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WATER-SALT EXCHANGE DURING BED REST OF VARYING DURATION

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16. Abstract

This work studies problems associated with the status of water-sodium metabolism under bedrest programs of varying lengbhs. The dynamics of electrolyte concentration in blood serum, functional status of kidney osmosis regulating function, and other problems are discussed.

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WATER-SALT EXCHANGE DURING BED REST OF VARYING DURATION

Yu. V. Natochin

Results of medical and biological testing of Soviet cosmonauts and American astronauts have presented an opportunity for establishing the most substantive changes occurring in the functional systems during varying periods of weightlessness [1, 2]. These changes involve, first of all, the cardiovascular system and (for flights of moderate duration) the musculoskeletal system. In analyzing the published data, it becomes clear that the disruption of water-sodium metabolism (or, more precisely, its adaptation to new conditions) plays a most important role in the physiological and biochemical mechanisms of these changes [3, 8]. Obviously, extensive and multifaceted study of the results of weightlessness requires numerous experiments which are more accessible than space flight. One widely used model which approximates a decrease in hydrostatic blood pressure, redistribution of fluid media, and a decrease in motor activity is bed rest, in which the observed changes in the human organism are to a certain extent similar to the phenomena associated with actual flight under conditions of weightlessness. /1*

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*Numbers in the margin indicate pagination in the original foreign text.

Data have been published regarding the effect of bed rest on various physiological systems [9 - 12]. The results of these studies have shown that the following changes take place in fluid phases and water-sodium metabolism: a decrease in the volume of blood plasma [13, - 15], hypercalcemia [16, 17], a decrease in the body potassium content (K. Hyatt, see note 12), an increase in the kidney excretion of calcium, nitrogen, sodium sulfur, phosphorus, and potassium [9, 13, 18]. An important question is which changes in the water-sodium metabolism are primary and which are secondary. This is a substantive question, since the means of correction are determined by the cause of electrolyte loss. If the loss is manifested as a different regulation of the balance, it is possible to compensate for the deficit by introducing supplementary quantities of salts or by strengthening their retention in the organism with the aid of hormone preparations. In the event that the electrolyte deficit is associated with a change in other functional systems, the introduction of excess electrolytes cannot normalize the balance or correct the defect. /2

On the basis of the above, it is possible to formulate and consider, as the present work attempts to do, certain unsolved and urgent problems associated with the status of water-sodium metabolism under bedrest programs of varying lengths:

1. the dynamics of electrolyte concentration in blood serum;
2. the relative role of the kidney in eliminating water and salt associated with the diet;
3. the functional status of the kidney osmosis regulating function;
4. volume regulation and the excretion of water and ions by the kidney;
5. the condition of the system regulating the exchange of sodium, potassium, and calcium, and transporting these ions within the kidney;
6. an analysis of the possible mechanisms for altering water and electrolyte metabolism.

A Short Description of the Experiments Performed

All the following experiments have been conducted with more than 60 healthy male volunteers between 20 and 39 years of age who were pronounced suitable by a special medical commission. In various experiments, the subjects were kept under bed rest conditions for periods of 5 - 182 days. To clarify the significance of the hydrostatic factor in the changes noted during the series of experiments, the subjects were kept with the head of the bed tilted at angles of 6°, 0°, -2°, -4°, -8°, and -12°. In addition, some of the subjects performed a complex of physical exercises (four-day cycle: three days of work and one day of rest) during the experiments. This permitted an /3 evaluation of the significance of limited motor activity in the observed shifts in water-sodium metabolism. During pre-experiment and recovery periods in the hospital, subjects were on an ordinary activity schedule and their intake of food and liquids was measures, as it was under kypokinetic conditions. Test samples were dessicated to a constant weight and incinerated to determine electrolyte concentration. Sodium and potassium content of blood plasma and urine was measured by pyrophotometry. Calcium was measured by atom absorptive spectrophotometry, osmotically active substances by cryoscopy, and creatinine by the Jaffe reaction. For evaluationg water-sodium metabolism and kidney activity, specific load tests were administered — water, sodium, potassium, and water deprivation.

Electrolyte Concentration in the Blood Serum

Ion stability of internal fluids — and especially of the blood plasma — is controlled by the activities of various organs and systems. Shifts in the ion concentration of blood serum reflect only extremely substantive changes in the ion balance, and therefore the constancy of the blood ion composition does not necessarily indicate that all is well with the ion regulating system. The results of 30-day hypokinesis show that during the entire period of observation the concentration of sodium and osmotically active substances in the blood serium did not change. Toward the end of the period, a decrease in the concentration of potassium and an increase in the concentration of calcium were observed among subjects who were kept in a horizontal or antiorthostatic position (Table 1).

Similar changes in the blood electrolytic composition were observed in subjects undergoing even longer period (six months) of bed rest in a -4° antiorthostatic position. Among six subjects undergoing 86-day hypokinesis, the calcium level of the blood serum rose to 4.92 ± 0.03 milliequivalents per liter, and for 178 day — to /5
4.96 ± 0.06 milliequivalents per liter, compared to 4.73 ± 0.05 in the pre-experiment period. It follows that hypercalcemia, having reached a certain level, does not increase even in the course of a half-year experiment.

Analogous data are obtained for the relationship of the change in blood serum potassium concentration and an increased bed rest period. In 26 days of hypokinesis, the same subjects experience a decrease in potassium concentration from 4.4 ± 0.09 to 4.0 ± 0.03 milliequivalents per liter. In 86 days, the potassium level was 4.2 ± 0.12 milliequivalents per liter, and in 178 days it was 3.9 ± 0.17 milliequivalents per liter. It follows, then, that kypokalemia was maintained at almost the same level throughout the whole six months of bed rest.

On the second day after the end of the 30-day hypokinesis experiment, hypercalcemia and hypokalemia persisted in all groups, as did increased osmolarity and hypernatremia (Table 1). In a few days the pre-experiment level of the blood ion composition began to be restored. Analogous data were also obtained for six-month bed-rest experiments, although the restoration of normal potassium and calcium levels in the blood serium required more time.

TABLE 1. CONCENTRATION OF ELECTROLYTES AND OSMOTICALLY ACTIVE SUBSTANCES IN BLOOD SERUM AT VARIOUS PERIODS IN THE 30-DAY HYPOKINESIS EXPERIMENT*

Experiment conditions	Tilt angle (°)	Sodium	Potassium	Calcium	Osmolarity
Pre-experiment	+6	I42±I,4	4,2±0,07	5,I±0,09	292±3,I
	-2	I42±I,8	4,4±0,09	5,0±0,I0	295±2,4
	- 6	I4I±2,0	4,2±0,II	5,2±0,I3	293±2,9
Bed rest					
2-day	+6	I45±0,7	4,2±0,I0	5,2±0,I3	295±2,0
	-2	I44±I,6	4,6±0,I2	5,0±0,09	297±I,9
	-6	I45±0,9	4,5±0,08	5,2±0,I0	298±3,I
12-day	+6	I43±0,9	4,I±0,II	5,2±0,I0	294±2,6
	-2	I4I±I,I	4,2±0,05	5,2±0,I2	293±3,7
	-6	I42±I,7	4,I±0,I4	5,3±0,08	295±I,2
27-day	+6	I42±I,9	4,0±0,I0	5,3±0,II	295±I,9
	-2	I44±2,3	4,0±0,08[x]	5,4±0,07[x]	297±0,8
	-6	I43 ±0,6	3,8±0,I2[x]	5,5±0,06[x]	297±2,7
Bed rest					
2-day	+6	I46±I,I[x]	3,9±0,I3[x]	5,4±0,07[x]	297±2,2
	-2	I47±I,7[x]	3,9±0,09[x]	5,5±0,I0[x]	303±2,0[x]
	-6	I48±0,9[x]	3,8±0,II[x]	5,5±0,I4[x]	302±I,7[x]
9- day	+6	I43±I,5	4,3±0,I0	5,0±0,09	290±2,9
	-2	I40±0,6	4,5±0,I4	5,I±0,I2	294±0,7
	-6	I42±I,2	4,I±0,07	5,2±0,I3	295±I,8
15-day	+6	I42±I,I	4,2±0,06	5,I±0,I2	29I±3,0
	-2	I43±0,9	4,4±0,08	5,I±0,08	293±2,I
	-6	I42±I,0	4,2±0,I0	5,2±0,I4	292±I,5

Comment: In each group, six subjects were tested for all conditions.

[x]Difference less than 0.05 compared to pre-experiment levels.

*Translator's note. Commas in numbers represent decimal points.

The Role of the Kidneys in Eliminating Water and Salts Under Hypodynamic Conditions

The relative stability of the blood ion composition during bed rest (disregarding the negative balance of sodium, potassium and calcium [9, 17, 18]) could depend on the change in relationship between ion demand and excretion by the kidneys or on a change in ion volume. In order to evaluate both possibilities experimentally, two series of experiments were conducted. In one experiment, the kidney excretion of salts as a percentage of their intake with nutriment was studied. In the other, the kidney reaction to various test loads was studied in the same subjects.

Under conditions of normal activity, the typical quantity of water consumed per day ranges from 2.3 to 2.5 liters according to our figures. Of this amount 1.7 to 1.8 liters were obtained from beverages, the liquid portion of the diet, and drinking water. On the very first day of bed rest, there was a significant decrease of water intake among all subjects to 1.4 - 1.2 liters per day (differences less than 0.01). In hypokinetic bed rest conditions, all subjects noted a dulled sense of thirst. If motor activity was not supplemented by physical exercise, water intake remained lowered during more extended periods of experiment also (Figure 1). With 2 - 2.5 hours per day of physical work on an exercycle, water intake remained at pre-experiment levels for a rather long time, but beginning with the 28th to 32nd day of the experiment it decreased, although it was still somewhat higher than in the group undergoing total hypodynamia.

Under conditions of our "normal activity" experiments, excretion of water by the kidney compared to intake reach an average of 54 - 60%. In the first days of transfer to bed rest, an increase in water loss through the kidneys was noted (Table 2).

It is worth noting that the greatest diuretic reaction was in the group of subjects in the antiorthostatic position. After a few days diuresis decreased, and thenceforward a wave-shaped change

TABLE 2. INFLUENCE OF TRANSFER TO BED REST ON ELIMINATION OF FLUID BY THE KIDNEY (MILLILITERS PER MINUTE, M ± m)*

Tilt angle	Elapsed time of experiment		
	Pre-experiment	24 hours	48 hours
+6°	0,8I±0,05	I,00±0,09	0,90±0,09
-2°	0,87±0,06	I,37±0,I2	0,94±0,I0
-6°	0,87±0,03	I,37±0,08	I,34±0,II

Comment: Six subjects participated in each experiment.

*Translator's note. Commas in numbers represent decimal points.

in the excretion of water by the kidney was noted in relation to water intake (Figure 2).

