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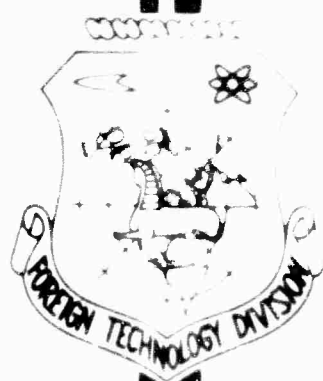
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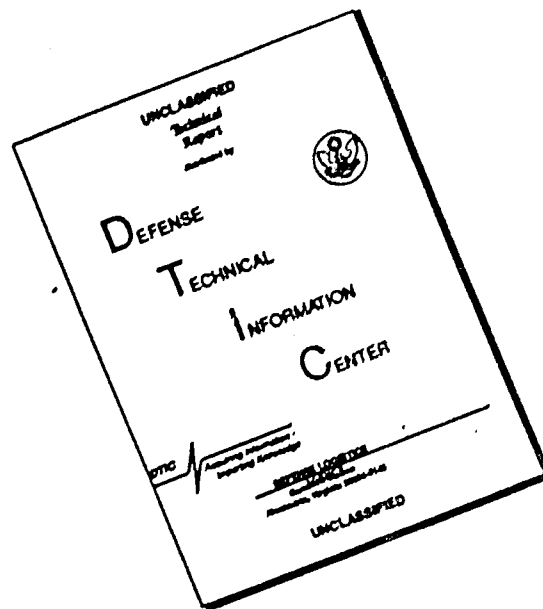
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**KISLORODNAYA
NEDOSTATOCHNOST'**

(Gipoksiya I Adaptatsiya K Ney)

Izdatel'stvo Akademii Nauk Ukrainskoy SSR
Kiev - 1963
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This collection presents research results obtained in the foremost laboratories of the Soviet Union working on the problem of hypoxia and adaptation of the organism to it.

Among other matters, the volume illuminates questions of the comparative physiology of adaptation and acclimatization of the organism to the high-mountain climate, contemporary concepts of the significance of the cell chemical mechanism in the process of adaptation to hypoxia are set forth, and data are presented on the importance of hypoxemia in the pathology of the childhood years and the role of the age factor in the reaction of the organism to hypoxia.

New facts are also communicated concerning the influence of hypoxia on the propagation of stimuli in the motor regions of the brain, on the influence that it exerts on bioelectric activity, oxygen partial pressure and the energy indicators of the cerebral cortex and subcortical formations. The problem of regional oxygen insufficiency and the importance of this problem in the development of myocardial infarct are examined. Light is also cast on the problems of oxygen starvation and the mechanisms that compensate it in heart failure. The question of foundations for the diagnosis of hypoxic states is raised.

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COMPARATIVE PHYSIOLOGY OF ACCLIMATIZATION TO THE CLIMATE
OF THE HIGH MOUNTAINS

N.N. Sirotinin

(Kiev)

Over a number of years, we have studied adaptation to hypoxia in the aspect of comparative physiology. In our papers* we have noted an increase in sensitivity and a decrease in resistance to oxygen insufficiency as the organism develops in both the phylogenetic and ontogenetic senses and the resulting amplification of the mechanisms for active adaptation to hypoxia. It would be of interest to cast light on the analogous problem in acclimatization to the climate of the high mountains, since this would clarify the capacity of the human organism to adapt to the hypoxic states that arise so frequently over the course of its lifetime.

For this purpose, we have collaborated with G.A. Leont'yeva over the past nine years in translocating representatives of all classes of vertebrates from Kiev to various altitudes on Mount El'brus. The amphibians taken there included 55 frogs (*Rana esculenta*) and 20 toads (*Bufo vulgaris*); among the reptiles, we selected lizards (*Lacerta viridis*) and Monitors (*Varanus griseus*), 20 individuals; grass snakes (*Tropidonotus natrix*), 6 individuals; racers (*Zamenis gemonensis*), 5 individuals, and bog turtles (*Emys orbicularis*), 45 individuals. The birds taken for the experiments were 45 chickens, 10 turkeys, 41 ducks and 10 geese; the mammals were 10 hamsters (*Cricetus cricetus*), 35 gophers (*Citellus suslicus*), 40 guinea pigs, 60 laboratory rats; 80

laboratory mice; 20 rabbits; 6 goats, 25 sheep, 2 suckling pigs, 1 Himalayan bear (*Ursus tibetanus*), 5 cats and 18 dogs. Also observed from time to time were 120 humans - participants in the expedition and test subjects. Some of these were at high mountain altitudes for the first time in their lives, while others had been there several times over 10 years and more; I personally was in the mountains for the first time 27 years previously.

The investigations were carried out at Kiev (Altitude 100 m) and at various altitudes on El'brus: Terskol (2100 m), Novyy Krugozor (3000 m), the 105th Piket (3400 m), Ledovaya Baza (3700 m), and the 11th Priyut (4200 m). We studied respiration (frequency, depth, pulmonary ventilation), blood circulation (pulse frequency, electrocardiograms, and for the humans, blood pressure), the blood picture (hemoglobin content, erythrocytes, reticulocytes), as well as the oxygen saturation of the blood; other investigations were also undertaken in addition to the above.

The studies were conducted on the second to third day of the altitude sojourn, after 5-10 days since it had begun, and after extensive acclimatization of the animals (gohpers, chickens, ducks) that were left on El'brus for a year or more. In some of the animal species and in some of the humans, we investigated the blood after the return to Kiev. The closest attention was given to the humans and the least to the small animals, in which, due to technical difficulties, it was not possible to devote thorough study to all of the indicators named above.

Results of investigations. We were unable to detect active adaptation in the form of increased frequency and depth of respiration and acceleration of cardiac activity at altitudes of 2100 m and above among the cold-blooded animals. Nor were we able to note a consistent increase in the quantity of hemoglobin or the number of erythrocytes and

reticulocytes. In some experiments, these indicators were observed to increase, most frequently among the frogs as compared to the other experimental animals, but it was found subsequently that this was a function of blood thickening due to intensified excretion of moisture from the surface of the skin at mountain altitudes. A certain tendency to active acclimatization was observed among the racers. Experiments of the same type were conducted by L.V. Bogdanova and N.M. Shumitskaya.* These authors obtained similar data.

The absence of active acclimatization to the high-altitude climate among the cold-blooded animals is, in our opinion, to be accounted for on the one hand by the fact that in the lower animals, vital activity can proceed to a considerable degree by anoxybiotic process and, on the other, to the fact that the reactivity of the cold-blooded animal organism to the influence of many different kinds of disturbances is less pronounced than in the case of warm-blooded animals, i.e., they are more stable, as we have noted in print on more than one occasion (1950, 1951, 1952).

TABLE 1

Frequency of Respiration, Number of Erythrocytes and amount of Hemoglobin in the Blood of Ducks at Various Altitudes

4 Давление (в мм.)	1 Казань (100 м)			Давление (в мм.)	2 Ледяной Восток (3700 м)			8 Увеличение числа эритроцитов (в тыс.)
	3 Кровь				3 Кровь			
	5 гемоглобин		7 число эритроцитов (в тыс.)		5 гемоглобин		7 число эритроцитов (в тыс.)	
	6 по Салли	%			6 по Салли	%		
12	76	12.8	2890	26	81	13.4	3690	800
19	71	12.4	2950	26	90	15.2	3320	970
17	75	12.4	2930	28	91	15.2	3840	910
15	72	12.4	2830	23	86	14.2	4310	1480
11	81	13.8	3250	20	92	15.4	3980	730
14	74	12.4	2910	25	86	14.2	3710	780
14	86	14.2	3060	26	91	15.2	4490	1430
22	87	14.4	2650	21	88	14.6	4280	630
16	102	17.0	4310	37	92	15.4	4070	-240
16	83	13.8	2810	35	86	14.2	4910	2100
15	74	12.4	2650	29	85	14.0	3350	690

TABLE 1 (CONT')

1) Kiev (100 m); 2) Ledovaya Baza (3700 m); 3) blood; 4) respiration (per minute); 5) hemoglobin; 6) after Sahli; 7) number of erythrocytes (in thousands); 8) increase in number of erythrocytes (in thousands).

In the birds, the high-mountain climate produces more distinct changes in respiration and blood circulation, and acclimatization to the climate is accompanied by an increase in the amount of hemoglobin and the number of erythrocytes. In ducks, it was possible to observe a certain increase in respiration rate and a minor increase in the blood hemoglobin content even at the altitude of 2100 meters, while in certain cases the number of erythrocytes also increased. Among the chickens, we did not observe consistently expressed criteria of active acclimatization at the 2100-m altitude. At the altitude of 3700 m, both the ducks and the chickens showed increased respiration rates, an increase in the amount of hemoglobin, and a greater number of erythrocytes (Tables 1 and 2). The depressed erythrocyte content in the blood of the chickens is apparently to be accounted for by their immaturity. Approximately the same shifts in the blood indicators were also noted in the geese and turkeys.

As we know, birds that live in the high mountains all the time are distinguished by their adaptation to hypoxia from birds whose habitat is the lowlands. Thus, Shtrol observed as early as 1910 that the relative weight of the heart, and particularly that of the right ventricle, was greater in alpine partridges than in ordinary partridges. According to Hall, Dill and Barron (1936), the hemoglobin of birds of the high mountains has a greater affinity to oxygen than the hemoglobin of birds whose habitat is the lowlands.

The adaptation mechanism of birds is less distinctly expressed in hypoxia of short duration. Thus, Khistend and Rendoll (1941) were unable to detect intensification of respiration during oxygen insuffi-

TABLE 2

Respiration Frequency, Number of Erythrocytes and Amount of Hemoglobin in Blood of Ducks at Various Altitudes

1 Киев (100 м)				2 Ледовая База (3700 м)				
4 Дышан- ие (в мин.)	3 Кровь			4 Дышан- ие (в мин.)	3 Кровь			8 Увеличение числа эри- throcytes (в тыс.)
	5 гемоглобин по Салли	6 %	7 число эритроци- тов (в тыс.)		5 гемоглобин по Салли	6 %	7 число эритроци- тов (в тыс.)	
43	56	9.2	2600	59	70	11.8	3350	1750
50	62	10.2	3010	59	85	14.2	3510	800
44	63	10.4	2990	68	84	13.8	3650	1660
54	70	11.6	3270	69	74	12.2	3780	500
46	66	9.2	2700	64	77	12.8	4090	1290
36	52	8.2	2000	44	70	11.8	3210	1210
32	62	10.2	2660	49	68	11.4	3730	1070
60	67	11.4	2830	57	78	13.0	3670	870
49	62	10.2	2770	58	75	12.6	3690	920
54	66	9.2	2530	52	75	12.6	3650	1420
66	62	10.2	3100	74	75	12.6	3940	810
52	57	9.4	2850	68	77	12.8	3410	530
57	62	10.2	2890	61	74	12.2	3370	460
37	66	11.2	3070	47	75	12.4	3750	680

1) Kiev (100 m); 2) Ledovaya Baza (3700 m); 3) blood; 4) respiration (per minute); 5) hemoglobin; 6) Hall, Dill and Barron; 7) number of erythrocytes in thousands; 8) increase in number of erythrocytes (in thousands).

ciency in Mallards, house sparrows, starlings and domestic pigeons. We were also unable to detect any distinct intensification of breathing due to hypoxia when chickens, ducks and geese were placed in the low-pressure chamber, although we did observe both accelerated respiration and an increase in the depth of respiration in these same species of birds at altitude in the mountains. Apparently this disagreement in the results is to be accounted for by the presence of auxiliary air cavities in the birds: during short-term hypoxia in the low-pressure chamber, the birds use the air reserve in these cavities; under prolonged hypoxia in the mountains, the partial pressure of the oxygen in the air sacs becomes equal to that in the external atmosphere, so that the birds experience more severe oxygen starvation and adapt to it by intensifying their pulmonary ventilation (Fig. 1).

Among the mammals, those investigated in greatest detail as re-

gards acclimatization to hypoxia were the white laboratory mice; in these animals, we regularly observed an increase in the number of erythrocytes and the hemoglobin content both at mountain altitudes and under the conditions of the low-pressure chamber (Sirotinin, 1934, 1936, 1938, 1940). However, it is difficult to use them in a comparison with the results of acclimatization experiments run on other animals, and, in view of this, we have recently been conducting the investigations simultaneously on various species of mammals. Since we are unable to present the results of all of our investigations, since they would occupy too much space, we note only that in all of the mammals studied we found an increase in the hemoglobin content and erythrocyte count of the blood in high-mountain acclimatization, but this was not expressed to the same degree in different species. The increase in these indicators depends on many conditions, and, in particular, on how quickly the animals are brought up to the mountain altitudes and how long they stay there. Table 3 shows the increase in the number of erythrocytes and the hemoglobin content in the mice.

We obtained approximately the same results in the experiments on the white laboratory rats. An increase in the oxidation surface of the blood when rats were acclimatized to hypoxia had been noted by Ye.M.



Fig. 1. Pneumograms of a duck. 1) At Kiev (100 m); 2) at Ledovaya Baza (3700 m); 3) time marker (4 sec).

Kreps et al. (1956) and Khenken (1958).

We shall dwell in somewhat greater detail on the investigations run with sheep, since there are certain departures between our results

TABLE 3

Number of Erythrocytes and Hemoglobin Content in Blood of Mice at Various Altitudes, Slow Ascent (after 10-day sojourn at Altitude of 2100 m)

1 Киев (высота 100 м)		2 Терскол (высота 2100 м)		3 105-й Пикет (высота 3400 м)		4 Увеличение	
5 Кровь		5 Кровь		5 Кровь		8	9
эритроциты (в тыс.)	% гемогло- бина	эритроциты в (тыс.)	% гемогло- бина	эритроциты (в тыс.)	% ге- могло- бина	эритро- цитов	гемо- глоби- на
6	7	5	7	6			
10430	82	11310	89	11990	95	1260	13
11460	93	10190	79	15540	112	4000	12
10030	86	10690	83	11230	94	1170	8
8080	71	10370	79	11270	83	3190	12
7990	63	10080	81	11540	81	3500	18
7830	67	10360	85	11470	75	3640	8
10130	81	9350	82	13880	101	3800	20
10240	82	11150	96	10540	86	300	4
8930	80	9240	73	9010	80	110	0
10540	80	11180	93	12670	92	2330	12
11300	74	11100	92	12070	83	770	9
10840	91	11930	93	12710	100	1870	10
11280	82	8730	78	11150	91	130	9
9130	80	11170	75	14230	98	5100	38
11420	95	11930	87	12490	99	1080	4
10120	79	9380	68	8380	75	1780	4
8530	45	7880	79	10820	82	5130	37

1) Kiev (altitude 100 m); 2) Terskol (altitude 2100 m); 3) 105th Picket (altitude 3400 m); 4) increase; 5) blood; 6) erythrocytes (in thousands); 7) % hemoglobin; 8) erythrocytes; 9) hemoglobin.

and those of the literature. Hall, Dill and Barron (1936) observed an increase in the hemoglobin content and erythrocyte count in sheep in an ascent through the Andes from sea level to 2800, 4710 and 5340 m. A.G. Ginetsinskiy and Z.I. Barbashova (1942) found that the oxygen capacity of the blood in mountain Gissar' sheep was lower than that in lowland sheep, and, on this basis, advanced the hypothesis that the mountain sheep adapt to hypoxia by changing their tissue processes. The same view has been taken by R.P. Ol'nyanskaya (1949), K.M. Bykov and A.D. Slonim (1949). A.P. Zhukov and V.A. Kozhevnikov (1947) and I.M. Arav and Ye.P. Smolichev (1947) noted a slight increase in erythrocyte count and a decline in the hemoglobin content when Pamir sheep were brought to the Gissar' and Darvaz mountains. However, N.N. Bulatova (1953) found that Central Asian mountain sheep not only had more hemoglobin than

TABLE 4

Increase in Erythrocyte Count and Hemoglobin Content in Blood of Kiev and Mountain Sheep Under the Influence of the High-Mountain Climate

Elevation (100 m)	1 Terskol (2100 m)				3 Novyy Krugozor (3000 m)				4 105th Picket (3400 m)			
	Erythrocyte count (millions)		Cayote & day		Erythrocyte count (millions)		Cayote & day		Erythrocyte count (millions)		Cayote & day	
	7	8	7	8	7	8	7	8	7	8	7	8
63	7040	7440	9280	48	9980	10210	60	10480	66	10780	68	10780
67	7780	7440	7440	45	9940	10010	61	10210	62	9700	61	9700
64	9110	10380	10380	57	9980	10570	57	10780	60	10810	71	12840
63	9120	9770	9770	56	9900	10080	57	10780	60	10810	70	12840
70	9730	10430	10430	60	10040	10710	68	10870	70	12840	70	12840
61	9820	10880	10880	62	9870	9880	57	11480	56	11480	70	12840
70	9820	12610	12610	61	9470	9880	55	10800	60	10800	71	12840
70	7880	10880	10880	62	10110	11630	68	11310	70	12370	70	12840
64	8880	9080	9080	58	8780	9800	68	10800	57	11710	70	12840
64	9080	9080	9080	61	8780	9800	68	10800	57	11710	70	12840
66	8330	8330	11430	60	10080	9840	58	10800	60	11270	60	11270
				66	11830	13460	71	13880	78	15430	86	15430
					13460	14680	77	14680	83	15770	86	15430
					14680	14680	70	14680	83	14930	86	14930
					14680	18120	88	18120	89	14940	86	14940
					18120	14880	80	14880	79	14440	86	14940
					14880	14880	80	14880	79	14440	86	14940

9 Киевские овцы

10 Горные овцы

1) Kiev (100 m); 2) Terskol (2100 m); 3) Novyy Krugozor (3000 m); 4) 105th Picket (3400 m); 5) second day of residence; 6) after 8 days; 7) erythrocytes (in thousands); 8) % hemoglobin; 9) Kiev sheep; 10) mountain sheep.

lowland sheep, but also more blood. N.N. Bulatova (1953) and P.A. Korzhuev, and I.S. Radzinskaya (1957) observed an increase in hemoglobin content, erythrocyte count and hematocrit number, averaging 20%, in sheep and cows when they were driven to their summer pastures in Dagestan at altitudes of 2000-3000 m.

In 1959, we studied 10 fine-fleeced lambs of the Kiev region, which were taken to the heights of El'brus. There, at the "El'brus" collective farm, we acquired five coarse-haired lambs of local origin, which were subjected to the same investigation at the same altitudes. The results of the investigations are presented in Table 4, from which we see that the erythrocyte count and hemoglobin content were higher in the mountain lambs and in the Kiev lambs. On the second day after arrival at the altitude of 2100 m, all of the Kiev lambs showed a drop in erythrocyte count and hemoglobin content. Then the amount of the latter increased. On ascending to higher altitudes, the number of erythrocytes increased both in the mountain lambs and in the Kiev lambs; the hemoglobin content increased in all of the mountain lambs and some of the Kiev lambs.

In 1960, we repeated this experiment using lambs and sheep at the same altitudes. It was found that not only the number of erythrocytes, but also the hemoglobin content increased in all of the animals. The data obtained were comparatively uniform, and this enabled us to derive average values (Fig. 2). Eight animals were left for the winter at Terskol (altitude 2100 m). On investigation, it was established that their erythrocyte counts and hemoglobin contents had remained at the initial values (about 10 million erythrocytes and 60% of hemoglobin). The possibility is not excluded that the absence of a rise in these blood indicators was a result of a poor food supply. It is of interest that a lamb that had been dropped by one of the ewes brought up from Kiev and

had been raised at the 2100-meter altitude showed higher erythrocyte counts and hemoglobin contents than its parents, with its figures closely approaching those of the mountain lambs.

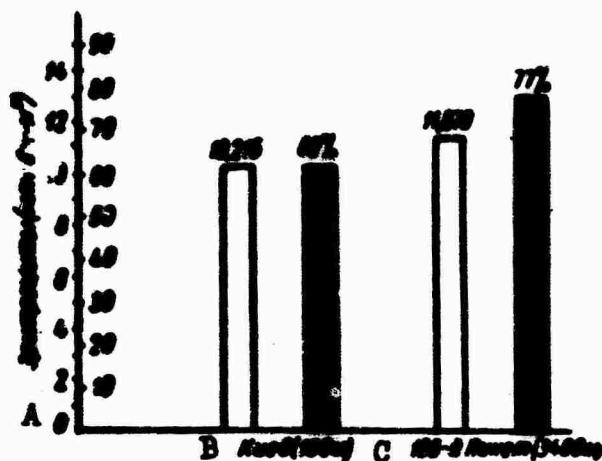


Fig. 2. Average erythrocyte counts (open columns) and hemoglobin contents (shaded columns) in 10 lambs at Kiev (100 m) and at the 105th Piket (3400 m). A) erythrocytes (about million per mm^3); B) Kiev (100 m); C) 105th Piket (3400 m).

We studied the oxygen saturation of the blood (using an oxyhemometer) on the same lambs at Kiev and on the heights of the El'brus, recorded respiration on a kymograph and took electrocardiograms. In both the mountain and the Kiev lambs, the oxygen saturation of the blood remained within normal limits right up to an altitude of 3400 m; the respiration frequency and the pulse rate changed insignificantly.

The data presented indicate that as regards high-mountain acclimatization, sheep do not differ particularly from other mammals. It may be that the authors who noted low blood indicators in lambs at high altitude investigated these animals on the first occasion on which they were at these altitudes, a time at which the number of erythrocytes and the hemoglobin content may fall off.

Rabbits, guinea pigs and dogs have served as the objects of high-mountain research for over half a century. Many authors have observed

an increase in their erythrocyte counts and hemoglobin contents at high altitudes (Misher, 1893; Kemp, Tsunts, Levi, Myuller, and Kaspari, 1905, and others). Abdergal'den, London, Kochneva, Rabinkova, Roske, Rozner and Vertkheymer (1927) studied hemopoiesis in angiotomized dogs at Halle (78 m), on Davos (1559 m) and at Muottas-Muregli (2450 m); at the high altitudes, they observed an increase in erythrocyte count in both the peripheral blood and the internal organs.

Beginning in 1930, we began a long series of studies on rabbits, guinea pigs and dogs and have noted an increase in hemoglobin content and erythrocyte count in them at high altitudes; N.M. Shumitskaya observed a rise in the number of reticulocytes in dogs. For the dogs, concurrently with the above studies, we recorded respiration on the kymograph and registered electrocardiograms, but dogs showed very little changes in respiration due to various factors, and this makes it difficult to detect distinctly expressed regular variations.

In the Himalayan bear, the erythrocyte count and hemoglobin content rose insignificantly at the altitudes of El'brus. According to Shumitskaya, an increase in the number of reticulocytes, which had not been detected under the conditions of Kiev, was also noted.

The largest number of studies into high-mountain acclimatization have been made on humans. The first such research dates from the end of the last century (Viol', 1890-1892; Myunts, 1891; Egger, 1893; Lavrinovich, 1898). Most of the research done recently indicates an increase in erythrocyte count and hemoglobin content at mountain altitudes. The question that had arisen earlier - as to whether this is a real increase or the result of redistribution of the blood - can now be regarded as solved: first we observe emergence of erythrocytes from the blood depots, and then, after two or three days, true hematogenesis begins. This is indicated by the rise in the number of reticulocytes in

the blood, with a leftward shift in their formula, and intensification of hemopoiesis in the bone marrow.

We observed an increase in erythrocyte count and hemoglobin content in participants in all of our expeditions into the mountains of the Caucasus, Pamir, Tien-Shan and Altai, which were undertaken on an annual basis from 1930 through 1940 and from 1949 to the present. In 1933, N.I. Vylegzhanin found us to have an increased number of reticulocytes with a shift to the left, and observation confirmed since then on more than one occasion, including recently by N.M. Shumitskaya. However, the increase in these indicators does not take place in strict parallelism with mountain altitude. It depends on a number of conditions: on the speed of ascent, the type of ascent (if the ascent is made on foot, the initial increase in the blood indicators is more sharply expressed due to the greater output of erythrocytes from the blood depots), on the interval of time that has elapsed from arrival at altitude when the investigation is made, and on individual peculiarities of the test subject. Usually, the erythrocyte shows the greatest increase, although in certain individuals it is the other way around, and the hemoglobin index rises by the greater amount.

Some authors reported long ago that the erythrocyte count dropped at high altitudes (Shauman and Rozenkvist, 1898; Kol'bryugge, 1898). On our expedition (1930), Z.I. Malkina found a drop in erythrocyte count in the present author on arrival at Adyl-Su (1670 m) from Kazan'; a decline in erythrocyte count and hemoglobin content was observed on occasion thereafter, most frequently on the second day of the high-altitude sojourn. In 1933, during the Pamir expedition, we attempted to register erythrolysis by analysis of urine to determine hemoglobin and bile-pigment content, but the results obtained were not unequivocal. Ya.G. Uzhanskiy described erythrolysis in posthemorrhagic anemia. In 1939,

during the Kazbek expedition, Ya.G. Uzhanskiy established such lysis among the participants of the expedition. Something similar was also observed in the experimental rats. On more than subsequent occasion we detected a drop in erythrocyte count and hemoglobin content on the second or third day of the high-altitude sojourn.

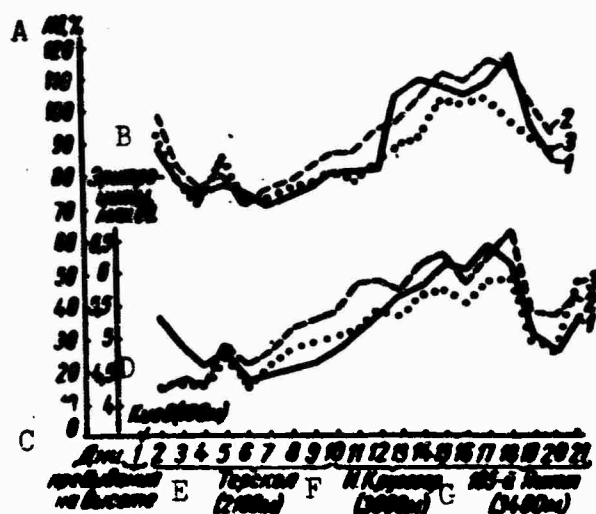


Fig. 3. Erythrocyte count and hemoglobin content in 3 test subjects at Kiev and at various altitudes on El'brus (daily observations). The peak in the rise curve on the fifth day at Terskol is associated with a hike in the mountains; on the 18th-19th days at 3400 m, the drop in erythrocyte count and hemoglobin content is seen distinctly. 1) E.V.G.; 2) G.I.V.; 3) M.I.G. A) Hemoglobin, %; B) erythrocytes, millions; C) days of sojourn at altitude; D) Kiev (100 m); E) Terskol (2100 m); F) Novyy Krugozor (3000 m); G) 105th Piket (3400 m).

During the sojourn at mountain altitudes, the erythrocyte count and hemoglobin content fluctuate, an effect that we ourselves have noted on more than one occasion, and one in which other authors concur (S. Zhikharev and T. Prelezhayev, 1936, and others). We noted that after acclimatization had intervened, approximately three weeks later, headaches and other symptoms of altitude sickness may make their appearance. N.M. Shumitskaya drew attention in 1959 to the fact that asthma sufferers began feeling poor at an altitude of 3000 m at approximately the time at which acclimatization steps in; this deterioration coincided with the drop in erythrocyte count and hemoglobin content.

Ya.G. Uzhanskiy showed that the initial erythrolysis may arise as a re-

sult of "autoaggression" on the part of autoantibodies against the erythrocytes. During the 1960 expedition, G.I. Vinogradov, M.I. Grutman and E.V. Gyulling made a special study of this problem, investigating autoantibodies against erythrocytes. Using the Boyden reaction, they detected an accumulation of autohemagglutinins in the blood serum on the 18th-19th days of the sojourn at high altitude, a point in time coinciding with the drop in erythrocyte count. Simultaneously, they observed a decline in the condition of the test subjects, although this was followed immediately by a rapid increase in erythrocyte count (Fig. 3). It appears that erythrolysis results in the formation of autoantibodies, which, during the time of their maximum accumulation, cause further erythrolysis, so that the products of the lysis activate hemopoiesis. It should be noted that this phenomenon may be manifested to different degrees and observed at different times. It depends on the titre of the antibodies that have formed and may not appear if they are present in small contents. In any event, these facts should be taken into account by all investigators studying hemopoiesis at high altitudes. It may be that the cases described in which the erythrocyte count dropped or failed to rise are associated with the above phenomenon.

On our test subjects, we studied the respiratory frequency (kymograph recording), pulmonary ventilation, cardiac frequency, electrocardiograms at rest and under metered loads of muscular work, with simultaneous investigation of the oxygen saturation in the blood. These oxymetric investigations were originally conducted during the expedition organized by the Physiology Institute of the Academy of Sciences Ukrainian SSR under Ye.M. Kreps and V.I. Voytkevich in 1954, and then by the present authors each year on the expeditions that followed; on one of the expeditions, we also studied the rate of bloodstream flow.

The investigations that we carried out indicate that the human organism, which is sensitive to hypoxia, begins to adapt to it quite early, in most cases basically by increasing pulmonary ventilation and in a minority of cases chiefly by intensifying the circulation of the blood. The erythrocytes, which at first increase in number due to output from the depots may be used quickly to some degree; the products of the erythrolysis activate true hemopoiesis. As the erythrocyte count and hemoglobin content increase, adaptation due to intensified respiration and blood circulation vacates into the background. In its turn, adaptation to hypoxia through an increase in the oxidation surface of the blood may be replaced by compensatory changes in the tissues.

All of the above bears testimony to the fact that higher animals, man included, possess varying, distinctly expressed mechanisms for active adaptation to hypoxia. Use of these properties of the organism with the objective of evolving a high-altitude therapy suggests itself in a natural manner.

Manu-
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[Footnotes]

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- 3 L.V. Bogdanova, "Ob adaptatsii k gipoksii nizshikh pozvonochnykh zhivotnykh" [On the Adaptation of Lower Vertebrates to Hypoxia]; N.M. Shumitskaya, "Sravnitel'no-fiziologicheskiye osobennosti funktsii krovotvoreniya u zhivotnykh v usloviyakh vysokogornogo klimata" [Comparative-Physiological Features of

the Hematogenesis Function in Animals Under the Conditions of the High Mountain Climate] (published in the present collection).

ON THE ADAPTATION OF LOWER VERTEBRATES TO HYPOXIA

L.V. Bogdanova

(Moscow)

On the basis of experimental studies carried out on representatives of various classes of animals, N.N. Sirotinin (1940, 1951, 1955) established that the lower the organization of the animal, the better does it withstand hypoxia.

A.N. Sokolov (1941) failed to observe adaptation to hypoxia in lower vertebrates. The experiments were run on fish (*Carassius aurantius*), frogs (*Rana esculenta*) and turtles (*Emys europaea*). When the fish were brought up to 10,000 m, the hemoglobin percentage did not change, while the erythrocyte count dropped very insignificantly. In the frogs after a two-hour "ascent" (10,000 m) and in turtles after two-hour and even seven-day residence in the low-pressure chamber, the erythrocyte counts and hemoglobin percentages dropped off slightly.

Z.I. Barbashova and N.N. Sirotinin (1941) failed to observe a marked rise in hemoglobin percentage, erythrocyte count or the oxygen capacity of the blood in experiments on reptiles [turtles (*Emys orbicularis*), grass snakes (*Natrix natrix*) and legless lizards (*Ophisaurus apus*)] placed in the low-pressure chamber (altitude 7000 m). N.N. Sirotinin concludes that these animals have no reaction to hypoxia, and that at best we may speak only of a "tendency to increased hemoglobin." Z.I. Barbashova suggests that reptiles have a special tissue type of acclimatization to hypoxia. Such adaptation would take the form not of a struggle on the part of the organism to "retain" oxygen in its blood,

but of adaptation of the tissues to function under conditions of oxygen insufficiency.

Al'tand and Parker (1955), conducting experiments on turtles (*Terapene carolina carolina*) in a low-pressure chamber at an "altitude" of 25,000-45,000 feet (18,000-13,500 m) observed no increase in the hemoglobin percentage or erythrocyte count regardless of the duration of the experiment (over 100 days). Nor was any stimulation of erythropoiesis observed, although blood-letting experiments on the turtles showed that they do have such a reaction. Placing the turtles in a gas mixture with low oxygen content (3%) resulted in a change in the nature of their respiration, but without noticeable hyperventilation. The authors come to the conclusion that the ability of turtles to withstand oxygen insufficiency is associated with the use of energy formed by anaerobic processes. It is interesting to note that turtles withstand hypoxia much more poorly at 36-38°C than at 20-23°C.

Bonne (1929) showed that for fish and frogs, a pressure of 10-20 mm hg in a 1-2-hour exposure each day for 6 days is not sufficient to stimulate erythropoiesis.

Ya.M. Britvan (1949), subjecting frogs to acute hypoxia by tying off the pulmonary arteries and poisoning them with cyanides, observed neither deeper nor more frequent respiration, but noted only a peculiar type of periodic respiration not normally observed in these animals.

At the same time, Gordon (1935) described stimulation of hematogenesis in the salamander (*Necturus maculosus*) during hypoxia. After 7 days' exposure in the low-pressure chamber to a pressure of 330 mm hg, immature erythrocytes and hemocytoblasts made their appearance in the peripheral blood.

K.P. Ivanov (1955, 1958) observed an increase in the number of formed elements in the blood by 90-110 thousand (20-22%) together with

increased pulmonary ventilation, even at altitudes of 2,000-3000 m, when frogs were periodically "raised" in the low-pressure chamber to an "altitude" of 10,000 m (3-4 hours a day for 10-15 days at a temperature of 4-6° C).

The author speaks of the high sensitivity of amphibians to hypoxia, and also indicates that they have certain adaptive reactions. In his opinion, turtles are less sensitive to oxygen insufficiency and their respiratory reaction appears only at an "altitude" of 8000-10,000 m.

These contradictions in the literature data were what prompted us to make these investigations.

The work was done from June to August 1958 with facilities of the Physiology Institute named for A.A. Bogomolets, Academy of Sciences Ukrainian SSR and during the El'brus expedition led by N.N. Sirotinin.

The first series of experiments was conducted in a low-pressure chamber. The experimental animals were frogs (*Rana esculenta*). The animals were divided into two groups. One group was "elevated" to the appropriate altitudes in aquaria filled with water, while the other "ascended" without benefit of aquaria, with the object of ascertaining whether the increase in erythrocyte count and hemoglobin content that was noted, for example, by Ivanov (1955) was a result of thickening of the blood due to evaporation from the surface of the skin.

In two experiments (Nos. 1 and 2), we "went up" together with the experimental animals in the chamber and conducted studies at altitudes of 2000, 3000, 4000, and 5000 m. Blood was taken from the frogs at the ventral vein, and respiration was recorded from a noose sewed through the mental region. In the frogs that ascended in aquaria filled with water, the hemoglobin content dropped from 54 → 50% to 75 → 55%, while in the frogs that went up without aquaria, it either also dropped to 68 → 58% or showed almost no change at 48 → 50%. The erythrocyte count

was 450,000 → 480,000. It is interesting to note that distinctly manifest periodic respiration appeared in three of the six animals at the altitude of 4000 m.

TABLE 1.

Change in Hemoglobin Content (in %) and Number of Erythrocytes (in thousands) in Blood of Frogs on Periodic "Ascents" in the Low-Pressure Chamber

1 № ан- им	2 Гемоглобин по Сали (в %)			3 Эритроциты (в тыс. в 1 мм ³)		
	норм	6-й подъем	8-й подъем	норм	6-й подъем	8-й подъем
		4	5		6	4
1	43	40	—	420	370	—
2	76	57	50	670	420	540
3	65	36	—	420	350	—
1	64	43	40	510	310	430
3	70	53	40	480	360	390
4	62	54	—	420	330	—
5	53	28*	—	420	220	—

Note: The No. 1 and 3 animals were in a water-filled aquarium; animals Nos. 1 and 5 were "raised" to altitude in an aquarium without water; *frog died immediately after was taken.

1) Frog No.; 2) hemoglobin after Sahli (in %); 3) erythrocytes (in thousands per 1 mm³); 4) normal; 5) 6th ascent; 6) 8th ascent.

Subsequently, we made an attempt to acclimatize frogs to hypoxia by raising them periodically in the low-pressure chamber. The possibility of such acclimatization was shown by Z.I. Barbashova (1956) in experiments on white mice.

For this purpose, the frogs were placed in the low-pressure chamber at an "altitude" of 10,000 m and a temperature of 20-23° C each day for six days, for 3-3.5 hours each day. The blood was analyzed before the experiment and after the sixth "descent" then the experimental animals were twice again taken up to an "altitude" of 10,000 m and the blood analyzed a second time. Several frogs died during the experiment: one in the water-filled aquarium (in the sixth "ascent"), two in the aquarium without water (after six "ascents") and three frogs that were taken up without water (their spleens had been removed previously). It

is interesting to note that under normal atmospheric pressure, the frogs whose spleens had been removed showed no differences in behavior from normal frogs.

The results of the experiment were consistent: the hemoglobin percentage and erythrocyte count fell in all cases (Table 1). In frogs raised periodically to the "altitude" of 10,000 m in the low-pressure chamber, no adaptive reaction on the part of the red blood was observed. The animals taken up without water also developed anemia instead of the expected thickening of the blood due to evaporation of moisture from the surface of the skin. The reaction of the frog organism associated with drying of the skin cannot be reduced simply to thickening of the blood. It would seem more probable that this reaction is considerably more complex and to be accounted for by invoking more profound mechanisms.

As we have already noted, the second series of experiments was carried during the expedition under natural conditions, at altitudes of 1) 58 m above sea level at Kiev; 2) 2100 m above sea level at Terskol; 3) 3000 m above sea level at Novyy Krugozor and 4) 3400 m above sea level at the 105th Picket. The studies were made on the 2nd and 6th-7th days of the sojourn at each new altitude. The temperature did not drop below 15° C. The experimental animals included amphibians and reptiles: frogs (*Rana esculenta*), turtles (*Emys europaea*), racers (*Zamenis gemonensis*) and lizards.

TURTLES (*Emys europaea*)

No adaptive reaction at all on the part of the red blood was observed in turtles at Terskol (altitude 2150 m). On the third day of the sojourn at this altitude, either no changes were noted (5 cases out of 12) or a slight anemia developed. After 10 days of residence at this same altitude, 2 cases showed a minor increase in hemoglobin percentage

(slightly more than in the preceding determination, but almost within normal limits); see Tables 2 and 3. At the altitude of 3000 m, 50% of the animals showed an increase in hemoglobin percentage and erythrocyte count. But this does not constitute stable acclimatization. Such changes might be more aptly referred to as an unstable reaction, the more so since four animals out of 6 did not reach the normal range in spite of the rise that they showed in these indicators. The incipient reaction was supplanted by intensified anemia as the high-altitude sojourn continued. Removal to the altitude of 3400 m either aggravated the anemia or produced no observable changes in 80% of the animals. Only in 2 cases did we note an increase in hemoglobin percentage and erythrocyte count. It would appear that this is the same unstable reaction (in turtle No. 8, the increased hemoglobin percentage dropped sharply after a few days). As a result of a month-long sojourn (stepwise ascent to altitude of 3400 m), 50% of the experimental animals developed severe anemia. In the others, the oxygen capacity of the blood either showed no change or changed very insignificantly, chiefly downward.

TABLE 2

Change in Hemoglobin Content (in %) in Blood of Turtles on "ascents" in low-pressure chamber

1 № чере- пане	2 высота в м						
	50	2150	2150	3000	3000	3400	2150
1	35-7	30	15	10-11	16	6	6-8
2	25-8	25	25	25	30	24	—
3	38-40	35	41	42	30	14	21-22
4	35			3 Погибла в дороге			
5	25-7	27	23	12	8-10	12	10-12
6	18-20	18	17	10	7-8	6-7	10
7	28-30	30	20	24	24	26	—
8	35	30-32	21	28-30	23	48	18
9	—	28-30	21	10-11	10-12	12	—
10	42	30	21	26	24	37	28-30
11	27-8	25	27-30	40-42	28	24-26	14
12	30-32	35	25	35		4 Погибла	
13	—	35-37	28	—	29	30-32	—
▲	32	31	27	32	28	26	22
●	27	25	21	10	11	9	93

Note. The triangle denotes average figures for the hemoglobin content in the blood of ani-

mals Nos. 1, 5, 6 and 9, while the circle precedes the averages for animals Nos. 2, 3, 7, 10, 11, 12 and 13.

1) Turtle No.; 2) "altitude" in m; 3) died in transit; 4) died.

TABLE 3

Change in Erythrocyte Count (in thousands) in Turtles on "Ascents" in low-Pressure Chamber

1 № чере- шек	2 высота в м			
	0	2100	3000	3600
1	610	450	100	120
2	350	220	450	370
3	720	470	600	220
4	450			
5	380	280	230	230
6	310	260	160	110
7	530	480	380	380
8	490	470	490	730
9	580	340	180	260
10	760	430	510	600
11	460	340	760	490
12	570	550	400	Потонул
13	—	470	390	4) 500
▲	560	430	500	420
●	420	360	180	180

Note. The triangle denotes averaged figures for the hemoglobin [sic] content in the blood of animals No. 1, 5, 6 and 9, while the circle precedes those figures for animals Nos. 2, 3, 7, 10, 11, 12 and 13.

1) Turtle No.; 2) "altitude" in m; 3) died in transit; 4) died.



Respiration curves for racer No. 6. a) At altitude of 2150 m; b) at altitude of 3000 m; time marker - 5 sec.

Nor was any adaptive reaction observed in respiration. Turtles normally breathe periodically and nonuniformly, and it is difficult to take respiration-pattern changes into account at an altitude of 3000 m.

Ivanov (1955) noted some change in respiration in turtles only at an "altitude" of 8000-10,000 m, while Al't'land and Parker (1955) ob-

served distinct changes in the nature of the respiratory curve on administration of a gas mixture containing only 5% of oxygen. In our experiments, 4 animals out of 12 showed a certain speedup in the respiratory movements, but at the same time 2 of them showed slower and another shallower respiration.

In the racers (*Zamenis gemonensis*), residence at an altitude of 2100 m produces no changes in the nature of respiration. When the altitude is increased to 3000 m, the animals react with a certain increase in respiratory frequency (see Figure).

In the frogs (*Rana esculenta*), neither an increase in the oxygen capacity of the blood (according to erythrocyte count and hemoglobin content) nor a respiratory reaction was observed at altitudes of 2150 and 3000 m.

INFLUENCE OF HYPOXIA ON THE CONDITIONED REFLEXES OF FISH

T.A. Aref'yeva

(Kiev)

It was established as a result of the researches of N.N. Sirotinin that the sensitivity of the organism to hypoxia increases as the organization of the central nervous system becomes more complex, and that the lower vertebrates are less sensitive to oxygen insufficiency than the higher vertebrates.

It is interesting to consider the effect of hypoxia on the functional state of the central nervous system - the system most sensitive to unfavorable disturbances of all kinds. In the literature available to us, we have not been able to find information concerning the influence of hypoxia in an aquatic medium on the functional state of the lower vertebrate central nervous system, particularly in fish, and hence made it the objective of the present work to investigate the influence of hypoxia on conditioned-reflex activity in fish.

METHOD

The experiments made use of goldfish (*Carassius auratus* L.) up to 10-15 cm in length. A system of positive and negative food-acquisition conditioned reflexes was developed by the technique of N.V. Prazdnikova (1953). On the conditioned signal, the fish would swim over to a glass bead and hold it, after which the reflexes were reinforced with food. A beam of colored light from a small electric bulb situated at a distance of 10-15 cm above the aquarium provided the conditioned light stimuli. The second conditioned stimulus was an electric bell mounted on the wall of the aquarium. The positive conditioned reflexes were developed to red light and the bell, and the negative reflexes to yellow light.

For various reasons, we were unable to use the technique employed in the studies of various authors for creating hypoxic conditions in water (Vintershteyn, 1908) by passing hydrogen or nitrogen through the water. We were unable to lower the oxygen content to below 1 cm³/liter by boiling the water to drive oxygen out of it, a fact not altogether satisfactory as regards the conditions of the experiment.

Studies of the conditioned reflexes of the fish were carried out in a low-pressure chamber for the first series, "raising" the aquarium with the fish to definite altitudes. "Elevations" to altitudes of 2000, 3000, 4000, 5000 and 6000 m were used (the respective partial oxygen pressures at these altitudes were 125, 110, 98, 86, and 74 mm hg). The exposure to each of these altitudes was 30 minutes.

In the second series of experiments, hypoxic conditions were set up in the water by placing the aquarium, which contained 15 liters of water heated to 30-50° C, in a low-pressure chamber under an atmospheric pressure corresponding to an "altitude" of 1500 m. The water was held at this atmospheric pressure for a definite period of time (up to 60 min) and vaseline oil poured in in an amount sufficient to form a layer up to 2-2.5 cm thick. When the surface of the water had been uniformly and completely covered by the layer of vaseline oil, we restored the atmospheric pressure in the low-pressure chamber to normal. A wire screen was placed under the oil film to prevent the fish from swallowing oil in their asphyxia. The content of oxygen dissolved in the water was determined by the Winkler method, and in cases in which the water contained a large amount of organic matter by the Rideal-Styuart method. At this point the fish were put into this water. They stayed there for 10 min, following which their conditioned-reflex activity was studied.

Four goldfish (*Carassium auratus* L.), Nos. 1, 4, 5, and 8, were used in the first series of experiments. "Ascents" were to altitudes of 2000 and 3000 m, 4000, 5000 and 6000 m.

At the altitude of 2000 m, the fish showed both normal and disturbed conditioned-reflex activity. No disturbance to conditioned-reflex activity were observed in fish No. 4. In fish Nos. 1, 5 and 8, we noted a disturbance of conditioned-reflex activity manifesting in non-performance of conditioned-reflex reactions. Not all of the conditioned

stimuli used in the experiment produced conditioned-reflex response reactions, as will be seen from the notes from the experiment of 28 September 1955 on fish No. 5 (see table). Of the 7 positive conditioned signals used, condition reflexes were obtained only with 3; disinhibition of differentiation was not observed.

Omission of conditioned reflexes to the light and bell was also observed in Fish No. 1 at an altitude of 2000 m. Of the five positive conditioned stimuli employed, a conditioned reflex was obtained to two (red light and bell).

In fish No. 8, there was no reflex to the bell at an altitude of 2000 m. The oxygen content in the water was $2.5 \text{ cm}^3/\text{liter}$.

Differentiation was not disturbed in the experimental fish at an altitude of 2000 m. At 3000 m, complete absence of conditioned reflexes (fish No. 1) was observed together with a drop in the percentage of positive responses.

On ascent to altitudes of 2000m and 3000m, the fish became somewhat, excited. They swam faster, and it was noticed in many cases that they were "swimming" at almost the same position, frequently butting their noses against the wall of the aquarium, with an oscillatory movement of the body. An increase in the number of between-signal responses was noted. When they were "elevated" to higher altitudes (4000, 5000, and 6000 m), the fish tended to lose equilibration, swimming only with difficulty. There were no conditioned reflexes in evidence at this time.

On investigating the oxygen content in water that had been at altitudes of 2000-6000 m for 30 minutes, we were unable to detect any significant drop in this content. The initial water had contained $3.5-5 \text{ cm}^3/\text{liter}$ of oxygen at a temperature of $20-22^\circ \text{ C}$. In water in which hypoxic conditions had been created by the technique described, the

Record of Experiment of 28 September 1955. Fish No. 5

Условный раздражитель 1	2 Наличие условного рефлекса	3 Время ус- ловного рефлекса	4 Возмуще- ние по ус- ловному	5 Примечание
Красный свет 6	+	4	+	Много межсигнальных реакций 7
Звонок-вибратор 8	+	2	+	Межсигнальные реак- ции 9
Желтый свет 10	-		-	
Красный свет 6	-		-	
Звонок-вибратор 8	-		-	Межсигнальные реак- ции 9
Желтый свет 10	-		-	
Красный свет 6	-		-	
Звонок-вибратор 8	+	2	+	
Красный свет 10	-		-	Межсигнальные реак- ции 9

1) Conditioned stimulus; 2) presence of conditioned reflex; 3) time of conditioned reflex; 4) unconditioned reinforcement; 5) remarks; 6) red light; 7) numerous between-signal reactions; 8) vibrator bell; 9) between-signal reactions; 10) yellow light.

oxygen content in one liter of water did not drop below 1.7 cm^3 . With the experiment set up in this way, the conditioned-reflex activity could change either as a result of hypoxia or as a result of the change in hydrostatic pressure. To differentiate between the effects of these factors, hypoxic conditions were created in an aquatic medium in advance (second series of experiments).

The conditioned-reflex activity of three goldfish was studied in water having an oxygen content of 3.3 to $0.22 \text{ cm}^3/\text{liter}$. No changes were observed in the conditioned reflex activity of the fish in water having oxygen contents of $3.3-1.0 \text{ cm}^3/\text{liter}$. Signs of disturbance to their conditioned-reflex activity were observed at higher degrees of hypoxia, when the oxygen content in the water was lowered below $1 \text{ cm}^3/\text{liter}$.

Fish No. 1 showed disturbance of its conditioned reflexes at an oxygen content of 0.5 cm^3 in 1 liter of water (see table). In this experiment, we noted the presence of two positive conditioned responses

to the 4 st muli employed. The motor activity of the fish showed no increase here.

In another experiment with the same oxygen content in the water ($0.5 \text{ cm}^3/\text{liter}$), we obtained identical data. The disturbance of conditioned reflex activity was more pronounced in fish No. 4 at the same oxygen content. Of the 5 positive conditioned stimuli used, only one (red light) produced a conditioned reflex. This fish entered asphyxia - it would rise frequently to the upper layers of the water. Its general state was characterized by excitability higher than normal.

Total absence of conditioned reflexes was observed in two experiments with fish No. 8 in which the water had oxygen contents of 0.6 and $0.5 \text{ cm}^3/\text{liter}$.

At an oxygen content of $0.22-0.29 \text{ cm}^3$ in 1 liter of water, there were no conditioned reflexes from any of the experimental fish. The fish swam up to the top layers of the water and swallowed water from just under the screen. If the screen was removed, they swam up to the oil film and swallowed small portions of it.

Spasmodic movements of the body, alternating with total immobility, were noted in fish No. 1 at an oxygen content of $0.22 \text{ cm}^3/\text{liter}$. It hung close to the screen at all times and swallowed water from the top layers. There were no conditioned reflexes.

It follows from the data given above that a disturbance to conditioned-reflex activity is noted in fish at oxygen contents below $1 \text{ cm}^3/\text{liter}$. The initial phase of the disturbances manifests in a drop in conditioned reflex activity, failure to produce specific conditioned-reflex responses to conditioned stimuli. Some of the fish showed no conditioned reflexes even when the oxygen content was lowered to $0.5 \text{ cm}^3/\text{liter}$. The higher degree of hypoxia between 0.3 and $0.22 \text{ cm}^3/\text{liter}$ and below this range produces complete disruption of conditioned reflex

activity in all of the fish.

DISCUSSION OF EXPERIMENTAL DATA

It has been established that the lower vertebrates are significantly more resistant to hypoxia than the higher ones. Toads withstand a drop in atmospheric pressure to 80 mm hg for several hours. Goldfish begin to perish when they are "elevated" in the aquarium to an atmospheric-pressure of 60 mm hg (N.N. Sirotinin, 1951). Asphyxia is observed in fish at oxygen contents of 0.4-0.5 cm³/liter (Vintershteyn, 1908). The oxygen threshold for trout is 1.26 mg/liter (Mints, 1954). According to Khlopin, Nikitin and Kuptsis, fish cannot exist in water containing less than 1 cm³/liter of oxygen. Water containing less than 3.5 cm³/liter of oxygen is not a suitable habitat for trout (Koenig, 1954). Data on the oxygen threshold for fish are contradictory, a fact possibly to be accounted for by the ecological peculiarities of the fish studied. Literature data on conditioned reflex activity in lower vertebrates under conditions of hypoxia are totally nonexistent, although numerous papers are accessible on the changes in the basic nervous processes - stimulation and inhibition - in oxygen insufficiency in higher vertebrates (Sirotinin, 1939; Lifshits, 1949, Kolchinskaya, 1953 and others).

In the experiments conducted, oxygen deficiency in the water caused an intensification of motor activity in the fish; they swam restlessly and rose to the upper layers of the water. In a number of cases of severe hypoxia, we noted that the fish were moving from side to side in a spasmodic manner. This state alternated with total immobility. A certain intensification of the excitation process could also be noted in studying the conditioned reflex activity (the number of between-signal reactions increased).

On the basis of the data compiled from two series of experiments,

it can be noted that a change in hydrostatic pressure has a stronger effect on the conditioned reflex activity of fish than does oxygen insufficiency. Conditioned reflex activity was disturbed when the oxygen content was adequate (quantity not allowed to drop below 1.7 ml/cm^3) but the hydrostatic pressure was left unchanged ("altitudes" of 2000 and 3000 m in the low-pressure chamber). In the subsequent series of experiments, conditioned reflexes were disturbed under considerably deeper hypoxia. In the series of experiments in which hypoxia was established in the water in advance, it was established that the fish show conditioned reflexes at a much deeper stage of oxygen insufficiency - when the oxygen content in the water is below $1 \text{ cm}^3/\text{liter}$. Partial disruption of conditioned reflex activity manifested in a lower percentage of positive reactions. Conditioned reflexes were totally absent when the oxygen content was lowered to $0.3-0.22 \text{ cm}^3/\text{liter}$. Distinct asphyxia was observed in the fish during this time: they swam up to the upper layers of the water and made deglutitory motions. This oxygen content represents the lower threshold and borders on the concentrations lethal for fish.

THE ELECTROCARDIOGRAM OF THE RACER UNDER NORMAL CONDITIONS
AND IN HYPOXIA

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(Kiev)

Our observations were made on 10 full-grown racers, *Coluber jugularis* and *Ptyas mucosus*, with body lengths ranging from 140 to 191 cm.

The electrocardiogram was registered in lead three, using a VEKS-01 vector electrocardioscope on animals in the normal gaseous medium and in rarefied media corresponding to altitudes of 3000, 6000, 9000 and 12,000 m. The temperature of the air surrounding the animals reached 17-18° C.

The animals, which were taped to the machine, occupied a horizontal attitude in the first series of experiments, while in the second series they were held in a vertical position. The prevailing conditions were such that the activity of the animals' cardiovascular systems was rendered difficult by the unfavorable position of the body relative to the gravity vector and the resulting hydrostatic pressure differences that appeared in the circulatory system.

Since no essential differences were noted between the EKG's of these two species of reptiles, the data obtained are collected in a single table.

Below we present the initial data characterizing the electrocardiograms of the racers as registered 20 min after the animals had been fixed: the R-R interval is 2.49 ± 0.22 sec, which corresponds to a pulse frequency of 24 beats per minute; P-Q is 0.40 ± 0.09 sec, QRS is 0.15 ± 0.03 sec, and Q-T is 0.98 ± 0.20 sec. The P deflection in nine animals out of ten was negative and equal to 0.20 ± 0.09 mv; a positive

Results of Analysis of EKG's of Racers in Horizontal and Vertical Positions in Normal and Rarefied Atmospheres

A Число серий записей в мин.	B Высота	C Продолжительность интервалов (в сек.)			F Амплитуда волны (в мВ)		
		P-Q	QRS	Q-T	P	R	T

F Горизонтальное положение

10	50 м	2,49 ± 0,22	0,40 ± 0,09	0,15 ± 0,03	0,98 ± 0,20	(1) + 0,14 (9) - 0,20 ± 0,09	1,19 ± 0,20	+ 0,29 ± 0,12
10	3000 м	2,16 ± 0,23 21,9/ мин.	0,40 ± 0,12	0,15 ± 0,03	0,88 ± 0,18	(1) + 0,14 (9) - 0,27 ± 0,06	1,19 ± 0,17	+ 0,27 ± 0,26
10	6000 м	2,22 ± 0,25 27,7	0,43 ± 0,12	0,17 ± 0,02	0,90 ± 0,17	(2) + 0,17 ± 0,04 (8) - 0,19 ± 0,07	1,10 ± 0,21	(8) + 0,29 ± 0,16 (2) - 0,23 ± 0,21
10	9000 м	1,81 ± 0,20 27,0	0,35 ± 0,23	0,18 ± 0,05	0,83 ± 0,14	(1) + 0,14 (9) - 0,17 ± 0,06	1,03 ± 0,25	(8) + 0,22 ± 0,16 (9) - 0,25 ± 0,08
10	12000 м	1,64 ± 0,14 33,1	0,35 ± 0,21	0,18 ± 0,04	0,72 ± 0,19	(1) + 0,14 (9) - 0,15 ± 0,06	1,00 ± 0,22	(6) + 0,26 ± 0,03 (9) - 0,37 ± 0,22
10	15000 м	1,96 ± 0,22 36,6	0,35 ± 0,35	0,19 ± 0,03	0,82 ± 0,18	(1) + 0,16 (9) - 0,12 ± 0,05	0,99 ± 0,25	(5) ± 0,49 ± 0,17 (9) - 0,28 ± 0,11
7	G (серия 60 мин.) H (серия после "спуска")	1,87 ± 0,12 38	0,29 ± 0,02	0,17 ± 0,01	0,63 ± 0,21	(1) + 0,22 (6) - 0,17 ± 0,06	1,15 ± 0,29	+ 0,49 ± 0,12

I Вертикальное положение

9	50 м	1,47 ± 0,16 40,8	0,38 ± 0,15	0,19 ± 0,11	0,59 ± 0,13	- 0,31 ± 0,17	2,45 ± 0,25	(5) + 0,43 ± 0,05 (4) - 0,22 ± 0,03
9	3000 м	1,35 ± 0,12 44,4	0,36 ± 0,02	0,19 ± 0,11	0,57 ± 0,14	- 0,34 ± 0,16	2,58 ± 0,18	(6) + 0,29 ± 0,05 (1) - 0,71
9	6000 м	1,82 ± 0,30 32,9	0,29 ± 0,09	0,16 ± 0,05	0,71 ± 0,12	- 0,31 ± 0,17	2,50 ± 0,19	(6) + 0,28 ± 0,04 (3) - 0,31 ± 0,05
8	9000 м	1,38 ± 0,16 43,4	0,29 ± 0,15	0,19 ± 0,1	0,55 ± 0,11	(1) + 0,16 (7) - 0,21 ± 0,17	2,22 ± 0,21	(8) + 0,50 ± 0,06 (2) - 0,40 ± 0,03
8	12000 м	2,00 ± 0,27 30,0	0,35 ± 0,11	0,22 ± 0,08	0,84 ± 0,5	- 0,29 ± 0,16	1,75 ± 0,12	(3) + 0,22 ± 0,03 (9) - 0,52 ± 0,04
8	G (серия 60 мин.) H (серия после "спуска")	1,36 ± 0,12 41,1 1,80 ± 0,26 33,3	0,29 ± 0,09	0,22 ± 0,08	0,76 ± 0,22	- 0,31 ± 0,26	1,40 ± 0,24	(2) + 0,51 ± 0,07 (4) - 0,43 ± 0,05 (2) + 0,61 ± 0,05 (2) - 0,30 ± 0,04

*The figures in parentheses indicate the number of observations.

A) Number of animals; B) altitude; C) duration of intervals (in sec); D) R-R and pulse frequency; E) wave amplitude (in mv); F) horizontal position; G) after 60 min; H) immediately after "descent"; I) vertical position.

P deflection was registered in one case (0.14 mv). The R deflection reached 1.19 ± 0.20 mv, and T was positive in all cases at 0.29 ± 0.12 mv (see table).

When the atmosphere was rarefied to the extent corresponding to 3000 m, we noted a 13.7% acceleration in the R-R intervals, and an increase in the variability coefficient of the figures characterizing P-Q, the EKG segment and the amplitude of the T-wave. The length of the Q-T intervals and the variability of the amplitudes of the P and R deflections diminished by 10.2%, but the average values of these waves did not change. When the gaseous medium was rarefied to the level corresponding to an "altitude" of 6000 m, the duration of the R-R intervals came to 89.1% of the initial value. The P-Q interval increased by 5% and the QRS interval by 13.3. The voltage of the R deflections dropped by 7.6%; in two cases, negative T-waves were produced.

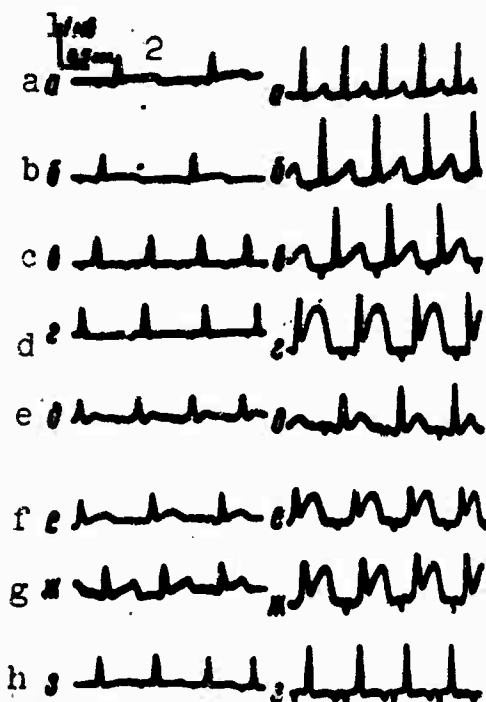
The changes in the EKG's of the racers became more distinct as the rarefaction of the gaseous medium in which they were situated was deepened. Toward the end of a sixty-minute sojourn in the rarefied atmosphere corresponding to the "altitude" of 12,000 m, the R-R, P-Q and Q-T intervals had been shortened by 21.5, 22.2, and 16.3%, respectively. The QRS interval had increased by 26.7%. The voltage of the R wave dropped by 16.8%. The positive and negative T-waves became higher (deeper).

Immediately after the animals had been returned to the normal gaseous medium, the most substantial changes were noted in the sizes of the R-deflections as compared with the level registered at the end of the "plateau;" at the "altitude" of 12,000 m, it had increased by 16.1%. All of the T-waves became positive. The shifts in the remaining elements of the EKG were less pronounced.

Under the physical load to which the cardiovascular systems of the

racers were subjected after they had been fixed in the vertical position, the reaction to hypoxia became even more pronounced. In the rarefied atmosphere corresponding to the 3000-m altitude, the R-R and Q-T intervals were shortened by 8.2 and 3.4%, the P-Q interval increased by 28.6% and the QRS showed no change. The voltage of the R-waves dropped by 5.3%. The voltage of the P- and T-waves also changed.

Three of the racers did not adjust to the conditions of the experiment. This conclusion was drawn on the basis of the manifest bradycardia (pulse slower than 10 beats per minute) and pathological changes in certain elements of the EKG (splitting of the R-wave, a considerable increase in the voltage of the T-waves, which differed in magnitude from the deflections on the EKG's of the other animals, and, finally, the appearance of a monophasic curve instead of the RQST complex).



Electrocardiogram of animal No. 6. On the left: EKG registration of animal when subjected to rarefied atmosphere in horizontal position; on the right: same, vertical position. a) EKG before experiment, 15 min after fixing animal on bench; b) after 5 minutes of residence at "altitude" of 3000 m; c) at "altitude" of 6000 m; d) 9000 m; e) 12,000 m, immediately after "ascent;" f) 12,000 m, after 30 min; g) 12,000 m, after 60 min; h) immediately after return to normal atmosphere. Calibration and sweep speed are indicated at the upper left corner. 1) 1 mv; 2) 0.5 sec.

It would hardly be advisable to average the results of the observations made on animals that did not respond well to the conditions of the experiment and were apparently in a preterminal state, since these data are so widely scattered. For example, in the orthostatic position, even in the normal atmosphere the amplitude of the R-waves came to 1.7, 2.0 and 3.4 mv in three different animals, while the T-waves were -0.28, -0.96 and -0.86 mv, and so forth. In view of this, the table presents data from the EKG's of those animals that withstood the experimental conditions satisfactorily.

The electrocardiogram of one of these animals is shown in the figure.

CONCLUSIONS

1. The data set forth in this paper give an idea of the basic elements of the electrocardiograms of *Coluber jugularis* and *Pituophis melanoleucus*.

2. A drop in barometric pressure causes no functional disturbances in the cardiovascular system as long as it is possible to avoid the effects of hypoxia or dysbarism.

3. Analysis of the data that we obtained indicates that the racers show, together with a distinct stability with respect to considerable lowering of the oxygen partial pressure in the inspired air, certain statistically dependable changes in the electrocardiogram, even when the gaseous medium is rarefied to the degree corresponding to an altitude of 3000 m (shortening of the ventricular Q-T complex and the R-R interval, drop in amplitude of T-waves, and so forth).

4. Use of the physical-load technique under the conditions of hypoxia makes it possible to obtain a wide variety of changes in the electrocardiogram.

COMPARATIVE-PHYSIOLOGICAL FEATURES OF HEMATOGENETIC FUNCTION
IN ANIMALS UNDER THE CONDITIONS OF
THE HIGH MOUNTAIN CLIMATE

N.M. Shumitskaya

(Kiev)

One of the most prominent adaptive reactions of animals and man in the mechanism of adaptation to hypoxic conditions is hematogenesis. The question as to what constitutes the hematogenetic reaction in higher vertebrates and man under the conditions of depressed oxygen partial pressure in the inspired air has been treated in rather complete detail in the literature.

Apart from an increase in the hemoglobin content and erythrocyte in the peripheral blood, we may draw reliable conclusions as to the bone marrow function under hypoxic conditions from the number and maturity of reticulocytes, which represent an early stage in the development of erythrocytes from nuclear normoblasts.

According to Zeyfart (1927), Marchevskiy (1934), Dabin (1934), Kozlovskaya and Kryukovaya (1934), Faynberg (1937), Gordon and Kleynberg (1937), Kudrin (1940), Sokolov (1940, 1941, 1944, 1946) and Beller (1958), humans, other mammals and birds show an increase in reticulocyte content together with the increases in erythrocyte count and hemoglobin content as a result of extended residence in a low-pressure chamber - 6-15 days at an "altitude" of 5-8 thousand meters.

These changes in the number of reticulocytes in hypoxia manifest even more clearly under the conditions of the high-mountain climate

(Barkroft, 1925, 1927; Vylegzhanin, 1933, 1937; Geyl'meyer, Reknagel', Al'bus, 1933; Gerke, 1935; Tal'bot, 1936).

Thus, while the problem of the active-adaptation mechanism for depressed partial oxygen pressure in the inspired air in mountains and under the conditions of the low-pressure chamber has been solved for the higher vertebrates and man, the question as to whether the lower vertebrates have analogous adaptive reactions to hypoxia on the part of the hematogenetic function is far from finally answered.

The present report gives only part of the data collected in a complex project carried out by staff members of the Laboratory of Comparative and Developmental Physiology of the Physiology Institute named for A.A. Bogomolets, Academy of Sciences Ukrainian SSR, a study devoted to the comparative-physiological study of the effect of hypoxia on the animal organism.

Data were obtained under laboratory conditions at Kiev (initial data) and during four expeditions to Mount El'brus, which were organized by the Institute of Physiology named for A.A. Bogomolets, Academy of Sciences Ukrainian SSR and implemented under the leadership of Active Member of the Academy of Medical Sciences USSR Prof. N.N. Sirotinin in the years 1955, 1956, 1957 and 1959.

METHOD

Preference was given to adult representatives of various classes of animals in this investigation. The exceptions were ducklings and chicks 2-3 months old.

Amphibians:

- | | |
|---|--------------|
| a) Pond frogs (<i>Rana esculenta</i>) | 7 specimens |
| b) Grass frogs (<i>Rana temporaria</i>) | 11 specimens |

Reptiles:

- | | |
|--|-------------|
| a) Common grass snakes (<i>Tropidontus natrix</i>) | 2 specimens |
|--|-------------|

b) Pond turtles (*Emys europaea*) 13 specimens

Birds:

a) Leghorn chickens 5 specimens

b) Geese 10 specimens

c) Ducks 7 specimens

d) Turkeys 9 specimens

e) Ducklings 7 specimens

f) Chicks 7 specimens

Mammals:

Orders:

1) Rodents: a) White laboratory mice 18 specimens

b) Hamsters (*Cricetus cricetus*) 5 specimens

c) Spotted gophers (*Citellus citellus*) 5 specimens

2) Carnivores:

a) Domestic cats 5 specimens

b) Mongrel dogs 10 specimens

c) Himalayan bear (*Ursus tibetanus*) 1 specimen

Total: 122 specimens

In addition to the above, 36 human individuals were studied. Of these, four were juveniles aged 13-17 years.

For all of the above-listed representatives of the animal world, dynamic studies were made on smears of peripheral blood to find the reticulocyte count in terms of 1000 erythrocytes. A blood analysis was run in Kiev prior to the expedition, at normal atmospheric pressure (58 m above sea level) and others during the expedition to El'brus: at Terskol (altitude 2000 m) on the 2nd or 10th day of the sojourn in the mountains, at Novyy Krugozor (altitude 3000 m) on the 9th-13th days, at Piket "105" (altitude 3400 m) and at Ledovaya Baza (altitude 3700 m) on the 13th-16th days of the expedition.

During the 1955-1957 expeditions, some of the animals and some of the expedition members were studied at Priyut-11 at an altitude of 4200 m above sea level, on the 17th-19th days of the stay in the moun-

tains.

The technique used in taking blood samples and preparing the smears for counting the reticulocytes was that generally accepted in practice.

Change in Number of Reticulocytes in Peripheral Blood in Representatives of Various Classes of Animals and Man at Various Altitudes on El'-brus

1	2	3	4	5	6	7
Вид животных	Класс (среднее значение)	%	Терскол, 2000 м (2-й день)	Новый Кругозор, 3000 м (10-й день)	Ледовая база, 3700 м (13-й день)	Приют-11, 4200 м (19-й день)
Лягушки: водные	8 3,22	100	+15,8	—	—	
травяные	9 6,27	100	-14,5	-15,9	-23,3	
Ужи	10 3,0	100	+33,3	+50,0	—	
Черепашки	11 38,6	100	+1,2	+16,6	+8,8	
Куры	12 59,2	100	+8,4	+52,7	+12,5	
Утки	13 85,5	100	+25,5	+49,1	+71,1	
Индюки	14 67,7	100	+15,8	+38,8	+98,5	
Цыплята	15 67,8	100	+19	+60	+87,3	
Гуси	16 62,2	100	+7,2	+43,3	+98,2	
Утята	17 86,8	100	+15,6	+46,7	+88,6	
Хомяки	18 10,9	100	+13,8	+95,3	—	+124,3
Мыши	19 72,5	100	+30	+62,3	—	+66,4
Сусляки	20 4,8	100	+187,4	—	—	
Собаки	21 5,1	100	+125,3	+252,9	+174,6	
Коты	22 4,6	100	+56,5	+117	+155,4	
Медведь	23 1,0	100	0	+100	+270	
Взрослые люди	24 6,56	100	+78,3	+156	+223	+258,2
Юноши	25 5,5	100	+84,5	+130	+218	

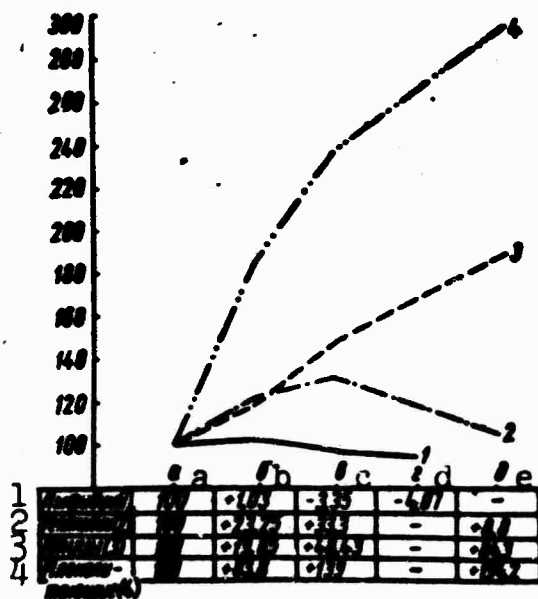
1) Species of animal; 2) Kiev (average data); 3) %; 4) Terskol, 2000 m (2nd day); 5) Novyy Krugozor, 3000 m (10th day); 6) Ledovaya Baza, 3700 m (13th day); 7) Priyet-11, 4200 m (19th day); frogs; 9) pond; 10) grass; 11) grass snakes; 12) turtles; 13) chickens; 14) ducks; 15) turkeys; 16) chicks; 17) geese; 18) ducklings; 19) hamsters; 20) mice; 21) gophers; 22) dogs; 23) cats; 24) bear; 25) adult humans; 26) juveniles.

The studies that we conducted showed that the ability of the organism to adapt under conditions of reduced oxygen partial pressure in the air inspired in the mountains is not manifest to the same degree in representatives of the various classes of vertebrates — the amphibians (pond and grass frogs), reptiles (grass snakes and turtles), birds (chickens, ducks, geese, turkeys, chicks and ducklings) and in the mammals (mice, hamsters, gophers, cats, dogs and bears), as well as in the adult and juvenile humans. It depends not so much on the altitude of the ascent, the rarefaction of the atmosphere, or the time of residence

under hypoxic conditions as on the species of the animal and the level of its organization in the comparative-physiological plan.

In the amphibians (grass frogs), we did not succeed in discerning any active adaptation of the organism to the hypoxia by way of hemato-genesis, in the form of an increase in the number of reticulocytes in the peripheral blood.

The slight increase in the number of reticulocytes observed at Terskol (2000 m above sea level) in some of the water frogs is more probably a result of thickening of the blood due to drying of the skin under the stiff breezes and strong sunlight that prevail in the mountains at these altitudes (see Table and Figure).



Dynamics of change in number of reticulocytes in peripheral blood of animals of various groups in the mountains: average data on the number of reticulocytes are plotted along the vertical in percent of the initial values; on the horizontal axis we present: a) The initial data (Kiev, 58 m); b) Terskol, 2000 m (second day); c) Novyy Krugozor, 3000 m (tenth day); d) Piket-"105," 3400 m (15th day); e) Ledovaya Baza, 3700 m (16th-18th days). 1) Amphibians 2) reptiles; 3) birds; 4) mammals.

The results that we obtained from investigations on the frogs disagree with the data of Ivanov (1955, 1958), but are in agreement with the material compiled by Bonne (1929), Sokolov (1940, 1941), Barbashova (1941) and Sirotinin (1949). The results of our experiments tend to

confirm Sokolov's opinion (1940) to the effect that amphibians do not have a blood depot or show true hematopoiesis in response to oxygen starvation.

Among the reptiles (grass snakes and turtles), our experiments showed an adaptive reaction of the organism to hypoxia - albeit not in all cases and not distinctly manifested - in the form of an increase in the number of reticulocytes in the peripheral blood as the elevation was increased to 2000, 3000, and 3700 m above sea level. Among the grass snakes, this proliferation of reticulocytes was more regular, thus supporting the viewpoint of N.N. Sirotinin (1951) that grass snakes, as representatives of the reptile group, already show a certain amount of adaptation to lowered oxygen partial pressure in the inspired air due to an increase in the oxydation surface of the blood.

Most of the turtles used in our experiments did exhibit a distinctly manifest additive reaction by the red blood in the form of an increased reticulocyte count with increasing time of residence in a rarefied atmosphere at various altitudes on El'brus . Some of the animals showed an "unstable" or "indistinct" reaction followed by a drop in the number of reticulocytes in the blood to a count below the initial count.

Among the representatives of the birds, we begin to note a distinct adaptive capacity of the organism that acclimates it to hypoxic conditions. It is characterized by a significant increase in the reticulocyte count in the peripheral blood, beginning with the 2nd day of the sojourn at the 2000-meter altitude and continues to develop with increasing altitude, increasing rarefaction of the air, and increasing time of residence under these conditions.

The capacity for active adaptation to the conditions of hypoxia comes particularly sharply to the fore in the higher mammals and par-

ticularly in man. This is manifested in the fact that a significant increase in the number of erythrocytes in the peripheral blood has taken place at an altitude of 2000 m above sea level, and, moreover, a left shift in the reticulocyte formula is noted at an altitude of 3000 m or higher even on the 9th-17th days of the mountain sojourn. In particular, not only do the numbers of preexisting group III and IV reticulocytes increase substantially in the peripheral blood, but the reticulocyte group II even makes its appearance as a function of the maturity stage of the latter (data from experiments on mice). All of this indicates a genuine stimulation of hematopoiesis (stimulation of the bone marrow) in mammals and man at these altitudes.

The research results that we have obtained confirm those of N.N. Sirotinin (1940, 1949, 1951, 1955) in indicating differing sensitivities to oxygen starvation for animals standing at different levels of the evolutionary ladder, and, as a function of this, differing degrees of development of the hypoxic active adaptation mechanisms among them.

CONCLUSIONS

1. Among representatives of the various classes of vertebrates - amphibia (frogs), reptiles (grass snakes, turtles), birds (chickens, ducks, turkeys chicks, ducklings) and mammals (mice, hamsters, gophers, cats, dogs, bears) and also in juvenile and adult human beings, all of which have attained different levels on the evolutionary ladder, the ability of the organism to adapt to conditions of depressed oxygen partial pressure in the inspired air in the mountains is expressed to different degrees. It depends on the species of the animal and the level of its organization.

2. The criteria for active adaptation to hypoxia on the part of the hematogenetic function as seen in changes in the number of reticulocytes in the peripheral blood are not observed in amphibians and be-

gin to make their appearance only in the reptiles (grass snakes, turtles).

3. The capacity for acclimatization to the conditions of hypoxia are manifested particularly clearly in the higher mammals and chiefly in man.

ON THE ROLE OF THE AGE FACTOR IN THE ORGANISM'S REACTION

TO HYPOXIA

N.V. Lauer

(Kiev)

Despite the research effort of comparatively long standing on the subject of hypoxia, age-related peculiarities of hypoxic states have been given little attention. Meanwhile, resolution of a number of aspects of this problem has acquired particularly urgent importance for prevention and elimination of oxygen deficiency due to various causes in the clinical treatment of numerous human disorders arising from the time of birth to extreme senility.

The complexity of this important problem is obvious. On the one hand, evaluation of pathological hypoxic states at any age must be based on proper understanding of the state and of the development of the organism itself, its various systems, its cell and molecular structures, the physiological peculiarities of the organs and of the regulatory mechanisms, the enzyme systems, the biochemical and other processes taking place in them. On even cursory examination of the tremendous distance covered by the mammalian organism, and by man in particular, from the time of its birth to extreme senility, it becomes obvious that complex interrelationships between the organism and its environment undergo changes in the process of individual development, each of them an expression of physiological features peculiar to its own ontogenetic stage.

On the other hand, the physiological features of an age level are

directly related to the species of the animal, to the time required for its embryonic development and life cycle, and to the rate at which the organism forms before and after birth. These age factors also depend on the maturity of the organism at the time of birth, on the complexity of the nervous system of full-grown specimens and on many other factors. This is why, even though a large amount of factual material on oxygen deficiency, on the states of functional systems and metabolism at early stages of ontogenesis has been collected and the progressive development of these stages to the mature state and the changes that take place in old age have been traced, there still remain open many questions concerning the age peculiarities of the physiology and pathophysiology of hypoxic states, further study of which is urgently required.

In evaluating the various phenomena related to the age peculiarities of hypoxic states, the situation as to early postnatal ontogenesis, during the short time when the response of the organism to oxygen insufficiency changes more than it does over a number of years in the adult state, is most open for discussion. Inadequate attention is again given to the fact that during the newborn phase, the specific peculiarities of the reactions to hypoxia are expressed considerably more distinctly than in maturity.

One of the most expressive over-all indicators of equilibrium between the organism and its environment is its ability to survive, its viability, under a given set of conditions. When we examine the changes in the resistance of an organism to hypoxia from the time of its birth to its old age, we are struck by the fact that newborn animals are distinguished by a special ability to withstand extremely severe degrees of oxygen insufficiency. Thus, for example, baby chicks survive 45 minutes in a nitrogen or at an altitude of 30 thousand meters, and puppies at 17 thousand meters; at birth, human babies survive when totally cut

off from oxygen supplies for 15-20 min, i.e., a degree of oxygen insufficiency absolutely lethal to adults.

Thereafter, the resistance of the organism declines progressively and settles at the level shown by the adults after an ontogenetic period that differs for each species. In puppies, resistance to hypoxia reaches the adult level at approximately 3-4 months. This does not, however, represent a linear progression, and certain age periods can be distinguished throughout the life of the organism - phases characterized by elevated sensitivity and lowered resistance to hypoxia.

One such period is that of puberty, which is highly complex as regards functional readjustments of the nervous and endocrine systems, the cardiac activity and respiration, and the emergence of a fine neurohumoral regulation of the functions (A.Z. Kolchinskaya).

Another age phase in the life of the organism that is characterized by definite anatomical-physiological changes in the respiratory apparatus, the heart and blood vessels, by a simplification and "coarsening" of differentiated structures, a lowering of sensitivity to nervous irritants, and limitation of the functional possibilities is old age. In old age, the resistance of the organism to oxygen insufficiency drops and the "altitude ceiling" is lowered. Data on peculiar features of reactions to hypoxia in the aged organism are presented in this collection, in the papers by A.Z. Kolchinskaya and M.M. Seredenko.

It is a well known fact that the higher divisions of the brain are most sensitive to oxygen insufficiency. Research conducted by A.Z. Kolchinskaya has shown that in juveniles and aged persons, disturbances to the higher nervous activity - softening of reflexes, an increase in the latent period and disinhibition of differentiation intervene under alpine conditions at lower altitudes than in children or adults. Data on disturbances to higher nervous activity represent objective indices to

the behavior of the organism under hypoxia as it varies during these age periods.

Unfortunately, the question as to the influence exerted by oxygen insufficiency on the basic nervous processes in newborn children has not yet been studied at all. It would be particularly interesting to study the earliest conditioned reflexes, which, according to a suggestion from V.A. Trochikhin, may be completed at this state of ontogenesis not in the cortex, but at some lower level.

Naturally, the resistance of an intact organism to hypoxia at various stages in ontogenesis is governed by a combination of many different factors. During the process of evolution, the higher mammals have developed reflex adaptive mechanisms, which are mobilized under conditions of oxygen insufficiency to supply the tissues and organs with oxygen at a level adequate to their needs. The function of external respiration, the circulatory system and the blood-forming system, which are regulated by central nervous mechanisms, support this complex process.

