSIOLOGICAL ASPECTS OF THE PROBLEM OF PROLONGED HYPOKINESIA

Ye. A. Kovalenko

In a century of scientific and technical revolution, /11* one of the foremost problems facing medicine is studying the effect on man of the progressively decreasing volume of muscle work due to mechanization and automation of production and also due to organization of public service and amenities.

The problem of studying hypokinesia (GK [gipokineziya, hypokinesis, HK]) is important for general clinical practice because usually a patient must spend some time or other in bedrest. The study of HK is necessary for space, aviation and naval medicine. The problem of partial HK is important also for successful development of animal husbandry and fur farming if one considers the broad expansion of the amount of agriculture and the number of wild animals in conditions which limit their motor activity. In other words, this problem has acquired great significance both for medicine and for the national economy.

The prolonged course of evolution of highly organized animals and man has always involved the constant necessity to improve intense muscle activity in order to move greater distances during hunting, to acquire food, protection from invasion, etc. At this time, this tendency, genetically connected to the long course of evolution, encounters the inevitability of significantly decreasing the volume of intense muscle work. In these cases won't a certain

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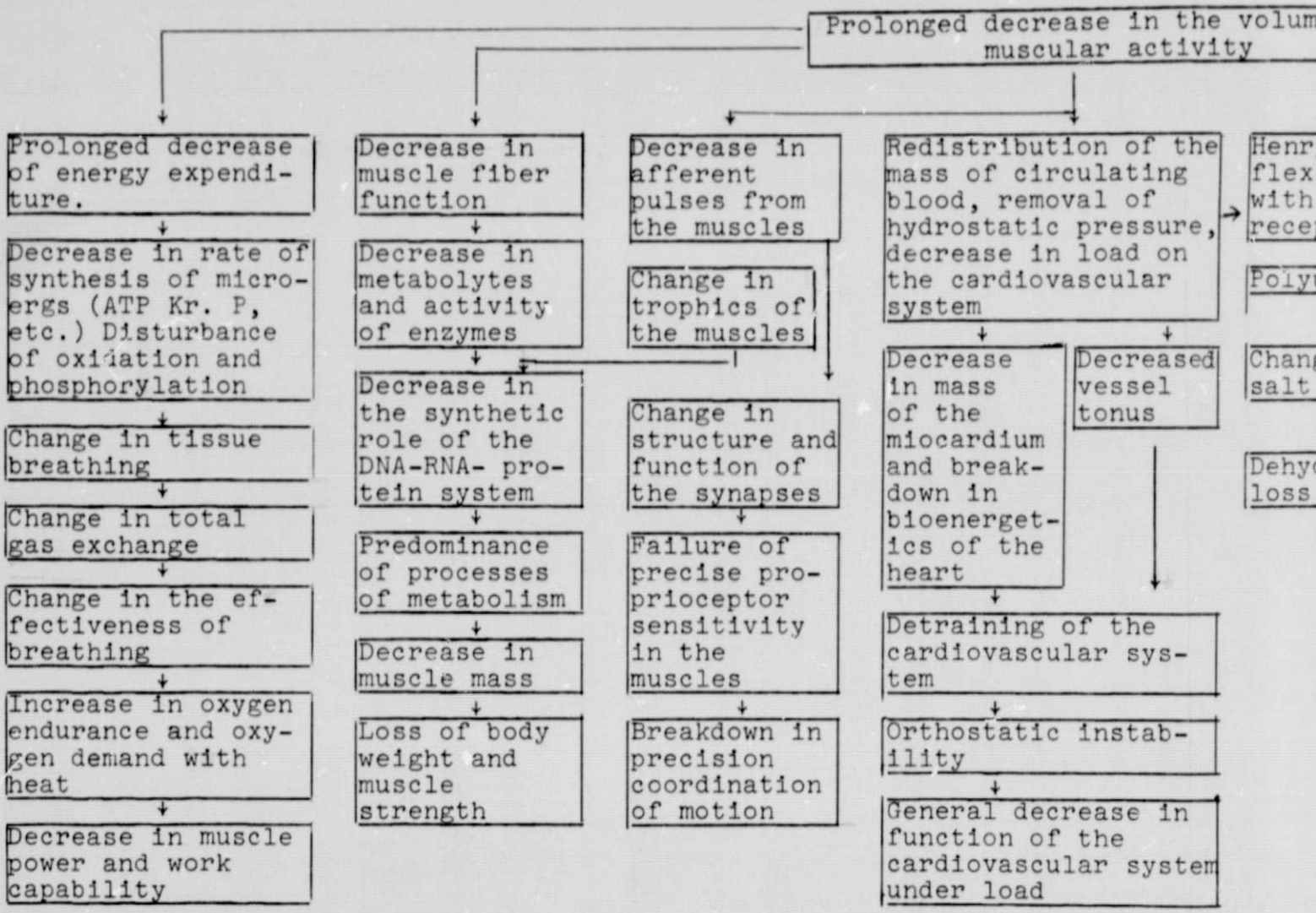
*Numbers in the margin indicate pagination in the foreign text

breakdown in the organism occur? Pathogenesis of these failures is necessary to explain and find approaches to the main question of this problem.