Among the subjects who performed physical exercise during bed rest, the elimination of fluids by the kidney in the first month of the experiment was lower than the pre-experiment amount, and less than in the total hypokinetic group (Figure 2). After 30 days of the experimental period, elimination of water by the kidneys increased. This was probably caused by lowered extrarenal losses, since body weight did not change substantially.

The elimination of sodium with the urine varies within wide parameters among healthy people. Even with standardized nutrition diets (but with individual discretion in the use of sodium chloride among the subjects), the excretion of sodium varied from 212 to 320 milliequivalents per 24 hours. During the first days of bed rest, the elimination of sodium increased among subjects in a horizontal or antiorthostatic position (Table 3). Not only did the absolute quantity of excreted sodium increase, but so did the elimination of sodium relative to the amount present in alimentation (Figure 3). Fifteen to twenty days after the beginning of hypokinesis, a tendency toward a decrease in the appetite for salt was manifested

TABLE 3. ELIMINATION OF SOIDUM (MILLIEQUIVALENTS PER 24 HOURS) BY THE KIDNEYS IN THE FIRST DAYS FOLLOWING TRANSFER TO BED REST (M ± m)

Tilt angle	No. of subjects	Pre-experiment	24 hours	48 hours
$+6^0$	6	268±26	237±21	274±18
-2^0	6	266±12	312±16	349±35
-6^0	6	250±10	351±29	300±16

among a majority of the subjects. The elimination of sodium by the kidney as a percentage of intake did not change, however (Figure 3). The excretion of potassium with the urine remained at pre-experiment levels during 15 - 20 days of bed rest, and then began to increase gradually (Figure 3). An analogous picture is characteristic of the elimination of calcium. /8

Functional Status of the Kidneys

Physiologically, the status of the kidneys can be adequately evaluated by a number of indicators, e.g., the level of glomerular filtration, osmotic dilution, and urine concentration under water load or fluid deprivation conditions. The process of osmotic concentration and dilution requires an adequate level of kidney blood flow, glomerular filtration, interrelationships between the operation of different nephron populations, the participation of all tubule segments, cells, and intercellular substances, etc. Therefore, the quantity of reabsorption and excretion of osmotically free water and the required level of the urine osmotic concentration for a given rate of urine elimination can serve as important indicators of the functional status of the kidneys and their regulating systems.

Glomerular filtration increases in the initial period of transfer to a horizontal or antiorthostatic position. A high level of fluid loss is noted, and then it is maintained at a level close to the pre-experiment figure (Figure 5). In the recovery period, during decreased urine elimination, there is a noticeable drop in the volume of glomerular filtration, but this is soon normalized (Figure 5).

In studying the osmosis-regulating function of the kidneys among cosmonauts, we have discovered that, in comparison with pre-flight quantities, post-flight morning urine tests show a drop in urine osmotic concentration despite decreased diuresis [6]. A similar picture is observed among subjects after a 30-day bed rest /9 period also. One day after a return to active movement, the urine osmolarity was less among all subjects who were kept in an anti-orthostatic position (-6°) and among five out of six who were in a horizontal position (-2°). Among those who were in a +6° position, no differences were exhibited. It should be emphasized that, among cosmonauts undergoing analogous periods of post-flight observation, changes in the relationship between the level of urine elimination and the lowered concentration of osmotically active substances in the urine were more apparent [6].

It was important first to establish whether this was caused by bed rest or whether it occurs at the moment when the body is transferred from a horizontal to a vertical position. Comparison of the urine composition of the subjects undergoing 27-day bed rest with pre-experimental figures did not display pronounced differences. It follows that under these conditions the functional status of the kidneys was not disturbed, and their altered capacity for osmotic concentration is a consequence of other regulatory influences. Since the activity of antidiuretic hormore (ADH) in the blood increases sharply after flight [5, 19], the change in osmotic concentration cannot be due to a deficit of ADH, but is probably related to a change in the cellular reaction to the hormone, particularly because of increased blood content of catecholamines [20], hypokalemia, hypercalcemia, etc. A graph showing a number of factors which decrease cellular reaction to ADH is presented in Figure 7.

Another possible cause of altered reaction to ADH could be post-flight activity against a different endocrine background of hypercalcemia and hypokalemia relative to the transport system of sodium and chlorine in the thick portion of Henle's loop (Figure 8). Increased reabsorption of sodium due to functional hypovolemia may also play an important role (Figure 8). It should be noted that the observed changes are extremely slight and are disclosed only under special experimental conditions and tonicity of the water economy system. This is explained by the fact that shifts in the ion composition of the blood are extremely slight, but since they act upon /1
the kidney continuously over long periods of time, they lead to a functional reorganization which is disclosed only in certain extreme conditions.

This point of view finds experimental support in the comparison of concentrations of osmotically active substances in morning urine tests collected after 27 days of bed rest and after the second day of the subsequent recovery period. Comparison shows that undergoing 30 days of hypodynamia does not destroy the kidney capacity to carry out its functions related to the urine osmotic concentration. The different relationship between osmolarity and diuresis was probably caused by lowered cellular reaction to ADH during the recovery period. At that time, against a background of hypokalemia and hypercalcemia, an excessive quantity of a number of hormones entered the blood [21], probably in response to the imbalance of blood volume with respect to vascular channel volume, which comes as a result of moving the body to a vertical position.

With increased experiment length, imbalance between the urine osmotic concentration (sodium concentration) and the diuretic volume was noted even during the period of hypokinesis. Thus, in a 91-day period of bed rest, five of the six subjects showed a decreased rate of diuresis averaging from 0.72 ± 0.04 to 0.57 ± 0.03 milliliters per minute with a practically unaltered amount of urine osmolarity. It should be noted that we observed an analogous phenomenon among immersed subjects, although in immersion these changes appeared sooner than in bed rest. It should be noted that the disturbance in

the relationship between urine osmolarity and diuretic volume following immersion appeared much sooner and was more pronounced. It follows then that increasing the length of both Earth-bound experiments and weightlessness can result in an altered reaction of the kidneys to the activity of regulatory systems. It is possible that such a lengthy condition (although not sharply expressed) of hypokalemia and hypercalcemia changed the sensitivity of the cells to ADH, not only under conditions of sharp gravitational forces, when /1
hormonal perturbation takes place, but also against a background of a relatively stable condition of the neuroendocrine system. Another possibility is that ion reabsorption increases when there is a comparatively water-permeable tubular wall, and a sufficient gradient of decreased urine osmolarity is not created when there is lessened diuresis.

Water load test. The decreased volume of blood and extracellular fluid as well as the insufficient blood volume of the central vascular areas, which were sharply pronounced among cosmonauts after their flights, found sharp reflection in water load functional testing. On the second post-flight day — and after a similar recovery period following Earth-bound experiments with bed rest and immersion — water testing (20 milliliters per kilogram of body weight) showed that the typical quantity of fluids excreted during the test was lowered (Figure 9). This is completely accounted for by the increased concentration of ADH in the blood, and can be viewed as a manifestation of the volume-regulating reflex.

The study of the reaction to water load during bed rest and with a varying degree of head declination has attracted a great deal of interest. During the 30-day experiment, elimination of water load did not differ from pre-experiment figures; under these conditions purgation of osmotically free water was not decreased for maximum diuresis. At the same time, in groups with an antiorthostatic bed-rest position of -6°, an increased purgation of osmotically active substances was noted in the second day of hypodynamia against a background of high diuresis (Figure 10). After ten hours of water deprivation among these same subjects, osmotic purgation was found to have occurred in the morning urine tests (Figure 11). This could be evaluated as a result of reflex saluresis due to an excessive volume of fluid in the central vascular areas.

In recovery periods following five days and 30 days of hypokinesis with head declination angles of +6° to -12° (Figures 10, 12), an identical reaction to water load was observed, i.e., an equal degree of fluid retention in the organism. Thus the change in water-sodium metabolism was the same as among post-flight cosmonauts. It follows, then, that bed rest experiments adequately model the condition of water metabolism which is typical of space flight. /1

Water load testing also provides extremely valuable information regarding the transport of a number of ions in the nephron. The creation of osmotically free water as well as osmotic concentration is linked to sufficient effectiveness of the cellular sodium reabsorptive systems. In the second day of bed rest after water loading, the subjects of all groups exhibited a greater elimination of sodium together with a decreased excretion of fluid (Figure 9). In addition, a difference in the degree of the increased rate of sodium excretion was established for varying angles of head declination, with the most pronounced effect in the -4° to -12° group (Figure 12). In the subsequent days of bed rest, a stationary condition of sodium metabolism began to be established. The relationship between the osmosis and volume regulation systems, on the one hand, and the excretion of sodium, on the other, did not differ from pre-experiment figures.

For 24 hours following the end of hypokinesis, all water-load test subjects showed a decreased elimination of sodium and osmotically active substances, together with a decreased excretion of water (Figure 9, 10). Analogous but less pronounced changes were observed in the analysis of urine collected during the first 24 hours following a return to regular motor activity. The difference was that quantitative intergroup differences — decreased elimination of water and sodium was greatest in the -6° group and least in the +6° group (Figure 13) — could be expressed with the water test. This could have been caused by peculiarities of hemodynamics, including the redistribution of the body fluids under varying degrees of antiorthostasis. Considering that among antiorthostatic subjects the typical quantity of hemoglobin decreased under conditions of its constant concentration in the blood [22] and that one could say that the volume of circulating blood in the 27 days of the experiment was lowered more than when the body was kept in a horizontal position, the compensatory retention of fluid and sodium after the experiment was greater, but their elimination by the kidneys was much less. Hemodynamic shifts resulting from the decreased volume of circulating blood and decreased blood flow to the organs of the thorax lead to increased secretion of ADH, aldosterone, renin, and forms of angiotensins [23, 24]. This can probably be explained by the decreased excretion (noted in the first days after return to ordinary activity) of fluid, sodium, osmotically active substances, and osmotically free water (Figures 9, 10). The displayed changes in the excretion of water, osmotically active substances, and sodium were probably a result not of the length of kypokinesis, but rather of the return to an orthostatic position, since analogous results were also obtained after five days of bed rest (Figure 12).

Sodium chloride load. The noted changes in osmotic and ion regulation were functional, and by the ninth day of the recovery period they did not even appear in the water load test. The change in water-sodium balance is therefore probably caused chiefly by decreased blood plasma volume and reflects a reactions which proceeds according to the Henry-Gauer reflex mechanism [25]. This supposition was supported by the results of a test in which a 0.9% sodium chloride solution (2% of body weight) was introduced into the organism in a single dose. In this test, in the second day of the recovery period, the excretion of fluid and sodium by the kidneys after isotonic load was significantly less than in the pre-experiment situation, while in the 39th day of kypokinesis the elimination of water and sodium was significantly higher than the pre-experiment level (Figure 14). During antiorthostatic hypokinesis, the decreased volume of extracellular (including vascular) fluid is probably adequate for the experimental conditions being studied. The volume-regulating system in hypokinetic conditions remains very sensitive and the kidney effectively eliminates excess quantities of the incoming isotonic solution, thus establishing a volume of extracellular fluid which is decreased in comparison to the pre-experiment level, but sufficient for hypokinetic conditions. Upon transfer to a vertical position and conditions of ordinary motor activity, the blood volume (decreased during bed rest) becomes insufficient to support optimal circulatory homeostasis, and the incoming sodium sodium chloride isotonic solution is retained to supplement the volume of extracellular fluid.