In the early stages of ontogenesis, the reactions to hypoxia on the part of the cardiovascular system, the respiratory organs and the blood differ from the corresponding reactions during other age periods.

In full-grown individuals suffering from acute hypoxia, an increase in the oxygen capacity of the blood due to redistribution of depot blood represents an excellent diagnostic index to the organism's ability to adapt to this disturbance.

In the newborn, an increase in the number of erythrocytes and the amount of hemoglobin is either not observed at all or very weakly manifest even at severe levels of hypoxia (N.V. Lauer, Yu.F. Dombrovskaya, L.I. Radchenko, Yu.V. Semenov). Using an x-ray technique in combination with the injection of contrast agents, it has been established that the

contraction reaction of the spleen to oxygen insufficiency in infants has a long latent time and a high threshold, intervening beyond the "altitude ceiling" of the adult animal, at approximately 13-14 thousand meters (Lauer). Changes in the erythrograms of newborn individuals under the influence of hypoxia also have their own age-conditioned characteristics (Semenov). It is possible that this results from the fact that the blood of newborn individuals contains many erythrocytes of extramedullar origin.

In prolonged hypoxia, the reticulocyte and erythrocyte counts and the amount of hemoglobin usually increase as a result of the stimulating influence of oxygen insufficiency on hematogenesis in the bone marrow. These indices show particularly distinct increases under the conditions of the high mountains in children of preschool and school age (Kolchinskaya), while hypoxic hemopoiesis is only weakly expressed in aged persons (Kolchinskaya, Seredenko).

The still almost uninvestigated question as to the influence of hypoxia on the extramedullar hematopoiesis is of great interest.

As life advances, the reactions to hypoxia on the part of the cardiovascular system also undergo changes. However, there remains much to be done in connection with this question. Thus, while the increase in the per-minute volume of the heart in adults is one of the most indicative adaptive reactions to hypoxia on the part of the cardiovascular system, there are still no definite data on the change in this hemodynamic phenomenon in hypoxia of premature infants. Starting from the fact that, unlike full-grown individuals, puppies do not respond to hypoxia by accelerating their cardiac activity, but instead slow it down (I.A. Archavskiy, L.A. Krasnovskaya, Lauer, V.D. Rozanova), we might assume that many hemodynamic reactions to hypoxia make their appearance at a later phase of ontogenesis. This is the more likely since the re-

relationships of mutual subordination between the vagus and systematic nerve centers (O.A. Mikhaleva) and the tonic influence of the vagus nerve centers on the heart (Arshavskiy) are not established immediately after birth.

In addition to its underdeveloped reflex regulation, the heart is distinguished in the newborn individual by resistance to hypoxia, strongly expressed automatism and the ability to resume its contractions after prolonged stoppage (Kulyabko, Andreyev et al.). In accordance with this, and on the basis of electrocardiography, the disruptions of cardiac activity in hypoxia in newborn (rabbits) begin at more severe levels of hypoxia than they do in full-grown animals (Lauer). A fact of great diagnostic importance is that the changes that appear in the EKG under the influence of oxygen insufficiency differ for the newborn and adults (N.V. Lauer and M.M. Koganovskaya).

Among the age-conditioned features in the reaction of the heart, our attention is attracted to the phase during which the organism arrives at sexual maturity. According to A.Z. Kolchinskaya, the heart becomes highly sensitive to oxygen insufficiency at this age; even at relatively moderate altitudes, juveniles experience hypoxic tachycardia with a more than 30% increase in pulse rate, while the electrocardiographic changes are more distinct than in adults under the same conditions. The cardiovascular system is found to be particularly sensitive to oxygen insufficiency in old age (Seredenko, V.V. Frol'kis).

The ontogenetic development of the external respiratory adaptive mechanisms is of great interest. In adults, compensation of oxygen insufficiency in the inspired air and the effectiveness of adaptation depend to a major degree on the extent to which pulmonary ventilation is increased. A rise in the MOD [Per-minute Respiratory Volume] is observed very early. Thus, for example, it appears in dogs even when the

oxygen content of the inspired air is lowered by 1-1.5% (Lauer, Kolchinskaya).

The external respiratory function is established as a gas-exchange function only afterbirth. At first, respiration is superficial, but this is offset by its high frequency (Kettle, A.F. Tur, M.S. Maslov, I. A. Arshavskiy, Yu.F. Dombrovskaya). In newborn and particularly in premature infants, the rhythm of respiration is easily disturbed and supplanted by periodic respiration (Denisova, Figurin et al.). Another unfavorable factor is the ratio of the dead respiratory space to the respiratory volume, which is comparatively large at this age.

Under hypoxia, newborn individuals show a weak reaction in increasing their pulmonary ventilation (Krasnovskaya, Mayatnikova, Lauer, Rozanova). It has been established that the reaction of the respiratory system to hypoxia is established at one year of age in infants and after 2.5-3 months in puppies (Krasnovskaya).

In addition, we note that in certain species, for example, in baby chicks (L.Ye. Pal'gova and V.I. Volobuyev, Adol'f and Khon) or rabbits (Lauer, Adamson), respiration may become more frequent in hypoxia even within the first few days after birth. However, these reactions are unstable and their compensatory effect is negligible. It will be possible to regard all of these problems as definitely resolved only when exact numerical data have been obtained on the changes in pulmonary and alveolar ventilation in hypoxia.

In this connection, it is necessary to emphasize that it is not only the existence of a reflex that is important, but also comparative evaluation of its stability, persistence and the value of its mechanism in adapting the organism to oxygen insufficiency.

In the light of data on the immaturity of specialized reflex mechanisms for adaptation to hypoxia and the instability of the vegetative-

function regulation, the high resistance to hypoxia of the automatic respiratory-center activity in the medulla oblongata and that of the vasomotor center (Lauer), which is quite distinct at this age, is of great importance for understanding the viability of newborn individuals under the conditions of acute hypoxia. Under a given set of hypoxic conditions, the nerve centers in newborn individuals function 10-14 times as long as in adults (Kaba, Kaba and Deni, Lauer).

It is necessary to stress, however, that the organism gets through prolonged oxygen inadequacy rather poorly at this early age, due to its anatomical-physiological peculiarities and the imperfect development of its regulatory mechanisms.

During the first year of life, as we know, children are gravely threatened by illnesses complicated by oxygen insufficiency. It is obvious that in the newborn, even slight degrees of oxygen insufficiency must be regarded as asphyxial, since the absence of a stable increase in pulmonary ventilation contributes to the accumulation of carbon dioxide in the blood.

For all ontogenetic stages with the exception of a short period immediately after birth, the increase in pulmonary ventilation is a highly important mechanism for compensation and adaptation of the organism to hypoxia. Among the various forms of mammals, an increase in the external respiratory function in hypoxia is observed more frequently than the reactions on the part of other functional systems working to transport oxygen.

As was shown by the investigations of A.Z. Kolchinskaya, the increase in ventilation during hypoxia in children takes place less efficiently than in adults as a result of increased respiratory frequency, despite the well-established reflex regulation.

According to data instability in individuals passing through pu-

berty, the effectiveness of adaptation to hypoxia through the external respiratory function is not as strongly expressed, a factor responsible for the higher degree of undersaturation of the blood with oxygen as compared to children and mature individuals under the same conditions (Kolchinskaya). The nature of the change in the effectiveness of adaptation through external respiration in old age, which is lower at this time, is of great interest.

In the light of the problems under consideration, we may not omit mention of various types of changes in metabolic processes during hypoxia as a function of the organism's age. It is sufficient to note that at minor and moderate degrees of hypoxia, the consumption of oxygen rises in mature animals and humans, as an effect of stress and amplification of many functions, chiefly the energy expended in contracting the respiratory musculature.

In contrast, the consumption of oxygen falls off in the newborn even in minor degrees of hypoxia (Kross, Tizard, Moor, Dauess and Mott, Maurek, Taylor and others). This mechanism is a very important factor in the ability of the newborn to withstand severe degrees of acute oxygen insufficiency. However, no matter how great the drop in the oxidation rate, the organism would hardly be able to withstand total lack of oxygen for such a long time (as, for example, the 45 minutes survived by newborn rabbits in nitrogen) if some other source of energy were not being used concurrently. During birth and immediately afterward, this energy source is found in the anaerobic processes (glycolysis) (Reyss, Gorovitts, Gimvich, Rosanova, Lauer). As a result, it is inevitable that interest arises in determination of carbon-metabolism changes during hypoxia, changes that also have their own age peculiarities.

Much is still lacking that is required for correct understanding of the sequence of the process in which the adaptive mechanisms develop.

Thus, for example, almost no study has been devoted to age-connected changes in the correlations between pulmonary ventilation, blood flow rate in the lungs and the diffusion capacity of the lungs. Also of extreme importance in this respect are investigations in the matter of the physiology of the respiratory and vasomotor centers, and their functional interrelationships not only normal conditions, but also under the conditions of the acute stress that arises in oxygen insufficiency.

The question as to the ontogenetic development of the higher control over the vegetative functions - a control associated with the cerebral cortex - merits particular attention. Our own data (see, in this collection, the paper by N.V. Lauer, A.Z. Kolchinskaya and V.V. Turanov entitled "Ob adaptatsii vzroslogo organizma k nedostatku kisloroda i znachenie vysshikh otdelov mozga v etom protsesse" [On the Adaptation of the Full-Grown Organism to Oxygen Insufficiency and the Importance of the Higher Divisions of the Brain in this Process]) and data in the literature suggest that despite the presence of specialized reflexes that are well-established in maturity, disassociation of the cerebral cortex lowers the effectiveness and adequacy of the organism's adaptation to oxygen insufficiency; this mechanism is of particularly great for man (Turanov).

Even a cursory examination of the available factual material makes it obvious that during its lifetime, the organism passes through age phases during which the stability and sensitivity to hypoxia, the external respiratory reactions, the vascular and blood-forming systems and the nature and effectiveness of adaptation to oxygen insufficiency have their own specific features - features inherent to the given stage in ontogenesis.

Although representatives of different mammalian forms under their own stages of individual development and it is hardly possible, even on

the basis of physiological characteristics, not to mention the nature of the hypoxic states, to distinguish exactly the boundaries of the ontogenetic phases, the principal criteria nevertheless permit us to distinguish 6 age periods on the basis of data obtained in our laboratory - periods characterized by distinctive turns taken in hypoxic states. In the very earliest postnatal ontogenesis we perceive two age periods:

First period (neonatal). This covers the time of birth and the first few days afterward (the duration depends on species). This phase is characterized by the capacity of the organism to withstand extremely severe degrees (as compared with other ages) of acute oxygen insufficiency with the phenomena of distinct homeostasis disturbance. The length of survival in hypoxia during this period is not related to the effectiveness of adaptation by amplifying external respiration and blood flow and increasing the oxygen of the blood, but is governed by the presence of embryonal, nonspecialized adaptation mechanisms, foremost among which are the high stability of the vitally important centers and the metabolic processes. The physiological importance of these mechanisms lies in adaptation to hypoxia during birth and to those complex functional readjustments that accompany the transition of the organism from intrauterine life to its extrauterine existence.

Second period. (suckling). This is characterized by a decline in the organism's stability to acute hypoxia and inability to withstand prolonged oxygen insufficiency. The latter is due to partial or complete loss of the embryonic adaptation mechanisms, a higher level of the oxidation processes, a relative decline in the rate of anaerobic glycolysis, the absence or incomplete development of specialized reflex mechanisms for adaptation to hypoxia and high instability of the vegetative-function regulation. This phase is singled out in the interests of clinical medicine. In children less than a year old, and particular-

ly during the first six months, illnesses complicated by oxygen insufficiency are distinguished by the severity of their course, as manifested in respiratory insufficiency coupled with extensive oxygen under-saturation of the blood.

Third period. (Childhood). As we have already noted above, the nature of changes that take place in higher nervous activity during hypoxia, the increase in the oxygen capacity of the blood (due to redistribution of blood) and the speedup of cardiac activity in the pre-school and school-age years differ little from these indicators in adults. At this age, the increase in hemopoiesis under the influence of hypoxia is more strongly manifest than in other age periods. The increase in pulmonary ventilation takes place in children basically by way of increased respiratory frequency and not by deeper respiration, which suggests a less economical path to the compensation of the oxygen insufficiency.

Fourth period. (Youth). This is characterized by increased sensitivity and lowered resistance to hypoxia and adaptation less efficient than that observed in adults.

Fifth period. (Maturity). As a result of increased reflex activity on the part of the external respiration, vascular and blood-forming systems, the presence of reflexes specialized for hypoxia and a certain degree of balance between the nervous and humoral system, the effectiveness of adaptation and the ability to survive homeostasis in certain ranges of oxygen insufficiency are more distinctly manifest during maturity than in other age periods.

Sixth period. (Old age). This is characterized by lowered resistance and increased sensitivity to hypoxia. The latter manifests in a pronounced lowering of the "altitude ceiling," early disruption of higher nervous activity - inertness of the reflex adaptive mechanisms,

functional instability and low effectiveness of adaptation to hypoxia.

ON THE ROLE OF THE AGE FACTOR IN ADAPTATION OF THE
HUMAN ORGANISM TO OXYGEN INSUFFICIENCY

A.Z. Kolchinskaya

(Kiev)

Very few studies have been devoted to the role of such an important factor as age in the reaction of the organism to hypoxia. The literature on this subject seems to give preference to comparisons of hypoxic states in newborn and full-grown organisms and to set forth data obtained for the most part in experiments on animals. There is almost no information on the effect of oxygen insufficiency on the growing, maturing or aged human organism.

The morphological and functional peculiarities of the organism in various age periods are so sharply manifest that we may even a priori assume that its reactions to oxygen insufficiency are functions of age.

Over 15 years, we have conducted studies to ascertain the age features of the organism's reactions to hypoxia. The reaction of the human organism to oxygen insufficiency was studied in individuals of preschool age, during puberty, maturity and old age.

In 1955, at a conference on the physiology and pathology of respiration, hypoxia and oxygen therapy, we presented data on changes that take place in the higher nervous activity of children of preschool age, boys and girls ranging from 14-17 years of age, adults (20-50 years) and elderly persons (age over 65 years) in a medium deficient in oxygen.

These investigations showed that under a given set of conditions prevailing in the external medium at altitudes up to 3000 m, the chang-

es in the higher nervous activity are least distinct in children of preschool age and most pronounced in the elderly individuals. During puberty, when the organism is particularly sensitive to oxygen insufficiency, the higher nervous activity was more noticeably disturbed than in middle-aged and very young individuals.

Later, our attention was concentrated on a study of the age-conditioned activity features of the most important mechanisms adapting the organism to oxygen insufficiency and taking an active part in the organism's "fight" for oxygen.

Changes in external respiration, cardiac activity and the erythrocyte composition of the blood were studied in hypoxic hypoxia on individuals from the various age categories enumerated above. Hypoxic hypoxia was induced in low-pressure chambers and by inhalation of gas mixtures deficient in oxygen. The effects of oxygen insufficiency were also studied under natural conditions at altitudes of 2000, 3000 and 4000 m in the mountains during the mountain expeditions of the Institute of Physiology named for A.A. Bogomolets to Mount El'brus.

The changes in external respiration in an atmosphere with a substandard oxygen content are so distinctly perceptible that it does not take a specialist to notice them. However, despite the fact that a large number of papers have been devoted to study of respiration in hypoxia since the time of P. Ber and I.M. Sechenov, a number of aspects of this problem, including even relatively primitive ones, have remained unclear to this day. One of these questions is that as to how the external respiration changes in individuals of various ages when there is a deficiency of oxygen in the surrounding air.

In a mature human placed in a state of total rest, oxygen insufficiency causes an amplification of external respiration and an increase in pulmonary ventilation. The literature data and our own suggest that

the increase in the per-minute respiratory volume (MOD) depends on the depth of hypoxia, the temperature of the ambient medium, individual peculiarities and fitness of the organism, the functional state of the organism and, in particular, that of its nervous system.

As we know, more than two-thirds of mature individuals in their middle years show an increase in external respiration at medium-low and medium altitudes, preferentially by way of an increase in depth of respiration; the frequency of respiration changes little under these conditions.

A decrease in the depth of respiration coupled with increased frequency in the respiratory rhythm of middle-aged individuals is regarded by a number of authors as a symptom of respiratory insufficiency. A further increase in the depth of respiration in a mature human individual that is not compensated by increased frequency suggests serious disruption of the respiratory act in hypoxia (Haldane).

In a mature organism subject to an external medium with a lower-than-normal oxygen content at medium-low and medium altitudes, the elevated pulmonary ventilation (Fig. 1) provides a sufficiently high level of oxygen saturation of the arterial blood (Fig. 2) and a constant level of oxygen consumption or even a level higher than that at normal atmospheric pressure.

In children of preschool age, oxygen insufficiency also causes an increase in pulmonary ventilation (see table). However, in contrast to the situation with the adult organism, the increase in per-minute volume in children aged 3-7 years takes place not by way of increased depth of inspiration, but preferentially by way of an increase in the frequency of the respiratory movements. As was shown by studies made at various altitudes (1000, 2000, 3000 m in the low-pressure chamber and 2000 and 3000 m in the mountains) the depth of respiration does not in-

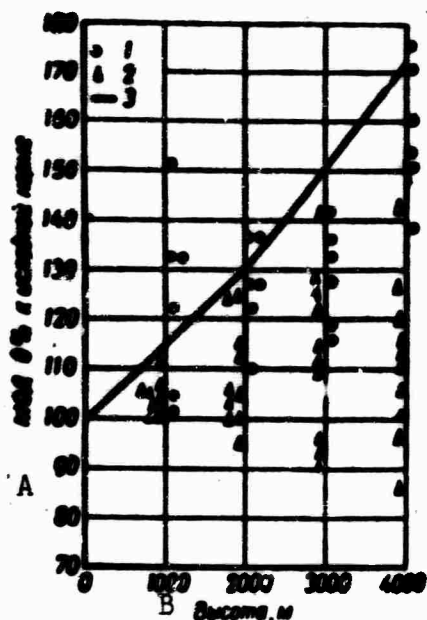


Fig. 1. Change in per-minute respiratory volume at various "altitudes" in the low-pressure chamber, as observed in persons of various ages: 1) Adults; 2) juveniles; 3) calculated ventilation. A) MOD in % of initial norm; B) altitude, m.

crease, but may even decrease.

The fact that children of preschool age increase their MOD at moderate altitudes by increasing the frequency of their respiratory movements and not by increasing the depth of respiration is obviously to be accounted for by the physiological features of respiration at this age. Under the conditions of a normal oxygen supply, respiration is more superficial and its rhythm more frequent in children 3-7 years old than in adults. With increasing age, respiration becomes deeper and less frequent (Gundobin, Maslov, Tur, Dombrovskaya, Shalkov and others). For this reason, increased respiratory frequency in hypoxia of children can hardly be regarded as a symptom

of respiratory insufficiency. However, more frequent respiration in children of preschool during hypoxia results in an increase in alveolar ventilation that is smaller than that observed in adults, and also lowers the reduced alveolar ventilation, which attests to lower effectiveness of the adaptation to oxygen insufficiency on the part of the external respiratory function during childhood.

It should be noted that in hypoxia, children retain the higher oxygen partial pressure in the alveolar air that is peculiar to them at normal atmospheric pressure. It is possible that this is one of the factors accounting for the lower degree of hypoxemia under the conditions of depressed oxygen partial pressure.

As with other vegetative functions, respiration undergoes significant changes during puberty - changes related to the over-all read-

adjustment of the neurohumoral factors regulating the functions of the organism, which frequently results in temporary physiological disfunctions. During this period, it is distinguished by severe instability. As regards type, respiration is mixed, alternating between the thoracic and abdominal types. With increasing age, the depth of respiration increases markedly, and this increase provides for increased pulmonary ventilation (Shalkov). Although the frequency of respiration during puberty approaches that of respiration in a mature individual, it nevertheless retains some of the features of the childhood type, continuing to be more frequent than in middle-aged adults.

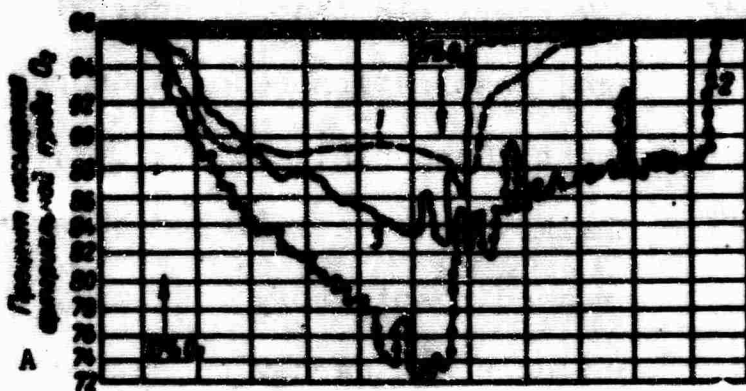


Fig. 2. Oxyhemograms of humans of various ages during short-term (5 min) breathing of a mixture of N_2 with 10% of oxygen. 1) Pavlik, aged 4; 2) Volodya, aged 14; 3) L.I.R., 24 years of age. A) Percentage O_2 saturation of arterial blood.

As our investigations showed, oxygen insufficiency gives rise to amplified respiration in teenage boys and girls, and at this age, as with mature individuals, they increase their pulmonary ventilation basically by increasing their depth of respiration (although 40% of the teenage male and female subjects showed increased respiratory frequency at altitudes of 2000, 3000 and 4000 m). However, the depth of respiration increases in teenagers of both sexes to a less significant degree than it does in adults, so that the increase in per-minute respiratory volume at medium-low and medium altitudes lags behind that observed in adults. As hypoxia progresses in teenagers of both sexes, the pulmonary

ventilation does not increase as rapidly and regularly as it does in adults, the reduced MOD diminishes and the alveolar ventilation is lowered. Adaptation of the organism to oxygen insufficiency through the external respiratory function is not accomplished as well during puberty as it is in middle age (Fig. 1). As a result of the inferior adaptation by the external respiratory system, hypoxemia is more strongly expressed in teenage boys and girls than in adults at corresponding altitudes (Fig. 2). The oxygen consumption drops markedly in teenage boys and girls during hypoxia.

Anatomical and functional changes in the respiratory organs in old age result in reduced ventilation of the lungs, the appearance of respiratory insufficiency manifest to varying degrees, and in a drop in the oxygen saturation of the arterial blood, i.e., in hypoxemia, even when the partial pressure of the oxygen in the inspired air is normal. The hyperventilation observed here in elderly persons is regarded by some authors as a barometer of the struggle against hypoxemia in old age (Bine and Bur, Vernan and Sebaun, Primak).

In old age, the respiratory insufficiency is aggravated by insufficiency of oxygen in the inspired air. We were able to follow only certain indices to hypoxic external respiration in 4 individuals aged 65-67 years. By comparison with that which was observed at normal atmospheric pressure in elderly persons, respiration was observed to be more frequent during the first few days of a sojourn in the mountains at an altitude of 2000 m when the subjects were in a state of rest in the horizontal position. The higher resting respiratory frequency persisted for a long time - to the 10th-12th day of the sojourn at this altitude. The speedup in respiration was more distinct at the 3000-m altitude.

At the altitude of 2000 m, periodic-type respiration was regis-

Respiratory Indices (Ira K., 6 years of age) at Various "Altitudes" in the low-pressure Chamber

1) Показатель внешнего дыхания	2) Нормальная атмосферическая давление	1000 м	2000 м	3000 м
3 Частота	22	23	25	27
4 ДО	172	174	180	189
5 МОД	3800	4000	4050	4300
6 МОД (редуцир.)	3430	3160	2780	2580
7 М. П. по O ₂	46	42	37	38
8 М. П. по CO ₂	67	68	48	41
9 А. В. по O ₂	2770	3040	3070	3270
10 А. В. по O ₂ (редуцир.)	2493	2700	2118	1962
11 А. В. по CO ₂	2810	2440	3080	3188
12 А. В. по CO ₂ (редуцир.)	2079	1927	2104	1908
13 Процент O ₂ в выдыхаемом воздухе	17,7	17,5	17,2	16,7
14 Процент O ₂ в альвеолярном воздухе	16,5	16,4	16,1	15,9
15 Процент CO ₂ в выдыхаемом воздухе	2,3	2,3	2,8	3,2
16 Процент CO ₂ в альвеолярном воздухе	3,8	3,8	4,0	4,3

1) External respiration indicator; 2) normal atmospheric pressure; 3) frequency; 4) respiratory volume; 5) per-minute respiratory volume; 6) per-minute respiratory volume (reduced); 7) metabolic index with respect to O₂; 8) metabolic index with respect to CO₂; 9) alveolar ventilation with respect to O₂; 10) alveolar ventilation with respect to O₂ (reduced); 11) alveolar ventilation with respect to CO₂; 12) alveolar ventilation with respect to CO₂ (reduced); 13) percentage of O₂ in expired air; 14) percentage of O₂ in alveolar air; 15) percentage of CO₂ in expired air; 16) percentage of CO₂ in alveolar air.

tered in individuals at "ripe old ages." The shortness of breath that set in during sleep caused considerable agitation. During the first few days of the sojourn at the altitude of 2000 m, even minor physical exertion winded the old ones and produced the sensations associated with oxygen deficiency.

The observations made permit us the conclusion that at each age the adaptation of external respiration to hypoxia has its own distinctive features. With growth and maturing of the organism, it is perfected, but it deteriorates significantly in old age.

A study of the state of the cardiovascular system on the basis of various indicators (frequency of cardiac contractions and its variation under physical load, arterial pressure, electrocardiogram) also brought out age-connected differences in the reaction of the system to hypoxia.

According to our data, the pulse showed almost no change up to an "altitude" of 3000 m in adults lying horizontally when the air in the low-pressure chamber is rarefied. At an "altitude" of 4000 m, their pulses rise by 5-10 beats per minute (9-12% of the initial norm), and 12-18 beats per minute (22-27%) at the 5000-m "altitude." Of 28 adults investigated as participants in mountain expeditions, the pulse was faster in 20 of them on the second day of the sojourn at the 2000-meter altitude, with the increase not exceeding 9 beats per minute in 15 of the people and amounting to 12-16 beats per minute in only 5 of them. On the average, middle-aged individuals showed a 5-beat increase in pulse rate at this altitude (8% of the initial norm).

Among 25 children of preschool age observed during the mountain expeditions, the increase in pulse rate during the first few days of the sojourn at 2000 m was more strongly marked than in the adults. In 18 children it was 9-30 beats per minute (in 7 of these children, the pulse speeded up by 20-30 beats), while only in 7 of the children was the pulse increase insignificant, by 2-6 beats per minute. On the average, the pulse-rate increase in preschool children at the 2000 m altitude was 14.8 beats per minute (17.6%) The children's pulses continued to increase in frequency during the entire three-week stay at the 2000-meter altitude.

It should be noted that although the pulse quickening at rest in the horizontal position was greater in children at 2000 meters than in the adults, an orthostatic test at the lowered atmospheric pressure showed pulse frequency changes that were smaller in preschool-aged

children than in adults. Thus, while the pulse quickened by 19% at normal atmospheric pressure (Kiev) in the adults on changing from the horizontal to the vertical position, and by 17% on the second day of the sojourn at the altitude of 2000 m, the children, on the other hand, showed 14% at normal atmospheric pressure (Kiev) and 8% at the 2000-meter altitude. Practically identical results were obtained in a test under physical load: in half of the children, 10 toe-touching exercises within 30 sec at the altitude of 2000 m produced a smaller increase (in percent of the initial norm) in the pulse frequency than at normal pressure (Fig. 3). The pulse rate returned to the initial norm either the same time as at normal atmospheric pressure or after a shorter interval of time after the effort.

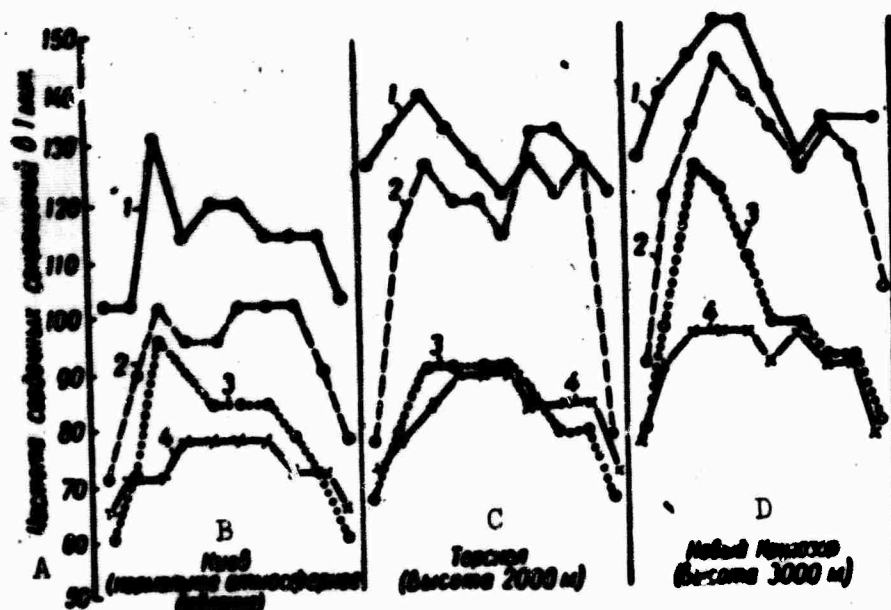


Fig. 3. Change in pulse frequency under the influence of physical load in individuals of various ages in the mountains. 1) Serezha, 5 years of age; 2) Zhenya, 14 years of age; 3) S.Ye., 30 years of age; 4) S., 65 years of age. A) Cardiac frequency, per 1 min; B) Kiev, (normal atmospheric pressure); C) Terskol, (altitude 2000 m); D) Novyy Krugozor (altitude 3000 m).

The pulse rates of the children increased at the 3000-meter altitude, both over the data obtained at Kiev (on the average, by 20.5%) and by comparison with the pulse rates recorded at 2000 m (by 3.5%). The absolute figures for the pulse quickening in the children were

larger than those for the adults.

The orthostatic test at the altitude of 3000 m resulted in a pulse quickening greater than that observed at 2000 m; the percentage increase referred to the initial norm averaged 14.8%. For the adults, the percentage of the initial norm was 20%.

The functional test also produced greater changes in the pulse rate at an altitude of 3000 m than it did at 2000 m, but the return of the pulse to the initial values did not take place more slowly than at normal atmospheric pressure (Fig. 3).

As shown by EKG data, the pulse frequency takes place in adults and in children at the expense of a shortening of the diastole. The P-Q and Q-T intervals show no change, in either the adults or the children. The heights of the EKG waves underwent insignificant changes: in adults and in children, the heights of the P and T waves became lower. In most of the adults, the R wave also subsided. We failed to note changes in the configuration of the EKG waves or a shift in the S-T interval at altitudes up to 3000 m, either in adults or in children. Thus, electrocardiography did not bring out any substantial disturbances to the children's cardiac activity at altitudes from 2000-3000 m.

Both the systolic and the diastolic blood pressures rose by 5-30 mm Hg in most of the children during the first few days of their sojourn at altitudes of 2000-3000 m.

In youths and maidens placed in the low-pressure chamber in the horizontal position in a state of rest, the pulse was observed to quicken by 2-20 beats per minute (3-36% referred to the original norm) even at an "altitude" of 2000 m, while at the "altitude" of 3000 m, the quickening was 7-30 beats per minute (10-54%) and at the "altitude" of 4000 m it was 10-30 beats per minute (16-54%), i.e., the pulse quickening in teenagers of both sexes as the air in the low-pressure chamber

was rarefied began at lower altitudes and was more pronounced than in adults.

Similar data were obtained under the conditions of the high mountains. On the second day of the sojourn at 2000 m, the pulse quickening observed in young boys and girls was sharper than in adults. In the teenagers, the pulse quickened by 6-18 and in some cases by 26-40 beats per minute. On the average, the pulse quickening was 14.2 beats per minute (14.3%).

The cardiac activity changes observed in teenagers of both sexes are particularly indicative when compared with the figures for adults when we come to the functional tests (Fig. 3). The orthostatic test and the physical-load test produced sharper changes in the frequency of cardiac contractions in teenage boys and girls at an altitude of 2000 m than at normal atmospheric pressure, together with sharper shifts than in adults under the same conditions.

At normal atmospheric pressure, the transition from the horizontal to the vertical position in teenage boys and girls caused an increase in the pulse rate by an average of 37.8%, at 2000 m this increase was 44.5%, and 4200 m it was 46.8%. The functional test with physical load produced similar results.

According to EKG's taken both in the low-pressure chamber and under the conditions of the mountains, the cardiac pause (the T-P interval) diminished in the teenage boys and girls beginning at altitudes of 2000-3000 m, while the P-Q interval did not change (only in one youth did it increase at the 4000-meter altitude). In some of the individuals tested at altitudes of 3000-4000 m, the Q-T interval was shortened beginning with altitudes of 2000-3000 m, and the height of the R wave decreased; the T-wave either did not change or diminished. We observed no shifts in the S-T interval.

It is evident from the data given above that although changes intervene in the electrocardiograms of teenage boys and girls at lower altitudes as compared with adults and children, the EXG does not show specific pathological changes in cardiac activity in the juveniles at altitudes not exceeding 4000 m.

In the teenage boys and girls, the blood pressure (systolic and diastolic) rises during the first few days of a stay in the mountains. In 4 min older than 65, the pulse frequency did not increase as significantly as it did in the younger persons on the second day of the sojourn in the mountains at an altitude of 2000 m. In three of the individuals tested, the pulse quickened by 5, 7 and 8 beats per minute, while in one case the pulse did not change at all. Of the three elderly persons taken up to the altitude of 3000 m, 2 showed slower pulse rates (slower by 6-20 beats per min), and the female test subject showed a quickening by 12 beats per min as compared with the Kiev norm. In the elderly persons, the orthostatic test at the altitude of 2000 m gave a smaller increase than in people in the other age categories (Fig. 3).

Gel'man and Braun, Berman and Sebaun, and MacFarland have noted a smaller increase in pulse rate under physical load in elderly persons as compared with other age groups. Gel'man and Braun report that elderly persons show a narrowing of the functional lability of the sinoatrial node and fixation of the pulse at more or less stable levels. Vernan and Sebaun also conclude that the heart is characterized in elderly persons by a progressive loss of its ability to adapt to load. According to MacFarland, the pulse frequency changes less in elderly persons than it does in young people during the first hour of a sojourn at 4240 m.

At 2000 m, and to a greater degree at 3000 m, the amplitude of the R and T waves decreased in elderly persons; in one of them, the dura-

tion of the QRS complex increased and it became quite drawn-out. In the others, no broadening of the QRS complex was observed. The P-Q interval did not change, although in one test subject the P-wave was smoothed out.

In healthy elderly persons, the systologic [sic] pressure showed no change on the second day of residence at 2000 m. On the 10th day of residence at this altitude, it rose, remaining elevated for the entire month of the stay in the mountains.

According to MacFarland, the blood pressure of persons of advanced age dropped during short-term hypoxia at an altitude of 4240 m, but had risen again by the second hour. However, both the decrease and the increase in systolic pressure amounted only to 2-4 mm, a statistically insignificant variation.

As we reported earlier (Kolchinskaya, 1955), temporary residence in the mountains causes nonuniform increases in the erythrocyte counts and hemoglobin content in persons of different ages. Very early, even on the fifth day of a sojourn at the altitude of 2000 m, we observe an increase in the erythrocyte count and hemoglobin content in children of preschool age. In this group, however, this increase reaches its maximum, as compared with other age groups, toward the end of a month's stay at altitudes of 2000-3000 m. The amount of hemoglobin and erythrocyte count in the circulating blood increased very slowly and sluggishly in elderly persons.

Thus, each of the age periods is characterized by certain distinctive features in the adaptation to hypoxia. This was shown with particular clarity for the organisms of newborn animals by N.V. Lauer (1959, 1961, 1963). As follows from the material presented above, the preschool age has its own unique reaction to oxygen insufficiency. The rhythm of respiration and the heartbeat becomes more frequent, and the

organism still manages to compensate, although not in an economical fashion, insufficiencies of oxygen in the surrounding air in the altitude range from 1000 to 4000 m. Under more chronic low-level hypoxia, intensified hematogenesis, which is most strongly manifest at this age under mountain conditions, also begins to acquire a certain role in the organism of the child.

In studying the acclimatization of the child's organism to hypoxia, it is also necessary to remember the fact that the smaller the child, the greater the amount of oxygen that its organism consumes in growing, and the smaller the amount of energy that it expends in performing muscular work (Gel'mreykh). This last circumstance cannot be without significance under the conditions of hypoxia, since the conflict between the limited access of oxygen to the organism and the organism's requirements will become smaller. The result of all this is that the child's organism adapts to hypoxic hypoxia comparatively well in the altitude range from 2-4 thousand meters above sea level. The absence of disturbances to the higher nervous activity of children at these altitudes serves to point up the good adaptation of the child's organism.

During puberty, adaptation to hypoxia on the part of the external respiratory function becomes more economical, but it is nevertheless somewhat perfect than in maturity. As a result of this, teenage boys and girls show higher degrees of hypoxemia than adults during hypoxia (Fig. 2), and, despite the fact that their cardiovascular systems react more strongly than those of adults, the tissues suffer from hypoxia. This important because the oxygen requirement of the tissues of the juvenile organism exceed those of the adult, particularly during physical work. Further testimony to the poorer performance of the juvenile organism in hypoxic hypoxia, as compared to that of the adult human, is found in the greater changes in the higher nervous activity of teenage

boys and girls at these same altitudes.

The activity of the hypoxic-adaptation mechanisms that provide for delivery of oxygen to the tissues in maturity is most efficient and economical. In the altitude range from 4000-5000 m, the amplification of external respiration and blood circulation can maintain the mature organism with regard to homeostasis and keep the functioning of the organism as a whole on a par with normality. Beyond this range of altitudes, the activity of only these adaptive mechanisms is found to be inadequate and "decompensation" sets in, a phenomenon observed in less severe hypoxic hypoxia in elderly persons.

CERTAIN DATA ON THE ANATOMICAL-PHYSIOLOGICAL CHARACTERISTICS
OF THE ORGANISM OF CHILDREN BORN AND RAISED IN
THE HIGH MOUNTAINS

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(Frunze)

The problem of acclimatization of the organism to altitude at various ages is among those to which little study has been devoted. The large population of children living year round at considerable altitudes poses the problem of studying the mechanisms by which the organism of the child adapts to mountain conditions, as well as establishment of physiological norms for children born and raised in mountainous terrain.

The literature gives only very little information on the anatomical-physiological characteristics of the organism of children born and raised in the mountains (Khurtado, Monge, Levi and Marton, Renger-Perel'man), and the children studied were natives of the Andes and Davos. No similar studies have been made at all as regards the mountains of Tien-Shan, although tens of thousands of children live here at altitudes of 1500-2500 m.

We have studied certain anatomical-physiological characteristics of the organism of these mountain children. Our investigations began with anthropometric measurements and studies of the cardiovascular, respiratory, hematogenetic and other systems of children of school age in practically perfect health, individuals born and reared at an altitude of 2050 m. About 8000 individuals ranging in age from 7 to 16 were

examined; in most cases, these were children of the Kirghiz nationality

The anthropometric measurements show that certain proportions of the body of the mountain child tend to differ from the corresponding indices for Kirghiz children in Frunze (altitude 750 m). The height of children born and reared at an altitude of 2050 m is somewhat shorter than for children of the same age who live in Frunze. The weight of the mountain children differs little from that of the Frunze children.

TABLE 1

Ratio of Chest Measurement to Height, in %

1 Age group	2 Mountains			3 Lowlands		
	Boys (750 m) 4	Boys (2050 m) 5	Difference (in %) 6	Boys (750 m) 4	Boys (2050 m) 5	Difference (in %) 6
7-10 yrs 7	48,17 %	48,35 %	+1,18	47,80 %	48,77 %	+1,27

*We calculated the ratio of chest girth to height for the Frunze children from data furnished by B. Mamytov (see Fizicheskoye razvitiye shkol'nikov g. frunze" [Physical Development of School Children in the City of Frunze], Trudy Kirg. ros. med. in-ta, [Transactions of the Kirghiz State Medical Institute] Vol. XII, 1959).

1) Age of children; 2) boys; 3) girls; 4) altitude of 750 m*; 5) altitude of 2050 m; 6) difference (in %); 7) 7-10 years.

Measurement of the girth at the chest is of particular interest. The chest measurements are somewhat larger for the mountain children than for children inhabiting the lowland locality. If we express the ratio of the chest girth to height in percent, our attention is drawn to the distinct increase of this index in the mountain children (Table 1).

The physiological significance of this phenomenon reduces to the fact that at a given or even lower height, the mountain children have broader chests, so that they are provided with better pulmonary ventilation. It is true that measurement of the lung capacities of these same

children did not show such a significant expansion as was found by Khurtado, Levi and Marton in children of Davos and the Peruvian Andes. In children who had been reared at altitudes above 2000 m, the vital capacity of the lungs was only slightly higher than the age norms, which are given by Miller, Dombrovskaya and Serebrovskaya (Table 3).

The respiration frequency in the mountain children differs little from the norms for the age, those values characteristic for lowland children (Table 2). The MOD per-minute respiratory volume is higher for the mountain children than for children living in lowland localities.

It is quite possible that the altitude of 2050 m is not yet sufficiently high to make these changes manifest as sharply as was noted in the studies of other authors (Khurtado, Monge and others), although even at this altitude we observe a tendency to those changes in the respiratory organs that are characteristic for inhabitants of the high mountains.

The state of the cardiovascular system was determined on the basis of several indices: the pulse rate, the blood flow volume, arterial pressure, electrocardiogram, data from capillaroscopy and the resistance offered by capillaries. The pulse-rate pattern of the mountain children can be inferred from the data of Table 4.

TABLE 2
Respiratory Frequency in Mountain Children

1	2	3	4	5	6
Пол	Возраст (в годах)	Пределы колебаний	Среднее арифметическое	Среднее квадратическое отклонение	Средняя ошибка
Мальчики . 7	7-10	16-30	22,3	2,8	0,3
Девочки . 8	7-10	16-30	22,9	3,6	0,4
Мальчики . 7	11-13	18-27	21,9	2,7	0,4
Девочки . 8	11-13	18-26	21,4	2,8	0,4
Мальчики . 7	14-16	18-26	21,4	3,1	0,4
Девочки . 8	14-16	18-26	22,6	2,6	0,7

- 1) Sex; 2) age (in years); 3) range of variation; 4) arithmetic mean; 5) root mean square deviation; 6) mean error; 7) boys; 8) girls;

TABLE 3

Pulmonary Vital Capacity (in cm³) in
Children Aged 7-10 Years

Автор	1	Мальчики 2	Девочки 3
Наша группа	4	1407	1211
Миллер	5	1319	1117
Домбровская	6	1380—1800	
Серебровская	7	1220—1679	
Израэли	8	1380	
Шалков	9	1400—1800	1200—1650

1) Source; 2) boys; 3) girls; 4) our data; 5) Miller; 6) Dombrovskaya;
7) Serebrovskaya; 8) Israelyan; 9) Shalkov.

On comparison of our data with those of other authors who had studied the pulse frequencies of children living in lowland localities, it was found that the mountain children had slower pulses than the lowland children. Relative bradycardia is encountered in children aged 7-10 years with particularly high frequency; in these individuals, the average frequency of cardiac contractions lies at the very lowest limit of the age norm. Bradycardia is detected less frequently at later ages. Relative bradycardia was found among the adult population of Tien-Shan by Yarkho, Mirrakhimov, Redlikh, Filatova and others, and in the Peruvian Andes by Khurtado.

Electrocardiograms were recorded with the object of more detailed study of the mountain children's cardiac activity. EKG's were recorded in three standard leads and six precordial leads. The EKG data for the high-mountain children do not differ greatly from the EKG's of children reared in the lowlands, although 15-17% of the children examined registered low wave voltages and 10% of all children had a high T-wave, a wave that exceeded all normal individual variations characteristic for this wave in lowland children. In occasional cases, mountain children showed S-T intervals higher or lower than the isoline and splitting of

R or S wave.

TABLE 4

Frequency of Heart Contractions in Mountain Children

Пол	1	Возраст в годах	2	Пределы колебаний	3	Среднее арифметическое	4	Среднее квадратическое отклонение	5	Среднее отклонение	6
Мальчики	7	7-10	60-110	79,3	8,6	0,9					
Девочки	7	7-10	54-106	78,7	10,2	1,1					
Мальчики	8	11-13	60-97	77,3	8,4	1,4					
Девочки	8	11-13	60-92	79,0	10,8	1,5					
Мальчики	8	14-16	56-96	77,0	9,7	2,6					
Девочки	8	14-16	60-102	73,0	6,6	1,7					

1) Sex; 2) age in years; 3) range of variation; 4) arithmetic mean; 5) root mean square deviation; 6) mean error; 7) boys; 8) girls.

On comparing the cardiac activity of children who live year-round in the high mountains with that of children who have only recently been brought up to this altitude, we can discern sharp differences. Although, according to A.Z. Kolchinskaya, the pulse rate considerably exceeds the initial norms for nonacclimatized children on the second day of a sojourn at the altitude of 2000 m, a normal contraction rhythm is characteristic for children born and raised in the high mountains, even with the relative bradycardia that results in more economical heart operation under mountain conditions. The determination of the blood flow rate with cytitone is reflected in Table 5.

As will be seen from Table 5, the blood flows more slowly in mountain children than in children who are inhabitants of lowland areas. Although the blood return time is 7-8 sec in children aged 7-10 years according to Leytes, it exceeds these values in the mountain children. According to Smirnov's data (6.1-6.9 sec) and those of Mishchenko (4-7 sec) and others, this retardation is even more pronounced. If we evaluate the bloodstream velocity in mountain children on the basis of "lowland" norms, then we find that in more than 50% of those investigated the blood flow rate was slower. Slower blood flow has also been

observed by Mirrakhimov in adult Tien-Shan locals. The slower blood flow velocity and a certain bradycardia may be of positive value in adapting the organism to the conditions of the high mountains. As a result of the slower blood flow and the elevated pulmonary ventilation, the saturation of the blood with oxygen is improved during its passage through the short [pulmonary] circuit, i.e., the blood becomes more completely arterialized. It might be assumed that with the increased pulmonary ventilation and slower blood flow, the oxygen saturation of the blood during its passage through the lungs will be more complete and, consequently, the extent of hypoxemia may be lower.

TABLE 5
Rate of Blood Flow in Mountain Children

Sex	Age (in years)	Range of variation (in sec.)	Arithmetic mean	Root mean square deviation	Mean error	
1	2	3	4	5	6	
Мальчики	7	7-10	4-15	8,9	2,3	0,2
Девочки	6	7-10	4-17	8,8	2,4	0,2
Мальчики	7	11-13	4-15	10,3	1,9	0,3
Девочки	8	11-13	4-17	9,9	1,9	0,3
Мальчики	7	14-16	6-17	10,9	2,6	0,7
Девочки	8	14-16	6-24	10,3	1,4	0,3

1) Sex; 2) age (in years); 3) range of variation (in sec); 4) arithmetic mean; 5) root mean square deviation; 6) mean error; 7) boys; 8) girls.

A study of arterial pressure in adult local inhabitants of the high mountains of Kirghizia showed that low arterial pressure is observed quite frequently and hypertonia occurs much more rarely than in lowland areas (Redlikh, Daniyarov, Aliyev, Volkova and others). Since we were particularly interested in the problem of arterial pressure indicators in Kirghiz mountain children, we conducted large-scale measurements of arterial pressure in children living at various altitudes. In all, we examined 7861 persons: 3502 at altitudes of 2050-2200 m, 2557 at an altitude of 1750 m and 1802 at an altitude of 750 m (Frunze).

The arterial pressure figures for Kirghiz children differed some-

what from the norms indicated by various authors for children of other localities. This difference was most sharply expressed in Frunze children, where the systolic and diastolic pressures were lower than in children of corresponding ages in lowland localities. In children living at altitudes of 1750 and 2200 m, the arterial pressure reaches higher values than in Frunze and differs less from the "lowland norms," as presented by Ostrovskiy and Braynina, Solov'yeva, Tur, Popov, Volyinskiy et al. and others for children of the central belt of the RSFSR.

The state of the capillaries was studied by capillaroscopy in 235 children. Basically, the capillaroscopic pattern of the mountain children showed almost no departures from normal. In only 25% of those investigated did the capillaries take the form of very short "commas," and in these cases the number in 1 mm was increased.

A study of capillary resistance (Nesterov method) showed that in approximately 40% of the mountain children, the strength of the capillaries was reduced. This is in agreement with the data of Mirrakhimov and Preobrazhenskaya, who found a similar phenomenon in adults native to the mountains.

On comparing the change in physiological reactions in children who were experiencing acute exposure to altitude and children living year-round in the high mountain, we note considerable differences between these reactions. While the children recently brought up into the mountains showed tachycardia, quickened respiration and activated hemopoiesis (A.Z. Kolchinskaya), all of which, in the final analysis, keeps the partial O_2 pressure of the blood from dropping too sharply, children born and reared in the high mountains achieved a similar result by another route. It is obvious that for them an increase in the measurements of the chest cavity is of greater importance - a change that results in better adaptation of the respiratory organs. The relative

bradycardia apparently permits the heart to work more economically. Finally, the presence of these adaptive reactions does not exclude tissue acclimatization and a possible decline in the oxygen requirement, such as very probably is also effected in acclimatized organisms in the mountains of Tien-Shan (A.D. Slonim, Barbashova and Ginetsinskiy, Barbashova, Filatova and others).

EXPERIMENTAL INVESTIGATION OF CARDIAC-ACTIVITY DISTURBANCES IN
HYPOXIA IN YOUNG PUPPIES

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There is an enormous body of literature on the problem of the effect of oxygen insufficiency on cardiac activity. The data of mountain expeditions, physiological researches and clinical treatment of cardiovascular and pulmonary disorders, all obtained with the aid of the achievements of modern engineering, have in recent years considerably broadened our conceptions of the functional possibilities of the heart and pathological disturbances to its activity in oxygen insufficiency.

However, the question of age in the nature of the disturbance to cardiac activity in hypoxia has not been given adequate study. Of particular interest in this respect is the early period of the organism's postnatal development, when both the heart itself and its innervation mechanisms are in a state of morphological and functional immaturity. Despite long study, the problem of hypoxia in infancy remains an extremely urgent one. The mechanisms by which the asphyxia that arises during birth, or secondary asphyxia, arises and their diagnosis and treatment and the grave course taken by illnesses complicated by hypoxia in children of breast-feeding age require study from all aspects.

Numerous circumstances make it difficult to ascertain the distinctive characteristics of early hypoxia in the clinic: the lack of initial data and exact information on the degree and duration of hypoxia in

children who are born in asphyxia, by the presence of assident phenomenon in the form of extravasation and edema of the brain, and the influence of intoxication preceding birth.

The task of the present investigation was to make an experimental study of changes in the electrocardiograms of puppies as a function of age under the influence of hypoxia, the latter very strictly dosed as regards severity and duration. In selecting the object of the investigation we settled on the puppies because they are more nearly comparable to children than other experimental animals as regards the maturity of the organism at birth and the manner in which the extracardial innervation develops.

METHOD

The investigations were run on puppies of three age groups (from 1 to 6 days and at two weeks and a month and a half), as well as on full-grown dogs. A total of over 100 animals were investigated. Oxygen insufficiency was induced by "elevating" the animals in a low-pressure chamber to a "height" of 15 thousand meters with one-minute "plateaus." EKG's were recorded from the extremities in lead two before the experiment and after the "ascent" in the low-pressure chamber, at thousand-meter intervals. More than a thousand electrocardiograms were recorded and analyzed in the low-pressure chamber during the experiments.

RESULTS OF INVESTIGATIONS

Under normal physiological conditions, the puppies that we studied in the first age group (1-6 days), the rhythm of the cardiac contractions was characterized by high frequency and instability (150-300 per 1 min). All EKG waves were clearly expressed. The EKG was distinguished by low amplitude, particularly in the R-wave, a deep S-wave and a comparatively long duration of the ventricular complex (0.18 sec).

In the two-week-old puppies, the cardiac rhythm was even more frequent and labile than in the newborn puppies. The EKG was characterized by an increase in the wave amplitudes. However, the amplitude of the P

and T waves had increased to a lesser degree than the R-wave; at this time, the S-wave had already diminished considerably; the duration of the ventricular complex averaged 0.17 sec.

In the puppies studied at one and a half months, the cardiac rhythm had slowed down from the earlier rate to 150-270 beats per 1 min, but was nevertheless still more frequent than in full-grown dogs (63-150 per 1 min). In puppies at this age, the EKG was characterized by a still greater increase in the R-wave (14.7 mm), a slight drop in the height of the P and T-waves as compared with the earlier age, an indistinct or totally lacking S-wave and a more rapid progression of the ventricular complex (0.15 sec).

In newborn puppies, the change in the rhythm of the cardiac contractions with increasing hypoxia is single-phased in nature and expressed in a slowing down of cardiac activity without a preliminary quickening, as has been observed in full-grown dogs and older puppies. Due to the fact that in newborn individuals suffering from hypoxia the cardiac activity slows down progressively, the heart still beats 195-200 times per minute even in the comparatively acute oxygen insufficiency developed at the "altitude" of 9 thousand meters, and at 48 times per minute at the "altitude" of 15 thousand meters.

Although it is still indistinct, puppies of the second age group show two-phased variations of the cardiac rhythm in hypoxia. Beginning at an "altitude" of 4-5 thousand meters, the rhythm of the cardiac contractions in these puppies becomes more frequent, reaching an average of 310 beats per minute at an "altitude" of 6 thousand meters, but this reaction is still unstable in the two-week-old puppies; at the "altitude" of 7 thousand meters, their cardiac activity begins to slow down; at 9-10 thousand meters, their pulses are even slower than they were to begin with, although at the "altitude" of 15 thousand meters, the pulse

has slowed to approximately the same level as in the newborn individuals.

In puppies of the third age group (1.5 months), the first phase of the reaction is a quickening of the heart rhythm in hypoxia that is more distinct as regards both extent and duration than in the two-week-old puppies. In both of these groups, the pulse begins to quicken at an "altitude" of approximately 4-5 thousand meters. At the age of a month and a half, however, this reaction is more stable, and the quickened heart rhythm is retained up to the "altitude" of 9 thousand meters, at which point it has reached its maximum, corresponding to 150% of the norm. In more acute hypoxia, the month-and-a-half-old puppies show a deceleration of cardiac activity; at the "altitude" of 11.5-12 thousand meters, the heart beats slower than normal, and an "altitude" of 15 thousand m the heartbeat rhythm averages 32 beats per minute, i.e., is decelerated more than in younger puppies under the same conditions.

The above data indicate that under identical conditions of progressively developing oxygen insufficiency, the nature of the change in the cardiac rhythm is a direct function of the age of the animal, in agreement with literature data (Arshavskiy, Krasnovskaya, Krasnovskaya and Mayatnikova, Lauer, Yenikeyeva and others).

Changes in EKG indices. In puppies of the first age group (1-6 days), the EKG indicators changed as follows under the influence of increasing oxygen deficiency: the amplitude of the P-wave remained virtually unchanged to an "altitude" of 10 thousand meters; at the "altitude" of 15 thousand meters, its height dropped by more than half in 71.6% of the experiments to average 1.3 mm (as against a norm of 3.1 mm). The R wave changed insignificantly up to an "altitude" of 12 thousand meters and then began to drop in more acute stages of hypoxia in 71% of cases (from a normal value of 7.1 to 3 mm at the "altitude" of

15 thousand meters); in 13% its height did not change and in 16% the R-wave increased slightly.

In 54.7% of the cases of progressive hypoxia, the S-wave subsided beginning at an "altitude" of 10,000 meters, did not change in 35.4% of cases and increased slightly in 9.9% of cases.

The amplitude of the T-wave changed very insignificantly in deepening hypoxia (up to and including its most acute stages) in the newborn animals (in 48.6% of cases, its height dropped slightly, in 32.2% it did not change and in 19.2% it increased slightly, and then only at the "altitude" of 14-15 thousand meters). The sharpening of the T-wave, which characterizes myocardial hypoxia in full-grown dogs, did not appear in the newborn puppies even at critical degrees of oxygen insufficiency. The typical criteria of acute oxygen insufficiency in newborn puppies are, instead, subsidence and rounding of the T-wave.

The duration of the P-Q interval in hypoxia at the early age is distinguished by constancy, and only at high "altitudes" (above 12 thousand meters) do we note an insignificant prolongation - from the normal value of 0.07 sec to 0.10 sec.

The change in the duration of the ventricular complex (Q-T interval) is clearly expressed in hypoxia in newborn puppies, and is characterized by the following indices: up to an "altitude" of 10-11 thousand meters, we observe a progressive increase in the interval (from 0.18 sec under normal conditions to 0.24 sec). At deeper stages of hypoxia, the prolongation of the Q-T interval increases more sharply and at the "altitude" of 15 thousand m it is 0.36 sec, i.e., it has doubled from the normal value.

The increase in the duration of the ventricular complex in newborn puppies suffering from oxygen insufficiency takes place basically as a result of an increase in the duration of the S-T interval, as well as

distension of the T-wave.

The hypoxic EKG changes in puppies of the second age group (two weeks) show the following pattern: the P-wave shows a tendency to become smaller with increasing oxygen insufficiency, as in newborn puppies - beginning approximately at the "altitude" of 10-11 thousand meters.

In a majority of cases (64%), the R-wave subsides, and in the others (36%), its amplitude remains unchanged; the R-wave was not observed to become higher in two-week-old puppies during hypoxia. As a rule, as the hypoxia became more severe in the two week old puppies up to an altitude of 4 thousand meters, the amplitude of the R-wave dropped slightly, then stabilized and increased a little at "altitudes" of 14-15 thousand meters, but did not reach its initial value.

In two week old puppies suffering from hypoxia, the S-wave remained unchanged in 53% of cases, diminished slightly in 29.4% of cases and rose slightly in 16.3% of cases of acute oxygen shortage.

Under the same experimental conditions, the T-wave began to increase gradually in 70.5% of cases at the "altitude" of 7 thousand meters, reaching 6.7 mm or 160% of its initial value at the "altitude" of 13 thousand m; in 29.5% of cases, the amplitude of the T-wave showed no change; in the two week old puppies we were unable to detect a drop in the height of the T-wave, as was noted in the newborn puppies suffering from hypoxia.

In our design of the experiment, the duration of the P-Q interval showed practically no change in two week old puppies as an effect of hypoxia. The duration of the ventricular complex in these animals shortened slightly at medium "altitudes" from 4 to 7 thousand meters) (in which they differ from puppies of the first age group), and then, as the hypoxia was aggravated, it became longer, reaching 0.25 sec or

150% of the initial value at the "altitude" of 15 thousand meters.

In puppies of the third age group (1.5 months), the changes in the EKG as an effect of hypoxia takes the following pattern: the P-wave changed in about the same way in hypoxia as in younger puppies. However, the change in the amplitude of the R-wave in hypoxia is definitely age-connected. In the month-and-a-half-old animals (in contrast to the puppies of the first two age groups), the R-wave definitely diminishes as hypoxia develops. At this age, the decrease in the amplitude of the R-wave begins at an "altitude" as low as 5 thousand meters. While the height of the wave is 60% of the initial value in newborn puppies at the "altitude" of 15 thousand meters, it is only 44% of the norm in the month and a half old puppies at the same altitude.

The height of the T-wave varied as follows in month and a half old puppies suffering from hypoxia: up to an "altitude" of 10 thousand meters, it did not change substantially, but in more severe hypoxia (in contrast to the two week old puppies), it rose sharply, reaching a maximum at an "altitude" of 12 thousand meters (190% of the norm); in even deeper hypoxia at "altitudes" of 13-15 thousand meters, the T-wave in these puppies decreased slightly but still remained in excess of its initial value.

The duration of the P-Q interval in puppies one and a half months old was extended from 0.06 to 0.12 sec at high "altitudes" (11-15 thousand meters), i.e., it was longer than in younger puppies under the same conditions.

At medium "altitudes" (from 6 to 10 thousand meters), the Q-T interval was markedly shorter, but beginning at an "altitude" of 11-12 thousand meters, it was again prolonged. The shortening of the Q-T interval noted at medium "altitudes" in the month and a half old puppies is more strongly manifest than in the two-week-olds, while the increase

in the duration of the ventricular complex that takes place in the older puppies in the terminal phase of acute hypoxia is considerably less distinct than in the newborn animals.

The changes in the size and form of the EKG deflections and the duration of the record's intervals at acute degrees of hypoxia in month and a half old puppies have begun to acquire the features observed in these changes in full-grown dogs and man. Thus, in month and a half old puppies brought to "altitudes" of 10-15 thousand m, we began to observe an increase and sharpening of the T-wave, the S-T segment was displaced above the isoelectric line, and in occasional cases the ventricular complex acquired a definitely single-phased appearance.

Thus, in analyzing the results of the investigations conducted, we must emphasize the presence of definite and clearly manifest age-connected peculiarities in the changes of the EKG in puppies under the influence of oxygen shortage. During the first few days after birth, we were unable to detect either the phenomenon of partial or total blockage or a rise and sharpening of the T-wave, or even fusion of the ventricular-complex peaks into a single-phase curve even in the most severe stages of hypoxia, i.e., the EKG changes that characterize disturbance of cardiac activity during oxygen insufficiency in full-grown animals were absent.

The data that we obtained make it possible to characterize the EKG changes in newborn puppies suffering from hypoxia in the following manner. When the organism is subject to slight and moderate degrees of hypoxia during the first few days after birth, we observe relative constancy of the EKG indicators; in acute stages of oxygen insufficiency, and particularly in the terminal stage, we note subsidence and rounding of the T-wave, as well as a distinct increase in the duration of the ventricular complex, basically in the form of longer S-T segment and T-

wave.

It is generally known that the heart of a newborn animal is distinguished by high stability against various types of disturbances by virtue of its well-developed automatism. It is necessary to note, however, that the absence in the newborn of the EKG changes typical for oxygen insufficiency in full-grown animals does not signify the absence of disturbances to cardiac function, but rather indicates the presence in these individuals of age-connected singularities in the pathology of the heart, singularities connected with the developmental state of the heart itself, extracardial factors and the nature of the tissue-metabolic processes.

ON THE INFLUENCE OF ACUTE HYPOXIA IN CHANGING THE ACID
RESISTANCE OF ERYTHROCYTES OF THE GROWING ORGANISM

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(Kiev)

In response to hypoxia, the organism develops a set of complex adaptation processes, calling upon various functional systems. A number of reactive changes also occur in the erythrocyte system of the blood. Among other things we observe in ephemeral acute hypoxia a fast reflex reaction in which the erythrocytes present in the organism are redistributed. The erythrocyte reserve is expelled into circulation from the various blood depots. The increase in the erythrocyte level increases the oxygen capacity of the blood, and, having thus expanded its transport capacity (transfer of oxygen), raises the resistance of the organism to oxygen shortage.

The erythrocyte redistribution reaction in acute hypoxia has been studied for a long time only from the aspect of its quantitative indices, i.e., through the change in erythrocyte count and hemoglobin content. Up to this time, little study has been devoted to qualitative changes in the erythrocytes as a result of oxygen starvation.

One of the methods for qualitative evaluation of the erythrocytes consists in determining their resistance to various types of injurious influences. Many methods exist for determining erythrocyte stability. Their osmotic, chemical, electrical, radiation, thermal, ultrasonic and mechanical resistances are determined. Among all of these methods, that in which the chemical (acid) resistance of the erythrocytes, a

method based on photoelectric registration of the dynamics of the hemolytic process, has come to the fore in recent years. The hemolysis is produced by treating the erythrocytes with a dilute (0.004 N) solution of hydrochloric acid. A graphic representation of the percentage distribution of the erythrocytes over the time of their decomposition in a thermostable hemolytic medium is known as an erythrogram. The technique was proposed by I.I. Gitel'zon and I.A. Terskov in 1957.

Recently, a number of papers have been published by authors who used this method in their investigations (A.I. Vorob'yev, O.S. Golosov, L.S. Solov'yeva, R.N. Shatilova, L.K. Kozlova, Yu.V. Kudryashov, M.L. Kukushkin, V.P. Makarov, S.E. Mochkina, C.A. Bershteyn and others). The erythrogram technique was approved at the All Union Conference on the Biophysics of Erythrocytes in 1959.

The stability of erythrocytes depends on many factors. The originators of the erythrogram technique take the position that the principal factor determining the stability of erythrocytes is their age. The peculiarities of erythropoiesis also influence the stability of the erythrocytes. The physical chemical state of the plasma and the erythrocytes is also important. In acute hypoxia, there is a possibility of a change in the age composition of the erythrocytes due to their emergence into the circulating blood from the various depots, the arrival of young erythrocytes from the bone-marrow reserve and older ones from the spleen.

Applying the erythrogram technique, I.I. Gitel'son and I.A. Terskov (1960) found in experiments on guinea pigs and white mice that in the initial phase of acute hypoxia, the stability of the erythrocytes does not diminish and may even rise due to the induction of younger forms into the blood stream. As the hypoxia is aggravated, we detect a drop in the stability of the erythrocytes. Studying the causes of the

diminished stability of the red blood cells, the authors set up experiments in two variants in which models of hypocapnic and hypercapnic acute hypoxia were created to obtain data indicating that the drop in stability is not associated with a change in the pH of the blood. The authors conclude that the drop in the stability of the erythrocytes is due to the accumulation of incompletely oxidized metabolism products in the blood. Together with this assumption, they do not exclude the possibility of injury to the erythrocytes by other disturbances in the physicochemical state of the plasma. All of these problems relating to changes in the qualitative composition of the erythrocytes in acute hypoxic states are of great interest, but the study that has been given them has been completely inadequate .

Recently, differences in the organism to oxygen starvation at early ages and in maturity have definitely been established.

First to report on this matter was P. Ber (1878). On more than one occasion, N.N. Sirotinin noted a drop in resistance to oxygen deficiency during the process of the organism's phylogenetic and ontogenetic development.

In his monograph entitled "Voprosy patofiziologii gipoksischeskikh sostoyaniy novorozhdennykh" [Pathophysiological Problems of Hypoxic States in the Newborn], N.V. Lauer (1959) analyzes literature data and a large volume of his own experimental results to arrive at the positive conclusion that young animals and newborn children show relatively high resistance to acute hypoxia.

There are also differences in the qualitative composition of the blood between early life and maturity. F.A. Lokshina (1937) found that the osmotic resistance of erythrocytes during the nursing period is higher than in adults, chiefly as a result of an increased number of highly stable forms with the same number of low-stability forms. Com-

paring the osmotic resistance of the erythrocytes in premature infants and nursing children, she detected higher stability of the red blood cells to hypotonic solution in the former category. This rise in the stability of the erythrocytes was due to an increase in the number of high-resistance forms and a drop in the content of low-resistance forms.

I.I. Gitel'zon, I.A. Terskov and L.V. Tikhanovich (1960) established in experiments on rabbits that the acid resistance of the erythrocytes is considerably higher in embryonic and newborn rabbits than in the full-grown animals. The erythrograms of the offspring are characterized by a sharp right shift due to the highly stable forms. During the process of embryonic development, the qualitative composition of the blood cells being produced changes continuously in the direction of lower erythrocyte stability, but by the neonatal period, the resistance of the erythrocytes still remains considerably higher than that observed in maturity.

Taking into account the fact that the organism's reaction to oxygen starvation is different in early life and maturity, and bearing in mind data on the age-connected peculiarities of the qualitative erythrocyte composition, it is natural to conclude that the nature of the shifts in the qualitative composition of the blood erythrocytes will also show differences in acute hypoxia between these age phases. We have been unable to find any information on this question in the literature available to us.

We perceived our task in the study of the erythrocyte reactions in the growing organism during acute hypoxic states. With this objective, we decided to use the erythrogram method to obtain an evaluation of the qualitative shifts in the erythrocyte composition of the blood in addition to the conventional quantitative characterization of the erythrocyte reactions. The present paper presents the first results of our in-

vestigations.

Experiments were run on 18 dogs, of which 6 were sexually mature (1.5-2 years), 6 newborn, 6 two-weeks-old and 5 a-month-and-a-half-old, the latter taken from a group that had "ascended" in the low-pressure chamber one month earlier, at the age of two weeks. Acute hypoxia was produced by "elevating" the animals in the low-pressure chamber, administration of oxygen-deficient gas mixtures through a spiograph, and constricting the trachea.

In analyzing the erythrogram, we worked from the recommendations of A.I. Vorob'yev and took the difference between the first and last readings of the optical density of the erythrocyte suspension undergoing hemolysis as the working figure.

The spherulation phase of the erythrocytes is not differentiated by this calculation method. In evaluating the erythrogram curve, we took into account the length of the erythrogram, the time and percentage of the maximum, premaximum and postmaximum lysis of the erythrocytes, the percentage content of low-stability (0.5-2 min), medium-stability (2.5-3.5 min) and high-stability cells available in the interval from 4 min prior to the end of hemolysis. These time intervals characterize the stability of the three basic groups of erythrocytes and are admissible as a qualitative criterion only for evaluation of canine erythrocytes, since the erythrograms of other species of animals may differ and the evaluation of the relative stability of the erythrocytes from their hemolysis times may differ with respect to the intervals adopted.

The originators of the acid-erythrogram technique found that the stability of mammalian erythrocytes (with respect to 0.004N HCl) lies in range from 1-20 min (1960).

Two series of experiments were run on full-grown dogs. In the first series, four full-grown dogs were "elevated" in the low-pressure chamber to an "altitude" of 5000 m. The total time taken for the "ascent" and "descent" with three-minute "plateaus" every 1000 m came to about 44 min. The 5000-meter altitude is physiologically equivalent to breathing air containing 11.2% of oxygen. The blood specimen was taken immediately after the "descent."

The results of the experiments indicated that in three of the dogs, the number of erythrocytes in 1 mm³ rose by 0.2-1.0 million, while the

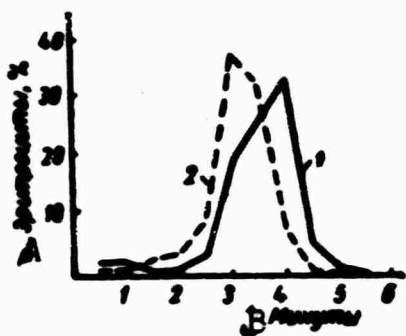


Fig. 1. Left shift in erythrogram of the full-grown dog Shkhel'da after an "ascent" to 5000 m. 1) Before "ascent"; 2) after "ascent." A) Erythrocytes, %; B) minutes.

stability decreased due to the larger number of low-stability cells and the smaller number of highly stable forms (Fig. 1). In one dog (Saturn), the number of erythrocytes dropped by 1.4 million. Here it was observed that the stability of the erythrocytes in this animal had changed somewhat due to the smaller number of low-stability cells (from 8 to 6.5%) and an increase in the number of highly stable cells (from 1.3 to 2.6%).

In the second series of experiments, in which the spirometer was used, a more severe state of hypoxia was induced.*

When 10 minutes had elapsed from the start of the experiment, at which point the oxygen content in the inspired air had fallen to 11-14% (which corresponds to an altitude of 3400-5000 m) and the oxygen saturation of the blood had decreased to 73-89%, it was not possible to detect any distinct tendency to increase the number of erythrocytes in the 6 full-grown dogs used in the experiment. On the other hand, the stability of erythrocytes had clearly diminished by this time. This was manifest in a change in the erythrogram curve due to an increase in the content of low-stability cells and a left shift in the medium-stability range. At 15 min from the start of the experiment, the oxygen concentration in the inspired air had dropped to 6.1-9.7% (which corresponds to an altitude of 6000-9400 m). The oxygen saturation of the blood fell to 43-75%. During this phase, all dogs were observed to have erythrocyte counts higher by 0.2-1.0 million, and a tendency toward higher erythrocyte stability was noted.

At 17-29 min from the start of the experiment, the oxygen content in the inspired air was down to 4.2-6.6%, which corresponds to an alti-

tude of about 9500 m, while the oxygen saturation of the blood had fallen to 24-40%. At the end of the experiment, there was a distinct erythrocyte reaction. Three of the dogs out of the six showed erythrocyte counts higher by 1.0-1.4 million, while the other three showed 0.7-0.8-million increases. At this time, the increase in erythrocyte stability and its approximation to the initial value was clearly in evidence. It is possible that this is due to an influx of fully viable cells from the reserve.

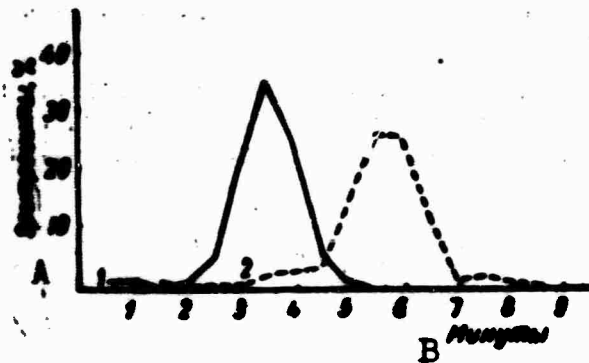


Fig. 2. Normal erythrograms of the full-grown dog Kazbek (solid line) and newborn puppy No. 2 (dashed line). A) Erythrocytes, %; B) minutes.

The results of 10 experiments on 6 full-grown dogs and 17 experiments on 12 puppies indicated the existence of age-connected differences in the qualitative erythrocyte composition. The erythrograms of newborn puppies differ sharply from those of full-grown animals (Fig. 2). From the erythrograms shown for the adult and newborn animals, it can be seen that the erythrogram of the "normal" newborn animal is shifted quite far to the right and drawn out to 8.5 min. In full-grown dogs, the time for total lysis of the erythrocytes is 5 ± 0.5 min. In the blood of newborn puppies we observed up to 70-78% of highly stable erythrocytes.

In inducing acute hypoxia in the puppies, we took their elevated resistance to oxygen starvation into account. Puppies of all age groups

were "elavated" to 8000 m with a 30-minute exposure. In some of the experiments the "height of the ascent" reached 10,000-12,000 m. In two of the six newborn puppies, acute hypoxia was induced by compressing the trachea (asphyxia). Our investigations showed that irrespective of the method used to induce acute hypoxia in newborn puppies, peculiar changes were to be observed in the qualitative erythrocyte picture. Under the conditions of moderate (8000 m) and severe hypoxia (asphyxia), the stability of the erythrocytes of the newborn puppies remains unchanged or even rises significantly. A sharp right shift in the erythrogram, with the maximum displaced to the right, was observed in three puppies out of the six (Fig. 3). In none of the full-grown dogs did we observe such right shifts in the erythrogram in acute hypoxia. In one puppy ("ascent" to 10,000 m), we found signs of a slight left shift in the interval of medium stability. We did not observe any distinct tendency to increase the erythrocyte count in the newborn puppies after acute hypoxia.

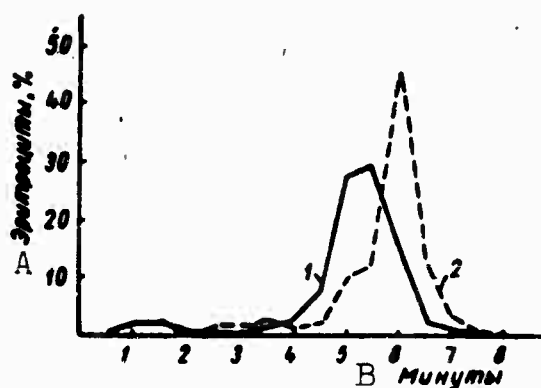


Fig. 3. Right shift in erythrogram of newborn puppy No. 3 after "ascent" to 8000 m with exposure lasting 30 min. Legend same as for Fig. 1. A) Erythrocytes, %; B) minutes.

In the two-week-old puppies we were unable to detect preservation or increase of erythrocyte stability with the same distinctness as in the newborn individuals. Only in two of the six two-week-old puppies did we observe an increase in erythrocyte stability. In the other four, the erythrocyte stability diminished as a result of the left shift in

the medium-stability interval (in one case, with a left shift of the maximum by 0.5 min, a decrease in the number of highly stable forms and an increase in the number of low-stability forms).

In the quantitative shifts, we noted a tendency to an increase in erythrocyte count. In contrast to the newborn and two-week-old puppies, all five of the month-and-a-half old puppies tested showed a considerable drop in the stability of the erythrocytes with a shift in the decomposition maximum by 0.5 min, an increase in the content of low-stability cells by 5-7% and a 2-8 or even 23% decrease in the highly stable forms. The quantitative shifts were of different kinds. In some puppies, the number of erythrocytes showed practically no change, while in others it was shifted toward a decrease or increase with small deviations from the initial value.

Thus, the data that we obtained indicate the existence of age-connected differences in the changes that appear in the qualitative erythrocyte composition during acute hypoxia. These differences come particularly clearly to the fore when we compare the erythrocyte reactions in full-grown and newborn animals. It can also be observed that there are differences between early life and maturity in the quantitative characteristics of the erythrocyte reactions as well. While almost all of the full-grown dogs showed the same type of shift in the number of erythrocytes at a given depth of acute hypoxia, there was no such consistency among the puppies.

It is necessary to note a divergence of our data from those of I.I. Gitel'zon and I.A. Terskov as regards the change in erythrocyte stability in the initial phase of acute hypoxia and the later, more profound phases (experiments on guinea pigs and white mice). In the experiments on full-grown dogs, we noted a drop in the stability of the erythrocytes in the initial phase and recovery of stability (approach to the initial

value) in the deeper phases. This is perhaps due to the specific peculiarities of the experimental animals.

The complex nature of the changes in the organism's internal medium during acute oxygen starvation makes it extremely difficult to establish the causes for the change in the acid-resistance of the erythrocytes in this state. To render palpable the nature of the qualitative changes in the erythrocytes, it is necessary to take into account that the resistance of the erythrocytes to various injurious factors determines certain of their properties. Hence it is very important to know exactly what properties of the erythrocytes are determined by its stability to dilute-acid hemolysis.

Our attention is also drawn to the disagreement between the rise in stability of the basic erythrocyte group and the absence of an increase in erythrocyte count. This lack of correspondence, which we observed in newborn puppies undergoing acute hypoxia, makes it difficult to account for the right shift in the erythrogram by arrival of more stable erythrocytes in the bloodstream.

The erythrogram technique is valuable for its objectivity and the possibility of differentiating the erythrocytes qualitatively. Use of this method to determine the qualitative characteristic of the erythrocyte shifts in hypoxia is important in itself, but establishment of the physiological significance of these shifts is of particularly great interest. At the present time, however, this question is still unclear and further research will be necessary to resolve it.

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The experimental data represent a fragment of a complex study made of adaptive processes to hypoxia by N.V. Lauer, A.Z. Kolchinskaya, V.V. Turanov and M.M. Seredenko.

SIGNIFICANCE OF HYPOXEMIA IN THE PATHOLOGY OF CHILDHOOD

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Hypoxemia and the closely related respiratory insufficiency lie at the roots of childhood pathology in a number of illnesses. During all of its age phases, the organism of the child is particularly sensitive to disruption of gas metabolism.

At the present time, infant mortality, usually during the first few days of life, occupies the foremost position among all causes of death in childhood. As we know, this problem has been the object of penetrating study on the part of obstetricians and pediatricians. Of particular importance to the pediatrician is the so-called intrauterine asphyxia, which causes the development of a number of disorders.

The problem of anoxia or hypoxia in the fetus is of exceptionally great importance, since preventive measures against birth injuries are related to it. It has been established that intrauterine asphyxia and birth trauma are very closely related to one another.

Experimental studies devoted to the problems of artificial intrauterine asphyxia indicate the development, as a result of oxygen starvation, of significant changes in the blood vessels and particularly those of the brain and lungs.

Intrauterine asphyxia may be of various origins, i.e., it may take the form of anemic, toxic, or circulatory hypoxia depending on the nature of the disturbance to the normal course of pregnancy.

According to data from the major birth clinics of Moscow, intra-uterine asphyxia has caused stillbirths in 32% of cases. Moreover, even after the child has been born (on the average, in up to 40% of cases), infants with confirmed diagnoses of intrauterine asphyxia may develop various forms of pathology, preferentially respiratory.

At the VIII International Congress of Pediatricians (Copenhagen, 1957), it was proposed that a number of forms of neonatal anoxia be distinguished - forms with disturbances to functions of the central nervous system and forms with derangement of functions of other organs and systems.

In view of this great importance of respiratory insufficiency during the first few days of the infant's life, we made an investigation of newborn infants that had come to the clinic with developed pneumonia and whose anamneses indicated various forms of asphyxia. We established that fertile soil was usually provided for the development of pneumonia in children in their first month of life by a special state of the lungs - the so-called pneumonosis.

The pneumonosis is associated with the presence of vascular dysfunction, extravasation and minor atelectasis and, as a rule, these changes are observed in children who have survived intrauterine and postnatal asphyxia.

On analysis of the external respiration indicators in a group of children in the first month of life, we were able, on the basis of pneumography data, to establish extremely superficial respiration as characteristic for this group of children - respiration closely resembling the Cheyne-Stokes and Kusmaul types.

As we know, one of the early symptoms of pneumonia in children less than a month old is early cyanosis. The presence of cyanosis has, so to speak, predetermined the development of hypercapnia and hypoxemia,

i.e., impoverishment of the organism in oxygen coupled with an increase in carbon dioxide concentration. However, on dynamic study of the gas composition of the blood, we were able to establish that the so-called hyperoxia, i.e., an increase in oxygen content, is observed in newborn infants and particularly in premature infants when the pneumonia develops. Also established was an increase in the amount of reduced hemoglobin, which indicates significant changes in oxidation-reduction processes.

Closely related to the above facts are problems of oxygen therapy and aërotherapy. Following the use of massive oxygen therapy - prolonged residence of the child in an oxygen tent in an atmosphere with a high oxygen content - reports began to appear in the literature indicating that prolonged oxygen therapy was dangerous and might result in the development of retrobulbar dysplasia and incurable blindness in the child.

It is known from practice that it is precisely among children in the first month of life, and among the prematurely born in particular, that oxygen therapy applied by the jet method from an oxygen bag may result in collapsoid with general pallor and adynamia.

In the light of our investigations, which indicate a high incidence of hyperoxia in children of this age group, the negative reaction described becomes understandable. Together with this, extensive aërotherapy normalizes the pneumogram and has a favorable effect on the gas composition of the blood.