At the present time, there is a good deal of work in the literature which discusses general and particular questions considering different aspects of possible pathology caused by prolonged HK [3,13,20,34,51]. However, we have not encountered works in which an attempt has been made to construct an overall system of HK pathogenesis from the position of pathologic physiology. The construction of such a system is still hypothetical but nevertheless it is necessary to attempt to present the features of the effect of the etiologic factor, the occurrence of basic pathogenetic links and the secondary processes. All of this would make it possible to discover the necessary method for further investigation and to eliminate the main links of failures which occur. It is completely obvious that the etiological factor, the main cause for development of the process, is prolonged decrease in the volume of muscle activity (see diagram). What does this effect lead to and where in the organism exactly should one look first for possible failures of various systems? Movement always involves expenditure of energy. Consequently, possible breakdown as a whole, apparently, must be sought for in the sphere of energy exchange of the organism. Further, motion is impossible without the material substratum which accomplishes this function. Such a substratum is the support motor apparatus, primarily, the muscles. Consequently, the second basic objective of our research must show the muscle system. It is natural that each movement is unthinkable without the complex regulating role of the neuroendocrine system and this regulation can change both toward direct breakdown of movement coordination and in relation to serious vegetative disorders which cause the

General Diagram of Hypokinesia Patho



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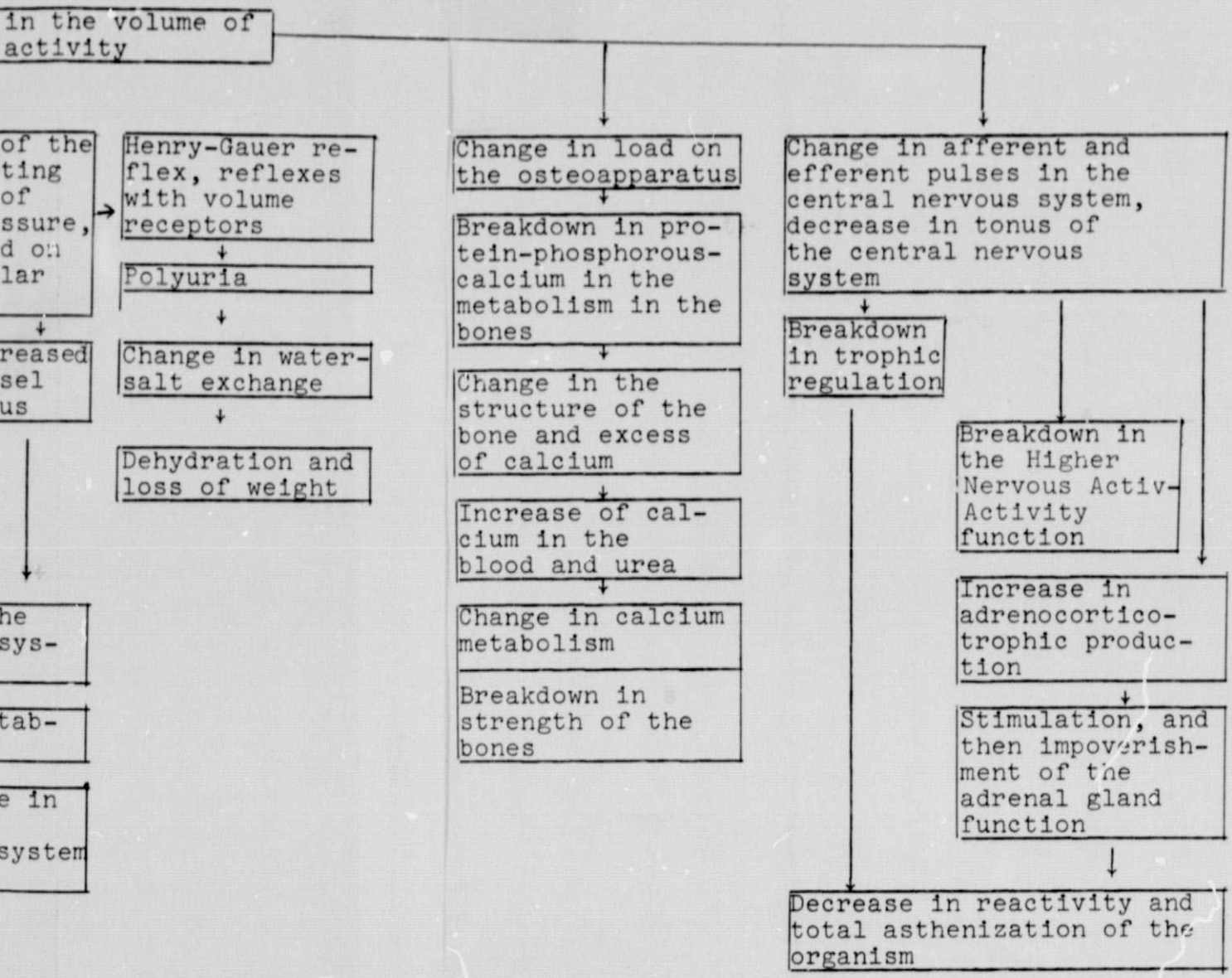

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trophic capability to improve the necessary volume of motion./13 In a case where prolonged HK occurs in conditions of bedrest, besides a decrease in muscular movement, one of the main pathogenetic links is also the removal of the hydrostatic component in the system of blood circulation caused by prolonged stay of man in a horizontal position. This moment, combined with the general decrease in load on the cardiovascular system, causes a whole sequential chain of failures in the form of detraining of the heart and vascular system.