Potassium chloride load. A negative potassium balance was observed during space flight [26]. Increased excretion of potassium by the kidneys is characteristic of bed rest also, and hypokalemia appears clearly in the blood. The study of potassium elimination by the kidney in a water test can provide important data regarding the condition of the potassium balance regulating system at various stages of hypodynamia, and show the role played by the antiorthostatic position in the genesis of these disturbances. Test results showed that, during the first two weeks of bed rest, no changes in the elimination of potassium by the kidneys were noted regardless of the bed angle. In the recovery period following five-day hypokinetic experiments — and after space flights of the same duration — no disturbances were noted in the kidney kaliuretic function during water-load tests (Figure 12). However, toward the end of a month's bed rest, regardless of hypokalemia, the kidneys excrete more /15
potassium, while during the recovery period the elimination of potassium is significantly lower than pre-experiment quantities (Figure 15). After nine days this function of the kidneys was completely restored (Figure 16). The data suggest that increased potassium loss during hypokinesis is due to two causes — muscular atrophy and a decreased ability of the kidneys to retain potassium.

Negative potassium balance during space flight (Figure 1) and during hypodynamia are probably caused by muscular atrophy. Of 4000 milliequivalents of potassium in the human body, more than 2500 are found in the muscles (Figure 17). Experiments conducted in conjunction with G. S. Arzamazov involving the introduction of supplementary quantities of potassium provide the opportunity to evaluate the role of the kidney in excreting potassium and to calculate the retention of potassium in the organism under varying conditions of potassium balance and muscular conditions. Subjects received a 10% potassium solution of one milliequivalent per kilogram of body weight in a single dose on an empty stomach. They were also given 250 milliliters of fruit juice containing seven milliequivalents of KCl. Compared to pre-experiment tests among subjects who were kept with the heads of their beds at a -4° angle for 34 days, potassium concentration in the blood rose after 45 minutes to 5.82 ± 0.30 milliequivalents per liter. It is significant that before hypokinesis a similar load increased potassium concentration in the blood to 5.19 ± 0.06 milliequivalents per liter after 45 minutes. Under bed rest conditions, despite hypokalemia before the load test, increased potassium concentration in the blood was greater. This might be associated with the decreased volume of the cellular depot, which the potassium enters after absorption from the intentine and whence it slowly passes into the blood to be excreted by the kidney. To indicate the volume of this depot, it is sufficient to state that the typical quantity of potassium ingested by the subjects in the load test exceeded all the potassium dissolved in their blood plasma and extracellular fluid (Figure 17). At the same time, potassium /1 concentration in the blood serum changed to a lesser degree, and therefore a greater portion of the potassium entered the cell. The kidneys reacted to the load with a more intensive excretion of potassium under conditions of lengthy (34-day) hypodynamia (Figure 18).

In a parallel group of subjects, who practiced physical training during their bed rest program, the excretion of potassium was the same as in the pre-experiment period. The results of this experiment support the conclusion that the potassium load test can be used for measuring the volume of the cellular depot and its ability to retain potassium. As muscular atrophy proceeds during hypodynamia, the cells' decreased ability to retain potassium is probably accompanied by increased excretion of potassium also. It is known that insulin activates the transfer of glucose and potassium to the cells. In our laboratory it was demonstrated that the introduction of a potassium load accompanied by glucose decreases the excretion of potassium by the kidneys. This was possibly caused by the transfer of large quantities of potassium to the cells. These results provide the basis for suggesting that during hypodynamia not only should the deposit of potassium be reduced, but also the assimilation of glucose should be lowered. In actuality, there are data showing that after ingestion of 100 grams of glucose, its concentration in the blood reaches the highest levels among people undergoing bed rest [27].

In 30-day bed rest programs, glucose homeostatis is maintained under conditions of a great increase in the insulin level (2.5 times normal) in the blood [21]. During hypodynamia pronounced changes are observed in endocrine status [21]. Consequently, another type of potassium load elimination can be caused by the altered hormonal regulation of potassium homeostatis, as well as by decreased potassium storage due to muscular atrophy. It might be supposed that the potassium load test reflects to a great extent the change in the condition of muscle tissues and other cellular storage areas of potassium, since the combination of physical training with bed rest for 34 days of hypodynamia did not cause a disturbance in the elimination of potassium.

Elimination of calcium. One of the more disturbing symptoms of extended periods of both bed rest and space flight is the constant loss of calcium. Experiments with hypodynamia can help to answer the question of the manner in which this condition is reflected in kidney function. How does the kidney process calcium? Can load tests be used for a more refined and precise evaluation of the condition of the nephron's reabsorption systems? Examination of calcium elimination during water testing at maximum diuresis as well as at various other stages has provided an unambiguous answer to these questions. Increased calcium excretion by the kidney develops

gradually during hypodynamia. It is absent in 2- and 12-day bed rest programs but clearly appears in 27 days (Figure 19). It must be emphasized that this is a specific calciuretic reaction, for the elimination of sodium in these tests does not differ from pre-experiment levels. This supports the data we previously obtained showing that there is no strict connection between the reabsorption systems of sodium and calcium, but such a connection appears in a number of instances [28]. This is seen even more clearly in the recovery period, when increased elimination of calcium takes place against a background of lowered potassium and sodium excretion (Figures 9, 16). Since the elimination of calcium is the same in groups kept in orthostatic, horizontal, and antiorthostatic positions, it follows that hypodynamia plays the chief role in the disturbance of the calcium balance and in the altered processing of calcium by the kidney. The diagram of calcium balance regulation (Figure 20) shows the activity of a number of factors during hypercalcemia, which develops as a result of bone demineralization. In the final analysis, the excess calcium entering the blood is eliminated by the kidney. This occurs against a background of an increasing parathyroid hormone level [21], which in ordinary circumstances aids in the increased reabsorption of calcium by the kidney. This shows once again that, under hypodynamic conditions, there is a change in the hormone /1
status and in the reaction to hormones which is typical for ordinary conditions.

The above testifies to the urgent need of experiments in which different variants of functional load tests might be combined with a multifaceted study of the endocrine system. The subjects' reactions to the load tests which were administered have supplied answers to a number of substantive questions about the problem under examination. Results of these tests have shown that the developing ion deficit in the organism does not lead to their retention but, on the contrary, increases their excretion by the kidney. This became clear during the introduction of potassium chloride and also during the water test.

Moreover, a load test consisting of an isotonic sodium chloride solution showed that the decreased volume of blood during hypodynamia not only did not slow the elimination of sodium but, on the contrary, hastened it. This was observed during the sodium-load test but not during the water-load test, which indicates differing reactions of volume-regulating and osmosis-regulating systems.

Further, during the water test under hypodynamic conditions, calcium excretion increases and sodium excretion decreases. This allows one to speak of the selective alteration of specific ion regulating reactions.

In conclusion, let us summarize the results which have been obtained regarding the condition of water-sodium metabolism and the kidneys during extended bed rest:

1. Functional capabiltiy of the kidney does not suffer; its alteration is caused by a different neurohumoral background.

2. An orthostatic position (compared to a horizontal or, especially, an orthostatic position) apparently hastens hemodynamic shifts, and this phenomenon causes more rapid and significant elimination of water and sodium, i.e., it is reflected in reactions associated with volume regulation.

3. Fundamental changes in the blood electrolytic condition are expressed by slight hypokalemia and hypocalcemia. Homeostatic mechanisms assure minimal shifts in the fluid composition of the of the internal medium. The kidneys react to a change of tissue metabolism by excess excretion of potassium and calcium.

4. Functional load tests (water, sodium, and potassium) made it possible to clarify the condition of separate ion regulating systems when, under ordinary conditions (without administration of such tests), shifts were minimal.

5. Hypodynamia evokes a change in tissue metabolism, there is a loss of electrolytes (which are not retained in the tissues), and the addition of electrolytes can be only symptomatic therapy for these conditions.

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Legends to the Figures

Figure 1. Water consumption (liters per 24 hours) during bed rest. Abscissa — days of experiment. Striped portion — water consumption in the pre-experiment period.

Figure 2. Elimination of fluid by the kidneys (in percentages of intake) during bed rest with hypokinesis (I) and in combination with physical exercises (II). Abscissa — length of experiment in days.

Figure 3. Elimination of sodium and potassium (in percentages of their intake with alimentation) during bed rest. Abscissa — length of experiment in days.

Figure 4. Elimination of calcium by the kidney (milliequivalents per 24 hours) during hypokinesis. Because of the absence of differences among groups of subjects kept in a horizontal position (-2°), and antiorthostatic position (-6°), and in a position with the head of the bed at +6°, the data for all groups are combined, and each dot represents the average quantity among 18 subjects. Striping — elimination of calcium in the pre-experiment period.

Figure 5. Rate of glomerular filtration (milliliters per minute) during bed rest. The beginning and end of bed rest are indicated by vertical dotted lines. Abscissa — length of experiment in days.

Figure 6. Relationship between concentration of osmotically active substances in the urine and diuresis (morning urine specimens. Ordinate — osmolarity of the urine (milliosmolarity per liter), abscissa — diuresis (milliliters per minute). Blank shapes — pre-flight/bed rest; dark — post-flight/bed rest.

Figure 7. Effects of various factors decreasing cell reaction to antidiuretic hormone (Yu. V. Natochin, 1976 [29].

Figure 8. Localization of the influence of hypokalemia and hypercalcemia on the kidney's functional condition.

Figure 9. Elimination by the kidneys of fluid (V) and sodium (U_{Na}.V) during the 4 hours after water load in percentages of output figures. Solid horizontal lines indicate pretest intervals of pre-experiment quantities. Abscissa -- days and periods of experiments.

Figure 10. Indicators of kidney osmosis regulating function during maximal diuresis following water load. Striped columns — C_{osm}, blank columns — C_{H_2O}. Abscissa — days and periods of experiment.

Figure 11. Indicators of kidney osmosis regulating function during water deprivation. Blank columns — diuresis; striped columns — $T^C_{H_2O}$. Abscissa — days and periods of experiment.

Figure 12. Kidney elimination of fluid (V, percentage of drinking water), sodium (U_{Na}.V), potassium (U_k.V) during water testing following bed rest experiments and space flights, both of 5-day duration.

C — control; o°, -4°, -8°, -12° — angle of head of bed during bed rest.

F — post-spaceflight.