Antibiotic and sulfa therapy produce no substantial effect on either the external respiratory indices or the gas composition of the blood, but complex treatment - the use of biogenic stimulants in combination with metered oxygen therapy with oxygen contents no greater than 40% in the inspired air - does; as we know, in children in the first month of

life, the variation of the blood gas composition does not have a strictly expressed hypoxemic or hypercapnic nature, and this must be taken into account in prescribing treatment.

The higher we go on the age ladder, the more distinctly is the combination of classical symptoms determining respiratory insufficiency drawn. In children older than 3 months of age, hypoxemia becomes clearly manifest, i.e., the oxygen content in the arterial and venous blood drops, and hypercapnia emerges, i.e., the carbon dioxide content rises.

Use of oxygen therapy for children of this age group is a highly effective method of treatment in the intricate system of complex measures taken against pneumonia.

As we know, intestinal toxicoses are accompanied by respiratory insufficiency, which frequently results in acute development of hypoxemia or develops slowly, contributing to the appearance of hypoxemia at a later time, but nongaseous acidosis, a consequence of which is occasionally the development of gaseous acidosis, i.e., hypercapnia, is found at the roots of this group of disorders.

When the pneumonia takes a grave course in older children, respiratory hypoxemia and hypercapnia are observed during the first few days of the illness, and are accompanied by changes in such indices of the oxidative processes as the vitamin C level and the levels of thiamine, carboxidase and glutathion. However, the difficult breathing observed in these children cannot be accounted for simply by the accumulation of carbon dioxide. Deceleration of the oxidation process in the tissues is of enormous importance in its development; it results in the formation of products that have not been fully oxidized - among others, lactic and pyruvic acids.

We conducted our observations under dynamic conditions and made an effort to juxtapose them with the development of relapses, protraction

of the pneumonia and its transition to the chronic form. We succeeded in establishing that the younger the child, the more slowly is the affected blood gas composition restored, despite normalization of the external respiration as registered by the pneumogram and the apparent onset of clinical recovery. The age-connected peculiarities of the adaptive reaction in hypoxemia are based on this fact.

The prolonged superficial respiration characteristic for all forms of respiratory disorders in children less than a month old is, according to Kholden, sufficient in itself to fatigue the respiratory center, with the result that respiration becomes even shallower and its frequency quickens. The oxygen expired here is a kind of recognition method for determining the reserve strength of the respiratory center and, in particular, inadequate development of the reflexogenic zones - sino-carotic and aortic - which is responsible for the weak adaptive reaction in this group of children.

Our clinical observations provided a basis for experimental studies carried out over the course of the last few years at the Central Scientific Research Laboratory of the 1st Moscow Medical Institute, Order of Lenin, with the participation of our colleagues A.S. Chechulin, A.N. Dombrovskiy and A.A. Rogov.

Inducing artificial oxygen starvation in rats at various ages, we determined the nature of respiration, the blood reaction, and erythrocyte diameter on these animals and then subjected their organs to morphological study after certain intervals of time had elapsed in acute oxygen starvation.

We established that newborn rats survived longer residence in a medium deficient in oxygen than the older animals in spite of their poor over-all adaptation, a result of their having gone over to anaerobic respiration.

The older the animal subjected to the experiment, the more distinct were its adaptation mechanisms and the more strikingly did the pattern of reaction on the part of the central nervous system emerge in the form of restlessness and spasms of the clonic and tonic types.

On morphological examination the organs of animals that had been subjected to acute oxygen starvation, a significant reaction on the part of the vascular and interstitial tissues of the lungs, blood vessels and parenchyma of the heart, liver and kidneys was observed (Fig. 1).

Thus, our hypotheses to the effect that asphyxia sets up a premonitory state for the development of pneumonia was confirmed by the experiment conducted (Fig. 2).

Under the conditions of the oxygen-starvation experiment, we established progressive development of a reaction on the part of the pulmonary interstitial tissues in the form of emphysema, swelling and solution of collagen fibers and subsequent development of sclerosis, i.e., we observed the changes typical of chronic interstitial pneumonia (Fig. 3).

Having established the inadequacy of local changes in the organs in oxygen starvation and the survival times of the animals, we subjected the tissues of a number of organs to histochemical analysis. We determined the activity of the oxidation-reduction process in the organs and tissues, i.e., essentially we attempted to investigate tissue respiration (Fig. 4).

Reactions to certain flavin enzymes and to cytochrome oxidase were also used. As a result of these investigations, we established that oxygen starvation causes diffusion of the respiratory enzyme out of the intracellular formation and that such pharmaceutical agents as vitamin B₁ raise the activity of the oxidation-reduction enzyme in the

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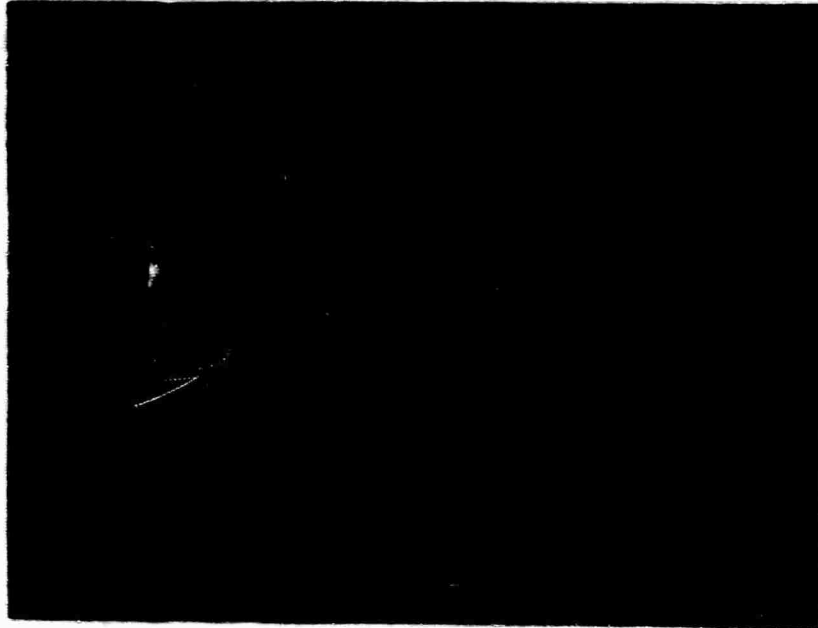


Fig. 1. Lung of 3-day old rat (2 hours of oxygen starvation). Thickening of interalveolar partitions due to proliferation of cells with basophilic protoplasm and hypochromic nuclei; transsudate in cavities of alveoli (Stain: hematoxylin-eosin, magnification 10 x 20).

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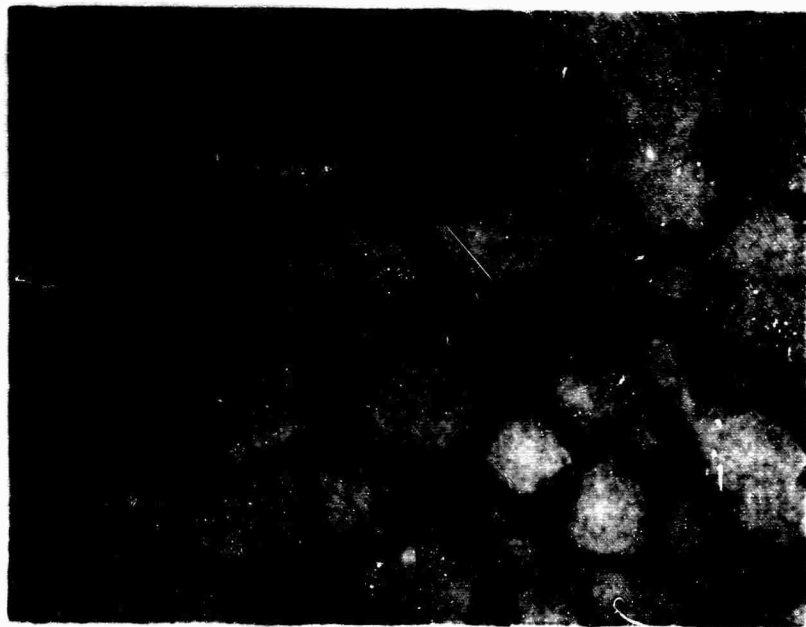


Fig. 2. Lung of 3-day-old rat (3 hours of oxygen starvation). Coarsening of argyrophilic fibers in vessel walls, increased argyrophilism of reticular fibers in alveolar walls (impregnation with silver according to Foote, magnification 10 x 10).

lung, heart, liver and kidneys only in animals a few days old.

Our investigations would not have been complete if we had limited ourselves to respiratory pathology, in which the classical hypoxemia and hypercapnia associated with disturbances to external respiration

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Fig. 3. Lung of 25-day-old rat after 28 days of oxygen starvation. Sclerosis of interalveolar partitions (Van Gieson staining, magnification 10 x 10).

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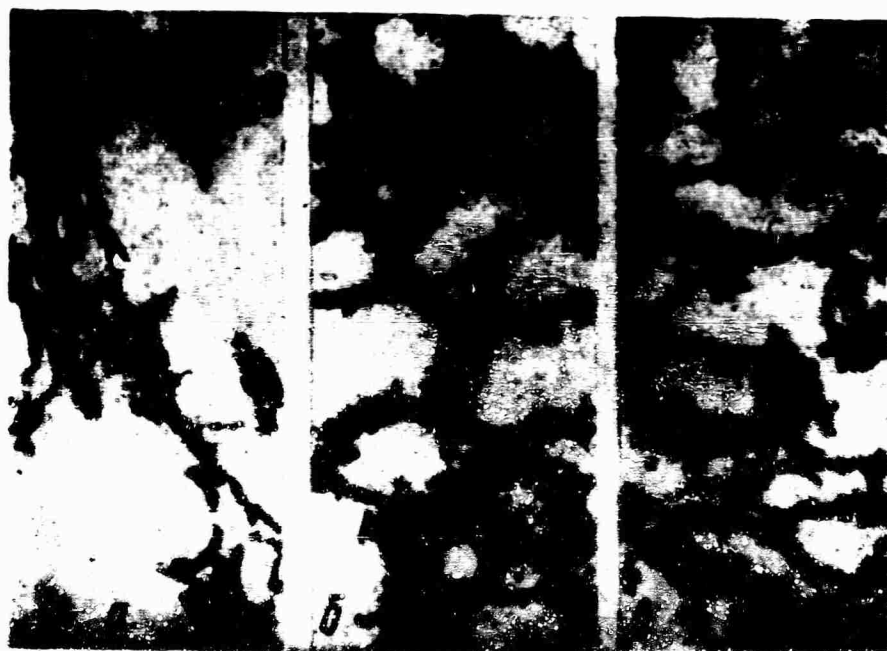


Fig. 4. Lung of 3-day-old rat. a) Control (normal animal); b) after acute oxygen starvation; c) after acute oxygen starvation against a background of vitamin B₁ injection (reaction with nitrotetrazol to DPN diaphorase).

come more actively into evidence, i.e., shortness of breath, coughing, lowered respiratory volume indicators, and the like. For comparison, therefore, we made an investigation of the state of the blood gases and external respiration in a group of children with cardiovascular pathology by taking under observation children who were suffering from rheu-

matism and at various stages in its course. In the acute phase of rheumatism, we established an infectious allergy without distinct injury to the cardiovascular system, together with hypercapnia and a low oxygen content in the venous blood. At the same time, the content of gases in the arterial blood remained almost within normal limits. The hypercapnia was particularly clearly manifest during the first phase of the illness, which to some extent accounts for the typical cyanotic-to-pinkish coloration of the face and mucous membranes. When the process abates, hypoxia, which is characterized by pallor of the integument, is aggravated. At the same time, the external respiration indices show virtually no change, so that we may assume that the disturbance to the gas composition of the blood in rheumatism without manifest cardiac insufficiency is due to significant shifts of the metabolic processes during precisely the acute phase of the rheumatism and to disturbed vascular permeability.

With rheumatic injuries to the heart accompanied by clinical symptoms of varying degrees of insufficiency, there is a manifest hypercapnia, which becomes more severe as the circulatory insufficiency develops. This indicates a circulatory nature for the hypoxemia associated with disturbed hemodynamics.

In our opinion, the disturbances to gas metabolism observed in the extraparoxytic phase of rheumatism, particularly in children suffering from chronic tonsillitis. In such children, dynamic investigation revealed a rather stable, if moderate, hypercapnia in the venous blood and, in cases of catarrhal disorders of the respiratory passages and pneumonia in particular, these disturbances of the blood gas composition were aggravated.

Also worthy of attention is the fact that in children going to rural schools, our data indicates that the disturbances to external res-

piration and the gas composition of the blood were considerably less severe not only in the extraparoxysmic phase, but also in cases of rheumatic cardiac failure - an observation to be accounted for by the long time that they have spent in the fresh air.

We conclude that our observations justify giving particular attention in cases of pathogenetic treatment to manifest or latent hypercapnia and hypoxia occurring in various childhood illnesses.

The aerotherapy widely employed in children's clinics, convalescence in sanatoria of patients suffering from recidive and chronic pneumonias and progressive healing of rheumatism sufferers in rheumatism sanatoria all bear witness to the expediency and effectiveness of these measures.

ON CERTAIN PECULIARITIES OF THE REACTION OF THE AGED ORGANISM TO
ACUTE HYPOXIA

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(Kiev)

Literature data on the features of the reaction produced by an organism to oxygen insufficiency at advanced ages are not extensive. At the same time, this problem has recently been attracting attention on the part of numerous investigators. There are references to the effect that physiological age is in itself characterized by the presence of a hypoxic state in the organism (Mil'man, Derviz, Sirotinin). Oxygen starvation of the organism is particularly aggravated in various illnesses frequently observed in old age (arteriosclerosis, pulmonary emphysema, and the like), in surgical episodes (thoracic surgery), in cases in which the individual is placed in a medium with inadequate oxygen in the air (travel by air, ascent into the mountains, employment in mountainous regions).

Investigations conducted previously by MacFarland, Kenter et al., Verman and Sebaun, Kolchinskaya, and Simonson have shown that the reaction of the aged organism to hypoxia does not take the same course as the reaction of a middle-aged organism, and that compensation is poorer in old age. However, these studies concern themselves only with specific functions of the organism, and, moreover, only small numbers of test subjects were examined.

The present paper represents part of an investigation devoted to ascertaining the age-connected features of the aged organism's reac-

tions to oxygen insufficiency.

The objects of the investigation were aged white rats 25-30 months old and old dogs, aged 12-17 years. Experiments were run simultaneously (for comparison) on corresponding animals in the prime of their lives. Hypoxia was induced either by rarefaction of the air in a low-pressure chamber or by administration of gas mixtures with progressively lower oxygen contents. The experiments were conducted on unanesthetized animals used to the experimental situation, in a state of relative rest.

The studies conducted showed that as the organism ages, its resistance to oxygen deficiency diminishes appreciably. Our experiments confirmed the data obtained earlier by A.Z. Kolchinskaya and then by N.V. Lauer and A.Z. Kolchinskaya on a lowering of the "altitude ceiling" in old rats. In experiments run in the low-pressure chamber (rate of "ascent" 10 m/sec, "plateaus" lasting 5 min), mature rats tied down on their backs died at a "height" of 10,000-11,000 m, while aged individuals died at altitudes of about 9,000 m. Similar results were also obtained on dogs in the unrestrained state. While middle-aged dogs survived "ascents" to "altitudes" of 11,000-12,000 m, old dogs began to perish at an "altitude" as low as 10,000 m, and less often at 11,000 m.

Also characteristic for the old animals was the appearance of ataxia, involuntary micturition and defecation. Thus, while middle-aged showed ataxia at an "altitude" of 7000-8000 m and involuntary micturition and defecation at 9000-10,000 m, the aged dogs manifested ataxia at an "altitude" of 6000 m in the overwhelming majority of cases and involuntary micturition and defecation at "altitudes" of 7000-9000 m.

We also studied changes in external respiration (frequency and depth of respiratory movements, type of respiration, per-minute respiratory volume) and the cardiac activity (from electrocardiographic data)

We made the following observations (Fig. 1) in our study of the

changes in respiratory frequency in mature and aged rats under the conditions of advancing oxygen insufficiency in the low-pressure chamber. As the air was rarefied, respiration speeded up in the middle-aged rats at an "altitude" of 1000-2000 m and reached its maximum at an "altitude" of 5000-7000 m (on the average, 30% as compared with the initial value). As hypoxia advanced, the respiration of these animals was observed to slow down and then, when the "altitude ceiling" was reached it stopped completely. With increasing age, the nature of the reaction to hypoxia on the part of external respiration changed. As in the middle-aged animals, the respiration of the elderly rats quickened and did so at the same "altitudes," although the quickening was less distinct (on the average, 12%); they showed the maximum quickening earlier, at the "altitude" of 4000-5000 m, at which point respiration became less and less frequent until it stopped completely and the rats died.

When the rats "descended" from the "altitude" of 7000 m (second series of experiments), the respiratory frequency gradually returned to its initial values, reaching the norm within 10-20 min after the "descent" for the middle-aged animals and after 20-30 min for the old animals. This suggests retarded normalization of respiration during the post-hypoxic period in the case of the old rats.

The changes in external respiration in oxygen insufficiency have been studied in greater detail in dogs placed in an altitude chamber ("ascent" to 5000 m, rate of "ascent" and "descent" 10 m/sec, "plateaus" of 3 min). It was not possible to identify any particular differences as a function of age in the variation of respiratory frequency. In most of the mature and aged dogs, an increase in the depth of respiration was noted first of all, and only in acute hypoxia did the frequency of the respiratory motions increase. Deepening of respiration resulted in increased pulmonary ventilation (Table 1).

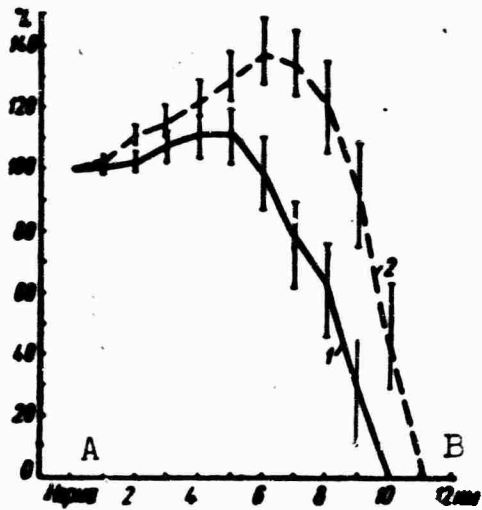


Fig. 1. Change in respiratory frequency in rats on "ascent" in altitude chamber (in % of initial value; average figures). 1) Old rats; 2) middle-aged rats. A) Norm; B) km.

As will be seen from Table 1, pulmonary ventilation began to increase from 1000-2000 m in the middle-aged dogs and rose progressively as the "ascent" continued. The increased pulmonary ventilation fell off again in the mature dogs during the "descent," reaching the initial values quickly. In the aged dogs, although the pulmonary ventilation began to increase at approximately the same "altitudes," the extent of its increase over the first thousands of meters of the "ascent" was larger

than in the middle-aged dogs. In the "descent" from 5000 m, the pulmonary ventilation reached its initial value at the end of the "descent" or immediately afterward in the middle-aged dogs, while in the old animals it remained at the elevated level for a long time.

Studies in which the animals breathed mixtures increasingly deficient in oxygen showed that old age is characterized by a type of normalization of the increased pulmonary ventilation that differs from that observed in mature animals. For example, more time was required for the initial values to be restored. Together with the increase in pulmonary ventilation with advancing hypoxia, an increase in oxygen consumption was also noted (Table 2).

As will be seen from Table 2, the middle-aged dogs showed approximately the same changes in oxygen consumption and pulmonary ventilation during both the increase and normalization of these indicators. In the old dogs, however, a direct relationship between the change in pulmonary ventilation and the oxygen requirement was observed only during the "ascent," while during the "descent" the picture was different.

TABLE 1

Change in Pulmonary Ventilation in Dogs in Altitude Chamber (in ml)

1 Высота (в м)	2 Контрольные собаки				3 Старые собаки			
	4 Казбек	5 Донгуз	6 Шхел- да	7 Сатурн	8 Бель- чик	9 Нерка	10 Жук	11 Чер- ныш
0	2500	2400	1800	2000	2600	3000	3100	2800
1000	2400	2400	2400	2600	3600	3800	4400	2800
2000	3200	3600	2700	3000	4200	4800	4200	3400
3000	3800	3800	3800	2600	4000	4800	5100	4600
4000	4300	4000	4600	4000	4400	7600	5400	5600
5000	5200	4700	5800	5400	5200	7600	6400	12000
12 «Спуск»								
4000	4400	3600	4600	4100	4600	7400	6000	9200
3000	3800	3200	4400	4000	3800	6400	5000	8000
2000	3600	2400	4200	3300	—	5400	5200	5700
1000	3400	2100	3400	2700	3600	5600	4700	5100
0	2400	2200	2800	2400	3000	5000	4400	3800

1) "Altitude," meters; 2) control dogs; 3) old dogs; 4) Kazbek; 5) Don-guz; 6) Shkhel'da; 7) Saturn; 8) Bel'chik; 9) Nerka; 10) Zhuk; 11) Chernysh; 12) "descent."

TABLE 2

Change in Oxygen Consumption in Dogs in Altitude Chamber (in ml per 1 kg of Weight)

1 Высота (в м)	2 Контрольные собаки				3 Старые собаки			
	4 Казбек	5 Донгуз	6 Шхел- да	7 Сатурн	8 Бель- чик	9 Нерка	10 Жук	11 Чер- ныш
0	5.3	6.0	5.7	5.0	5.5	4.1	3.7	5.1
1000	4.5	5.5	6.0	5.3	5.9	4.4	4.6	4.7
2000	6.0	6.9	6.1	5.5	6.3	4.9	—	5.1
3000	6.9	6.6	7.3	4.6	6.1	4.5	4.3	6.2
4000	7.4	6.5	8.3	6.6	6.1	7.3	4.8	6.7
5000	8.3	7.1	9.5	8.3	7.6	7.3	5.5	11.8
12 «Спуск»								
4000	7.7	5.8	8.4	6.9	7.9	7.6	5.7	12.6
3000	7.3	6.2	8.3	6.7	7.5	6.9	5.4	11.0
2000	6.6	5.2	8.0	5.9	—	6.5	6.4	8.8
1000	6.1	4.9	7.2	5.4	7.7	6.7	6.6	8.5
0	4.7	5.4	6.7	5.0	6.8	6.4	6.3	6.0

1) "Altitude," meters; 2) control dogs; 3) old dogs; 4) Kazbek; 5) Don-guz; 6) Shkhel'da; 7) Saturn; 8) Bel'chik; 9) Nerka; 10) Zhuk; 11) Chernysh; 12) "descent."

Firstly, in the "descent" from 5000 to 4000 m, the oxygen requirement of the aged dogs not only did not decrease with the decrease in pulmonary ventilation, but even increased slightly. As the hypoxic effect diminished and then ceased altogether, the pulmonary ventilation of the old dogs did not normalize as well as in the middle-aged dogs; the oxygen requirement returned to the initial values even more slowly than

the ventilation. Despite the significant increase in pulmonary ventilation and oxygen requirement, the oxygen saturation of the arterial blood fell more sharply in the older dogs (Fig. 2). In the initial stage of hypoxia (experiments on the spiograph), no particular differences in the oxygen saturation of the arterial blood were observed in dogs of different ages, but even at an oxygen content of about 13-14% in the inspired air (corresponds approximately to an altitude of 3000-4000 m), the arterial blood in these animals began to show oxygen contents lower than those of the middle-aged dogs, and as the oxygen content in the inspired mixture fell further, it was found to have lower and lower saturations.

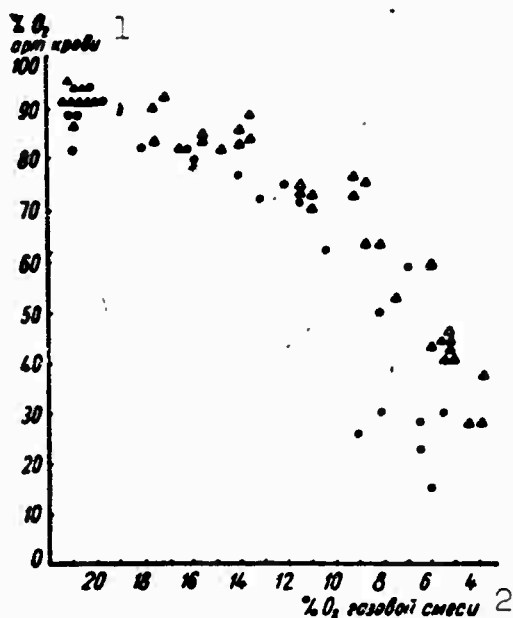


Fig. 2. Change in oxygen saturation of arterial blood as hypoxia develops in dogs. The triangles denote the percentage oxygen saturation of the arterial blood in the mature dogs and the circles the same quantity in old dogs. 1) % of O₂ in arterial blood; 2) % of O₂ in gas mixture.

It is interesting to compare the elimination of oxygen shortage in old and young animals during the post hypoxic period.

It was found that in the middle-aged animals, the pulmonary ventilation, oxygen requirement and oxygen saturation of the arterial blood returned to their initial values within the first few minutes of breathing ordinary air. In the old dogs, however, despite the increased pulmonary ventilation and the elevated oxygen requirement, the phenomenon of hypoxemia does not disappear until air containing a normal amount of oxygen has been breathed for a considerable time (Fig. 3).

As compared with the higher mammals, for which quickening of the cardiac activity by way of adaptation is characteristic in hypoxia, a progressive reduction in the pulse rate

is typical for rats. The investigations that we carried out indicated that under the conditions of the altitude chamber, mature rats maintain their pulse rates at the initial level up to an "altitude" of 4000-5000 m, and then we observe a gradual slowdown of the cardiac activity; at "altitudes" of 8000-9000 m, a sharp drop in the pulse rate begins. In old rats, the gradual decrease in the number of heartbeats begins at "altitudes" of 1000-2000 m, and the precipitous drop is noted at "altitudes" from 5000-7000 m. In a "descent" from an "altitude" of 7000 m, the cardiac activity of the rats normalizes in approximately 20-40 min after "descent," irrespective of the age of the animals.

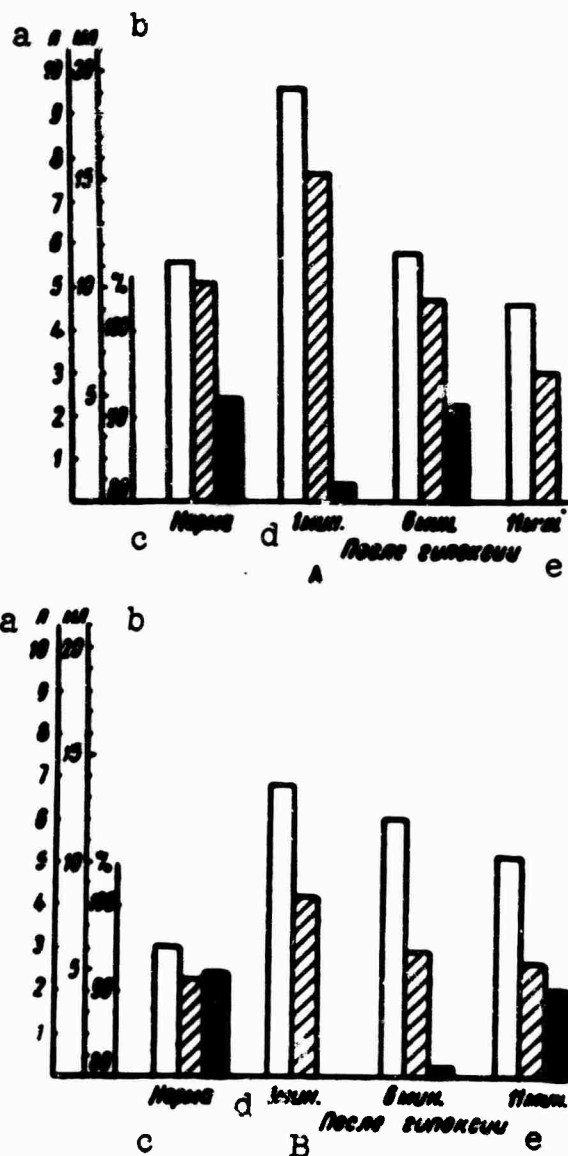


Fig. 3. Variation of pulmonary ventilation, oxygen consumption and arterial-blood oxygen saturation in dogs after hypoxia. Open bars: pulmonary ventilation (in liters); cross hatched bars: oxygen requirement (in ml per 1 kg of weight); shaded bars: percentage oxygen saturation

of arterial blood; A) Mature dog; B) aged dog. a) liters; b) milliliters; c) normal; d) 1 min; e) after hypoxia.

The changes in the electrocardiogram indicate higher sensitivity to hypoxia in the heart of the old organism as compared with middle age. In middle-aged rats at "altitudes" of 4000-6000 m, we observe an increase in the R and T-waves, and, beginning at an "altitude" of 7000-8000 m, a sharp change in the S-T line. It took the form of a convex arc situated above the isoelectric line and frequently rose higher than the R-wave. The same type of change was also observed in the old rats, but the "altitude" at which these changes were observed was "lower," at 1000-2000 m.

When experiments were conducted in the altitude chamber, an increase in pulse rate was observed in the mature dogs beginning at "altitudes" of 1000-3000 m and continuing as hypoxia developed. During the "descent," the pulse rate returned rather rapidly to the initial values, often reaching the norm at an "altitude" of 3000-2000 m. The cardiac activity quickened in the old dogs at approximately the same "altitudes," but its return to the initial value took longer and an increased pulse rate was observed in a number of cases even after the barometric pressure had been normalized.

The electrocardiogram changes in dogs reduce basically to a slight decrease in the R and T-waves or to deepening of a normally negative T, and do not reflect any particular dependence on age in the "ascent" to 5000 m. This attests to a drop in the stability of the elderly organism against acutely developing hypoxia. This is supported by the drop in the "altitude ceiling" in aged rats and dogs, the earlier appearance of ataxia, the involuntary micturition and defecation observed in the aged dogs, and the earlier slowdown of respiration in aged rats during "ascent" in the altitude chamber. The decrease in the pulse rate, which

sets in at lower "altitudes," and the changes in the electrocardiograms of the aged rats, also appearing at lower "altitudes," and the greater increase in pulmonary ventilation in the aged dogs indicate increased sensitivity of the elderly animals to deficiency of oxygen in the inspired air. Despite the increased pulmonary ventilation and oxygen requirement that are noted with advancing hypoxia in both mature and aged dogs, the phenomena of hypoxemia are more distinctly expressed in the aged animals, and this suggests that the amplification of the external respiratory function is not sufficiently effective. This last would appear to be associated with inadequate alveolar ventilation due to the increased physiological dead space in old age. In the normalization of the physiological functions as the hypoxia diminishes and disappears, our attention is drawn to the more drawn-out return to the initial values of pulmonary ventilation, oxygen requirement and pulse rate in the aged dogs, a partial explanation for which may be found by the more protracted hypoxemia and the intensified activity of the respiratory and cardiac muscles in the aged animals during the post hypoxic period. There is a possibility that the increased oxygen requirement, of longer persistence after survival of oxygen insufficiency in the old dogs, is also partly the result of accumulation of larger amounts of incompletely oxidized metabolism products in the blood and changes, as yet unclear to us, taking place at the level of the tissue processes.

ON THE AGE-CONNECTED PECULIARITIES OF THE REACTION OF THE HEART TO
HYPOXIA

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and V. V. Fro l'kis

(Kiev)

Myocardial hypoxia is one of the most commonly encountered pathogenic mechanisms that disturb the function of the heart during operation of various etiological factors. Indeed, cardiac hypoxia may be caused by insufficiency of the coronary blood supply, noncorrespondence between the oxygen requirement of the myocardium and the amount supplied to it, primary disturbances to the various enzyme systems of the heart, and the various forms of hypoxemia. All this makes it understandable why clinical medicine specialists and experimenters show unfläging interest in study of the changes that take place in cardiac activity during hypoxia.

At the present time, there is a distinct inconsistency between the clinical and experimental approaches to study of the effect of hypoxia on cardiac activity. Under the natural conditions of human life, those with which the clinical medicine specialists are constantly coming into contact, the phenomena of manifest hypoxia of the myocardium most frequently arise during definite age periods - those of "ripe" and senile old age. To support this, it is sufficient to recall such hypoxic syndromes as coronary insufficiency and myocardial infarct, which occur most frequently in persons of the oldest age groups. The very fact that these disorders arise in elderly persons indicates the existence of met-

abolic peculiarities and reactivities of the organism in this age period, factors that determine the development of these pathological processes. At the same time, experimental study of cardiac hypoxia on examples furnished by specific disorders is undertaken without consideration of the most important age-connected peculiarities of animals and in the overwhelming majority of cases, on younger animals.

Like any tissue reaction, the changes that take place in the heart during hypoxia must necessarily and naturally depend on the strength of the stimulus in operation (the degree of oxygen starvation) and on the initial functional state of the reacting system. From this standpoint, the nature of the metabolic processes taking place in the myocardium acquires great interest for determination of the age-connected peculiarities of the myocardial changes in hypoxia. At the present time, a certain amount of factual material has been accumulated (N.N. Sirotin et al., 1960; F.Ya. Primak, 1961), material that testifies to the occurrence of hypoxic shifts in the organism in aging.

It was important to ascertain the degree to which these hypoxic shifts affect the metabolism of the heart in the healthy older animal. It is perfectly obvious that this initial metabolic level will in many respects determine the peculiarities of the heart's reactions to other conditions that result in myocardial hypoxia.

The oxygen requirement of the myocardium, the rate of the glycolysis processes, and the lactic acid content and glycogen content in the cardiac muscle were determined in animals of various age groups - rabbits aged 1-2 days to 3-3.5 years and rats aged from 3-4 weeks to 2-2.5 years. This manner of analyzing the metabolic processes enables us to give a general characterization of the relationship between the aerobic and anaerobic phases of respiration, which depends in many respects on the oxygen supplied to the functioning heart. All calculations were made for both the raw and dry weight of the tissue, since the water content in the cardiac muscle changes with age. The results of all the

investigations were processed by the variational-statistical method, with calculation of the mean probable error ($\pm m$) and the series confidence ($t > 3$).

The maximum oxygen consumption rate is observed in the myocardium of the rabbit at an age of 4-5 weeks: immediately after this, the intensity of tissue respiration begins to decrease, reaching its lowest values in aged animals. The rate of oxygen consumption in rabbits (QO_2) at an age of 4-5 weeks is 6.95 ± 1.3 , while at ages from 3 to 3.5 years it is 2.61 ± 0.96 . Approximately the same type of variation is observed in rats. Together with the decline in tissue respiration during aging, the organism exhibits amplification of glycolysis. This is indicated by the increased quantity of lactic acid in the myocardium in aged rabbits, a decrease in the amount of inorganic phosphorus and a decrease in the glycogen content. Thus, in rabbits 4-5 weeks old, the content of lactic acid in the heart (in mg %) is 99 ± 32 , at 1.5-2 years it has risen to 123 ± 7.9 , and at 3-3.5 years to 162.1 ± 13.2 . Converted to dry weight, the quantity of lactic acid was found to be 480,542 and 711 mg % in the respective age groups. The content of glycogen in rabbits aged 1.5-2 years was equal to 2607.6 mg %, while in animals that had lived to 3-3.5 years it was 1352 mg %. These relationships between the heart's oxygen consumption and the amounts of lactic acid in it are reflected in Fig. 1.

Thus, as the organism aged, we noted a change in the proportions between the anaerobic and aerobic phases of respiration. In old animals, the specific weight of the oxidative processes diminishes and the rate of the anaerobic reactions rises. As we know, intensification of anaerobic reactions in the tissue is frequently a kind of compensatory reaction directed toward maintaining a certain level of metabolism under the conditions of developing hypoxia.

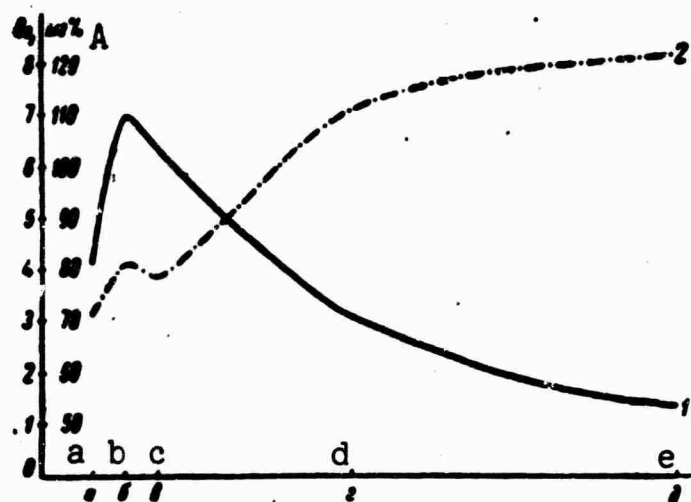


Fig. 1. Variation in rate of tissue respiration and content of lactic acid in hearts of rabbits at various ages: 1) QO_2 ; 2) lactic acid in mg %; a) Newborn animals; b) 2-week-old animals; c) 4-5 weeks; d) 1.5-2 years; e) 3.5 years. A) mg %.

The types of metabolic change that we have described as taking place in the heart of the aged animal can be used as part of the evidence for hypoxic shifts during aging of the organism. This is why the heart of the aged animal must be particularly sensitive to pathological processes that result in hypoxia of the myocardium. Thus, even under normal conditions, we note in aged animals a certain strain on the adaptive mechanisms, manifested in a change in the relationship between anaerobic and aerobic metabolic paths in the cardiac muscle.

It would be of particular interest to study the changes in cardiac activity during hypoxia developed in coronary insufficiency and myocardial infarct. Both of these syndromes are results of varying degrees of mismatch between the oxygen requirement of the heart and the amount supplied to it.

Thus, both the vascular and the cardiac factors are of definite importance in the mechanism by which coronary insufficiency arises. The data given above concerning the reduced rate of tissue respiration in aged animals makes understandable the essential role taken by the cardiac factor in the mechanism of coronary insufficiency during this age

period. However, this is not the only thing bearing on the specifics of coronary-insufficiency development in aged animals. It has been shown by the studies of V.V. Frol'kis and his colleagues that during aging of the organism, the sensitivity of the heart and vessels diminishes with respect to nervous factors and is enhanced with respect to humoral factors. The change in the reactivity of the heart and vessels in old age casts light on certain peculiarities in the development of coronary insufficiency, in the mechanism of which neurohumoral factors are of no small importance.

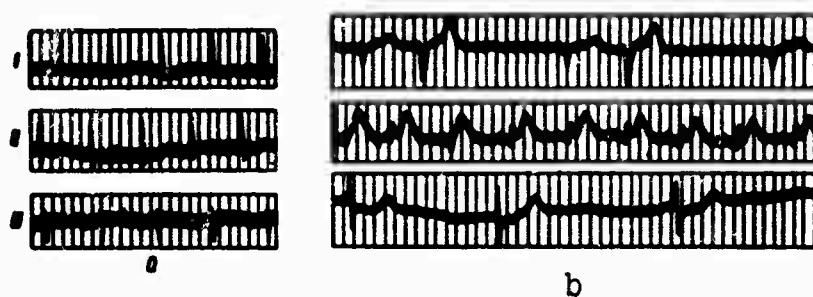


Fig. 2. Electrocardiographic changes after injection of 0.6 units/kg of pituitrine into young (a) and aged (b) rabbits; I, II, and III indicate leads.

Experimental coronary insufficiency is easily reproduced by intravenous administration of pituitrine to the animals. This model is interesting in view of the fact that, as we know, vasopressin may play a certain role in the development of coronary insufficiency in man. The administration of pituitrine causes manifest myocardial hypoxia that registers on the electrocardiogram. V.V. Frol'kis and D.A. Kuz'minskaya established that depression of tissue respiration, resulting from limitation of the blood supply to the myocardium, is observed on administration of pituitrine.

Experiments on 16 aged rabbits and 14 young ones showed that in the older animals, the phenomena of coronary insufficiency arrives when smaller quantities of pituitrine are injected.

Figure 2 shows the essential changes that take place in the car-

diac activity of the aged animal on intravenous injection of 0.6 units of pituitrine for each 1 kg of weight. We note on the electrocardiogram numerous extrasystoles, changes in the position of the S-T segment relative to the isoelectric line, and a sharp rise in the T-wave. In the young animals, this same dose of pituitrine produced no substantial changes in the electrocardiogram. In 5 experiments out of 15, administration of 0.6 units of pituitrine per 1 kg of weight to the aged animals caused profound changes in the activity of the heart, changes terminating in fibrillation and the death of the animals. In young animals, administration of pituitrine in twice the dose resulted only in manifest phenomena of coronary insufficiency, after which the cardiac activity consistently returned to normal.

In experiments, the phenomena of coronary insufficiency can be reproduced by use of carbocholine, which, as we know, causes a drop in blood pressure and contraction of the coronary vessels. On administration of carbocholine, coronary insufficiency develops against a background of distinct bradycardia due to its direct action on the m-choline-reactive systems of the heart.

In experiments on 20 rabbits of different ages, we determined the sensitivity of the heart to carbocholine. In aged animals, changes in the heart rhythm and phenomena of coronary insufficiency arose at lower carbocholine concentrations. Figure 3 shows the electrocardiographic changes that arise in an old animal and a young one on administration of the same dose of carbocholine.

Thus, the administration of chemical agents (pituitrine, carbocholine) causes changes in coronary blood circulation and hypoxic phenomena, and these are more distinctly manifest in the old animals. These peculiarities of the appearance of coronary insufficiency in aged animals are determined firstly by the elevated sensitivity of the heart

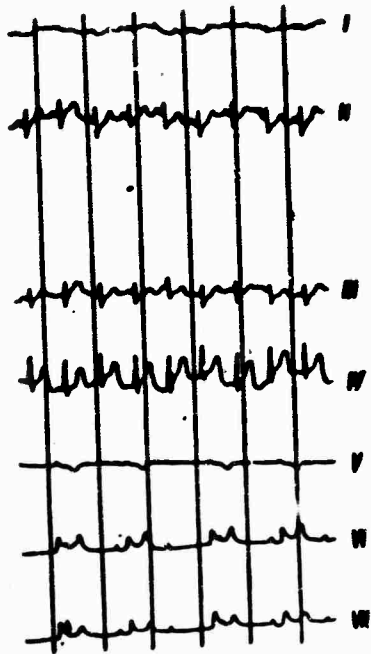


Fig. 3. Electrocardiographic changes after administration of 5 µg/kg of carbocholine to young (curves I-IV) and old (curves V-VII) rabbits. Bradycardia and acute myocardial hypoxia develop in the old animal.

and vessels to humoral factors, and, secondly and obviously, by the described changes in the relation between the anaerobic and aerobic phases of respiration in the hearts of the old animals.

In accordance with the conceptions of Raab (1959) and Khegglin (1959), a factor of substantial importance in the mechanism of coronary insufficiency is an increase in the content of catecholamines in the cardiac muscle - substances that accumulate in large quantities under various types of stress, such as physical overwork, emotional overexcitement and other states. Becoming fixed in the heart, the catecholamines sharply increase the oxygen requirement of the myocardium. Under these conditions, even normal coronary blood circulation may prove inadequate and myocardial hypoxia may arise.

It might be assumed that for the older animals, injection of adrenalin under such conditions would result in even further aggravation of oxygen starvation. The sensitivity of the heart to adrenalin was determined on 50 rabbits and cats. As we know, adrenalin causes substantial changes in the activity of the heart, acting both directly on the cardiac muscle (sharp increase in requirement for oxygen, increased instability of the sinus automatism, amplification of contractility of the myocardium) and indirectly by raising the tonic effect of the vagus nerve on the heart (bradycardia). We showed that in the old animals, the sensitivity of the heart to the direct effect of adrenalin is increased. However, the action of adrenalin through the nerve

centers is more distinct in young animals. Thus, adrenalin in a dose of 6 $\mu\text{g}/\text{kg}$, which does not produce changes in the electrocardiographic indicators in young animals, produces significant shifts in the old ones - a sharp deepening of the Q-wave, a rise in the S-T segment, and a change in the amplitude of the T-wave. In a dose of 12 $\mu\text{g}/\text{kg}$, adrenalin very frequently produces numerous polytopic extrasystoles of the paroxysmal tachycardial type in old animals. On injection of larger doses of adrenaline, the changes in rhythm and amplitude of the waves also appear in young animals. They show the bradycardia even more strongly than the aged animals. Thus, the hypoxic shifts in the old animals are more sharply expressed than in the young ones on administration of adrenalin.

In the human organism, situations occur in which the phenomena of coronary insufficiency arise as a result of simultaneous action of adrenalin and pituitrine. It must be remembered that the vasopressin secreted in various states of stress (A.V. Tonkikh, S.I. Teplov, A.I. Il'ina) contributes to subsequent secretion of adrenalin. The combination of adrenaline and pituitrine produces coronary insufficiency by virtue of simultaneous action of cardiac and vascular factors, since spasm of the coronary vessels sets in here together with a sharp increase in the heart's oxygen requirement.

In this connection, it was found interesting to establish the reactions of young and aged animals to these two substances. Subliminal doses of adrenalin and pituitrine were administered to aged and young animals. This treatment resulted in the electrocardiographic manifestations of hypoxia, and, in the old animals, simultaneous introduction of adrenalin and pituitrine caused sharper shifts in the cardiac activity, changes that considerably exceed the effect due to either substance administered alone. Thus, the hypoxic shifts in the myocardium

of the aged animals appear on application of considerably smaller quantities of the chemical substances.

The age-connected peculiarities of the heart's reaction to hypoxia are clearly manifested when we study experimental myocardial infarct. In experiments on 30 aged and 27 young rabbits, we studied the development of experimental myocardial infarct on tying off the circumflex branch of the left coronary artery. The higher sensitivity of the hearts of the aged animals to restriction of the myocardial blood supply manifested in the fact that in this age. A larger number of cases of fibrillation of the heart were noted than in the young animals. In the old animals, development of cardiac fibrillation was observed in 33% of cases, but only in 12% of cases in the young animals. The fluttering of the heart in myocardial infarct may be regarded as a reaction of the heart to acute hypoxia.

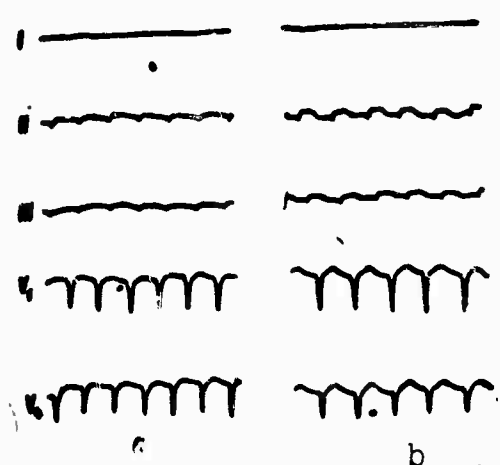


Fig. 4. Electrocardiographic changes after tying off coronary artery in an old rabbit. a) On the third day after ligature, a $QS_{2,3}, V_1 V_4$ wave is registered and the S-T interval approaches the isoelectric line and is shifted slightly; b) on the fifth day, a second sharp increase in the S-T interval upward from the isoelectric line; I, II, and III are lead numbers.

The second significant deviation of the S-T interval from the isoelectric line just after it has almost returned to normal testifies to the higher sensitivity of aged rabbits to hypoxia as compared with young ones. In an old rabbit on the third day after ligature of the coronary artery, the S-T interval has risen only insignificantly above the isoelectric line, but on the fifth day we again note a considerable rise on this interval (Fig. 4).

Further testimony to the greater sensitivity of aged animals to hypoxic shifts is borne by the peculiarities of

the animals' reaction to various stimuli during experimental myocardial infarct. Aged and young animals were subjected to hypoxia ("elevation" in the altitude chamber to "altitudes" of 3500 and 7000 m) and orthostatic tests, and adrenalin, pituitrine and carbocholine were administered intravenously. All of these disturbances ultimately lead to myocardial hypoxia by varying the oxygen saturation of the blood and the influx of blood to the heart in accordance with the nature of the test, and by producing spasm in the coronary vessels for a sharp increase in the oxygen requirement of the cardiac muscle.

In all of these tests, the aged animals with myocardial infarct reacted more sharply than the younger control rabbits. This age-connected difference manifested most clearly on administration of pituitrine and during the orthostatic test. In these two tests, the inflow of blood to the heart changes substantially, in one case due to coronary arterial spasms and in the other as a result of the drop in total oxygen pressure.

Comparison of the changes in the functional state of the heart during the various functional tests enables us to conclude that the aged animals with experimental myocardial infarct are extremely sensitive to deterioration of the myocardial blood supply. This fact indicates that the development of collateral blood circulation is of particular importance for aged animals among the compensatory processes that intervene after the coronary artery has been tied off.

In aged animals, the tissue adaptive reactions to hypoxia are found to be under strain even under physiological conditions; among other things, anaerobic respiration is intensified. This renders understandable the described elevated sensitivity of the heart in aged rabbits to another important adaptive mechanism related to change in the level of blood supply to the myocardium.

Thus, the singularities of metabolism in the heart as the organism ages, and changes in the sensitivity of the heart and coronary vessels to the action of nervous and humoral stimuli determine the special nature of the myocardial reaction to hypoxia induced in a wide variety of ways. These facts must be taken into account in analyzing specific features of the course of a number of pathological processes that lead to the development of hypoxia as the organism ages.

AN EARLY INDICATOR OF THE ADAPTIVE REACTION OF MUSCLE TISSUE
TO DEVELOPING SENESCENT HYPOXIA

S.I. Fudel'-Osipova and F.I. Grishko

(Kiev)

Among the complex problems that confront investigators studying aging of the organism, the lack of clarity as to why the oxidizing ability of the tissues diminishes with increasing age is one of considerable importance. This question is illuminated in a number of papers based on both examination of humans (E. Baldwin et al., 1948; Bine and Burl'yer, 1960; H. Wilcox, 1957; N. Lassen et al., 1960) and in experiment on animals (S. Barrows et al., 1958; A.A. Pashkova, 1960). Emphasizing the importance of studying the phenomena of hypoxia, N.N. Sirotnin made reference to its development and manifestation in various forms in the senescent organism. To this day, however, it remains unclear why the absorption of oxygen and its consumption by the tissues should fall off during aging. Exactly where is the first cause of this phenomenon to be sought? It is well known that during aging, complex structural changes that reduce, in general terms, to a decrease in the amount of vital tissue and an increase in the amount of connective tissue take place in all tissues of the organism. Still, the vital elements that are preserved also lose the structure characteristic for them as aging progresses and acquire new forms (V. Martynov, 1937; V. Osaulenko, 1958; Berg, 1958, et al.). The question naturally arises as to whether or not the decline in tissue oxidation processes, i.e., some degree of hypoxia, should be accounted for by precisely this decrease

of the active elements in them.

Exact conversion of the tissue oxygen consumption to mass of active substrate would make it possible to obtain a perfectly concrete conception of the oxidizing ability of the tissue as a function of its retention of specific structural elements. Such an attempt was made by O. Rozental', M. Bovi and G. Uogoner in 1941 in a determination of respiratory capacity, dehydrase activity and glycolysis in ox cartilage. They found that the decline in respiration takes place more rapidly than the drop in the number of cartilage cells. From this they conclude that the decline in respiration is a function of reduced activity of enzymes. Thus it would appear that the drop in tissue respiration cannot be accounted for solely in terms of a reduced content of active elements, although for a final decision on this question it would be necessary to have factual data obtained on different types of tissues.

The literature data devoted to the problem of enzyme activity in tissues of aged animals are highly contradictory. Thus, working with white rats with ages up to two to three years, G.G. Ivanov (1939) observed an increase in the dehydrase activity of some tissues (brain, cardiac muscle, skeletal muscle, etc.) and a decline in others (liver, kidneys). Ye.I. Sazonova (1960) found that the activity of liver succinoxidase increases, while that of succindehydrase does not change. S. Barrows, M. Inget, M. Shok (1958) and M. Ross and J. Ely (1954) observed no changes in enzyme reactions in aged animals. Consequently, it is obviously not always possible to link the decrease in the tissue oxygen consumption of aged animals with a drop in enzyme activity.

Thus, while the presence of tissue hypoxia in old age has definitely been established, the cause of this phenomena is unclear, and further research in this direction will probably enable us to form a certain conception as to its cause and, consequently, to map out ways to

counter it.

The biological and morphological changes that set in in the muscles of humans and animals with increasing age have been under study for a number of years in the biology laboratory of the Gerontology Institute (Kiev). Since experimental studies permit more detailed and exact establishment of age-connected changes in the tissues of the organism, we regarded it as expedient to concern ourselves with age-connected changes in the tissue respiration of animals. An investigation of oxygen absorption by muscle tissue and comparison of the data obtained on the structural states of the muscle fibers enabled us to derive a certain amount of information on the relationship between the phenomena of tissue hypoxia and structural changes in the muscle fibers.

Experiments were set up on white rats of different ages, beginning from one day and ending at 37 months. In the present report, we shall discuss only the material obtained in investigating mature and aged rats. Tissue respiration was determined on a Warburg apparatus in Meyerhoff's bouillon on muscle that had been ground up on ice (Chepinoga, 1939). The experiments were run at $t^{\circ} + 38^{\circ}$ and a pH of 7.21. To determine the structural integrity of the muscle tissue, we separated out a bundle of muscle fibers from the muscle being studied and split it up into individual fibers under the binocular microscope. Here the muscle fibers were stained quickly with 0.1% cresyl blue, followed by bleaching with a 4% acetic acid preparation. With this method of staining, the nucleus and transverse striation are rendered easily visible. The thickness of the muscle fibers did not change as a result of such staining - a fact of which we satisfied ourselves by comparing the diameters of muscle fibers in the unstained and stained preparations. The diameters of the muscle fibers were measured using an ocular micrometer under the microscope, and the number of nuclei on a segment 1265 microns in length was estimated with the same instrument. All of the material obtained was processed statistically and found to be fully reliable.

It is evident from the table that 15-month-old rats have the highest rate of tissue respiration. At 24 months, the respiration has

Rate of Tissue Respiration in Rats of Various Ages

Возраст рыска в ме- сяц	2 QO ₂ мышцы	3 Количество ядер в мышеч- ном волокне	4 Толщина мышечного волокна (в мк)	5 Исчерченность мышечного волокна
10	18,47 ± 1,21	62 ± 4,80	105 ± 3,10	Хорошо
15	24,56 ± 2,66	61 ± 3,81	104 ± 5,01	Хорошо 6
24	16,58 ± 0,78	104 ± 9,16	100 ± 6,20	Хорошо
30	16,17 ± 1,82	28 ± 7,07	80 ± 3,87	Не везде хо- рошо 7
37	13,08 ± 0,18	23 ± 1,63	74 ± 1,34	Не везде хо- рошо

1) Age of rat in months; 2) QO₂ of muscle; 3) number of nuclei in muscle fiber; 4) thickness of muscle (in μ); 5) visibility of striation in muscle fiber; 6) good; 7) not good everywhere.

dropped by 8 μl, and by 37 months by 11.50 μl, i.e., by almost 50% as compared with the 15-month rats.

Measured over a one-hour period at various times during the experiment, the oxygen absorption by animals of different ages proceeds in about the same manner. In Fig. 1a, we see the parallel lay of the three curves indicating the nature of the respiration of rats at three different ages: 15, 32 and 37 months. These curves differ from one another only in that the younger the animal, the higher is the curve situated; this serves as an indication to the higher respiration rate at less advanced ages.

The decline in tissue respiration in old animals may depend both on a decrease in the amount of active substrate and a decrease in enzyme activity. In this case, it is obvious that both processes occur, since if the only important factor was the decrease in the amount of substrate, with the enzyme activity remaining unchanged, then the curves from rats of the more advanced ages would not show the same uniform decline as the curves for the young rats.

Microscopic examination of the muscle-fiber structure showed that the thickness of the fibers was considerably smaller in the old animals

as compared with the young ones. The rats aged 12-15 months had the thickest muscle fibers (104-105 μ), and the first signs of muscle-fiber thinning begin to appear at 24 months. The thickness drops to 80-74 μ in the 32-37-month-old rats. The amount of connective tissue between the fascia increases in the aged animals. Thus, the protoplasmic active substrate in the muscles diminishes as the animal grows older.

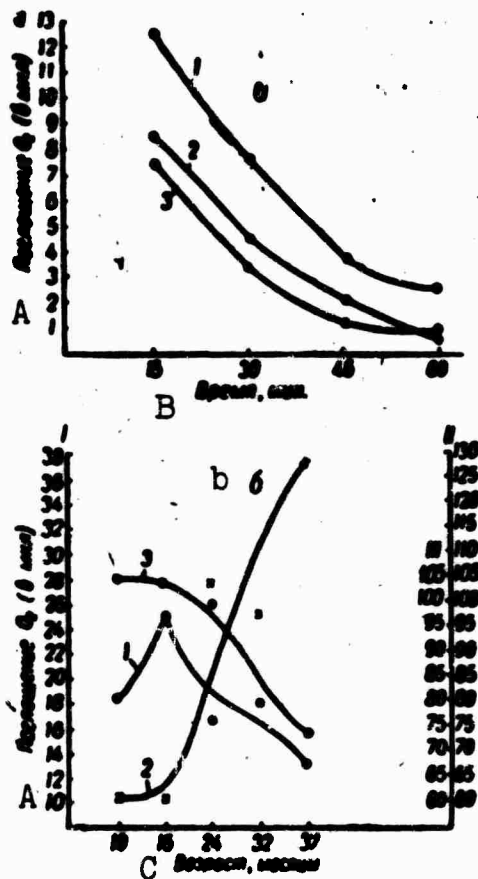


Fig. 1. a) Absorption of oxygen by muscle tissue over one hour; 1) 15-month-old rat; 2) 32-month-old rat; 3) 37-month-old rat. b) oxygen absorption by muscle tissue (I), Thickness of muscle fibers in μ (II) and number of nuclei in them (III) for rats of different ages. A) O_2 absorption (in μl); B) time, min; C) age, months.

Concurrently with senescent muscular atrophy, the muscle fibers show a drop in the clarity with which the transverse striation is outlined and an increase in the number of nuclei. In our opinion, this last phenomenon deserves particular attention. In muscle fibers, the nuclei are centers of the assimilation processes, in exactly the same way as the mitochondria, according to contemporary conceptions, perform the role of oxidative metabolism centers (Ivanov and Yur'yev, 1961; A. Miller, D. Konoli, M. Gabriyel', M. Gandi, 1959; Ye. Venbakh, I. Garbus, 1959; B.V. Kedrovskiy, 1959, et al.).

While the majority of cells in the aged organism have lost their ability to divide, a fact that some authors regard as an effect of aging, the nuclei begin to divide at a high rate in muscle fibers, and the older the organism, the

larger the number of nuclei that can be counted in a cell. This was

pointed out by I. I. Mechnikov in his time. If we take into account what we said above concerning the role of the nuclei in the assimilation processes, then it is natural to assume that the intensified division of nuclei that begins at this age is a compensatory reaction to the drop in the oxidative processes in the cell. If we take this standpoint, however, then it is necessary to adopt the position that the "transport" of oxygen to the muscles diminishes with increasing age. Since, as we know, atherosclerosis does not occur in rats, it is necessary to find some other causes responsible for the hypoxic state of the muscle tissue. Oxygen supply may be disturbed either by an increase in the tone of the small blood vessels or by thickening of the membranes of both the alveolar capillaries and the capillaries in the muscle tissue. Future research must also answer this question.

Atrophic processes in the senescent organism do not affect all muscle fibers to the same degree. It is frequently possible to observe senescent rats that have no distinctly manifest structural changes in their muscle fibers. It is found that in these cases, muscular respiration is proceeding at a rather high level.

Take, for example, Experiment No. 18. Female rat, aged 32 months, muscle tissue QO_2 25.8 μ l, number of fine muscle fibers 55-70 μ in diameter only 35%, number of fibers with increased nuclear content (90-100 and more) only 12%. It is evident from this example that in this particular animal there were no signs of tissue hypoxia, since the compensatory reaction, which consists in intensified division of nuclei, is indistinctly in evidence.

In certain experiments with the same proportions of thick and thin muscle fibers, it was possible to observe an increase in the number of nuclei present in the cells, just as in Experiment No. 18. In our opinion, the appearance of a large number of nuclei indicates a certain de-

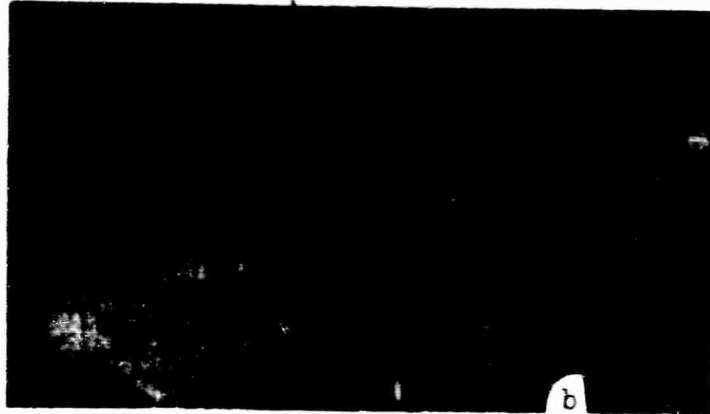
gree of oxygen starvation of the organism. And, indeed, the oxygen consumption by the muscle tissue was found to be low in these cases.

This can be demonstrated by reference to Experiment No. 38 as an example. Female rat, 32 months, QO_2 of muscle tissue $10.95 \mu l$, thin muscle fibers with diameters from $55-70 \mu$ amounting only to 32%, number of nuclei in all muscle fibers, irrespective of diameter, very large, at 90-150. As will be seen from the examples presented, it is possible to observe differing degrees of hypoxia in the 32-month-old rats, but if it is present it is always accompanied by intensified division of nuclei.

In 37-month-old rats, there is always a distinctly manifest tissue hypoxia - the QO_2 is low. With very rare exceptions, their muscles consist of thin muscle fibers $55-70 \mu$ in diameter, and all of these fibers contain large numbers of nuclei (over 100).

Muscle fibers from a young, 15-month-old rat (Fig. 2a) and an aged rat at age 37 months (Fig. 2b) were microphotographed. The muscle fibers of the young rat have distinctly manifest transverse striation, are 100μ thick, and rod-shaped nuclei are spotted along the fiber in insignificant numbers. In the muscle fibers from the aged rat, the transverse striation is vague, the fibers are thinner (65μ) and we see in them a very large number of nuclei, among which oval-shaped nuclei occur in groups.

Analysis of the data obtained indicates that the oxygen consumption by the tissue diminishes with the development of the atrophic changes peculiar to advanced age. The phenomenon of tissue hypoxia, however, is more distinctly manifest the larger the number of thin muscle fibers in the given tissue and the larger the number of nuclei present in them. Figure 1b clearly shows the relationships that exist between QO_2 , the thickness of the muscle fiber and the number of nuclei



**GRAPHIC NOT
REPRODUCIBLE**

Fig. 2. Muscle fiber structure (native preparations). a) Muscle fibers of 15-month-old rat; b) muscle fibers of 37-month-old rat. Stain: cresyl blue. Magnification 10x7.

present in the muscle fibers. The QO_2 curves and the thickness of the muscle fibers come down with increasing age, while the curve indicating the number of nuclei in the muscle fibers in the various age periods rises monotonically.

In our opinion, the increase in nucleus count in the muscle fibers of aged animals, an increase that runs concurrently with the rise in level of tissue hypoxia, is one of the compensatory mechanisms. The products that the nucleus secretes into the cytoplasm stimulate the mitochondria and, consequently, the oxidative processes as well. Muscle tissue, whose energy expenditure is particularly high in warm-blooded animals, comes into a particularly difficult situation as hypoxia develops. The hypoxia, and, perhaps, some other stimuli as yet unknown to us that appear as the organism ages, cause intensified division of nuclei. It may be assumed that the increased number of nuclei is capable to some extent of retarding the development of muscle-fiber atrophy as it sets in under the conditions of oxygen insufficiency as a result of disturbance to various assimilative processes. The presence of a large number of nuclei in muscle fibers that have not yet begun to thin, together with depressed QO_2 , as observed in some of the cases (for example, in Experiment No. 18) may be regarded in exactly the same way.

Thus we consider that the appearance of a large number of nuclei serves as one of the early criteria of aging and the onset of tissue hypoxia.

INFLUENCE OF HYPOXIA ON PROPAGATION OF STIMULI IN THE
RESPIRATORY FORMATIONS OF THE BRAIN

S.A. Dolina and G.P. Konradi

(Leningrad)

A number of investigations have established the possibility of increasing the excitability of the central nervous system at a minor degree of hypoxia and lowering it by inducing a considerable degree of oxygen insufficiency. For example, in our laboratory, T.V. Popova established that such a two-phased change in excitability during hypoxia produced by blood-letting is observed with respect to the exteroceptive and interoceptive vasomotor reflexes, as well as in pressor and depressor effects caused by direct excitation of the cerebral cortex and medulla oblongata.

With the objective of obtaining a farther-reaching characterization of the influence exerted by hypoxia on this state of the central nervous system, we undertook to study the influence of varying degrees of hypoxia on the propagation of an excitation produced by stimulating the cerebral cortex. To clear up this question, we compared the magnitude of the threshold voltage of the current producing the minimum motor effect with the voltage of the current necessary to evoke generalized spasms.

The experiments were performed on rats with a unipolar electrode implanted in the region of the projection of the frontal cortical lobe after removal of the insulation from a point 0.3 mm in diameter. A lead plate on the animal's tail served as the indifferent electrode. The stimulus was provided by a series of pulses at a frequency of 200 in

1 sec, from an IES-01 stimulator. Stimulation lasted for 1 sec. The threshold voltage necessary to evoke local contraction of the contralateral extremity (porog lokal'nogo sokrazhcheniya, local contraction threshold, PLS) and the voltage just adequate to produce generalized spasms (porog generalizovannykh sudorog, generalized spasm threshold, PGS) were determined. Hypoxia was induced by rapid rarefaction of the air in an altitude chamber. The investigations were conducted after a 40-minute residence in the altitude chamber at the "altitude" in question. Each series of experiments was performed on eight to ten rats after four or five days had elapsed since implantation of the electrode in the cortex of the brain.

A consistent result of "elevating" the rats to an "altitude" of 1500 m was a drop in the PLS to $66 \pm 6.8\%$, on the average, of the initial value, which was taken as 100, with a simultaneous rise in the PGS to $154 \pm 9.9\%$ of the initial value. As a result of the opposite directions taken by the changes in the PGS and PLS, the difference between these quantities had increased at an "altitude" of 1500 m by $152 \pm 28.9\%$ of the initial value as registered at normal barometric pressure. A statistically quite reliable increase occurs in the excitability of the directly stimulated cortical elements with such an indisputable decrease in the ability of the stimulus to propagate to the formations whose participation in the reaction is necessary to produce general spasms (according to numerous recent data, induction of subcortical structures into the excitation is necessary to produce this effect; see Gasto, 1959). The drop in the sensitivity of rats to corazol observed at the "altitude" of 1500 m is in agreement with this, while a 40 mg/kg dose of corazol injected subcutaneously produced spasmodic attacks in five rats out of 20 at normal barometric pressure. The same dose, administered directly before an "ascent" to the "altitude" of 1500 m, resulted in an attack of spasms in only one rat out of 20. With a 60 mg/kg dose of corazol, we note at an "altitude" of 1500 m a dis-

tinct weakening of the spasm attacks produced by the corazol and a decrease in their duration and frequency.

At "altitudes" of 7000 and 8000 m, the relationships are somewhat less distinct. A weakening of the spasmodic seizures produced by corazol is also noted at the "altitude" of 7000 m (these experiments have not yet been performed for higher "altitudes"). The magnitude of the PLS increased at the "altitude" of 7000 m in 60% of cases (on the average, by 60%), while in 40% of cases it decreased (by an average of 30%), while the PGS rose at this "altitude" (by an average of 34%). In view of the consistency of this effect and the increase in the PLS in six cases out of ten, the average value, taken over all cases, of the difference between the PGS and PLS at the "altitude" of 7000 m increased by 60% ($\pm 19.8\%$), a figure at the boundary of statistical reliability. At the "altitude" of 8000 m, the PLS had risen in all animals by an average of $40 \pm 12.2\%$, while the PGS had risen in three rats and diminished in five, so that the difference between the PGS and PLS in five cases was 50% smaller, and in three cases 50% larger than the initial value.

Thus, we can speak of an unquestionable decrease in the excitability of the cortical motor neurons to direct stimulation at an "altitude" of 8000 m (this is already noted at an "altitude" of 7000 m), and of a certain tendency to easier propagation of the excitation leading to general spasms. This last point is in agreement with literature data (Gell'gorn) to the effect that the onset of spasms caused by direct stimulation of the subcortical formations is facilitated in hypoxia.

It is necessary to note that in all cases in which we (S.A. Dolina, 1962) observed a particular tendency to go into convulsions (in a genetic strain of rats producing audiogenic spasms and in rats that had been sensitized by a previous attack of spasms), we consistently ob-

served significant narrowing of the interval between the PLS and PGS. On the other hand, when we achieved a drop in sensitivity to the spasm-inducing agents by long-term administration of very slowly increased doses of camphor, this was accompanied by a very sharp increase in the difference between the PGS and PLS values. It is therefore necessary to acknowledge that the ability of an excitation process to radiate out far beyond the limits of its focus of origin is not directly related to the excitability of the neurons in this focus with respect to direct stimulation.

A large amount of material has been accumulated in the study of instinctive and conditioned reflexes to indicate that the degree of excitation localization in the reflex arcs of unconditioned and conditioned reflexes is achieved by an inhibition process opposed to the excitation process. The convulsive attack can probably be regarded as an extreme degree of disturbance to the inhibitory process that limits the excitation process. Hence we assume that slight degrees of hypoxia result not only in elevated excitability of the cortical cells, but also strengthen the inhibition process limiting the induction into the excitation of elements that do not belong to the focus directly stimulated. This does not exclude the possibility that the decrease that we established in the ability of the stimulus to radiate at an "altitude" of 1500 m is related to desynchronizing excitation of the elements in the reticular formation that activate the cortex, with a simultaneous reciprocal suppression of those reticular formations excitation of which promotes synchronization of the cortical potentials (Moruzzi 1960). As we know, this synchronization is regarded as characteristic for the compulsive attack. It is also possible that the effect of hypoxia at the "altitude" of 1500 m depends not so much on its direct influence on the brain as on reflex effects from the aortocarotid chemo-

receptive zone, excitation of which causes stimulation of the divisions in the reticular formation that activate the cortex. It must also be remembered that the effects that we observed might be related to the increase in the brain's blood supply that intervenes at a certain degree of hypoxia.

The effects of hypoxia at "altitudes" of 6000-8000 m can be regarded as consequences of the decrease in cortical excitability and stimulation of the reticular formations that facilitate the synchronization processes (see Bonvalle and Dell). This appeal to changes in the subcortical divisions caused by hypoxia is, of course, still purely hypothetical in nature, and this interpretation is presented only as one of the theoretically admissible ways toward an explanation. However, irrespective of the interpretation of the phenomena described, their interest consists, in our opinion, in the fact that they characterize the effect of hypoxia not only on the excitability of nerve cells in the cerebral cortex, but also its effect on the ability of an excitation to radiate from these cells to other formations of the brain.

The facts obtained indicate that a degree of hypoxia, not yet sufficient to lower the content of oxyhemoglobin in the blood, increases the ability to limit the excitation process to a definite focus and thus promotes retention of the mosaic (I.P. Pavlov) of excitation foci in the cortex of the brain. It would be of interest to juxtapose these facts with the exceedingly important data of N.N. Sirotinin concerning therapeutic application of hypoxia in treatment of psychoses.

AN INVESTIGATION OF THE BIOELECTRIC ACTIVITY OF THE CEREBRAL
CORTEX AND CERTAIN SUBCORTICAL FORMATIONS IN ACUTE HYPOXIA

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The development of acute hypoxic hypoxia in warm-blooded animals and man causes significant changes in the functional state of the central nervous system (P. Behr, 1878, V.V. Pashutin, 1881; D. Barcroft, 1927; N.N. Sirotinin, 1933-1941; D. Holden, 1936; V.V. Strel'tsov, 1938; E. Opits, 1942; I.R. Petrov, 1949-1952, and others).

Due to the fact that disturbances to the activity of the brain are responsible for the gravity of the pathological state in hypoxia and its outcome, a large number of experimental studies have been devoted to the question of the influence exerted by oxygen starvation on the central nervous system. In spite of this, however, the mechanism by which the brain's activity is disturbed remains in many respects uninvestigated.

Among the various methods used to investigate the mechanism by which hypoxia influences the central nervous system, electroencephalography is of definite importance.

In the development of acute oxygen starvation, both in practically healthy persons and in animals, we note consistent changes in the bioelectric activity of the cerebral cortex, changes that correlate to a certain degree with certain symptoms of disturbance to the activity of the brain. As has been shown by the studies of G. Berger (1934), A. Davis, H. Davis and W. Thompson (1936), A. Kornmyuler, F. Pal'me and Kh.

Shtrukh'gol'd, P.I. Shpil'berg (1943) and G.V. Altukhov and V.B. Malkin (1949-1950), the changes in the bioelectric activity of the human brain during the development of acute hypoxia are phased. We can clearly distinguish two or three sequentially developing phases: 1) activation of high frequency oscillations; 2) activation of the alpha-rhythm and 3) dominants of the slow high-voltage oscillations - the delta-waves. This last phase appears in the development of severe derangements of the brain's activity (convulsions, impaired consciousness, and so forth.

Experiments on animals have made it possible to investigate EEG changes more thoroughly in the development of acute oxygen starvation, since it was found possible to study even extremely grave hypoxic states. Three basic stages in the variation of the bioelectric activity of the cerebral cortex have been described as functions of the degree to which oxygen starvation has advanced: 1) activation of high-frequency oscillations - the desynchronization phase; 2) predominance of slow rhythms of high amplitude - the hypersynchronization phase and 3) extinction of bioelectric activity - the depression phase (F. Bremer and A. Thoma, 1934; V. Noel', 1950; P. Dell and M. Bonvalier, 1953; O. Kreuzberg, et al., 1957; M.N. Livanov and O.N. Parfenova, 1945; V.B. Malkin, 1955, and others).

Up to the present time, the basic object of study in acute oxygen starvation has been the bioelectric activity of the cerebral cortex, while considerably less attention has been given to investigation of the bioelectric activity of subcortical formations. At the same time, it is extremely important to study the intercentral relationships to ascertain the mechanism by which hypoxia influences the brain.

With the purpose of studying this problem, we studied the bioelectric activity of the cortex and that of certain subcortical formations simultaneously in animals during the development of acute hypoxic hypox-

1a.

During the work, we made an effort, firstly, to establish general relationships between the changes in bioelectric activity in different regions of the cortex and subcortex, and to ascertain the singularities specific for each structure; secondly, to determine the developmental sequence of the changes in bioelectric activity in various structures of the brain.

METHOD

Experiments were performed on rabbits, in which the bioelectric activity of the sensomotor region of the cerebral cortex, the hippocampus, the hypothalamus and the reticular formation of the midbrain were studied during the development of acute hypoxic hypoxia.

The biocurrent leads were bipolar from chronically implanted electrodes. Needle electrodes for registering the cortical biopotentials were implanted in the sensomotor region through a trephined hole, without exposure of the dura mater. The biopotentials were tapped from the subcortical formations by means of constantan electrodes, 30 μ in diameter, covered with glass insulation. The electrodes were introduced with a stereotaxic instrument designed by the experimental workshops of the Bogomolets Physiology Institute using the coordinates of Sawyer, Eneret and Green. The electrodes were fixed to the cranial bones with dental cement. The biopotentials of the brain were registered on an Alvar ink-writer electroencephalograph simultaneously with the record of the electrocardiogram and respiratory movements.

In a special series of experiments on animals in various stages of hypoxia, the reticular formations or hypothalamus was stimulated electrically. Here we used an Alvar Neurovar electronic stimulator, which generates square-shaped electrical pulses.

Acute hypoxic hypoxia was induced in the experimental animals by

"elevating" them in an altitude chamber to an "altitude" of 12,000 m. The rabbits were kept at the "altitude" of 12,000 m until the bioelectric activity of all divisions of the brain being registered had become totally extinct.

With the purpose of determining exactly the positions of the electrodes in the brain, we ran a morphological control, which indicated that the electrodes had been introduced quite exactly into the desired region of the brain.

RESULTS OF INVESTIGATIONS

A total of 38 experiments was run on 20 rabbits. In the normal state, before the "high-altitude ascent," rapid rhythms of the order of 15 cycles and more could be traced clearly on the EEG in the lead from the sensomotor region of the cortex simultaneously with slow oscillations of the order of 4-8 cycles (the latter not uniformly manifest in the different animals). The average level of cortical bioelectric activity varied from 60 to 100 μ v among the various experimental animals.

Subcortically in the reticular formation of the midbrain and hypothalamus and in the lead from the hippocampus, the average level of bioelectric activity was of the order of 40-80 μ v and only in occasional experiments did it reach 90-100 μ v.

As a rule, the slow rhythm (4-6 cycles) predominated in the EEG traces from these regions; they came particularly clearly to the fore in recordings from the hippocampus and subthalamic region, where oscillation forms of the same type, with frequencies of 4-6 per second, were frequently observed. In the hippocampus, even slower oscillations of the order of 1-0.5 cycle and below were manifest against a background of such activity in certain animals.

During the development of acute oxygen starvation in the experimental animals, consistent changes in the bioelectric activity of the

brain were detected. They appeared at different times in traces from different formations of the brain and were phased. Basically, despite the distinct individualism of the EEG's, it was possible to distinguish three phases in the variation of the EEG, phases that reflected advancing oxygen starvation of the brain.

The first phase consisted in activation of high-frequency oscillations; it made its appearance even during the "ascent" to altitudes of 2000-8000 m (at a "rate of climb" of 100 m per second). This phase of the changes in bioelectric activity was detected in 11 out of 20 experimental animals (in 21 experiments out of 38). It appeared most distinctly in leads from the sensomotor region of the cortex, the reticular formation and in the tap from the hypothalamus. With increasing number of rapid oscillations, and despite the increase in their amplitude, the average level of bioelectric activity fell off somewhat: in the reticular formation to 25-40 μ v, and to 50-60 μ v in the lead from the sensomotor region of the cortex. During this period, the slow rhythm at 4-6 cycles became more regular in the traces from the hippocampus and, in certain experiments, in the leads from the hypothalamus.

These changes in the bioelectric activity of the brain took place against a background of distinctly manifest compensatory respiratory reactions, the latter taking the form of increased frequency and depth of respiration. The initial changes in respiration were noted at "altitudes" of the order of 1000-2500 m, i.e., somewhat in advance of the unmistakable first phase of the change in the brain's bioelectric activity.

The increases in the high-frequency oscillations in the leads from the sensomotor region of the cortex, the reticular formation and, in some experiments, from the hypothalamus, were detected almost simultaneously, and only in two experiments was it possible to observe on de-

tailed analysis of the curves that the changes in the bioelectric activity in the reticular formation appeared slightly before those in the cerebral cortex.

As the hypoxia advanced further with the attainment of altitudes of 9000-12,000 m, and, in some of the animals, during the first 10-30 sec at the "altitude" of 12,000 m, the nature of the bioelectric activity changed substantially. The high-frequency oscillations faded and high-amplitude slow oscillations appeared, exhibiting frequencies of the order of 2-3 sec [sic] and lower. Despite the individual differences in the manner in which the EEG changed, predominance of the slow oscillations at a definite stage in the development of hypoxia could be noted in almost all of the experimental animals (in 19 out of 20 animals, and in 36 experiments out of 38).

As a rule, the slow high-frequency oscillations appeared in the traces from all regions of the brain studied. Only in certain experiments were they found to be vaguely manifest in the lead from the hippocampus, where an increase in the amplitude of the ultraslow oscillations was noted in some experiments.

Thus, the second phase of variation of the bioelectric activity during the development of acute hypoxia can be characterized by the domination of slow oscillations with a considerable (by a factor of two or three and more) increase in the average level of the bioelectric activity.

In the majority of experiments, it was exceedingly difficult to establish the sequence in which the slow oscillations appeared in the leads from various structures of the brain. They appeared almost simultaneously in the reticular formation, the sensomotor region of the cortex and the hypothalamus. In six experiments, we noted that the slow oscillations appeared earliest in the traces from the reticular forma-

tion, while in five experiments they appeared first in the lead from the sensomotor cortex. As a rule, it was only in the lead from the hippocampus that the slow oscillations appeared later than they did in traces from other regions of the brain, and they were not distinctly manifest in all experiments.

A fact of definite interest is that "spindles" appeared in the experiments in the background trace of the EEG from the sensomotor region or, less frequently, in the lead from the reticular formation. During the time in which the slow waves were dominant, they appeared again between groups of high-voltage slow oscillations.

As a rule, profound derangements of central nervous activity appeared simultaneously with development of the second EEG phase: clonic spasms, disappearance of motor reflexes to pain stimuli, disappearance of the corneal reflex, and so forth. The cardiac activity was also found to be profoundly disturbed, as attested to by the development of bradycardia with total or partial atrioventricular block, as well as by the appearance of a polytonic ventricular extrasystole. Thus, the second phase corresponded in time with the development of uncompensated oxygen starvation.

The second phase can be arbitrarily broken down into two periods: a period in which the amplitude of the slow oscillations increases and a period in which their amplitude and frequency diminish, periods that immediately precede the development of total depression of bioelectric activity.

Suppression of bioelectric activity is the terminal phase in the variation of the EEG in acute hypoxia. It does not appear immediately in many experiments. Segments of "silence," i.e., the complete absence of bioelectric activity, make their appearance between individual groups of slow oscillations. The bursts of bioelectric activity become

shorter and shorter, the periods of "silence" become steadily longer and, finally, bioelectric activity ceases completely. This phase in the variation of the bioelectric activity appears during the development of an extremely grave hypoxic state. Usually, it coincides in time with the appearance of hypoxic apnoea and with the development of terminal respiration.