Thus, the main etiologic factor of HK is a prolonged decrease in the volume of muscle activity. This factor causes prolonged decrease in energy expenditure. As is known, muscular contraction improves with decomposition of the existing reserves of ATP [adenosine triphosphate] and its transformation to ADP [adenosine diphosphate]; after this, as a result of the oxidation processes and phosphorylation accompanying them, resynthesis of ATP sets in. This process, with constant and fairly stressful work occurs intensely, smoothly and systematically. It is natural to think that with HK, the rate of decomposition and synthesis of the rich energies of phosphorous compounds will slow down and be insufficient. A study especially carried out in model tests on rats of oxidation phosphorylation and its regulation in the Barburg apparatus in the tissues of the skeletal muscles, the miocardium and liver, and also in the mitochondria during prolonged (up to 100-170 days) HK showed the following. In the skeletal muscle, the level of phosphorylation decreases from 19.9 $\pm$ 1.31 to 13.7 $\pm$ 1.48 MA of phosphorous ($P < 0.05$) to the 45th day of HK, and in the heart -- from 24.3 $\pm$ 1.95 to 14.3 $\pm$ 3.6 MA ($P < 0.05$) with breathing a succinate and approximately as much when breathing α-ketoglutarate [25-27].

In these same tests, sharp changes in the relationship of mitochondrial breathing in the third and fourth (according to Chance) metabolic states were noted; this resulted in a sharp decrease in the value of breathing control (2-2.5 as opposed to 6-7 in the control). In this way, the increase in mitochondrial breathing in the fourth and weakening of breathing in the third metabolic state attests to the decrease in the degree of conjugation and energy regulation of breathing [14,25,27,38]. Thus on the basis of these data, it is apparent that prolonged HK actually causes a decrease in the ATP synthesis rate due to a decrease in the degree of conjugation of oxidation phosphororylation, that is, it occurs like detraining of energy synthesis. Besides, a change was noted in tissue breathing which, in the final analysis, can affect the value of total gas exchange [38]; then here, one observes an interesting principle. In a person with prolonged HK, as a rule, a certain decrease in basic metabolism was noted, by 10-22% [21,42,75]. A similar principle was observed in dogs in HK [23,27]. In truth, in rats, as body weight decreased and there was a relative increase in body surface (according to Rubner's law) and also as a result of interrupting oxidation phosphorylation, an increase in gas exchange was noted [10,25,28]; the decrease in intensity of gas exchange causes a definite decrease in pulmonary ventilation in man. Besides, when carrying an adequate physical load after prolonged HK, on the other hand, a very sharp increase in oxygen demand and oxygen deficiency occurs and also the coefficient of oxygen utilization decreases. This was established both in man and in animals[10, 20,42]. The result of failure of processes of energy exchange, biological oxidation and total gas exchange, both fully apparent with physical loads, is a sharp decrease in the efficiency of gas exchange and work capability [2]. It is

pointed out that even after 22 days of HK, in man, a decrease in work capability by 16% occurs, and the increase in oxygen deficiency with muscle load increases by 61-137% of the control. Besides, upon completion of the test, one observed a /14
decrease in the coefficient of reduction of oxygen demand by 34% and a sharp increase occurred in the consumption of oxygen per unit of work (by 50% and more). There are similar data on the sharp increase of oxygen demand and oxygen deficiency with physical load and even when carrying out an orthostatic test after HK [10,48,75]. All of this speaks to the sharp changes and loss in effectiveness in regulation and the decrease in efficiency of gas exchange processes and energy supply of the functions.

The next most important link in the chain of failures which occur is the breakdown of structural supply of the functions. "Atrophy from misuse" occurs. Naturally, this process first of all affects the skeletal muscles and the heart muscle.

A decrease in the function of muscle fibers results in a decrease in the constant level of stimulation of synthetic processes in muscle tissue. In these cases, production of metabolytes and activity of enzymes directed at activation of synthetic processes in the working organ decreases. It was established that regulation of metabolism occurs by change in the rate of enzyme reactions. In usual conditions, their intensity is provided by the use of only part of the existing molecules of the enzyme in a cell, the other part being unused; usually, one is inactive and would be in the reserve of the cell. An increase in function of the cells results in mobilization of the reserve of the enzyme molecules, their activation (transformation of the proenzyme to enzyme), and this increases the number of molecules of the enzyme in a

cell with an increase in any functional load. It is natural to suppose, and experimentally shown [41,53,54], that in hypokinesia conditions, a decrease in functions of the enzyme systems occurs. Consequently, such an important link of cellular regulation of functions and metabolism, like enzyme activity, and besides this, the isoenzyme spectrum of enzymes in the blood serum are subjected to significant changes [41, 50]. Stressful, intense work of a given tissue and its separate structures creates conditions where the function of this organ is required for its necessary plastic supply [39,40]. In conditions of prolonged absence of this periodic stimulation of the genetic apparatus of cells, weakening of protein synthesis occurs according to the DNA→RNA→protein system. In ordinary conditions of normal functioning, systematically the expenditure of energy reserves in the muscle in the form of ATP, the presence of periods of constant and fairly intense expenditure of macroergs and the formation of products of decomposition are a constant stimulating factor resulting in a sharp increase in the synthesis of nucleic acids in proteins, in an increase in the amounts of working tissue of a given organ. In the case of prolonged hypodynamics, systematic stress periods are absent for expenditure of macroergs in the muscle system and the miocardium. As we have already said, weakening of energy regulation of the processes of biologic oxidation occur [14,27,37] and all of this, in the final analysis, causes a decrease in synthetic processes. If one takes the equilibrium between breakdown and synthesis of a given structure as the constant standard, adequate for its functional load, then with HK, at first, predominance of catabolism can occur over the anabolism processes, and then a new dynamic equilibrium of the processes is established. All these theoretical hypotheses have factual support.