Figure 13. Rate of sodium excretion by kidneys during water tests Abscissa — time (minutes) after water load (arrow). Ordinate — elimination (microequivalents per minute). —●— — control; --o-- — 48 hours of hypokinesis; —△— — 27 days of hypokinesis; —▲— — 48 hours of recovery period.

Figure 14. Rate of sodium excretion by kidneys during test with 0.9% solution of sodium chloride. Abscissa — time (hours) after load. Ordinate — elimination of sodium (micro-equivalents per minute).
C — control; 39B — 39 days of bed rest; 2R — 2 days (48 hours) or recovery period.

Figure 15. Potassium excretion rate by the kidney during water test. Abscissa — time (minutes after water load. See Figure 13 for key to signs. /25

Figure 16. Elimination of potassium (U_k.V) and calcium U_{ca}.V) for 4 hours after water load in percentages of pre-experiment figures. Solid horizontal lines indicate pretest intervals of pre-experiment quantities. Abscissa — days and periods of experiment.

Figure 17. Potassium balance. I — diagram of distribution in the organism. II — influence of space flight on potassium balance (Leach, et a., 1975 [26]); elimination of potassium load during hypodynamia.

Figure 18. Rate of potassium excretion by the kidneys after potassium chloride load. Abscissa — time (hours) after laod (arrow). Ordinate — elimination of potassium (micro-equivalents per minute)
Special signs: heavy line — pre-experiment period; line with solid triangles — 39-day hypokinesis; line with circles — 39-day bed rest with physical training; line with blank triangles — 48 hours after bed rest.

Figure 19. Rate of calcium excretion by kidneys during water test. Abscissa — time (minutes) after water load.
Signs: see Figure 13.

Figure 20. Diagram of altered regulation of clacium balance during hypodynamia.

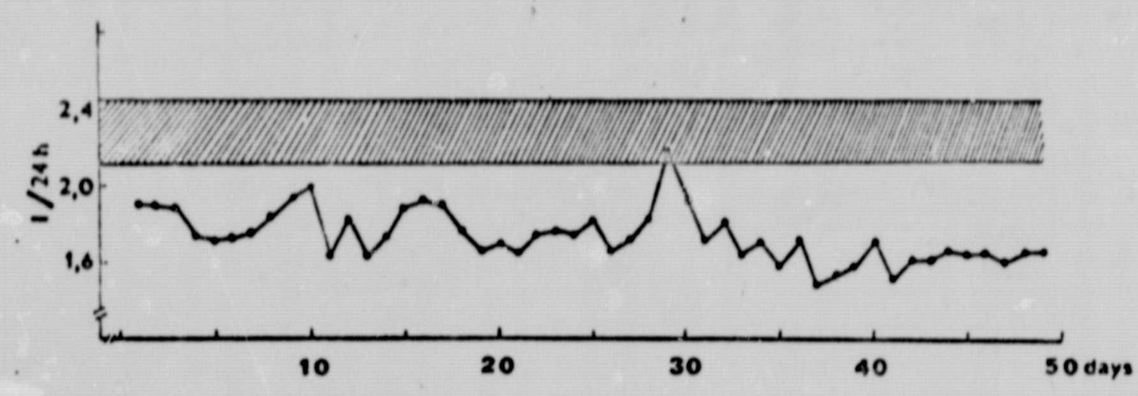

Figure 1

Figure 2

/27

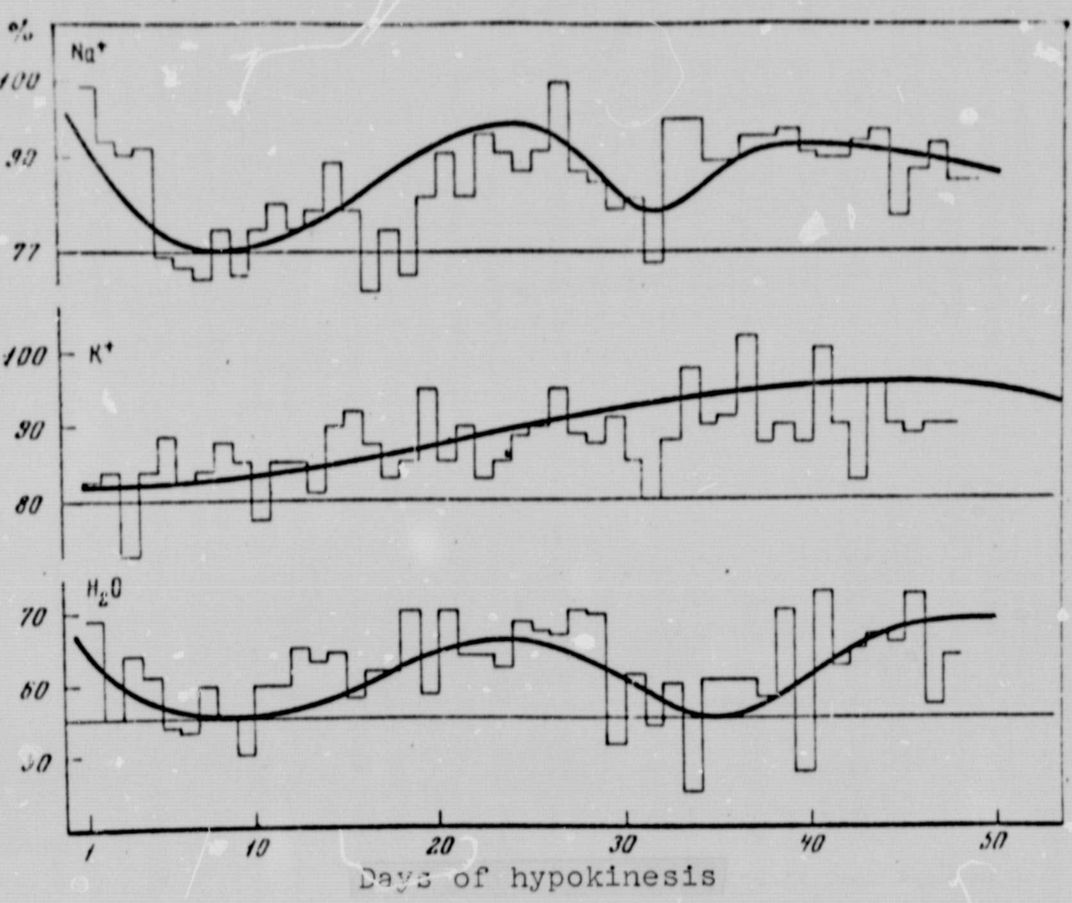
%
Na+
100
90
77
100
K+
90
80
H2O
70
60
50
1
10
20
30
40
50
Days of hypokinesis