In six experiments, the suppression of bioelectric activity was noted at first in the lead from the reticular formation, and only then in the leads from the sensomotor region of the cortex. In seven experiments, on the other hand, depression of the biocurrents occurred first in the lead from the sensomotor cortex, and later in the trace from the reticular formation. In 16 experiments, suppression of the bioelectric activity of the sensomotor cortex, the reticular formation and the hypothalamus was noted almost simultaneously. The bioelectric activity of the hippocampus, as a rule, was maintained for the longest time.

Rapid return of the animals to normal barometric pressure, i.e., "descent from altitude," when done while they were still breathing, i.e., before terminal respiration had definitely ceased, resulted in gradual restoration of the bioelectric activity of the brain and all vital functions. Restoration of bioelectric activity took place faster with shorter suppression phases of the EEG at "altitude."

During resuscitation, we noted that all of the phase changes in the EEG that had been observed during the development of hypoxia were run through in reverse order.

In most of the experiments, the bioelectric activity appeared first in the lead from the sensomotor region of the cortex, and only later in the leads from the subcortical formations and hippocampus. In ten experiments, the appearance of bioelectric activity in the lead from the sensomotor cortex preceded the onset of EEG restoration in

other leads by 5 sec and longer. In nine experiments, restoration of bioelectric activity was noted simultaneously in the leads from the cortex and from the subcortical formations, and only in three experiments did the bioelectric activity first reappear in the lead from the subcortical regions.

In ten experiments, electrical stimulation was applied to the hypothalamus (six experiments) or the reticular formation (four experiments) in various phases of the variation of bioelectric activity. The stimulation was provided at the threshold current value, i.e., the value that would provoke a slight motor reaction from the animal before the "ascent to altitude."

In all experiments, we noted a rise in the electrical stimulation threshold during the development of hypoxia while the slow high-amplitude oscillations were dominant in the EEG (phase II) and during suppression of bioelectric activity (phase III), i.e., in no experiment did we note even a weak motor reaction on the part of the experimental animal in response to stimulation.

During the phase in which bioelectric activity was being restored, the electrical threshold remained abnormal for a long time. Here the restoration of electrical excitability was observed only some time after the EEG had apparently recovered.

In two experiments, the slow oscillations were observed to be supplanted by high-frequency oscillations in the lead from the reticular formation directly after stimulation of that formation; here, the slow oscillations in the lead from the sensomotor region of the cortex also became somewhat less distinct.

During the phase in which bioelectric activity had been suppressed, it was found possible on stimulation to produce spontaneous activity of the stimulated region for a certain time. Following stimulation of the

hypothalamus during the phase in which the high-amplitude slow waves dominated, it was observed in four experiments out of six that suppression of the bioelectric activity of the stimulated region occurred considerably later than in other regions of the brain as hypoxia advanced.

Analysis of the experimental data brings out certain individual differences in the sequence of changes in the bioelectric activity of the brain between different experimental rabbits. Despite this, however, we can distinguish three basic phases characterizing the change in bioelectric activity with rapidly advancing hypoxic hypoxia: 1) activation of high-frequency oscillations; 2) dominance of slow high-amplitude waves; 3) suppression of bioelectric activity.

These phases appear in the EEG both in the lead from the sensorimotor region of the cortex and in the leads from the reticular formation and hypothalamus. In EEG traces from the hippocampus, it was not possible to observe a phase in which high-frequency oscillations were activated.

The presence of consistent phase variations in the EEG in taps from different formations of the brain indicates that they reflect a nonspecific reaction of the neurons to a strong stimulus. We might also arrive at this conclusion on the basis of the fact that such EEG phase changes have been observed not only in the various forms of hypoxia, but also in hypoglycemia (Gell'gorn), narcosis (Robiner et al.) and other disturbances.

Dell and Bonvalier showed that the activation of high-frequency oscillations in a lead from the cortex during hypoxia is due to irritation of the chemoreceptors in the sinocarotic zone, which results in excitation of an ascending activating reticular formation and determines the corresponding desynchronization reaction in the cortex. The experiments that we performed show that the hypothalamus is also drawn into

this reaction, in addition to the reticular formation.

The development of the second phase may be governed in the cortex both by the direct inhibiting action hypoxia on the cortical neurons and by the suppression of their activity due to a decline or complete cessation of the activating effect of the reticular formation on the cortex. The appearance, in some experiments, of slow waves in the lead from the sensomotor region of the cortex somewhat in advance of the same phenomenon in the lead from the reticular formation provides a basis for the assumption that the second phase is due, at least in these experiments, to the direct inhibiting effect of hypoxemia on the neurons.

The cortical and subcortical development sequence in the second and third phases - the latter consisting of suppression of the brain's bioelectric activity - suggests a complex systemic character for the reaction of the central nervous system in hypoxemia, and not a simple layer-by-layer "switching-out" of its various divisions, as has been assumed by some investigators (V.V. Strel'tsov, A.A. Volokhov and others).

In this connection, the fact that the bioelectric activity of the cortical sensomotor region is restored first after the animals have been returned to normal respiration conditions is highly noteworthy.

Thus, in ephemeral acute hypoxic hypoxia producing complete suppression of bioelectric activity (lasting up to 1 minute) in the sensomotor region of the cortex, the hippocampus, the reticular formation and the hypothalamus, the sequence of phase changes in the EEG cannot be reduced, either during the time in which hypoxemia is being aggravated or during resuscitation, to the simple model of layer-by-layer "top-to-bottom" inhibition of various regions of the brain and their corresponding "bottom-to-top" restoration during the posthypoxic period.

POLAROGRAPHIC METHOD IN STUDY OF TISSUE HYPOXIA IN THE LIVING
ORGANISM

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(Moscow)

Under the influence of many factors encountered in high-altitude flight - rarefaction of the atmosphere, excess pressure in the lungs, acceleration - hypoxic states may arise in the organism - states whose study is of great practical and theoretical interest for aviation and space medicine.

A much-neglected and, at the same time, one of the most interesting and important aspects of the problem of oxygen starvation is that of hypoxia and the oxygen supplied directly to the tissues, and, primarily, to the tissues of the brain as the organ most sensitive to oxygen deficiency.

The methods of in vivo study of hypoxic states, which were, until recently, within the province of the physiologist and pathophysiologicalist, enabled us to judge the oxygen supply being furnished to the tissues only indirectly. Only in recent years has a method been developed for determining the oxygen partial pressure (pO_2) directly in the tissues - the method of polarographic analysis. The theoretical foundations of this technique and the principles employed in its practical utilization in analytical chemistry and engineering were worked out by the Czech scientist Ya. Geyrovskiy (1922).

The polarographic technique has been used in physiological research by Davis and Brink (1942), Montgomery (1958), and Clark et al.

(1953), and also by A.L. Byzov and G.D. Smirnov (1951), I.D. Entina and V.A. Yakovlev (1951), A.D. Snezhko (1956), Ye.A. Kovalenko (1959, 1961), Ye.M. Khvatova (1961) and N.V. Sanotskaya (1960).

The essentials of this technique reduce to the following. If a voltage of 0.4-0.6 v is impressed upon two electrodes placed in a solution of electrolyte or in the tissue of a living organism, which is a colloidal solution, then reduction of the O_2 present in the given medium begins at the cathode, with formation of H_2O_2 ($O_2 + 2H + 2e = H_2O_2$) and then reduction of the H_2O_2 to water ($H_2O_2 + 2H + 2e = 2H_2O$). This naturally causes a current to flow in the circuit - a current whose magnitude is proportional to the amount of oxygen diffusing toward the cathode per unit of time, i.e., to the oxygen concentration in the solution. Consequently, the O_2 concentration in the solution can be inferred from the value of the current registered.

For in vivo determination of the O_2 partial pressure in the tissues, the polarographic analysis procedure departs from the classical version in using a solid platinum electrode instead of the mercury electrode. A nonpolarizing electrode (Dubois-Reymond electrode, a calomel electrode or a silver chloride electrode) is used as the anode. The voltage is applied to the electrodes from a direct-current battery; the current that arises in the circuit, which is of the order of fractions of a microampere, is registered by means of a sensitive galvanometer.

Research is performed under ordinary laboratory conditions with this polarographic apparatus - at normal barometric pressure and constant gravitational field.

The polarographic apparatus has been improved for experiments to be performed in a rarefied atmosphere.* This technique makes it possible to determine pO_2 in several regions of the brain (cortex and sub-

cortex) under the conditions of the altitude-chamber experiment and is essentially as follows.

An operation is performed in which two composite electrodes are implanted in the brain of a dog; the electrodes are made of plexiglas and each encloses two platinum needles of differing lengths (from 4 to 16 mm for the cortex and subcortex). These electrodes become the cathodes. The anodic electrode is either an ebonite rectal electrode with a silver-chloride attachment or a specially developed ear clip of our own design with a silver chloride plate and a screw that makes it possible to vary the amount of contact between the electrode and the skin and to regulate the interelectrode resistance within certain limits. The use of such anodic electrodes eliminates the possibility of evaporation of liquid from the latter's surface and formation of bubbles of desaturated gas within the electrodes when the atmosphere is rarefied. Moreover, the secure location of the electrodes makes it possible to conduct oxygen polarographic analysis even when the accelerations are considerable. A diagram of the polarographic apparatus is presented below (see Fig.1).

The operation of the implanted electrodes during respiration of various gas mixtures in "ascents" in the altitude chamber can be checked immediately after the operation if an acute experiment is planned, or, on the other hand, 10-15 days later, when the animal is to be used for chronic experiments.

Electrodes were regarded as satisfactory if they could be used to register a proportional increase in the pO_2 in the brain during respiration of gas mixtures with the oxygen concentration increasing (from 20 to 100%) and with diminishing pO_2 during inspiration of mixtures deficient in oxygen. The oxygen partial pressure registered during inspiration of air is taken as 100%.

A particularly valuable criterion for proper performance of the

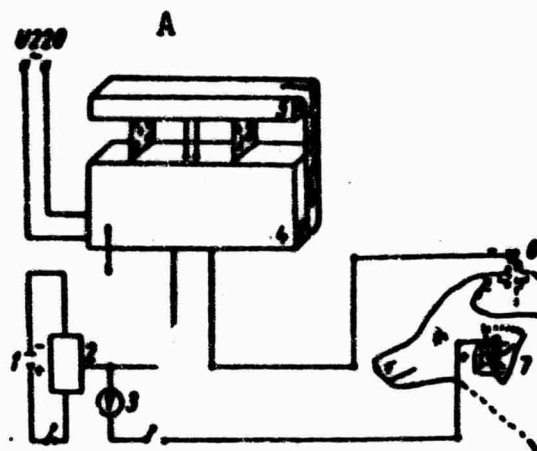


Fig. 1. Diagram of polarographic apparatus for direct determination of O_2 pressure in tissues of dog brain. 1) Direct-current source; 2) variable resistance; 3) voltmeter; 4) direct current amplifier; 5) recording mechanism; 6) platinum electrodes in brain (cathodes); 7) silver chloride ear electrode (anode). A) $U = 220$ volts AC.

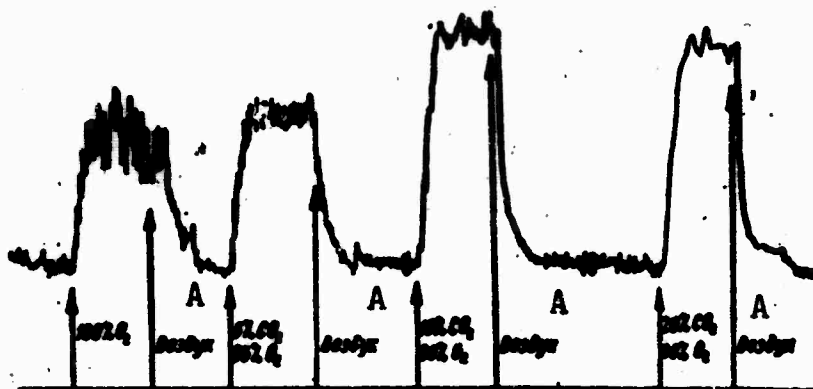


Fig. 2. Change in rhythm of pO_2 in brain tissues during respiration of gas mixtures with different contents of O_2 and CO_2 . A) Air.

polarographic apparatus is obtained by "elevating" the animal in the altitude chamber to an "altitude" of 10,000-10,500 m during respiration of pure oxygen. Here the pO_2 in the tissues of the brain should be the same as on the ground during respiration of atmospheric air, since the partial pressure of O_2 in the alveolar air is approximately the same in these two cases.

Using the polarographic apparatus described, we performed several series of experiments with altitude-chamber "ascents" and barometric pressure drops, respiration of gas mixtures, and even during spinning on the centrifuge. The results obtained give a clear conception of the

high promise of the polarographic method for study of hypoxic states.

Under ordinary conditions, when the dogs were breathing air, a number of experiments showed a kind of rhythm in the brain-tissue oscillations of the oxygen pressure, at a frequency of 4-8 per minute; the amplitudes of these oscillations sometimes reached as high as 20% of the initial pO_2 level. A similar observation was also made in the studies of A.D. Snezhko (1957) and those of Davis and Bronk (1957). The nature of this rhythmicity has not yet been made clear. In our experiments we established a considerable increase in the amplitude of the rhythmical pO_2 fluctuations during respiration of 100% oxygen and a sharp decrease or even the disappearance of the oscillations during respiration of gas mixtures with high CO_2 contents (Fig. 2). Considerable variations in the pO_2 rhythm were also observed during acceleration. These facts, together with the data of other authors, provide support for the assumption that the rhythmical variations of pO_2 reflect a periodicity in the metabolic processes or fluctuations in blood-vessel tone in the brain. However, this problem requires further study.

During a slow "ascent" in which the animals were taken up to an "altitude" of 12,000 m without oxygen and left at this altitude for two minutes, we observed a drop in the pO_2 in the cortex by an average of 50% and in the subcortex by 70%. Here, violent manifestations of acute oxygen starvation were frequently noted (convulsions and suspension of respiration). "Ascent" to this altitude with oxygen caused a drop in the cortical and subcortical pO_2 by no more than 20-25%.

The same drop in pO_2 was observed while the animals were in residence at an "altitude" of 3600-4000 m without O_2 , i.e., in these cases only a moderate oxygen starvation of the brain tissues was noted. These data permit inferences as to the maximum permissible degrees of hypoxia in the brain tissue and provide a conception of the levels of oxygena-

tion of tissues in various divisions of the brain under various conditions of oxygen supply.

During rapid "ascents," such as simulate depressurization of an aircraft's cabin at altitudes of 15,000, 17,000 and 20,000 m, the dogs showed a distinct drop in the pO_2 of the brain tissues within 30-10 seconds, respectively. The pattern of acute oxygen starvation developed immediately after this, terminating in collapse of the animal, convulsions, and, within 120-60 seconds, total cessation of respiratory movements. Further residence at these "altitudes" resulted in the death of the animal.

The rate and extent of brain-tissue deoxygenation increased with increasing "altitude." This fact accounts for the shortening of the "reserve time" in the dogs (this is the time from the moment of collapse to stoppage of respiration) that was observed as the "altitude" increased, and requires a critical attitude toward the statement Shtruhgol'd et al. (1951) to the effect that an altitude of 15,000 m is equivalent to cosmic space as regards O_2 deficiency.

In experiments in which oxygen was breathed under excess pressure, using an external compensating counterpressure on the body under ground-level conditions and during "ascents" to altitude, it was established that the pO_2 in the brain tissues is determined by the excess pressure in the lungs, the effectiveness of the compensating apparatus and the "altitude of ascent." Thus, under ground conditions, given an increase in intrapulmonary pressure to 150 mm of mercury and adequate compensation of the latter by an external counterpressure, the pO_2 in the brain tissues increased by two or three times. In cases in which the excess pressure in the lungs was not effectively compensated, the pO_2 fell below the initial level, indicating the development of circulatory derangements.

Breathing oxygen under an excess pressure amounting to 150 mm hg together with the atmospheric pressure in combination with an effective counterpressure on the animal's body during the "ascent" to "altitudes" up to 30,000 m permits maintenance of the pO_2 in the brain tissues at 60-70% of the initial level. Under these conditions, therefore, the animals' organisms are in a state of moderate oxygen starvation, since such pO_2 values are observed in ascents without O_2 to moderate altitudes (4000-5000 m) or during respiration of 100% O_2 without excess pressure at an altitude of 12,000 m.

A decrease in the excess pressure in the lungs, like a decrease in the effectiveness of the compensating devices under the conditions of flight, results in a considerable drop in the brain's pO_2 , which sometimes falls to 30% of the initial level.

The data obtained in this series of experiments indicate the possibility of using the polarographic technique for oxygen determination in combination with other research methods to evaluate the effectiveness of experimental oxygen-breathing equipment that sets up an elevated pressure in the respiratory passages.

Use of the polarographic technique has made it possible to obtain interesting data also during prolonged acceleration. It was found that under these conditions, the pO_2 in the brain tissues drops (Fig. 3). Here the degree to which the pO_2 declines is determined chiefly by the magnitude of the g-force. Also of essential importance is the latter's direction relative to the longitudinal axis of the animal's body. Thus, it became possible for the first time in obtaining not indirect, but direct proof of the development of tissue hypoxia in the brain under the influence of acceleration. Comparison of the data obtained on pO_2 with the results of varying other physiological functions enables us to form a conception of the severity of the developing hypoxic state and

evaluate the effectiveness of the various countermeasures taken under these conditions.

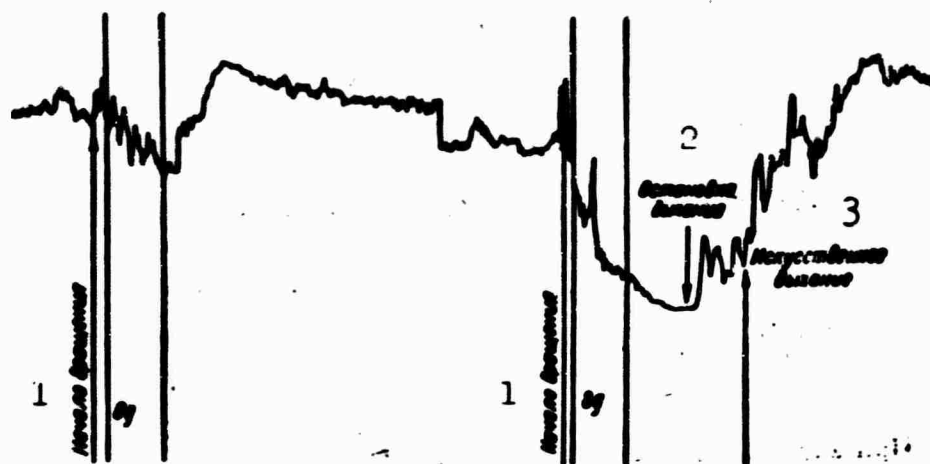


Fig. 3. Variation of pO_2 in dog brain tissues during operation of g-forces in the head-to-pelvis direction. 1) Start of spin; 2) respiration stops; 3) artificial respiration.

The use of the polarographic technique in experiments on animals breathing various gas mixtures made it possible to establish that the pO_2 in the brain tissues depends not only on the partial pressure of this gas in the inspired mixture, but also on the latter's CO_2 content. Thus, addition of 5-10% of CO_2 (replacing nitrogen) to the air causes pO_2 to rise to 130-160%. Further, while respiration of a hypoxic mixture (5% O_2 and 95% N_2) for three minutes lowers the pO_2 on the average to 45%, addition of 10% of CO_2 to this mixture lowers the pO_2 only to 75% on the average. These data indicate the importance of the part taken by carbon dioxide in hypoxic states of the brain and make possible a new approach to study of the mechanism by which carbogen [oxygen with admixture of carbon dioxide] exerts its influence in oxygen starvation.

A study of the influence of various pharmaceutical agents (adrenalin, caffeine, cytitone, lobeline) on the pO_2 level indicated that the oxygenation of the brain also depends to a considerable degree on the state of blood circulation in the brain tissues. Thus, on intravenous administration of adrenalin, we observe a sharp undulating increase in

pO_2 in the tissues of the brain. This fact suggests the possibility of experimental study of the action of various pharmaceutical agents on the level of oxygen supplied to the brain.

It can be stated on the basis of the data presented above that in vivo determination of pO_2 in the tissues of the brain under the influence of rarefied atmosphere, acceleration, breathing of oxygen under excess pressure and mixtures of gases, as well as on administration of various pharmaceutical agents to the organism, places in the hands of the experimenter a valuable technique for study of the oxygen supplied to the tissues of the brain while the factors enumerated are in operation.

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Ye.A. Kovalenko, in journal entitled "Pat. fiziol. i eksperiment. terapiya," [Pathological Physiology and Experimental Therapy], 1961, 2, page 66.

OXYGEN PRESSURE IN TISSUES OF DOG BRAIN DURING
RESPIRATION OF GAS MIXTURES

Ye.A. Kovalenko, V.L. Popkov and I.N. Chernyakov
(Moscow)

In studying the organism's reactions to changes in the gas composition of the air inspired, it is necessary to have an idea of the partial pressures of the gases in the alveolar air, the blood and directly in the tissues. Among these problems, the latter is at present the one most neglected and at the same time the most important, since until recently there has been no reliable technique for in vivo determination of the gas pressures in the tissues of the living organism.

METHOD

With the purpose of in vivo study of the dynamics of oxygen pressure (pO_2) in dog brain tissue during respiration of various gas mixtures, we employed the polarographic method of determining the O_2 using platinum electrodes implanted in the brain.* Simultaneously with pO_2 , certain indices to the basic physiological functions were recorded in individual experiments using an eight-channel ink-writer oscillograph: EEG, EKG, pneumogram, and EMG of the external oblique abdominal muscles, the pulmonary ventilation and arterial pressure.

The gas mixtures used in the experiments consisted of nitrogen, oxygen and carbon dioxide in various proportions (see table). A special apparatus was developed to permit quick preparation of a gas mixture of the desired composition and feed it into the respiratory passages of the animal (Fig. 1). The apparatus consists of three bottles (1) with

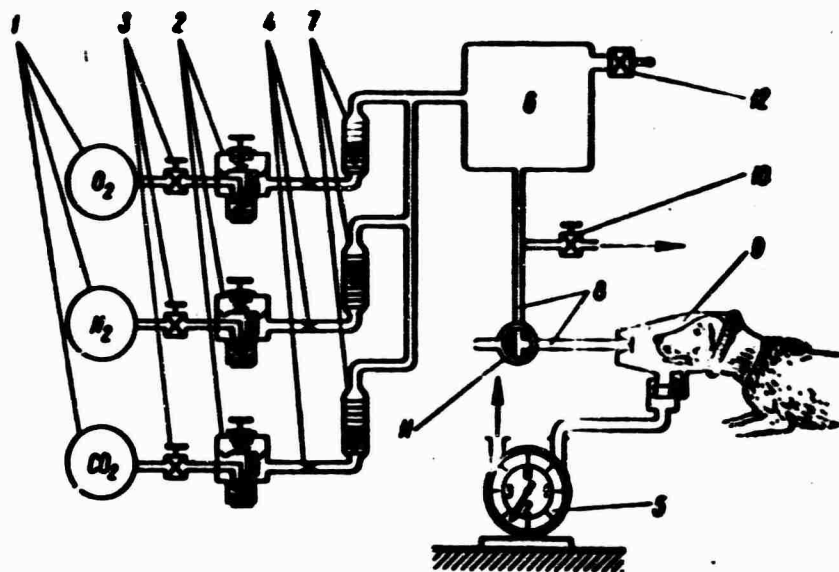


Fig. 1. Diagram of apparatus for preparation of gas mixtures. A description is given in the text.

capacities of 40 liters each operating at a pressure of up to 150 atm, three pressure reducers (2) with the valves (3), which cut the pressure to 1-3 atm, three nozzles (4) with diameters of 0.3 and 0.15 mm to set up a steady flow of gas, sections of rubber tubing, a mixer (6) and rheometers (7). The latter make it possible to establish the required percentage composition of the gases in the mixture from the volume of each gas fed into the mixer. A Douglas bag (12) is connected to the apparatus as an auxiliary capacity for cases in which the pulmonary ventilation exceeds the volume of gas fed into the apparatus from the bottles (over 5 liters/min). The mixing chamber of the apparatus is connected to a mask or "space helmet" (9) via the hose (8) with its side extension (10). The gas mixture is ducted through the side pipe to a continuous-duty "Oksitest" gas analyzer to permit steady monitoring of the oxygen concentration in the mixture. The side pipe is also used for periodic sampling for control analyses of the carbon dioxide content in the mixture in a Holden apparatus or a "GUKh-1" instrument. Access of atmospheric air to the lungs was cut off by turning a three-way petcock, and the animal then began to breathe the gas mixture under investiga-

tion. The expired air passed through a gasmeter (5), so that it was possible to measure the pulmonary ventilation. In all cases the gas mixture was breathed for 3 minutes. The brain oxygen pressure registered during respiration of atmospheric air was taken as 100%.

A total of 204 experiments were performed on 10 dogs with implanted electrodes.

RESULTS OF EXPERIMENTS

Variation of pO_2 in brain tissues during respiration of gas mixtures with various oxygen contents. The oxygen partial pressure in the tissues of the brain was maintained at a level constant for each experiment in the majority of cases in which atmospheric air was breathed. It is necessary to note, however, that this pO_2 level showed periodic fluctuations not connected with the pulse or respiration rhythms: the amplitude of the fluctuations sometimes reached 8-10% of the average pO_2 value, while the frequency varied in the range from four to eight per minute.

Breathing pure oxygen resulted in an increase in pO_2 in the cortex and subcortex, on the average by a factor of one and a half (see table). As a rule, the rhythmical fluctuations of pO_2 in these experiments increased in amplitude, reaching 20-30% of the initial level in some cases (Fig. 2).

The increase in the brain-tissue pO_2 only by a factor of one and a half to two during respiration of 100% oxygen, when the partial pressure of this gas in the alveolar air and, consequently, in the blood as well, is increased by a factor of approximately 6.5, indicates that there is no direct proportionality under these conditions between the pO_2 in the tissues and that in the blood. There is justification for assuming the presence of a direct positive correlation between these indices. The physiological mechanism of this relationship requires

O₂ Partial Pressure (pO₂) in Brain Tissues During Respiration of Various Gas Mixtures

1	2	3	3									
Газовая смесь	Воздух (исходный)	Воздух + 5% CO ₂	Воздух + 10% CO ₂	O ₂ -10% N ₂ -90%	O ₂ -15% CO ₂ -5% N ₂ 80%	O ₂ -10% CO ₂ -10% N ₂ 80%	O ₂ -5% N ₂ -95%	O ₂ -5% CO ₂ -5% N ₂ -90%	O ₂ -5% CO ₂ -10% N ₂ -85%	O ₂ -85% CO ₂ -5%	O ₂ -90% CO ₂ -10%	
4 В коре												
5 pO ₂ в % (средняя величина)	100	165	123	159	77	92	120	48	68	82	233	300
6 Крайние значения pO ₂ в %	—	123-222	98-157	104-250	50-92	82-108	100-157	26-83	48-88	72-133	126-600	145-750
7 Количество измерений . .	140	15	14	14	12	8	9	10	8	9	11	12
8 В подкорке												
5 pO ₂ в % (средняя величина)	100	150	127	160	58	64	109	37	45	78	209	405
6 Крайние значения pO ₂ в %	—	125-200	100-160	105-204	50-62	40-89	94-125	21-52	30-60	—	138-350	172-487
7 Количество измерений . .	64	10	6	7	5	4	4	4	3	1	8	8

1) Gas mixture; 2) air (initial); 3) air; 4) in cortex; 5) pO₂ in % (average value); 6) extreme values of pO₂ in %; 7) number of measurements; 8) in subcortex.

study. At the moment, however, we can still advance the hypothesis that one of the factors preventing a directly proportional increase in the brain-tissue pO₂ with increasing pO₂ in the blood is the spasm of the intracranial vessels that has been noted by many authors during breathing of mixtures with high O₂ contents (Lambertson, 1960; Vomek, 1961, and others).

It must be noted that during respiration of 100% oxygen, the pulse slackens somewhat and the pulmonary ventilation drops noticeably (by 0.6-0.8 liter/min from an initial ventilation of 3 liters/min); there are no distinct changes in other indicators. A drop in the mixture's oxygen content to 10-5% caused a consistent drop in the brain-tissue pO₂ - down to 77-48% in the cortex and even further - 57-36% - in the subcortex (see table and Fig. 2).

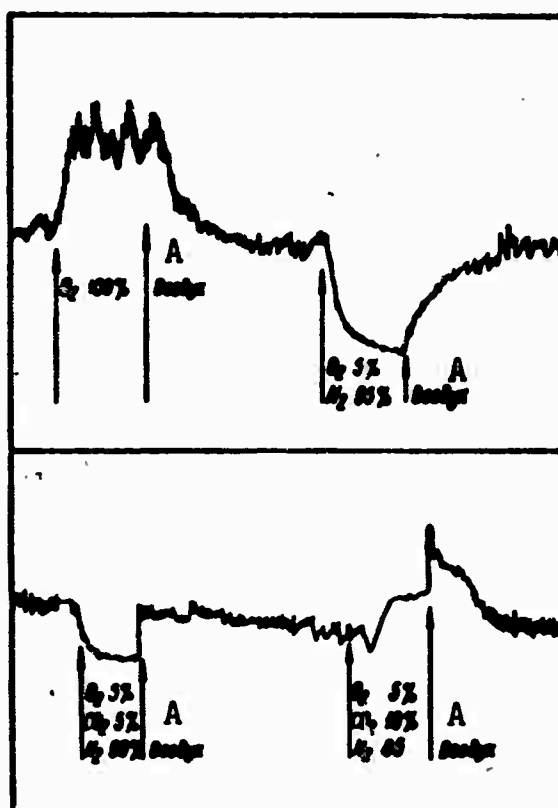


Fig. 2. Oxygen partial pressure in cortex of brain during respiration of pure oxygen, a hypoxic mixture without carbon dioxide and a hypoxic mixture with 5 and 10% of carbon dioxide added (experiment No. 12 on 17 June 1961, dog Omega). A) Air.

It is of interest that the most clear-cut drop in the subcortical pO_2 was also observed in the experiments of Ye.A. Kovalenko (1961) in "ascents" by an animal to an "altitude" of 12,000 m without oxygen.

On respiration of a hypoxic mixture, the pO_2 rhythm was suppressed to some degree. Simultaneously with the lowering of pO_2 in the brain, hypoxic mixtures caused a quickening of the pulse (by 10-40 beats per minute), a certain quickening of respiration, a marked increase in pulmonary ventilation (by 1.5-2 liters/min), some increase in the AD [arterial pressure], an intensification of bioelectric activity in the skeletal muscles and the appearance of high-amplitude slow oscillations on the EEG. In occasional cases, respiration of an oxygen-deficient mixture (5%) was observed to be accompanied by convulsions and even cessation of breathing. The lowest pO_2 in the brain tissues were registered here. After 6-8 minutes had elapsed since respiration was switched

to atmospheric air, these changes in the physiological indicators returned to their normal level.

Variation of pO_2 during respiration of gas mixtures with elevated CO_2 content. It was ascertained in subsequent experiments that the pO_2 level in the brain tissues is determined not only by the oxygen concentration in the inspired air, but to an even greater degree by the content of carbon dioxide gas in the latter.

Thus, addition of 5-10% of carbon dioxide gas to the air (at the expense of the nitrogen) raised the pO_2 to 123-158% in the cortex and to 127-160% in the subcortex (see table and Fig. 3). The rise in the brain pO_2 during respiration of air with 10% of carbon dioxide was approximately the same as for respiration of pure oxygen. The rhythm of pO_2 diminished in amplitude with increasing concentration of carbon dioxide gas in the mixture.

The changes in the other physiological functions during these experiments can be reduced to the following. With a slight decrease in the frequency of respiration, the depth increases sharply, with the result that pulmonary ventilation is expanded considerably (by a factor of three or four). We also note a marked rise in the electrical activity of the respiratory muscles, particularly during the inspiration phase; the AD [arterial pressure] increased. During respiration of the mixture, the pulse frequency was close to normal, and sometimes even subnormal. During the first minute after respiration had been switched from atmospheric air, a sharp quickening of the pulse was noted (by 20-40 beats per minute), a fact apparently reflecting the heart's reaction to the drop in AD after the carbon dioxide had been cut off. Under the conditions of hypercapnia, the EEG showed slow high-amplitude oscillations at a frequency of four or five per second, these forming a background for still more frequent oscillations. These EEG changes appar-

ently reflect the appearance of the narcotic effect of hypercapnia.

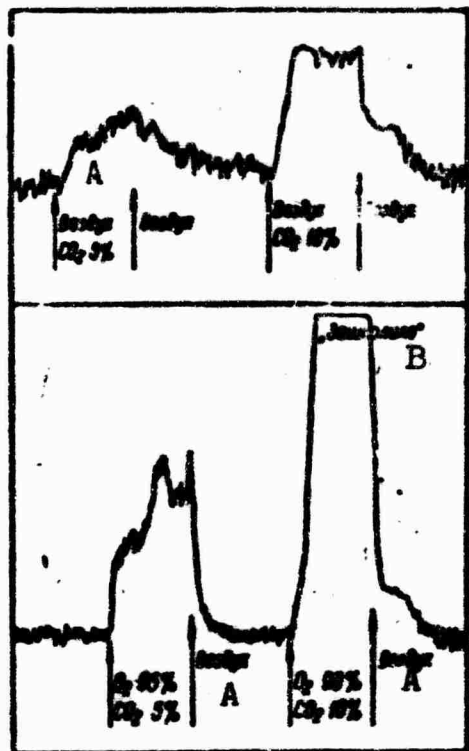


Fig. 3. Oxygen partial pressure in brain cortex on addition of 5 and 10% of carbon dioxide to air and to oxygen (experiment No. 12, on 17 July 1961, dog Omega). A) Air; B) off the scale.

Analysis of the facts enumerated here, as well as literature data (P.N. Al'bitskiy, 1911; N.V. Veselkin, I.I. Golodov, 1946; K. Ye. Serebryannik, 1946; F.L. Bukh, 1949; I.K. Petrov, 1949; M. Lambertson, 1960; Kadrov and Naumenko, 1954; V.A. Skripin, 1960; Vomek, 1961; N.V. Sanotskaya, 1961) permit us to advance a hypothesis as to the factors that elevate the pO_2 in the tissues of the brain during respiration of air with a high CO_2 content. Such factors may include: increased pulmonary ventilation, which results in an elevation of pO_2 in the alveolar air and in the blood, increased blood flow in the vessels of the brain, a right shift of the oxyhemoglobin dissociation curve and, finally, a drop in the or-

ganism's oxygen consumption.

The next group of experiments studied the variation of pO_2 in the tissues of the brain during respiration of oxygen with 5 and 10% of carbon dioxide added. The oxygen partial pressure in the brain rose in these cases to a considerably greater degree than for respiration of 100% oxygen alone, averaging, respectively, 232-300% in the cortex and 209-405% in the subcortex (see table and Fig. 3). Our attention was drawn to the fact that in many of the experiments, pO_2 rose by a factor of six to eight in the brain. All of this attested to a sharp increase in the oxygen supply to the tissues of the brain when carbon dioxide was added to the oxygen. It seems to us that these data are of great

practical interest for clinical medicine.

Variation of pO_2 in brain tissues during respiration of hypoxic mixtures with carbon dioxide added to them. As we have already indicated, respiration of a hypoxic mixture (5% oxygen) causes a sharp drop in the brain-tissue pO_2 , which goes down to 48% in the cortex and 36% in the subcortex. When 5% of carbon dioxide gas is added to this mixture (at the expense of the nitrogen), the drop in pO_2 was distinctly smaller: the pressure was 68% in the cortex and 44% in the subcortex. An even higher level of pO_2 in the brain tissues could be maintained during respiration of a mixture with 5% oxygen by adding 10% of carbon dioxide to it. Here the oxygen partial pressure came to 82% in the cortex and 78% in the subcortex (Fig. 2).

During respiration of a mixture with 10% oxygen and 10% carbon dioxide, we even observed an increase in the pO_2 above its initial level, within the following limits: 120% in the cortex and 108% in the subcortex. These data indicate that the addition of carbon dioxide to the inspired mixture with a lowered partial oxygen pressure may, under certain conditions, substantially improve the oxygen supply to the tissues of the brain.

The increase in the brain-tissue pO_2 that intervenes on combined action of hypoxia and hypercapnia cannot be accounted for in terms of the increase in pulmonary ventilation (by a factor of five or six) observed in these experiments, nor by an increase in the blood supply to the brain, since when there is a sharp drop in the pO_2 in the alveolar air, both of these factors would be more likely to result in deoxygenation of the brain than in an increase in the latter's pO_2 . Hence it is natural to assume that the decisive factors in maintaining pO_2 at a sufficiently high level under these conditions was a drop in the oxygen consumption by the brain cells. The EEG data provide an indirect con-

firmation of this in indicating a decline [sic] of the hemoglobin dissociation curve to the right, as was also reported in his time by I.I. Golodov (1946).

Data obtained in experiments with the pO_2 under the combined influence of hypoxia and hypercapnia permit a new approach to the solution of the question as to the role of carbogen and more concrete understanding of the physiological importance of carbon dioxide in the oxygen supply to the brain in hypoxic states of the organism.

CONCLUSIONS

1. The oxygen partial pressure in the tissues of the brain depends on the percentage content of oxygen in the inspired mixture. As the oxygen concentration in the mixture is increased to 100%, the pO_2 in the cortex and subcortex rises, on the average by a factor of one and a half to two. Simultaneously with this, we observe a marked decrease in pulmonary ventilation. No distinct changes are noted in other indicators.

2. When the oxygen content in the mixture is lowered to 10-5%, the pO_2 diminishes, on the average, to 77-48% of the initial value in the cortex and to 57-37% in the subcortex. Under these conditions, we observe distinct hypoxic changes in the physiological functions under study.

3. A gas mixture corresponding in oxygen content to air but having an elevated carbon dioxide concentration (5 and 10%) produced an increase in the pO_2 of the cortex and subcortex to 125-160%, respectively.

An even greater increase in the pO_2 of the brain, reaching 250-400%, is observed during respiration of a mixture consisting of 95-90% of oxygen and 5-10% of carbon dioxide (carbogen). These facts justify advancing the hypothesis that the pO_2 level in the brain depends not only on the partial pressure of this gas in the alveolar air, but also

on the state of blood circulation in the brain, changes in the oxygen consumption of the tissues and, probably, on shifts in the oxyhemoglobin dissociation curve.

4. Addition of 5-10% of carbon dioxide to the inspired gaseous mixture produced a sharp increase in pulmonary ventilation, a rise in arterial pressure, an increase in the frequency and amplitude of the abdominal-muscle EMG, a slackening of the pulse and the appearance of a theta rhythm in the EEG.

5. During respiration of a mixture with a lowered oxygen content (10 and 5%) but with 5-10% carbon dioxide added to it, we note a considerably smaller drop in the pO_2 of the brain tissues as compared with respiration of the same mixtures without the carbon dioxide gas. In occasional experiments, the oxygen partial pressure in the brain reached the initial level or even surpassed it in the former case. These facts permit more concrete understanding of the physiological role of carbon dioxide in the oxygen supply to the brain tissues in hypoxic states of the organism.

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A detailed description of the technique will be found in the paper by Ye.A. Kovalenko in the journal "Patol. fiziol. i eksperim. terapiya." [Pathological Physiology and Experimental Therapy], 1961, No. 2, page 66.

ENERGY INDICES TO STATE OF CENTRAL NERVOUS SYSTEM IN HYPOXIA

V.A. Berezovskiy

(Kiev)

An opinion commonly encountered in physiological literature is that shutting off one or both carotid arteries produces no distinct hypoxia in the brain (Andreyev, 1933; Petrov, 1949; Karlil and Greyson, 1956, and others). Despite its high sensitivity, the electroplethysmographic method also indicates the absence of any significant changes in the blood supply to the brain when a carotid artery is tied off (Kedrov and Naumenko, 1954). At the same time, it is well known that the central nervous system is very highly sensitive to an insufficiency of oxygen, a drop in the supply of which results in disturbances to higher nervous activity (Sirotinin, 1934; Altukhov, 1955; Zvorykin, 1953; Kuklin, 1960) and to readjustment of the metabolic processes in the brain (Kreps, 1958; Shapot, 1952; Gayevskaya, 1951, and others). Hence, even quite apart from the abundance of collaterals, shutting off one of the arteries cannot but produce changes on the part of the nervous tissue. The lack of information concerning these changes may be the result of inadequate sensitivity of the methods that have been used up to now (Chenykayeva, 1958).

Geyerovskiy's development (1922) of polarographic analysis and the possibility of applying this method for dynamic determination of the oxygen partial pressure in the brain under the conditions of the chronic experiment (Davy et al., 1942-1944; Entina and Yakovlev, 1951; Meyer and Deni-Braun, 1955; Snezhko, 1956-1957; Sanotskaya, 1960; Mizrani,

Beran, Spredli and Garvud, 1960; Kovalenko, 1961, and others) have considerably broadened our capabilities in this direction. On the other hand, the development of semiconductor physics and the creation of highly sensitive thermistors make it possible to investigate with high accuracy the temperature fluctuations in the central nervous system (Ludwigs, 1954; Karmanov, 1956; Parolla, 1958), and this enables us to draw inferences as to the rates of metabolic processes in the tissues (Voronin, 1942; Gramenitskiy, 1952; Semenov, 1952; Klossovskiy, 1951-1961; Berezina, 1954; Berezovskiy, 1960).

The oxygen partial pressure in the brain tissue was determined using platinum electrodes mounted in threaded organic-glass plugs 8 mm in diameter, which were implanted in the brain. The surface of the electrode was coated with a film of KhVL-21 [polyvinyl chloride lacquer] with the exception of the free face end. The depth of immersion in the brain tissue through the pinhole in the dura mater did not exceed 2-3 mm. The anode was a silver-chloride rectal electrode fashioned in the form of a rod or olive. A steady voltage of about 0.6 volt from a high-capacity storage battery was employed. The voltage drop across a dissipative load of the order of 2-3 kilohms was fed to the input of an automatic electronic self-recording potentiometer, the EPP-09. Preliminary step-down of the resistance P_{sh} in the measuring bridge of the potentiometer makes it possible to raise its electrical sensitivity to 150-200 microvolts per scale [division]. In practice, a sensitivity of 1 microvolt per scale [division] (with a trace width of 280 mm) is quite adequate. The possibility of shifting the instrument's null by varying the resistance P_n (2) makes it possible to eliminate the circuit compensating the constant component.

Temperature changes were determined by means of MT-54 semiconductor microthermistors, which were implanted in various regions of the brain down to contact with the surface of the cortex. The thermistor was connected into an arm of the direct-current bridge with a power of up to 30 μ v dissipated in it (Karmanov, 1956). The imbalance current was applied to the input of an EPP-09 multichannel automatic-recorder potentiometer. The temperature sensitivity of the apparatus runs up to 0.002 mm (Berezovskiy, 1960, 1961). The experiments were performed on

dogs under the conditions of the acute and chronic experiments.

The data obtained indicated that shutting off any of the four main arteries of the neck results in a manifest reaction on the part of the brain tissue. A few seconds after the artery has been clamped, a drop in the oxygen partial pressure level begins in the tissue and its temperature begins to rise (Fig. 1a).

Clamping one carotid artery for 3 min results in a more strongly manifest drop in the oxygen partial pressure in the brain as compared with tying off one vertebral artery for the same period of time. Even sharper changes are observed when two arteries are clamped simultaneously. The amount by which the temperature rises also increases correspondingly (Figs. 1c and 2).

Changes of a similar nature - a drop in the oxygen partial pressure and an elevation of brain temperature - are observed in various disturbances that lead to oxygen insufficiency in the central nervous system: inspiration of gaseous nitrogen for 1-3 min, mechanical asphyxia, injection of a sodium nitrite solution into the blood, blood-letting or ligation of the four arteries of the neck. Such manipulations, which produce gross disturbances in the oxygen supply to the brain, result in a catastrophic rise in the temperature of the brain while the temperature of the arterial blood going to it remains relatively stable. While ligation of one neck artery causes a temperature rise of the order of $0.08-0.15^{\circ}$ C, which returns to the initial level immediately after blood flow in it has been restored, mechanical asphyxia or subtotal blood-letting raises the temperature of the brain by $1-1.5^{\circ}$ C, a level maintained for 10-30 min and longer, depending on the nature and severity of the disturbance (Fig. 3).

Measurement of the temperature of the blood draining from the brain indicated that during gross disturbances to the brain's oxygen

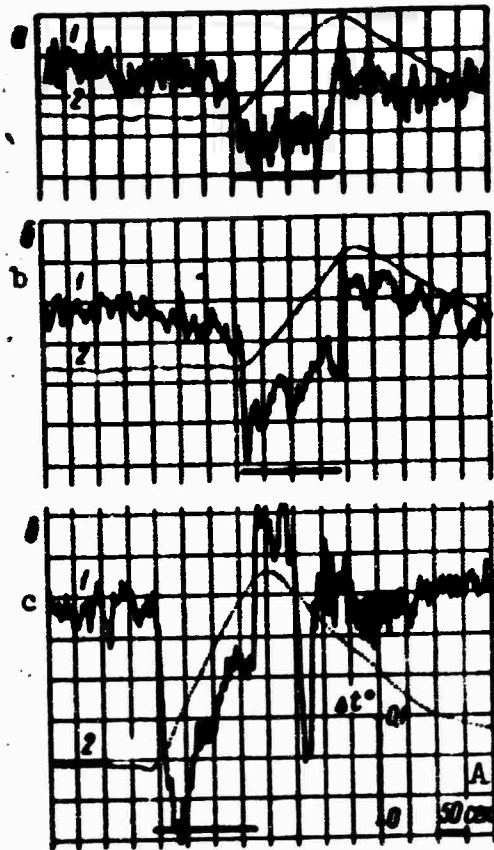


Fig. 1. Changes in oxygen partial pressure and temperature in the brain cortex of a dog on ligation of carotid arteries under the conditions of the acute experiment (morphine narcosis): a) Changes intervening after right common carotid artery had been tied off for three minutes: 1) Oxygen partial pressure; 2) temperature of brain cortex. The duration of ligation is indicated by the heavy horizontal line. Vertical division is 50 sec [sic]; b) changes intervening after left common carotid artery had been tied off. Same nomenclature; c) changes intervening on simultaneous ligation of both carotid arteries for three minutes. Same nomenclature. A) 50 sec.

supply, a temperature increase occurs in the venous blood. While the venous blood in the jugular vein has a temperature lower than that of the arterial blood in the common carotid artery under normal conditions, the temperature of the draining blood during asphyxia may exceed that of the arterial blood by an appreciable margin.

The rise in the temperature of the brain when the blood supply to it is interfered with has been noted by numerous investigators (Voronin, 1942; Semenov, 1952; Gramenitskiy, 1952; Parolla, 1958, and others). However, the two latter authors regard the temperature rise in the brain during hypoxia as a consequence of dilation of the blood vessels in the brain and an amplified blood supply to it.

The data that we obtained, which attest to a rise in the temperature of the venous blood draining from the brain during its hypoxic state, unquestionably indicate participation, in this case, of the brain's own heat production, which rises sharply during oxygen starvation.

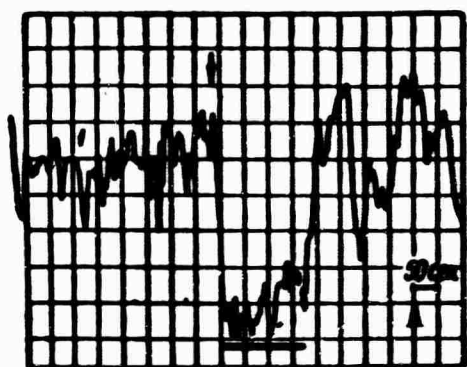


Fig. 2. Changes in oxygen partial pressure in cortex of dog brain on ligation of two carotid arteries under the conditions of the chronic experiment. The arrow designates the moment at which ligation was performed; segment 1 is its duration. The vertical division is 50 sec [sic].

As we know, anemization of the brain is characterized by transitory diffuse excitation (Petrov, 1949; Shapot and Gromova, 1954; Duan-Hau-Shen, 1959, and others). Shutting off only the anterior arteries of the brain in a dog disturbs internal inhibition and increases the motor activity of the animal (Kosmarskaya, 1947; Kuklina, 1957).

Biochemical studies affirm that during hypoxia, there is an increase in the oxygen consumption of the brain (Marshak, Ardashnikova, Aronova, Blinova, Voll, 1948; Komisarenko et al., 1954; Gayevskaya, 1954, and others), the amount of ammonia formed increases (Gerard and Meyerhof, 1927; Richter and Dauson, 1948; Pertseva, 1958). Simultaneously, the ATF [adenosine triphosphate] level drops sharply (Kurokhtina, Malkiman, Parfenova, 1950), with the degree of the effect depending on the intensity of the initial excitation. Thus, the excitation of the central nervous system in hypoxia under ordinary environmental temperature conditions may result in the disappearance of ATF; on the other hand, hypoxia induced against a background of preliminary inhibition of the central nervous system's functions in hyperthermy produces less distinct changes in the ATF content of the brain tissue (Gayevskaya and Nosova, 1960).

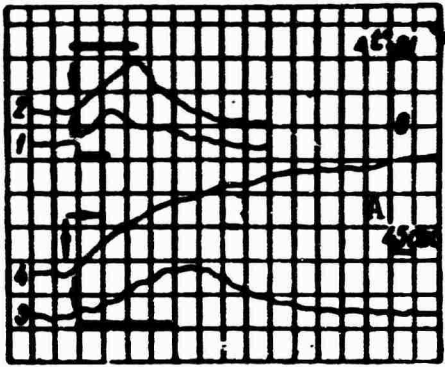


Fig. 3. Changes in temperature of cortex of dog brain under the conditions of acute experiment with disturbances to blood circulation in the vessels of the neck. 1) Ligature of one carotid artery for 1 minute; 2) ligature of one carotid artery for 2 min; 3) ligature of one carotid artery for 3 min; 4) one carotid artery tied off. Same nomenclature. Vertical pressure 45 sec [sic].

Excitation of the specific activity of any organ is accompanied, by virtue of the second law of thermodynamics, by an increase in its heat production (Hill, 1921; Marshak, 1948; Putilin, 1953; Slonim, 1952; Al'pern and Arlozorov, 1940; Trincher, 1960, and others). This increase in heat production takes place in proportion to the increase in the rate of the metabolic reactions, thus creating an opportunity for dynamic monitoring of the level of the energy-producing processes in the tissue under investigation (Meyerhof, 1926; Tauson, 1950).

It may be assumed that as an irritating factor, hypoxia (Frol'kis, 1958) results in diffuse excitation of the nervous structures with a sharp increase in the rate of the exothermic reactions in which high-energy compounds are decomposed, manifesting in an increased level of heat production by the brain.

It is possible that the degree to which the temperature of the brain rises, which is proportional, within certain limits, to the degree of oxygen starvation, may be used as an index to the degree of hypoxic excitation of the central nervous system. The sensitivity of this index is confirmed even for such a disturbance as ligature of one of the arteries of the neck, an intervention that may produce only minor, transitory circulatory disturbances that impair the oxygen supply to the tissues of the brain.

The drop in oxygen partial pressure that is noted when one of the arteries of the neck is temporarily tied off may arise either as a re-

sult of circulatory insufficiency or as a result of the brain's increase in oxygen consumption as an effect of the hypoxic excitation. The fact that the oxygen partial pressure gradually returns to normal when one of the arteries is clamped for 5-15 min speaks in favor of the first hypothesis. This, however, does not exclude the second hypothesis. Tying off two carotid or vertebral arteries causes more prolonged disturbances to the oxygen content in the tissues, disturbances that may be in evidence for several tens of minutes to several hours.

The return of the temperature to the initial level usually lags behind the recovery of oxygen partial pressure. We frequently observe a phase in which the oxygen content has reached the initial level, while the temperature has only begun to fall back, lagging behind by several minutes. It is possible that the brain tissue's intrinsic heat capacity plays a certain role in this effect. However, the longer delay periods that are observed in occasional cases permit the assumption that the "metabolic tail," i.e., the retention of the stressed metabolic-process level for a certain time after the hypoxic disturbance, plays the leading role in this phenomenon; this would also account for the retention of an elevated brain temperature at a time when the oxygen partial pressure in the tissue has returned to its initial value.

There is no doubt that in the intact organism, hypoxia produces simultaneous changes in the activity of many systems, including the circulatory compensatory reactions. It is an unquestionable fact that there is an increase in the rate of blood supply to the brain and a dilation of the brain's blood vessels. However, as has been shown by data from measurements of oxygen partial pressure in the tissue, these mechanisms prove inadequate when the arteries of the neck are shut off, so that the oxygen partial pressure in the brain is found to have been depressed immediately following the intervention. It would appear that

this initial hypoxia is the cause of excitation of nervous elements and the phenomena attending the excitation..

As was shown by experiments performed earlier (Berezovskiy, 1961), the temperature of the dog brain under an intact skull is higher than the temperature of the arterial blood in the common carotid artery. The same temperature relationship was reported earlier by Faytel'berg and Lampl' (1935), Semenov (1952) and others. On the basis of this relationship, an increase in the blood supply to the brain can lead only to an intensification of its cooling. The rise in temperature, which is observed both during transitory hypoxia with the arteries of the neck tied off and in asphyxia of the brain when blood circulation has stopped completely, must apparently be connected to decomposition of high-energy compounds with liberation of large quantities of energy.

CONCLUSIONS

1. Temporary ligation of one of the four main arteries of the neck in the dog produces a drop in oxygen partial pressure and a rise in temperature in the brain tissue.

2. The state of diffuse excitation that arises during hypoxia of the central nervous system is accompanied by an increase in heat production on the part of the brain.

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[Transliterated Symbols]

175 ш - sh - shunt - shunt

175 н - n - nagruzka - load

INFLUENCE OF ASPHYXIA ON THE ELECTROCORTICAL EFFECTS
OF ACETYLCHOLINE

Ye. A. Markova

(Ternopol')

A state of asphyxia develops in many pathological processes; hence the study of its influence on the functional state of the organism's systems persistently attracts the attention of researchers.

According to our earlier investigations (1959) and literature data (Litvin, 1959), asphyxia lowers the sensitivity of the cardiovascular system to small doses of acetylcholine.

As we know, injection of acetylcholine into the carotid artery on the way to the brain causes a diffuse desynchronization of the brain's potentials (Moruzzi and Hart, 1950; Rinal'di and Khimvich, 1955; Longo, 1955), resembling excitation of the ascending reticular system.

In the present investigation, we have made it our task to study the influence of asphyxia on the electrocortical effects of acetylcholine. The work was done with Prof. F.N. Serkov as scientific consultant.

METHOD

Experiments were performed on 20 rabbits without narcosis. Asphyxia was induced by connecting a rubber bag containing 4 liters of air to a tube inserted into the trachea. On the development of terminal respiration, the bag was disconnected and, if necessary to restore the functions, artificial respiration was applied.

The biocurrents were tapped by a bipolar arrangement from the cortex of the brain. Platinum electrodes mounted in threaded plexiglass

plugs were used for this purpose. Such an electrode would be secured tightly in a trephined opening made in the parietal region of the skull. As a rule, the dura mater was not damaged. The biocurrents were tapped from one hemisphere and, in some experiments, concurrently from both. The EKG recording was made with a 16-channel ink-writer oscillograph of the "Kayzer" system. The acetylcholine was injected into the common carotid artery on its way to the brain in a dose of 2-10 γ .

RESULTS OF EXPERIMENTS

In accordance with the data of other investigators (Rinal'di and Khimvich, 1955), we observed a distinctly manifest desynchronization reaction in our experiments on intracarotid injection of 2-10 γ of acetylcholine into intact rabbits (Fig. 1a).

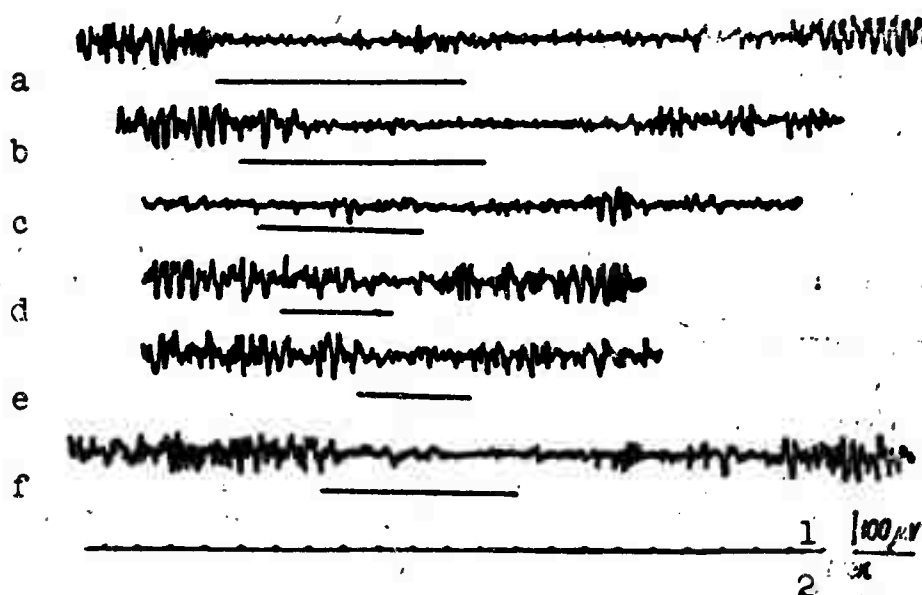


Fig. 1. Changes in electrocortical effects of acetylcholine during asphyxia. a) Before asphyxia; b) 1 min after onset of asphyxia; c) 3 min after onset of asphyxia; d) 30 sec after withdrawal of asphyxia induction; e) 2 min after asphyxia; f) 10 min after asphyxia. The solid line indicates the time of injection of the acetylcholine. 1) 100 μ v; 2) 1 sec.

The asphyxia itself caused desynchronization of the cortical rhythms, which was manifest to different degrees at different times during the development of asphyxia. During the initial stage of asphyxia, when the desynchronization that it produces is not yet in evidence, the

electrocortical effect of acetylcholine occupies a somewhat shorter time interval (Fig. 1b).

With increasing intensity of the asphyxial state against a background of some desynchronization of the cortical activity, the administration of acetylcholine intensified the desynchronization, but this effect was not pronounced (Fig. 1c).

In the deep stages of asphyxia, when the ECoG showed slow potential oscillations, the electrocortical reaction to acetylcholine had disappeared or was manifest even more weakly (Fig. 2c).

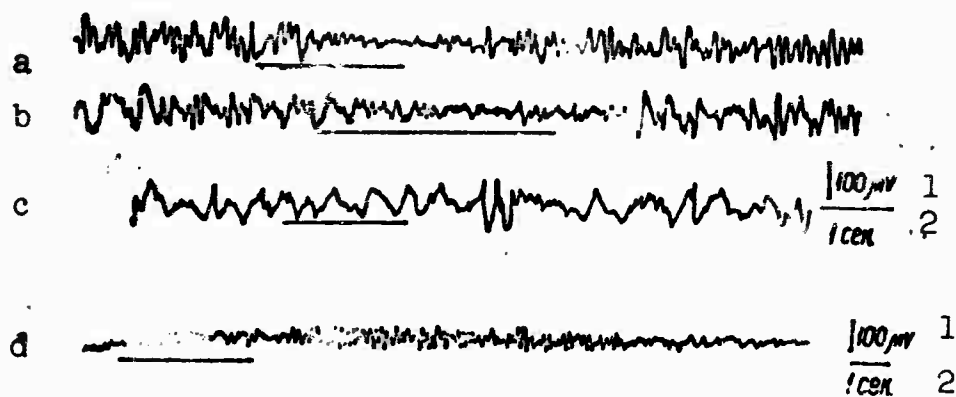


Fig. 2. Changes in electrocortical effects of acetylcholine during asphyxia. a) Before asphyxia; b) 1 min after the onset of asphyxia; c) 7 min after onset of asphyxia; d) 3 min after asphyxia. 1) 100 μ v; 2) 1 sec.

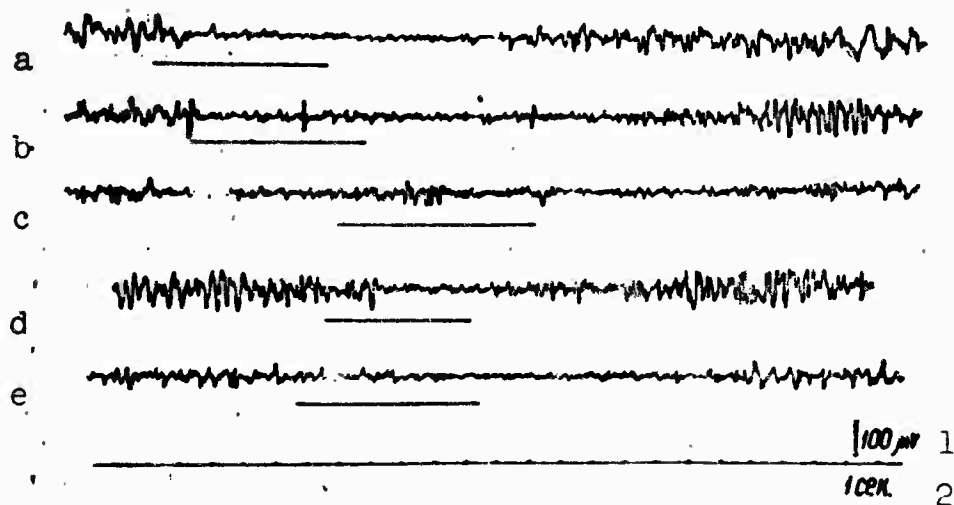


Fig. 3. Changes in electrocortical effects of acetylcholine during asphyxia. a) Before asphyxia; b) 4 min after onset of asphyxia; c) 9 min after onset of asphyxia; d) 1 min after asphyxia; e) 6 min after termination of asphyxia. 1) 100 μ v; 2) 1 sec.

At certain stages in asphyxia, when the desynchronization of cortical activity produced by the asphyxia was already quite strongly in evidence, the injection of acetylcholine produced, instead of an aggravation of the desynchronization, an outburst of synchronized potentials of considerable amplitude, with a rhythm of 4-6 per second (Fig. 3c).

The disappearance of the electrocortical reaction to acetylcholine in asphyxia is a reversible phenomenon, since after the situation inducing the asphyxia has been withdrawn, while the EKG gradually returned the initial indices, the reaction to acetylcholine reappeared. At first, it was brief and weakly manifest (Fig. 1, d and e), but then it returned to the same level as in the initial state (Fig. 1g [sic]).

It should be noted that, not only in asphyxia, but also during the process of functional restoration after it has been withdrawn, the injection of acetylcholine against a background of the desynchronization of cortical activity caused by the asphyxia frequently produced an electrocortical reaction in the form of an outburst of synchronized high-amplitude slow-rhythm potentials (Fig. 2d).

In our investigations, therefore, we were able to confirm the fact that desynchronization of the cortical electrical activity arises in response to intracarotid injection of small doses of acetylcholine.

Irrespective of the mechanism by which this electrocortical reaction arises, i.e., regardless of whether it is a result of disturbance to the choline-reactive systems of the reticular formation, as was assumed by Rinal'di and Khimvich (1955) or, on the contrary, a result of irritation of receptors in the vessels, its realization is interfered with during asphyxia.

The cause of this disturbance may be either oxygen insufficiency or an excess of carbon dioxide. It is known that hypercapnia in itself

results in excitation of the reticular formation and desynchronization of cortical activity (Gell'gorn, 1953). The desynchronizing effect of acetylcholine is probably impeded against this background. It is true that in our experiments, the desynchronization reaction was suppressed on injection of acetylcholine when the content of carbon dioxide in the inspired air had not reached high concentrations. Consequently, it would seem that oxygen shortage rather than excessive carbon dioxide was the factor suppressing this reaction.

The disturbances to the electrocortical effects of acetylcholine in asphyxia are reversible in nature. During restoration of the functions, the changes in the electrocortical effects of acetylcholine develop in a sequence that is the reverse of what we observe during asphyxia.

Cases in which outbursts of synchronized potentials instead of desynchronization of the cortical activity appear in response to the administration of acetylcholine require special analysis. Similar potential outbursts were observed by F.N. Serkov (1955) and N.V. Bratus' (1956) in the anterior divisions of the brain in response to irritation of interoceptors, and by V.V. Russev (1959) in response to sensory stimuli against a background of bromide effects.

The explanation for this fact is more probably to be sought in the doctrine of N.Ye. Vvedenskiy, according to which the same stimulus produces different reactions depending on the functional state of the central nervous system.

CONCLUSIONS

1. The development of asphyxia causes a progressive reversible disappearance of the electrocortical effects of acetylcholine. During the process of restoration of the functions, they return to the initial state.

2. Against a background of cortical-activity desynchronization during asphyxia and subsequent restoration of functions, an outburst of synchronized potentials of considerable amplitude and slow rhythm is frequently observed during intracarotid injection of acetylcholine.

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[List of Transliterated Symbols]

183 ЭKoГ = EKoG = elektrokortikogramma = electrocorticogram

INFLUENCE OF ANOXIA ON THE PHYSICAL ELECTROTONUS OF
SMOOTH MUSCLE

M.F. Shuba

(Kiev)

The appearance of physical electron [sic] (FE) in excitable tissues is governed by polarization of the protoplasmic membrane under the influence of a constant electric current. Here the excitability of the tissue in the region of the physical cath- and anelectron [sic] undergoes changes. However, as the literature data indicate (D.S. Vorontsov, "Obshchaya elektrofiziologiya," [General electrophysiology], 1961), FE is also easily produced on appropriate physical models. Hence the question arises as to whether the formation of the FE in the excited tissues is due chiefly to purely physicochemical processes in the protoplasmic membrane or, to the contrary, to metabolic processes. To clarify this question, we made an investigation of the influence of anoxia and potassium cyanide on the FE of smooth muscle.

We selected smooth muscle as the object of investigation because, as we know, metabolism in this tissue is depressed by comparison with other tissues. Moreover, as our investigations showed, the FE of smooth muscle differs sharply from the FE of, for example, nerve or striated muscle.

METHOD

The object of investigation was the smooth sphincter muscle of the frog stomach. Having been excised from the body of the frog, the stomach was cut along its minor curvature and the mucous membrane removed,

after which a strip of the circular muscle fibers was cut out of its anterior part. In some experiments, the serous lining was also removed from the muscle strip. Then the muscle strip with the polarizing and lead electrodes applied to it was mounted under slight tension in a humid, hermetically sealed chamber. Observation began three or four hours after the muscle had been placed in the chamber. The polarizing current was taken from a bank of storage batteries through a potentiometer. The polarizing and lead electrodes were chlorinated silver wires, which were placed in glass cannulas with Ringer's solution. The end of the cannula in contact with the muscle was wrapped tightly in cotton moistened in Ringer's solution. The distance between the polarizing electrodes was 7-10 mm, that between the near polarizing electrode and the proximal lead electrode was 1-2 mm, and that between the leads was 15-25 mm.

Anoxic conditions were set up in the chamber by passing pure nitrogen through it. Before entering the chamber, the nitrogen was purified of O_2 and CO_2 impurities by passing it through two successive pyrogallol tanks. The pyrogallol was dissolved in caustic potash. To increase the area of contact between the gas and the absorbent, it was deliquesced with agate filters (No. 2).

Potassium cyanide (KCN) was used as a cell-respiration inhibitor. So that the potassium concentration in the Ringer's solution would not increase when the KCN was added to it, we prepared a Ringer's solution in which the KCl was replaced by a corresponding quantity of KCN. Mixing this solution in various proportions with the normal Ringer's solution, we produced the desired KCN concentration in the solution. Since KCN decomposes quite rapidly in solution, its concentration diminishes progressively. For this reason, a fresh KCN solution was prepared for each individual experiment.

RESULTS OF EXPERIMENTS

As we know, hydrocyanic acid and its salts are specific inhibitors of enzymes with a metallic prosthetic group. These substances block the respiratory enzyme cytochromoxidase, with the result that the tissue loses its ability to reduce oxygen and oxygen starvation sets in. In our experiments, the potassium cyanide concentration ranged from 1 to 2.5 mM. In the experiment whose results are shown in Fig. 1, KCN concentration was 2.5 mM. The polarizing current was near the threshold at $3 \mu\text{a}$. When the muscle was treated with KCN at the end of the ascending part of the cathelectrotonic potential (KEP) there arose a well-defined negative local potential (Fig. 1a).

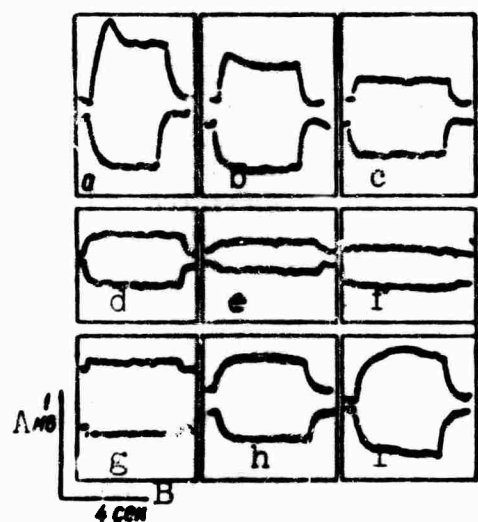


Fig. 1. Influence of KCN on FE. a) Normality; b, c, d, e, f, g) after 10, 30, 45, 60, 120 and 125 minutes of treatment with KCN, respectively; h, i) after 60 and 120 minutes, respectively, had elapsed since rinsing off of KCN. A) 1 mv; B) 4 sec.

Even at the 10th minute of KCN treatment of the muscle, the amplitude of the KEP and that of the negative local potential that appears on it had diminished markedly (Fig. 1b). Subsequently, as the KCN continued to act on the muscle, the KEP amplitude gradually dropped to zero, and the local potential no longer appeared on it (Fig. 1, c-f). Nor was subsequent application of a considerably higher polarizing current ($15 \mu\text{a}$) accompanied by the appearance of an electrotonic potential (Fig. 1g). The small, fast deflection of the curve on the electrogram under consideration is not connected with physiological processes taking place in the protoplasmic membrane. This so-called fast part of the electrotonic potential arises under certain conditions even on killed muscle, and even when the resistance of the solution

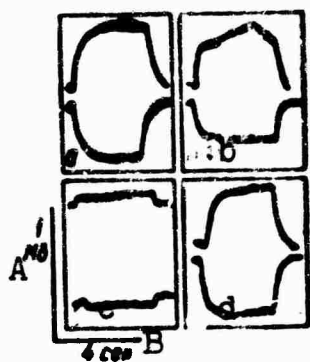


Fig. 2. Influence of nitrogen in FE: a) Normality; b, c) after 120 and 180 minutes, respectively, of subsequent oxygen treatment. A) 1 mv; B) 4 sec.

surrounding the muscle is increased.

The above-described changes in the KEP were found to be reversible, since the amplitude of the electronic potential was gradually restored (Fig. 1, h, i) after the KCN had been rinsed from the muscle. The amplitude of the anelectrotonic potential (AEP) also diminishes when the muscle is treated with KCN (Fig. 1, a-g). Here, at the 60th and particularly at the 12th [sic] minute of treatment with KCN, the amplitude and shape of the

AEP and KEP show virtually no differences (Fig. 1, d and e). After the muscle had been washed with a normal Ringer's solution without KCN, the amplitude of the AEP gradually recovered (Fig. 1, h and i), although even during the second hour, it was still below the level prevailing before KCN treatment. Thus, suppression of cell respiration by potassium cyanide results in a decrease in the FE. The extent of the FE decrease depends on the concentration of the inhibitor.

In connection with the FE decline under treatment with KCN, it was felt worthwhile to trace the influence of muscular anoxia on it. The results of one of these experiments are given in Fig. 2.

In this experiment, the level of the polarizing current was near the threshold at $5 \mu\text{a}$. As a result, a small but rather persistent negativity appears at the end of the ascending part of the KEP under normal conditions (Fig. 2a). At the 120th minute of passage of pure nitrogen through the humid chamber, the KEP amplitude dropped markedly, and the appearance of the negative-going local potential is delayed (Fig. 2b). Subsequently, as passage of nitrogen through the chamber continued, the amplitude of the KEP became smaller and smaller, and had finally dropped to zero by the end of the third hour (Fig. 2c). Subsequent pas-

sage of pure oxygen through the chamber resulted in a rather rapid recovery of KEP amplitude (Fig. 2d). As will be seen from this figure, the AEP amplitude also diminishes gradually to zero as an effect of anoxia (Fig. 2, a-c). This is accompanied by a decrease in the rise time of the AEP amplitude (Fig. 2b). Subsequent passage of pure oxygen through the chamber resulted in recovery of the AEP (Fig. 2d). It should be noted that if there was a small oxygen impurity in the nitrogen used, the amplitude of the cathelectrotonic and anelectrotonic potentials did not decrease under these conditions.

The amplitude of the electronic potential depends, other conditions the same, on the permeability state of the protoplasmic membrane. The higher this permeability, the smaller will be the number of ions repelled by the cathode and anode of the polarizing current that will be detained on the surface of the membrane. Accordingly, the amplitudes of the cathelectrotonic and anelectrotonic potentials will also be reduced. On this basis, it should be assumed that the FE decrease taking place, as described above, under the influence of KCN or anoxia is due to an increase in the permeability of the membrane of the smooth-muscle cells to ions.

From this it follows that the permeability of the protoplasmic membrane and, consequently, also the formation of the FE, do not represent a purely physicochemical phenomenon, but a phenomenon intimately related to metabolism. In this connection, we note that Frezer and Keynes (1959) link the increase of, for example, the Na content in striated muscle fibers under the influence of KCN not so much with suppression of active secretion of Na from the fibers as with an increase in its intake as a result of increased permeability of the protoplasmic membrane.

As concerns the recovery of the FE under oxygen treatment, however,

it is governed by a decrease in the ionic permeability of the membrane of the smooth-muscle fiber.

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[Transliterated Symbols]

188	ФЭ = FE = fizicheskly elektroton = physical electrotonus
190	КЭП = KEP = katelektroton = cathelectrotonus
191	АЭП = AEP = anelektroton = anelectrotonus

ON THE POTENTIAL ADAPTIVE-COMPENSATORY FUNCTIONS OF THE ORGANISM

IN HYPOXIA

I.M. Kyazen

(Moscow)

An enormous number of investigations have been devoted to the problem of adaptation and acclimatization to hypoxia (M.P. Brestkin, Z. I. Barbashova, G.Ye. Vladimirov, M.Ye. Marshak, N.N. Sirotinir, V.V. Strel'tsov, L.A. Orbeli, D.Ye. Rosenblyum, I.P. Rasenkov, Dzh. Barkroft, Ye. Van-Lip, Dzh. Kholden and others), but nevertheless many of its aspects, in particular questions as to the limits of adaptation and ways to increase the potential compensatory capacities of the organism, remain as yet to a significant degree unresolved.

From the standpoint of general biology, the problem of the organism's protective functions is so pressing that the entire XVI Session of the Academy of Medican Sciences of the USSR was devoted to its consideration (P.K. Anokhin, N.V. Davydovskiy, V.V. Parin, I.R. Petrov, V.N. Chernigovskiy and others).

In the present article, we set forth, in generalized form, the data that we have accumulated from study of the limits of adaptation, stability and endurance of the animal and human organism to oxygen insufficiency under the conditions of flight, residence in the altitude chamber and residence at mountain altitudes.

Under the conditions of flight, and especially in modern supersonic high-altitude aircraft, the flight crew is frequently under conditions of high emotional stress, a result of the special nature and com-

plexity of the tasks to be performed within extremely short time intervals. Emotional stress, which itself is accompanied by a sharp increase in respiratory and pulse frequencies, may, in some cases, give rise to secondary hypoxic manifestations as a result of hyperventilation. These manifestations may occur under the influence of acceleration and other extreme stimuli.

To evaluate the functional state of the organism in hypoxia, it is important to observe not only the reactions of its individual systems, but also to study its ability to perform work.

In setting up an investigation whose primary objective is to ascertain the role of the nervous and humoral mechanisms that regulate and compensate the organism's functions under the influence of hypoxia, and to determine the relationships that develop here between the various regulatory systems in the intact organism, it would appear most promising to proceed from the propositions of I.P. Pavlov, who demonstrated that the importance of nervous and humoral regulatory links is not the same for different organs and systems.

Accordingly, we employed the neuroglandular apparatus of the gastrointestinal tract as the indicator object in a study of general-physiological phenomenon.

It has been established in experiments on both animals and humans that oxygen starvation first affects the neural triggering mechanisms regulating the secretory functions of the digestive glands. Consequently, the more directly the performance of the glands is monitored by the central nervous system, the more rapidly and strongly will the hypoxic changes be manifested and the more rapidly will the secretory disturbances recover to their initial level. Those secretory functions that also depend to a considerable degree on the humoral regulation mechanisms, and particularly those in whose regulation local intramural in-

nervation machinery participates, are distinguished by relatively high stability.

Under the influence of oxygen insufficiency, the digestive glands react, as a rule, by cutting back their secretion, although the "altitude threshold" established for dogs under altitude-chamber conditions is different for each gland. Thus, it is 3500-4000 m for the salivary glands, 8000 m for the intestinal glands and 6000 m for the bile-forming function. The thresholds of changes in enzyme activities are also different: 4000-5000 m for enzymes of the digestive group, 3500-4000 m for carbonic anhydrase and diaminoxidase, 8000 m for succindehydrase and 10,000 m for cytochromeoxidase. Varying degrees of sensitivity are noted even within a given organ in an intact functional system: the secretory function of the glands in the floor and body of the stomach is inhibited at an altitude of the order of 4500 m, while the secretory function of the pyloric glands is not disturbed even at an altitude of 8000 m. These "altitudes thresholds" by no means exclude the possibility that even lower altitudes may also have a certain effect on the functional state of the glands on longer exposures.

The consistent variations that have been established with respect to the salivary, gastric, intestinal and other glands provide a certain conception of the correlation conditions between the individual functions of the intact organism in oxygen starvation. Our attention is first drawn to the shifts in the relationships between the secretion of juices and enzymes on the one hand and the excretion of salts, acids, protein bases, urea, uric acid, sugar and other components on the other hand. While the appearance of amylase in the saliva of dogs under the conditions of oxygen insufficiency reflects the adaptotrophic influence of the sympathetic nervous system, intensified secretion of incompletely oxidized and other metabolism products with the juices attests to a

compensatory role of the glands in the regulation of acid-base equilibrium with retention of the organism's other constants. For example, a rise in the activity of carbonic anhydrase in the blood and a drop in its activity in the salivary gland with a simultaneous decrease in the secretion of hydrochloric acid correspond to an adequate level of exchange of HCO_3 and Cl ions in the erythrocyte and in the gland cell as a result of adaptive readjustment of the entire complex respiration process.

High-altitude ascents for training purposes tend to smooth the above disturbances both during the actual sojourn under hypoxic conditions and in the aftereffect. The shorter the aftereffect, the more reliable is our judgement as to the limits and level of the homeostatic reactions.

Residence at mountain altitudes (2000-4000 m) is responsible for an increase in the organism's stability against subsequent (after 2.5-3 months) effects of considerably greater degrees of atmospheric rarefaction (6000-8000 m) under the conditions of the altitude chamber. However, as the number of such "trips up" increases, a limit appears, above which changes in the functional state of the glandular apparatus represent a kind of signal indicating the breakdown of the acclimatization that has been acquired. The investigations were expanded in view of the unquestionable practical importance of this fact.

The special-purpose experiments performed at the time by the participants in the El'brus expedition are highly illustrative in this respect. Experimental subject M. (female) had, in the preceding two years, done systematic work in the altitude chamber at various altitudes and participated twice in expeditions to El'brus. In establishing the general condition of M. as an initial background, our attention was drawn to hypersalivation quite far beyond normal limits. This function-

al manifestation had not been observed before. On the move from Terskol to the Eleventh Priyup [shelter], at an altitude of 3700 m, the typical picture of altitude sickness emerged. After a few hours of rest, M. felt better, and her general condition was satisfactory thereafter during the sojourn at the 4200-m altitude under a strict regimen. The high level of salivation, which exceeded the initial rate by a factor of 1.5-2.5, was characteristic for the entire two months sojourn in the mountains. There was no doubt that the peculiar nature of the changes in the secretory process, which is regulated basically only by complex-reflex nervous mechanisms, was connected with the generally uncomfortable state of the test individual. Three months after the return from the expedition, in the very first test in the altitude chamber at an "altitude" of 3700 m, the same altitude-sickness symptoms were observed. This state passed rapidly on "descent" to 2200 m and was repeated consistently in subsequent "trips up."

In experiments that the author performed on himself, the symptoms of oxygen insufficiency were observed at an altitude of 4800 m against a background of normal ability to work and a feeling of general well-being. Together with the complete disappearance of hydrochloric acid from the gastric juice, it was noted that the musculature maintained the abdominal prelum. These phenomena were quite persistent, and were observed at various high altitudes, after the descent from "Pastukhov's Shelter" and on the lowland. Only after 20 days was it possible to note subsidence of the symptoms, followed by their disappearance. In these self-observations, the altitude of 4250 m was the threshold, and a further increase in altitude by 550 m, which involved physical exertion on the move, resulted in certain disturbances to the general state of the organism. Their precursors were sharp disturbances in the content of free hydrochloric acid at altitudes of 2200 and 4250 m. In experiments

performed after three months of rest, no abnormalities whatsoever in the state of health were observed during a four-to-five-hour exposure under the conditions of the altitude chamber at an "altitude" of 4800 m, nor after flights lasting five to six hours.

In the general schedule of work done at I.P. Rasenkov's laboratory (Yu.M. Lazovskiy, N.V. Malkiman, V.M. Rubel', M.M. Khazen, S.I. Filipovich and others), a great deal of attention was also devoted to structural-morphological changes in the glands. It was established that animals kept at an "altitude" of 8000 m for four to six hours the first effects were observed in the mucous membrane of the body and the floor of the stomach. Stereotyped repetition of the "ascents" (every one or two days, total number of "trips up" ranging from 3 to 63) led to increased injury to the structural elements. Almost continuous necrobiosis of the investing epithelium and necrosis of occasional small arteries were observed; principal and accessory cells were transformed into an indifferent-type epithelium, the number of parietal cells decreased sharply, and so forth. However, beginning at about the 15th "ascent," regeneration phenomena began to come into evidence, reversing the development until those acute changes that had accumulated during the preceding disturbances had vanished completely (Yu.M. Lazovskiy, 1941).