As has been pointed out [63,64], with HK in animals, a significant decrease occurs including labeled amino acids in the muscle proteins. A decrease in the percentage content of proteins in the gastrocnemius muscle which progresses during prolonged periods of HK was established in rats [9]. Moreover, a decrease of both sarcoplasmic and miofibral protein was noted on the 30th and 60th days of HK in the extremity muscles.

A persuasive proof of the significant decrease in synthetic processes in the muscles is the decrease in weight both of the separate muscle groups and the bare carcass of animals (skeletal and muscular system) during prolonged HK (up to 100 days), and also the sharp decrease in total body weight (by 25-30%) and decrease in growth in the process of autogenesis [2,3,10,23,24,]. During HK in humans, as a rule, one observes a lesser decrease in body weight. During a 70 day experimental HK, a weight decrease occurs from 2 to 6.4 kg and a negative nitrogen balance is noted with loss on the average of 8 g of protein per day [57]. Also one observes a decrease in the neighborhood of the femur and tibia muscles, that is, a decrease in muscle mass especially on the extremities [48]. /15

It is natural that in these conditions with sharply indicated breakdowns in synthetic processes and a decrease in plastic supply of functions, detraining of the complex effect of the trophic role of the vegetative nervous system plays a very significant role [20,47]. However, this question requires a special and very detailed consideration and we will not pause here to discuss it but only mention its extremely important role. It is necessary to devote attention to the fact that the decrease in volume of muscle

activity, naturally, results both in a significant decrease in the efferent pulse of the total complex of necessary signals causing motor actions and stress of muscle fibers, and in a sharp decrease in reverse flow of afferent pulses which inform the central nervous system and a number of systems of the organism as to functional changes occurring in the muscles. This process of reverse communication with adequate trophic effects is subject to the greatest changes during HK [13,17,20]. The decrease in volume of efferent and afferent effects and decrease of the the volume itself and frequency of muscle contractions results in a change in the state of the contractile apparatus of the muscles and also breakdown of the structure and functional synapses and mediate processes. An unusual "physiological enervation" of the muscles occurs. Biochemical changes during HK in the muscles reminds one of those which occur during an initial enervation of the muscles. The excitation threshold of the gastrocnemius muscle increases in rats even during 30 day hypodynamics (from 4-6 to 10-16 V). The character changes both in single contractions of muscles (maximum stress decreases to 26%, duration of contraction increases to 170%, time of half weakening increases to 150%, the rate of development of stress drops to 21%, etc.) and in tetanic contraction (maximum stress drops to 29% and time of reaching maximum stress increases to 256%, the rate of stress development decreases to 11%). The content of myoglobin and glycogenolysis in the muscle decreases [3]. As is apparent, a sharp decrease in the contractile apparatus of the muscle and metabolism in them occurs. In man, the muscle strength decreases sharply, the statistic and dynamic strength of the muscle tonus during HK decreases. Endurance in prolonged work on a veloergmeter was weakened to 57% of the initial after 62 days of HK, etc. [20,47,48]. Besides, not only strength

and endurance of the muscles decreased but also the retention of motor habits and coordination of motion was lost [15]. Sharp disturbances occurred of these simple biomechanical acts, like holding a vertical pose, capability to walk, getting up from a lying position into a sitting or standing position.

Prolonged HK leads to a breakdown in motor performance (synergy) which is apparent in severe disorders of such purposeful and coordinated acts as standing, walking, and the enervation ratios lying as their basis [15, 58]. Thus, in functions of the muscular system, there are energy, structural and regulatory links. The main blow to these systems would appear to be the sharp and systematic decrease in muscle function.

The next most important link in HK pathogenesis is the sharp decrease in load on the cardiovascular system. The study of this pathogenesis link has been given and is being given a great deal of attention due to the vitally important role of this system and its vulnerability during HK [17,20, 23,34,49,51]. Here one must point out the two most important factors which can play a leading role in the chain of changes which occur. First of all, this is a decrease in load on the cardiovascular system due to a decrease in oxygen demand with a decrease in energy expenditure and, secondly, removal of the hydrostatic component in hemodynamics when the body is in a horizontal position, that is, mechanical removal of pressure of the column of blood in the vessels of the lower part of the body, which always exists in a vertical position of the organism. A decrease in demand for oxygen in the substrata of oxidation results in a decrease in the heart function and a decrease in hydrostatic pressure increases the venous return of blood to the right auricle. At first, as redistributior

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of blood increases during the horizontal position in people, an increase occurs in the stroke and minute volumes of blood [17,49]. Then as the duration of hypodynamics increases, a sharp decrease in stroke and minute volume of the heart occurs and a gradual decrease in the original increase in intrathoracic volume of blood [52]. On the EKG, during prolonged hypokinesia (70 days) one notes a slow-down in conductivity, a decrease in amplitidue of the RT waves, a decrease in the relationship of the size of the T wave in different sections, periodic shifting of S-T segment, and also a change in the repolarization process [8,17]. To a certain degree, one can develop a fairly adequate blood supply to the heart especially in conditions of high physical load. At the present time, it is shown that prolonged HK essentially worsens the functional state of the heart [18,49].