Figure 3

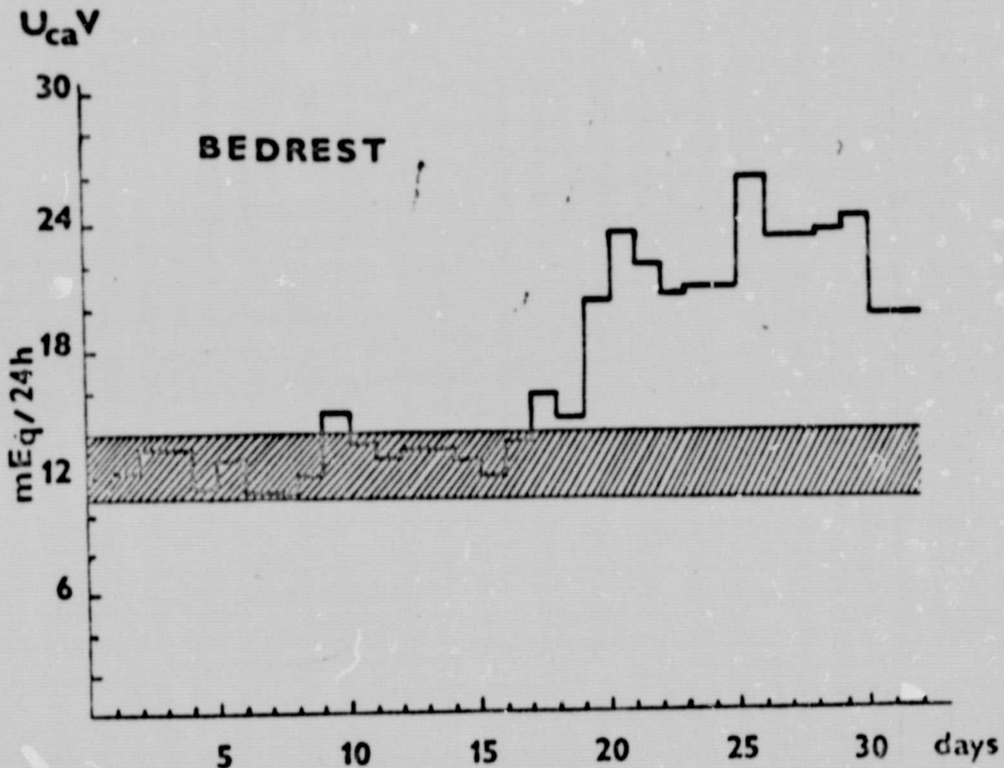

Figure 4

/27

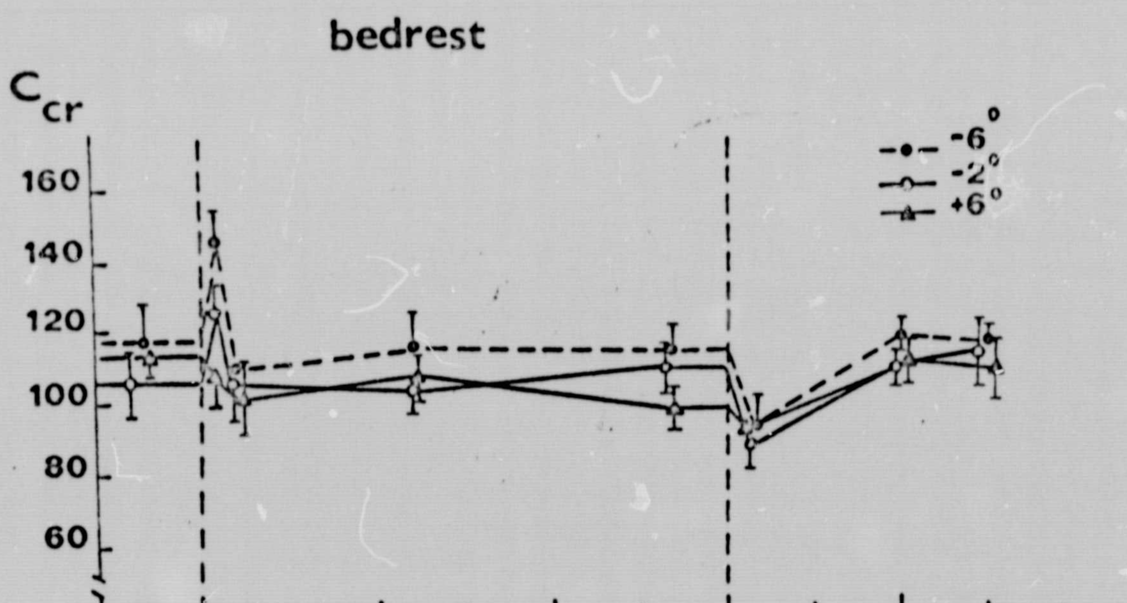

Figure 5

/28

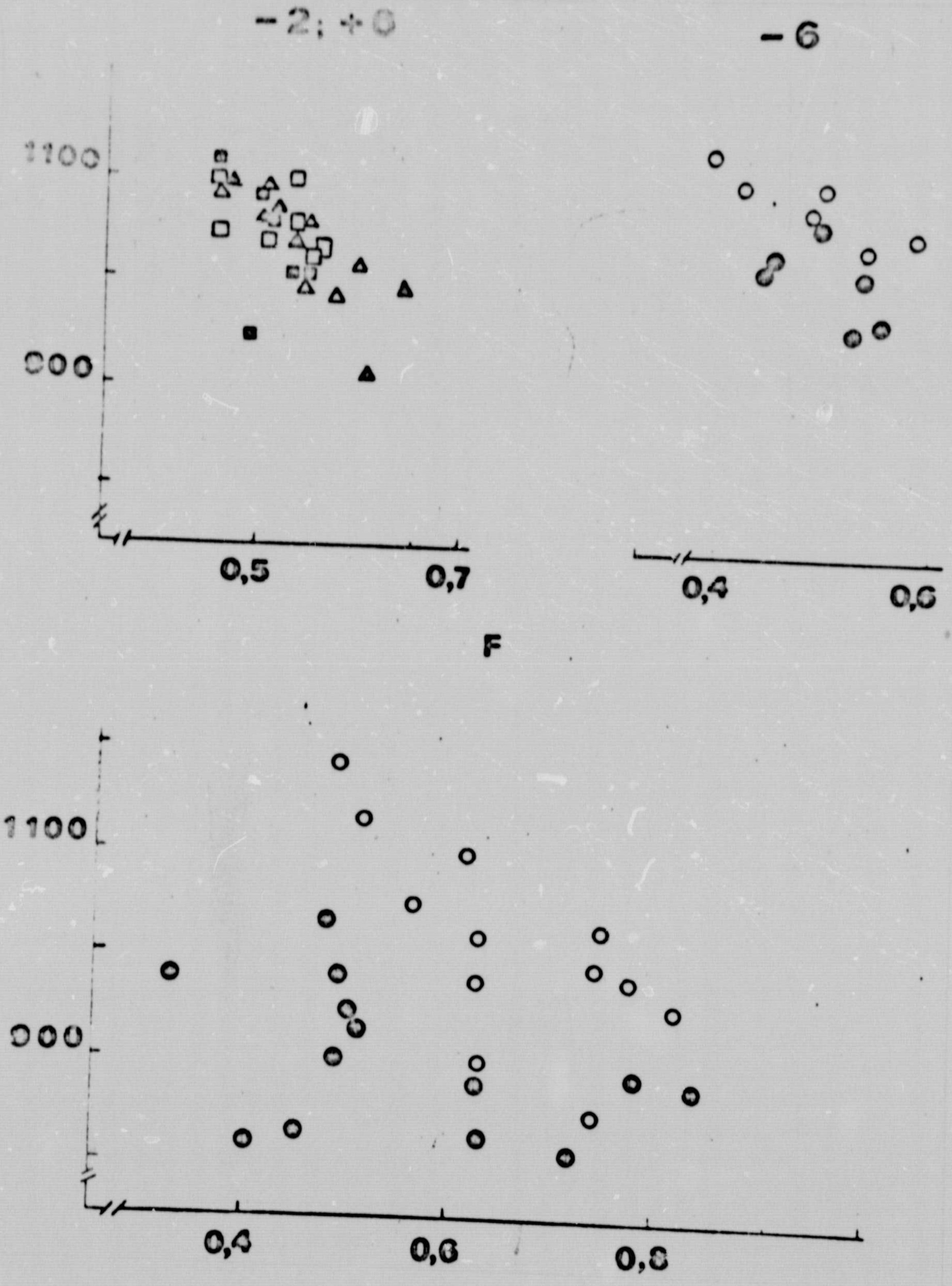

Figure 6

/30

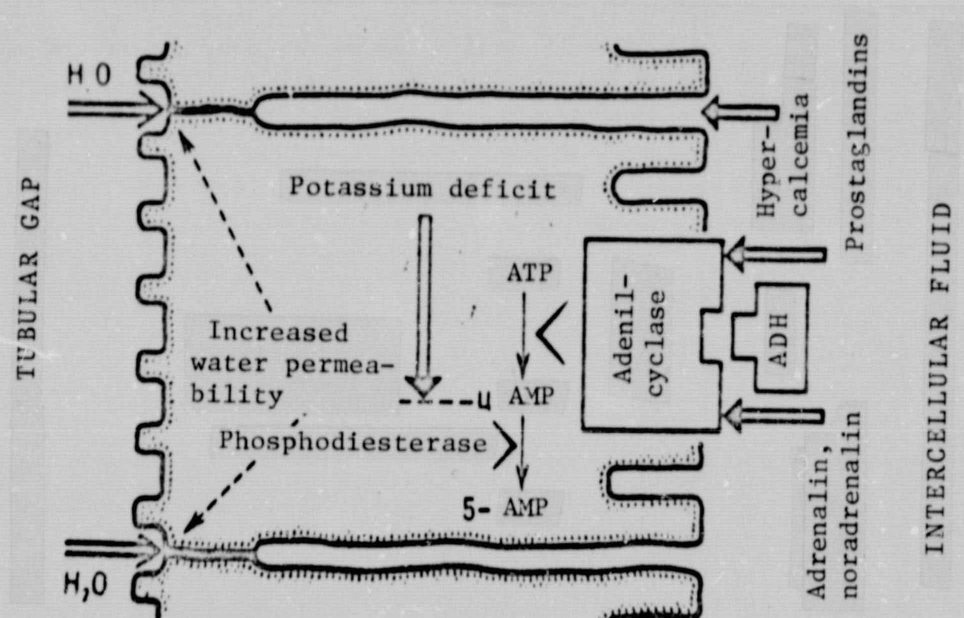
H O
H,O
TUBULAR GAP
Potassium deficit
Increased
water permea-
bility
Phosphodiesterase
ATP
AMP
5- AMP
Adenil-
cyclase
ADH
Hyper-
calcemia
Prostaglandins
Adrenalin,
noradrenalin
INTERCELLULAR FLUID

Figure 7

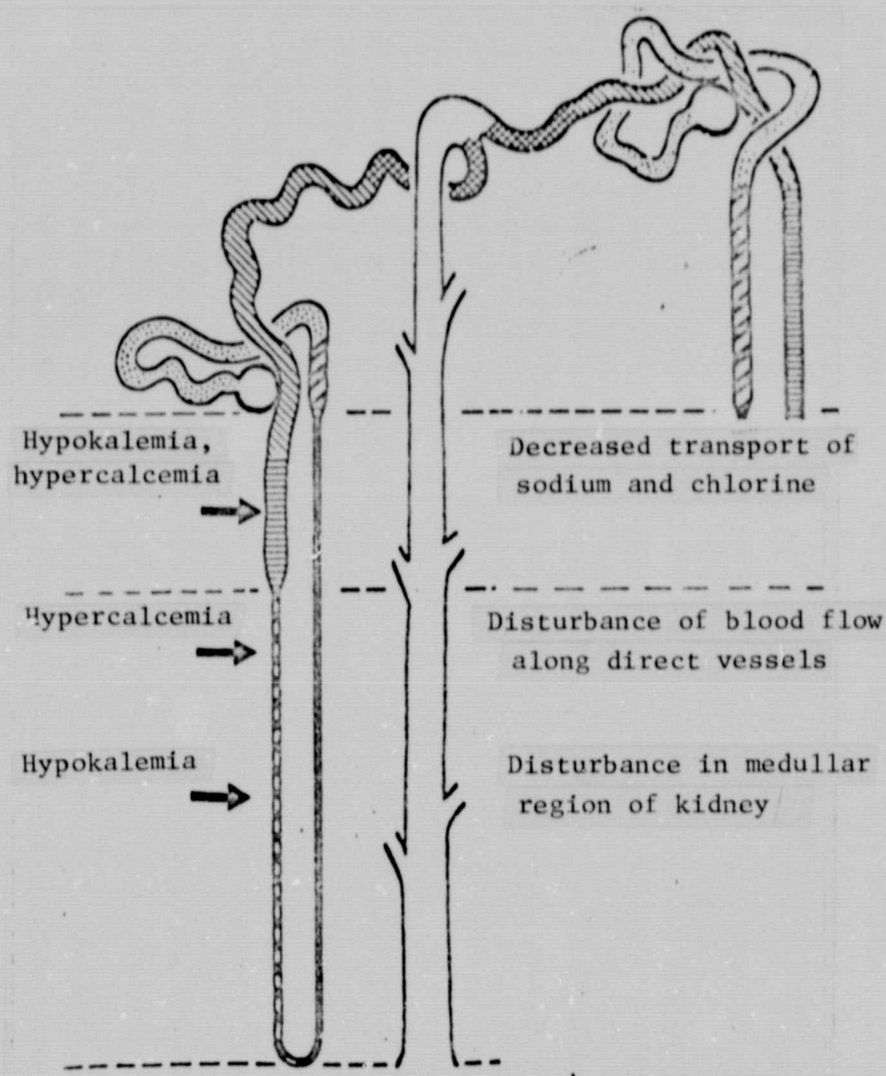
Hypokalemia,
hypercalcemia
Decreased transport of
sodium and chlorine
Hypercalcemia
Disturbance of blood flow
along direct vessels
Hypokalemia
Disturbance in medullar
region of kidney