Major fundamental importance should be attributed to the facts given above, since they attest to the presence of potential, long unsuspected adaptive-compensatory resources of the organism. It may be concluded that in the general system of digestive glands, the region of the base and body of the stomach acquires a special regulatory importance under the conditions of hypoxia, and the next thing that occurs to us is its endocrine role in the processes of hematogenesis.

Analysis of the literature data indicates that in prolonged hypoxia, the first observed stage of degenerative exhaustion of the adrenal

cortex is supplanted by a stage in which it recovers fully (L.L. Langley, 1942; G. Soyer, 1950; Dzh. Stikney and Ye. Van-Lir, 1953). Since the structural changes in the glands of the body and floor of the stomach coincide in time (from 2 to 12 weeks) with the structural changes in the adrenal cortex and are obviously governed by the same factors, it is natural to assume that the work of these organs is coordinated.

We established a link between the secretory activity of the gastric glands and the activity of the hypophyseal-adrenal system in acceleration experiments on animals and humans (I.M. Khazen, P.M. Suvorov, I.L. Vaysfel'd, A.S. Barer, 1957, 1958, 1959, 1961). It was shown in these experiments that, as in hypoxia, the rate of restoration of the disturbed secretory functions of the gastrointestinal tract takes place more slowly and in a different manner than that of the respiratory and circulatory functions. Thus, under certain specific experimental conditions, the shifts in the bioelectric activity of the brain and heart had been adjusted by the 3rd minute, while a long aftereffect running to several hours was characteristic for the gastric glands. For prognosis and judgement of the course of adaptation, therefore, it is necessary to take into account all aftereffect reactions on the part of those functional systems that provide a certain conception of the correlation between the functions of the intact organism that arises under the influence of a given irritant.

As concerns the question as to the "limit of resistance" to hypoxia, we cannot but acknowledge its highly relative signification. The stability limits can be broadened considerably by taking rigorous account of the characteristics of the stimulus and the initial functional state of the organism. The latter, however, is determined by the state of the neural and humoral regulatory systems and by all the peculiarities of metabolic processes. The morphological readjustments described

above, which reflect general compensation and repair phenomena, also speak in favor of an increase in the capabilities of the organism to adapt to hypoxia. These statements explicitly broaden the content of the "adaptation energy" concept introduced by G. Selye in his stress theory.

It follows from all of the above that the tactics of prophylactic intervention must be defined in terms of measures that make it possible to prevent exhaustion of the neural and humoral regulatory mechanisms and, first and foremost, the mechanisms of the higher divisions of the central nervous system. Normalization of metabolic processes, and therewith stabilization of the organism's constants by use of carbohydrates and various pharmaceutical agents has long been within the range of attention of numerous scientists.

We established the high effectiveness of a preferentially carbohydrate diet with an adequate specific content of proteins and other nutrients in it during the period in which the animals were being acclimatized on El'brus (altitudes 2000-4200 m). As compared with those on an ordinary mixed diet, these animals were subsequently (after 2.5-3 months) found to be considerably more resistant in the altitude-chamber test to "altitudes" of the order of 8000 m in a six-hour exposure, and also in a flight lasting five hours at an altitude of 3300-4880 m.

The resistance of the animals also increases under the influence of a purposive schedule of vitamin administration. Among the ten water-soluble vitamins tested in our laboratory, thiamine, citrine, ascorbic and paraaminobenzoic acids were found most effective (F.P. Kosmolinskiy).

The effectiveness of the vitamins as factors elevating the organisms's resistance to hypoxia by activating tissue enzymes and increasing the activity of the pituitary-adrenal system was judged on the ba-

sis of the general condition of the animals, their conditioned-reflex activity, changes in the "altitude ceiling," and the extent of the morphological disturbances.

On the basis of the observed importance of neurohumoral mechanisms in the regulation of enzyme activities, we made an attempt to improve the resistance of the organism to hypoxia by application of ultrahigh-frequency currents. In designing these experiments, we proceeded from the peculiarities of the biological effects of ultrahigh-frequency currents, and, in particular, from their property of significantly enhancing autocatalytic processes. Animals that had first been irradiated with UVCh showed distinct resistance in tests in the altitude chamber at an "altitude" of 8000 m, with a four-hour exposure period. No substantial abnormalities in the general functional state of the animals were observed, nor were the secretory processes of the digestive glands disturbed.

It is clearly evident on the basis of this example in which the activity of the digestive glands was studied during the operation of extreme irritants that the better we recognize the qualitative laws governing adaptive-compensatory processes, the better will be our ways and means for increasing the organism's stability to hypoxia. The problem under investigation is of unquestionable interest not only for aviation and space medicine, but also for the physiology of work and athletics.

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УВЧ = UVCh = ul'travysokochastotnyy = ultrahigh-frequency

ON THE ADAPTATION OF THE MATURE ORGANISM TO OXYGEN INSUFFICIENCY
AND THE IMPORTANCE OF THE HIGHER DIVISIONS OF THE BRAIN IN
THIS PROCESS

N.V. Laver, A.Z. Kolchinskaya and V.V. Turanov

(Kiev)

Despite the fact that the reaction of the mature organism to oxygen insufficiency in the surrounding air has been studied quite thoroughly and usually serves as the standard with which hypoxic states in other age periods are compared, the mechanisms by which the mature organism adapts to hypoxia have not been studied adequately at this time.

The literature has accumulated a great deal of information on short-term or long-term effects of oxygen insufficiency on individual organs and systems of the mature organism - the organs of respiration, blood circulation, hematogenesis, and others that participate in supplying the tissues with oxygen. However, most of these data were obtained from study of one or another function in isolation. Obtained under varying sets of conditions and on different objects, they are not grown to the requirements of contemporary physiology, since the activity of individual adaptive mechanisms in the process of adaptation to hypoxia in the intact organism are so intertwined that this process can be understood only as a result of study of the reciprocal effects of some functions and systems on others.

Study of the coordination and regulation of the adaptive-mechanism activity is one of the foremost problems involved in hypoxic states. It is therefore natural that to understand the development of the adap-

tive mechanisms in ontogenesis, it is necessary to acknowledge the great importance of study of the part taken by the central nervous system in the mature organism's adaptation to hypoxia. In the early stages of individual development, the genesis and intervention of the functions of the central nervous system and, in the later stages of ontogenesis, its readjustment, cannot but effect changes in the organism's response to disturbances of the external medium.

All of the above considerations formed the bases of a research program into the age-connected peculiarities of the organism's reaction to oxygen insufficiency that was carried out in the Age Physiology Laboratory of the A.A. Bogomolets Physiology Institute of the Academy of Sciences Ukrainian SSR (see also the works of N.V. Lauer; A.Z. Kolchinskaya; V.V. Turanov; N.V. Lauer, M.M. Koganovskaya, O.R. Kostenko, M.S. Bondarevskiy; M.M. Seredenko; Yu.V. Semenov in the present collection).

An attempt at simultaneous study of the activities of the various adaptive mechanisms concerned with the oxygen supply to the tissues was undertaken; particular attention was given here to ascertaining participation of higher divisions of the brain in these reactions.

A great amount of experimental material that has been collected in the USSR and abroad leaves no doubt as to the participation of the cerebral cortex in regulation of the vegetative functions at normal atmospheric pressure. While not yet available in large volume, data obtained in study of the role of the higher divisions of the brain in the organism's reactions to oxygen insufficiency tend to confirm these general propositions.

It has been shown by many investigators that the level of development of the nervous system, the functional state of the higher divisions of the brain or their anatomic or physiological intervention have a marked effect on the organism's resistance to oxygen insufficiency

(Sirotinin, Petrov, Gubler, Machinskaya, Lauer, Lauer and Kolchinskaya).

In the present communication we report data obtained in an experimental study of the significance of the brain cortex in forming the adaptive reactions of the mature organism to oxygen insufficiency. In these researches, an attempt has been made to evaluate the mutual relationships between the adaptive functional systems in the same group of normal animals, and to study their activity in hypoxia after these same animals had been surgically or pharmaceutically decorticated.

METHOD

The work was performed on full-grown dogs that had undergone prolonged training under the conditions of normal oxygen partial pressure for performance of an acute hypoxia experiment without use of narcosis.

The external-respiration indices were studied: frequency, respiration- and per-minute respiratory volumes (DO and MOD, respectively), and alveolar ventilation. The frequency of respiration, the DO and the MOD were registered on a spirograph. The hemodynamic indicators were recorded: the pulse frequency on an electrocardiograph and by means of a membrane manometer (on kymograph tape); the blood pressure was measured in the femoral artery with a Ludwig manometer. In the course of the experiment, the saturation of the arterial and venous blood with oxygen was determined using a cuvette oxyhemometer, and the oxygen content of blood taken from the femoral arteries and vein was found by the Van Slyke manometer method.

The erythrocyte count and hemoglobin content and the hematocrit indicators were determined. The oxygen consumed by the animal during the experiment was registered on the spirograph. The oxygen requirements before and after the experiment were also determined by the Douglas-Holden method.

The experiments were performed under the conditions of acute hypox-

1a. In some of the experiments, hypoxia was induced by rarifying the air in a large-volume, well-ventilated altitude chamber ("ascent" at a rate of 10 m/sec with 3-5 minute "plateaus" at "altitudes" of 3, 5, 7, 8, 9, and 10 thousand meters). In other experiments, the animals breathed a gas mixture produced in the spiograph with progressively diminishing oxygen content. Carbon dioxide was absorbed by special absorbers. During the course of the experiment, the content of oxygen in the inspired mixture was determined systematically.

Special investigations were conducted under the conditions of the high mountains during an expedition to El'brus with short sojourns in the mountains ranging upward from 2-3 days.

After thorough study of the indices enumerated above at normal oxygen content, and then under the conditions of hypoxia, we conducted analogous investigations on the same animals but in a state of anesthetized sleep, which was induced by administration of the minimal soporific doses of chloral hydrate (150 mg/kg) and chloralose (45-70 mg/kg). Subsequently these same dogs were surgically decorticated, first by one hemisphere and then, after a few months, by the other. The reactions of the dogs to oxygen insufficiency were investigated repeatedly after each of these operations.

The experiments performed indicated that the external respiratory function began to intensify very early in the normal dogs as the oxygen partial pressure in the inspired air was lowered (Table 1).

In the altitude chamber experiments, pulmonary ventilation began to increase at an altitude of 1 thousand m in 8 out of 10 dogs, and in the other 2 dogs at an altitude of 2 thousand m. The maximum increase in pulmonary ventilation was reached at "altitudes" of 7, 8 and 9 thousand m, and more severe degrees of hypoxia produced a lowering of the MOD. In these same 10 dogs, the first signs of an increase in pulmonary

ventilation were registered in the experiments with hypoxic mixtures when the oxygen content in the mixture had dropped to 20% in 2 dogs, to 19% in 6 dogs, to 18% in 2 dogs and to 16% in one dog.

Analysis of the quantitative external respiration indices (Fig. 1) indicates that the increase in pulmonary ventilation observed in normal mature animals at slight and moderate degrees of oxygen insufficiency takes place primarily through an increase in depth rather than an increase in the frequency of respiration. The frequency of respiration also rose at high altitudes. Respiration quickened to a somewhat greater degree in hypoxia in the females than in the males, and at lower altitudes (17.5-16% of oxygen, as compared to 15-10.5% of oxygen in the males); see Table 2.

Reducing the pulmonary ventilation indices to standard conditions (temperature, pressure and humidity), as is customary in determination of gas volumes, showed that in most of the normal dogs the reduced pulmonary ventilation either is maintained at the initial level or increases slightly with increasing oxygen deficiency up to an "altitude" of 9 thousand meters.

It follows from the data obtained that as hypoxia mounts, the reduced alveolar ventilation* does not increase at moderate altitudes, and, furthermore, diminishes at high altitudes (5, 6, 7, and 9 thousand meters).

Together with the amplification of the external respiratory function in mature dogs as the oxygen insufficiency became more severe, there was a progressive increase in the pulse rate (Fig. 1). In the majority of cases, a distinct quickening of the pulse in control dogs was registered beginning at "altitudes" of 2-3 thousand meters.

The quickening of cardiac activity, which began in normal dogs at an "altitude" of 2000 m (and in the majority of cases at an "altitude"

TABLE 1

Variation of External Respiration Indices in Mature Dogs in the Altitude Chamber

1	2	3	4												
			0	1	2	3	4	5	6	7	8	9	10	11	
Класс собак	в. в	Высота, тыс. м	760	670	586	526	460	404	355	310	270	233	200	170	
		Барометр. давление	760	670	586	526	460	404	355	310	270	233	200	170	
		5	20.9	18.6	16.0	14.5	12.7	11.2	9.9	8.6	7.5	6.5	5.5	4.5	
		5	20.9	18.6	16.0	14.5	12.7	11.2	9.9	8.6	7.5	6.5	5.5	4.5	
6	Капитанка	11.5	7	22	36	40	42	38	44	—	—	—	—	—	
			8	263	183	175	171	221	227	—	—	—	—	—	
			9	5.8	6.6	7.0	7.2	8.4	10.0	—	—	—	—	—	
11	Машка	11.0	10	5.2	5.1	4.8	4.3	4.2	4.4	—	—	—	—	—	
			10	20	18	20	18	25	27	36	32	56	49	—	—
			10	200	189	300	358	331	331	306	356	411	368	—	—
12	Цыганка	13.5	10	4.0	3.4	6.0	10.0	8.6	9.6	11.0	11.4	23.2	16.0	—	
			10	3.6	2.6	4.1	5.9	4.3	4.0	4.2	3.7	6.3	4.2	—	—
			10	12	13	12	14	12	16	20	30	34	92	—	—
13	Алмаз	9.5	10	234	339	300	286	350	300	320	407	418	—	—	
			10	3.4	4.1	3.6	4.0	4.2	4.8	6.4	12.2	14.2	—	—	
			10	3.1	3.1	2.5	2.4	2.1	2.1	2.1	3.9	3.8	—	—	
14	Жуль	9.0	10	15	15	16	17	17	16	17	18	21	36	—	
			10	173	210	275	232	259	275	353	468	315	278	—	—
			10	2.6	3.6	4.4	4.8	4.4	4.4	6.0	8.4	6.6	19.0	—	—
15	Марс	8.5	10	2.3	2.8	3.0	2.8	2.2	1.9	2.3	2.7	1.8	2.3	—	
			10	18	16	24	24	25	32	—	—	—	—	—	
			10	156	250	167	167	169	188	—	—	—	—	—	
16	Дружок	9.0	10	2.5	3.1	2.7	2.4	2.2	2.6	—	—	—	—	—	
			10	22	17	17	19	20	24	24	28	28	—	—	
			10	127	129	200	221	210	316	242	—	—	—	—	
17	Дезик	13.0	10	2.8	2.2	3.4	4.2	4.2	7.6	5.8	—	—	—	—	
			10	2.5	1.7	2.3	2.5	2.1	3.3	2.2	—	—	—	—	
			10	18	16	13	24	24	26	26	72	64	—	—	
18	Венера	9.5	10	156	188	222	334	233	239	292	84	—	—	—	
			10	2.8	3.0	4.0	8.0	5.6	6.2	7.6	6.0	—	—	—	
			10	2.5	2.3	2.7	4.7	2.8	2.7	2.9	1.9	—	—	—	
19	Рыжик	9.9	10	20	19	22	22	28	28	28	30	38	—	—	
			10	110	137	164	255	222	243	286	333	390	—	—	
			10	2.2	2.6	3.6	5.6	6.2	6.8	8.0	10.0	14.8	—	—	
18	Венера	9.5	10	2.0	2.0	2.5	3.3	3.1	3.0	3.0	3.2	4.0	—	—	
			10	20	26	24	26	29	25	30	34	37	52	82	
			10	170	185	192	185	200	224	227	176	211	235	181	
19	Рыжик	9.9	10	3.4	4.8	4.6	4.8	5.8	5.6	6.8	6.0	7.8	12.2	14.8	
			10	3.1	3.7	3.1	2.8	2.9	2.5	2.6	1.9	2.1	2.8	2.8	
			10	12	12	16	15	1	22	25	38	70	62	56	
19	Рыжик	9.9	10	153	167	175	219	225	223	270	186	271	210	193	
			10	1.6	2.0	2.8	3.5	3.6	4.9	6.0	9.6	13.0	16.8	10.8	
			10	1.4	1.5	1.9	2.1	1.8	2.2	2.3	3.1	3.5	3.9	2.1	

Symbols: Ch. d. - Frequency of respiration (in 1 min); DO - respiratory volume (in ml); MOD - per-minute respiratory volume (in liters); MOD (red.) - per-minute respiratory volume, reduced (in liters).

1) Name of dog; 2) weight, kg; 3) "altitude" in thousands of meters; 4) barometric pressure; 5) % O₂ in gas mixture; 6) Kashtanka; 7) Ch. d.; 8) DO; 9) MOD; 10) MOD (red.); 11) Mashka; 12) Tsyganka; 13) Almaz; 14) Zhulya; 15) Mars; 16) Druzhok; 17) Dezik; 18) Venera; 19) Ryzhka.

of 3000-4000 m) reached its maximum increase (by 124-249% of the initial norm) at an "altitude" of 7-10 thousand meters (in 13 dogs out of 15).

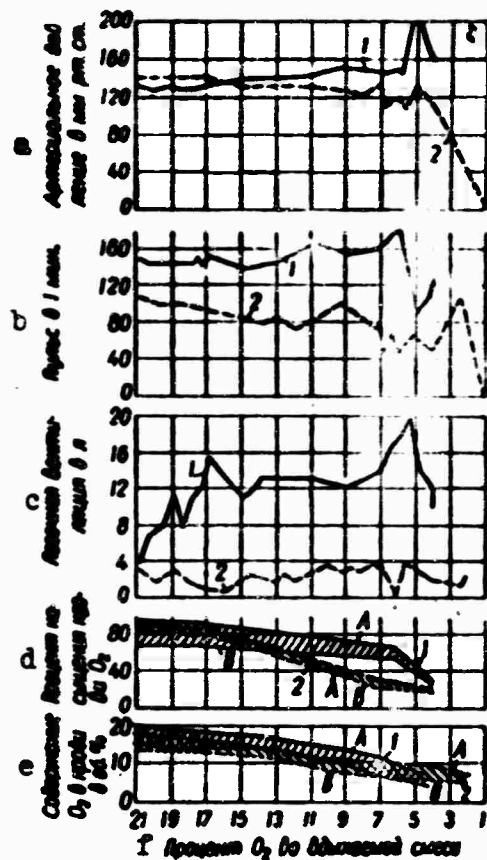


Fig. 1. Variation of arterial pressure (in mm Hg). Pulse rate, MOD, percentage of oxygen saturation of arterial blood and hypoxic oxygen content in waking and sleeping dogs. 1) Dogs awake; 2) dogs asleep. A) Femoral artery; B) femoral vein. a) Arterial pressure in mm of mercury; b) pulse, beats in 1 minute; c) pulmonary ventilation in liters; d) percentage O_2 saturation of blood; e) content of O_2 in blood, volume-%; f) percentage of O_2 in inspired mixture.

Before the content of oxygen in the inspired mixture had dropped to 16-16.5%, the level of the arterial pressure in the normal dogs showed no change (Fig. 1); when the oxygen content fell from 17 to 9-7%, a progressive increase in the level of arterial pressure to 140-170 mm Hg was noted; under more acute hypoxia (below 7% of oxygen in the gas mixture), the rise in blood pressure became very sharp, with its level reaching 220-270 mm Hg. In this phase, the rise in blood pressure was attended by a slackening of the pulse. A critical drop in blood pressure followed immediately after a quick ascent.

Analysis of the data that we obtained indicates that in the control dogs, an increase in pulmonary ventilation sets in at degrees of hypoxia at which hemodynamic shifts are still not in evidence. In the

initial stage and at moderate levels of hypoxia, the increase in MOD preserves the oxygen saturation of the arterial blood at a rather high level. Thus, up to an altitude of 4 thousand meters (12.5% oxygen in the inspired air), the oxygen saturation of the arterial blood drops relatively little in normal dogs -- to 81-83%; beginning at an altitude of 4.8 to 6.8 thousand meters (11.5% oxygen), the oxygen saturation of the blood decreases to 78-70%, and only at altitudes from 7 thousand meters (8.5% oxygen in the inspired mixture and less) do we observe a decrease in the oxygen saturation of the blood below 60% (Fig. 1).

A determination of the oxygen content in the arterial blood by the Van Slyke manometer method showed that when the oxygen in the inspired mixture is lowered to 15-13% and even to 6.5%, its content in the blood is kept at a rather high level in normal dogs (Fig. 1).

The relatively high oxygen content in the arterial blood at low saturation may be accounted for in part by an increase in the oxygen-carrying capacity of the blood, such as usually occurs in normal dogs in acute hypoxia as a result of an increase in the number of erythrocytes in the circulating blood.

Experiments performed on these same dogs in a state of anesthetized sleep, or after decortication by one or both hemispheres showed that intervention by the higher divisions of the brain has a distinct effect on the organism's reaction to hypoxia.

It is first of all necessary to note that adaptation to hypoxia by intensification of external respiration is not as good after removal of the brain cortex as compared to the normal state; such animals differed from normal animals in that the increase in pulmonary ventilation begins at a more severe level of oxygen deficiency, approximately at an "altitude" of 4-5 thousand meters.

The effectiveness of adaptation to hypoxia on the part of external

TABLE 2

Variation of External Respiratory Indices in Mature Dogs on Inspiration of an Oxygen-Deficient Gas Mixture

A Name of animal	C Characteristics of gas mixture										B Respiratory indices									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
P Almyra	Ch. d.	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
	DO	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202
Kashanay	Ch. d.	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	DO	171	171	171	171	171	171	171	171	171	171	171	171	171	171	171	171	171	171	171
L Koshin	Ch. d.	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14	14
	DO	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202
M Carryn	Ch. d.	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
	DO	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189
N Puzan	Ch. d.	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
	DO	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170
O Byrnan	Ch. d.	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
	DO	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202	202
P Amos	Ch. d.	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21
	DO	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170	170
Q Xyan	Ch. d.	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
	DO	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189
R Akent	Ch. d.	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17	17
	DO	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189
S Akent	Ch. d.	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	DO	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189	189

Symbols: Ch. d. - Frequency of respiration (in 1 min); DO - respiratory volume (in ml); MOD - per-minute respiratory volume (in liters); MOD (red.) - per-minute respiratory volume, reduced (in liters).

A) Dog's name; B) weight, kg; C) corresponding altitude, thousands of meters; D) barometric pressure; E) % of O₂ in gas mixture; F) Donguz; G) Ch. d.; H) DO; I) MOD; J) MOD (red.); K) Shkhel'da; L) Kazbek; M) Saturn; N) Ryzhly; O) Druzhot; P) Almaz; Q) Zhulya; R) Dezik; S) Myshka.

respiration is also impaired because the pulmonary ventilation in these animals rises much more slowly (Figs. 1 and 2) than in the fully con-

scious state, while the reduced pulmonary and particularly the alveolar ventilation lags far behind the initial level.

The decrease in reduced alveolar ventilation in dogs in which sleep was induced by chloral hydrate is particularly marked. Special experiments performed with chloralose showed that the absolute minimum saporiphic dose of chloralose - 40-45 mg/kg (not all dogs were put to sleep by administration of chloralose in these quantities) produced, in cases in which the animal did fall asleep, a marked suppression of adaptation to hypoxia by external respiration, although this effect was not as pronounced as in sleep induced by chloral hydrate (Lauer, 1960; Lauer and Kolchinskaya, 1960-1961).

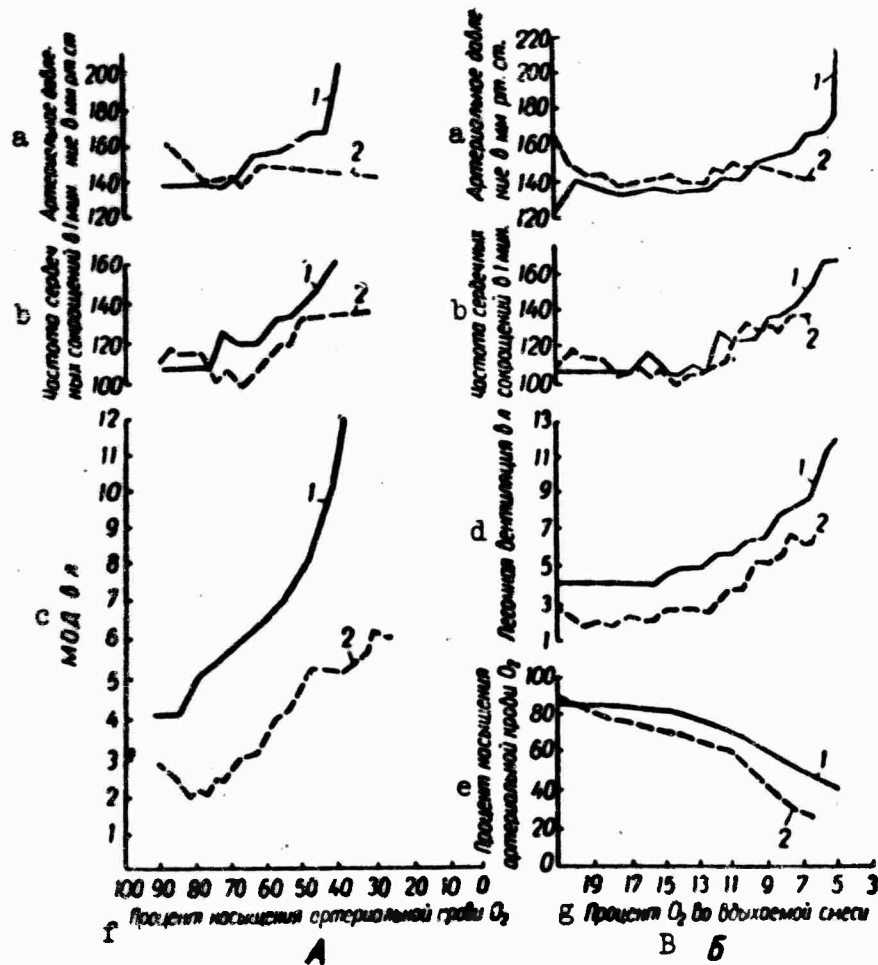


Fig. 2. Variation of arterial pressure, pulse frequency and MOD in dogs in the waking and sleeping states, plotted against percentage saturation of arterial blood with oxygen (A) and against oxygen content in inspired mixture (B). Symbols the same as in Fig. 1. a) Arterial pressure in mm of mercury; b) pulse frequency; c) MOD in liters; d) pulmonary ventilation in liters; e) percentage saturation of arterial blood with O₂; f) percentage saturation of arterial blood with O₂; g) percen-

tage of O_2 in inspired mixture.

An indication that the poorer adaptation to hypoxia during anesthetized sleep must be attributed to exclusion of the brain cortex is found in the experiments made with decorticated animals. Our observations showed that a distinctly manifest suppression of the external respiratory augmentation response to hypoxia occurs in dogs over 1-2 months after removal of the cortex of one hemisphere, as compared with the response of the same dogs prior to the operation. After 3-4 months, however, the respiratory reaction to hypoxia was restored.

As we know, bilateral decortication of dogs is followed by sharp excitability and violent respiratory reactions to the most diverse types of stimuli (Asratyan, Merkulova, Goryunov, Vaksleyger, Lauer and Kolchinskaya), and this makes it difficult to bring out the respiratory reaction directly to hypoxia. However, special experiments set up with the purpose of isolating the dogs from external stimuli, with meticulous verification of the initial pulmonary ventilation data showed that after removal of the cortex from both hemispheres of the brain, the respiratory reaction to hypoxia is diminished. As a rule, the MOD of decorticated dogs did not increase in altitude-chamber experiments running up to "altitudes" of 4-5 thousand m, while in experiments with gas mixtures a marked increase in pulmonary ventilation also began when the oxygen content had dropped below 12.5%. When the oxygen in the inspired mixture was cut down to 9.6%, the pulmonary ventilation of the decorticated dogs had risen by 33%, and only when the oxygen content had been lowered to 8.5% had their MOD's doubled.

It is interesting to note that while the reduced MOD was maintained at the initial or a slightly higher level in the control animals when the oxygen content in the inspired air dropped to 8%, as noted above, this index dropped to 73-83% of the initial level at the same degree of

hypoxia in the dogs lacking cerebral cortex.

By way of illustration, we present a curve (Fig. 3) obtained in an experiment with oxygen-deficient gas mixtures on the dog Zhuchka (12 months after removal of the cortex from the second hemisphere), from which it is seen that her low level of pulmonary ventilation varied little, not only at minor degrees of hypoxia, but even when the oxygen content had been lowered to 9-10%, i.e., under conditions in which the MOD's of the control dogs had usually risen by 178-600% with respect to the initial value.

The weakening of the external respiratory reaction to oxygen insufficiency in dogs after removal of the cortex from both cerebral hemispheres is observed not only in acute hypoxia, but also under high-mountain conditions (Lauer, Kolchinskaya, Turanov, Semenov).

After removal of the cortex from both hemispheres, the pulse frequency increased in the dogs that we studied. In hypoxia, the pulse was maintained at a more frequent level than was observed in normal animals under the same conditions.

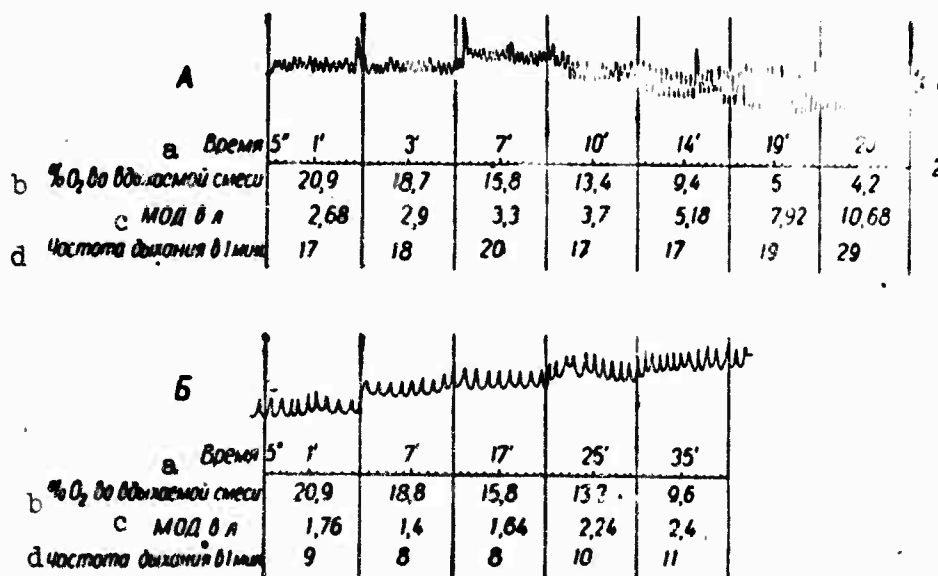


Fig. 3. Variations in frequency and depth of respiration in normal (A) and decorticated (B) dogs during inspiration of oxygen-deficient gas mixtures. 1) Kymographic record of respiration; 2) time marker. а) Time; б) % O₂ in inspired mixture; в) MOD in liters; г) respiratory frequency, cycles² in 1 min.

The minimal soporific doses of chloral hydrate or even larger doses of chloralose (80-100 mg/kg) produced a quickening of the pulse in control dogs even at normal atmospheric pressure. As a result, when hypoxia developed during unconsciousness in these animals, the quickening of the pulse, expressed as a percentage of the initial norm, under the influence of oxygen insufficiency was less strongly manifest than during waking under the same conditions. It is necessary to point out, however, that in absolute figures, the pulse frequency at low degrees of hypoxia (16-14% of oxygen in the inspired air) was higher in dogs that had been put to sleep, while at severe degrees of hypoxia, the pulse of these dogs quickened to a lesser extent than at the same "altitudes" in the waking state. Together with this, the change in blood pressure during hypoxia is not as great in the sleeping animals as in the waking ones; particularly indistinct in the acute phases of hypoxia is the second phase of the reaction on the part of the blood pressure (Fig. 1); the sharp preterminal peak in blood pressure that is observed in normal dogs is almost completely absent here. At moderate degrees of hypoxia, the level of the average arterial pressure was higher than normal in the sleeping dogs.

The drop in the effectiveness of adaptation to hypoxia on the part of external respiration, the quicker pulses and the high level of blood pressure result in a pronounced decrease in the oxygen saturation of the blood, even at minor degrees of oxygen insufficiency; in acute hypoxia, undersaturation of the blood with oxygen becomes particularly distinct in dogs with the brain cortex excluded.

It follows from the data given above that adaptation to oxygen insufficiency takes place in normal mature animals chiefly through amplification of the external respiration, as indicated by the earlier increase (at an "altitude" of 1-2 thousand meters) in pulmonary ventila-

tion, which increases consistently as the content of oxygen in the inspired air falls off.

The preservation of relatively high alveolar ventilation indices provides for saturation of the blood with oxygen at a rather high level during hypoxia in normal dogs. The reaction to hypoxia on the part of the cardiovascular system arises at a more acute degree of hypoxia.

As indicated by our observations, functional exclusion or surgical removal of the brain cortex has a distinct effect on the organism's reaction to hypoxia. Adaptation to hypoxia through the external respiration deteriorates, as indicated by the indicators of reduced pulmonary and alveolar ventilation. The lowered effectiveness of adaptation to hypoxia by external respiration, the more frequent heartbeats and the relatively high level of blood pressure cause a manifest decrease in the oxygen saturation of the blood in dogs in a state of anesthetized sleep, i.e., a higher degree of hypoxemia, even at relatively slight degrees of hypoxia. In acute hypoxia, the undersaturation of the blood with oxygen becomes particularly distinct. These data, obtained as they were on dogs, are in full agreement with the results of investigations by V.V. Turanov (published in the present collection), who established a marked drop in the effectiveness of adaptation to hypoxia in humans during natural and medication-induced sleep.

Needless to say, the question as to the mechanisms by which the higher divisions of the brain influence the organism's adaptation to oxygen insufficiency in its various aspects is a highly complicated one. On the one hand, it is known quite well that in natural or anesthetic sleep, the organism's oxygen requirement falls off. Under the conditions of mounting hypoxia, as was shown by our experiments, the oxygen requirement of decorticated and drugged dogs either increases to a lesser degree than during waking or even decreases. These data suggest

that exclusion of the brain cortex, for which a high level of oxidation processes is characteristic, lowers the organism's over-all oxygen requirement and thereby alleviates the conflict that arises in the organism when the amount of oxygen in the inspired air is reduced. On the other hand, exclusion of the brain cortex results in a weakening of the external-respiratory reaction to oxygen insufficiency. Although hypoxemia is more pronounced in the the decorticated animals, the external respiration is augmented to a lesser degree here and in the control dogs. It is difficult to say what is behind this phenomenon - a rise in the excitability threshold of the receptor apparatus or a drop in the excitability of cells in the respiratory center.

All of these problems require special investigations. At the present time, however, we can already affirm that the disturbance to higher regulation of the vegetative functions that sets in as a result of excluding the brain cortex causes a diminution of the reflex activity that is at the bottom of the adaptation of higher mammals to oxygen insufficiency.

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[Footnote]

207 The alveolar ventilation was determined by the Bohr formula. The anatomical dead respiratory space was determined on the carcasses of the animals.

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[Transliterated Symbols]

205 $\Pi O = D O =$ dykhatel'nyy ob'yem = respiratory volume

205 $MO\Omega = MOD =$ minutnyy ob'yem dykhaniya = per-minute respiratory volume

208 Ч.д = Ch. d = Chastota dykhaniya = respiratory frequency

208 ред. = red. = redutsirovanny = reduced, adjusted

ON THE PROBLEM OF ADAPTATION OF ADULT HUMAN ORGANISM
TO OXYGEN INSUFFICIENCY

V.V. Turanov

(Kiev)

Despite the fact that a large number of investigators have concerned themselves with the question of the adult human organism's adaptation to air oxygen insufficiency and a great many facts have been accumulated on the amplification of the adaptive-mechanism functions (external respiration, cardiac activity, red blood, and etc.), certain contradictions and unclear points remain in the factual material itself and in the analyses applied to it. These contradictions have arisen from many causes: different authors have obtained data under differing hypoxic conditions and on different individuals, using differing techniques; in many cases, the state of the test subjects at various altitudes in the mountains, with varying rates of "ascent" in the altitude chamber, etc., have not been taken into account. Inadequate attention has been paid to research at moderate altitudes. Authors have on many occasions studied the changes of only a single function of the organism, out of context with other adaptive mechanisms.

At the same time, the complex process of adaptation of the whole organism to hypoxia can be understood only as a result of juxtaposition of the changes in the activities of the various adaptive mechanisms.

Proceeding from the above considerations, we performed experiments on one and the same individual, with attention to the changes that arose in the basic systems participating directly in adaptation of the human

to oxygen deficiency. For this purpose, we studied the external respiratory indices (MOD, frequency and depth of respiration), cardiac activity (pulse frequency and electrocardiographic data), changes in erythrocyte count and hemoglobin content in the blood (after Sahli) and the oxygen saturation of the arterial blood (after Krepes).

The studies were made under altitude-chamber conditions and at various heights on El'brus. The "trip up" in the altitude chamber took place at a rate of 10 m/sec to the "altitude" of 5000 m with five-minute plateaus" every thousand meters, during both the "ascent" and the "descent." The pulmonary ventilation was registered using a contact-type gas-flow meter.

TABLE 1
Respiratory Frequency During Hypoxia in the Altitude Chamber

1 "Высота" подъема	2 Испытуемые					
	Э. Г.	А.	М. С.	В. А.	В. Я.	В. П.
	3	4	5	6	7	8
9 Норма	16	10	10	12	12	12
10 1000 м	14	10	14	12	15	12
2000 "	14	12	14	12	15	12
3000 "	12	10	12	12	15	12
4000 "	12	10	11	12	14	12
5000 "	12	11	14	12	12	14

Respiratory Frequency in the Mountains

Условия	12 Испытуемые									
	М. С.	А.	А. З. К.	М. Н.	С. Я.	В. Т.	В. Ф.	Л. Р.	В. А.	И. К.
11	5	4	13	14	15	16	17	18	6	19
Киев . 20 . . .	10	10	12	20	13	10	8	16	12	10
21 Терскол (2000 м)	7	7	17	19	13	9	12	13	10	12
22 Ледовая база (3800 м) . .	10	10	16	—	13	7	12	15	8	12

1) "Altitude" of ascent; 2) test subject; 3) E.G., 4) A.; 5) M.S.; 6) V.A.; 7) V.Ya.F.; 8) V.P.; 9) under normal conditions; 10) 1000 m; 11) conditions; 12) test subjects; 13) A.Z.K.; 14) M.N.; 15) S.Ya.; 16) V.T.; 17) V.F.; 18) L.R.; 19) I.K.; 20) Kiev; 21) Terskol (2000 m); 22) Ledovaya baza (3800 m).

We present data that we obtained in an investigation of external respiration on healthy individuals under hypoxic conditions.

As will be seen from Table 1, the respiratory frequency in the state of rest (lying down) slackened in most cases during hypoxia, with

TABLE 2

Per-minute Respiratory Volume in the
Altitude Chamber

Условия 1	2 Испытуемые					
	Э. Г. 3	А. 4	М. С. 5	В. А. 6	В. Я. Ф. 7	В. П. 8
9 Нормы	5400	3400	6600	4000	5200	5200
1000 м	5800	3600	8800	4000	5400	5400
2000 м	5800	4000	9000	4400	6000	6600
3000 м	6400	4600	8600	5800	6300	6600
4000 м	7000	5000	11200	7000	8400	7800
5000 м	7800	5700	12300	9600	8400	8600

Per-minute Respiratory Volume in the
Mountains

Условия 1	2 Испытуемые									
	М. С. 5	А. 4	А. З. К. 10	М. Н. 11	С. Я. 12	В. Т. 13	В. Ф. 14	Л. Р. 15	В. А. 6	И. К. 16
17 Киев	6600	3000	4600	9000	9600	6000	3500	5200	4100	4000
18 Терскол (2000 м)	7800	7000	5950	9500	9100	8100	5000	6000	5300	4800
19 Ледовая база (3800 м)	10000	4800	7200	—	10400	6300	6800	7100	6500	6200

1) Conditions; 2) test subjects; 3) E.G.; 4) A.; 5) M.S.; 6) V.A.; 7) V.Ya.F.; 8) V.P.; 9) under normal conditions; 10) A.Z.K.; 11) M.N.; 12) S.Ya.; 13) V.T.; 14) V.F.; 15) L.R.; 16) I.K.; 17) Kiev; 19) Terskol (2000 m); 20) Ledovaya baza (3800 m).

a slight quickening in only a few of the test subjects. The same individuals under the same conditions showed pulmonary ventilation increases instantly with aggravating hypoxia. The increase in MOD was observed as soon as the altitude of 1000 m in most of the experimental subjects (Table 2).

It follows from the data given that in most of the test subjects, the increase in MOD is to be accounted for by deeper breathing, which was noted even at moderately high altitudes. Only in the weaker, untrained individuals was the MOD at moderate altitudes due to a quickening of the respiratory rhythm, although the depth of their breathing also increased sharply at high altitudes, while the respiratory frequency remained at the initial level.

Adaptation to hypoxia by increasing the depth of respiration instead of its frequency is more favorable to the organism, since in this

TABLE 3

Variation of Respiration Depth in Altitude Chamber

1 "Высота" подъема	2 Испытуемые					
	Э. Г.	А.	М. С.	В. А.	В. Я. Ф.	Н. П.
	3	4	5	6	7	8
9 Норма, м	340	340	660	330	430	430
1000 »	414	360	630	330	360	450
2000 »	530	333	640	360	400	550
3000 »	580	460	710	470	420	550
4000 »	580	500	800	580	560	650
5000 »	650	520	880	800	560	700

Variation of Depth of Respiration in the Mountains

10 Условия	2 Испытуемые									
	М. С.	А.	А. З. К.	М. Н.	С. Я.	В. Т.	В. Ф.	Л. Р.	В. А.	И. К.
	5	4	11	12	13	14	15	16	6	17
18 Киев	600	300	380	300	730	600	400	325	350	400
19 Терскол (2000 м)	660	1000	350	500	700	900	416	170	320	400
20 Ледовая база (3800 м)	1000	800	450	—	800	900	550	171	312	516

1) "Altitude" of ascent; 2) test subjects; 3) E.G.; 4) A.; 5) M.S.; 6) V.A.; 7) V.Ya.F.; 8) N.P.; 9) normal altitude; 10) conditions; 11) A.Z.K.; 12) M.N.; 13) S.Ya.; 14) V.T.; 15) V.F.; 16) L.R.; 17) I.K.; 18) Kiev; 19) Terskol (2000 m); 20) Ledovaya baza (3800 m).

case the detrimental effect of the dead space is smaller and the alveolar ventilation figure is higher. Thus, for example, the pulmonary ventilation of test subjects A.Z.K. and L.R. increased in the mountains, in A.Z.K. through the frequency of respiration, and in L.R. through increased depth of respiration. At Terskol (2000 m), the alveolar ventilation had increased correspondingly: in A.Z.K. by 750 ml as compared with the "Kiev" norm, and in L.R., with deeper respiration, by 1160 ml (Table 3). On adjusting the pulmonary ventilation figures of the test subjects we can easily satisfy ourselves that in the adult human, the MOD deficit is a small figure — ranging from 200 to 1500 ml at altitudes of 3000-4000 m, and that this deficit in pulmonary ventilation is the smaller the deeper was the respiration of the individual in question. The nature of respiration did not change within the altitude range stud-

TABLE 4

Variation of Pulse Frequency During Hypoxia in the Altitude Chamber

"Высота" подъема	1	2 Испытуемые					
		Ф. 3	Д. 4	А. 5	Г. 6	В. 7	С. 8
9 Нормы		64	60	64	72	64	76
1000 м		64	60	64	72	64	76
2000 "		66	60	68	76	64	76
3000 "		72	60	80	76	64	80
4000 "		80	64	84	84	72	80
5000 "		96	76	88	96	86	88
4000 "		80	68	80	80	72	80
3000 "		76	64	71	80	68	76
2000 "		66	60	76	72	64	76
1000 "		64	60	64	72	64	76
0 "		64	56	64	72	64	76

Variation of Pulse Frequency in the Mountains

Условия	10	2 Испытуемые									
		Т. 11	Ф. 3	Р. 12	А. 5	В. 7	С. 8	К. 13	К. А. З. 14	Я. 15	Н. 16
17 Киев . . .		62	50	64	64	68	76	46	72	48	56
18 Терскол (2000 м)		60	48	80	60	80	64	52	68	52	66
19 Ледовая база (3800 м) . .		64	84	80	76	100	84	64	88	60	—

1) "Altitude" of ascent; 2) test subjects; 3) F.; 4) D.; 5) A.; 6) G.; 7) V.; 8) S.; 9) normal altitude; 10) conditions; 11) T.; 12) R.; 13) K.; 14) K.A.Z.; 15) Ya.; 16) N.; 17) Kiev; 18) Terskol (2000 m); 19) Ledovaya baza (3800 m).

ied. The adaptation of the organism to hypoxia is also contributed to by intensification of cardiac activity.

In experiments under the conditions of the altitude chamber, a marked quickening of the pulses of individuals in a state of rest (lying down) was observed, as will be seen from Table 4, beginning at an "altitude" of 3000-4000 m. In the mountains, the pulses of 50% of the test individuals were even somewhat slower as the altitude of 2000 m (Terskol) than in Kiev. It is necessary to note that in the mountains, the duration of the effect of the rarefied air was incomparably longer (around the clock). On this basis, a 2000 meter altitude in the mountains can be completed with the same "altitude" in the low-pressure chamber.

A study of the electrocardiographic data indicated that no patholog-

ical changes are observed up to an altitude of 5000 m. Beginning at an altitude of 3000 m, the heart pause was slightly shortened (the T-P interval was reduced), and the voltage of the R-wave increased insignificantly. The latter may reflect an increase in the load on the ventricles of the heart and thus testify indirectly to an increase in its systolic volume.

Thus, it follows from the data given above that the reaction to hypoxia on the part of the heart manifests at higher altitudes than the response in external respiration. Obviously, at low altitudes (1000-2000 m), an increase in the per-minute respiratory volume is found adequate to maintain the oxygen partial pressure within the normal range.

At higher altitudes (3000-4000 m), an increased MOD is no longer adequate (a pulmonary ventilation deficit arises). At this moment, the reaction on the part of the heart and red blood comes clearly into evidence: the pulse frequency increases, together with the per-minute volume of the heart, and the erythrocyte counts and hemoglobin content in the blood stream show a rise.

The resultant of the above reactions is the degree of oxygen saturation of the arterial blood. Below we present data on the oxygen saturation of the blood in our test subjects under the conditions of the altitude chamber.

The percentage oxygen saturation of the arterial blood in mature humans begins to drop markedly from an "altitude" of 2000-3000 m. At the "altitude" of 5000 m, the oxygen situation of the blood drops in most of the test subjects to 81-88%, and to 76% in only one. During the "descent," the percentage saturation returns gradually to normal (at an "altitude" of 1000 m, or on "descent" to 0). The deficit in the oxygen saturation of the blood is compensated to a certain degree by an increase in hemoglobin content and intensified cardiac activity. However, this

compensation is found inadequate at high altitudes for rapid ascents, as manifested in the discomfort of our test subjects at an altitude of 3800 m in the mountains and 5000 m in the altitude chamber.

As has been shown by the studies of Sirotinin, Arkhangel'skoy, Petrov, Gubler, Machinskoy, Lauer and Kolchinskoy, Turanov and others, the cortex of the brain plays an important role in coordinating and regulating the vegetative functions of the various physiological systems in the adaptive reactions of the organism to change in conditions in its environment. On the basis of these observations, the necessary attention has been devoted to the state of the central nervous system in study of the human organism's adaptation to hypoxia.

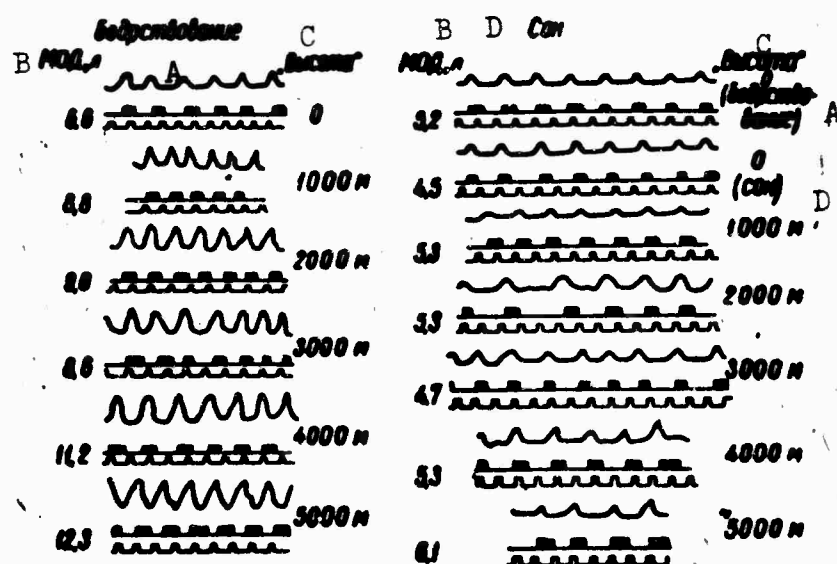


Fig. 1. Variation of external respiration in test subject M.M.S. during "ascent" in the altitude chamber while awake and asleep. The upper line is the respiration trace; the central line is the lung ventilation marker; the lower line is the time marker. The MOD (in ml) is keyed on the left and the "altitude" (in thousands of meters) on the right.

A) Waking; B) MOD, liters; C) "altitude"; D) sleep.

We studied the changes in external respiration, cardiac activity, and shifts in the oxygen saturation of the blood in the same experimental subjects after putting them to sleep with nembutal (nembutal dose of 0.2). During the nembutal sleep at normal atmospheric pressure, the pulmonary ventilation diminished markedly (Fig. 1).

No quickening of respiration was observed during an "ascent" in the altitude chamber. The respiration depth and pulmonary ventilation increased to a much lesser degree than in the waiting state, i.e., the adaptive respiratory reaction was less distant during sleep. Thus, in the waking state the pulmonary ventilation of test subject M.S. increased by 33% at an "altitude" of 1000 m, while during sleep it rose by 18%; at an "altitude" of 8000 m, it rose by 32% in the waking state and 10% during sleep. The maximum increase in pulmonary ventilation was observed at an "altitude" of 5000 m; in the waking state it rose by 90% and during sleep by 35%. During drugged sleep (Fig. 2), profound changes in the nature of respiration were observed when the air in the altitude chamber was rarefied: periodic respiration of the Cheyne-Stokes type appeared at an "altitude" of 4000-5000 m and was retained during the "descent" to "altitudes" of 4000-3000 m. Thus, when test subject E.G. was "taken up" in the altitude chamber while asleep to an altitude of 4000 m, the type of respiration did not change; only at an "altitude" of 5000 m did we register the Cheyne-Stokes periodic type of respiration; this type of respiration persisted in this [male] test subject even during the "descent" down as far as "altitudes" of 4000-3000 m. At these same "altitudes," but in the waking state, the nature of his respiration remained normal (Fig. 3). During natural sleep in the mountains, we also observed periodic respiration in our subjects at altitudes of 4200-5300 m. The pulmonary ventilation dropped sharply during this time.

The data shown indicate that during sleep, the pulmonary ventilation increase is considerably smaller than during waking when the test subjects were in hypoxia. It is found to be inadequate to provide the organism with the necessary quantity of oxygen.

During drugged sleep, rarefaction of the air in the altitude chamber produced a quickening of the cardiac rhythm in our test subjects,

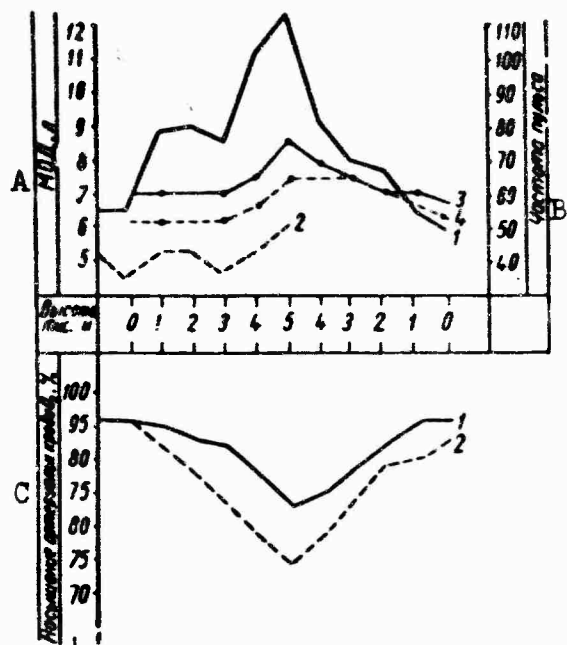


Fig. 2. Changes in MOD, pulse frequency and oxygen saturation of blood of test subject M.M.S. during "ascent" in altitude chamber, during waking and sleep. 1) Waking; 2) sleep; 3,4) pulse frequency in beats per 1 min. A) MOD, liters; B) pulse frequency; C) O₂ saturation of arterial blood, %.

just as it had in the waking state, beginning at an "altitude" of 3000-4000 m. However, in contrast to the waking state, the pulse continued to speed up during sleep even during the "descent" to an "altitude" of 4000 m. In most of the test subjects, the maximum pulse quickening was observed at an "altitude" of 4000 m after "descent" from an "altitude" of 5000 m. The latter would apparently be explained in terms of the extent of hypoxemia remaining, as was indicated earlier, higher during sleep even after

the pressure has been raised in the chamber (Fig. 2). Thus, while asleep, the pulse of the same test individual M.M.S. also began to quicken beginning at an "altitude" of 4000 m, reached a maximum at 5000 m and then,

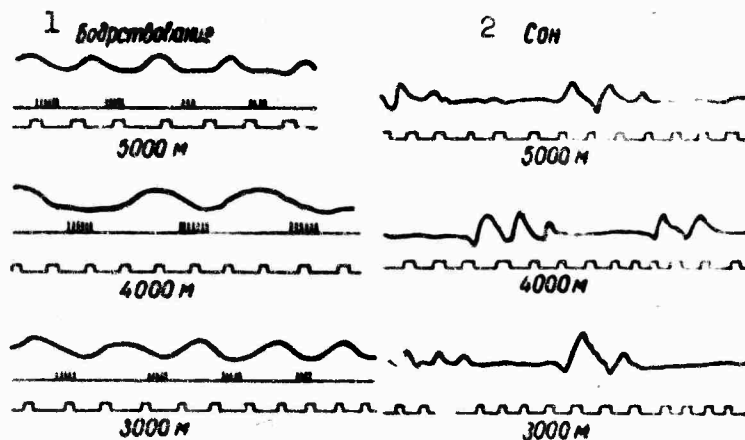


Fig. 3. Change in nature of respiration in test subject E.G. during "ascent" in altitude chamber in waking and sleeping states. 1) Waking; 2) sleep.

despite the fact that the pressure in the chamber had been raised to the respective altitudes of 3000 m and 4000 m [sic], remained just as fast as it had been at the "altitude" of 5000 m.

Normalization of the pulse frequency in this test individual was considerably slower during sleep than in the waking state. Only after the "descent" had been completed (normal barometric pressure) did his pulse frequency reach the initial value. Similar changes in pulse frequency were also noted in other test subjects.

Also characteristic is the pulse variation in another test subject. The maximum quickening of his pulse was observed not at the "altitude" of 5000 m, but at an "altitude" of 4000 m during the "descent." It follows from this that the reaction on the part of the heart is, as it were, delayed during sleep, becoming inadequate to the changing conditions of the environment.

It appears that the high degree of arterial hypoxemia that we observed in mature humans during sleep (Fig. 2) is also to be accounted for in terms of inadequate pulmonary ventilation.

As is shown by the oxyhemograms, sleep at normal atmospheric pressure produces a drop in the percentage saturation of the arterial blood with oxygen. On the other hand, as the air in the altitude chamber is rarefied, the percentage oxygen saturation of the arterial blood in the same individuals is lower during sleep. The hypoxemia that arises during sleep also persists longer during the "descent" than in the waking state. Thus, for test subject V.P., the percentage oxygen saturation of the blood during a sleeping "ascent" in the altitude chamber was 3-8% lower than in the waking state: 88% awake and 80% asleep at an "altitude" of 5000 m. During the "descent" while awake, the percentage oxygen saturation of the blood reached 93% even at an "altitude" of 2000 m, while during sleep it had reached 78% at this same altitude, i.e., the

extent of hypoxemia remained significant even when normal atmospheric pressure was restored.

The data presented above suggest that during sleep, the activity of the adaptive mechanisms deteriorates, and that fine and rapid adaptation to varying environmental conditions no longer occurs.

During natural and drugged sleep, the human organism's reactions to hypoxia — on the part of his respiratory system and cardiac activity — become less sensitive; with increasing oxygen shortage, they are delayed in time, and manifest at higher degrees of hypoxia and less strongly: on the other hand, on the return to a medium with a normal oxygen content in the inspired air, more time is required for their normalization as compared with the waking state.

Tabulation and analysis of the data obtained on one and the same test subject indicate the following. At moderately high altitudes, the respiratory organs react first to oxygen insufficiency — the per-minute volume of the lungs is increased by increasing the depth of respiration, by the frequency of respiration and the pulse usually remain without any particular changes. At higher altitudes (3000-4000 m), we observe an increase in pulse frequency, and the erythrocyte count and hemoglobin content in the blood rise.

As is indicated by both the literature dated and our own, the functional state of the brain cortex is of great importance in the adaptation of man to hypoxia.

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[Transliterated Symbol]

220 MOI = MOD = minutnyy ob"yem dykhaniya = per-minute respiratory
 volume

SIGNIFICANCE OF THE FUNCTIONAL STATE OF THE CENTRAL NERVOUS SYSTEM IN
THE INTERACTION MECHANISMS OF THE RESPIRATORY AND VASOMOTOR CENTERS
IN VARIOUS FORMS OF HYPOXIA

Ya.M. Britvan

(Vinnitsa)

Few today share Busby's (1915) suggestion that there exists a single center regulating respiration and blood circulation. I.R. Petrov (1935) maintained that the vasomotor center possesses only independent mechanical excitability, while its chemical excitability is effected through the respiratory center. Excitation impulses radiate constantly from the respiratory center to the vasomotor center.

Subsequently, I.R. Petrov (1949) acknowledged that various interrelationships between the respiratory and vasomotor centers are possible. The same standpoint has been taken by V.N. Chernigovskiy (1943), D.A. Biryukov (1946), M.A. Kondratovich (1954), V.V. Frol'kis (1959) and others. It should be noted that the mechanisms of interaction between the respiratory and vasomotor centers under pathological conditions remain rather neglected.

In our previous communication (1962), it was indicated that the interaction between the respiratory vasomotor centers is different in different stages of hemic hypoxia and depends on the rapidity, severity, and duration of its course. In the initial stage of a rapid, acute, massive loss of blood, we observe, together with a sharp drop in arterial pressure, excitation of respiration and inhibition of the brain cortex function as determined from its electrical activity.

When hemic hypoxia was developed slowly by fractional bloodletting and intoxication with methemoglobin-forming agents, the arterial pressure gradually diminished, and the initial phase of respiratory excitation is frequently combined with an amplification of the cortical electrical activity. Parallel reactions, irradiation or inductive behavior of the respiratory and vasomotor centers are noted in the transitional stage of hemic hypoxia. Our observations also indicated that in hemic hypoxia, the interaction between these centers also depends on the initial functional state of the central nervous system as affected by narcosis, administration of phenamine and aminazine and exclusion of the arterial-pressure regulators.

In the present report, we shall analyze data on the interaction of the respiratory and vasomotor centers in other forms of hypoxia - transfusion and anaphylactic shock, asphyxia, and elevated intracranial pressure. The respiration, arterial pressure and the biocurrents of the brain were registered simultaneously. The potentials of the cortex and, in some of the experiments, those of the thalamic division as well, were recorded with a cathode oscillograph or an "Alvar" pen-recorder apparatus.

In the experiments of N.A. Viyevskiy, transfusion shock was induced in rabbits by intravenous administration of banked human blood. In the case of anaphylactic shock, sensitization was by triple injection of normal force serum. The reacting dose was administered on the 18th-21st day after the first serum injection.

The initial functional state of the central nervous system was varied by administration of phenamine in a dose of 5 mg/kg of weight and aminazine in the same dose. Both the phenamine and the aminazine were administered 30-35 min before inducing the shock.

The investigations showed that in the initial stage of either form

of shock, the arterial pressure rises together with the excitation of respiration. In the transitional stage of shock hypoxia, suppression of the respiration (frequent superficial rhythm) is at first combined with arterial pressure held below the initial values. In many of the experiments, this drop below the initial values resulted in the appearance of stereotyped third-order waves of varying amplitude and frequency, sometimes in synchronism with periodic respiration. The appearance of terminal respiration types was always accompanied by a catastrophic drop in arterial pressure.

In rapidly progressing shock, a sharp drop in arterial pressure intervened soon after the phase in which it was elevated; this was accompanied by suppression of the brain-cortex electrical activity. The appearance of periodic phenomena in the fluctuations of vascular tonus and respiration was normally noted in more protracted forms of the shock. In these experiments, we first observed an intensification and quickening of the fundamental-rhythm biocurrents or an enlivening of the high-frequency biopotentials on the electrocorticogram. Slow, high-voltage potentials then appeared. As the shock deepened, the fundamental rhythm and high-frequency potentials were suppressed, and the voltage and frequency of the delta-oscillations also diminished. On the development of terminal respiration types or slightly earlier, the brain-cortex biocurrents vanished completely.

In rabbits to which phenamine had been administered, the reaction of the respiratory and vasomotor tensors and the electrical activity of the brain cortex resembled those of control animals. However, after the administration of phenamine, frequent irregular or chaotic respiration occurred together with seizures of general motor excitation. Phenamine promoted the development of severe heterotransfusion shock, usually with a lethal outcome. The course of anaphylactic shock varied to a lesser

degree.

In rabbits to which aminazine had been administered first, the initial phase of respiratory excitation was indistinct, and the phase in which the arterial pressure rose was also rather vague or totally absent. As a result of the protracted course of the shock, slow delta-waves were registered for a long time on the electrocorticogram. It should be noted that after administration of aminazine, it was not always possible to produce a severe shock with a lethal outcome. As the hypoxia reversed its course, respiration reached the initial level considerably in advance of arterial pressure, and the electrical activity of the brain cortex recovered even later.

Thus, we may speak of a dependence of the reactions of the respiratory and vasomotor centers on the current functional state of the central nervous system, which is an effect of the successive development of the successive development of stages in hypoxia. A two-phased reaction of these centers in nonanesthetized animals is characteristic, with a first phase in which activity is quickened and a second in which it is suppressed. These phases do not have uniform durations. Thus, the excitation phase of the respiratory center is generally shorter, and the suppression phase longer; on the other hand, the rise in arterial pressure is of short duration and intervenes later. Hence the interaction of the respiratory and vasomotor centers changes throughout the development of the actual hypoxia.

Figure 1 reflects the various aspects of this interaction in one of the experiments with anaphylactic shock on an unanesthetized rabbit. As will be seen from the figure, prior to administration of the reacting dose of serum, the initial normal respiration, arterial pressure and brain-cortex electrical activity have been registered (1). After administration of the reacting serum dose (1), a slight drop in arterial

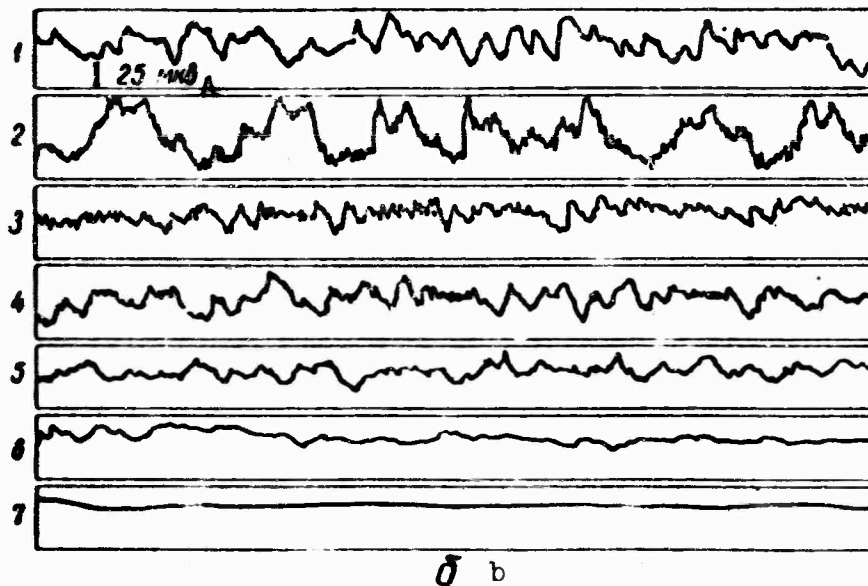
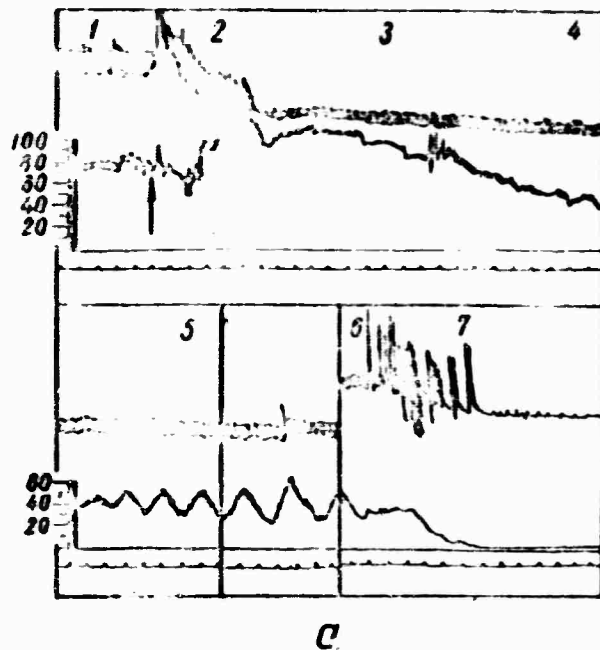


Fig. 1. Changes in respiration, arterial pressure and electrical activity of brain cortex in an unanesthetized rabbit in anaphylactic shock. a) Legend, top to bottom: respiration, arterial pressure; arrow indicating time of serum reinjection, arterial pressure zero line, 10-second time marker; b) electrocorticograms, time marker 1 sec. The numerals 1-7 indicate the times at which the electrocardiograms (6) were recorded. A) 25 μ v.

pressure occurred in combination with vigorous excitation of respiration, with the latter retained even under conditions under which the arterial pressure exceeds its initial level (2).

The excited respiration is supplanted by suppressed respiration, although the arterial pressure remains high (3). Subsequently, frequent superficial respiration persists under the conditions of lowered arter-

ial pressure (4), and the latter acquires the nature of stereotyped slow third-order waves (5). Agonal excitation of respiration and the "last gasps" were registered against a background of vasomotor center paralysis (6 and 7).

It is worthy of note that the initial excitation of the respiratory and vasomotor centers arises against a background of profound cortical inhibition, which is manifest in the high-voltage slow delta-waves with frequencies of one or two per second. As hypoxia deepens, the electrical activity of the brain cortex diminishes progressively and vanishes on the appearance of terminal respiration (lower half of figure).

The asphyxia experiments were set up by Ye.A. Markova. Rapidly advancing asphyxia was produced in cats by totally cutting off access of air to the respiratory tracts and maintained for 5-8 minutes; gradual asphyxia was induced by having the animals breathe air in an enclosed space and lasted for 26-50 minutes.

In unanesthetized and phenaminized animals, concurrent excitation of the respiratory and vasomotor centers was observed in initial asphyxia; here, breathing became considerably deeper, with frequent deep intercalary inspirations, and the arterial pressure rose steeply and steadily. Seizures of general motor excitation were accompanied by a transitory rise in arterial pressure. Suppression of the fundamental rhythm and high-frequency potentials was registered quite early on the electrocorticogram, and slow high-voltage delta-waves appeared.

In the transitional stage of hypoxia, a drop in the arterial pressure and a slackening and voltage decrease in the slow electrical activity were observed together with a slackening of the respiratory rhythm and a lowering of its amplitude. With the onset of terminal respiration, the arterial pressure was 10-20 mm Hg, and the brain cortex biocurrents

had vanished. A distinctive feature of protracted asphyxia consisted in the quickening and amplitude increase of the waves of the fundamental rhythm in the initial stage, in combination with long-persisting deepening and quickening of respiration.

Deep ether narcosis weakened the excitation phase of the motor and respiratory centers considerably, preventing the appearance of the deep "gasps." The results of one of the experiments using ether anesthesia are shown in Fig. 2.

As will be seen from Fig. 2, the cats breathed uniformly, showed normal arterial pressure and slow regular electrocorticogram waves before asphyxia was induced (1). In the initial and transitional stages of short asphyxia, we note a slackening and slight deepening of respiration and an insignificant rise in arterial pressure with enlargement of the second-order waves. The electrocorticogram shows a sharp drop in the amplitude of the slow waves (2). In the terminal stage of asphyxia, respiration stops, the arterial pressure drops to 20 mm Hg and the brain cortex biocurrents vanish (3). Two minutes after the beginning of independent function restoration, sporadic respiration with occasional "gasps" and short delays in inspiration appeared, the arterial pressure rose to 100 mm Hg and the electrical activity of the brain cortex was suppressed (4).

Ye.A. Markova also studied the reflex excitability and functional mobility of the respiratory and vasomotor centers under the conditions of asphyxia. The excitability was determined from the stimulation threshold and the functional mobility from the reactions of the centers to stimulation of the central segment of the tibial nerve by induction currents of various frequencies.

The experiments indicated that with the development of asphyxia, the reflex excitability and functional mobility of the centers diminish

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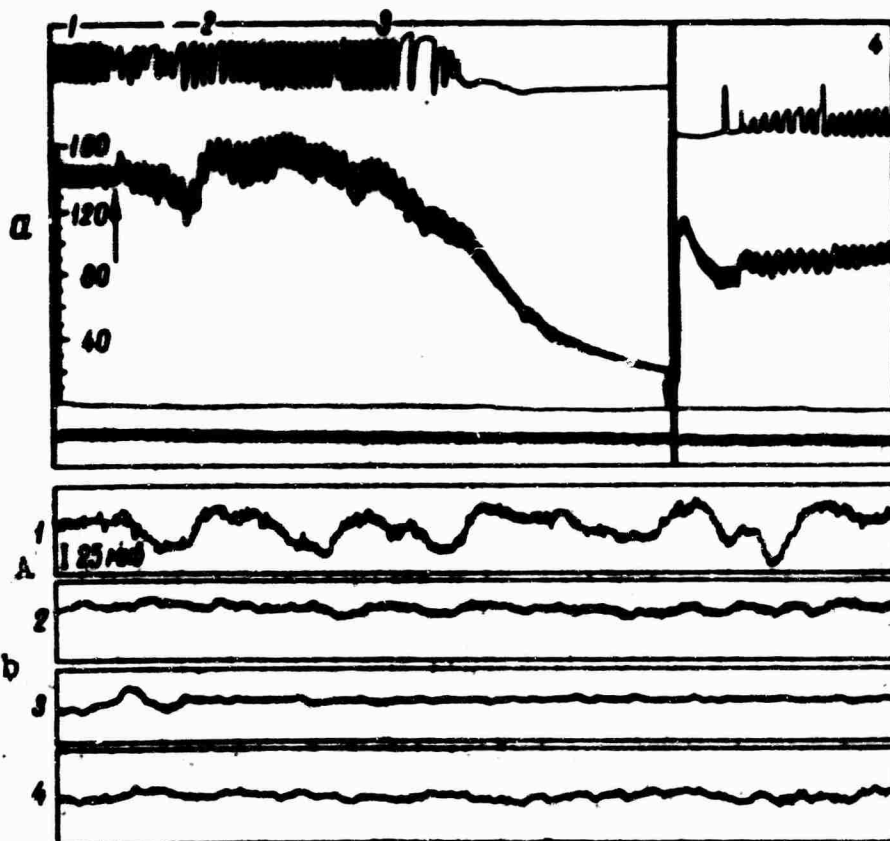


Fig. 2. Changes in respiration, arterial pressure and electrical activity of brain cortex in a cat under ether anesthesia during short-term hypoxia. Symbols same as in Fig. 1. The arrow indicates the time at which the tracheal passage was blocked. A) 25 μ v.

concurrently, and that the equalizing reaction of the centers is supplanted first by a paradoxical and then by an inhibitory reaction. Phenamine raises the initial reflex activity of the respiratory and vasomotor centers considerably, while ether narcosis depresses it. It should be noted that deep ether anesthesia and the administration of phenamine have a negative influence on the processes by which the organism's functions are restored.

Thus, in contrast to shock, the interaction of the respiratory and vasomotor centers is more standard in asphyxia, and the changes in the initial and transitional stages of asphyxia run concurrently. This can be accounted for by the combined effects of hypoxia and hypercapnia in asphyxia. Only in the final stage of asphyxia do we note dissociation of the functions: paralysis of the vasomotor center is accompanied by

"loosing" of the lower respiratory tracts.

In the investigations of S.S. Krokmal', the intracranial pressure of cats was elevated by extradural infusion of Ringer's solution under a pressure of 200-250 mm Hg. The sudden, rapid and transitory rise in intracranial pressure produces a sharp increase in arterial pressure, suppression of respiration and complete disappearance of the brain cortex biocurrents with suppression of the currents in the thalamic division, in which slow regular delta-waves are most frequently registered.

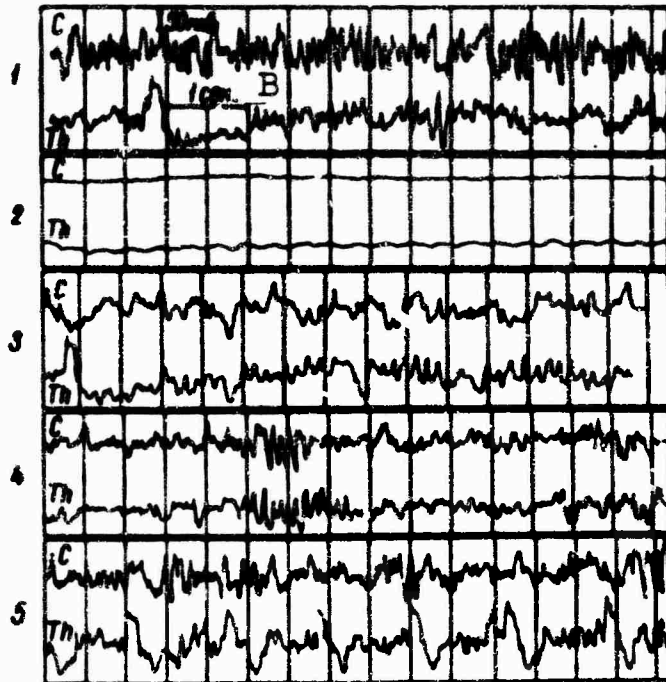
On an increase in intracranial pressure that is less severe but lasts longer, we observe infrequent respiration of the periodic type, a smaller rise in arterial pressure, third-order waves, and suppression of biocurrents in the cortex and thalamic division of the brain. The changes take the reverse course when the functions are restored. Figure 3 shows data from one of the experiments with a short-term rise in intracranial pressure. As will be seen from the Figure, the initial figures for the cats were within normal limits (1). On sudden extradural infusion of Ringer's solution under a pressure of 250 mm Hg, the respiratory center reacts in two phases. The second phase, in which respiration ceases, is accompanied by a sharp increase in arterial pressure to 230 mm Hg, the electrical activity of the brain cortex vanishes simultaneously and that of the thalamic division is greatly suppressed (2). On removal of the conditions supporting the increase in intracranial pressure, the arterial pressure returns to the normal level, while respiration is characterized by a frequent rhythm, initially of the periodic type. The electrical activities of the cortex and thalamic division of the brain take a long time in returning to the initial level (3-5).

In cats to which aminazine was administered, the pressor reaction of the arterial pressure was indistinct or absent, despite the considerable rise in intracranial pressure. In none of the experiments did the



a

A



b δ

Fig. 3. Changes in respiration, arterial pressure and the electrical activity of the cortex and thalamic division of the brain in unanesthetized cat on elevation of intracranial pressure. a) Legend, top to bottom: respiration, arterial pressure, bar indicating time during which intracranial pressure was raised, zero line of arterial pressure, 10-second time marker; b) corticogram (C), thalamogram (Th). A) 50μv; B) 1 sec.

arterial pressure rise above the initial level. The phase in which the arterial pressure drops and respiration is suppressed, together with the biocurrents of the brain, develops soon afterward. Restoration of the organism's functions is usually not observed.

The results of all our investigations indicate that the interaction

of the respiratory and vasomotor centers is not the same in different stages of hypoxia produced by blood transfusion and anaphylactic shock, asphyxia and elevation of the intracranial pressure. There is a dependence of the reaction of these centers on the rapidity, intensity and duration of the hypoxia. The interaction of the respiratory and vasomotor centers during the process in which the functions of the organism are restored is similarly irregular. All of this indicates that the reactions of the centers depend on functional changes related to their current activity.

The investigations also show that the interaction of the respiratory and vasomotor centers in shock and asphyxia and on elevation of the intracranial pressure depends on the initial functional state of the central nervous system, which is affected by narcosis and the administration of phenamine and aminazine. Certain differences are noted in asphyxia, apparently as a result of the combined effects of hypoxia and hypercapnia.

In all forms of hypoxia studied, we note an initial significant rise in arterial pressure, in contrast to the case of hemic hypoxia. As in hemic hypoxia, we detect high sensitivity of the brain cortex to oxygen insufficiency, and an inhibition process of the protective type develops in it at an early phase.

DECREASE IN THE ORGANISM'S RESISTANCE TO OXYGEN STARVATION
UNDER THE INFLUENCE OF NARCOTICS

A.I. Ulovich

(Moscow)

The importance of the problem of the combined action of narcotics and oxygen starvation on the organism is determined primarily by the fact that most of the basic complications of narcosis are associated with oxygen starvation. Oxygen starvation is regarded as the principal cause of one of the grave complications of narcosis - suppression of respiration. It is ascribed an important role in the development of circulatory insufficiency and in the etiology or pathogenesis of heart stoppage on the operating table. A definite relationship with the effect of the fourth complication of narcosis - postoperational disturbances to higher nervous activity - on the narcotized organism is also noted. Suppression of respiration, with developing circulatory insufficiency up to the point of collapse is also observed in the use of narcotic hypnotics and analgesics in hypoxic states of therapeutic patients (Arkhir patol. [Archives of Pathology], No. 3, 1962, page 60).

This problem is also of theoretical importance. The helpful influence of narcotics was originally affirmed in a study of the influence of a number of narcotic substances on the course of experimental oxygen starvation.

Attempts have recently been made to substantiate the position that there are two aspects to the effect of narcotics in oxygen starvation: helpful and detrimental. By the detrimental effect, we mean an increase

in the sensitivity of the narcotized organism to oxygen starvation and a decrease in its resistance to it.

The majority of studies on which it was concluded that narcotics have a positive effect in oxygen starvation were performed with lethal degrees of hypoxia. Here, an index frequently used for this effect was the prolongation of the narcotized animals' survival time, which could have been a result of a delay in extinction of the narcotized organism's functions during the stage of irreversible changes. However, in experiments with anemic hypoxia induced by sodium nitrite administered subcutaneously to the narcotized animals, the increase in survival time might have been a consequence of a delay in its infusion into the blood stream.

In connection with the circumstances outlined above, we made it our task to study the resistance of narcotized animals to moderate degrees of oxygen starvation. Here we assumed that only the survival rate could be used as a dependable index to the organism's resistance. Since narcotics have been used in oxygen starvation with a view to lowering the sensitivity of the central nervous system to oxygen insufficiency and limiting the consumption of oxygen by the tissues, we used narcosis of medium depth, under which, in contrast to light narcosis, we could expect a higher probability of both a decrease in the sensitivity of the central nervous system and a decrease in the tissue oxygen consumption.

Our first observations, which date from 1954-1955, indicated a distinct decrease in the survival of narcotized mice in anemic hypoxia induced by the administration of the methemoglobin forming agent sodium nitrite. Subcutaneous injection of 19 mg/kg of weight resulted in the death of 11.3% of the control mice. Mice that had been narcotized first died in a considerably higher percentage of cases (Farmakol., toksikol. [Pharmacology and Toxicology], No. 5, 1955, page 27).

Under the influence of a dose of 1200 mg/kg of body weight of urethane, introduced intraabdominally, the fatality rate of the mice on the administration of the same sodium nitrite dose increased to 60%, and under the influence of chloral hydrate in a dose of 300 mg/kg to 64.8%. An increase in the death rate of the mice to 37% was also observed under the influence of chloralose administered intraabdominally in a dose of 80 mg/kg of weight. Codeine phosphate, a substance that depresses the central nervous system, had a similar effect.

In analogous experiments on rats, a decrease in the survival rate of the narcotized animals, albeit a smaller one, was also observed. A 97-mg/kg dose of sodium nitrite caused death of control rats in 21.1% of cases. Rats narcotized with urethane at the same level of hypoxia perished in 37.8% of cases, while those narcotized with chloralose perished in 35% of cases.

The same relationship was brought out in experiments on cats, to which sodium nitrite was administered intravenously in a dose of 25-26 mg/kg of body weight. At this sodium nitrite dose, four cats of 11 control animals perished, while four cats out of six that had been narcotized with urethane expired (Farmakol. i toksikol., No. 3, 1961, page 28).

Experiments were performed on 22 rabbits in a moderate degree of hypoxic hypoxia. The animals breathed through masks a gas mixture containing 13.4% of oxygen for 6-7.5 hours. Five control animals withstood respiration of this gas mixture without apparent complications. Respiration remained rhythmical and amplified during the entire experiment, with a marked increase in depth. The blood pressure, which sometimes fell off toward the end of the experiment, remained in the range of the initial level or even slightly higher. As a rule, rabbits that have been narcotized with urethane, sodium amyral and chloralose died in hypoxic

hypoxia within 25 minutes to 4.5 hours. Of ten previously narcotized rabbits, only two survived for six hours. In moderately deep urethane and chloralose narcosis. All seven rabbits to which sodium amytal and chloralose were administered after one hour of hypoxia died between 1 hour and 2 hours and 40 minutes after their administration (Arkhi v patol., No. 3, 1962, page 60).