Cardiac activity becomes less "economical" which is apparent in the increased frequency of cardiac contractions, the change in phase structure of the cardiac cycle and the decrease in systolic volume of blood, the decrease in force of cardiac contractions. The regulation of circulation changes sharply which is expressed in the change in rhythm of cardiac activity (it becomes clear that there is an increase in frequency of cardiac contractions during small load and even in a state of rest), in distortion of the Ashner reflexes and cardiac components of the orthoclinostatic reflex, and also the reflex of physical load [18,52]. Roentgenologic study of the heart made it possible to establish an important fact. After 70 days of hypodynamia, the dimensions of the heart in a man decrease by 12.9-17.9%. The total area of the heart on the X-ray in the test subjects decreased from 166 to 135 cm^2, that is, by 31 cm^2. In tests on rats, after 120 days of HK, a 4.26% decrease in heart

weight was observed. Besides, in the miocardium of hypokinetic rats, one noted a decrease in the oxygen requirement of the tissue to 38 ± 6.2 mm^3/100 mg/g in comparison with the control (62 ± 4.8 mm^3/100 mg/hr) [27,28,30]. Electron microscopic study of the miocardium in these animals showed that unequal swelling of the mitochondria occurs, a decrease in cristae of the mitochondria, an absence of their strict orientation, and also swelling of the endothelia capillaries and breakdown in the structure of cellular membranes [24,27]. As is apparent, not only the cardiac function suffers but also a sharp decrease in heart mass occurs and a change takes place in its ultramicrostructural elements; the processes of biological oxidation depend on them and tissue breathing of the miocardium suffers, and consequently, its functioning. Also a definite change occurs in the vascular system. In HK conditions, first of all, a systematic increase in oxygen demand is weakened due to the absence of a fresh volume of muscular activity. This results in a decrease in stroke and minute volume of the blood, and consequently, in a decrease in venous return. Naturally, all of this causes a definite change in functioning of the vessel alveus and a change in tonus of the vessels. A gradual decrease in the /17
volume of circulated blood occurs because the latter, to a considerable degree, depends on the periodic increase in oxygen demand of the tissues. An opinion exists that the "oxygen regulation mechanism" in the tissues can sometimes even play a more important role than the nervous regulatory mechanisms. This was shown with full enervation of vegetative nerves of the muscles, but during conditions where regulation is retained in them, blood circulation is only dependent on oxygen demand of a given tissue [73]. The deresulting decrease in vascular tonus can cause a decrease in lability of vascular tonus, constantly trained during function of the muscle groups which, in turn, causes

a breakdown in regional blood circulation and causes a decrease in capillarization of the tissues and a breakdown in the structure of capillary walls [6]. The most important pathogenetic link in the disturbances in hemodynamics during prolonged hypokinesia when remaining in bed is removal of hydrostatic pressure on all large vessels located along the longitudinal axis of the body. Adopting a horizontal position and prolonged lack of motion results in redistribution of the mass of circulatory blood, in removal of pressure of blood weight on the vessels of the lower half of the body. A gradual detraining occurs of a large part of the vascular alveus, detraining of the muscles, contracted vessels of the lower half of the body and loss of turgor of tissues, etc. All of this, with adequately long effect, results in the fact that if man again adopts a vertical position, then a significant part of the blood flows toward vessels which are detrained with low tonus in the lower half of the body and orthostatic collapse can occur, anemia of the brain and loss of consciousness. Special attention is given to the danger of this threat occurring as one of the most serious consequences of prolonged HK [13,1720]. Thus, on the part of the vascular system, very serious disturbances occur which can be qualified as its total detraining and development of marked orthostatic instability.

The following phenomena are closely connected to the pathogenetic link of removing hydrostatic pressure of the blood and its redistribution in the organism. In the first period of transferring from a vertical position of the body to a horizontal, redistribution of blood occurs in the organism, its flow to the heart increases and overflow of the blood in the auricle and small vessels. In a series of works (69-72], it has been clearly indicated that an increase in intrathoracic volume of blood includes a reflector mechanism, in particular, the baroreceptors of the heart