Figure 8

/32

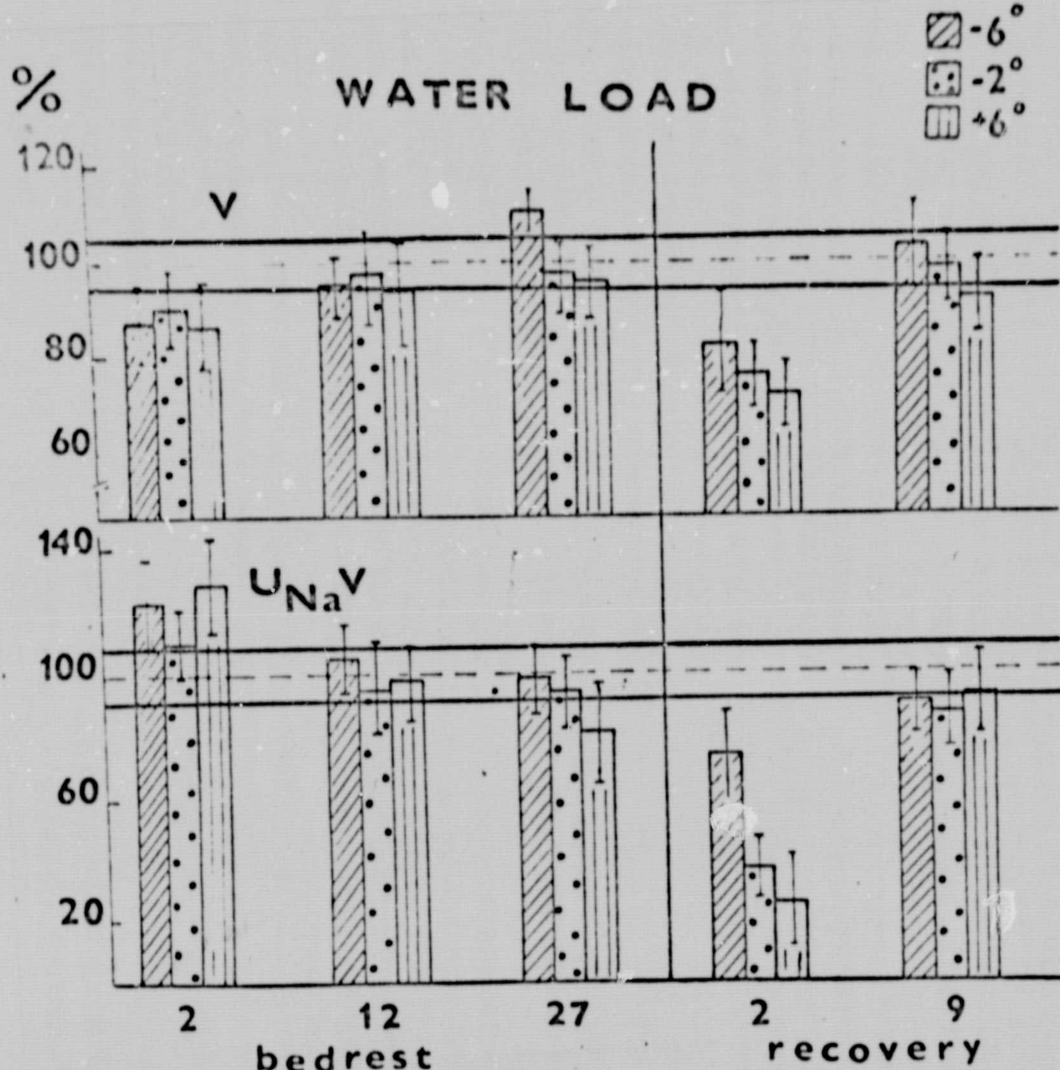
%
WATER LOAD
-6°
-2°
+6°
120
V
100
80
60
140
$U_{Na}V$
100
60
20
2
12
27
2
9
bedrest
recovery