Thus, a decrease in the survival rate of narcotized animals was observed in both anemic and hypoxic hypoxia, but it was more distinct in the latter form. This can be accounted for in terms of a number of aspects, but the principal cause probably consists in the fact that the hypoxic hypoxia did not diminish, while progressive reduction of the methemoglobin to hemoglobin resulted in a gradual diminution of the extent of oxygen starvation.

The type of respiration, level of blood pressure, and the contents of oxygen and carbon dioxide in the arterial blood during oxygen starvation as we examined them in the experiments on cats and rabbits indicated sharper deviations from the initial physiological level in the narcotized animals as compared with those that were not drugged.

Intraabdominal administration of sodium amytal to the rabbits after one hour of hypoxia resulted in a immediate considerable slackening of respiration in some of the cases. Even 5 minutes after injection of the narcotic, the number of respirations dropped by almost half (from 72 to 38 respirations per minute). In animals not suffering from oxygen starvation, the same sodium amytal dose produced no marked change in respiratory frequency during this time. A distinct slackening of respiration — an indication that it had been depressed — was also observed at the time of administration of sodium nitrite to cats under urethane narcosis.

The rhythm of respiration was also disturbed in animals that had been narcotized with sodium amytal and chloralose. We observed prolonged

periodic respiration, respiration by occasional gasps. Cheyne-Stokes respiration developed during oxygen starvation under chloralose narcosis. The respiratory rhythm was not disturbed in oxygen starvation in animals that had not been drugged. The undulating type of respiration curve sometimes observed prior to the experiment and at the onset of hypoxia was subsequently replaced by uniform respiration.

Like respiration, the blood pressure of nondrugged rabbits was within the physiological limits during oxygen starvation. Anemic hypoxia in undrugged cats proceeded with frequent periods in which the excitability was elevated, with a rise in the blood-pressure level. In cases in which the cats perished, the blood pressure dropped during the phase of terminal respiration.

The blood pressure was lowered on combined application of narcotics and oxygen starvation in either sequence. Injection of sodium nitrite against a background of narcosis resulted in a very slow but nevertheless distinct decline in blood pressure during administration.

A drop in blood pressure following the collapse type was observed during the first 3-5 minutes after injection of sodium amytal into rabbits against a background of hypoxia. Following intraabdominal administration in a dose of 100 mg/kg, the blood pressure dropped by 38-60% of the initial level. Under chloralose narcosis, distinct oscillations of the blood pressure corresponded to periodic respiration.

In the control rabbits, the oxygen saturation of the arterial blood had fallen on the average from 93.6 to 76.2% after one hour of breathing a gas mixture containing 13.4% of oxygen. The oxygen saturation of the arterial blood decreased at most to 64.4%, and that of the venous blood to 29.7%. The true content of oxygen in the arterial blood diminished on the average by 2.5 volume-% with respect to the initial level.

In narcotized rabbits, extremely low indices were noted for both the percentage oxygen saturation of the arterial blood and the oxygen contents in the arterial and venous blood after an hour of breathing this gas mixture. In rabbits drugged with sodium amytal, the oxygen saturation of the arterial blood decreased during this time to 26.7% in some cases, while the corresponding figure for the venous blood was 14.3%. The true oxygen content decreased considerably in certain cases, amounting to 3.9 volume-% for the arterial blood and 2.1 volume-% for the venous blood.

Manifest shifts in the blood gas balance were also noted in drugged cats not subject to oxygen starvation; this indicates the development of hypercapnia during narcosis and a tendency toward insipient hypoxia.

To evaluate the data obtained, we consider it admissible to invoke the basic concepts of the stability of the organism as a self-regulating system, as set forth by the biologist Ashby,* the general sense reduces to the following.

The organism resists disturbance by diverse environmental factors by virtue of its ability, developed over the course of evolution, to control its own functions. The brain, which executes the highest regulatory function, was developed as an organ for adaptation to external environmental conditions. Regulation has the purpose of maintaining constancy of the internal medium within certain physiological limits: the body temperature, pH, sugar content and other constants. By maintaining the internal medium constant, the regulatory system thus ensures stability of the organism and ultimately its survival. Hence the death of the organism is an expression of the impossibility of regulating the functions, while survival is to be regarded as a direct indication of the organism's stability.

The stability of an organism, which characterizes its regulatory

capabilities, can be evaluated on the basis of the reaction of the organism's various systems to stimuli. An irrefutable proof of stability is maintenance of functions and constants within the physiological limits, together with rapid return of the functional systems to the initial level after a deviation under the influence of the factors being studied.

In accordance with these conceptions, our collection of data on the reduced survival rates of the drugged animals in oxygen starvation, on the disturbances of the rhythm and nature of respiration in these animals, the drop in blood pressure and, moreover, the inability of the drugged organism to maintain a high level of oxygen in its arterial blood, as well as the wide fluctuations of its carbon dioxide content, all indicate that the stability of the organism has been reduced in this state.

These concepts provide a general theoretical explanation for the drugged organism's stability decrease during oxygen starvation. To the extent that the brain, which performs the highest regulatory function, was developed as an organ of adaptation to environmental conditions, its depression by narcotics will naturally and necessarily result in a decrease in the regulatory capabilities of the organism during oxygen insufficiency.

Our data indicate a detrimental influence of narcotics in the doses that produce anesthesia of moderate depth, when they are administered in oxygen starvation. We have noted that with increases depth of narcosis, the detrimental effect is amplified. The literature contains data indicating that small doses of narcotics also have a detrimental influence.

In examination of the data on the positive influence of narcotics, our attention is first drawn to the inconsistency of the effects observed in almost all of the experiments. In some cases, amounting occasion-

ally to one third, a decrease rather than an increase in the survival time of the drugged animals in lethal hypoxia was observed. In occasional cases, transitory anemia of the brain in drugged animals hastened their death, while it did not in control animals. Survival of drugged animals under conditions of rapid rarefaction of the air in an altitude chamber and a rapid return to atmospheric pressure was also observed only in some cases.

Moreover, survival of some of the drugged animals in lethal altitude-chamber hypoxia was observed only under strictly defined experimental conditions: rapid regulation of atmospheric pressure, i.e., restoration over a short time interval. The ability of some of the drugged rabbits to survive a considerably larger number of transitory anemias of the brain was also observed under quite specific experimental conditions - in experiments with anemia lasting 15 sec. It is possible that in such ephemeral anemia, the functional stability of some of the drugged animals was retained by the stimulation of glycolysis by the narcotics.

As regards survival of some drugged rats with tied-off carotid arteries while all of the control rats died, we have yet to satisfy ourselves that this inconsistent but unquestionably positive effect of the narcotics will be observed in representatives of other animal species and in other forms of oxygen starvation. In our experiments on cats to which we administered the minimal lethal dose of sodium nitrite (30 mg/kg), neither urethane nor sodium amyral nor chloralose narcosis to moderate depth saved the animals from death.

As we have already indicated, an increase in the survival time of drugged animals or an increase in their ability to withstand "altitude" in the low-pressure chamber was frequently noted as an indicator of positive effect, but it is one that in many cases may be a result of prolongation of the terminal period, which may be supported basically by

glycolysis. In this case, therefore, the influence of narcosis on the organism's response to oxygen insufficiency will not consist in a direct lowering of its sensitivity to oxygen deficiency.

In experiments with tissue hypoxia induced by cyanides, survival of previously narcotized animals may not be linked directly to the narcosis. The literature points to the possibility that the cyanides may be rendered innocuous by bonding to "active" or phosphorylated sugars, the content of which may be increased in certain forms of narcosis. Even in this case, the influence of narcosis may not be associated with a direct lowering of the organism's sensitivity to hypoxia.

Data on improved restoration of central nervous system functions in the frog after anemization under the influence of narcotics are open to question. The opposite effect has been noted in such experiments.

The absence of a consistently positive effect, the justification of certain conclusions on the basis of rigorously defined experimental conditions and, furthermore, the arbitrary evaluation of the individual data, render less satisfactory conclusions to the effect that narcotics have a positive effect in oxygen starvation. In addition to the shortcomings noted and the sparsity of the data indicating a certain positive effect from the use of narcotics, our attention is drawn to the fact that experimental investigations in this direction have not been sufficiently elaborate, failing to take into account chronic hypoxia and pathological states. This prohibits our drawing the general conclusion that narcotics have a positive effect in oxygen starvation and precludes extending this conclusion to the case of clinical practice. The proposition that narcotics have a two-sided effect in oxygen starvation cannot be regarded as a definitive solution to this problem.

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*U.R. Eshbi [Ashby], Vvedeniye v kibernetiku [Introduction to Cybernetics], 1956.

THE REFLEX MECHANISM OF PERIODIC RESPIRATION IN HYPOXIA

A.I. Khomazyak

(Kiev)

The mechanism of periodic respiration has been examined on more than one occasion in specialized research into the physiology and pathology of breathing. The net results of these studies are generalized in the work of N.N. Sirotinin (1933), D. Holden and D. Priestly (1935), K. Heimans and D. Cordier (1940), M.V. Sergiyevskiy (1950), M.Ye. Marshak (1961) and others. There will probably be no further doubt of the general statement that hypoxia is the most frequent cause of periodic respiration. At the same time, the specific mechanisms of periodic respiration remain somewhat neglected.

The hypothesis most widely accepted at the present time is that periodic respiration is a result of changes in the interrelationships between the carbon dioxide and oxygen concentrations in the blood. Hyperventilation in hypoxia causes hypocapnia, which results in lowered excitability of the respiratory center and in apnoea. During apnoea, carbon dioxide accumulates, and this is a condition for the appearance of the next respiratory cycle.

Ya.M. Britvan (1940) maintains that the appearance of periodic respiration is determined by the functional state of various divisions of the central nervous system.

The former, and possibly both, of the standpoints set forth above are based on the idea that the chemoreceptors of the carotid sinuses are of a certain importance in reflex stimulation of respiration when the

oxygen partial pressure in the arterial blood decreases. We have drawn attention to the change in the sensitivity of the specific regulators of oxygen tension in the blood and the consequent change in the basic role of reflex inhibition of respiration from the carotid chemoreceptors in the genesis of periodic respiration.

Experiments were set up on 80 full-grown dogs weighing from 8 to 36 kg. In the basic experiments, we used morphine (0.0025/kg)-chloralose (0.030-0.0100/kg) narcosis of moderate depth. Using a Brody-Starling electrokymograph and a six-channel "Cardiovar" instrument, we made synchronized records of the respiratory pressure fluctuations in the trachea or the respiratory excursions of the rib cage, the oxygen saturation of the blood in the carotid artery, the arterial and central venous pressure, and the pressure in the chambers of the heart and the pulmonary artery (electronic manometers). The oxyhemograph sensor was mounted in a tube cuvette tied into the carotid artery before the left carotid sinus.

The animals breathed 2-10% oxygen in nitrogen through a wide tracheal cannula with a system of valves or, in another version of the experiments, from a closed bag without valves. In other experiments, periodic respiration was induced by intravenous injection of sodium amytal, which was individually dosed. The thorax was left closed in all of the experiments, and the pressure in the chambers of the heart and the main blood vessels was registered through catheters.

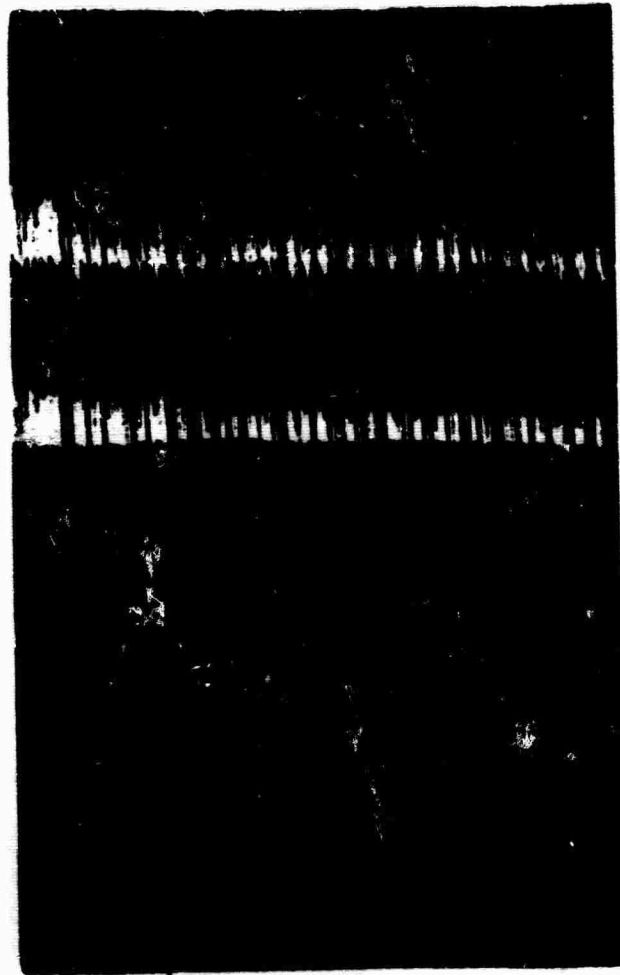
The general reactions on the part of respiration and circulation on inspiration of gas mixtures containing subnormal oxygen concentrations were described in special reports (A.I. Khomazyuk, 1961). The reaction to hypoxia is registered after the oxygen saturation of the blood in the carotid artery has fallen - respiration is sharply intensified, the force and frequency of the heart beats increase, the arterial pressure rises in the aortal circulatory system, and the systolic pressure rises and the diastolic pressure decreases in the pulmonary artery. The average pressure in the pulmonary artery is subsequently raised as a result of the development of tissue hypoxia.

After a short period of hypoxia (40-120 seconds), i.e., in most of the experiments before respiration was depressed, the animals were switched to respiration of air or oxygen. The first breath of air produced apnoea, which intervenes immediately after the oxygen saturation of the blood in the carotid artery has been raised. The oxygen saturation of the blood never reached the initial level after the first breath of air, but stayed considerably below it. Consequently, reflex inhibition intervened at a much-changed sensitivity threshold, which had appeared against a background of hypoxia.

During the period of apnoea, the oxygen saturation of the blood again falls off, and this triggers reflex restoration of breathing. The increase in the oxygen saturation of the blood in the region of the carotid chemoreceptors again induces apnoea. Periodic respiration arises in this manner in all experiments as the animal is brought out of the hypoxic state. In occasional experiments, this phase of the respiration is limited to a few periodic cycles or only two or three periods of apnoea, after which the sensitivity of the receptors to oxygen has been restored.

The restoration of chemoreceptor sensitivity after inhalation of the oxygen-deficient gas mixture has been stopped can be traced in Fig. 1. Each phase of respiration is accompanied by a rise in the oxygen's saturation of the carotid blood and by a reflex inhibition of breathing. After each respiration period, the inhibition threshold rises and gradually the sensitivity of the chemoreceptors returns to normal. Oxygen breathing causes stronger inhibition, but the sensitivity to oxygen is restored more rapidly and periodic respiration ceases. As we know, inspiration of oxygen restores regular rhythm to the respiration.

Prolonged hypoxia, and, to an even greater degree, rapid intravenous administration of narcotics (particularly barbiturates) even in



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Fig. 1. Male dog, weight 24 kg, morphine-chloralose narcosis. Reaction of respiration and circulation in recovery period after inspiration of 2.4% oxygen in nitrogen. Legend for curves (top to bottom): respiratory pressure fluctuations in trachea, pressure in pulmonary artery in mm Hg (electronic manometer, pressure in right ventricle of heart in mm Hg (electronic manometer), average pressure in pulmonary artery in mm of water, pressure in femoral artery in mm Hg, oxygen saturation of blood in carotid artery, stimulus time marker; 5-second time mark.

small doses, causes persistently periodic respiration (these methods of producing periodic respiration are used most frequently by experimentors. Figure 2 demonstrates a variant of periodic respiration that arose after fast injection of chloralose. In this case, as in all of the other experiments, we can trace the direct and inverse relationships between respiration and the oxygen saturation level of the blood. An increase in the oxygen saturation of the blood, which does not, however, reach the normal levels, causes an inhibition of respiration, but immediately afterward a considerable drop in the saturation restores respiration. Thus

it is logical to conclude that a change in the partial pressure of oxygen rather than carbon dioxide produces the respiratory periodicity. The length of the respiratory periods and the periods of apnoea is determined by the rate of change of the oxygen partial pressure in the blood, by the latent period of the chemoreceptor reflexes and by the extent to which the sensitivity threshold has changed. It is highly probable that a change in the functional state of the respiratory center under the influence of variations in the carbon dioxide concentration in the blood may be of importance in the pathogenesis of periodic respiration. It is obvious, however, that respiratory periodicity also arises in cases of lowered ventilation (overdoses of narcotics), when the periods of apnoea cannot be accounted for in terms of hypocapnia.

To analyze the reflex mechanism of period respiration, a series of experiments was performed with administration of ganglionic blocking agents (4-8 mg/kg of hexamethonium) and transection of the vagus nerves. Both of these interventions failed to eliminate completely the possibility of periodic respiration as the animal was coming out of hypoxia.

Bilateral denervation of the carotid regions prevented the appearance of regular respiratory periodism of the Biot or Cheyne-Stokes type. Profound hypoxea was capable in these experiments of depressing and stopping respiration. After inspiration of the oxygen-deficient gas mixture ceased, respiration was restored progressively without phases of inhibition. In occasional experiments, isolated deep "gasps" or an irregular rhythm, neither of which could be regarded as regularly periodic, were observed against the background of progressive respiratory recovery.

The investigations made indicate a direct significance for reflex inhibition of respiration as a result of stimulation of the carotid sinus chemoreceptors in the appearance of periodic respiration during experimental hypoxic hypoxia.

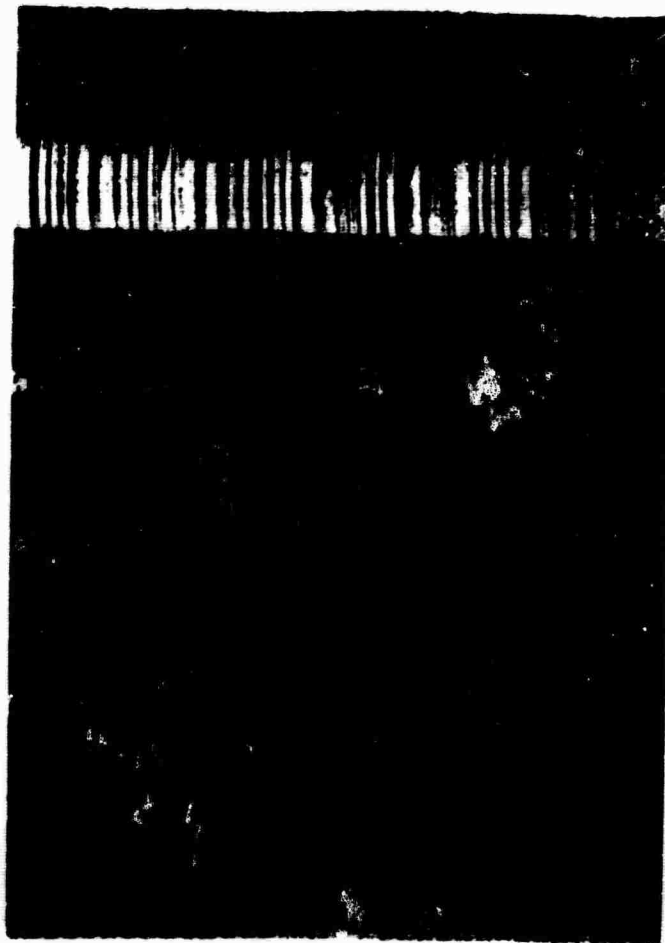


Fig. 2. Male dog, weight 18 kg, morphine-chloralose narcosis. Periodic respiration after rapid administration of chloralose. Legend for curves (reading down): respiratory fluctuations of pressure in trachea, pressure in left ventricle in mm Hg (electronic manometer), pressure in pulmonary artery in mm Hg (electronic manometer), oxygen saturation of blood in carotid artery, average pressure in pulmonary artery in mm Hg, pressure in femoral artery in mm Hg, average central venous pressure, stimulus time marker, 5-sec time marker.

It is probable that a kind of adaptation of the carotid chemoreceptors takes place during hypoxia - manifesting in a sharp decrease in the "upper" threshold of their sensitivity, i.e., sensitivity to elevation of the oxygen saturation of the blood. The threshold of sensitivity to hypoxemia must obviously be regarded as higher. In any event, we have an example of a paradoxical reaction when a slight increase in the oxygen saturation of the blood against a background of acute hypoxemia causes reflex inhibition and periodicity of respiration, frequently also in synchronism with changes in blood circulation.

We suggest that the considerations set forth above cannot come into

conflict with other data on the importance of the various divisions of the nervous system, including the brain cortex, in the pathogenesis of periodic respiration, although the specific carotid chemoreflex is the proximate mechanism by which the respiratory periodicity arises in hypoxia. We have not studied the participation of chemoreceptors in the aortic arch nor that of other oxygen-sensitive receptors. In accordance with conceptions of their importance in regulating respiration, we may advance the hypothesis that they also participate in this mechanism.

ON THE REGULATION OF GAS EXCHANGE IN HYPOXEMIA

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(Leningrad)

The problem of the changes that arise in gas metabolism during hypoxemia, and particularly those that occur in the process of short-term or long-term acclimatization in the mountains, is of considerable interest. On the one hand, this is due to the fact that the level of oxygen consumption is a criterion of the oxygen requirement of the tissues and, consequently, may determine, for a given oxygen saturation of the blood, the degree to which the tissues are suffering from oxygen starvation. On the other hand, the level of oxygen consumption reflects the rate of the vital processes in the organism, and their variations under the influence of oxygen insufficiency. These two aspects of the problem as a whole, although they can be substantiated by a considerable amount of factual material, still require examination from all aspects as problems of metabolic regulation and its evolution due to the extreme contradictions found among the data obtained by different investigators.

At the present time we have at our disposal three groups of facts (research trends), working with which we can illuminate this problem in experiment and under the conditions of the natural life of animals. The first group establishes relationships in the changes of energy expenditures and oxygen requirement by the organism as a whole during short-term experimental disturbances. The general conclusion drawn from these numerous experimental data* is the fact that in experimentally induced hypoxia, the oxygen consumption is held at a constant level up to a cer-

tain limit, after which gas metabolism begins to fall off. In homoiothermal organisms, this latter effect is always accompanied by a considerable drop in body temperature. It has been established by the investigations of Dzhayya and Dzhelineo (1938) and Dzhayya and Markovich (1950, 1955) that there is an intimate relationship between the threshold value of oxygen partial pressure and the temperature of the medium at which a lowering of the organism's oxygen requirement begins.

This "barocoefficient" is the ratio between the oxygen requirement per 1 kg of weight per hour and the oxygen partial pressure in mm Hg. The data of Dzhayya and his co-workers, which were obtained on laboratory rats, indicate irrefutably that the oxygen requirement drops significantly faster than the oxygen partial pressure as the temperature of the environment is lowered, i.e., as the oxygen requirement resulting from chemical heat regulation increases.

Facts testifying to an increase in the general stability of the organism ("altitude ceiling") and a drop in its oxygen consumption under the combined action of hypoxea and high environmental temperature had been obtained even earlier in our laboratory by N.A. Arkhangel'skoy (1949). However, such relationships are far from always observed in short-term subjection to oxygen starvation. Certain investigators have described the so-called hypoxic paradox — a phenomenon in which a rise in oxygen consumption is observed in response to a lowering of the partial pressure in the environmental medium. This has been observed in dogs and in humans. The hypoxic paradox has been accounted for in terms of an increase in the activity of the respiratory musculature and the intensity of blood circulation, such as usually occurs in acute hypoxia. Thus, examination of the experimental data does not lead us to any definite conclusions if we limit ourselves to experiments on the usual laboratory animals (rats, dogs) or to data from studies of humans. For all

of these organisms, a hypoxic medium - in its varying degrees - and the hypoxemia that arises in response do not constitute an adequate stimulus. Depending on the reaction of the auxiliary systems - respiration and blood circulation - there occurs either an increase or a decrease in gas exchange. In deeper degrees of hypoxemia, we observe the relationships expressed by the Dzhayya "barocoefficient" presented above. A considerable correction has recently been introduced into this scheme as a result of the investigations made in our laboratory by K.P. Ivanov (1959), who established a definite relationship between the oxygen requirement at various stages of hypoxia and the electrical activity of the skeletal musculature. In these experiments, which were performed on rabbits without anesthesia, it was shown that in deep degrees of hypoxemia, a sharp decrease in oxygen requirement is accompanied by a simultaneous sharp decrease in the electrical activity of the skeletal musculature. In the presence of the hypoxic paradox, the electrical activity of the muscles is found to be enhanced, and unchanged when the oxygen requirement remains steady. Consequently, the changes in gas exchange during hypoxemia are based not only on a shift in respiration and blood circulation, but also the state of excitation of the skeletal musculature - the temperature-regulation tonus. As has been shown by the investigations of K.P. Ivanov, these excitation states of individual muscle fibers, which have no external manifestation, result in a considerable rise in gas metabolism in the individual muscle when studied in situ, and also in a simultaneous enhancement of gas metabolism in the organism as a whole (Ivanov, 1960). Consequently, the reaction of the general metabolism to hypoxemia depends on the excitation state of the skeletal musculature.

If in laboratory animals hypoxemia produces a rather wide variety of changes in gas metabolism, then it would be natural to seek an answer

to the problem posed by investigating animals for which limitation of oxygen supply is an adequate stimulus. It has been established by experimental studies made in our laboratory by L.G. Filatova (1958, 1961) that in many wild animals, for example, in the yellow suslik and the long-eared hedgehog, the oxygen requirement rises by 36-45% during a "trip up" in the altitude chamber. Both of these mammalian species hibernate - i.e., they enter a state accompanied by considerable hypoxemia and a simultaneous decline in gas metabolism. However, the hypoxic paradox occurs when hypoxemia is created in the low-pressure chamber. Consequently, this method of inducing hypoxemia is not an adequate stimulus for the animals in question - a stimulus capable of producing a drop in the demand for oxygen. The latter has been found possible only by the use of ways of inducing hypoxemic states that are adequate for the individual species of animals.

It had been established as long ago as the 1946-1958 investigations of L.G. Filatova that when the hedgehog curls up into a ball a considerable drop in oxygen consumption (by 43%) is observed. It was also found that the saturation of the arterial blood at this time drops to 12% by volume of oxygen. The data obtained by A.F. Davydov (1961) indicate a close relationship between the described changes in gas metabolism in the hedgehog and the pattern of skeletal-musculature electrical activity. On curling up into a ball, the hedgehog shows an increase in the biocurrents of its circular skin musculature and a drop in the electrical activity of the femoral muscles. Consequently, even in this case, a drop in gas metabolism is observed against a background of lowered muscle tone. However, this effect is observed only on a stimulus adequate to the hedgehog (an increase in the dead space of the respiratory tracts on curling up). It is possible that we have here complex reflex relationships among individual muscle systems (Slonim, 1961). Another example of

a drop in gas metabolism can be found in the gas-exchange depression recently studied by our colleagues A.F. Davydov and A.R. Makarova during diving (immersion in water) in the seal. It was shown in these investigations that short-term immersion of a young seal (in the stage of development in which diving takes place) causes a 35% decrease in oxygen consumption. The recovery period after 10 minutes of immersion is found to be very short (no longer than 5 minutes), after which we observe a drop in the level of metabolism. An investigation of the skeletal-muscle bio-currents during immersion showed a sharp drop in the tone of the musculature. It is observed only at the point at which pulmonary respiration ceases (the head goes under) and is reflex in nature. A sharp slackening of the pulse is noted simultaneously.

Thus, both curling up for the hedgehog and driving into water for the seal produce a half drop in the organism's demand for oxygen, an effect that cannot be interpreted in any other way than as a phenomenon of profound adaptation to hypoxemia that has developed in the course of evolution.

A second group of research results concerning the effect of hypoxemia on gas metabolism encompasses data obtained during short-term sojourns of human beings and animals in the mountains. The numerous facts extracted at various times by the various investigators point to a slight increase in gas metabolism in man, accompanied by an increase in pulmonary ventilation. Subsequently, these changes smooth out and the basic metabolism in the mountains returns for all practical purposes to the level normal for the lowlands (Bykov and Martinson, 1933; Slonim et al., 1949; Bedalova, 1959; Khurtado, 1959, and others). Only under the conditions of Tien-Shan have a number of investigators established a rather persistent depression of basal metabolism in man. This drop in basal metabolism is accompanied by a decrease in the erythrocyte count in the blood, low-

ered blood pressure, and reduced pulmonary ventilation. These phenomena are expressed particularly distinctly at altitudes of 1500-1750 m. On ascent to higher altitudes, the level of gas metabolism rises somewhat, although it remains depressed in a number of cases (Slonim et al., 1949; Slonim, 1952; Fantalis, 1960; Filatova, 1954, 1961; Mirrakhimov, 1962), an effect linked by a number of investigators (Slonim, 1962; Filatova, 1961; Mirrakhimov, 1962) with a depression of the thyroid function under the conditions of the Tien-Shan mountains. Our attention is also drawn to the fact that under the conditions of the Caucasus at the same altitudes, we observe a rise in gas metabolism and blood stream time and an increase in the erythrocyte count and hemoglobin content (Bedalova, 1959, 1962). The phenomenon of thyroid-function depression in animals and humans in Kirgizia has been established by a number of authors (Akhunbaev, 1957; Malyshev, 1958; Turmambetov, 1959). It should be noted that gas-metabolism changes in the mountains cannot reflect solely the influence of hypoxemia, since simultaneously with the ascent into the mountains, the temperature of the environment also drops significantly. The latter has a stimulating effect on gas metabolism, and even if it remains constant, this is not yet enough to justify including the absence of a depressive effect of hypoxemia on gas metabolism. Nor was any drop in gas metabolism observed in rodents indigenous to high altitudes (Slonim, 1962).

In this connection, it is of great interest to examine the changes in gas metabolism that occur in farm animals in the mountains - great-horned cattle, horses and sheep. In these animals (mature), according to a number of investigators (Rittsmann and Benedikt, 1938; Akhmedov, 1958; Makarova, 1955; Romanovskaya, 1960; Slonim, 1960, and others), there is no chemical temperature regulation at all in a zone of moderate environmental temperatures. Under these conditions, therefore, the influence of

hypoxemia is not masked by the stimulation of metabolism that occurs on cooling.

A considerable drop in the oxygen saturation of the blood of sheep in the mountains was first noted by Hall, Dill and Barron (1936), and subsequently studied in detail by Z.I. Barbashova and A.G. Ginetsinski (1942). The latter authors were the first to advance the hypothesis of areactive acclimatization, whose foundation is the change in the tissue processes rather than stimulation of respiration, blood circulation and hematogenesis. The data of Barbashova and Ginetsinski have been confirmed in our laboratory by R.P. Ol'nyanskaya et al. (1946, 1949) on sheep, and then by other investigators - Arav (1960), A.N. Yevdakov (1954), and Ye.P. Basenko (1958) - on sheep, by A.P. Kostin (1958) on great-horned cattle, and by Yu.O. Raushenbakh (1958) on horses and sheep.

The nature of the physiological reactions in acclimatization to altitudes is different for different species and breeds of animals. Thus, for example, the depression of gas exchange at altitude is more distinct in local fat-tailed sheep as compared with lowland thin-fleeced sheep. Mongrel thin-fleeced sheep of various generations occupy an intermediate position (Ol'nyanskaya et al., 1946, 1949). Thus, the tissue areactive type is more characteristic to breeds of animals that have adaptation to mountain conditions. Closely related data were obtained by Yu.O. Raushenbakh (1958) on horses when they were driven through the mountains from an altitude of 2000 to an altitude of 3000 m above sea level. In a lowland group of horses, the respiratory frequency and pulse rate were found to be higher than in the foothill and mountain groups. Also apparently of great importance is the initial background (altitude) from which the animals are taken up into the mountains. This problem has not yet been studied.

A.P. Kostin (1958) established that when great-horned cattle of the

Red Prairie [steppe] and Kuban' Black Sea breeds were driven up, the relaxation of respiration, blood circulation and hematogenesis was much better expressed in the lowland Red Prairie cattle than in the Kuban'-Black Sea animals, which have long been bred in the foothills of the Northern Caucasus. Age-connected differences were also observed: calves of the Red Prairie breed showed a type of altitude acclimatization approximating the areactive type, with smaller shifts on the part of respiration, blood circulation and hematogenesis as compared with the full-grown cattle.

Of great importance in the analysis of all these data is the factor of nutrition on the high-mountain pastures. Generous foddering with green vegetation stimulates the formation of hemoglobin in the animals (as compared with wintertime conditions in the stall). Hence in evaluating the data obtained, it is necessary to compare with control groups that have been left at lowland altitudes under the same feeding conditions.

The third group of factors, as yet the smallest in number, concerns long-term acclimatization of animals and humans to the mountains. The majority of researchers indicate that the level of metabolism remains unchanged during long-term acclimatization in permanent residents of the middle and high mountains (Khurtado, 1959; S.M. Bedalova; Kravchuk, 1962). Under these conditions it is necessary to take into account the influence of low temperature, of which we spoke above. This might possibly account for a certain rise in gas metabolism that is usually observed under these conditions (+9-12%). A drop in basal metabolism was also observed by M.M. Mirrakhimov (1962) and I.A. Fantalis (1960) in year-round inhabitants of the Tien-Shan.

As yet, research material on animals is extremely sparse. R.P. Ol'-nyanskaya (1949) observed sheep of lowland origin over a number of gener-

ations at an altitude of 2600 m. The areactive acclimatization type was observed, with a decrease in metabolic level, frequency, erythrocyte count and hemoglobin content. It goes without saying that research must be continued in this direction, even though the periodic driving of the animals into the mountains limits opportunities for this very severely.

The nonuniform reactions of animals of different species, with their different origins (ecogenesis) and degrees of acclimatization to mountain conditions, advances, as a biological problem of major importance, the search for a mechanism by which the tissue processes can adapt to low barometric pressure. The question also arises as to whether we should regard the drop in oxygen consumption that takes place in the mountains, and the consequent phenomena of so-called areactive adaptation, as the objective of physiological phenomena directed toward adjusting the organism to the environment under these essentially extreme conditions.

The facts set forth above suggest that the suppression of temperature-regulation tone is one of the universal mechanisms by which the oxygen adapts to oxygen starvation. While such a drop in gas metabolism intervenes only at very low oxygen partial pressures in animals with poor adaptation to these conditions, for example, in rabbits, which moves these phenomena closer to Dzhayya's "initial pressure," the same drop in demand for oxygen sets in in animals with good adaptation to mountain conditions even on relatively slight hypoxemia — for example, at the medium altitudes and relatively moderate muscular loads encountered in summer pasture. However, we do not yet have at our disposal data on the changes in temperature-regulation tone in the mountains in animals and man. This important problem, which represents indisputably a gap in our knowledge, requires circumstantial study.

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*A.D. Slonim, Trudy konferentsin po vysokogor'yu [Transactions of Conference on the High Mountains], Frunze, 1962, page 327.

ON THE PROBLEM OF DECOMPENSATION AND COMPENSATION
OF THE HUMAN RESPIRATORY FUNCTION

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(Moscow)

It is known that the hypoxic or respiratory form of hypoxia is governed by a drop in the oxygen partial pressure in the inspired air, and by pathological changes in the respiratory system that interfere with gas exchange.

Research has been concentrated for the most part on the phenomena connected with inadequate oxygen supply to the organism. Less attention has been given to the development of the pathological process in the respiratory system, which may considerably aggravate and sometimes compensate to some extent for the phenomena due to inadequate access of oxygen to the organism. This has been shown in the studies of N.N. Savitsky, A.A. Tregubov, B.Ye. Botchal and T.I. Bibikova, Kompo, Kurnan, Ross'ye and others.

Research carried out in our laboratory over the course of the last three years (I.A. Panchenko, L.G. Malyshev, M.A. Chaplik) have been devoted to physiological analysis of the phenomena that develop during pathological processes in the respiratory system. They were performed on individuals suffering from chronic bronchitis, pneumosclerosis and emphysema at varying levels, as well as on patients who had survived surgical collapse and resection interference occasioned by pulmonary tuberculosis, i.e., on patients with chronic injuries to the lungs and respiratory tracts.*

Indicators characterizing resistance to respiration, alveolar ventilation and certain other conditions of pulmonary gas exchange were stud-

ied. The rate of expiration, the composition of alveolar air and a number of other indicators were determined simultaneously with respiration of the activity currents of the respiratory muscles and the dynamics of the arterial blood.

The studies were performed using various functional tests. Study of the dynamics of ventilation and pulmonary gas exchange (Búlau spiograph), also under varying sets of conditions, was combined with registration of the dynamics of blood oxygen saturation and other factors. Thus, several physiological functions were registered, and this facilitated discernment of the mutual relationships among the observed phenomena.

The investigations performed indicated that hypoxia apparently produced by topological processes of identical nature (chronic bronchitis, pneumosclerosis and emphysema) nevertheless had various mechanisms of disturbance to respiration at its worst. In one group of cases (in chronic bronchitis, pneumosclerosis and manifest secondary emphysema of the lungs), distinct criteria of alveolar hypoventilation, obviously governed by the resistance to the air current in the respiratory tracts due to their chronic irritation and secondary changes in the elasticity of the pulmonary tissue (emphysema) were detected. Here were registered a delay in expiration, increased residual volume, a change in the composition of the alveolar air toward a lower oxygen content and an increase in the carbon dioxide partial pressure. A change in the partial pressures of the gases in the alveoli — particularly in the case of oxygen — always results in contraction of the pulmonary arterials and a rise in pressure in the pulmonary circulation (Euler and Lillienstrand). In our observations, this was supported by the signs of change in the right half of the heart, as registered on the electrocardiogram.

Simultaneously, the alveolar hypoventilation resulted in incomplete arterialization of the blood. The causal relationship between these processes was confirmed by the fact that inspiration of oxygen, which eliminated the alveolar hypoventilation, also completely eliminated the hy-

poxemia.

We felt it necessary to ascertain the degree to which the set of phenomena described above was actually related to increased respiratory resistance in patients of this category. Our judgments in this matter were based on data obtained during registration of the activity currents of the respiratory muscles, which was done at rest and during functional tests, in combination with determination of the aspiration rate and the size of the dead volume (Fig. 1). It was found that the biocurrents of the intercostal muscles, which are elevated even at rest in these illnesses, rose sharply on imposition of additional respiratory resistance, as well as during work. The hypoxemia also became more pronounced. The increase in activity was more significant during the inspiration phase, which, according to Campbell, is always a proof of increased respiratory resistance, since its purpose is to overcome the latter.

L.L. Shik and I.A. Morozova, noting the increase in the activity currents of the respiratory muscles in pulmonary emphysema, also concluded that it was connected with resistance to respiration. The importance of respiratory resistance has also been confirmed by the fact that inspiration of oxygen, which eliminates hypoxemia, only partially reduced the bioelectric activity of the respiratory muscles. Thus, it had become quite obvious that an increased resistance to respiration due to aspects of the development of the pathological process itself was at bottom of the complex of pathological phenomena that we observed in the patients studied. It was precisely this that gave rise to the complex chain of mutually involved pathological reactions. It is appropriate to note that the patients whom we studied were, as a rule, poorly adapted to physical work, and that the gas-metabolism indicators obtained on them showed considerable deviations from what they should have been.

We are far from regarding the respiratory function disturbances

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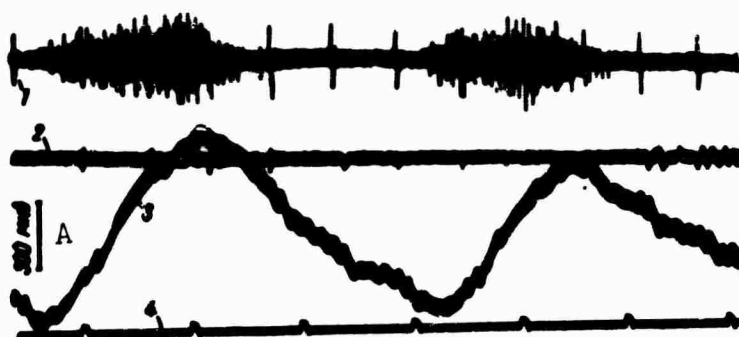


Fig. 1a. Patient L. Chronic bronchitis, moderate pneumosclerosis, distinct emphysema of the lungs. Activity currents of respiratory muscles at rest. 1) Activity currents of intercostal muscles; 2) activity currents of external oblique muscle of abdomen; 3) pneumogram; 4) time marker, 1 sec. The EKG is seen superimposed on the electromyogram in this figure and in all figures to follow. MVL 43% of par, rate of forced expiration 54% of ZhYeL in 1 sec, residual volume 53% of OYeL. The alveolar air contained 7% carbon dioxide and 12.6% oxygen. The oxygen saturation of the blood at rest was 88%, 100% during oxygen breathing and 8% during work. The oxygen deficiency (47%) was not compensated for 10 minutes. A) 300 μ v.

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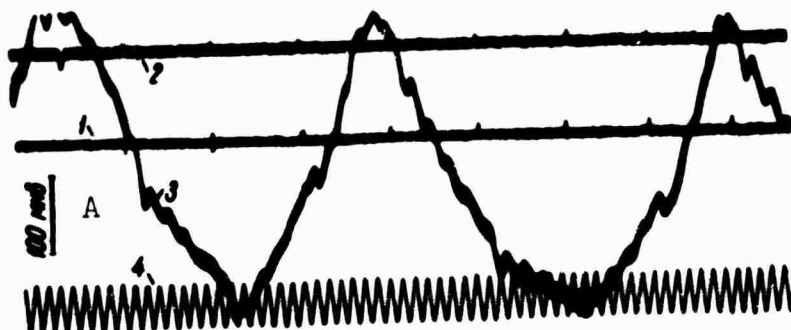


Fig. 1b. Patient O. Chronic bronchitis, mild pneumosclerosis, moderate pulmonary emphysema. Action currents of respiratory muscles at rest. Legend items 1, 2, 3 same as for Fig. 1a; 4) time marker, 0.1 sec. MVL 76% of par, rate of forced expiration 84% of ZhYeL in 1 sec, residual volume 32% of OYeL. Composition of alveolar air: 5.4% carbon dioxide, 14.3% of oxygen. Oxygen saturation of the blood 87% at rest, 92% during oxygen breathing and 3% during work. The oxygen deficiency (27%) was compensated in 5 min. Action currents of the respiratory muscles were not registered. A) 100 μ v.

described solely as the result of mechanical impediment of air flow in the tracheobronchial tree. Here there is no question that regulatory disturbances are also of importance.

It is highly probable that chronic inflammatory processes in the respiratory tracts and lungs are accompanied by changes in reactivity, functional instability and, as is characteristic for altered tissues,

show the parabolic type of reaction to pulses to the central nervous system (N.Ye Vvedenskiy, M.V. Latmanizova). The pathological processes are undoubtedly accompanied by a change in the peripheral nervous apparatus in the respiratory tracts and lungs. In tuberculosis, this has been established by F.L. Abramson, R.Yu. Drabkina, and others. Such changes may cause pathological afferentation of the respiratory center and change its functional state. As we know, a change in the angioreceptors of the aortic arch in atherosclerosis gives rise to a change in the state of the vasomotor center (V.I. Filistovich). Proliferation and atrophy of the angioreceptors has been observed in rheumatism (V.K. Beletskiy); these effects may be due to subversion of the vasomotor regulation (L.N. Pankova).

There were substantial differences in the manner in which the respiratory function changed in another group of patients studied. As regards the nature of the pathological process, they were distinguished by the fact that chronic bronchitis in these patients was accompanied by pneumosclerosis, while the emphysema was insignificant or mild. Determination of the residual volume and alveolar-air composition on such patients showed no substantial deviations from the norm, and their expiration rates were also normal. Respiratory muscle action currents were not registered at rest or were very weak; when additional respiratory resistance was imposed, and during work, we noted irregular and slight increases in these quantities (Fig. 2a).

Taken together, the results of the investigation make it obvious that in this group of patients, there is no consistent increase in respiratory resistance, so that they did not develop alveolar hypoventilation. The changes in gas exchange could, obviously enough, have been only local in nature, as is characteristic for pneumosclerotic areas; they could easily have been compensated by the undamaged parts of the lungs.

But how to explain the occurrence of arterial hypoxemia in these? First of all, the nature of the functional tests, for example, the insignificance of the increase in oxygen saturation of the blood in oxygen breathing, is already sufficient to suggest hypoxemia of a different nature as compared with that of the first group of patients. This has, moreover, been confirmed by literature data. As we know, ramifications of the pulmonary artery are brought into the pathological process in sclerosis of the interstitial tissue, and the pulmonary circulation is modified. Among other things, anastomoses between precapillary pulmonary arteries and veins (I.V. Davydovskiy, I.K. Yesipova) and loop-type arteries (A.V. Ryvkind) form in the sclerotic patches. But since the collateral blood flow is not effective as regards gas metabolism, hypoxemia develops in such patients. At the same time, the collateral blood flow compensates to a certain extent the pulmonary hypertension that could develop as a consequence of the shortening of the bloodstream. In actual fact, the electrocardiograms of such patients show no signs of changes in the right heart. It is necessary to note that these patients were well-adapted to work and no substantial deviations of their gas-metabolism indicators were noted during it.

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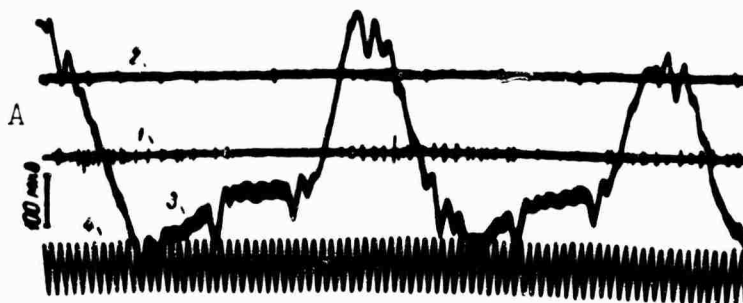


Fig. 2a. Patient Sh-n. Condition after resection of upper part of right lung (2 years and 6 months later). Action currents of intercostal muscles at rest. 1) Action currents of right intercostal muscles; 2) action currents of left intercostal muscles; 3) pneumogram; 4) 0.1-sec time marker. MVL 50% of par, rate of forced expiration 96% of ZhYeL in 1 sec, residual volume 40% of OYeL. Oxygen saturation of blood 90% at rest, 94% during oxygen breathing and 4% during physical labor. Oxygen shortage (32%) eliminated in 7 min. A) 100 μ v.

Thus, examination of two groups of patients indicated that the changes in their respiratory functions were not identical, and that the pathogenesis of the disturbances is a function of aspects of the pathological process. These investigations were helpful in bringing out certain aspects of the influence of increased respiratory resistance and the resulting changes in pulmonary hemodynamics on the respiratory function. Also brought out were certain peculiarities in the bloodstream changes — features associated with pneumosclerosis and obviously of an adaptive nature. The impression was created that these mechanisms are not equivalent as regards pathophysiological significance.

For more complete orientation to the nature and importance of these phenomena, we examined patients who had undergone economic and extensive pulmonary resections in connection with tuberculosis. These investigations showed (and this was common to the majority of patients observed) the absence of signs of resistance to the air stream in the respiratory tracts — the rate of forced expiration and the residual volume did not deviate substantially from par, while the action currents of the respiratory muscles, which were registered at rest and during work, did not, as a rule, deviate from the corresponding figures in healthy control persons. Only in occasional cases did we note insignificant changes in the electromyogram on the side of the operation. Here, according to x-ray data, the pleural deposits and adhesions that were always observed — which were responsible for local variations in the elasticity of the lungs — did not influence the alveolar ventilation, obviously for the same reasons as in pneumosclerosis. Nevertheless, arterialization of the blood was lower in a number of cases, even in spite of oxygen breathing. The entire combination of physiological indicators suggested that here, as in pneumosclerosis of the lungs, the hypoxemia is a result of an increased admixture of venous blood. In these cases the source of the

latter could have been arteriovenous anastomoses in the zones of pulmonary tissues that had undergone fibrous modification as a result of a specific process (Blazi and Katena), as well as arteries of the loop type, which were detected by V.S. Zhdanov in pleural adhesions.

To obtain satisfactory information as to the importance of increased aerodynamic resistance in the development of respiratory insufficiency, a group of patients with massive sutures and pleural deposits and with advanced fibrosis of the pulmonary tissue was studied. Characteristic for this group of individuals was the presence of profound changes in the elastic properties of the tissues. Together with this, and in contrast to chronic bronchitis and secondary obstructive emphysema, they showed no substantial increase in tracheal bronchial resistance. These were patients with resections of part of the lung that had been preceded by an extensive tuberculous process, as well as patients with corrective thoracoplasty. Those studied also included several persons on whom thoracoplasty had been effective.

Morphological studies made by V.S. Zhdanov indicate that in sclerosis of the pleurae and interlobular septa, zones of pulmonary tissue are found to be inclosed in fibrous rings, so that the functional activity of the lungs is restricted - particularly that of their subpleural divisions. The pleural deposits result in the development of subpleural emphysema, i.e., in a local decrease in the elasticity of the lungs. In thoracoplasty, the fibrous changes in the pulmonary parenchyma, while obviously aggravating these phenomena, are still not accompanied by distinct diffuse changes in the respiratory tracts. All of these persons showed manifest intensification of the respiratory muscle action currents, preferentially on the side on which the operation had been performed, i.e., exactly where the x-rays indicated there were massive adhesions and pleural deposits and, in some cases, fibrous changes in the

lung (Figs. 2a and 2b).

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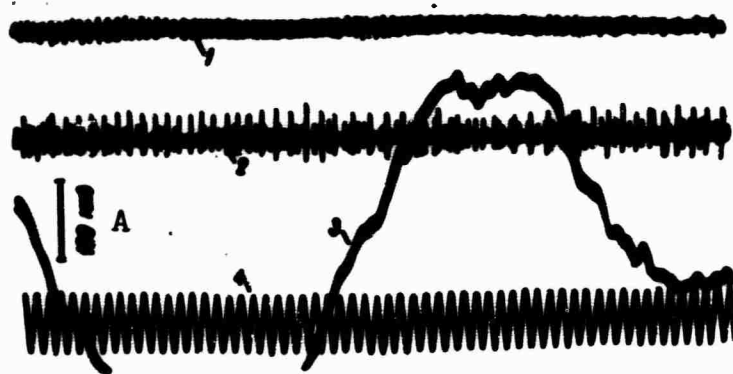


Fig. 2b. Patient S. State after sinistral thoracoplasty (6 years later). Action currents of intercostal muscles at rest. Legend same as for Fig. 2a. MBL 68% of par, rate of forced respiration 87% of ZhYeL in 1 sec. In the alveolar air: 5.4% carbon dioxide, 14.3% oxygen. Oxygen saturation of blood 91% at rest, 94% during oxygen breathing and 4% during physical work. Oxygen deficiency (34%) eliminated in 6 min. A) 100 μ v.

Consequently, the changes in the electromyograms of these patients were associated with changes in the elastic properties of these tissues and, possibly, also with constant tension of the respiratory muscles due to deformation of the rib cage. This idea is supported by the relatively uniform and constant intensification of the biocurrents over the entire course of the respiratory cycle. The latter may be a consequence of a change in the afferentation of the respiratory center as a result of constant stimulation of proprioceptors of the respiratory muscles and the interoceptors of the pleura and lungs. Let us note that the changes in the electromyogram were asymmetric and predominantly on the side of the operation. Another proof of the reflex nature of the phenomena described above was the fact that oxygen breathing, which reduced the hypoxemia to some degree, had no influence at all on the bioelectric activity of the intercostal muscles. It is possible that the pleurothoracic reflex, which has its closure at the level of the cervical and thoracic segments of the spinal cord, acquired a certain significance here (D.A. Kocherga).

The above phenomena, together with the modified rate of expiration,

residual volume and gas composition of the alveolar air, indicate that in these cases the resistance to respiration is due not to diffuse changes in bronchial freedom of passage and an increased aerodynamic resistance, factors detrimental to the exchange of air and gases, but to a decrease in the elastic properties of the lungs and pleura and a change in the tone of the respiratory muscles. These changes have their own distinctive features and are responsible for the local disturbance to the respiratory mechanics.

The nonuniformity of pulmonary gas exchange, which was scarcely perceptible at rest in this group of patients, became more distinct under physical load. The latter frequently produced a deviation of the gas-exchange indicators, one associated with inadequate adaptability to the work.

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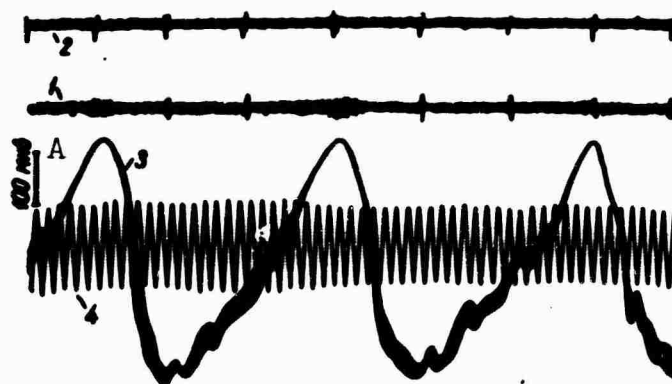


Fig. 3. Patient I-v. Condition after resection of left lung (2 years later). Action currents of intercostal muscles. Legend same as for Fig. 2a. ZhYeL 48%, MVL 57% of par; rate of forced expiration 85% of ZhYeL in 1 sec. Composition of alveolar air: carbon dioxide 5.2%, oxygen 14.6%. Oxygen saturation of blood 91% at rest, 96% during oxygen breathing and 14% under physical load. Oxygen deficiency (32%) made up over 6 min. A) 100 μ V.

All of the above satisfies us that the increase in aerodynamic resistance is an important factor in the disturbance to the respiratory functions and, consequently, in the development of hypoxia. Its mechanisms are also brought out to some degree.

In patients that have undergone removal of a lung, a slight and ir-

regular increase in the arterial pressure, one that could not be eliminated by breathing oxygen, was noted during rest. The biocurrents of the respiratory muscles were also increased very slightly and irregularly while these patients were resting, and only on that side of the rib cage opposite from that on which the operation had been performed. This is apparently a compensatory reaction whose purpose is to amplify the ventilation of the remaining lung (Fig. 3), and could have been stimulated by a drop in the oxygen partial pressure in the arterial blood. No other substantial deviations in the respiratory function at rest were observed (with the exception of a reduction in certain respiratory volumes). During work, however, these persons developed considerable hypoxemia — the drop in arterialization of the blood reached 9-14%. We observed "work hypoxemia" of such distinctness only in certain patients with considerable pulmonary emphysema. In these cases, we regarded it as a result of acceleration of blood flow and shortening of the time of contact between the alveolar air and the blood of the pulmonary capillaries as a result of the shortening of the pulmonary bloodstream by the destructive process.

During work, the action currents of the respiratory muscles were intensified only slightly in pneumectomized patients. This also attested to a different nature for the "work hypoxemia" in these patients as compared with those suffering from secondary emphysema. This would mean that a completely different, specialized "work hypoxemia" mechanism went into operation on pneumectomy. It is obvious that in these cases, despite the opening and possibly even the formation of additional capillaries in the remaining lung, as reported by Monal'di, I.K. Yesipova and Ye.V. Ryzhkov, its vascular network is inadequate to accommodate the per-minute blood volume, which has been increased as a result of the exertion. As a result, some of it is shunted into the veins through arterio-

venous and anastomoses, bypassing the pulmonary capillaries and thereby taking some of the load off the pulmonary-artery system. However, it would appear that this is not the only cause of the significant level of "work hypoxemia" observed. It is necessary to assume that the per-minute volume of the blood, which is increased as a result of exertion, is so out of correspondence with the capacity of the vascular tract of the single lung that the pressure in the pulmonary artery system rises sharply. It comes to exceed the pressure in the bronchial arteries. Under such conditions, poorly arterialized blood may move out of the pulmonary artery through arterioarterial anastomoses and enter the bronchial arteries, something that is compensated to a certain degree by pulmonary hypertension, but the hypoxemia rises sharply simultaneously with this. We are aware that experimental proofs of the operation of arterioarterial anastomoses on ligature of the pulmonary artery are given in the work of Alley et al. The presence of a certain degree of pulmonary hypertension in pneumonectomized patients is confirmed by changes in the right heart that are registered on the electrocardiogram. Also apparently to be explained in terms of pathogenetic peculiarities is the fact that in these patients, the changes in pulmonary gas exchange under moderate exertion were frequently indistinctly manifest, intensifying as the load was increased.

Summarizing the facts set forth above, we can state that in the intricate set of phenomena that develop on injury to the lungs, the increase in resistance to respiration must be acknowledged to have basic importance. Here the tracheobronchial resistance, which triggers a complex chain of phenomena aggravating the hypoxea, is most important. The change in pulmonary hemodynamics must be singled out from among these as having prime importance. The distinctive nature of the changes in pulmonary hemodynamics produced by the pathological processes was indi-

cated earlier.

The high importance of tracheobronchial resistance in the development of hypoxia is obviously a result not only of its influence on the intrapulmonary processes. Data available to us suggest that the peculiarities of respiratory regulation have unquestionable significance here. However, this problem requires a special examination.

We must not omit mention of yet another interesting fact -- the absence of a direct and consistent relationship between the presence of hypoxemia and the capacity of the patients for physical work. It was found that this capacity is lowered when the hypoxemia is due to alveolar hypoventilation and is not limited to the case in which the lowered arterialization of the blood is a result chiefly of collateral blood flow. Thus, it has become obvious that hypoxemia as such cannot be an un failing indication of oxygen starvation in the organism without determination of its nature. In this phenomenon we perceive adaptive changes in the tissue processes.

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268 *Patients in the therapeutic ward (Prof. L.I. Fogel'son, director) under the observation of Candidate of Technical Sciences O.V. Lebedeva and Physician T.P. Sidorkina and patients in the tuberculosis ward (Prof. S.Ye. Nezhlin, director), who were under the observation of Candidate of Medical Sciences S.V. Melamed, were studied.

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[List of Transliterated Symbols]

271 MBJ = MVL = minutnaya ventilyatsiya legkikh = per-minute pulmonary ventilation

271 XEJ = ZhYeL = zhiznennaya yemkost' legkikh = vital capacity

271 OEJ = OYeL = obshchaya yemkost' legkikh = total pulmonary capacity

THE ROLE OF RESPIRATION THROUGH THE SKIN IN COMPENSATING DIFFICULT OR
DISTURBED PULMONARY GAS EXCHANGE IN MAN

N.M. Petrun'

(Kiev)

As we know, cutaneous respiration plays an extremely important role in lower animals in supplying the organism with oxygen and dissipating carbon dioxide. In the process of evolution, as the various functions and systems of the organism were perfected, cutaneous respiration became inadequate and has been gradually replaced by the superior pulmonary respiration. In man at normal environmental temperatures, the organism's exchange of gases with the external medium is accomplished 98-99% through pulmonary respiration and only 1-2% through cutaneous respiration.

It has been shown by a number of investigations (Lavoisier, 1777; Foyt, 1878; A.A. Mittel'shtedt, 1934; A.B. Lekakh et al., 1935; N.K. Witte, 1943, and others) that during residence of a human under the conditions of high temperature of the surrounding air, pulmonary gas exchange shows a slight decrease.

Thus, N.K. Witte (1943) undertook special investigations to clear up the question as to whether the heat production of a man performing physical labor involving various degrees of exertion changes as the air temperature rises from 10 to 45°. It was established that in the performance of a given physical task (requiring moderate or heavy exertion), heat production rises slightly simultaneously with a rise in air temperature to 35°. At a higher air temperature (45°), however, heat production

falls off, and diminishes further the heavier the physical work: in work requiring moderate exertion, heat production diminishes by 2%, while during heavy work it falls off by 15-17% of the initial values.

It is difficult to accept the idea that the rate of metabolism in the organism decreases in the performance of a given physical task at a higher air temperature, i.e., that the organization works, as it were, with a smaller expenditure of energy. The hypothesis that arose from this was that at high air temperature, the role of respiration through the skin might increase, so that not all of the carbon dioxide produced in the organism is excreted and not all of the oxygen is absorbed by the lungs and registered through the respiratory gas exchange. This hypothesis was confirmed in investigations that we conducted specifically for this purpose, studying cutaneous respiration in the human under various temperature conditions. The results of these investigations indicated that while the absorption of oxygen and excretion of carbon dioxide through the skin are increased by a factor of 2-2.2 at rest with the air temperature elevated to 40°, this increase in respiration through the skin reaches significant levels during the performance of physical work: 1.6-8 and 10% of the pulmonary gas exchange, i.e., it increases more than six fold.

If the data that we obtained on cutaneous respiration are combined with those of N.K. Witte (1943) on gas exchange through the lungs in man in the resting state and during the performance of physical labor at various air temperatures, then it is found that no decrease in heat production occurs at high air temperature either in individuals performing physical labor or in individuals in a state of rest (see Table).

Data on Human Heat Production at Various Air Temperatures (in %), Obtained with Account of Oxygen Absorption through the Skin

Условия исследования 1	2 Температура воздуха (в °C)				
	18	24	28	35	45
Покой 3	101,3	—	109,4	112,6	116,1
Легкая работа 4	101,3	—	—	110,6	105,4
Работа средней тяжести 5	101,3	101,3	106,6	110,9	107,4

1) Conditions of investigation; 2) air temperature (in °C); 3) rest; 4) light work; 5) moderately heavy work.

In physical labor, therefore, we observe an apparent decrease in heat production, the more so as the air temperature rises. This is accounted for by an increase in gas exchange through the skin and is a result of failure to take the latter into account in determining heat production by way of the respiratory gas exchange. In actuality, the increase in heat production at elevated air temperature is the same (for the same physical work) as in the state of rest.

Subsequently, we carried out special investigations to study the influence of elevated oxygen concentrations in the air surrounding the skin on the rate at which it penetrates the skin and on the extent of pulmonary gas exchange. The entire body of each test subject, with the exception of the head, was closed in a lightweight diving suit in which an elevated oxygen concentration was produced (70-80%). The results of these studies indicated that the absorption of oxygen through the entire surface of the skin averaged, in the state of rest, 5407 ± 412 cm³/hour, while the amount of carbon dioxide excreted was only 96.5 ± 7.1 cm³/hour. If these data are compared with figures for gas exchange through the skin in a man under normal environmental conditions, it is observed that the quantity of oxygen absorbed by the skin is 33 times as large, while the amount of carbon dioxide excreted is, to the contrary, 45% smaller than the normal value.

At the same time, one hour of residence of the test individuals in the diving suit with its elevated oxygen content also had a considerable influence on the oxygen requirement of the lungs. The absorption of oxygen by the lungs gradually declined, and was 25% smaller even 30 minutes after the beginning of the experiment; after an hour, it had dropped by 31% of the initial value. No substantial change was noted here in the amount of carbon dioxide excreted by the lungs. Nor did the oxygen saturation of the arterial blood show any significant change; however, the oxygen content in the venous blood increased considerably.

If we take into account the increase in oxygen diffusion through the skin and the decreased consumption of this gas by the lungs, it is found that in actuality, almost no changes take place in the human's oxygen consumption under the conditions described earlier. This, in turn, attests to an extensive ability to compensate pulmonary respiration, which sometimes tends to fall behind, by gas exchange through the skin.

The above suggests that a human organism placed under conditions of existence to which it is not accustomed will amplify its cutaneous respiration considerably, and this will compensate for various degrees of impediment to the pulmonary gas exchange. This path by which oxygen enters the organism may also be effective in such states of the organism as asphyxia, hypoxia and a number of pathological processes (skin disorders, pulmonary tuberculosis, cardiac insufficiency, burns, and so forth).

In their observations of blood circulation and carbon-dioxide and oxygen diffusion through the skin of a stump and a healthy extremity, A. G. Zhironkin and Ye. G. Zykina (1948) observed that when the blood circulation through the blood vessels of the stump is artificially impeded, a considerable increase in oxygen diffusion into the tissues through the skin takes place. If, however, the factor interfering with blood circula-

tion continues to operate, then the oxygen absorbed in larger quantity through the skin is no longer capable of compensating the increasing hypoxia of the stump tissues. As a result, the metabolism of the tissues is subverted at a certain degree of hypoxia. It acquires a desoxidative nature, and this results in a decrease in the formation and excretion of carbon dioxide.

In a study of cutaneous respiration in persons suffering from certain dermatitides (sun eczema, the discoid form of red lupus, athlete's foot), undertaken jointly with Z.A. Korniyenko, we observed a considerable increase in cutaneous respiration in these patients (by a factor of three-six), which reached 6-8% of the pulmonary respiration, with the intensity of gas exchange through the skin depending on the degree to which it had been injured. This increase in cutaneous respiration in subjects suffering from the above dermatitides can be accounted for by disturbance of the peripheral blood flow on the affected areas.

Ya.K. Volovik (1961) collected even more interesting data in a study of cutaneous respiration in tuberculosis patients, both before surgical intervention and after resection of one lung or part of a lung. While the pulmonary gas exchange was considerably depressed in these patients, respiration through the skin, on the other hand, had increased considerably, thus compensating the inadequate pulmonary gas exchange to a certain extent.

Similar data were observed by Enders (1928) in persons suffering from Basedow's disease, as well as by Kin and Rakkov (1954) in individuals suffering from cardiac insufficiency, anemia and polycythemia, hyperthyroidism and hypothyroidism.

Working with O.V. Dol'nitski, we observed significant changes in cutaneous respiration in children after burns had been suffered on the body. We established that the gas exchange was considerably higher (by

a factor of three-five) through the scar tissue, which is abundantly supplied with blood vessels running very close to the surface of the body. In the event that scar tissue appearing after extensive healing of the burned surface was still characterized by inflammatory infiltration, so that the scars had become courser, painful, cyanotic in color and brittle, then the gas-exchange pattern observed was somewhat different from that in the previous case. Both the absorption of oxygen and the excretion of carbon dioxide through scar tissue were considerably lower in this case than that through healthy skin on the symmetrical region of the body.

The stepped-up gas exchange through the skin of these patients is testimony to the effect that an oxygen shortage arises in their skin. This provides a basis for the assumption that placing such patients in an atmosphere containing an elevated quantity of oxygen might be effective, since this would make up for the oxygen insufficiency present to a certain degree. This assumption is further supported by the fact that when a human is placed under conditions of elevated oxygen concentration, the oxygen is absorbed by the skin 20-30 times faster than under normal atmospheric conditions.

Recently, data supporting our hypothesis have been obtained at the pediatrics surgery clinic of the Kiev Medical Institute. Under the direction of Professor A.R. Shurinok, staff workers of the clinic applied the technique of saturating the organism with oxygen, not only through the lungs, but also through the skin to sick children suffering from severe pneumonia with suppurative processes in the lungs and pleurae, and also to critical-list patients with extensive skin burns. The data obtained indicate that the oxygen deficit in the organism is reduced considerably in these patients due to more intensive absorption of the gas through the skin.

It becomes obvious on the basis of everything said above that cutaneous respiration is capable of compensating, to a certain degree, inadequacies of pulmonary gas exchange, such as arise in the organism when it resides under conditions to which it is not accustomed (high temperature, heavy physical labor, and so forth).

No less important is the use of the skin path for delivery of oxygen to the organism in those cases when this is required for a patient. Obviously, it would be expedient in treatment of many patients to use the skin path for delivery of oxygen to the organism in combination with administration of abnormally high oxygen concentrations through the lungs. This procedure might be found more effective in a number of cases than the subcutaneous injection of oxygen into the organism, such as is so extensively practiced in dermatology clinics.

ON THE EFFECT OF NORMAL BAROMETRIC PRESSURE ON THE GAS COMPOSITION OF
THE BLOOD OF ANIMALS THAT HAVE UNDERGONE REMOVAL OF A LUNG

V.A. Losev

(Kiev)

One of the urgent problems that arise in clinical thoracic-surgery work is study of the mechanisms by which the respiratory function is regulated when considerable portions of a lung are excluded from the respiratory process.

Clinical and experimental data on the gases of the blood in cases of pulmonary resections reflect contradictory results. The clinical observations include the work of T.N. Shamarina and V.I. Burakovskiy (1953), Yu.M. Repina (1954), R.M. Izabolinskoy, N.I. Mokrik and R.P. Vel'tman (1957), and A.L. Gofman (1958). Some of these authors (Shamarina and Burakovskiy) do not find hypoxemia after pneumonectomy; on the other hand, others (Repin, Izabolinskaya et al., Gofman) detect more or less pronounced venous and arterial hypoxemia. The existence of these contradictions can be explained to some degree by the fact that the studies of different authors were not performed at the same point in post-operational time, while the surgery had arisen out of various diseases. Also to be taken into account is the fact that the clinician encounters a number of deviations in the activity of the various systems and organs that might be associated with the surgical intervention in itself, with the patient's condition before the operation, and also with the entire previous development of the disorder.

There are not very many experimental studies illuminating this prob-

lem (S.M. Lipovskiy, 1953, 1957). However, in connection with what we have said, there is a need for them, since they make take a certain part in uncovering the mechanisms of respiratory insufficiency and refining compensatory adaptations directed toward its elimination.

Our earlier experimental investigations (N.N. Gorev, V.A. Losev and L.P. Cherkasskiy, 1959; V.A. Losev, 1959, 1960; V.A. Losev, V.T. Sviriyakin and L.P. Cherkasskiy, 1959) indicate that the disturbances to the respiratory function that arise arise immediately after resection of the lung are closely related to the compensatory processes mobilized by the organism. It was shown that in the initial period after surgery, diffusion of the blood gases tends to suffer; this applies primarily to arrival of oxygen and elimination of carbon dioxide. The poor performance of the respiratory apparatus results in a disturbance to coordination between the blood and air supplies to the lungs, with the consequence that the arterial blood is not fully saturated with oxygen. Simultaneously with this, we observe compensatory reactions - the oxygen capacity of the blood is increased and the rate of oxygen transfer from the blood to the tissues rises, as indicated by the increased oxygen difference between the arteries and the veins. A later phase (two to six months after the operation) is characterized by an increase in the oxygen content of the blood and by normalization of the carbon dioxide concentration of the alkaline reserves of the blood and the oxygen evacuated with the urine. Long after the operation (one to two years later), the oxygen saturation of the blood has risen and the arterial venous difference has increased.

In the light of the data obtained, we may conclude that an organism that has lived for some time with one lung adapts to the conditions of its environment to a considerable extent by compensating the functional disturbances observed in the early post operational period. There is no

doubt that this adaptation to the new conditions of existence is achieved by readjustment of certain of its functions and a certain amount of stress on the compensatory processes. To establish the degree of this stress, animals were placed in a state of artificially induced hypoxia.

As we know, the peculiar changes that take place in an organism under hypoxic conditions persist for a certain time after the subnormal barometric pressure has ceased to act (Holden and Priestley, N.N. Sirotnin, M.G. Danilov and others).

We investigated the gas content and alkaline reserves of the blood in animals before a "trip up" to "altitude" and immediately after removal from the altitude chamber.

The experiments were set up on 18 rabbits that had undergone pneumonectomy 1-1.5 years previously, and on 9 control rabbits. After each animal was placed in the altitude chamber, the atmosphere in the chamber was rarefied to a conventional altitude of 6000-10,000 m over 30-50 minutes. This was followed by a gradual (over 20-25 minutes) return of the pressure to atmospheric, at which point the rabbit was immediately pulled out of the pressure chamber and blood taken at once for examination.

It has been shown by the studies of a number of author's (Mosso, 1897; Cardier, 1936; Berzinger, 1937; Holden and Priestley, 1937, N.N. Sirotnin, 1939; M. Bergert, 1939) that under the conditions of subnormal barometric pressure, excessive elimination of carbon dioxide from the organism sets in as a result of hypoxemic hyperventilation; this results in a lowering of the H_2CO_3 content in the carbonate buffer $[(H_2CO_3)/NaHCO_3]$ and gaseous alkalosis arises as a result. However, the gaseous alkalosis that arises is compensated by a drop in the quantity of $NaHCO_3$, since the renal compensatory mechanism is switched in and the excess of alkaline bases is excreted with the urine, so that the blood pH remains normal. In those cases in which the compensation mechanisms prove inadequate, a persistent disturbance to the acid-base equilibrium arises and gaseous alkalosis manifests in animals in the form of muscular rigidity,

spasms and fibrillar twitching of individual muscle groups, respiration of the periodic type, and the like. Similar signs of gaseous alkalosis were observed in our experiments on rabbits that had undergone the operation when they were "lifted" to an "altitude" of 6000-8000 m, but they were manifest to a considerably lesser degree in the control animals - those that had not been operated upon - despite the fact that the latter were "taken up" to a higher "altitude" (9000-10,000 m) in most cases and were kept under the hypoxic conditions for a longer time.

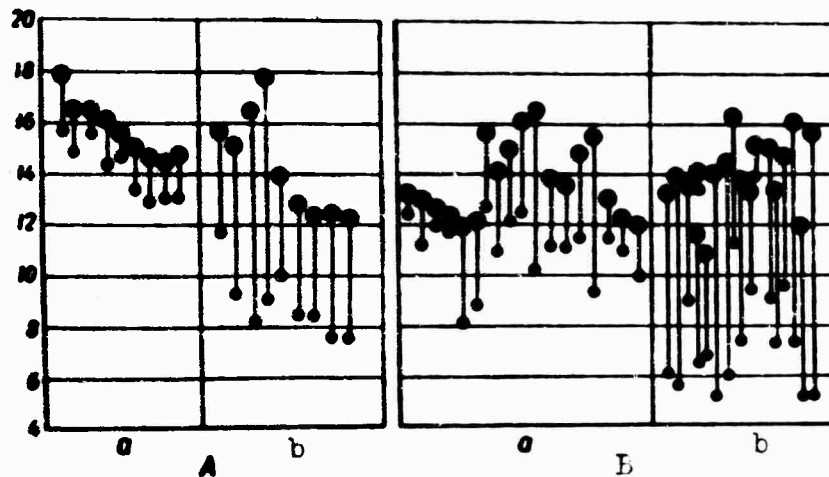
On examination of blood drawn immediately after extraction of the rabbits from the pressure chamber, we were no longer able to detect alkalosis, although the decrease in the total quantity of blood carbon dioxide and the small (by comparison with the initial data) drop in the alkali reserves that were detected in the animals that had undergone the operation may be regarded as a sign of incomplete restoration of acid-base balance. Such shifts were not observed in the experiments with the control group of rabbits. This is testimony to the effect that normal animals have greater compensatory abilities than those that have undergone surgery.

The changes in the gas composition of the arterial and venous blood in animals subject to subnormal barometric pressure are represented schematically on the figure, from which it is evident that the arterial blood of the rabbits contains approximately the same amount of oxygen before and after the altitude-chamber experiment. This fact, which was noted both for the control group (see A on the figure) and for the group of rabbits with pulmonary resections (B on the figure), indicates that the arterial hypoxemia that arises in the rabbits under the influence of lowered barometric pressure is eliminated very quickly under the conditions of normal atmospheric pressure.

These observations find a confirmation in the work of other authors,

and in particular that of M.G. Danilov, who, in a study of the influence of oxygen starvation on gas exchange, noted a distinct rise in the percentage of oxygen absorbed from the inspired air in dogs after they were taken out of the altitude chamber.

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Change in oxygen content of arterial (○) and venous (●) blood (in % by volume) before and after rabbits were subjected to subnormal barometric pressure. A) Indices from control groups of rabbits; B) indices for rabbits subjected to pneumonectomy. a) Before sojourn in altitude chamber; b) after altitude chamber.

Together with normal oxygen content in the arterial blood, both the control and postoperational rabbits showed low oxygen indices in the venous blood after the altitude-chamber experiment. The drop in oxygen level in the venous blood of the animals indicates an elevated oxygen requirement from the tissues, both under the conditions of depressed barometric pressure and during a certain span of time after the sojourn in the altitude chamber. It should be emphasized that the degree of venous hypoxemia differed between the control and experimental animals. After the altitude-chamber experiments, the oxygen saturation of the venous blood showed a greater decrease in rabbits that had undergone removal of a lung. As is clear from the figure (see A), the oxygen content in the venous blood of the control group averaged 13% by volume before the experiment, while after the oxygen-starvation experiment this index had decreased to 9% by volume. In the animals with one lung, the oxygen level

in the venous blood had dropped, on the average, to 5% by volume after the altitude-chamber experiment, as compared with an initial 11% by volume (see B on the figure). It must be remembered here that the extent to which the pressure is lowered in the altitude chamber was not the same for the two groups of rabbits: for the control group, the highest conventional altitude of "ascent" was 9000-10,000 m, while for the group of pneumonectomized rabbits, this "altitude" was generally limited to 6000-7000 m, since further "ascent" threatened the lives of the animals.

The distinct venous hypoxemia observed in the animals after the altitude-chamber experiment and the increase in the arteriovenous oxygen difference associated with it may be regarded as a compensatory reaction of the organism following the hypoxia - a reaction whose purpose is to reduce the oxygen deficiency of the tissues. A low oxygen content in the venous blood being drained from the tissues indicates that they are absorbing a large amount of oxygen, a considerable part of which would appear to be expended on oxidation of the intermediate metabolism products that have accumulated. Thus, in investigating the gas composition and alkaline reserve of the blood, it was found that the capacity of animals with one lung to adapt to marked levels of hypoxia is lower than in normal rabbits.

ON THE INFLUENCE OF HYPOXIA CAUSED BY DECREASE IN ATMOSPHERIC PRESSURE
ON CARDIAC ACTIVITY OF ANIMALS THAT HAVE UNDERGONE PNEUMONECTOMY

L.P. Cherkasskiy

(Kiev)

Removal of a lung causes a variety of reactions on the part of the organism, reactions whose purpose is to adapt it to the new conditions. Of great interest in characterizing the distinctive nature of the life of an organism with one lung is study of the question as to the level of its adaptive capabilities at various points in time after the operation. As regards evaluation of the states of the cardiovascular system from this standpoint, data were obtained in P.K. Anokhin's laboratory (1954, 1956) indicating that during the phase immediately after removal of a lung (for ten days and longer), compensation is not stable and is easily upset under the influence of the disturbances applied (water, physical load and overheating). We have also determined that short-term and relatively sparing disturbances applied during the first few days after the operation cause a distinct pathological reaction of the heart in the animal (1960).

In view of the importance of studies pertaining to more remote times after operation, and the importance of investigating the influence of hypoxia under the conditions described, we performed appropriate experiments using the altitude chamber on animals at various points in time after removal of a lung.

METHOD

The subjects of observation were 46 rabbits, which were examined

2-3.5 months after pneumonectomy (10), 5-7 months afterward (17) and 10-26 months after the operation (19 animals). A total of 59 experiments were performed on animals with one lung, while control experiments were run on 17 normal animals.

Having been secured to the bench, the rabbits were placed in the altitude chamber and, as the atmospheric pressure was reduced, electrocardiograms were recorded at each kilometer of the "ascent," using the standard and two chest leads. In the majority of experiments, the respiratory movements were also registered synchronously. The atmospheric pressure was lowered at a rate corresponding to a "trip up" by 1 km in the course of 3 minutes; then the pressure was held at the level thus attained for 2-2.5 minutes, followed by continuation of the "ascent" in the same regimen (to no higher than 10 km).

RESULTS OF EXPERIMENTS

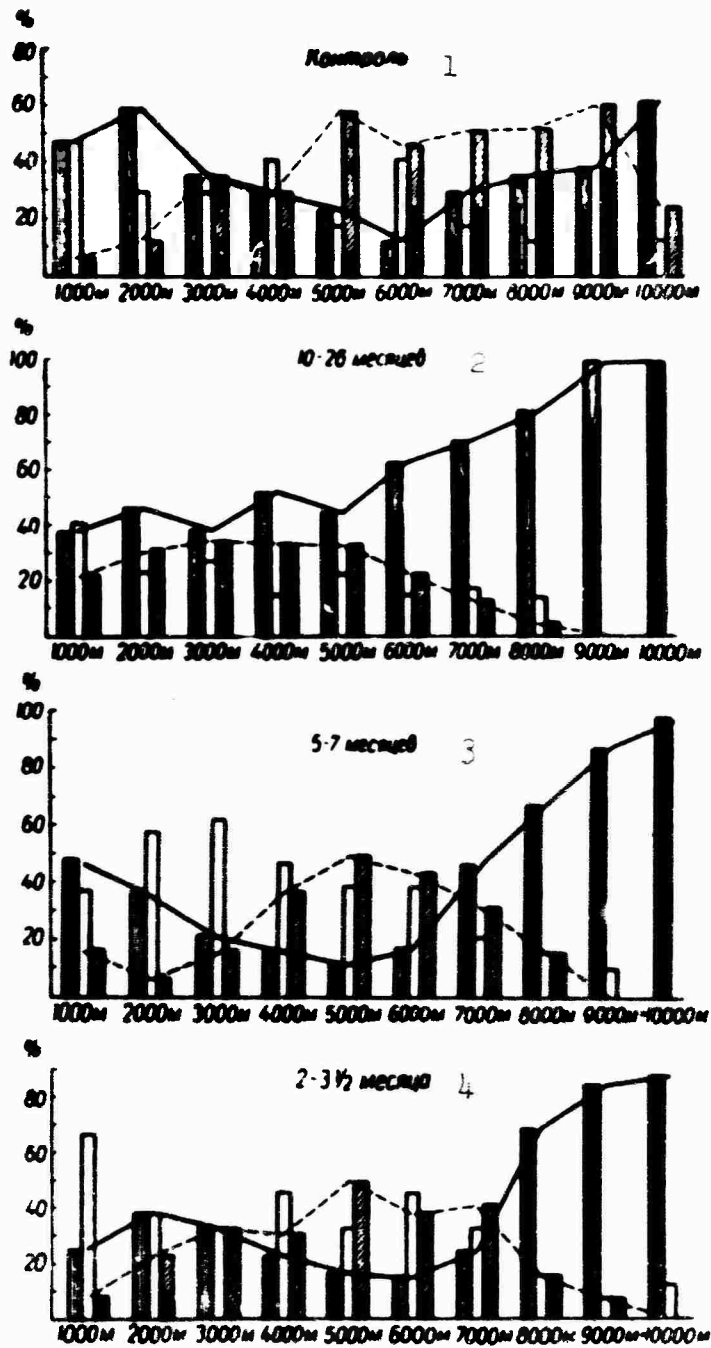
There are essential differences in the external manifestations of the reactions between the experimental and control animals. In the normal rabbits, distinct signs of a deterioration in the general condition, which we can judge from the difficult, strained respiration, usually intervene after the atmospheric pressure has been reduced farther than in the case of the experimental animals (more frequently at an "altitude" of 9-10 km). In the rabbit that had undergone surgery, and preferentially in the groups studied 10-26 months after the operation, intensified panting respiratory movements, which were more distinct on the unoperated side and were accompanied by "time keeping" movements of the head and extremities, and retraction of the head were observed in many cases at an "altitude" of 6-7-8 km. The impression created was that in itself, the act of respiration was difficult physical labor for the animal. Distinct signs of asphyxia were noted in occasional experiments.