auricle are stimulated and cause a decrease in production of antidiuretic hormones by hypophysis, and this, changing reabsorption in the kidneys and kidney filtration increases diuresis. Polyuria which occurs in the first stages of hypodynamia results in a gradual decrease in the fluid part of the blood which is expressed in the increase in the hematocrit index. Then, exit of intra and extracellular fluid into the circulation system occurs, and a definite dehydration of the tissues develops, a certain dehydration of the organism takes place. It is natural that the change in water volume begins to correspond to a loss of electrolytes, primarily Na and K [12,22,69,70]. It is interesting that an increase in diuresis and outgo of Na and K occurs in the organism not only due to reflector stimulation of baroreceptors of the heart and small vessels, which overflow with blood, but also due to other less clear mechanisms. In tests on rats, when redistribution of the blood does not occur from the lower half of the body to the upper and an increase in its flow to the heart and small vessels, because the animals, all the time, are in a horizontal natural position in conditions of prolonged 100-day HK, all show an increase in diuresis to 18 ± 1.5 ml of urine in 24 hours as opposed 10 ± 2.9 ml in the control. At the same time, one observes an increase in generation of Na from the organism [28]. In these animals, one also notes a change in the magnitude of maximum hydration capability of the tissues and an increase in their sorption capability (decrease in tissue resistance) determined by the D. N. Nasonov [45]. This phenomenon, in D. N. Nasonov's opinion, usually is accompanied by an increase in viscosity (coagulation) of cytoplasm. The primary mechanism for development of dysfunction of the water and salt metabolism during HK with an absence of the Henry-Gauer reflex from the auricle, attests to the fact that other less clear mechanisms exist in the

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pathogenesis of these links with hypokinetic disorders. On the whole, it is apparent that during HK, disturbance of the water and salt metabolism occurs and a certain degree of dehydration of the organism can develop. However, this process is usually marked only in the first HK period [20], and later on it weakens or disappears.

The next important link in the pathogenesis of prolonged HK is a decrease in load on the bone apparatus, especially clear in a case of lengthy stay in bed when the mechanical effect of force on the bone is decreased not only due to a decrease in muscle contractions and muscle tone but also due to the moving small deformations caused by gravitation on elements of the bony structure when the body is in a vertical position. This is an important mechanism but little attention has been given to it [23]. Even in 1892, Yu. Wolf pointed out the dependence in bone structure, orientation of the structural elements and mass of its component substances on the force and direction of mechanical load. It has been shown that the deforming force causes such a change in bone structure as is necessary in order to more adequately withstand its force. The primary links which occur during HK changes in the bony system, apparently are the following. The first signals when removing load and decreasing deformations can be pulses from the nerve extremities in the periosteum, in the region of vessels or even in the elements of the bone itself. This pulsation naturally has appropriate trophic effects on the entire complex of fine regulation for maintaining bone structure, in particular, protein, phosphorous and especially calcium metabolism, by changing the interaction of hormone activity of the parathyroid gland, and also through functioning of

elements of the thyroid gland, as a result of changes in production of tyrocalcitonin [1,46,67,74,75]. In the chain of disturbances which occur, special attention must be given to synthesis of those important amino acids such as glycine and hydroxyproline which take an active part in the formation of the bony matrix, that is, its protein composition. However, the cause for change in bone structure can involve other effects. It was observed [66] that during mechanical load, bending and stress of the bone and its microstructure, an electrical charge occurs. It was established that in the bone structure, between the hydroxylapatite and collagen crystals a piezoelectric effect occurs which changes the mechanical stress to electrical. The value of the potential which occurs is proportional to the force applied to the bone. The negative potential which arises causes an accumulation of osteoblasts and stimulates synthesis of bony tissue in those sections and, on the other hand, with lessening of the load on the bone, the function of osteoclasts begins to predominate. Moreover, the presence of the difference which occurs in potential during load on the bone creates an "electric pump" stimulating flow of charged molecules, ions of mineral substances and chemical radicals. This creates an additional mechanism for supplying this section of tissue and results in stimulation of synthesis of bone structure, corresponding to the direction of load on a given section of bone [66]. During prolonged HK, these processes of stimulation of plastic metabolism in the bony tissue will be absent. All of this leads to a certain change in metabolism in the bone tissue. During prolonged HK in animals (rats and dogs) a decrease in /19
inclusion of Ca^{45} was established [4,36,55]. The decrease in mineral saturation of bony tissue and exit of Ca from the bones is noted in humans which is particularly apparent

in the decrease in optical density of bones in persons with prolonged HK. The data of roentgenophotometry indicated a decrease in density of calcaneus by 11.8% during 70-day HK in bed [33]. A study of this question on rats during 100-130-day HK showed that in animals, besides the decrease in inclusion of Ca^{45} in the femur by 21%, a decrease occurs in its inclusion in teeth by 15.6% and in the mandibular bone by 19.4%, that is, disturbance of calcium exchange does not have a regional, but apparently, a systemic character. Moreover, it was established that besides this, one observes a sharp and earlier change in phosphorous and amino acid-glycine metabolism [27,23]. In other words, with prolonged HK, a complex change occurs in the protein-phosphorous-calcium metabolism in the bones and other calcified tissues. Egress of Ca from basic storage in the bones results in increase in its content in the blood [4, 20] and increased removal with urine and feces. During 70-day HK in humans, outflow of Ca with urine in the final test had increased by 36%, and with the feces, by 38% [57]. The increase in content of Ca in the blood and urine, in turn, can cause a number of important consequences. A change in the blood coagulation system can occur [16], serious reasons for the formation of kidney stones can arise [62], calcification of the blood vessels increases, and the contractile properties of the muscles can change [48], etc. Inasmuch as disturbance of the protein-phosphorous-calcium metabolism has a systemic character during HK, the latter can facilitate a breakdown in strength of the teeth and caries can occur [55]. Outflow of Ca from the bone and the occurrence of osteoporosis can result in a decrease in the strength of the bone system. Particular attention is given to the pathogenesis link of HK in a more detailed study of the breakdown