Figure 9

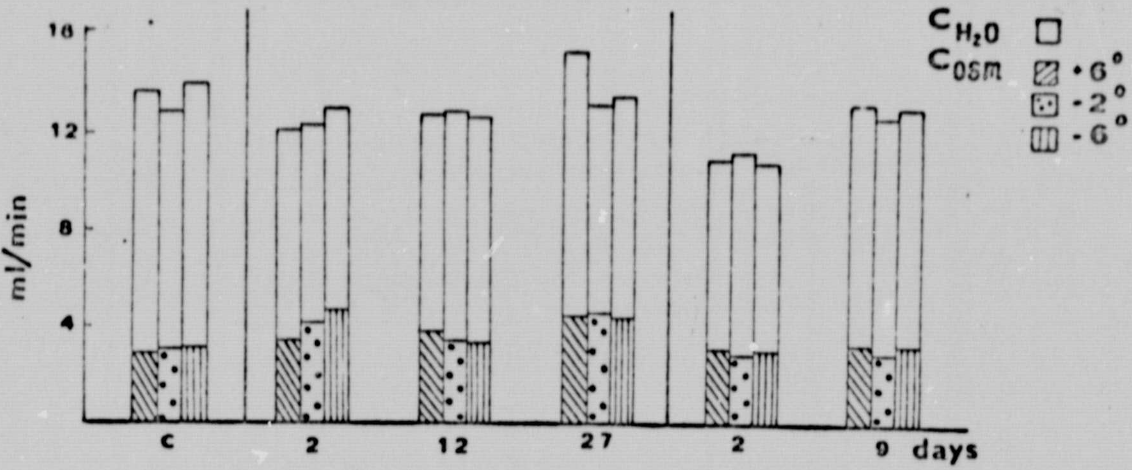

Figure 10

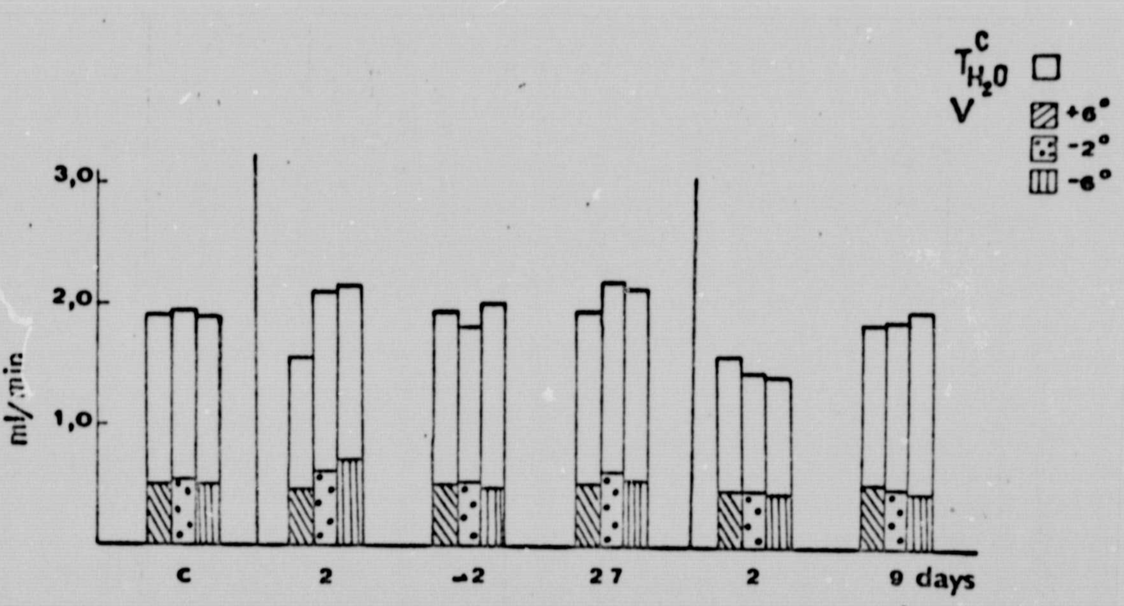

Figure 11

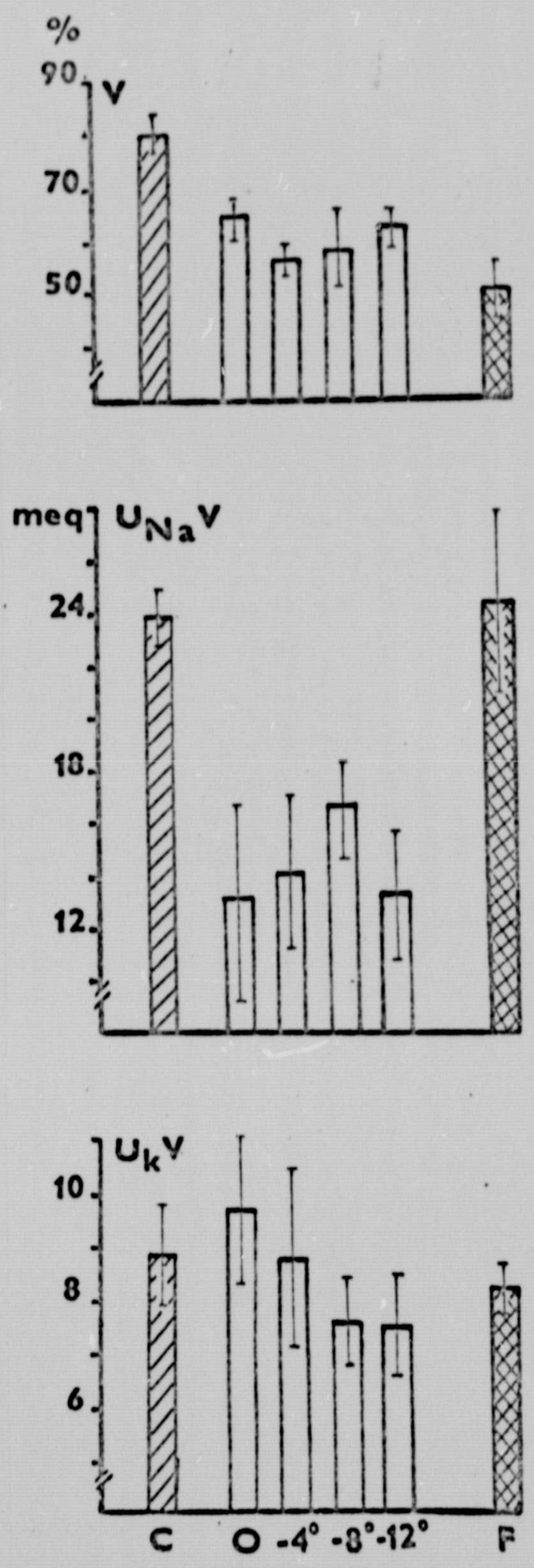

Figure 12

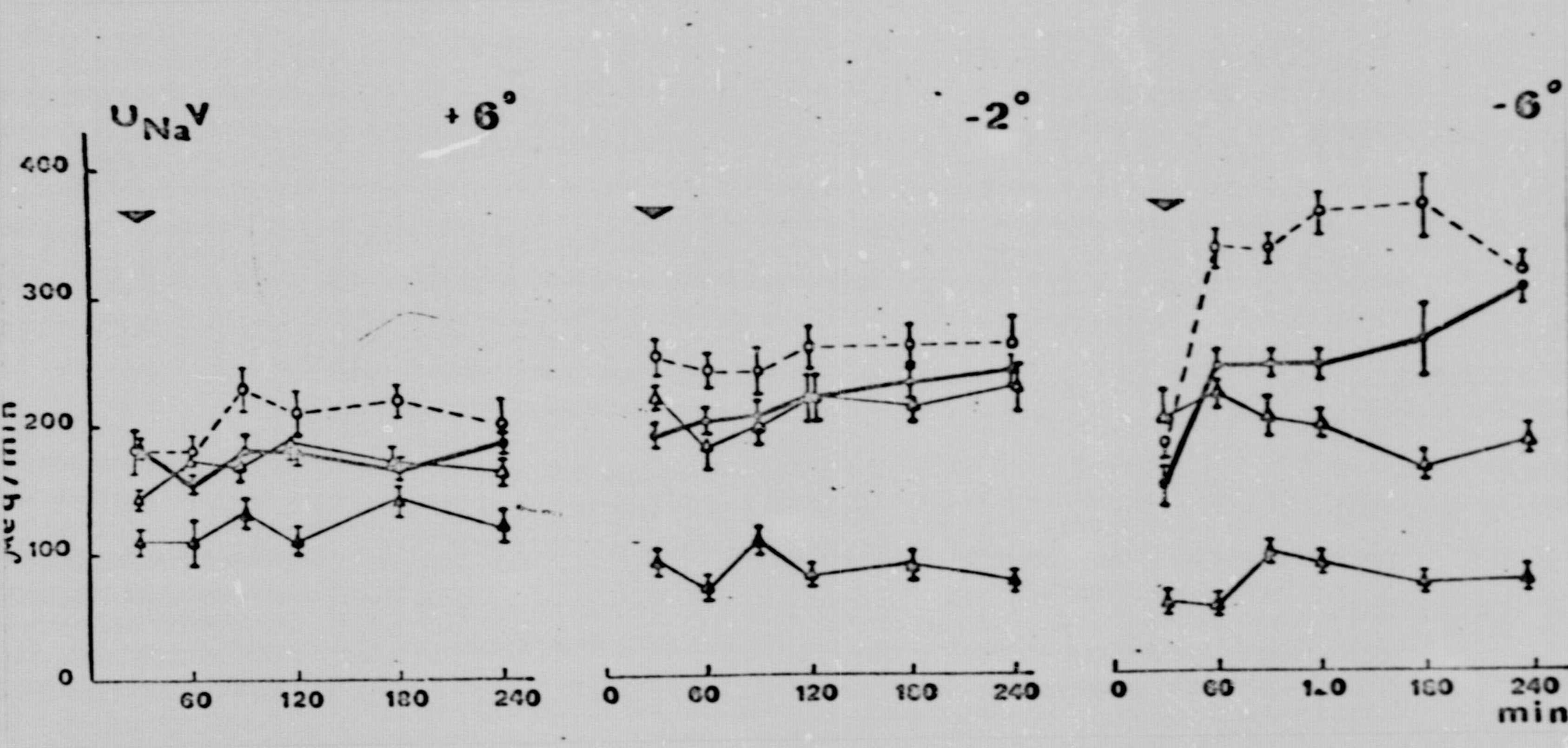

Figure 13

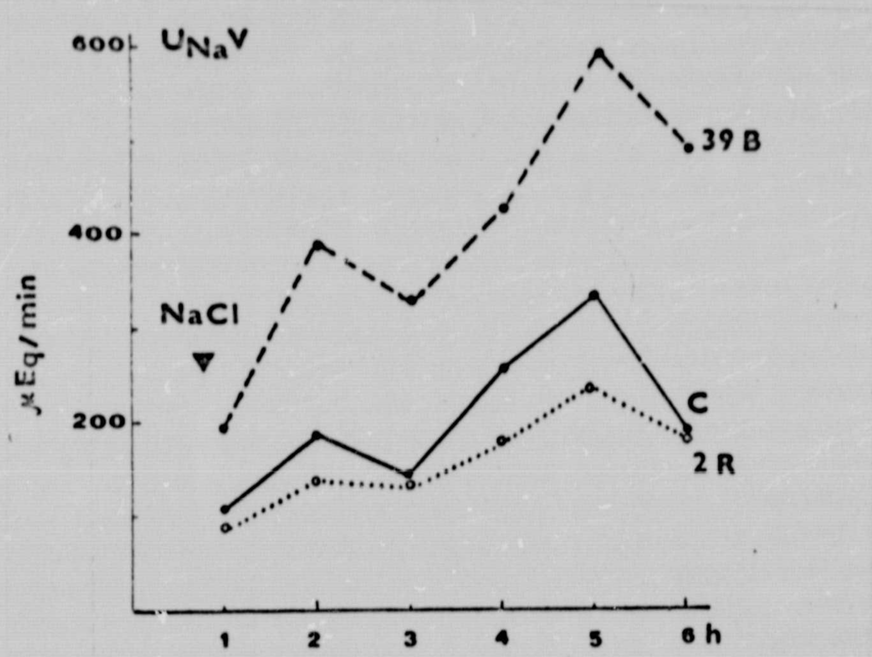

Figure 14

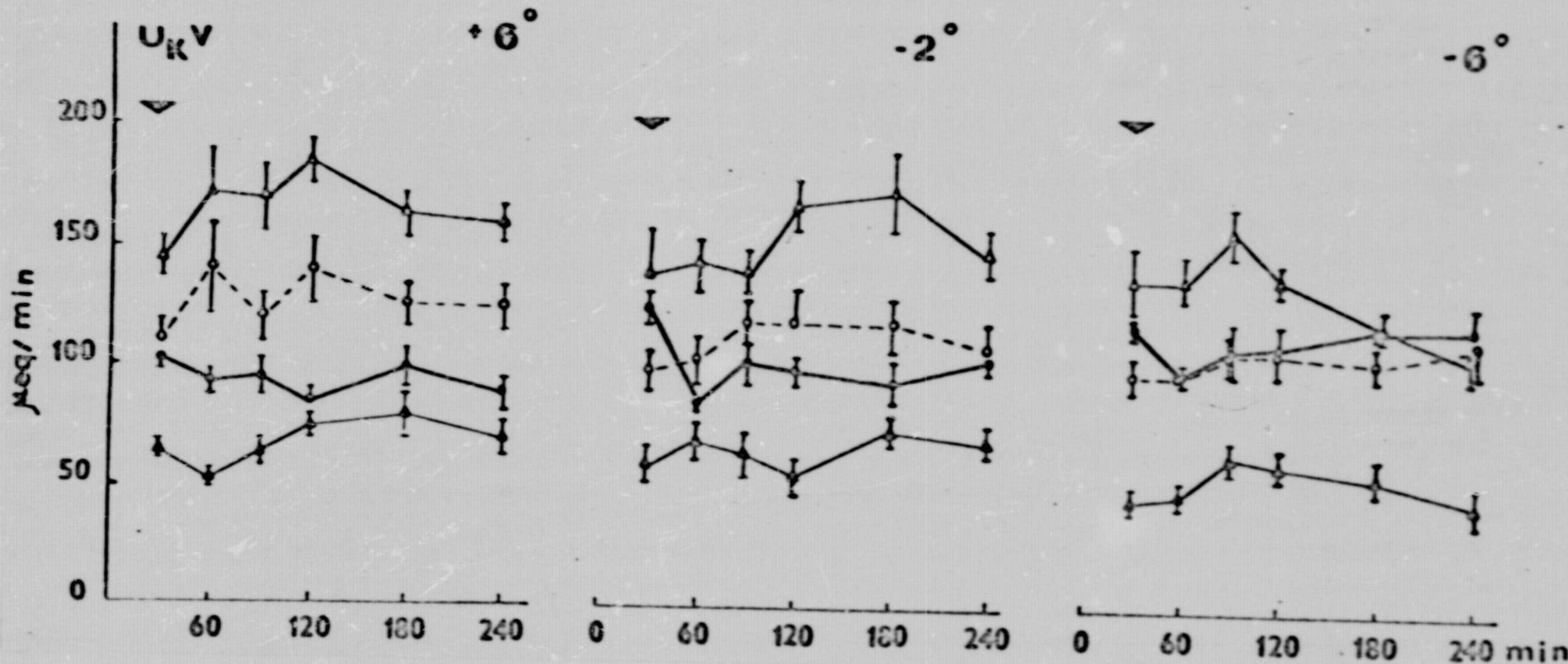
UKV
+6°
-2°
-6°
200
150
100
50
0
µeq/ min
60 120 180 240
0 60 120 180 240
0 60 120 180 240 min