Changes in cardiac activity that distinguish the nature of the one-lunged experimental animals' reaction from that of the control animals were also brought out quite clearly. It is necessary to note that the pulse rate is regarded as one of the most important criteria for evalua-

ting the circulatory reaction to hypoxia (Koch, 1936; M. Sirotinin, 1941; Aleksandrov and Yegorov, 1947; Lauer, 1959, and others). When the atmospheric pressure is lowered we can frequently distinguish two phases in the reaction of the heart — a phase in which the rhythm is quickened, followed by one in which it slackens. Continuation of the "ascent" results in a third phase in the organism's reaction to the treatment — a phase characterized in the terminal stage by paralysis of the extracardial nerve centers and the death of the animal. Together with the change in pulse frequency, the elements of the electrocardiogram also undergo modifications. The literature contains data on this problem, obtained in study of both healthy humans and experimental animals (Borgard and Koch, 1934; Mirolyubov and Chernogorov, 1934; Koch, 1936; Lauer, 1959, and others).

We have not succeeded in finding in the literature any indications as to the nature of the reactions of the cardiovascular system in animals with one lung to lowering of the atmospheric pressure.

In our observations (Fig. 1) on the control animals, in agreement with the literature data, the pulse frequency shows a tendency to increase in the course of the atmospheric-pressure decline. In animals investigated 10-26 months after pneumonectomy, cases of slight quickening of the rhythm at an "altitude" of 1 or 2 km are even more frequent than in the control group, an observation that may indicate earlier triggering of the adaptive mechanisms. However, the rhythm was quickened in the control group in nearly a third of the experiments at the "altitudes" of 3 and 4 km, while in the group of animals that had undergone surgery, there were a considerable number of experiments in which slackening of the rhythm set in. As the pressure in the altitude chamber was lowered further, the differences in the reactions of the experimental and control animals became more pronounced. In the control group, at an "alti-



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Fig. 1. Dynamics of changes in cardiac frequency in animals at various points in time after removal of a lung and in control animals, with diminishing atmospheric pressure. Legend: open bars - no changes (variations within $\pm 2\%$ of the initial rhythm in each experiment); diagonally hatched bars - quickening of the rhythm; vertically hatched bars - slackening of rhythm; black bars (inside hatched bars) - unusually distinct (by more than $\pm 10\%$) deviations of the rhythm from the initial figure. The height of a bar indicates the percentage of experiments in the number taken as 100% for each given "altitude." The curves connect points corresponding to the percentages of experiments with deceleration (solid line) or acceleration (broken line) of the cardiac activity. 1) Control; 2) 10-26 months; 3) 5-7 months; 4) 2-3 1/2 months.

tude" of 5-9 km, the rhythm was quickened as compared to the initial level in more than half of the experiments, and quite considerably in a

number of cases - by 20-30% and more. Only at an "altitude" of 6 km was a quickening of the rhythm noted in the experimental-animal group - in one-fourth of the experiments, and subsequently this was observed in no more than 5-13% of all experiments. At the 9-km "altitude," there were no longer any cases of quickened rhythm at all. At the same time, from 7 km on, a deceleration of the pulse was observed in the overwhelming majority of cases. To this it should be added that due to the significant disturbance of the cardiac-activity rhythm, which could be noted visually during electrocardiography, and the difficult general condition of the animals at the indicated remote points in time after the operation, the "ascent" was terminated and the investigated stopped in 17 experiments at the "altitude" of 6 km (two experiments), 7 km (two experiments), 8 km (five experiments) and 9 km (eight experiments). In the control group, the "ascent" was stopped for the same reasons at an "altitude" of 8 km in three experiments and at 9 km in one experiment.

In the experiments on animals that had undergone surgery, the slackening of the pulse was combined in most cases with distinct arrhythmia, usually of the sinus type. In view of the labored respiration observed when the atmospheric pressure was lowered, we might expect that these disturbances to the rhythm are functions of the unusual nature of the respiratory movements under the conditions of the experiment. A check of this hypothesis by registering the respiratory movements in synchronism with the electrocardiogram did not bring out any connection between arrhythmia and the respiratory movements (Fig. 2). In the cases being described, we may speak of arrhythmia as a sign of serious derangement of the cardiac activity. Nevertheless, it would appear to be of a functional nature: a rise in the atmospheric pressure in the altitude chamber results in rapid normalization of the rhythm.

Less distinct manifestations of arrhythmia were also observed in

the control animals, but relatively seldom and only when the atmospheric-pressure drop was considerable, corresponding to an altitude of 8-10 m. In addition to the arrhythmia, other changes appeared in the electrocardiogram. In seven experiments of the basic group, we noted a shift in the mean electrical axis of the QRS complex (to the right in six of them). In the control group, the axial shift appeared in two experiments (shift to the left). In some of the experiments on the post-surgical animals, a drop in the voltage of the R-wave, a shift in the level of the RS-T segment, and a change in the amplitude and direction of the T-wave were noted (Fig. 2).

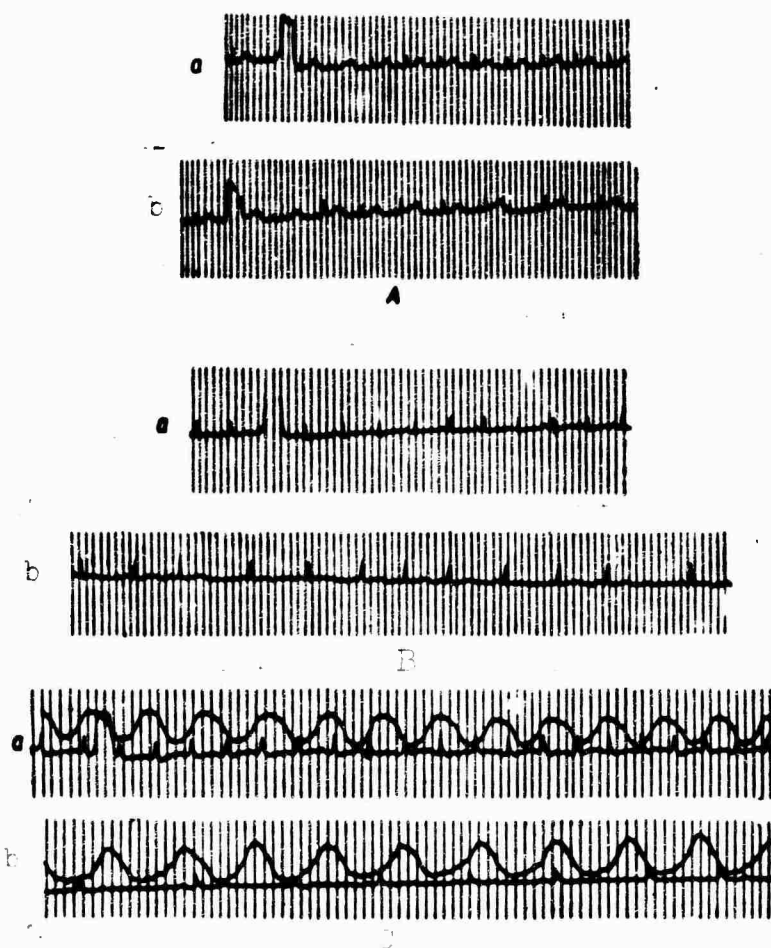


Fig. 2. Altitude-chamber experiments. EKG record (left chest lead) and respiration trace. A) Rabbit No. 54: a) before experiment; b) 14 months after operation; altitude of "ascent" 6000 m; B) rabbit No. 56: a) before experiment; b) 15 months after operation; altitude of "ascent" 6000 m; C) rabbit No. 163: a) before experiment; b) 10 1/2 months after operation; altitude of "ascent" 1000 m.

In animals observed 5-7 months after removal of a lung (Fig. 1), persistent shifts in the cardiac activity were noted beginning at an "altitude" of 7 km. At this "altitude," almost half of the experiments showed a slackening of cardiac activity, while less than one-third of the control group produced such experiments. At the same time, a minor quickening of cardiac activity is registered in almost a third of cases, but more than half of the experiments in the control group were of this type. The tendencies noted at "altitudes" of 8 and 9 km manifest with better definition. In almost all experiments, a significant slackening of the pulse was accompanied by sinus arrhythmia, which was distinctly manifest in half of the cases. The arrhythmia arose at 7-8 km (seven experiments) or at a higher "altitude."

In the group of experiments conducted on animals 2-3.5 months after pneumonectomy (Fig. 1), considerable differences in the pulse as compared with the control appear at 8 km, when almost half of the experiments (twice as many as in the control group) show slackening of the pulse by 10-30%. Arrhythmia also appeared in this group of experiments at the 8-km "altitude" (five experiments); in six experiments it appeared only at 9 km, and in two not at all. The arrhythmia was usually not severe and was considerable at the "altitude" of 8-9 km in only four experiments. Even though the slackening of the pulse rate set in after the pressure had been lowered quite far in the altitude chamber, and the attendant arrhythmia was usually not strongly manifest, other changes in the electrocardiogram came out quite clearly in some of these experiments. For example, in the experiment on rabbit No. 234 two months after sinistral pulmonectomy, a decrease in pulse rate was observed at "altitudes" of 8 and 9 km, although distinct changes in the T-wave had been noted beginning at 5 km. Toward 6 km, the T-wave became negative and remained so for the entire subsequent "ascent" to 9 km and throughout the

"descent" period (Fig. 3); only after the experiment had been completed did the configuration of the T-wave return to normal. In another experiment (rabbit No. 224; 2 months and 8 days after the operation), the slackening of pulse rate began at 9 km, and at the 7th km it increased sharply (from 253 to 308 per minute). Simultaneously with this, however, extrasystology made its appearance (Fig. 3).

Comparison of the results from experiments performed on animals 2-3.5 months, 5-7 months and 10-26 months after removal of the lung provides a convincing indication, based on a number of indicators, that the difficulties experienced by the organism as a result of increasing artificially induced hypoxia appear most often in animals in the remote post-operational period.

To generalize to some degree from the data set forth above, and comparing them with the results of investigations made earlier in the laboratory into various aspects of the functional state of the cardiovascular system and blood picture, it must be noted that observation of animals with one lung over a rather long span of time following pneumonectomy (up to 26 months) indicates that the organism of the experimental animal has a capacity to preserve, within certain limits, the state of compensation of the disturbed functions that has been achieved during the first few months after the operation, and the resulting equilibrium with the environment. Under these conditions, however, the extent of the potential for adaptation to difficult situations is markedly lower. The phase shift in the heart's reaction to lowered atmospheric pressure that is observed even in normal animals takes place differently in animals at remote stages following pneumonectomy (10-26 months after the operation). The first phase (quickenning of the rhythm) is shortened; the second phase (slackening of the rhythm) sets in early in most cases, at a relatively low "altitude," and is complicated by other disturbances to car-

diac activity. As a result, the time interval within which the adaptive reactions might develop is found to be shorter. All of this indicates that in animals with one lung, the adaptive mechanisms do not, in the majority of cases, go into action with sufficient strength in the remote post-operational period and that they are exhausted comparatively quickly when abnormal demands are placed on them.

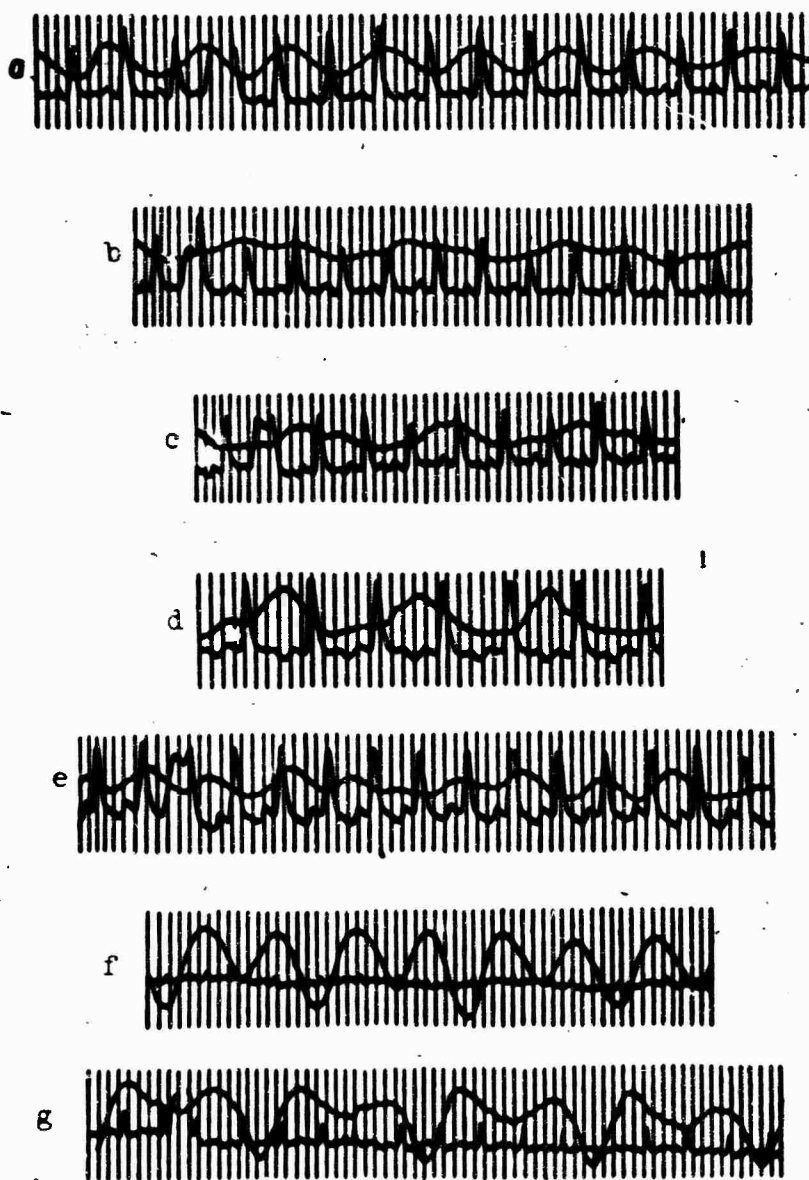


Fig. 3. Altitude-chamber experiments. EKG and respiration traces. Rabbit No. 234. a) 2 months after operation; b) altitude of "ascent" 5000 m; c) altitude of "ascent" 6000 m; d) altitude of "ascent" 9000 m; e) "descent," 4000 m; f) altitude of "ascent" 7000 m (lead II); g) altitude of "ascent" 7000 m; CR₅ lead.

It is necessary to point out that these differences in the reactions of the experimental and control animals to hypoxia affected to a lesser

degree those groups of animals that were studied 5-7 and 2-3.5 months after the operation. Even at later times, we observed cases in which this reaction differed little from the reaction of normal animals. The number of such experiments increases as we recede in time toward the operation. Hence, it is important that not only the reactions of the experimental animals were different, but also that in a number of experiments, this difference was quite indistinct. Taking into account the fact that the degree to which the accident partial pressure was reduced in the altitude chamber was quite high in these experiments, we may not omit to stress that in the cases described we still note considerable reserve capabilities in the organism of the experimental animal. To this it should be added that despite the shifts - quite distinct in many experiments - in the cardiac activity at high "altitudes," stopping the "ascent" and normalizing the atmospheric pressure in the altitude chamber eliminates the pathological phenomena that had developed at "altitude" in quite short order. Removal of a lung undoubtedly reduces the organism's reserve capabilities, and in particular those of its cardiovascular system, for adaptation to hypoxic conditions, particularly at remote points in post-operational time; nevertheless, the processes in which the disturbed functions are compensated develop after the operation in a direction such that experimental animals with one lung are, in many cases, quite capable of resisting rather considerable degrees of artificially induced hypoxia.

REGIONAL OXYGEN INSUFFICIENCY

M.Ye. Marshak

(Moscow)

In the overwhelming majority of cases of oxygen insufficiency (or oxygen starvation) observed in humans in hypoxic hypoxia, the amount of oxygen consumed by the organism is practically the same as under normal conditions, but this situation is achieved as a result of the number of regulatory mechanisms coming into play. There are a variety of ways in which the various organs are supplied with oxygen here. Thus, records made in our laboratory of the degree of oxygen saturation of the arterial blood and the blood in the jugular and femoral veins when the oxygen content in the inspired air was reduced indicated that the difference between the oxygen content in the arterial blood and the blood of the jugular vein decreases during hypoxia, while the arteriovenous difference increases in the blood in the extremities. This permits us the conclusion that normalization of the oxygen supply to the muscles of the extremity in hypoxia is provided to a certain degree by using more of the oxygen from the arterial blood, and otherwise by an increase in blood supply to the tissues.

When the oxygen content in the inspired air is lowered considerably - in cases of acute hypoxia, as was noted in our laboratory in studies performed on humans and animals - the amount of oxygen used by the organism is smaller than its requirement, so that an oxygen deficiency develops and is aggravated as the hypoxia continues. Only in the recovery period, after the subject has been switched to breathing atmospheric

air, is this deficit made up. The magnitude of the oxygen deficit in these cases is an over-all index to the oxygen insufficiency; we may not, on the basis of these data, draw inferences as to how the regional oxygen supply changes in acute hypoxia.

At the same time, the nonuniform supplies of oxygen to the various organs, the nonuniform regional oxygen deficit in acute hypoxia, is governed by the activity of a number of regulatory mechanisms that increase the organism's tolerance to hypoxia. The polarographic investigations of changes in the oxygen partial pressure in the brain and muscles of the extremity in acute hypoxia that were carried out simultaneously at our laboratory indicated that when the oxygen partial pressure in the muscles of the extremities is reduced by a considerable margin, the oxygen tension in the brain changes relatively slightly.

A clear-cut example of regional oxygen insufficiency can be found in cases in which the influx of blood to an organ or part of an organ is cut off. This is observed in vascular thrombosis or on artificial blockage of the blood stream, for example, by application of a tourniquet to the extremity. Regional ischemia develops distally from the point at which the artery is obstructed or compressed. Polarographic studies of the oxygen-tension changes in the muscles of the lower leg after application of a tourniquet to the thigh indicated that the oxygen partial pressure has dropped to zero after a few minutes. Cutting off the blood supply to an extremity also results in a gradual drop of the skin and muscle temperatures. Immediately upon removal of the tourniquet, the muscle temperature of the extremity to which it had been applied rises. Here, as a rule, the temperature rises quite far above the initial level — the so-called reactive hyperemia, which reflects a considerably amplified blood influx, sets in. The latter is usually explained in terms of a drop in vascular tone due to the influence exerted on the vessel

walls by metabolism products formed in the ischemized extremity.

We established that following a repeated application of the tourniquet to the extremity for 15-30 minutes each day or every other day over a span of three to four weeks, the reactive hyperemia following removal of the tourniquet gradually disappears (Fig. 1). When a certain time has elapsed after the second application of the tourniquet, the reactive hyperemia following temporary ischemia of the extremity reappears.

We may advance the hypothesis that the absence of reactive hyperemia after the second temporary ischemia results from biochemical shifts that have intervened in the tissues of the ischemized extremity.

In these experiments, which were performed on rabbits without anesthesia, we were able to satisfy ourselves that during the first few minutes after application of the tourniquet in the second phase of ischemia in the extremity, the muscle temperature of this extremity dropped not only as a result of stoppage of the blood supply, but also as a result of a conditioned-reflex increase in the tone of the muscles and contraction of the vessels. Figure 2 represents the dynamics of the muscle-temperature variation in the right and left extremities when the tourniquet was applied to the left extremity after a three-week period in which tourniquets were placed on both extremities each day for 20 minutes. As will be seen from Fig. 2, for three minutes after application of the tourniquet to the left thigh only, the muscle temperature dropped uniformly in the muscles of both extremities; only after three minutes did the muscle temperature of the left extremity (to which the tourniquet had been applied) continue to decrease, while the muscle temperature of the right extremity began to rise (single application of the tourniquet to one extremity causes only insignificant muscle-temperature fluctuations in the other extremity).

These data may serve as yet another illustration of the importance

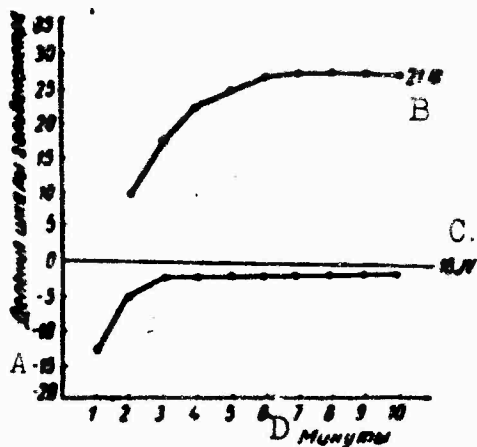


Fig. 1. Muscle temperature in lower leg after removal of tourniquet applied to thigh (explanation in text). A) galvanometer scale divisions; B) 21 March; C) 18 April; D) minutes.

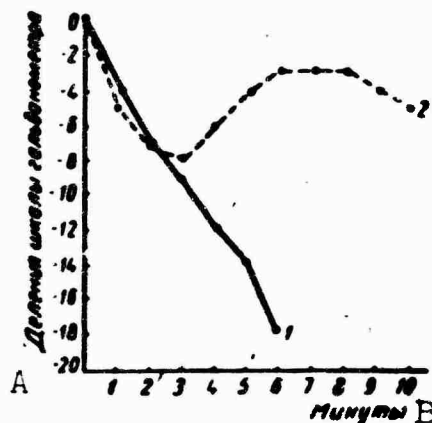


Fig. 2. Muscle temperature in right and left lower legs after application of tourniquet to left thigh. 1) Muscle temperature of left lower leg; 2) muscle temperature of right lower leg (explanations in text). A) Galvanometer scale divisions; B) minutes.

of conditioned-reflex effects, which manifest not only in general, but also in regional repeated oxygen insufficiency. Myocardio infarct may serve as an example of regional oxygen insufficiency affecting only part of an organ. Under experimental conditions, myocardial infarct is induced by tying off a branch of the coronary artery.

Our laboratory made a detailed investigation of the influence of local myocardial ischemia on the oxygen partial pressure in various zones of the cardiac muscle (V.K. Sanotskaya). An investigation of the oxygen partial pressure in the myocardium was made by the polarographic method, using special electrodes that could be securely fixed in the heart muscle. It was established that after ligation (or compression) of a branch of the coronary artery, the oxygen partial pressure drops very sharply in the ischemized zone of the myocardium. Adjacent to this zone is a region of the myocardium known to us as the boundary zone (it is not the same in different experimental animals), in which, after a branch of the coronary artery has been tied off, we also observe a cer-

tain drop in oxygen partial pressure. On regions of the myocardium remote from the ischemized zone, the oxygen tension either did not change at all or increased or decreased.

It must be assumed that the drop in oxygen partial pressure in the boundary zone of the myocardium is due to an effect in which this region of the myocardium is supplied with blood to some extent through ramifications of the ligated branch. The correctness of this hypothesis is confirmed by the results of experiments in which the influence of breathing pure oxygen on the oxygen tension in various zones of the myocardium was investigated after a branch of the coronary artery had been tied off. It was found that inspiration of oxygen has virtually no effect on the level of the oxygen tension in the zone of total myocardial ischemia. In areas remote from this zone, inspiration of oxygen caused a considerable rise in the oxygen tension in the myocardium, to the same level as was observed before the coronary branch had been tied off; a distinct rise in oxygen partial pressure was observed here in the boundary zone as well. This fact is of great importance not only from the theoretical standpoint, but also for clinical practice.

The data cited above suggest that the helpful effect of oxygen therapy in myocardial infarct consists chiefly in elimination of the myocardial oxygen insufficiency in the zone bordering the zone of total ischemia. This reduces the size of the myocardial zone with more or less pronounced oxygen insufficiency developed after ligation (or obstruction) of a branch of the coronary artery.

Literature data and the results of our studies of the influence of elevated carbon dioxide concentration in the inspired air on regional blood circulation placed before us the question as to the expediency of adding a small quantity of carbon dioxide to the oxygen inspired under the conditions of local myocardial ischemia. This was established in our

laboratory in a series of animal experiments. It was found that following ligation of a branch of the coronary artery, inspiration of a mixture of oxygen and 3-5% of carbon dioxide causes a greater increase in the oxygen tension both in zones of the myocardium remote from the ischemized zone and in the boundary zone; the latter is of particularly great importance. It must be supposed that an increase in the carbon dioxide tension to some degree neutralizes the local vasoconstrictor influence of high oxygen pressure in the arterial blood. A rise in the carbon dioxide tension of the blood counteracts a slight drop in arterial pressure that frequently attends inspiration of oxygen. Moreover, an increase in the carbon dioxide partial pressure in the arterial blood facilitates passage of oxygen from the blood into the tissues by reducing the affinity of hemoglobin to oxygen.

ON TWO CHEMORECEPTOR MECHANISMS OF THE CAROTID SINUSES

S.S. Krylov

(Leningrad)

In 1951, Nielsen and Smith showed that when a human inspires a mixture of the gases O_2 and N_2 with a subnormal oxygen content, addition of carbon dioxide to this mixture is not accompanied by a marked increase in the volume of pulmonary ventilation until the CO_2 partial pressure in the blood reaches the normal (about 30 mm Hg) level. Only when this level is exceeded does CO_2 produce a considerable increase in the pulmonary ventilation. As the CO_2 partial pressure in the blood increases further, the increase in pulmonary ventilation rises as a function of the CO_2 -tension level.

In 1963, V.G. Startsev established that when cytisine acts on the carotid chemoreceptors, we observe amplified motor activity and secretion of gastric and intestinal juices. At the same time, the action of cyanide on these chemoreceptors is accompanied by inhibition of the gastric and intestinal activity (see also Startsev, 1958, 1959). These data have been confirmed by the present author (S.S. Krylov, 1960) in corresponding experiments with acetylcholine and sodium cyanide.

A 1958 monograph of Heimans and Heil set forth the results of experiments by Neil in which it was shown that when animals inspire a gas mixture with a subnormal oxygen content, electrical activity is intensified in some of the nerve fibers of the sinus nerve - fibers in which no changes occur when there is an excess of CO_2 in the inspired air. Conversely, other nerve fibers register excitation in response to CO_2 and

at the same time do not produce changes in response to oxygen insufficiency.

It is extremely difficult to account for these data within the framework of the hypotheses that had accumulated by the middle '50's concerning the excitation process of the carotid chemoreceptor apparatus.

Thus, according to the "acetylcholine" hypothesis, excitation of the sensitive terminals of the sinus nerve in the carotid sinus takes place solely by way of acetylcholine (or a similar substance) secreted by the chemoreceptor cells on any disturbance to glomera capable of producing excitation in it (Schweitzer and Wright, 1938; Euler et al., 1939, 1941; Lillstrand, 1951, 1954; Lundgren et al., 1952, 1954; Abo, 1947; Ishimova, 1948; Ross, 1959).

From the standpoint of the "oxygen" hypothesis (Vinder, 1937; Vintershteyn, 1955, 1956), the immediate and only cause of excitation of the sinus-nerve terminals in the glomus is an increase in the concentration of hydrogen ions that arises by formation of carbonic acid with an excess of CO_2 , and (given equivalent disturbances) in O_2 insufficiency, by accumulation of acidic incompletely oxidized products.

Finally, according to the hypothesis of M.L. Belen'kiy (1952; see also S.V. Anichkov and M.L. Belen'kiy, 1962), the unique cause of excitation in the carotid sinus is a disturbance in the metabolism of macroergic compounds in its chemoreceptor cells.* Here the excitation of the sinus-nerve terminals in the glomus is associated with an increase in the decomposition of these compounds (chiefly ATF).

If we view from the standpoints of these hypotheses the nature of the information received by the central nervous system as a result of excitation of the carotid sinuses, we note the following. From the standpoint of the "acetylcholine" hypothesis, the equals sign is placed between such conditions as hypercapnia and hypoxia, since under these con-

ditions the sensitive terminals of the sinus nerve are excited by acetylcholine, which means that the information produced by the receptor devices in the glomera is not rigorously defined. The "acid" and "energy" hypothesis, in contrast to the "acetylcholine" viewpoint, imply a more specific nature for the information. According to the "acid" hypothesis, excitation of a glomus represents information pertaining to acidotic shifts, while according to the "energy" hypothesis it is information concerning a threat to the energy metabolism of the tissues. It follows from this that there are profound differences between these three hypotheses as regards the mechanism by which the sensitive terminals of the sinus nerve are excited and, consequently, as regards the nature of the information generated by the carotid sinuses. At the same time, each of these hypotheses is universal in nature, i.e., for each hypothesis the mechanism that it postulates for excitation of the carotid chemoreceptor devices is the only process that could possibly be responsible for the excitation that arises in the carotid sinus.

The experimental results of Nielsen and Smith, Startsev and Neil presented at the beginning of this article stand in direct disagreement with this last conclusion. Nor can be reconcile with any of these hypotheses data on the influence exerted on the carotid chemoreceptors by substances that have cholinolytic effects and by anticholinesterase compounds. According to a majority of authors, the former eliminate and the latter intensify the exciting action on the glomus, and at the same time exert no influence at all on the hypoxic excitation of the carotid chemoreceptors (see surveys by Heimans and Neil, 1958; Anichkov and Belen'kiy, 1962).

All of these data necessitated making a new pharmacological analysis of the chemical sensitivity of the carotid-chemoreceptor devices.

For the most part, this work was done using a technique developed

specifically for this purpose - one of perfusion of a preparation of the sinus reflexogenic zone that had been completely isolated from the organism of the animal (cat) (Krylov, 1956), which made it possible to characterize the excitation process in the carotid sinus exactly by registering the sinus-nerve biocurrents and thus to determine exactly the composition and temperature of solutions perfused through the preparation. The following data were obtained as a result.

It was established on investigation of glomic chemoreceptor excitation induced by acetylcholine and substances with similar effects (nicotine, cytosine) that excitation of the chemoreceptors occurs immediately upon administration of a single dose of acetylcholine to the sinus. This excitation is very short in duration. It lasts a few seconds and disappears quickly. Nicotine and lobeline produce a similar excitation of the chemoreceptors when administered once. When the carotid sinus is subject to the action of acetylcholine for an extended time, excitation of the chemoreceptors continues quite persistently (many minutes); here, the intensity of the excitation decays very slowly. On the other hand, when the glomus is subject to prolonged treatment with nicotine (or cytosine), strong excitation of the chemoreceptors lasts only 2-3 minutes, and then dies out rapidly; by the end of the fourth minute, as a rule, the action currents of the sinus nerve have returned to the initial level. In this period of the continued action of nicotine (or cytosine), the ability of the carotid sinus to respond to acetylcholine excitation is exhausted completely. At the same time, there is no change at all in the chemoreceptor-exciting effect of sodium cyanide, 2,4-dinitrophenol, lactic acid and potassium chloride. Other substances that block n-choline receptors (curare, paramion, tetraethylammonia, hexamethonium) have exactly the same effect on the sinuses as nicotine or cytosine in the second (blocking) phase of their action.

In analysis of the hypoxic excitation of the carotid sinus, and in study of the glomic effect of 2,4-dinitrophenol — a substance that disturbs the phosphorylation processes associated with respiration — the following observations were made. On a single injection of sodium cyanide or dinitrophenol into the current of Ringer's solution perfusing through the preparation of the sinus reflexogenic zone, the excitation continues for about two minutes and then gradually dies out. At the peak of the excitation, we frequently observed considerable suppression of the electrical activity in the sinus nerve. In experiments in which prolonged sodium-cyanide or dinitrophenol treatment was applied to the carotid sinus (during perfusion of solutions of these substances through the preparation), excitation of the carotid chemoreceptor apparatus arose, as in one-shock treatment, not immediately, but 10-15 seconds after perfusion was begun. The excitation continued for 2-3 minutes, and, as a rule, had ended by the fourth minute. The action currents of the sinus nerve returned to the initial level during this time in which the cyanide or dinitrophenol solution was being perfused. Introduction of acetylcholine, lactic acid and potassium chloride into the flow of perfusate against this background was invariably accompanied by an increase in the electrical activity of the sinus nerve. This represents testimony to the effect that under conditions in which the carotid sinus has ceased to react to prolonged treatment with cyanide or dinitrophenol, its ability to respond by excitation to acetylcholine, "acidic" conditions in the medium (to lactic acid) and to potassium chloride is still retained in full.

In analyzing hypoxic excitation of the carotid sinus, it was also established that anticholinesterase substances do not affect the sensitivity of the chemoreceptor apparatus to sodium cyanide. It was further shown that on a considerable alkaline shift in the pH of the carotid

sinus, its capacity to respond by excitation to sodium cyanide is not substantially affected.

It is necessary to note the following point in evaluating the exciting effect of acid on the carotid sinus. When lactic acid is introduced into the current of Ringer's solution being passed through the isolated preparation of the sinus reflexogenic zone, a sharp quickening and amplitude increase appears in the action currents of the sinus nerve - an effect that might be regarded as excitation of the glomic chemoreceptors. This excitation arises immediately after introduction of the acid and ceases after a few (10-15) seconds. Acid excitation of the sinus is quite similar in nature to the exciting effect of acetylcholine.

The following are among the other peculiarities noted in the exciting effect of lactic acid on the glomus: when the choline receptors of the sinus are blocked, its ability to respond with excitation to lactic acid is retained, as is the exciting effect of the acid on the glomus while, for example, sodium cyanide is acting continuously on the sinus, when the excitation produced by it (the cyanide) disappeared completely.

It was established in an investigation of the sensitivity of the carotid sinus at various temperatures that a drop in the temperature of the glomus even to 10-12° has no fundamental effect on its ability to respond by excitation to acetylcholine (and substances with similar effects), to lactic acid and to potassium chloride. When the temperature of the glomus is depressed, the first phase of the exciting effect of sodium adenosine triphosphate on it is also preserved. At the same time, when the temperature of the sinus is lowered to 20° and the more so at lower temperatures, the exciting effect of sodium cyanide and 2,4-dinitrophenol on the chemoreceptors vanishes just as completely.

On assembling all data (including those borrowed from works of other investigators, but chiefly the results of the present experiments)

characterizing the excitation of the carotid sinus, it can be seen that there is a fundamental difference between the excitation of the glomus induced by acetylcholine and acid on the one hand and, on the other, the excitation caused by sodium cyanide and 2,4 - dinitrophenol.* Essentially, it consists in the fact that excitation of the carotid sinuses by substances of the first group (i.e., acetylcholine and acid excitation of the chemoreceptor devices) may arise and proceed under conditions such that hypoxic excitation cannot occur (or excitation equivalent to it). This forces us to the conclusion that the mechanism of acetylcholine and acid excitation of the carotid sinuses must differ basically from, and be independent of, the mechanism of hypoxic glomic excitation. A general conclusion that may be formulated as follows proceeds from this: two chemoreceptor mechanisms, two independent processes, each of which is responsible for a definite excitation that is peculiar to it, may be realized in the carotid sinuses - and herein there probably lies the basic essence of the chemoreceptor principal of the sinus reflexogenic zone (Krylov, 1960, 1962).

If, adopting these premises, we consider the carotid chemoreceptors as devices that inform the central nervous system, then the information that they generate may be represented in the following form.

It can be assumed that acid excitation of the carotid chemoreceptors, which, in the last analysis, results in a sharp increase in pulmonary ventilation, is, on the basis of its origin, an appraisal of the central apparatus of the nervous system that acid metabolism products (either incompletely oxidized products such as lactic acid or final products such as carbon dioxide) have accumulated in the tissues of the organism, and the carotid sinus in particular, and must be eliminated from the organism. Elimination of these products is possible by way of excretion in the respiratory process (in the case of accumulation of in-

completely oxidized products, it is first necessary to oxidize them to carbon dioxide), and this requires increased pulmonary ventilation.

From this standpoint, acetylcholine excitation of the carotid chemoreceptors may probably be added to acid excitation (and, apparently, to hypoxic excitation as well) under conditions that are extremely difficult for the organism, as yet another of the reflex stimuli to respiration. Highly compatible with this point of view are results obtained in Gesell's laboratory (1942), an acid shift in the pH may amplify the effect of acetylcholine by inhibiting the activity of cholinesterase, which is suppressed to a considerable degree under acid conditions. These data permit the assertion that the effect of acid and acetylcholine on the carotid sinuses take the same direction and have the same significance — chiefly in that they increase the pulmonary ventilation volume.

To a considerable degree, the pulmonary ventilation volume and the hemoglobin content of the blood determine the level of acid-base balance in the organism, and this, in turn, governs directly the degree to which the mechanism of carotid-chemoreceptor acid excitation is brought into play.

Remembering here that the pulmonary ventilation volume determines the level of acidotic shifts in the organism, we may regard the mechanism of carotid-sinus acid excitation as one of the adaptations for regulating acid-base balance in the organism, while acid excitation itself would be seen as informing the central nervous system of the acidotic shifts in the organism.

As concerns hypoxic (and equivalent) excitation of the carotid chemoreceptors, it is distinguished by one extremely important circumstance. When the carotid sinuses are put out of action, the unprepared organism is incapable of responding by excitation of respiration to conditions of acute hypoxia. Furthermore, after the carotid sinuses have been excluded

by a resection of the sinus nerves (Heimans et al., 1931, 1933) or after extirpation of the carotid sinuses (Belen'kiy, 1952), acute hypoxia suppresses respiration and produces a general depression of the animal, a characteristic of the basic role of the carotid sinuses in the organism during acute hypoxia.

If we consider hypoxic excitation of breathing from the standpoint of the partisans of the "acid" hypothesis, chiefly Winder and Winterstein, who assume that during hypoxia, as a result of glycolysis, acid products accumulate in the carotid sinus and thereby increase the concentration of hydrogen ions, with the result that the chemoreceptors are excited, then it is necessary to assume that glycolysis and the formation of acid products in hypoxia are possible only in the carotid sinuses, since their exclusion during acute hypoxia tends to suppress respiration. This assumption is found to be rather improbable, since it does not have any experimental confirmation.

In view of the fact that the organism has highly effective "stand-by" systems capable, in the absence of the carotid sinuses, of assuring excitation of respiration when there is a significant acid shift in pH, it is extremely difficult to accept the proposition that these systems are not in a position to react to the presence of acid products formed in the tissues during hypoxia when the carotid sinuses have been removed. All this tends to suggest that some mechanism other than that assumed by the supporters of the "acid" hypothesis must lie at the bottom of hypoxic excitation of the carotid sinuses. It is most probable that a disturbance to the metabolism of the macroergic compounds, and ATP in particular, is behind this mechanism — an idea developed by M.L. Belen'kiy (1952; see also Anichkov and Belen'kiy, 1962). It follows from this that in contrast to acid and acetylcholine excitation of the glomera, their excitation in hypoxia and under conditions corresponding to it represents

appraisal of the central nervous system of a threat to the oxidative processes, chiefly to the energy metabolism of the tissues.

Considering all of these data, we see that the research results of Nielsen and Smith, Startsev and Neil as cited above are satisfactorily explained in terms of two independent chemoreceptor mechanisms in the carotid sinuses, and that these data themselves confirm the new conception as to the functioning of these sinuses.

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[Footnotes]

- 311 *For the sake of brevity, the hypothesis of M.L. Belen'kiy will subsequently be referred to as the "energy" hypothesis.
- 316 *A certain difference between acetylcholine and acid excitation, consisting in the fact that when the choline receptors of the sinus are blocked, acid continues to exert an exciting influence on the glomus, is apparently not fundamental, since there are very points of similarity between the exciting effects of acetylcholine and acid on the sinuses and only this single difference. The latter should rather be regarded as a result of the action of acetylcholine and acid (hydrogen ions) on different parts of the same receptor system, instead of attempting to postulate the presence of separate receptor systems in the carotid sinus, one of which responds to acetylcholine, while the other responds to an elevation of the hydrogen-ion concentration.

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[Transliterated Symbol]

- 311 $AT\Phi$ = ATF = adenzintrifosfat = adenosine triphosphate

INFLUENCE OF OXYGEN STARVATION ON INTEROCEPTIVE REFLEXES
(FEMORAL-ARTERY CHEMORECEPTORS)

R.Z. Pozdnyakova

(Frunze)

It has been established from the time of Heimans that the leading role in maintaining a stable oxygen partial pressure in the blood must be ascribed to the chemoreceptors in the carotid and aortal reflexogenic zones, which possess exceedingly high sensitivity to changes in the organism's internal environment.

It has been shown subsequently by the work of Soviet scientists (Bykov, Chernigovskiy, Galkin et al.) and foreign authors that chemoreceptors situated outside the carotid and aortal zones also respond to changes in oxygen partial pressure, and especially changes in the pH of the arterial blood.

If we consider the participation of peripheral-vessel and tissue chemoreceptors and their role in maintaining homeostasis, then the question naturally arises as to whether their excitability under the conditions of oxygen starvation changes, and if it does, then how it does. Clarification of this question acquires even greater significance as a result of the fact that there has been almost no studies devoted to changes in the excitability of the peripheral-vessel chemoreceptors under the conditions of oxygen insufficiency, nor many works concerned with the reflex response on the part of these interoceptors in hypoxia. The present paper is devoted to clarification of these questions.

We studied interoceptive reflexes from the chemoreceptors of the

femoral artery under the conditions of transitory and more chronic hypoxic hypoxia and under the conditions of local circulatory oxygen insufficiency. The criterion on the basis of which we judged the excitability of the femoral-artery chemoreceptors under the conditions of oxygen insufficiency was the change, during hypoxia, in the interoceptive reflexes — the change in the threshold concentration of lactic acid solution whose injection into the femoral artery of a dog would produce a reflex reaction of the arterial pressure and respiration.

Concurrently with registration of the interoceptive reflexes under normal conditions and when the dogs were in hypoxic hypoxia, we investigated such indicators as the oxygen and carbon dioxide contents of the arterial blood and the blood pH.

In all of the experiments that we set up, transitory hypoxic hypoxia was induced by use of a mixture of nitrogen with 10% of oxygen. The animal breathed this mixture for 20-25 minutes. The influence of more protracted hypoxic hypoxia (one to three days) on the interoceptive reflexes was studied in the mountains at an altitude of 3200 m. Local circulatory hypoxia was induced by tourniqueting the femoral artery for various times (from 10 to 90 minutes).

Lactic acids in solution concentrations ranging from 0.001 to 1% was used as the stimulus. It was injected into the femoral artery in the central direction, against the blood flow, in an amount figured to produce 0.5 ml per 1 kg of the animal's weight. In the experiments with circulatory hypoxia, the lactic acid solution was always administered in 2-ml quantities.

The experiments were run on dogs that had been anesthetized by intravenous injection of sodium thiopental.

Under the conditions of transitory hypoxic hypoxia induced by breathing a mixture of nitrogen with 10% of oxygen, the oxygen content in the arterial blood of the experimental dogs dropped from the normal value of 17.57 to 14.51% by volume, while the carbon dioxide content diminished correspondingly from 31.27 to 27.93% by volume. The actual reaction of the blood changed in the direction of alkalosis. We detected a drop in the threshold concentration of lactic acid solution: thus, while the threshold concentration had varied in the range of 0.05-0.1%

in the acid solution in dogs with normal pO_2 , this threshold solution concentration, that which produced a reaction on the part of the arterial pressure and respiration, was lower, varying from 0.001-0.01% in the solution during the acute hypoxia. In response to stimulation of the chemoreceptors, the arterial pressure dropped in all dogs, both under normal conditions and during short-term hypoxic hypoxia. Respiration showed changes in far from all cases on stimulation of the femoral-artery chemoreceptors, and these variations consisted in a decrease in amplitude and frequency of the respiratory movements.

For the sake of clarity, we present one of the experiments of this series (Fig. 1). As will be seen from Fig. 1, the normal threshold concentration, whose injection into the femoral artery produced a reflex lowering of the arterial pressure, was a 0.05% acid solution. Against the background of developed hypoxia, a similar reaction was noted on administration of a 0.01% solution of the acid. Then the pressure dropped to 18 mm Hg. The changes in respiration were much less distinctly manifest.

In experiments conducted in the mountains at an altitude of 3200 m, the hypoxemic state of the animal during the first three days of the sojourn there, just as with transitory oxygen starvation, was characterized by a drop in the oxygen content of the arterial blood (from 18.01 to 15.24% by volume), by a decrease in the carbon dioxide content (from 37.14 to 31.66% by volume, and by a pH shift in the blood in the direction of alkalosis.

The interoceptive reflexes were also found to have been intensified against this background of an internal medium modified by hypoxia. In the control dogs (at Frunze), the threshold concentration that produced the initial changes in pressure and respiration varied from 0.1-0.5% of the acid in the solution. At the 3200-meter altitude, the same reaction

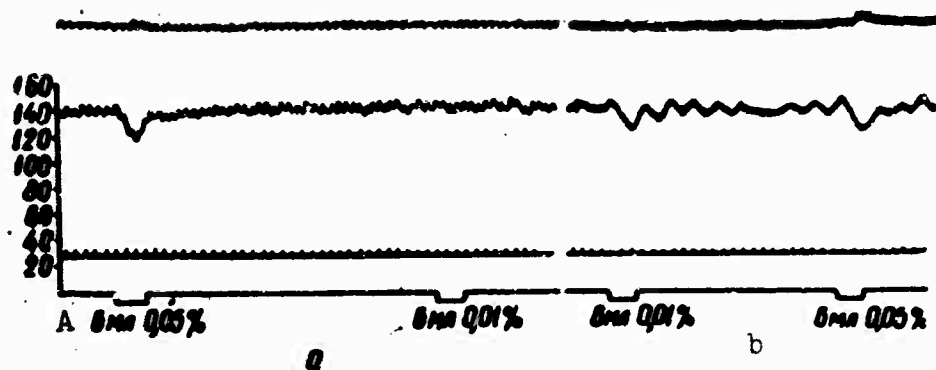


Fig. 1. Experiment run under conditions of experimentally produced hypoxia (breathing of a mixture of nitrogen with 10% of oxygen). Change in arterial pressure and respiration on administration of a stimulant into the femoral artery of a dog. a) Under normal conditions; b) under the conditions of hypoxia. Curves (from top to bottom): respiration, arterial pressure, time marker, stimulant marker. A) 6 ml of 0.05% [solution].

was observed in unacclimatized dogs on administration of 0.001-0.005% solutions of lactic acid into the femoral artery. On stimulation of the chemoreceptors, under both normal and hypoxic conditions, the arterial pressure diminished in almost all of the dogs. The respiratory changes were manifested in decreased amplitude of the respiratory movements, but the magnitude of these changes was considerably greater in hypoxia than under normal conditions.

Figure 2 reflects one of the experiments of this series. In the control dog, the threshold concentration was found to be 0.01% of acid in the solution, and its injection into the femoral artery lowered the arterial pressure by 12 mm Hg. In an unacclimatized dog taken to the mountains, the analogous reaction was noted on injection of a 0.005% solution of the acid. Here the arterial pressure dropped by 24 mm Hg. The respiratory changes were also distinctly manifest.

Thus, our experiments with transitory and more protracted (one to three days) hypoxic hypoxia produced quite similar results, which suggest that a moderate degree of hypoxia strengthens the arterial-pressure and respiration reflex reaction from the chemoreceptors of the peripheral vessel (femoral artery). At the altitude of 3200 m, however, this

strengthening was more distinct than during hypoxia induced by inhalation of a gas mixture with 10% oxygen. To judge from the drop in oxygen content in the arterial blood of the dogs, this may probably be accounted for by the milder degree of hypoxia in the mountains. It would also appear that we may not exclude the action of other factors in the high mountains: temperature, ultraviolet radiation and others, which might possibly contributed to amplification of the reflex reaction.

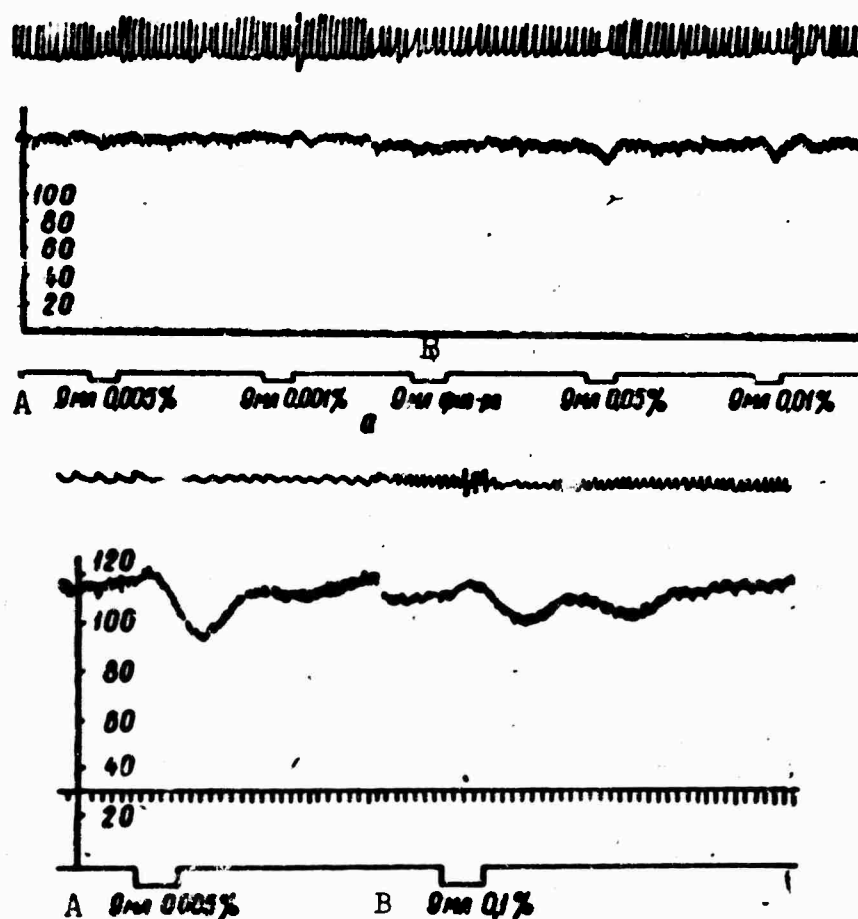


Fig. 2. Change in arterial pressure and respiration on injection of a stimulant into the femoral artery of a dog. a) At the town of Frunze; b) in the mountains, at an altitude of 3200 m above sea level. Legend same as in Fig. 1. A) 9 ml of 0.005% [acid solution]; B) 9 ml of physiological solution.

To eliminate the influence of oxygen starvation on the cortical terminal of the interoceptive analyzer (as arises in experiments with hypoxic hypoxia), while still maintaining the effect of oxygen insufficiency at its periphery, we set up a series of experiments with local circulatory hypoxia. We chose ischemic hypoxia as a means of inducing local oxygen starvation, reasoning that we could, in these experiments, ascertain not only the influence of the oxygen-insufficiency factor directly on

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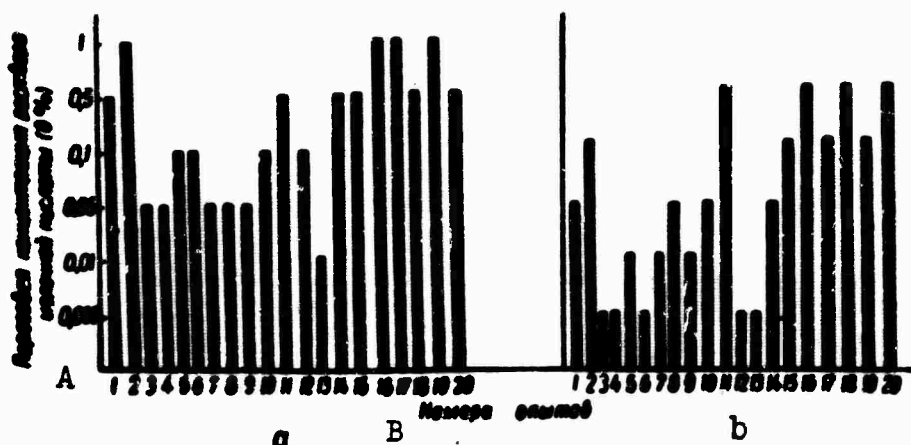


Fig. 3. Threshold concentrations of lactic acid solution, producing reflexes from vascular chemoreceptors. a) Under normal conditions; b) under the conditions of transitory circulatory hypoxia induced by shutting off blood supply to the extremity of the dog for 10-15 minutes. A) Threshold concentration of lactic acid solution (in %); B) experiment No.

the chemoreceptors, but also answer the question as to whether parallelism exists in the action of different forms of hypoxia (hypoxic and circulatory) on the interoceptive analyzer.

Experiments performed under the conditions of local oxygen insufficiency on intact and isolated dog extremities showed that in short-term hypoxia (10-15 min), the threshold concentration of lactic acid solution was depressed as compared with data obtained while the extremity was receiving its normal blood supply and in cases when the stimulant was administered immediately (within 2-3 min) after application of a temporary clamp to the femoral artery.

Figure 3 reflects the lowering of the threshold lactic acid concentrations under the conditions of transitory circulatory hypoxia. As will be seen from Fig. 3, the threshold concentration varied from 1-0.1% of acid in the solution when the extremity was receiving its normal blood supply, while under the conditions of transitory (10-15 min) circulatory hypoxia, the range of variation of the threshold concentration was 0.5-0.005% of the acid in solution.

Aggravation of the hypoxia, induced by prolonging the time during which the blood supply was interrupted to 60-90 min, resulted in total

suppression of the interoceptive reflexes from the chemoreceptors of the main vessel in the extremity. The reflex nature of the response reactions obtained in our experiments is demonstrated by the short latent period and by the absence of changes in arterial pressure and respiration on injection of the stimulant into the femoral artery when the extremity had first been denervated (Fig. 4).

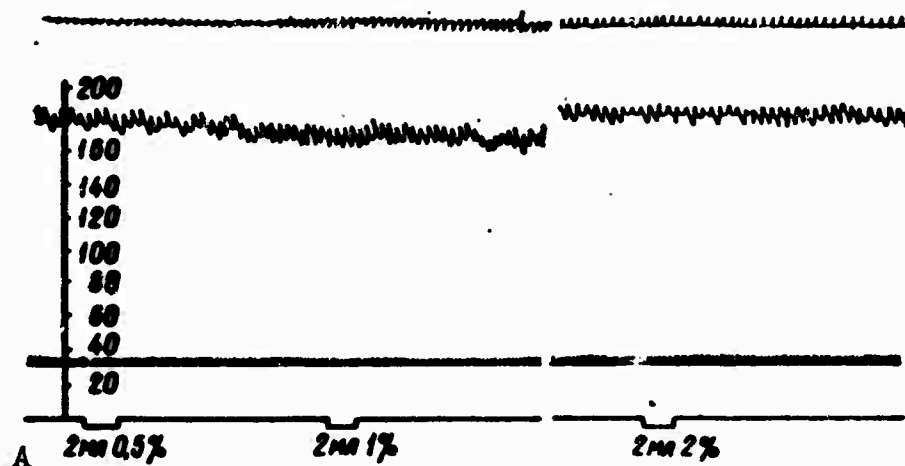


Fig. 4. Experiment indicating the absence of reflex reaction of arterial pressure and respiration on stimulation of femoral artery chemoreceptors in previously denervated dog extremity. A) 2 ml of 0.5% [acid solution].

The clearest proof of the reflex nature of these response reactions is found in experiments with crossed-over blood circulation, in which the isolated extremity of a dog, retaining only the nerve connections to the organism of the host, was switched into the circulatory system of a donor dog. Stimulant injected into the femoral artery of the isolated extremity of the recipient dog produced a change in its respiration and pressure, while no effect was observed in the donor dog on such administration.

On the basis of the studies made, therefore, we may arrive at the conclusion that under the conditions of transitory and, accordingly, mild hypoxic and circulatory hypoxia, the interoceptive reflexes from the chemoreceptors of the peripheral vessels are intensified, and that an increase in the excitability of the peripheral end of the interocep-

tive analyzer is responsible for this. This does not, however, exclude the possibility that under the same conditions the excitability of the central part of the interoceptive analyzer is also increased.

DEVELOPMENT OF EXPERIMENTAL MYOCARDIAL INFARCT IN ARTERIAL HYPOTONIA

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(Kiev)

The question as to the state of the coronary blood circulation in chronic arterial hypertonia has been given altogether inadequate study. Occasional data in the literature concern studies of the coronary circulation in acute experimental hypotonia (Eckenhoffer et al., 1948; Heckel, Sanchetta and Kleinermann, 1956; Lin et al., 1956). Of particular interest are the question as to the state of the heart's blood supply in chronic arterial hypotonia and the closely related question as to the features of the course of experimentally induced focal ischemia of the myocardium in chronic arterial hypotonia.

Our investigations were performed on rabbits in which arterial hypertonia had been induced by removal of the adrenal glands. Together with the stable decrease in arterial pressure — chronic arterial hypertonia — the animals showed characteristic changes in the electrocardiogram and shifts in the electrolytic composition of the blood. Examination of the electrocardiograms of animals with experimental arterial hypotonia brought out a distinct tendency toward slackening of the cardiac rhythm and prolongation of the heart's electrical systole; transitory changes in the T-wave were observed (two phased configuration with negative phase first), together with a sharpening and narrowing of the base of the T₁ and T₅ waves and changes in the voltage of the R-wave.

These changes in the waves and intervals of the electrocardiogram

could be treated as a reflection of changes in the exchange of electrolytes in the myocardium. Studies conducted in connection with this to determine the potassium and sodium contents in the blood of experimental animals (M.N. Levchenko and N.G. Kochemasova) brought to light a considerable increase in potassium content coupled with a decrease in the sodium content of the blood of animals with experimental suprarenal hypotonia (see Table). In some of the hypertonic rabbits, it was possible to detect (from the electrocardiogram) signs of focal damage to the myocardium.

Change in Content of Sodium and Potassium in Blood Serum of Rabbits with Experimental Hypertonia

1 № кролика	2 До удаления надпочечников		5 После удаления надпочечников	
	3 Na, мэкв/л	4 K, мэкв/л	3 Na, мэкв/л	4 K, мэкв/л
12	133.9	3.4	128.2	3.7
20	152.1	4.0	117.8	4.8
58	148.2	4.4	131.7	5.0
59	158.6	3.9	152.1	5.0
65	152.6	3.8	148.6	4.5
66	—	4.6	—	5.4
67	—	4.6	—	4.7
68	—	4.5	—	6.3
69	—	4.4	—	4.4
70	—	3.9	—	7.6
72	165.0	4.7	144.3	5.0
73	152.1	3.9	140.0	5.8
75	155.5	4.3	143.4	5.1
78	155.0	4.5	154.3	5.2
79	168.2	5.2	133.0	6.9
82	156.5	5.2	150.0	7.5
84	141.2	4.3	136.9	5.2
85	154.3	4.1	136.9	5.6
90	141.2	4.6	139.1	5.0
96	145.2	4.3	136.9	4.7
97	161.6	4.1	136.8	4.4
104	144.3	4.6	141.2	5.6
Среднее 6	153.2	4.3	139.5	5.3

1) Rabbit No.; 2) before removal of suprarenals; 3) Na, meq/liter; 4) K, meq/liter; 5) after removal of suprarenals; 6) average.

In a second series of experiments, 15 rabbits with experimental hypotonia showed focal disturbance to the blood supply of the myocardium. Closing the lumen of a coronary artery in animals with chronic arterial

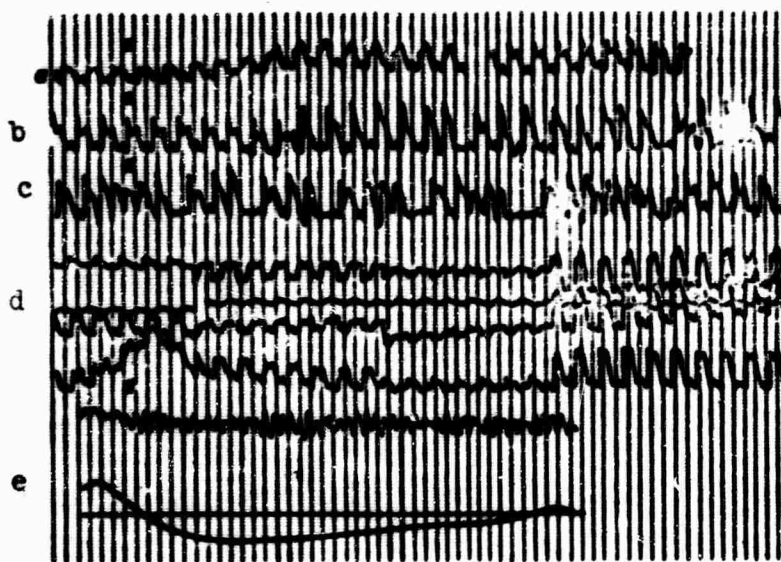


Fig. 7 Dynamics of electrocardiogram changes in rabbit No. 65 with experimental hypotonia after tying off a branch of the coronary artery. Experiment of 3 February 1961.

One minute (a) after closing the lumen of a branch of the coronary artery, we note a rise in the S-T segment, and this increases progressively (b). In the fourth minute (c), we observe polytopic extrasystololy, which goes over into short attacks of ventricular fibrillation. (To provide a more complete characterization of the changes observed, we present the electrocardiogram in the standard, amplified extremity and preordial derivations (d). The EKG changes indicate the presence of an extensive ischemic focus encompassing the anterior, posterior and lateral walls of the heart. After 9 minutes, the ventricular fibrillation has developed and death of the animal follows (e).

hypertonia was accompanied by a sharp drop in arterial pressure, changes in the electrocardiogram, and a higher mortality rate among the animals in the first few minutes after closure of the coronary lumen, as compared to the control group.

The electrocardiogram changes were characterized by a severe disturbance to the cardiac rhythm - extrasystolic arrhythmia of a polytopic type, usually against a background of diminishing pulse rate. Attacks of paroxysmal tachycardia were noted frequently, and frequently terminated in ventricular fibrillation and death of the animals. A sharp rise in the RS-T segment, inversion of the QRS complex, and prolongation of the electrical systole were observed. The Q-wave appeared much earlier in animals with hypotension than in the control animals with normal tone (Fig. 7).

The electrocardiographic investigations indicated that focal ischemia induced against a background of chronic arterial hypertonia causes the development of a more extensive necrotic focus and a broader zone of injury and hypoxia in the myocardium.

Morphological examinations of the hearts of these animals performed in the pathological anatomy department of the A.A. Bogomolets Kiev Medical Institute (department director Professor Ye.I. Chaika) by Yu.S. Kozachuk, confirmed this conclusion fully. In experimental myocardial infarct in animals with arterial hypotonia, a zone of extensive extravasation can be observed even macroscopically in the infarcted region, with softening and acute aneurysmatic dilatations of the wall in fresh cases. Morphological examination of the hearts of rabbits with experimental hypotonia showed a collaptoid state of the venous, arterial and capillary systems with distinct paresis of the vessels, which were severely distended and overfilled with blood. Also noted were extensive perivascular extravasations, sometimes in the form of layered hematomas, only in the zone and around the periphery of the ischemic focus distal from the ligature, but frequently also above the ligature. It was possible to note the appearance of so-called "lakes" of hemostases and lymphostases, stases with hemosiderin, which had formed, in all probability, prior to ligature (Fig. 2). These changes contributed to the graver development and course of the myocardial infarct.

On histological and histochemical examination, the disappearance of glycogen was noted in the ischemic zones, and intensive leucocytic infiltration was detected in the marginal zones (Fig. 3). Subsequent observations here included nuclear fragments, a macrophagic reaction with phagocytosis of the necrotized muscles, and basophilia of the intermediate substance.

All infarcted zones showed profound derangement of blood circulation



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Fig. 2. Rabbit No. 75. Experiment of 30 October 1961. Death 9 minutes after closing the lumen of the coronary-artery branch. The phenomena of stasis with formation of hemosiderin in the myocardial vessel outside the necrotic focus. Stain: hematoxylin-eosin. Magnification 200x.

Fig. 3. Rabbit No. 67. Experiment of 16 November 1961. Death two days after closing lumen of coronary artery branch. Leucocytic infiltration into boundary zone of necrosis. Edema of the myocardium outside the infarction focus. Stain: hematoxylin-eosin. Magnification 100x.

with distinct stases, and sometimes thromboses; severe tissue edema as a manifestation of the increased permeability of the vascular walls; subsequently, basophilia and insipient desmolysis of the connective tissue.

The more severe course that we observed in experimental myocardial infarct during arterial hypotonia can be accounted for by a number of factors. It would appear that one of the important aggravating factors is the disturbance to the permeability of the vessel walls, noted in experimental arterial hypertonia by M.F. Sirotina, a staff worker in our

laboratory (1962). The results of these functional studies are in agreement with the conclusions of Yu.S. Kozachuk, which were drawn on the basis of morphological examinations.

The more serious disturbances to cardiac activity in myocardial infarct in animals with arterial hypertonia can also be accounted for in terms of changes in the electrolytic composition of the blood and tissues — changes characteristic in suprarenal hypertonia.

The more distinct changes in the electrocardiogram during focal ischemia and necrosis of the myocardium against a background of chronic arterial hypotonia would appear to be due to the disturbed conductivity and the appearance of heterotopic foci of excitation in the ischemic zone of the myocardium. These changes may be due to a considerable extent to disturbance of the potassium and sodium balance in the cardiac muscle. The disturbance of the blood's electrolytic composition has been established by our studies. Investigations are being conducted at the present time into the contents of electrolytes in the myocardium in experimental focal myocardial ischemia of healthy rabbits and rabbits with experimental arterial hypotonia.

The experimental investigations carried out produced new proofs of the importance of deviations in vascular permeability and electrolyte exchange in the development and outcome of ischemic necroses of the myocardium in general and during arterial hypotonia in particular.

EXPERIMENTAL INVESTIGATIONS OF HEMODYNAMICS IN MYOCARDIAL INFARCT

M.M. Povzhitkov

(Kiev)

Study of the pathogenesis of hemodynamic changes during myocardial infarct have attracted the attention of numerous investigators in recent years. The sharp drop in the arterial pressure level that is frequently observed in acute myocardial infarct may be a factor aggravating the course and prognosis of the disorder. The question as to the mechanism of these changes had recently been an object of discussion among researchers. Some authors maintain that shock sets in in acute infarct as a result of acute cardiac insufficiency (Wiggers, 1945; Pisha and Gammmer, 1960; A.V. Vinogradov, 1962, and others); others conclude that it is a result of acute vascular insufficiency (Shimert, 1952, and others). Few experimental studies have been made in this field.

Investigations of hemodynamic changes during experimental myocardial infarct, which most of the authors have conducted with the chest open, cannot be regarded as satisfactory, since opening the rib cage in itself exerts considerable influence on the hemodynamics. Moreover, it has been shown (Ovsyshcher, 1959) that exposure of the heart causes substantial changes in the cardiac activity as a result of cooling. It is understandable that, despite the difference between the conditions of experimental research and clinical work, study of the pathogenesis of myocardial infarct under the conditions of chronic experiment can bring investigators closer to understanding of certain cardinal problems in the pathogenesises of hemodynamic disturbances in myocardial infarct, dis-

turbances that arise during the first few minutes and hours of its onset.

We investigated certain hemodynamic indicators in experimental myocardial infarct in chronic experiments on 15 dogs.

METHODS

Dogs weighing 15-30 kg underwent surgery for application of a provisional sliding loop of our design at one-third of the way down the descending branch of the left coronary artery. The chest was then sutured

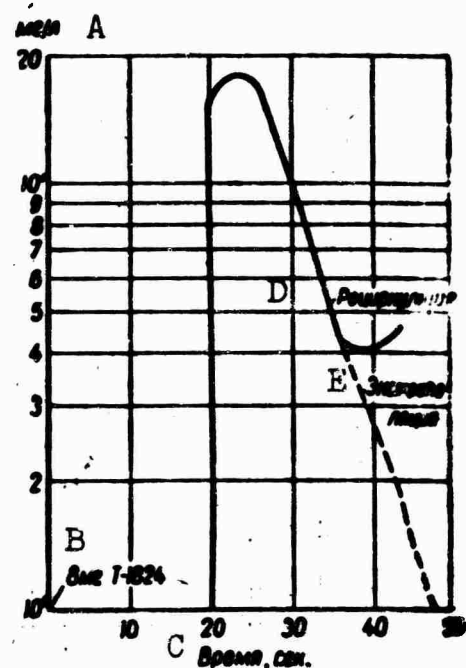


Fig. 1. T-1824 dilution curve for the dog Nayda before closure of lumen of left coronary artery. The arrow indicates the instant at which the dye was injected. A) mg/liter; B) 8 mg of T-1824; C) time, sec; D) recirculation; E) extrapolation.

layer by layer, air was evacuated from the pleural cavity, and the ends of the ligature, which were brought out to the outside, were imbedded under the skin on glass beads. The lumen of the coronary artery was blacked 7-14 days after the operation, when the changes associated with the thoracotomy had disappeared. The basic criterion for judging this was the return of the basic electrocardiographic, ballistocardiographic, hemodynamic and hematological indices to their initial values. In some of the experiments, the coronary arteries were obstructed by injection of mercury into them through a catheter passed to the orifice of the aorta from the left carotid artery. Closure of the coronary-artery lumen was preceded by study of electrocardiogram (EKG) in the standard, amplified-extremity and precordial derivations according to Wilson, the ballistocardiogram (BKG) (M.M. Povzhitkov, 1961), the average arterial pressure

(A.D._{sr}) and respiration. Also determined were the minute (MO) and stroke (UO) volumes of the heart, the cardiac index (SI), the mass of circulating blood (MTsK), the total peripheral resistance (OPS), the blood stream time and blood return time and the hematocrit index. The MO was determined by the Hamilton dye method (1932) in a modification for experimental research purposes. A one-percent solution of Evans' blue (T-1824) was prepared. A calibration curve was plotted from 10 points with dye concentrations in the plasma ranging from to 10 mg per

1 liter, using an FEK "M" photoelectrocalorimeter. The dogs' femoral arteries and veins were prepared under morphine-chloralose anesthesia. A polyethylene catheter 8-10 cm long was inserted into the vein; a plexiglas cuvette open at both ends was inserted in the artery after prior heparinization of the animal with a cannula. The dye dilution curve was registered using a [Soviet] O-57 oxyhemometer, whose signal, after amplification by a direct-current amplifier, was fed to a registering device in the form of an electromagnetic ink-writer. The oxyhemometer's photoelectric sensor was pushed on over the cuvette, which had recesses to provide for securing it.

Thus, the method that we used was that of absolute oxyhemometry. Before the dye was injected, the animal was switched to breathing pure oxygen to exclude spontaneous changes in the oxygen saturation of the blood, which depends on respiration and other factors. The dye was injected quickly into the vein in an amount corresponding to 0.5 mg per 1 kg of the animal's weight. After 5-10 minutes had elapsed after administration of the dye, 5 or 10 ml of blood were drawn from the animal for determination of the MTSK and calibration of the dye dilution curve. The dye concentration (in mg/liter of blood) was determined on the saturation curve each second until the recirculation wave appeared, and the data obtained were transferred to semilogarithmic paper (Fig. 1). The descending branch of the dilution curve was extrapolated to the zero line to determine the time required for the full blood circuit. The MO was determined by Hamilton's short formula: $MO = I \cdot 60 / S$, where I is the amount of dye administered and S is the sum of the concentrations of the dye during its first circuit. The OPS was determined by the formula $OPS = P \cdot 1332 / D$ dynes·sec·cm⁻⁵, where P is the average arterial pressure in mm Hg, D is the heart volume in ml/sec, and 1332 is a coefficient for converting relative resistance units into absolute units. The surface area of the animal's body was calculated first for determination of the cardiac index (SI).

EXPERIMENTAL RESULTS

In most of the experiments that we performed, a drop in arterial pressure was noted after the lumen of the coronary artery had been closed. In some of the experiments, the arterial pressure recovered after a transitory (1-2 minutes) drop and even exceeded the initial level by

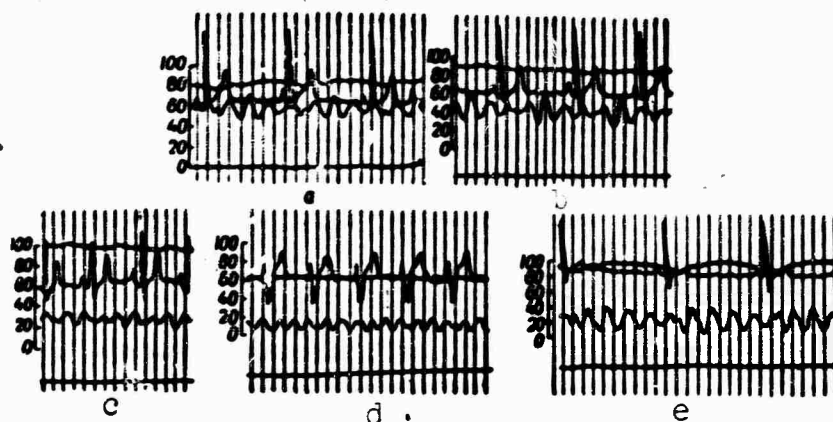


Fig. 2. Changes in arterial pressure, EKG, BKG and respiration in the dog Strelka in experimental myocardial infarct. a) Before closing lumen of descending branch of left coronary artery; b) after 1 minute; c) after 2 hours; d) after 24 hours; e) after 14 days.

10-20 mm Hg. At the same time, the BKG showed changes suggesting disturbances to the contractile functions of the myocardium: fused H_I waves and splitting of the J-wave (V.Dok, G. and R. Mandel'baum, 1953; A.V. Mareyev, 1961, and others). The MO dropped considerably and the blood flow and circulation times increased. The OPS rose substantially, while the MTsK and the hematocrit number did not change. On the EKG, we noted only an insignificant rise in the RS-T segment in the precordial leads. Distinct changes in the EKG were observed after 24 hours: polytopic extrasystoly, displacement of the RS-T segment, disturbances to the auriculoventricular and interventricular conductivity. The BKG showed a drop in the amplitude of all waves, and particularly the waves of the systolic complex; splitting and twining of the J-wave were more sharply manifest. The arterial pressure was found to be subnormal by a considerable margin. The MO remained low, and the blood flow and circulation times increased. The OPS decreased, although the initial values were not attained. The MTsK and the hematocrit index showed no substantial change.

After 14 days had elapsed since closure of the coronary artery lumen, we noted a tendency toward normalization of the EKG, BKG, MO, UO and the other indices that we were studying. Among all of the indicators,

the changes in the MO and BKG were most persistent (Fig. 2).

It should be noted that 24 hours after obstruction of the coronary artery, when the changes in the cardiac muscle were most strongly manifest, we observed a certain recovery of the MO, obviously due to mobilization of reserve capabilities in the intact divisions of the myocardium. In those cases in which compensation of the cardiac contractile insufficiency took place by way of tachycardia, the blood flow and circulation times were found to be reduced.

The table presents the results of study of certain hemodynamic indices. It will be seen from the table that in the first 30 minutes after the lumen of the coronary branch had been closed, the MO decreased by an average of 39%, and was down 24.1% after 24 hours and 26.1% after 14 days; the decrease in the UO is considerably more pronounced - by 47, 50.5 and 3.9%, respectively. The blood flow and circulation times increased during the first 30 minutes by 20 and 32%, on the average, but after 24 hours in those experiments in which considerable tachycardia was noted, this time even became shorter (experiments No. 18 and 23). The total peripheral resistance was found to be elevated at these same points in time for all animals, with the exception of experiment No. 22, in which a sharp drop in arterial pressure was observed in the dog after obstruction of the coronary artery.

DISCUSSION OF EXPERIMENTAL RESULTS

The hemodynamic changes in experimental myocardial infarct present a rather distinctive pattern. Immediately after obstruction of the coronary artery, we observe disturbances in the contractile function of the myocardium, manifest in a drop in the MO and UO and characteristic changes in the BKG. Analysis of the interrelationships between the average arterial pressure (AD_{sr}), MO and OPS, specifically $AD_{sr} = MO \cdot OPS$, indicates that the level of arterial pressure depends on the functional

Variation of hemodynamic Indicators in Experimental Myocardial Infarct

a	b	C MO (s)			E VO (s)			I AUK (s)			G PPM (s)																		
		A	B	C	A	B	C	A	B	C	A	B	C																
18	Tobuk h	1.81	1.6	-11.0	1.9	1.3	1.76	-4.4	23.2	21.8	15.0	11.1	60.8	28.3	0	1.1	1.1	0	1.0	-9.1	1.0	9.1	6.7	3.0	1.7				
22	Uzayv l	2.27	1.13	-37.0	1.1	-23.0			11.0	8.1	26.1	9.1	-11.6			1.5	1.5	0	1.5	0	0	20.1	20.0	1.70	+161.5	62	-1.7		
20	Medved' j	5.5	3.5	-61	5.2	-5.5			50.9	42.1	36.1	36.1	-29.1			2.3	2.3	0	2.0	11.3	0	106	108	0	111	133.3			
23	Hadia k	2.8	2.0	-28.6	2.1	-13.2	2.61	6.8	38.8	13.8	61.5	18.2	-53.1			2.2	2.2	0	2.3	4.5	2.1	-4.6	72	111	100.0	1.3	67.5	68	-5.6
19	Dzhek l	2.3	1.5	-37.0	2.2	-4.1	2.25	2.2	19.1	10.0	17.7	13.7	28.3			1.3	1.3	-5.2	1.3	-5.2	1.5	1.9	16.8	16.8	16.8	33.3	96	-20.0	
16	Peestryu m	2.7	1.95	69.8	1.1	-18.2			33.7	8.8	73.9	8.7	71.2			1.3	1.2	7.7	1.0	-23.1		40	120	50.0	166	300.0	140	+75.0	
21	Aza n	1.2	2.2	1.6	1.86	55.8	2.11	-42.7	35.0	18.3	-17.7	10.3	70.6			1.3	1.2	-1.5	1.23	-8.3	1.23	8.3	120	120	0	180	+50.0	81	-30.0
Средние показатели O team		3.08	1.88	-39.0	2.81	-7.8	2.26	-26.7	39.9	16.4	-47.0	15.3	50.3			1.58	1.52	-3.8	1.48	-6.4	1.45	8.3	109	123	12.8	157	+44.0	97	-11.0

a	b	P PPM (s)			Q PPM (s)			R PPM (s)			S PPM (s)																		
		A	B	C	A	B	C	A	B	C	A	B	C																
18	Tobuk h	13.0	11.0	17.7	9.9	30.8	13.0	13.0	21.0	22.5	7.1	15.0	-25.6			100	125	+25.0	105	+5.0	105	4.32	6256	+43.7	437	+0.4	4656	+2.3	
22	Uzayv l	8.5	16.3	191.0	11.0	61.7			90.5	39.0	46.3	31.0	151.2			150	85	-43.4	90	40.0		283	4737	-10.0	364	-32.0			
20	Medved' j	19.0	10.0	0	15.0	1.94			17.0	19.0	11.7	25.0	17.0			105	125	+19.0	100	-4.8		13.6	2889	+86.0	133	+0.8			
23	Hadia k	21.0	21.0	0	16.0	-21.0	22.1	1.7	27.0	31.0	25.0	35.0	-7.4			138	130	-5.8	120	-13.0	110	30.3	3942	1200	+31.0	394	+0.1	3368	-14.6
19	Dzhek l	9.0	11.0	+23.0	8.0	-11.2	11.3	61.0	19.0	24.0	21.0	11.8	21.7			90	100	+11.0	90	0	100	11.0	3104	1536	+78.0	3208	+3.3	3362	+14.4
16	Peestryu m	15.0	19.5	30.6	19.0	26.6			22.0	31.0	51.5	24.0	12.2			24.5	+29.0	-13.0	80	-30.5	105	7.7	3428	4048	+76.5	4633	+35.2		
21	Aza n	7.0	9.0	128.5	9.0	28.5	11.0	-57.1	13.0	23.0	66.6	18.0	120.0			20.0	+33.3	110	100	-9.0	70	22.3	2263	2839	+59.4	3007	+31.7	2855	+16.2
Средние показатели O team		11.9	11.3	120.1	12.8	17.5	15.8	-32.7	20.2	23.8	32.6	22.3	10.3			115	109	-5.3	93	-19.2	99	14.0	1416	4654	+42.0	3477	+1.7	3807	+2.6

Note: A) 30 minutes after closure of the lumen of the left coronary artery, in absolute numbers and in percentages of initial indices; B) after 24 hours; C) after 14 days. Other nomenclature is explained in the text.

a) Experiment No.; b) name of dog; c) MO (in liters); d) normal; e) UC (in cm²); f) MTsK (in liters); g) cardiac rhythm (min⁻¹); h) Tobik; i) Dzheim; j) Medved'; k) Nayda; l) Dzhek; m) Peestryu; n) Aza; o) averages; p) blood flow time (in sec); q) blood circulation time (in sec); r) arterial pressure (average) (in mm HG); s) OPS (in dynes·sec·cm⁻⁵);

state of the myocardium and on the OPS. In those cases where a decrease in the MO is covered by a considerable increase in the OPS, no drop in arterial pressure is observed (Dzhil'bert, 1954; Fridberg, 1961).

We cannot bring ourselves to agree with those authors who regard the disturbances in the contractile capability of the heart as the cause of shock in acute myocardial infarct (Wiggers, 1945, and others). The contractile function of the myocardium is always disturbed as a result of obstruction of a coronary artery, but the shock pattern does not de-

velop in all cases, obviously depending to a considerable degree on the state of the OPS. A sharp drop in the OPS is an important factor in the development of hypertonia subsequent to infarct.