of the regulatory role of hormones such as parathyroid and tyrocalcitonin. An increase in the latter regulatory link of calcium metabolism apparently, is one of the promising approaches for correction of the dysfunctions which occur [61]. It is necessary to keep in mind that the bone system is one of the basic reservoirs of cerebral bone and a decrease in load on the skeleton can be the origin for changes in the hemopoiesis system. Serious attention has been devoted to this question in recent years [31] indicating a decrease in the number of erythrocytes per 1 mm^3 of blood during HK at 500,000 to 1,000,000 [7].

A decrease in anti-infection resistance occurs in conditions of prolonged hypodynamia. Changes both in nonspecific anti-infection resistance and specific immunologic reaction were successfully established during 70-day hypodynamia in humans. These changes result in the decrease of conventional pathogenic activity and saprophytic automicroflora, which grow in the organism and also facilitate activation of latent infection for diffusion of agents introduced from outside. During hypodynamia for 70 days, there were cases of illness with catarrh of the upper respiratory tracts, rhinitis,bronchitis, otisis, sties, caries, exacerbation occurred of pulpitis, cholecystitis, nettle rash, and in one test subject even acute phlegmonos appendicitis [59-65]. All of this is evidence of the fact that a general change occurs in reaction capability of the organism to a number of factors including infection.

What changes occur in the nervous and endocrine systems? During hypodynamia, a sharp decrease occurs in afferent pulsation which is fairly intense and systematic during ordinary motor activity. In these cases a decrease in the constant toning effect of motion occurs primarily on the

reticular formation of the brain. It is well known that proprioceptor pulsation is the activator of reticular formation of the hypothalmic-cortico system, and this, in turn, creates a definite toning of functions of the cerebral cortex [11]. /20 In these same HK conditions, a marked decrease in tone and function of the cortex and subcortex occur. With a detailed analysis of the EEG in humans, even with a 10-day HK, an increase in the number of slow waves is found and a decrease in the number of β-waves. These changes occur in all sections, but the most marked are in the foremost sections of the cerebral cortex. A significant weakening in mastery of the rhythm of light flashes by the cortex, occurs especially in the high frequency zone. Significant changes occur in the skin galvanic reaction, almost completely disappearing after hypodynamia [60]. A combination of all the indices studied during HK indicated a definite connection in EEG changes, sensitivity of the components of the orienting reaction and precision in conventional motor reaction. Moreover, it was established that mental activity decreases. During HK, fatigue increases, a certain weakening in memory occurs, errors are more frequent, logical thinking is more difficult, etc. [5,38,43,44,56]. During HK, emotional disturbances occur, irritability increases, a change in mood is noted, sleep is disturbed, the person falls asleep slowly, sleep is light, pretraining motor activity increases [43,44]. Neurological changes occur. Asymmetry of tendon and skin reflexes and smoothing of the right nasolabial wrinkles with decrease in muscle force on this side are apparent; deviation in speech occurs on the right, etc. In other words, a set of symptoms arise usually indicating neuropathology like the syndrome of pyramid insufficiency. The left hemisphere of the brain, on a background of a general decrease in the level of neurodynamics during HK,

is more overloaded (sound, reading, writing, speech) with functions and asthenization of it sets in more rapidly; and as a result earlier disturbances in the left hemisphere [34,35,43,47,48]. As a whole, one can note that HK is accompanied by a significant combination of afferent stimulation of the brain cells resulting in a prevalence in them of the retarding process and a decrease in their work capability. Acute asthenization of functions of the central nervous system, its reflector and associated activity occurs. One of the systems involved earliest in the chain of dysfunctions during prolonged HK is the vegetative nervous system. Disturbance occurs in its adaptation and trophic functions which is apparent in the many indices of transport systems and metabolism of substances [20,34,35]. Disturbance occurs in the humoral length of the regulatory function. Observations and studies during 120-day HK in humans showed that at first an increase in discharge into the blood of catecholamines and corticosteroids occurred caused by the unusual circumstances of the test and by volitional increase of limitations of ordinary life activities and suppression of natural desires for activity [34,35]. It is interesting that in the tests on rats, attention is devoted in the first period of HK (the first 15 days) to two-fold increase in the content of corticosterone, a adrenalin and noradrenalin in the blood and adrenal glands and an increase in the concentration of ACTH in the blood. In the first period of HK, the latter increased to 200% in comparison with the control [19,25]. Then, thanks to inclusion of adaptation mechanisms, a condition occurred which provided a more economical system of operation for the nervous and endocrine systems on a background of prolonged decrease in total stimulation and toning effects. In the second month of HK, the content of corticosteroids and catecholamines decreased [19,25]. With the time period

of HK increasing, detraining of the nervous-vegetative system and humoral regulation of functions developed, exhaustion of the endocrine regulation link occurred and the content of catecholamines and corticosteroids decreased even below normal; in the case of applying different stimuli, the response reactions of the hypothalmus-hypophysis-adrenal gland system was characterized not by an increase, but by decrease in discharge of ACTH, corticosteroids, etc., apparently a gradual impoverishment of this hormonal link in regulation occurred. A gradual almost threefold decrease in the concentration of 11-HCS and a less marked decrease in the level of 17-HCS in the urine at the end of the first month of hypodynamia was noted in persons during prolonged (70-day) hypodynamia [57]. During prolonged HK, an increase in secretion of aldosterone can occur but, a specific feature of its effect is primarily the absence of a typical effect of aldosterone like the marked retention of Na at the kidney level and an increase in the volume of blood plasma [30]. /21