Figure 15

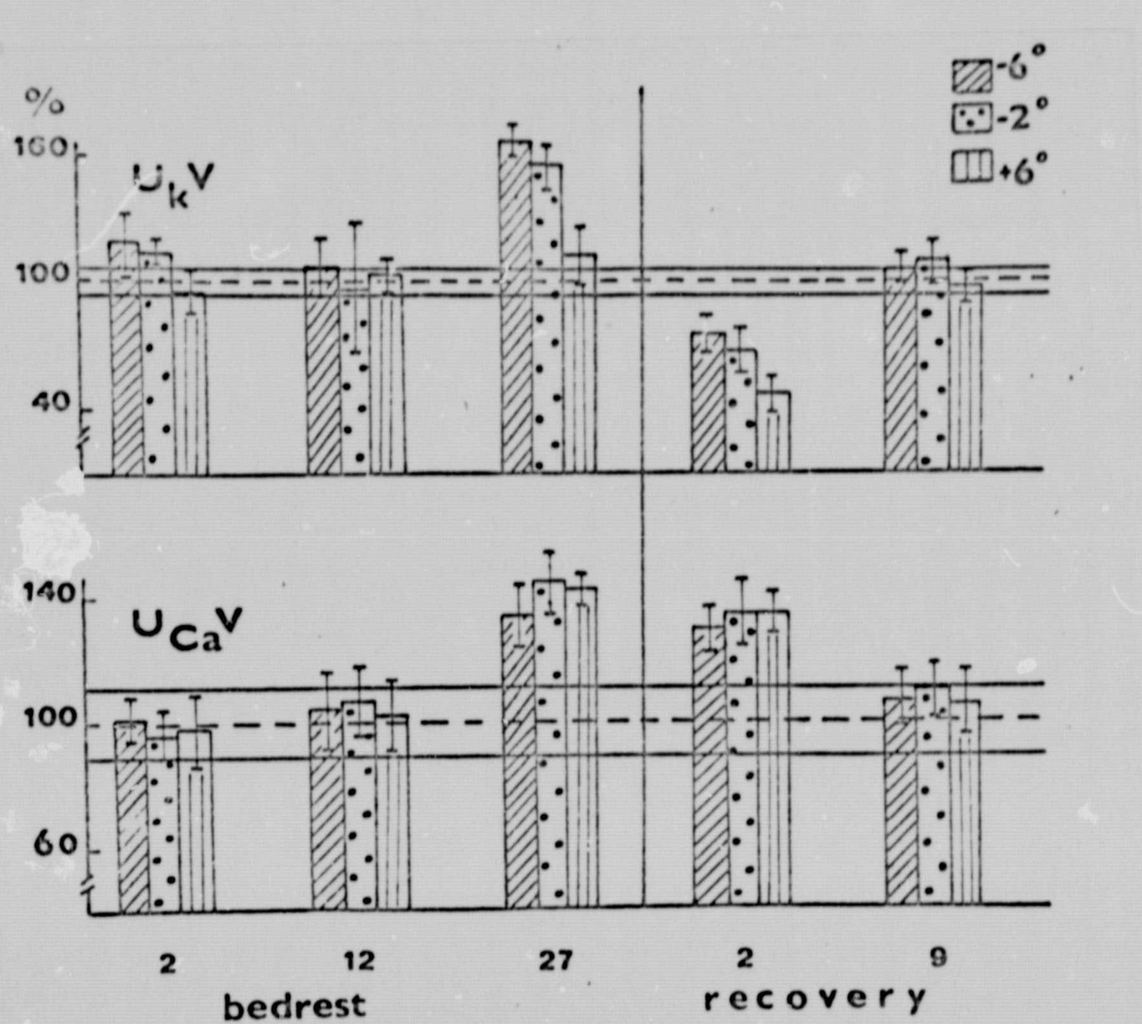

Figure 16

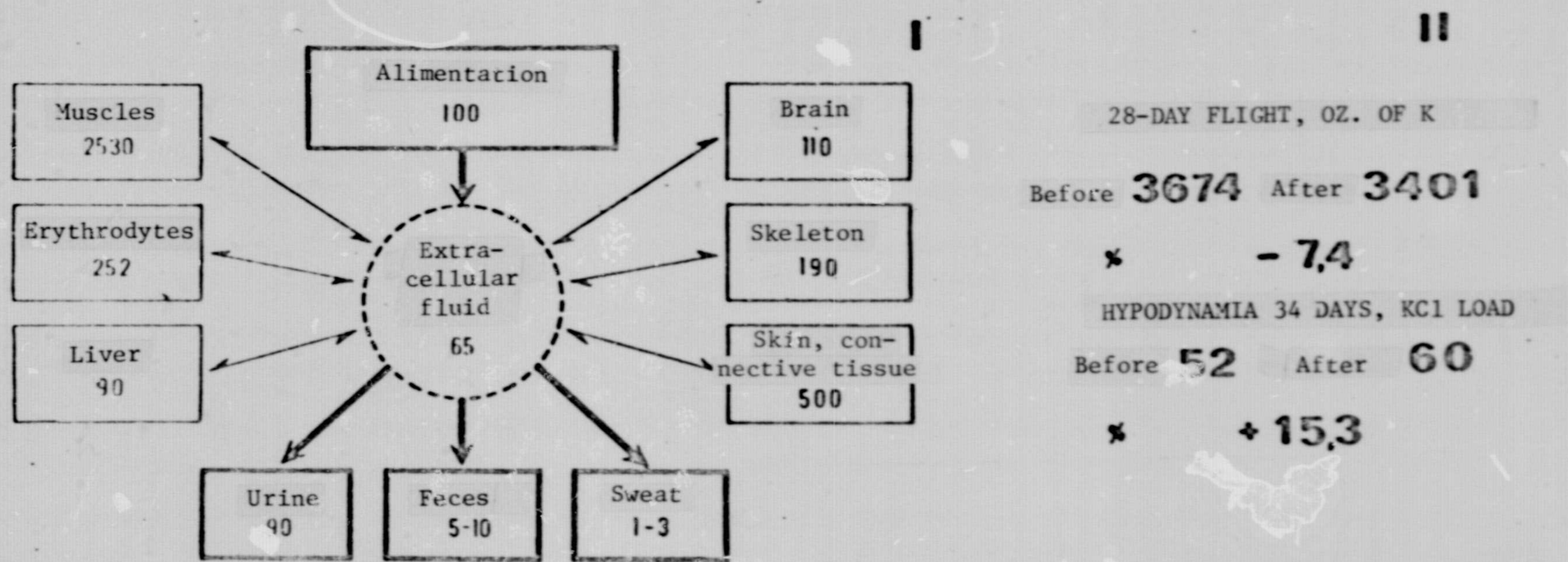
I
II
Alimentacion
100
Muscles
2530
Erythrodytes
252
Liver
90
Extra-
cellular
fluid
65
Brain
110
Skeleton
190
Skin, con-
nective tissue
500
Urine
90
Feces
5-10
Sweat
1-3
28-DAY FLIGHT, OZ. OF K
Before 3674 After 3401
% - 7,4
HYPODYNAMIA 34 DAYS, KCl LOAD
Before 52 After 60
% + 15,3

Figure 17

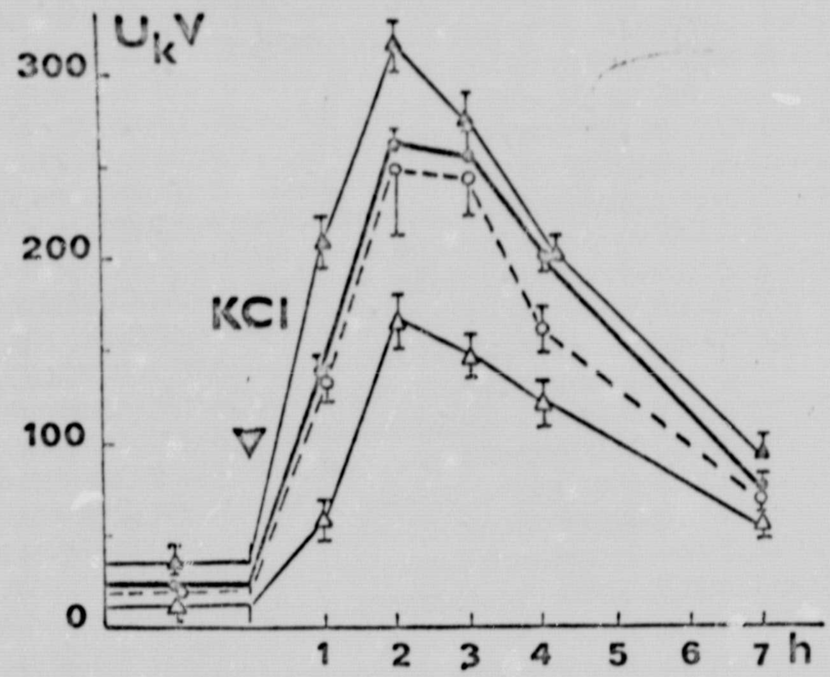

Figure 18

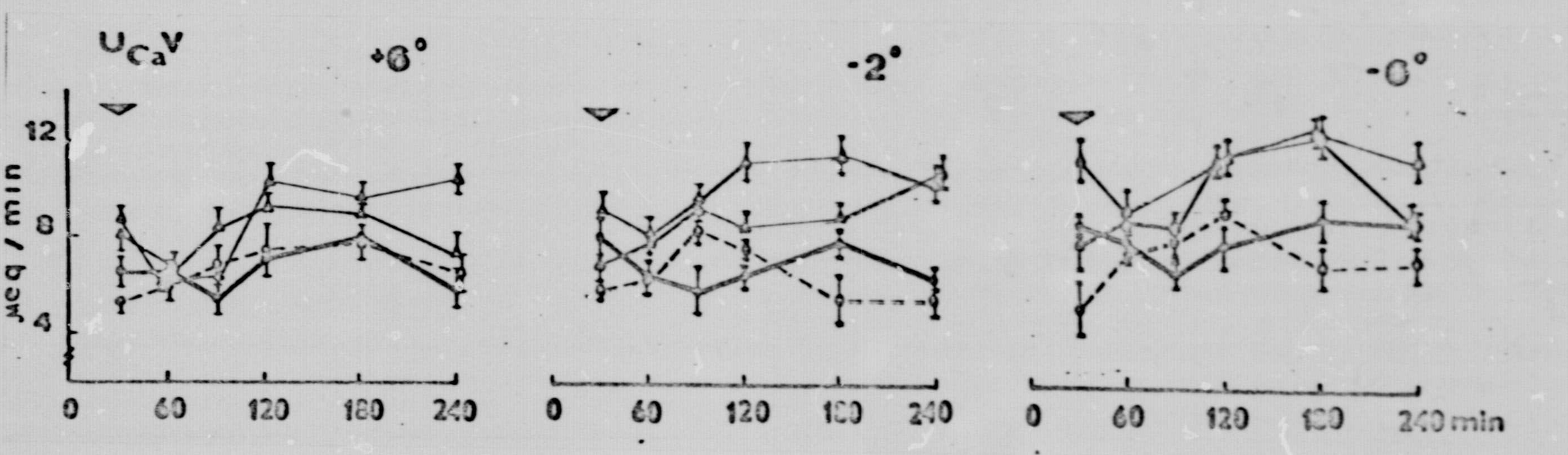

Figure 19

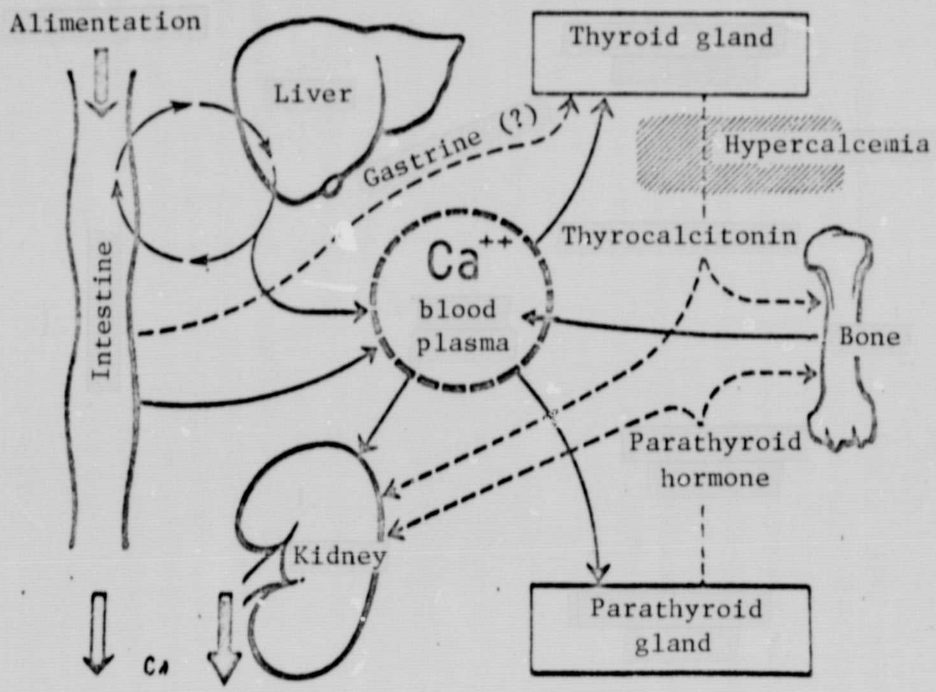
Alimentation
Liver
Thyroid gland
Gastrine (?)
Hypercalcemia
Thyrocalcitonin
Intestine
Ca^{++}
blood
plasma
Bone
Parathyroid
hormone
Kidney
Ca
Parathyroid
gland

Figure 20