But one should not exclude another apparently, more probable mechanism involving the gradual exhaustion of aldosterone secretion and decrease in reabsorption of water in the kidneys and increase in removal of Na. There is no clarity here yet. Besides this, it is necessary to keep in mind that with prolonged HK one cannot exclude a decrease in discharge of somatropic hormone as one of the most common regulators of autogenesis and synthesis of proteins in tissues with an absence of constant stimulating effect of affection on the hypothalmus as a result of "atrophy from disuse." As a result of the increase in discharge of steroids in the first HK period in the rats, L. V. Serova successfully observed a definite involution of the thymus, an increase in decomposition of thymocytes and further attrition of the thymus, and also a general decrease in resistance and

sorption capability of the tissues [25].

In other words, once again this attests to the predominance of processes of catabolism over synthetic in the tissues and dysfunction of equilibrium between them. One must note that the creation of HK in an experiment on animals (with artificial limitation of mobility in the cells) or the creation of HK in humans, with constant volitional forces and all inconveniences involved in prolonged strict bedrest, one can create at first a prolonged stress situation. A state of peculiar "chronic stress" occurs explained both by disruption of ordinary natural living conditions not involved with prolonged lack of motion and also directly connected with it. Strictly speaking, for studying pathogenesis of prolonged HK itself we should be interested only in the second factor. However, separating it from the whole complex created by HK is practically impossible. Going from the existing experiences of our work and literary data, we have attempted however to approximately determine the time period for different stages of "chronic stress" arising during prolonged HK. In the first place, this is an anxiety reaction with more marked increase in discharge of corticosteroids continuing up to the 15th to 20th days of HK. Then during the second month of remaining in HK, a certain adaptation of primary changes occurs which is noted in tests on humans [13,17,20,34,35,49] and finally (3 to 4 months or more), the last stage sets in where barely marked adaptation is continued or, as one observes in animals, attrition of a number of functions sets in primarily of the nervous-endocrine regulation link which is well defined by sharp suppression of the complex of the central nervous system and hypophysis of the adrenal cortex [19,25].

Thus, in spite of the obvious systemization and absence of a number of clearly defined factors and links in this chain, one can hypothetically present an overall system

of prolonged HK (see diagram), first of all as an existing etiologic factor in view of prolonged decrease in the volume of muscle activity. This results in a sharp decrease in bioenergy consumption in the organism and a decrease in the necessary plastic provisioning of this function. The most important link in the chain of dysfunctions occurring is detraining of the cardiovascular system and the appearance of orthostatic instability. Closely connected to this pathogenesis link is also disturbance of the water-salt metabolism resulting in an increase in discharge of water salts from the organism. A decrease in bioenergetics, structural provisioning of the functions and regulatory link of functional coordination of the muscles creates an unusual type of pathology in the form of "atrophy from disuse", a decrease in load on the bone system, it causes dysfunction of calcium metabolism which can have a systemic character. A sharp decrease in afferent and efferent pulses involves the whole chain of disturbance of the central nervous system which is apparent both in dysfunction of higher nervous activity and in changes of the reflector regulation at lower levels. Disturbance of the vegetative nervous system, a decrease in its trophic functions, takes on special importance. Total asthenization of the nervous system and its regulatory functions occurs. As to the humoral link regulation, the occurrence, especially in the first stages of hypodynamia, unusual stress reactions which gradually on a background of no muscle activity produce exhaustion and detraining of the nervous and endocrine link in function regulation all deserve attention. Apparently, as the basis of everything presented, one can consider that an adequately long HK can qualify as a unique "hypokinesis disease". What proof is there for this? Fairly often in modern life we encounter a certain degreee of limitation of muscle activity for a comparatively short time, however we observe then not

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a fast recovery from a precise disease but more rapidly a total detraining of the organism. Apparently, all of this work is related to the duration and degree of HK effect. I. P. Pavlov wrote: "What is a pathologic state? It is an encounter, a meeting of the organism with any kind of extreme condition or, more probably, with an unusual dimension of an everyday condition... If the disturbance does not remain on a single organ, but insists on expanding further, we again, for a new harmony, study the functional connection of organs and, finally, determine that moment and mechanism when the combined force of the organism as a whole is exhausted."[1] Obviously this concept of a great philosopher makes it possible to consider that with adequately prolonged HK such detraining, unusual "pre-illness" of the organism occurs which later on can develop into a "hypokinetic disease" with a number of characteristic symptoms; then a person will not be able to carry out the ordinary patterns of life, walk, work, fulfill elementary motions, inherent in a healthy person.

We must keep in mind that a number of the positions indicated in our article are very disputable but the presentation itself of questions at the beginning of the study of the problem is extremely important and necessary for selecting the approach for a scientific search and further deepening of research.

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