As we know, the OPS level is determined by the tonic state of vessels in various regions of the body; in some of the vascular basins, vasoconstriction may prevail, while in others vasodilatation predominates. In most cases of post-infarct shock, we note signs of peripheral vasoconstriction, although this may be accompanied by a considerable decrease in the vascular resistance of vessels in the internal organs and, as a result, the OPS is found to be low. This point has been stressed by a number of authors (Fridburg, 1961; A.V. Binogradov, 1962, and others).

In our studies of regional vascular peripheral resistance, using the resistometric technique in experimental myocardial infarct of cats, it was possible to show that the principal role in maintaining the arterial pressure level is to be ascribed to the state of peripheral resistance of the visceral blood vessels. A rise in the resistance of the peripheral vessels is observed both in cases of shock and in cases where shock does not occur. Kuhn et al. (1960) showed that if the resistance to blood flow is increased by introducing a balloon into the descending aorta of a dog suffering from shock increased by massive embolism of the coronary arteries, the result is a persistent increase in arterial pressure despite the decrease in MO. The use of medication of the mesatone or levarterenol type in myocardial infarct has been found highly effective, both in experimental studies (A.V. Vinogradov, 1962) and in the clinic for urgent therapy of acute myocardial infarct. This provides circumstantial confirmation of the importance of increasing the systemic arterial resistance to compensate the cardiac contractile insufficiency, and also assist in mapping out possible paths of therapeutic intervention.

CONCLUSIONS

1. An increase in the minute and stroke volumes of the heart and in the blood flow and circulation times, together with changes in the ballistocardiogram during the first few minutes after obstruction of a coronary artery indicate early disturbance to the myocardium contractile function.

2. A considerable drop in the vascular tone of the internal organs in experimental myocardial infarct may cause a drop in general peripheral resistance, and this would appear to be one of the important factors in the development of post-infarct shock.

3. The arterial pressure level in myocardial infarct depends on the relationship between the changes in heart minute volume and the level of general peripheral resistance. Changes in the general peripheral resistance are, in turn, the result of changes, frequently operating at cross purposes, in the peripheral resistance in the various vascular basins.

4. Within certain limits, the rise in general peripheral resistance may be regarded as a compensatory reaction of the organism whose purpose is to improve blood supply to vitally important organs.

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[List of Transliterated Symbols]

- 335 $AD_{cn} = AD_{sr}$ = arterial'noye davleniye, sredneye = arterial
pressure, average
- 335 $MO = MO$ = minutnyy ob"yem = minute volume
- 335 $yo = UO$ = udarnyy ob"yem = stroke volume
- 335 $CI = SI$ = serdechnyy ideks = cardiac index
- 335 $MIK = MTsK$ = massa tsirkuliruyushchey krovi = mass of circula-
ting blood

335 ОПС = OPS = obshcheye perifericheskoye soprotivleniye =
general peripheral resistance

336 ФЕК = FEK = fotoelektrokolorimetr = photoelectrocalorimeter

OXYGEN STARVATION AND THE MECHANISMS COMPENSATING IT IN CONGENITAL
HEART DEFECTS OF THE BLUE AND PALLID TYPES

L.L. Shik

(Moscow)

Of great importance in comprehensive study of the oxygen-starvation problem are comparative investigations of the mechanisms by which it arises and is compensated in various forms of pathology.

This assists in bringing out the specific peculiarities of the various types of hypoxic states and verifying the applicability of relationships established in study of certain forms of oxygen starvation to other forms. In view of these considerations, the present report examines the problem of the origin and compensation of oxygen starvation in certain forms of congenital cardiac defect.

Among the numerous and staggeringly varied types of congenital heart defects, we have selected those most frequently encountered - the pallid defects (persistent ductus arteriosus Botalli, defect in interatrial septum, defect in interventricular septum) and blue defects (Fallot's tetrad, i.e., a combination of intraventricular septal defect with stenosis of the exit passage from the right ventricle). All of these defects represent deviations from the basic circulatory scheme of man and the higher animals.

In defects of the pallid type, arterial blood from the greater circulation (aorta or the left divisions of the heart) passes through an abnormal orifice (communication) directly into the pulmonary circulation (into the pulmonary artery or the right divisions of the heart), where

it is mixed with venous blood. This overflow of blood from left to right has a consequence that the blood minute volume flowing through the pulmonary capillaries exceeds (occasionally by several times) the minute volume of blood passing through the capillaries of the greater circulation. The reversed situation arises in blue-type cardiac defects: thus, in Fallot's tetrad, part of the blood from the right ventricle passes, due to the stenosis of its exit channel, through the defect into the exit channel of the left ventricle. As a result, mixed blood (of both venous and arterial composition) enters the aorta, and in greater quantities than it does the pulmonary artery. The minute volume of the greater circulation (MOB) exceeds the minute volume of the pulmonary circulation (MOM) in such defects.

Thus, the MOB is unequal to the MOM in either type of congenital heart defect. In defects of the pallid type, it is generally considered that all tissues and organs suffer from inadequate blood and oxygen supply due to the spillage of the blood from the MOB into the MOM. In defects of the cyanotic type, the blood going to the tissues through the greater-circulation arteries is mixed, i.e., it has a depressed oxygen partial pressure. Hence, although formerly hypoxia arises in either case as a result of disturbances to blood circulation, it is only in defects of the pallid type that it can be characterized as circulatory hypoxia. In defects of the blue type, the basic factor responsible for the hypoxia is lowered oxygen partial pressure in the blood in the greater-circulation arteries, i.e., the shift that is characteristic for hypoxic (respiratory) hypoxia. In the exposition to follow, therefore, we shall compare results obtained in a study of patients with blue-type defects with the thoroughly studied changes that take place in the physiological functions in hypoxic hypoxia, particularly during prolonged residence in the mountains. For this reason we raise the point that the classification of

hypoxic states adopted by the Kiev conference in 1948 should be supplemented under the heading "Hypoxic Hypoxia," which contains an enumeration of its causes, by a special subheading reading "As a Result of Admixture of Venous Blood to Arterial Blood." This formulation would reflect not only the causes of the hypoxia created in blue-type heart defects, but also that resulting from certain disturbances to pulmonary circulation ("shunting" of pulmonary capillaries).

Investigations of external respiration conducted in the Physiological Laboratory of the Surgical Institute named for A.V. Vishnevskiy by R.S. Vinnitskaya on patients with defects of the pallid and cyanotic types showed that the respiratory minute volume (MOD) and alveolar ventilation are considerably better in the latter than in the former. The amplified ventilation of the lungs in patients with Fallot's tetrad manifests in the fact that the MOD is in excess of the desirable volume, the O_2 utilization coefficient (ratio of O_2 consumed to the MOD) is depressed and so is the alveolar CO_2 pressure. As we know, the same changes in respiration are observed during prolonged sojourns in the mountains.

In patients with blue-type defects and in healthy individuals in the mountains, it appears that the hyperventilation is due to the same cause (the lowered O_2 partial pressure in the alveolar air) and is governed by the same mechanism (reflex intensification of breathing, produced by stimulation of chemoreceptors in the sinocarotic and cardioaortic regions). We note that following surgical treatment, which results in a lessening of the arterial hypoxemia, the MOD and the alveolar CO_2 pressure approached the normal values. However, the importance of the identical respiratory changes is fundamentally different in the two types of cases under consideration. In the mountains, hyperventilation represents an adaptive reaction that lowers the extent of arterial hypox-

emia (admitted at the expense of the hypocapnia that developed at the same time). In patients with defects of the cyanotic type, the compensatory significance of hyperventilation consists in prevention of hypercapnia, but in no way does it substantially lessen the extent of hypoxemia. This fundamental difference may serve as a clear example illustrating the following general proposition: compensatory reactions that appear under pathological conditions due to reflex mechanisms that have taken shape during the evolutionary process and provide for adaptation of the healthy organism's reaction may acquire a new significance.

This applies in particular to the increase in the oxygen capacity of the blood that is consistently observed in cases of Fallot's tetrad — an increase associated with a higher erythrocyte count (6-9 million per mm^3 of blood) and hemoglobin content (18-25 g per 10 ml of blood). The adaptive importance of these shifts — the decrease in the extent of venous hypoxemia — is basically the same as under the conditions of prolonged mountain sojourn. In Fallot's tetrad, however, this leads to a relative increase in the oxygen tension of the arterial blood, since the venous blood being mixed with the arterial blood is richer in oxygen as a result of the erythremia. This compensatory effect is specific, and is not observed in the mountains.

We also determined the minute volumes of the greater (MOB) and pulmonary (MOM) circulations by Fick's principle, with the heart-sounding operation performed by Yu.D. Bolyanski and with determination of the oxygen saturation and content in the arterial and mixed venous blood. As would be expected, the MOM was depressed, and, despite the spillage of venous blood into the aorta, the MOB was within normal limits in the majority of patients (in 18 out of 31), and moderately depressed (in 6) or elevated (in 7) in the others.

On the average, the MOB came to 102% of the normal value. Thus, as

a rule, no compensatory increase was observed in the minute volume. This is in conformity with the fact that, as we know, this increase is characteristic only for the first few days of a sojourn in the mountains and is absent when acclimatization has been achieved.

In patients with cyanotic heart defects, the oxygen saturation of the arterial blood varies over a broad range as a function of many factors, and primarily in dependence on the extent of the stenosis of the passage out of the right ventricle, which to a considerable degree determines the amount of venous blood mixed with the arterial blood.

According to our data, the saturation averages around 80%, and in the majority of cases lies between 70 and 90%.

As we now, in healthy individuals living year-round at high altitudes, we frequently observe even lower oxygen saturations of the blood. At the same time, the general condition and prognosis is quite grave in Fallot's tetrad. It appears that for a given degree of oxygenation of the blood and erythremia, compensation of oxygen shortage is far superior in the mountains to that seen in patients with cyanotic heart defects.

Not having an opportunity to devote adequately complete consideration to this question in the present report, we should like only to draw attention to the relationships that take shape in the organism under physical stress, which, at least partially, account for the difference noted above.

Actually, in acclimatized individuals living in the mountains, the performance of moderately heavy physical work does not produce any substantial lowering of the alveolar O_2 pressure or the extent to which the arterial blood is oxygenated at the expense of an increase in pulmonary ventilation over that observed at sea level.

Due to the adaptive increase of the oxygen capacity of the blood, the oxygen content in the venous blood and the minute volume change here in almost the same way as at sea level. In contrast, physical exertion in patients with blue-type heart defects produces a very sharply manifest drop in the oxygen saturation of the arterial blood. The reason for this decrease is specific for this form of hypoxia and cannot be compensated by an increase in pulmonary ventilation and the oxygen capacity of the blood. Indeed, the extent of venous-blood spillage into the arterial stream depends on the relationship between the resistance of the stenotic exit passage of the right ventricle to blood flow, on the one hand, and the vascular resistance of the greater circulation on the other. In physical labor, the latter, as we know, diminishes considerably, so that the spillage of venous blood from the right ventricle into the aorta increases sharply. It must also be taken into account that during muscular activity, the oxygen content of the venous blood is lowered. The combined effect of these two factors -- the increased inflow of venous blood into the aorta and the decreased content of oxygen in it -- is responsible for the very sharp drop in the oxygen saturation of the mixed arterial blood. As has been shown by an investigation conducted for this specific purpose in our laboratory, it is basically persistent even when pure oxygen is breathed while the work is being performed.

Thus, since a given degree of arterial hypoxemia arises in the mountains and in blue-type cardiac defects as an effect of different causes, the changes that it undergoes under physical load are completely different: in the mountains, the adaptive reactions protect the organism from further aggravation of the hypoxia during work; in cardiac defects, on the other hand, a sharp intensification of the oxygen starvation arises, indicating that the compensatory possibilities of the organism are not adequate to these conditions.

In pallid cardiac defects, the basic compensatory reactions are directed toward preservation of an adequate blood supply to the organs and tissues, i.e., toward maintenance of the necessary minute volume in the greater circulation despite the spillage of blood from it into the pulmonary circuit. No significant compensatory reactions arise here on the part of external respiration and the blood system.

The measurement of the MOM and MOB indicated that, despite extensive spillage of blood from the greater circulation into the pulmonary, the MOB is below normal only very rarely. Thus, a considerable increase in the MOB was found in only two out of 31 cases of persistent ductus arteriosus Botalli, in seven out of 30 cases of interatrial septum defect and in two out of 28 cases of interventricular septal defect (for a total of 11 patients out of 89). In the overwhelming majority of patients, the MOB was in the normal range of variation or even elevated (on the average, it came to 115% of the normal value). Accordingly, the extent to which the venous blood was saturated with oxygen was normal or even slightly above normal.

Thus, the possibility of oxygen starvation setting in was totally excluded in most of the patients by compensatory reactions that provide for normalization of the MOB. These reactions consist in a lowering of the peripheral vascular resistance in the greater circulation and intensification of the heart action. The former reaction is manifested in a lowering of the average (and minimum) arterial pressure, which is sometimes incorrectly explained as due to a drop in the MOB. In actuality, this decrease takes place with a normal or even increased MOB due to a decrease in the peripheral resistance - an adaptation that assists in reducing spillage of blood from the aorta into the pulmonary artery in cases of persistent ductus arteriosus Botalli.

The intensification of heart action must be acknowledged to have

basic compensatory importance. Actually, maintenance of the normal MOB under the conditions of blood leakage from the greater circulation into the pulmonary circulation is possible only provided that the MOM is increased, frequently to a very high level. According to our data, the MOM was 255% of normal in patients with unclosed ductus arteriosus Botalli, 264% in patients with interatrial-septum defect and 199% in those with intraventricular defect. In some of the patients, the MOM exceeded the normal values by factors of three to four and sometimes even five. Here we frequently observe an increase in the pressure in the pulmonary artery, a pressure which depends not only on the MOM increase, but also on secondary changes in the incipient sclerosis of the pulmonary vessels.

Thus, analysis of the compensation processes in pallid-type defects brings us to the conclusion that in the majority of cases the organism is suffering not so much from oxygen starvation as from the continuous stress on the systems that protect it from hypoxia. This conclusion is in agreement with the basic clinical realities, which are extremely grave and frequently fatal: decompensation of the hypertrophized myocardium and hypertension of the pulmonary circulation. Both of these are results of a chronic, continuous sharp increase in the heart action and the MOM, which can initially, for a number of years, protect the organism from circulatory hypoxia.

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[List of Transliterated Symbols]

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|-----|--|
| 344 | МОБ = MOB = minutnyy ob'yem bol'shogo kruga = minute volume of greater circulation |
| 344 | МММ = MOM = minutnyy ob'yem malogo kruga = minute volume of pulmonary circulation |

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МОД = MOD = minutnyy ob"yem dykhaniya = respiratory minute
volume

HYPOXIA, HYPOXIDOSES AND AUTOALLERGY: THEIR IMPORTANCE
IN INTERNAL PATHOLOGY

F.Ya. Primak

(Kiev)

Increased demand for oxygen is the proximate response not only to all types of everyday loads imposed on the organism, but also to many pathological displacements that occur in it. However, the increasing consumption of oxygen can be covered by a corresponding increase in the supply of it in far from all cases. It is in such cases that the state of oxygen deficiency or hypoxic phenomena arise. These phenomena are compensated by a whole range of mechanisms. The compensatory amplification of external respiration and the respiratory function of the blood in oxygen insufficiency has been studied more or less adequately. Tissue respiration, on the other hand, has been given considerably less attention. Little is known of the directivity and regulation of tissue respiration under the conditions of routine physiological loads, and even less in the case of pathological states of the human organism. And the statement that hypoxia occurs in any illness obliges us to turn redoubled attention to the distinctive features of hypoxic shifts primarily under clinical conditions. Moreover, the stepped nature that has been observed in the development of hypoxia, consideration of compensatory shifts, and the appearance of increased sensitivity, a kind of sensitization to it, permit us to speak of a certain consistency in the aggravation of the hypoxic manifestations in the development of the complications that accompany it.

Study of hypoxic states in the internal pathology supports the conviction that the various manifestations of hypoxia are frequently encountered in the internal medicine clinic. The specific nature of these manifestations, their combinations and their persistence from time to time acquire certain distinguishing features peculiar to a given form of internal pathology. At the same time, systematic study of oxygen exchange under clinical conditions makes it possible to register the peculiar type of staged development of the hypoxic states that we have already noted.

This stepwise development of hypoxic manifestations might, for example, be observed in hypertonia. Thus, in patients in the initial stage of hypertonia, arterial hyperoxemia is frequently encountered, and in rather high degrees, together with elusive venous hypoxemia. However, subsequent "normalization" of the oxygen composition of the arterial and venous blood from time to time indicates deterioration of the compensatory-mechanism function, since a sudden drop of a previously high arterial venous oxygen difference (if even to the normal level) may be one of the essential criteria of tissue hypoxia and the hypoxidosis that accompanies it, i.e., mountain functional and morphological changes of the vascular-tissue and perivascular structures; changes caused by long-standing hypoxia or even by the development of extreme sensitivity to hypoxic shifts. Thus, for example, the autoallergic syndrome is frequently one of the criteria of developed hypoxidosis. The organic disorders that develop immediately following this sign, like the phenomena of a focal exacerbating infection, are often combined with a subsequent deterioration of oxygen exchange, right down to the point at which assimilation of oxygen is blocked and the manifestations of anaerobic metabolism becomes stronger. Such a sequence can also frequently be traced during intensifying manifestations of circulatory insufficiency with

distinct edema. Here, first the signs of venous hypoxia, then arterial and then finally tissue hypoxia are particularly clearly seen. Morphological investigations have shown that in cases of acute terminal edema, including edemas that have developed on soil provided by circulatory insufficiency, profound changes arise first in the connective-tissue structures with their networks of blood and lymph vessels and also occasionally in different ways in various organs and systems. "The exceptional polychromatism and polymorphism of the connective-tissue elements essentially indicates different degrees of injury to the collagen substance precisely during the edemas" (F.Ya. Primak).* It is decay of the tissue protoplasm, a significant decrease in the activity of synthetic processes in the tissue elements that has been responsible for the presence of sharp changes in various structures of the organism in general and particularly in the connective tissue, skeletal muscles, myocardium and even in the smooth musculature. As we see, here morphology brings out clearly the consequences and seriousness of the mounting changes in tissue metabolism, where disturbances of oxygen exchange acquire prime importance.

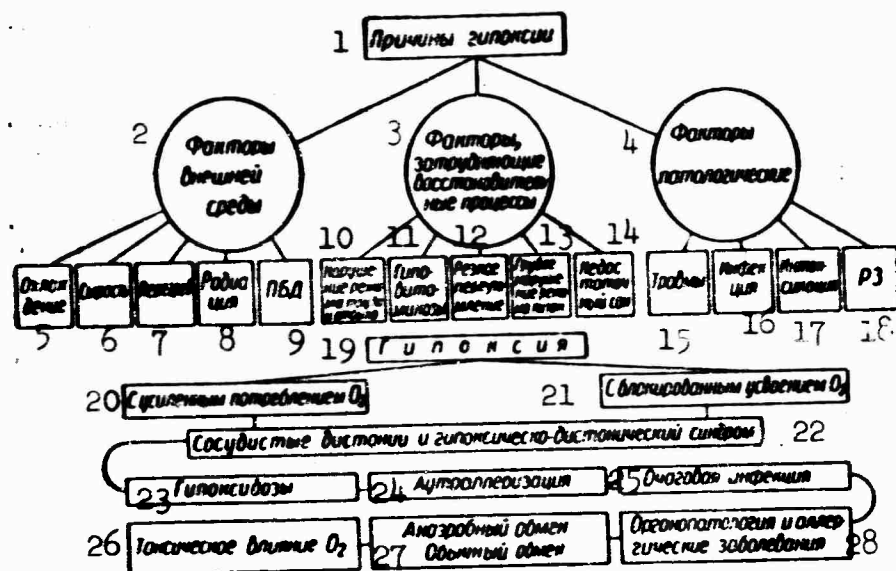
A repeated investigation of the gas composition of the blood in persons suffering from severe forms of endocarditis enables us to identify patients in whom the mounting manifestations of arterial hypoxemia are combined with signs of tissue hypoxia. But the disturbances to the vascular-structure function, including the increasing manifestations of capillaritis with severe damage to the vascular endothelium, should be regarded as one of the essential signs of hypoxidosis and the autoallergia that accompanies it.

The hemorrhagic syndrome of sudden onset and the complex pattern of thromboembolic phenomena observed in many endocarditis patients are also explained to a certain degree by autoallergic shifts that arise as

a result of decompensated hypoxia. The occurrence of the latter is indicated not only by a considerable drop in the arterial venous oxygen difference, but also by burgeoning signs of vascular dystonia. The phenomena of capillaritis, increasing vascular-tissue permeability, and instability of the arterial blood pressure and pulse pressure frequently form parts of the complex picture of tissue hypoxia. The combination of hypoxic manifestations with signs of vascular dystonia comes out so clearly in a number of disorders that it is even appropriate to speak of a hypoxic-dystonic syndrome. As has been shown by clinical experience, the great distinctness and persistence of this syndrome represent an essential criterion for those forms of aggravating tissue hypoxia in which, as a result of autoallergic shifts, one or another form of organic pathology arises. Depending on the localization of the changes that take place, however, we observe manifestations of hypoxic-dystonic states now in purely localized form and again with more extensive morphological modifications - those combined, as we have already noted, under the term "hypoxidoses." It is these associated phenomena of autoallergia, however, that account for the unusual acuteness of the reactive shifts in the organism attending any new conditions that cause the hypoxia to exacerbate.

As further examples of such disorders, in addition to the numerous cases of suddenly exacerbating manifestations of focal infraction, we may cite certain forms of chronic pulmonary disorders with increasing pneumosclerosis and asthmatic syndrome; disorders of the gastrointestinal tract with hypoxic-dystonic states and phenomena of hypoxidosis embracing preferentially the region of the portal basin; the initial forms of myocardial damage of the serous-myocarditis type; certain disorders of the liver, and so forth. Nevertheless, clinical observations enable us to link these numerous examples of internal pathology with the devel-

opment of hypoxidosis and autoallergia in attendance upon them. The link between the rising manifestations of vascular-tissue permeability on the one hand and the functional and morphological changes in the vascular-tissue structures under the conditions of increasing hypoxia and the other would explain the mechanism by which the manifestations of hypoxidosis are aggravated by autoallergia.



Development of hypoxidoses and their complication.

1) Causes of hypoxia; 2) external environmental factors; 3) factors impeding recovery processes; 4) pathological factors; 5) cold; 6) rawness; 7) overheating; 8) radiation; 9) PVD [not identified]; 10) disturbance of work and rest schedule; 11) hypovitaminosis; 12) severe overwork; 13) gross disturbances to nutritional regime; 14) insomnia; 15) trauma; 16) infection; 17) intoxication; 18) RZ [not identified]; 19) hypoxia; 20) with increased O_2 consumption; 21) with assimilation of O_2 blocked; 22) vascular dystonia and hypoxic-dystonic syndrome; 23) hypoxidoses; 24) autoallergia; 25) focal infection; 26) toxic effect of O_2 ; 27) anaerobic metabolism; normal metabolism; 28) organic and allergic disorders.

In studying the vascular-tissue permeability in persons with manifest hypoxia and vascular dystonia, we observe them to show a considerable increase in the amount of fluid escaping from the vascular stream, as well as an increase in the amount of albumin in it. This circumstance is of essential importance both in the exacerbation of the manifestations of hypoxidosis and in the development of subsequent autosensitization due to native proteins sweated out of the vascular stream. Reexam-

ation of the same patients indicates that the development of the hypoxic-dystonic syndrome, and then of hypoxidosis and the autoallergic state with its various complications may serve to explain the increasing manifestations of hypoxia. The appearance of the latter and the development of further changes in the organism up to the point at which anaerobic metabolism and the toxic effect of oxygen prevail is represented schematically in the figure.

This scheme, which illuminates the pathogenetic importance first of hypoxia and then of hypoxidosis and autoallergia in internal pathology, also accounts for the importance of abnormally high vascular-tissue permeability in a set of disorders associated with exacerbation and increasing frequency of hypoxic manifestations. It also accounts for the high frequency of serous inflammation as the earliest and most frequent complication of tissue hypoxia, which results in various distinct forms of organic pathology. The blocking of oxygen assimilation entered first on the diagram and then the predominance of anaerobic metabolism, sometimes considerably later, enable us to understand many aspects of acute and chronic vascular pathology taking the form of the most frequently occurring hypoxidosis and autoallergia. This is why study of hypoxic manifestations and precise definition of the subsequent functional and morphological changes in the vascular-tissue structures (which we unify in the concept of hypoxidosis) and establishment of criteria for the attendant autoallergia are of such great importance for internal pathology.

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*Primak, F.Ya., Terminal'ni nabryaki m'yaziv [Terminal Muscular Edema], Vid-vo AN URSR [Acad. Sci. UkrSSR Press], Kiev, 1937, page 188.

ON THE BASIC MECHANISMS COMPENSATING HYPOXIA
IN CHRONIC CIRCULATORY INSUFFICIENCY

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(Kiev)

The organism calls upon a number of different mechanisms to compensate oxygen insufficiency — changes in external respiration and blood circulation, the volume of circulating blood and the oxygen capacity of the blood, an increase in the efficiency of oxygen utilization, complex readjustment of metabolism and others.

In chronic circulatory insufficiency that has developed in patients with rheumatic heart damage, the compensation of hypoxia proceeds in a distinctive fashion, but its mechanisms have not yet been clarified adequately.

We studied the compensatory reactions of the organism in patients with chronic circulatory insufficiency in the active and latent phases of rheumatism. For this purpose, we investigated the curves of oxygen and carbon dioxide fixation, the gaseous composition of the arterial and venous blood, the oxygen capacity of the blood, total and reduced glutathione and the distinctive features of tissue metabolism, on the basis of the arterial venous difference between substances that represent the principal source of energy for the tissues (sugar, lactic and pyruvic acid, fatty acids, ketone bodies and amino-acid nitrogen). The quantity of circulating blood and the rate of exchange of the dissolved substances between the tissues and the blood were investigated by the isotope method. The mass of circulating blood was determined by the Hevesy method as modified by D.N. Strashchesko and B.E. Tartakovskiya, using erythrocytes tagged with P^{32} ; the exchange rate of the solutes was taken into account on the basis of the rate at which the P^{32} was elimin-

inated from the intracutaneous depot.

In patients with heart defects (basically, combined mitral defect), an increase in the oxygen consumption of the blood was observed even before the appearance of the clinical signs of circulatory insufficiency and in stage I. In 12 out of 17 patients examined, the arterial venous oxygen difference and the percentage utilization of oxygen by the blood were increased. An increase in the venoarterial carbon dioxide difference and, in some of the patients, an increase in the consumption of energy substances corresponded to this. In one-third of the patients, an increase was noted in the arteriovenous sugar difference and the venoarterial lactic acid difference together with a normal level of these metabolites in the blood. Together with this, there was an increase in the metabolism of reserve energy sources – the concentration of amino acid nitrogen in the serum of the arterial and venous blood increased (in almost half of the patients), and its arterial venous difference was higher.

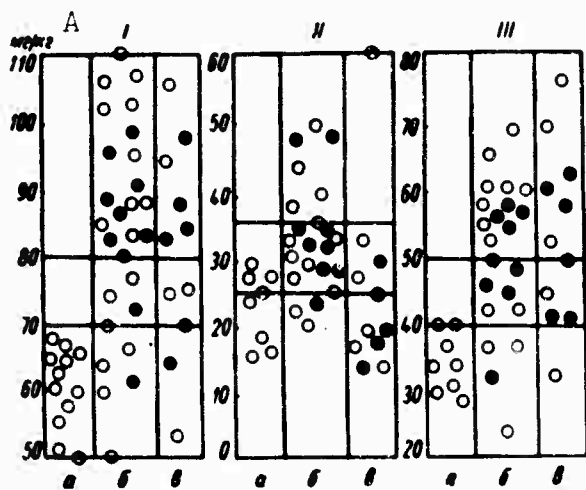


Fig. 1. Quantity of circulating blood. I) Volume of whole blood; II) total erythrocyte volume; III) plasma volume. a) Heart defects without distinct circulatory insufficiency; b) chronic circulatory insufficiency in inactive phase of rheumatism; c) circulatory insufficiency against a background of endomyocarditis. ○) Without edema; ●) with edema. A) mg/kg.

The increase in fat metabolism was characterized by elevated mobilization of fat from the tissues (the arteriovenous difference for the fatty acids was frequently negative, in contrast to the situation in healthy persons) and by a high consumption of ketone bodies. It is suggested that the increase in oxygen consumption and the expenditure of energy substances is a compensatory mechanism that provides for the normal vital activity of the tissues when the supply of blood to them is cut down.

Our attention is drawn to the consistent decrease in the mass of circulating blood in the patients (Fig. 1). The consistent decrease in the mass of circulating blood that we identified in heart defects even before the appearance of distinct decompensation criteria is in agreement of the data of the V.V. Parin and F.Z. Meyerson, Ya.I. Mayzel', K.G. Abramovich and V.F. Zelenina to the effect that the reduction in blood minute volume in such patients must also be regarded as an adaptation of the organism to relieve the circulatory apparatus.

In stage IIA of circulatory insufficiency, the increase in the blood's utilization of oxygen comes out even more clearly. A high arteriovenous oxygen difference and a high utilization percentage were found in 24 of 31 patients. As a rule, the oxyhemoglobin dissociation process in these patients proceeded normally. The increased rate of transfer of oxygen from the oxyhemoglobin to the tissues was achieved as a result of the increased carbon dioxide tension of the blood. While the oxyhemoglobin dissociation curves did not leave the normal range of variation (Fig. 2a), the carbon dioxide-fixation curves were pushed down slightly, and this, with the normal content of carbon dioxide in the blood, resulted in an increased partial pressure from this gas in the majority of patients, particularly in the venous blood.

At the same time, the consumption of energy substances increased.

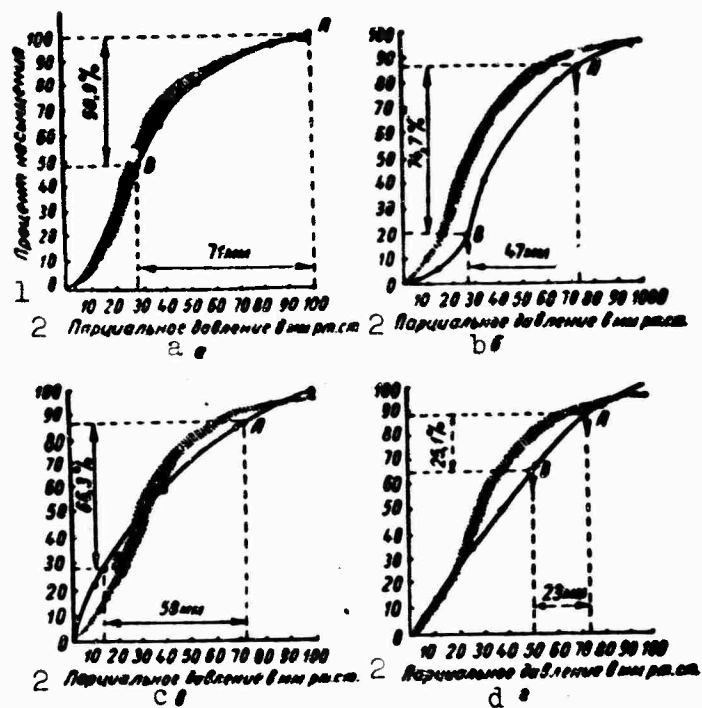


Fig. 2. Oxyhemoglobin dissociation curves. a) Patient K. IIA circulatory insufficiency; b) patient L. IIB circulatory insufficiency in inactive phase of rheumatism; c) patient S. Rheumatic endocarditis. IIB circulatory insufficiency; d) patient L. Persistent septic endocarditis. III circulatory insufficiency; vertical axis: O_2 saturation percentage; horizontal axis: pO_2 in mm Hg. 1) Percentage saturation; 2) partial pressure in mm Hg.

In a third of the patients, we observed a considerable arteriovenous difference in sugar at a normal level of glycemia. In more than one-third of the patients, we found an increase in venous lactacidemia, with the corresponding rise in the venosoarterial lactic acid difference. A tight relationship was observed between the extent of the increase in the venosoarterial difference and the increase in the venous-blood concentration of lactic acid (Fig. 3).

Statistical analysis indicated a close relationship between these quantities. In stage I, the linear correlation coefficient r was 0.63, and in stage IIA it was 0.76 (an r of 0.3 indicates a weak relationship, between 0.3 and 0.5 the relationship is moderately strong; from 0.5 to 0.7 it is marked and from 0.7 up we have a high degree of correlation). Closer examination of the nature of the relationship showed that a near-

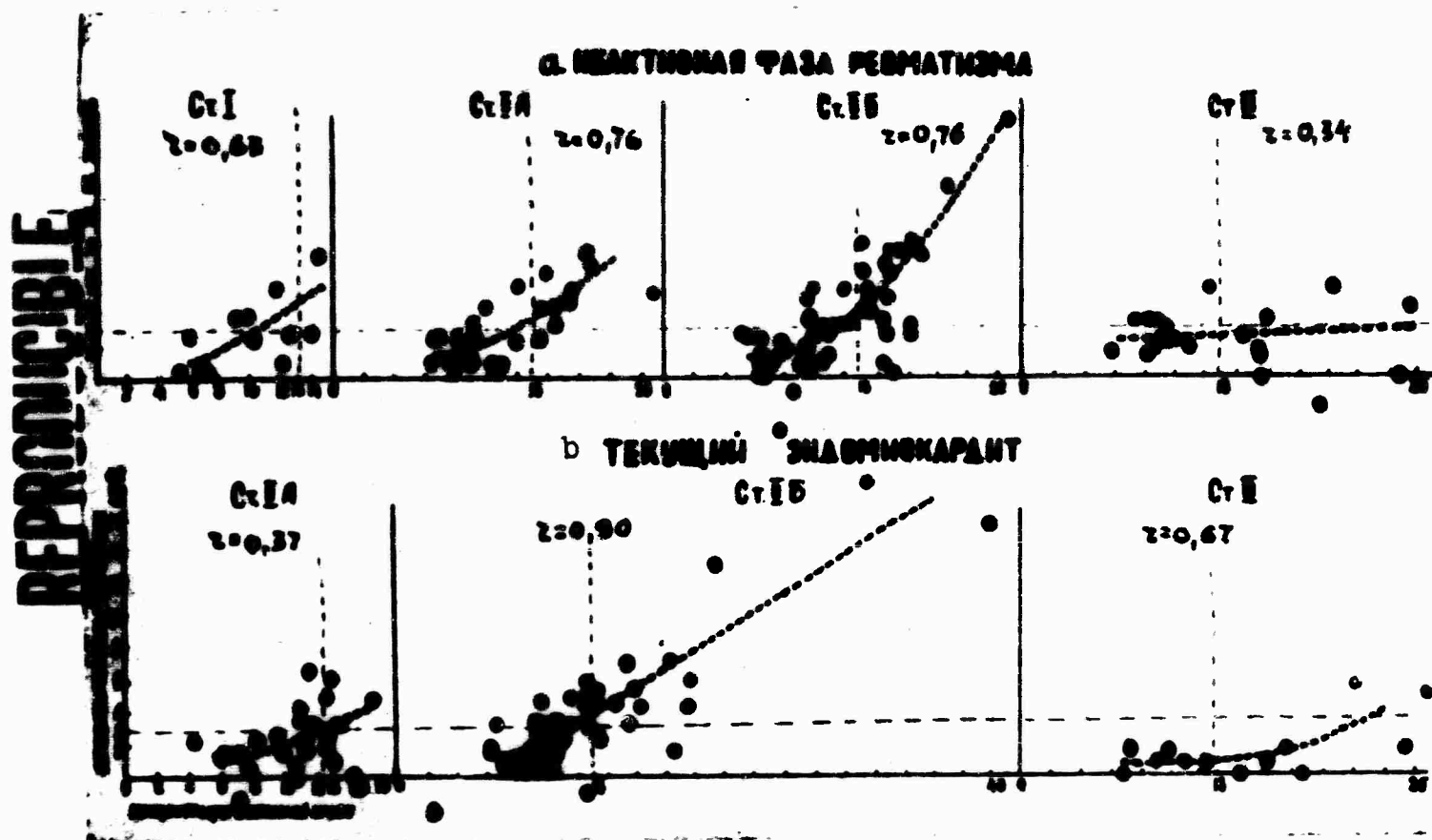


Fig. 3. Lactic acid in circulatory insufficiency. Venosoarterial difference. Each circle denotes the venosoarterial difference (along the axis of ordinates) as plotted against the lactic acid concentration in the venous blood (axis of abscissas). The curve of average values of the venosoarterial difference reflects its variation with increasing lactic acid concentration in the venous blood; r is the linear correlation coefficient. a) Inactive phase of rheumatism; b) current endomyocarditis. 1) mg-%; 2) stage; 3) venosoarterial difference; 4) concentration in venous blood.

ly linear parabolic type is most probable.

Even in the early stages of decompensation, we determined an increase in nitrogen metabolism, with a higher content of amino acid nitrogen in the blood serum and a rise in the arteriovenous difference. The intensification of fat metabolism was particularly distinct, with an increase in the rate of transfer of fatty acids from the tissues into the blood and a high consumption of ketone bodies by the tissues (Fig. 4). The closeness of the correlation between the arteriovenous difference of the ketone bodies and their concentration in the arterial blood was greatest in this stage (r equal to 0.79).

There is a possibility that the intensified consumption of ketone bodies in the early stages of decompensation is one of the compensatory factors associated with the increase in fat metabolism, which possesses high calorific value. Even in stage IIA, some of patients showed an increase in the mass of the circulating blood. The rate of transfer of the dissolved substances from the tissues to the blood was slowed down insignificantly. In a later stage of decompensation, IIB, the most important compensatory mechanism supporting the increased transfer of oxygen to the tissues was a drop in the affinity of the hemoglobin for oxygen. In half of the patients observed, it manifested in a shift of the dissociation curves toward the right and downward, with a sharp lower inflection (Fig. IIb). In contrast to the initial stages of circulatory insufficiency, the content and tension of the blood carbon dioxide dropped in stage IIB, and the increased transfer of oxygen from the hemoglobin could come about only through a decrease in its affinity for oxygen.

The arterial venous difference and the percentage utilization of oxygen by the blood in these patients were particularly (Fig. IIb). However, by virtue of the drop in the affinity of the hemoglobin for oxygen, the oxygen tension in the venous blood, which is a direct index to the extent of circulatory hypoxia, dropped less significantly. Together with this, a number of patients in serious condition showed no decrease in the oxygen affinity of the hemoglobin under the conditions of distinct oxygen starvation, which apparently ought to be regarded as a disturbance of an important compensatory adaption to hypoxia in these persons.

In most of the patients suffering from chronic circulatory insufficiency, the oxygen capacity of the blood remained normal. Only in a small number of patients (14 out of 91) did we observe an increase. In the later stages, particularly in stage III, the oxygen capacity of the

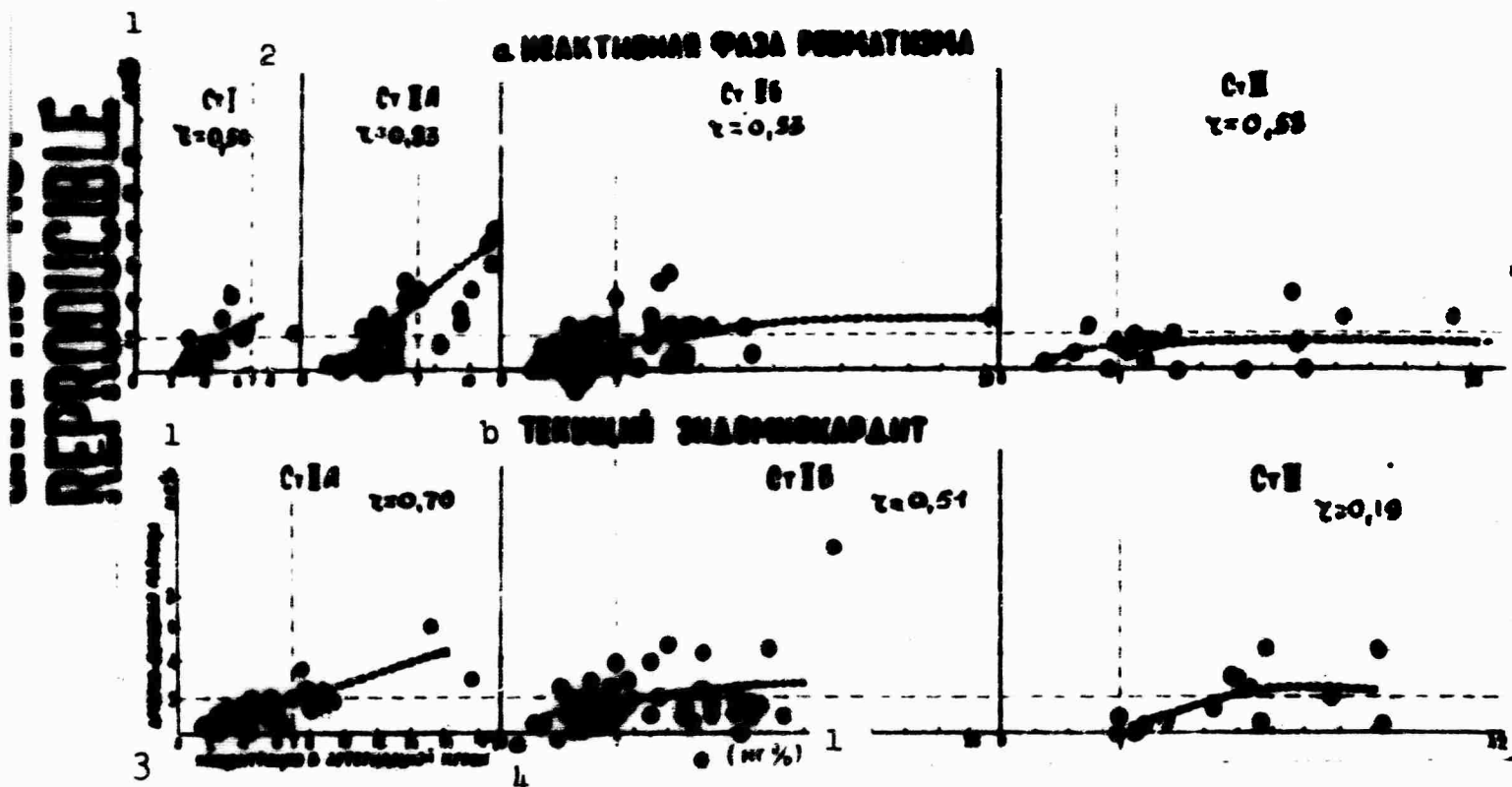


Fig. 4. Ketone bodies in circulatory insufficiency. Arteriovenous difference. Axis of ordinates: arteriovenous difference; axis of abscissas: concentration of ketone bodies in arterial blood. r is the linear correlation coefficient. a) Inactive phase of rheumatism; b) current endomyocarditis. 1) mg-%; 2) stage; 3) arteriovenous difference; 4) concentration in arterial blood.

blood sometimes decreased. Hyperglobulinemia was also observed comparatively rarely (only in about one-fifth of the patients).

The increase in circulating blood mass observed in most patients in stage IIB (in 24 out of 38) took place basically by an increase in the volume of plasma (Fig. 1).

In some of the patients with combined mitral cardiac defect, in whom decompensation manifested in a considerable enlargement of the liver and stagnation effects in the lungs in the absence of peripheral edema and ascites, the amount of circulating blood was normal or even slightly subnormal. To a certain degree, this confirms the conception according to which the leading factor contribution, on the one hand, to the increase in circulating blood mass and, on the other, to the appearance of edemas and ascites, is the retention of sodium and water in the organism

due to the increased production of aldosterone.

The total erythrocyte volume was within normal limits in the majority of patients suffering from chronic circulatory insufficiency. An increase was observed only in some of the patients with an increased amount of circulating whole blood (in 7 out of 24), which corresponded to a moderate frequency of hyperglobulinemia and an increased oxygen capacity of the blood in these patients.

Thus, a change in the volume of circulating blood took place chiefly through a change in the plasma volume and, consequently, could not have any substantial compensatory value in improving the oxygen supply to the tissues. The change in blood oxygen capacity also has limited significance in compensating hypoxia in chronic circulatory insufficiency.

In later stages of circulatory insufficiency, changes in metabolic processes with an increase in the anaerobic phase and utilization of oxidation-reduction systems come more clearly to the fore.

Very frequently (in 40% of patients), we detected a rise in the lactic acid concentration in the venous blood. An increase in the veno-soarterial lactic acid difference was noted even more frequently - in half of the patients. The linear correlation coefficient between them was high (0.76) in stage IIB. Consequently, despite the clear clinical signs of liver damage, its resynthesizing function remains satisfactory in stage IIB, and in many patients was even above normal. Actually, an increase in lactic acid concentration in the arterial blood was observed three and a half times more frequently than in the venous blood (in only 6 out of 55 patients).

It appears to us that this fact reveals one of the important compensatory mechanisms that supports reduction of glycogen reserves in the organism for some time during hypoxia. It is known that 12 times as much

material is expended in anaerobic splitting to produce the energy formed by total oxidation of glycogen. To maintain biological equilibrium, the increase in glycogenolysis must be compensated by an increase in the resynthesis of lactic acid. This would apparently account for the frequently observed great arteriogenous sugar difference in these critical patients, a difference which, in combination with the abnormally high venous lactacidemia and the large venosoarterial lactic acid difference, can provide an idea of the intensity of anaerobic glycogenolysis and the compensatory resynthesis of lactic acid. Simultaneously with this, glyconeogenesis processes are enhanced by protein decomposition — in the patient studied, the amino acid nitrogen content, the arteriovenous difference and the percentage of oxygen utilization by the amino acids were all increased.

Increased ketonemia was observed quite often in stage IIB — in half of the patients. At the same time, the arteriovenous difference and the percentage utilization of ketone bodies diminished, indicating depressed oxidation of these substances in the tissues.

In harmony with these data were the changes in the glutathione content of the blood. In patients with chronic circulatory insufficiency, as observed, chiefly in stages IIB and IIB-III, a distinct tendency toward a higher content of total glutathione in the venous blood and a higher proportion of this substance to the erythrocytes. The arteriovenous glutathione difference was considerable, as regards both the reduced and oxidized forms.

The rate of exchange between the tissues and the blood in stage IIB is distinctly disturbed: the elimination of P^{32} from the intracutaneous depot was retarded considerably.

Thus, in state IIB, the decreased influx of blood and oxygen into the tissues is for a long time compensated by increased utilization of

oxygen and readjustment of the the metabolism with amplification of anaerobic processes. The increased rate of the glycogenolytic processes is compensated to a considerably degree by an increase in the resynthesis of lactic acid. Utilization of the glutathione oxidation-reduction system is intensified.

In stage III of circulatory insufficiency, we observed, together with a sharp drop in the affinity of hemoglobin to oxygen and high utilization of the latter, a normal or depressed consumption of oxygen and elimination of carbon dioxide (with a drop in the arteriovenous oxygen difference to 3.4% by volume and in the venosoarterial carbon dioxide difference to 2.6% by volume. The latter reflected the development of histotoxic hypoxia (Fig. 2d).

The profound metabolic disturbances were increasingly associated with suppression of the ability of the tissues to consume energy-producing substances and a depressed resynthesizing function of the liver. Hyperlactacidemia was observed equally frequently in both the venous and arterial bloods in half of the patients. The arteriovenous sugar, lactic acid, and ketone-body differences decreased or vanished as their concentrations in the blood rose to high levels. The relation between the venosoarterial lactic acid difference and the concentration of the acid in the venous blood, which is very clear in other groups of patients and in healthy individuals, became less distinct in stage III, indicating profound derangements of the metabolic processes and their regulation.

It should be noted that dystrophic processes with depressed consumption of energy-producing substances and exhaustion of the compensatory mechanisms that provide for constancy of the organism's internal medium develop very gradually in the inactive phase of rheumatism and reach profound degrees only in stage III of decompensation.

The processes described above unfolded somewhat differently in de-

compensation that developed against a background of current endomyocarditis. The compensatory mechanisms that are brought into play in circulatory insufficiency are suppressed quite rapidly in current endomyocarditis.

The oxyhemoglobin dissociation process was disturbed, as manifested in the change in the dissociation curves from their normal S-shape to approximate a hyperbola. The compensatory decrease in the affinity of hemoglobin for oxygen was indistinctly expressed or totally absent, with the result that the phenomena of stagnation and hypoxic hypoxia were sharply intensified, and histotoxic hypoxia appeared early in some of the cases (Fig. 2c, d). An increase in the blood oxygen capacity was noted even less frequently than in the inactive phase of rheumatism (in 11 out of 141 patients). At the same time, a decrease was observed in the majority of patients (in 90), particularly when the process took a severe course; this would correspond to a decrease in the number and total volume of erythrocytes in the patients.

Very rarely did we note a rise in the level of total and reduced glutathione in the blood (in only 7 out of 74 patients). In the severe forms of endocarditis, both the total glutathione content and its content in each erythrocyte (Gabbe coefficient) showed a consistent decrease (Fig. 5). Intensification of the anaerobic processes, with an increase in anaerobic glycogenolysis, set in early, but the intensified resynthesis of lactic acid in the liver was suppressed. Hyperlactacidemia was observed almost equally frequently in stages IIA and IIB, in both the venous and the arterial blood.

Restitution of glycogenesis was apparently accomplished to a considerable degree by the least favorable path - through an increase in glyconeogenesis from the products of protein metabolism. It was precisely these patients who showed the highest content of amino acid nitrogen and

the greatest - usually positive - arteriovenous difference in this substance.

A rise in the rate of fat metabolism was characteristic. High ketonemia accompanied all of the severe forms of endocarditis, but the ability of the tissues to oxidize ketone bodies, the arteriovenous difference and the utilization percentage of these bodies decreased at a particularly early point in time.

The differences in the course taken by the metabolic processes in the various stages of decompensation were less distinct than in the inactive phase, and were obliterated in the more severe forms of endocarditis. Dystrophic processes in the tissues, with suppression of their ability to consume oxygen and oxidize energy-producing substances, together with the suppression of the resynthesizing function of the liver, processes that developed slowly during the inactive phase of the rheumatism, sometimes over a number of years, emerged quickly on decompensation against a background of current endomyocarditis, reaching a critical in the more acute forms within a few months, and sometimes even within a few weeks.

A considerable slowdown of the passage of P^{32} from the tissues into the blood stream was established by the radioactive method in the later stages of decompensation. It was particularly sharply manifest in some of the patients during current endomyocarditis (increase in the half-elimination time of P^{32} from the cutaneous depot to 90-115 min, as against 15-18 min under normal conditions).

On the other hand, the distinct decompensation phenomena and the profound metabolic disturbances were found to be reversible when the basic rheumatic process was successfully treated. If, however, it was not possible to arrest the current rheumatic process, the phenomena of circulatory insufficiency developed with catastrophic speed, and late

irreversible decompensation phenomena developed in a relatively short time.

The above outlines a certain consistent relationship in the compensation of hypoxia in chronic circulatory insufficiency:

1. Even before the distinct clinical signs of circulatory insufficiency appear and in the initial stages of decompensation (stages I-IIA), the utilization of oxygen rises in response to the decrease in the amount of blood arriving at the tissues, as does the consumption of energy-producing substances by the tissues (sugar, ketone bodies, amino acids), without any significant accumulation of intermediate metabolism products in the blood.

The increased yield of oxygen by [sic] the tissues is provided for by intensification of oxyhemoglobin dissociation due to the increased carbon dioxide tension of the blood. In stages I and IIA, our attention is drawn to a rise in fat metabolism, with increased mobilization of fats from the tissues and an increased consumption of ketone bodies in the tissues.

2. In a later stage of circulatory insufficiency (stage IIB, hypoxia is compensated chiefly at the expense of reduced affinity of hemoglobin for oxygen and the adjustment of metabolism with intensification of anaerobic processes. Intensification of anaerobic splitting of carbohydrates is for some time compensated by a rise in lactic acid resynthesis in the liver, and by intensified processes of glyconeogenesis from mitogenous products. Utilization of the glutathione system is increased.

3. In patients suffering from heart defects with latent circulatory insufficiency, the amount of circulating blood is lower than normal. It increased as decompensation developed and progressed. The amount of circulating blood was increased chiefly through changes in the plasma volume and, consequently, is of limited compensatory value in these pa-

tients. An increase in the oxygen capacity of the blood is observed infrequently and apparently has no significant role in compensating hypoxia in chronic circulatory insufficiency stemming from rheumatic damage to the heart.

4. In the third stage of decompensation, the ability of the tissues to consume oxygen and energy-producing substances is lowered, histotoxic hypoxia develops, and resynthesis of lactic acid in the liver is suppressed. The regulatory mechanisms have been exhausted. The dependence of the venoarterial lactic acid difference on its concentration in the venous blood, and that of the arteriovenous ketone body difference on the concentration of ketone bodies in the arterial blood, which were extremely close in stages I, IIA and IIB, vanish in the decompensation stage III. The constancy of the organism's internal medium has been disturbed.

5. In circulatory insufficiency that has developed against a background of current endomyocarditis, the compensatory mechanisms are suppressed comparatively quickly — the hemoglobin dissociation process is disturbed, histotoxic hypoxia develops early, the oxygen capacity and glutathione content of the blood fall, and anaerobic processes are intensified, while the lactic acid resynthesis process in the liver slows down and the consumption of energy-producing substances in the tissues decreases.

When the rheumatic process subsides, the manifest decompensation processes and profound metabolic disturbances are found to be reversible.

CONCERNING HYPOXIA IN ATHEROSCLEROTIC HEART DAMAGE

A.L. Mikhnev and N.S. Zanozdra

(Kiev)

Atherosclerotic myocardiosclerosis is, together with rheumatism, the most frequent and widespread cause of heart trouble, disturbances to the heart's contractile function and the development of stenocardia, myocardial infarct and circulatory insufficiency.

Atherosclerotic damage to the heart may be a consequence of various factors, and primarily of the progress of a general atherosclerotic process, although it can be stated with confidence at the present time that hypoxic shifts in the organism are of unquestionable importance here as well, as attested to by clinical observations and scanty but convincing research studies.

In his monograph entitled "Atherosclerosis," A.L. Myasnikov presents data to the effect that the level of oxidation reduction processes is subnormal in atherosclerosis patients — an effect associated by some authors with hypofunctioning of the thyroid gland. Thus, K.K. Maslova noted a marked decline in thyroid function and basal metabolism in atherosclerosis patients.

Ye.A. Tolochkova found a majority of atherosclerosis patients examined to show changes in the gas composition of the arterial and venous blood. A.S. Fridman, M.N. Zolotova-Kostomarova and N.G. Stepanov, V.A. Patreyeva, M.V. Ignat'yev and others also report to this effect.

V. Khuper ascribes prime importance to hypoxia in the development of atherosclerosis.

We studied 120 patients suffering from atherosclerotic myocardiosclerosis, determining their external respiration indices, the gas contents of the arterial and venous blood and, for some of them, the curves of oxyhemoglobin dissociation and carbonic-acid fixation. There were 79 male patients and 41 females. For the most part, the ages of the patients ranged from 50 to 60 years. For convenience in presenting the data obtained, we subdivided the patient group studied into three subgroups. A first subgroup consisted of 52 persons in whom it had been possible to establish moderately distinct signs of atherosclerotic myocardiosclerosis combined with stage II hypertonia (classification of the MZ SSSR [USSR Ministry of Health]). In patients of the second subgroup (38 persons), we noted distinct signs of myocardiosclerosis, coronary insufficiency and stage I-II-III general disturbances to circulation stemming from hypertonia.

To the third subgroup (30 persons), we assigned patients suffering from atherosclerotic myocardiosclerosis, stenocardia, and circulatory insufficiency without hypertonia. Some of these patients had previously suffered myocardial infarct.

In patients of the first and second subgroups, the increase in respiratory frequency, respiratory minute volume (MOD) and 1-minute oxygen absorption were marked, as was the decrease in the respiratory depth and reserve, carbon-dioxide elimination rate and respiratory coefficient. Particularly noticeable was the change in these external respiration indices as the circulatory insufficiency progressed. Thus, respiratory frequencies above 20 in 1 minute were observed in 50 persons, while the MOD varied from 8 to 12 liters in 1 minute in 33 of them, for the most part in the second subgroup.

The impression created was that the increase in respiratory fre-

quency, MOD and oxygen absorption in 1 minute represented testimony to the stress under which the external respiratory apparatus was operating, while the decrease in the depth and reserve of respiration and the respiratory coefficient indicated its relative inadequacy.

We determined the blood gases on 38 individuals (17 of first subgroup and 21 of the second), and normal figures (98-94% for the oxygen saturation of the arterial blood were noted in only three of the patients; depressed values (from 93 to 90%) were observed in 13 (with a majority of 11 in the first subgroup), and low indices (from 89 to 85 and below) in 22 individuals (here patients of the second subgroup formed the majority of 19). The oxygen saturation indices of the venous blood were lowered to the same degree (in 24 individuals, this index varied from 39 to 30%).

Basically, the arterial and venous hypoxemia in patients suffering from atherosclerotic myocardiosclerosis was in correspondence to the gravity of the damage to the heart muscle and appeared to contribute to the appearance of certain compensatory mechanisms. These would include, in addition to the stressed functioning of the external respiratory apparatus, an increase in the percentage utilization of oxygen by the tissues and in the oxygen capacity of the blood. The percentage of tissue utilization of oxygen in patients of the second subgroup was doubled (70-80%), while the oxygen capacity of the blood had increased to 26-27% by volume.

The quantity of carbon dioxide in the venous and arterial blood increased only in certain patients of the first group, particularly when pneumosclerosis was present; a decrease in this quantity was noted in many persons of the second subgroup coupled with circulatory insufficiency.

For more thorough study of the hypoxic shifts, we determined oxyhe-

moglobin dissociation curves in 17 patients (6 of the first subgroup and 11 of the second) and the carbon dioxide fixation curves in 8 patients. A shift in the curves was observed in 12 patients, of whom 11 showed a shift to the right and downward, while only one showed a shift upward and to the left. The upward and leftward shift of the oxyhemoglobin dissociation curve was noted in patient K., who was suffering from manifest pneumosclerosis, pulmonary emphysema and pulmonary-cardiac insufficiency. The shift of the curves to the right and downward in 3 persons of the first subgroup and 8 of the second subgroup depended largely, but not always, on the presence of circulatory insufficiency. In manifest cases of atherosclerotic myocardiosclerosis with disturbance to the contractile function of the myocardium, the oxyhemoglobin dissociation curves lost their S-shape and acquired the shapes of hyperbolas.

In accordance with the degree of atherosclerotic heart damage and disturbance to its contractile function, the oxygen partial pressure in both the arterial and the venous blood showed a decrease, while the oxygen transfer gradient - i.e., the difference between the oxygen partial pressure in the alveolar air and that in the arterial blood - became steeper.

In the persons whom we examined, the carbon dioxide fixation curves were also shifted downward; the carbon dioxide partial pressure had risen markedly in both the venous and arterial blood. In some patients, the carbon dioxide partial pressure in the venous blood was extremely high at 70-80 mm Hg.

In patients of the third subgroup (30 persons), almost all of the external respiration indices were depressed. The respiratory frequency, for example, was greater than 20 in 1 minute in only five persons, while the MOD exceeded 8 liters in 1 minute in four patients. The figures for respiratory depth and reserve, elimination of carbon dioxide and absorp-

tion of oxygen in 1 minute and the respiratory coefficient were particularly low, the latter dropping below 0.80 in 18 patients.

Such a reaction of the external respiratory apparatus, which is obviously not adequate to the needs of the organism, not only lowered the ventilation function of the lungs in patients of the third subgroup, but also made it difficult for the gases to diffuse in the pulmonary circulation. This was attempted to by a drop in the percentage oxygen saturation of the arterial and venous blood. Thus, in patients with low external-respiration indices, distinct arterial hypoxemia (85-88%) was observed even without derangement of the general circulation; of 16 patients examined, 14 showed subnormal percentage saturations of the arterial and venous blood. We had also observed a decreased percentage oxygen saturation of the arterial and venous blood in an earlier study of atherosclerotic patients (A.L. Mikhnev, V.P. Bezuglyy, N.V. Osadchaya).

In patients of the third subgroup, the compensatory reactions in response to hypoxia were considerably less distinct as compared to patients of the first and second subgroups. Not all of the patients showed increased hemoglobin contents and erythrocyte counts, nor an increase in the blood oxygen capacity. Only in occasional patients did the oxygen capacity of the blood reach the level of 21-22% by volume with adequately high utilization of oxygen by the tissues (60-70%); in most of the patients, this indicator was normal or even subnormal.

At the same time, profound hypoxic shifts in patients of the third subgroup were indicated by a decrease in oxygen partial pressure in the arterial and venous blood, a rise in the oxygen transfer gradient and the carbon dioxide partial pressure in both the arteries and the veins. The shifts of the oxyhemoglobin dissociation curves downward and to the right were indistinct, and in two patients with second-stage circulatory

insufficiency, the shift of the curves did not occur at all, although the oxygen partial pressure in the arterial and venous blood was depressed markedly. As in patients of the first subgroups, individuals of the third subgroup showed a distinctness of hypoxic shifts corresponding to the clinical and electrocardiographic pattern of damage to the myocardium and coronary vessels.

Thus, hypoxia - the earliest concomitant to atherosclerotic heart damage - appears in many respects to predetermine the disturbance of the myocardial contractile function. And while hypertonia may also play a certain role in this respect in patients of the first and second groups, hypoxia occupies one of the foremost positions in persons of the third subgroup as a cause of the emergence and development of circulatory insufficiency.

All of this no doubt dictates the use of certain therapeutic measures. Oxygen therapy and therapeutic exercises may be effective in countering hypoxia in atherosclerotic patients; this would apply in particular to breathing exercises that tend to lower the frequency and deepen respiration, improving the ventilation capacity of the lungs and diffusion of gases in the pulmonary circulation.

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[List of Transliterated Symbols]

- 373 M3 CCCP = MZ SSSR = Ministerstvo Zdravookhraneniya SSSR = USSR
Ministry of Public Health
- 373 МОД = MOD = minutnyy ob'yem dykhaniya = respiratory minute
volume

PATHOGENESIS OF ARTERIAL HYPOXEMIA IN RHEUMATIC HEART DISEASE

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(Kiev)

Determination of the oxygen content in the arterial blood has been adopted extensively as a part of clinical practice. Most operations in thoracic surgery, oxygen therapy, and therapeutic exercising are conducted with oxymetric monitoring. Knowledge of the degree to which the arterial blood is saturated with oxygen also permits us to press closer to a determination of the compensatory potential of pulmonary respiration and to detect disturbances to pulmonary circulation. Considerable importance is attached to this index in studies of patients with disorders of the cardiovascular system. However, the literature presently available shows no consistent opinion as to the level of oxygen saturation of the arterial blood in rheumatic heart disease, and in cases with arterial hypoxemia, its pathogenesis is complex and in many cases disputable.

The majority of authors maintain that in patients with diseases of the cardiovascular system, the oxygen saturation of the arterial blood is usually not affected in the stage in which circulation is compensated (Kharrop, Karraso, Blum, A.M. Gurova and others). However, the opinion has been advanced that it may be subnormal even in the stage of circulatory compensation (I. Boytkevich and D.Ya. Shurygin, V.I. Il'inskiy and G.S. Kiseleva). Many authors find that the oxygen saturation of the arterial blood is lowered markedly only in the presence of distinct signs of cardiovascular insufficiency (N.D. Strazhesko, V.Kh. Basilenko,

N.A. Kurshakov, A.G. Dembo, I.F. Lulakov and others). I.V. Bazilevich and N.M. Turovets, S.I. Vul'fovich and L.I. Georgiyevskaya note arterial hypoxemia only in patients with stage III circulatory insufficiency and in occasional cases in stage II. Some authors find that arterial hypoxemia is altogether uncommon in cardiovascular insufficiency (Eppinger, B.M. Shershevskiy, Dotreband). The question as to the degree to which activation of the rheumatic process influences the oxygen content in the arterial blood has been neglected.

To shed light on these questions, we studied 124 patients with rheumatic heart disease in various stages of circulatory insufficiency and with varying activities of the rheumatic process. In the patients observed, we determined the blood gases by the Sechenov-Van Slyke method, the uniformity of the air distribution in the lungs, spirometry, pulmonary gas exchange, oxyhemography, pneumography, etc., in complex with other studies.

The oxygen saturation of the arterial blood decreased only in a few patients with mild mitral heart defects, and in many in whom the heart defects were manifest in the stage of circulatory compensation and in most patients with mounting circulatory insufficiency. On the average, the oxygen saturation of the arterial blood in the stage of circulatory compensation was at the lower limit of the normal range: $M = 94.1 \pm 4.6\%$. It should be noted that of the 45 patients of this group, the oxygen saturation of the arterial blood was found to be markedly depressed in 14. In patients with stage IIA circulatory insufficiency, the average was $M = 90.5 \pm 6.2\%$, while in patients with IIB circulatory insufficiency $M = 88.9 \pm 4.7\%$, and in stage III, $M = 91.5 \pm 2.8\%$.

Irrespective of the degree of the circulatory insufficiency, the oxygen saturation of the arterial blood decreased in patients with pro-

tracted septic endocarditis (the difference is statistically significant as compared with the other groups).

The question as to the pathogenesis of arterial hypoxemia in the patients studied is rather complex. When the values of arterial blood oxygen saturation are compared in each individual case with other indices of pulmonary respiration and data from general clinical examination, no consistent pathogenetic factor was detected in the appearance of arterial hypoxemia.

Most characteristic for all patients with arterial hypoxemia was an increase in the stagnation of blood in the lungs and the resulting decrease in total pulmonary capacity. On this basis, it might be assumed that the drop in arterial blood oxygen saturation in patients with rheumatic heart disease set in as a result of the decrease in total pulmonary ventilation and inadequate absorption of oxygen. However, a study of pulmonary gas exchange showed that the decrease in total lung volume does not result in a decrease in ventilation and absorption of oxygen in 1 minute. Even in patients with a total pulmonary volume below 50% of normal, the ventilation of the lungs and the absorption of oxygen per 1 min were found to be much higher than in the normal state. Thus, in patients in the dystrophic stage of circulatory insufficiency, the total capacity of the lungs (vital capacity + residual air) M was $69 \pm 9.4\%$ of the normal value, while the absorption of oxygen in 1 min $M = 114 \pm 22.5\%$, and the pulmonary ventilation $M = 177 \pm 41.9\%$.

As a result of the high pulmonary ventilation, the oxygen partial pressure in the alveolar air was found to have increased: $M = 116 \pm 11.1$ mm Hg.

Thus, the mechanism indicated above to account for the appearance of arterial hypoxemia must be regarded as unsubstantiated, the more so since the blood minute volume was considerably below normal for the

given absorption of oxygen per 1 minute. In many patients with arterial hypoxemia, the uniformity of air distribution in the lungs was thrown off. It changed particularly substantially in stage II and III circulatory insufficiency. In patients with actively proceeding endocarditis, as compared with the inactive phase of the rheumatism, more significant focal difficulties in bronchial passage were detected.

It should be noted that the uniformity with which air is distributed in the lungs was determined here by the method of L.L. Shik, A.M. Kulik and M.G. Shneyderovich with slight modifications, and by a modified method with seven-minute inhalation of oxygen. Both of these methods produce data of a specific kind and should complement one another.

Many authors assume that nonuniform ventilation of the lungs may be the basic cause of arterial hypoxemia (Holden, N.N. Savitskiy, A.A. Tregubov, B.P. Kushelevskiy, A.M. Blinova and M.Ye. Marshak, A.G. Dembo et al.). Actually, the most significant arterial hypoxemia was observed in patients with particularly acute deviations from uniformity in the pulmonary air distribution, and improvement of the air-distribution uniformity in the lungs in these patients was accompanied by a rise in the oxygen saturation of the arterial blood. In 19% of cases, however, together with normal oxygen saturation of the arterial blood we also detected a pronounced deviation from uniformity in the distribution of air in the lungs, and in some of the patients with arterial hypoxemia the degree to which the uniformity was upset did not always correspond to the degree to which the oxygen saturation of the arterial blood had been lowered. In such cases it appears necessary to take into consideration the state of the regulatory mechanisms that coordinate pulmonary ventilation and pulmonary circulation, as well as other factors. Among the latter, no small importance attaches to impeded diffusion of oxygen through the hemorespiratory barrier. This was indicated by a de-

terioration in the utilization of oxygen in the inspired air with the uniformity of pulmonary air distribution comparatively close to normal. In recent years the phenomena of oxygen diffusion the hemorespiratory barrier have also been linked with the time of contact between the blood and the air in the pulmonary capillaries (Kurnan, Richards).

From this standpoint, we can account for the following apparently paradoxical facts: in patients with combined mitral heart defects, re-cidive endocarditis and predominantly dextral circulatory insufficiency, the oxygen saturation of the arterial blood ($M = 84.9 \pm 4.8\%$) was found to be lower than when sinistral insufficiency predominated, in which case $M = 91.1 \pm 7.6\%$ (statistically reliable difference). In the inactive phase, the oxygen saturation of the arterial blood was higher: $M = 94.1 \pm 6\%$, although in certain patients low-side indicators were also noted.

In analyzing the results of our study of pulmonary respiration in patients with predominant sinistral circulatory insufficiency, it was possible to note higher figures for pulmonary ventilation, absorption of oxygen in 1 min, the oxygen partial pressure in the alveolar air and the slowdown of pulmonary circulation as compared with the figures for other patients. This provides a basis for the idea that in patients with predominantly sinistral circulatory insufficiency, the percentage saturation of the arterial blood with oxygen was higher than when dextral circulatory insufficiency predominates, as a result of superior coordination of the pulmonary circulation due to a higher oxygen partial pressure in the alveolar air and longer contact between the alveolar air and the capillary blood.

The fact that the oxygen saturation of the arterial blood was more distinctly depressed in patients with actively proceeding endocarditis, particularly the subacute septic type, as compared with inactive phase

of rheumatism is worthy of attention. It can be assumed that the disturbance to the uniformity of air distribution in the lungs and the raising of the hemorespiratory barrier, which manifested in smaller residual air volume, had an influence on this. These same patients showed a more accelerated pulmonary blood flow (as determined by the magnesia method) as compared with the inactive phase, and this resulted in a shorter oxygenation time and might, in the presence of the above changes in the lungs, further aggravate the arterial hypoxemia. If enzymes are a factor in the oxygenation process (Tomas), then it may be assumed that when endocarditis is proceeding actively, and in cases of the subacute septic type in particular, in which many enzymatic processes are disturbed, this factor also figures in the appearance of arterial hypoxemia. It would appear that a change in the properties of the hemoglobin itself and in the pH of the blood (A.A. Tregubov, R.M. Povolotskaya) also has a certain significance here.

During sojourns in the oxygen tent, most of the patients showed oxygen saturations reaching 98-100% in the arterial blood. In some patients, however, this percentage did not rise even to the lower limit of the normal range, thus providing a basis for the suspicion that venous blood is entering the arterial stream, detouring around the pulmonary capillaries (S.I. Vul'fovich, Ross'ye, Yulikh, Pal'me et al.). In occasional cases, we observed a decline in the oxygen saturation of the arterial blood (from oxyhemography and pneumography data) with respiratory arrhythmias - undulating and Cheyne-Stokes respiration. The widest fluctuations of the arterial-blood oxygen-saturation index during a single period reached a maximum of 18-20%. Thus, we may arrive at the following conclusions:

1. The oxygen saturation of the arterial blood began to fall even in the early stages of development of the rheumatic process; it had de-

creased markedly when the cardiac defects became manifest with increasing circulatory insufficiency, particularly in subacute septic endocarditis.

2. The pathogenesis of arterial hypoxemia in rheumatic disease of the heart is complex. The drop in the oxygen saturation of the arterial blood is the result of a disturbance to the uniformity of air distribution in the lungs, impaired diffusion of oxygen through the hemorespiratory barrier, admixture of venous blood into the arterial stream, shunting the pulmonary capillaries, and respiratory arrhythmia. In the individual groups of patients, and in each patient taken alone, we observe a combination of various factors. The significance of each of them in the development of arterial hypoxemia depends on the course and severity of the rheumatic process and the development of cardiac defects and circulatory insufficiency.

BASAL METABOLISM AND EXTERNAL RESPIRATION IN CHRONIC ARTERIAL
HYPOXEMIA CAUSED BY CONGENITAL HEART DEFECTS

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(Moscow)

Congenital heart defects are of interest to the physiologist studying external respiration not only from the standpoint of functional diagnostics, but also from a general theoretical standpoint.

There is a group of patients suffering from congenital hemodynamic anomalies of the so-called "blue type," in which chronic arterial hypoxemia is created immediately after birth. This group may serve as an example of the elaboration of long-term adaptations to chronic oxygen starvation due to a drop in the oxygen partial pressure in the arterial blood.

Problems of the external respiration of patients with blue defects are discussed in the specialized papers of R.A. Meytin (1954), R.A. Meytin, V.Ya. Shapovalov and L.F. Sherdukalev (1956), I.S. Shiryayev (1959), B.M. Lipovetskiy (1958), Bing et al. (1948), Devison et al. (1953) as well as in papers concerned with description of congenital heart defects and their surgical treatment (A.N. Bakulev and Ye.N. Meshalkin, 1955; K. Littman and R. Fono, 1954; P. Wood, 1956, et al.).

Nevertheless, it appears to the present authors that certain questions - particularly those concerning the relation between external respiration and the energy exchanges in the organism in this type of chronic hypoxemia - have not yet been adequately clarified. We shall attempt to make this analysis in the present paper.

We ran basal-metabolism tests on 150 patients with congenital heart defects, who had shown arterial hypoxemia, including 100 with a diagnosis of "Fallot's tetrad." The diagnoses were made by physician-surgeons of the A.V. Vishnevskiy Surgery Institute of the Academy of Medical Sciences USSR on the basis of complex clinical examination and soundings of the heart, and were confirmed in surgery.

In Fallot's tetrad, the basic hemodynamic disturbances involve venous blood entering the arterial stream, bypassing the lungs, and a decrease in the quantity of blood flowing through the pulmonary circulation. Patients of this group are more suitable for analysis of the problem that we set up than are patients with other blue defects (of the type of Eisenmenger's complexes) and overstrain of the pulmonary circulation, as a result of which they may show changes in external respiration due to factors other than hypoxemia.

TABLE 1

Average Weight, Height, Basal Metabolism and Pulmonary Ventilation Date by age Groups

Возраст, лет	Число больных	Вес, кг	Рост, см	Основной обмен в % отклонения от нормы	КИ O ₂ , мл/л	Мод. % к норме	ДК
1	2	3	4	5	6	7	8
3-6	14	15,9	106	+ 7,4	29,7	137	0,76
7-9	22	20,9	121,0	+ 3,1	31,1	150,8	0,76
10-12	22	22,7	126,2	+ 1,9	31,0	138,6	0,77
13-15	9	26,1	150,9	+ 6,7	32,3	139,1	0,82
16-20	15	31,3	162,1	+ 1,0	30,6	136,7	0,75
21 и старше	8	32,4	160,0	+13,0	35,8	135,9	0,77
10 всего	100	-	-	+4,2	31,6	141,2	0,77

1) Age, years; 2) number of patients; 3) weight, kg; 4) height, cm; 5) basal metabolism in % deviation from norm; 6) KI of O₂, ml/liter; 7) MOD, % of norm; 8) DK; 9) 21 and older; 10) total.

We studied the basal metabolism (for two days on each patient), using the Douglas-Holden method on some patients and the A00Z-SKTB (Kazan') apparatus on others, with oxygen breathing (in addition to

consumption of O_2 , the elimination of CO_2 can also be taken into account with this apparatus). Then we calculated the deviations of the basal metabolism from the norm as computed from the tables of Harris-Benedict, the O_2 utilization coefficient in ml/liter (KI of O_2), and the respiratory coefficient (DK). The vital capacity (ZhYeL) and its fractions were measured with the patient in the standing position. The oxygen saturation of the arterial blood (at rest) was determined in a cuvette oximeter on a specimen of arterialized blood taken from a finger after warming the hand. Among the special techniques used for studying the external respiration, the residual air was measured on some of the patients (by the method of diluting helium in a VNIIM10 apparatus), as was the resistance of the air passages (using a VNIIM10 pneumotachograph); this was complemented by electromyography of the respiratory muscles. Table 1 presents average data on the weights, heights and the quantities characterizing energy metabolism and pulmonary ventilation by age groups.

TABLE 2

Distribution of Patients by Age and by Deviation of Basal Metabolism from Normal

Возраст, лет 1	Общее число больных 2	3 Отклонение от нормы в %				
		ниже -30 до -21 % 4	от -20 до -11 % 5	норма ±10 % 6	от +11 до +20 % 7	от +21 % и выше 8
3-6	14	—	1	6	3	4
7-9	32	3	4	14	7	4
10-12	22	1	3	14	2	2
13-15	9	—	—	7	—	2
16-20	15	1	2	8	3	1
21 и старше 9	8	—	—	4	1	3
Итого 10	100	5	10	53	16	16

1) Age, years; 2) total number of patients; 3) basal metabolism in percent; 4) below -30 to -21%; 5) from -20 to -11%; 6) normal ±10%; 7) from +11 to +20%; 8) from +21% up; 9) 21 and older; 10) total.

As has been noted more than once in clinical handbooks, and as proceeds from the tabular data given, children with chronic hypoxemia

lag behind healthy children in weight and height. The difference is particularly significant in children aged from 7 to 12 years. The average anthropometric indices for healthy children of this age are higher by approximately 10 kg and 10 cm than the averages for our patients.

The mean deviation of the basal metabolism from the norm as calculated from the actual weight and height ranged from +1 to +7% in all groups of children and adolescents; in the adult patients, the average deviation from the norm was +13%. It is necessary to note, however, that the mean deviation does not reflect those disturbances to metabolism that occurred in these patients. Table 2 shows the distribution of the patients by deviation of the metabolism from normal. In only half of the patients was the metabolism within the normal range of variation, i.e., $\pm 10\%$; 32 had elevated metabolism (extreme deviation up to +53%), while 15 showed an extreme deviation to -31%. In the group of patients aged 7-9 years, deviations from normal are encountered in more than half of the cases - in 18 patients out of 32.

Thus, the disturbances to the metabolism did not all go in the same direction. Bing assumes that the depressed metabolism that he observed in patients with arterial hypoxemia might be accounted for in terms of adaptation of the tissues to chronic hypoxemia. However, we observed a decrease in metabolism in our patients only in a small number of cases. On the other hand, despite the chronic hypoxemia, a tendency toward increased metabolism that became stronger with increasing age was noted.

If, however, we adopt this standpoint in considering the correspondence with the age norms, it can be stated that the amount of oxygen consumed per minute and, accordingly, the energy metabolism averaged lower in these patients than in healthy children, and in proportion as the patients lagged behind healthy individuals in height and weight.

It is difficult to say whether this is an adaptation to chronic hypoxemia or a pathological shift resulting from it, but it seems to us that the latter is more likely.

TABLE 3

Oxygen Saturation of Arterial Blood (data averaged over age groups and distribution of patients by severity of hypoxemia)

Возраст, лет 1	Общее число больных 2	3 Распределение больных по интенсивности гипоксемии					Среднее процентное HbO ₂ 8
		69% HbO ₂ и ниже 4	70-79% HbO ₂ 5	80-89% HbO ₂ 6	90% HbO ₂ и выше 7		
3-6	12	2	4	4	2	78.2	
7-9	25	9	11	2	3	72.8	
10-12	13	6	5	2	—	71.0	
13-15	7	—	2	5	—	81.3	
16-20	7	1	3	2	1	80.6	
21 и старше 9	6	—	3	3	—	81.0	
Всего 10	70	18	28	18	6	75.8	

1) Age, years; 2) total number of patients; 3) distribution of patients by severity of hypoxemia; 4) 69% HbO₂ and lower; 5) 70-79% HbO₂; 6) 80-89% HbO₂; 7) 90% HbO₂ and higher; 8) average percentage of HbO₂; 9) 21 and older; 10) total.

Hypoxemia is manifest in all patients (Table 3). The HbO₂ index of the arterial blood averaged around 76%, 78% in the youngest group of children, 73% in the group of children aged from 7-9 years, 71% in the 10-12-year age group and around 81% in children of all older age groups. The gravity of the clinical state of the children in the first three groups generally matched the decrease in the HbO₂ percentage of the arterial blood. An exception is found in patients in whom we observed attacks of cyanotic shortness of breath, which caused a sharp deterioration of the patient's state as compared with the state in which he was examined. In the older age groups, there was in general no strict correspondence between the clinical severity of the disease and the HbO₂ percentage in the arterial blood.

Our attention is drawn to the increase in pulmonary ventilation,

which may be related to the constant stimulation of the chemoreceptors in the sinocarotic and cardioaortic zones by the subnormal pO_2 in the arterial blood. The hyperventilation was noted both with reference to the necessary oxygen consumption (on the average, the MOD was 141% of normal) and with respect to the actual oxygen consumption (on the average, the KI of O_2 was 31 ml/liter as against a norm of 40 ml/liter). Here the respiratory frequency was not increased in the overwhelming majority of cases, so that the pulmonary ventilation was increased by deepening breathing, i.e., by true alveolar hyperventilation.

TABLE 4

Comparison of Oxygen Saturation of Arterial Blood with Respiratory Minute Volume in Patients with Fallot's Tetrad

Respiratory Min. Volume % of normal	Number of Patients	Respiratory minute volume in % of normal					
		100% or lower	101 to 120%	121 to 150%	151 to 200%	201% or more	
Up to 90	9	3	2	1	—	—	
Or 89 to 80	10	3	2	1	4	1	
Or 79 to 70	11	5	5	7	6	2	
Or 69 or down	12	1	1	4	7	5	
Total	13	75	12	13	20	17	8

1) Percentage of HbO_2 in arterial blood; 2) total number of patients; 3) respiratory minute volume in % of normal; 4) 100% and lower; 5) from 101 to 120%; 6) from 121 to 150%; 7) from 151 to 200%; 8) from 201% up; 9) [down] to 90; 10) from 89 to 80; 11) from 79 to 70; 12) from 69 down; 13) total.

The most pronounced hyperventilation occurred in the group of children aged from 7 to 12 years, and it was somewhat less marked in younger children and in adult patients. We found no direct correlation between the increase in hypoxemia and the increase in MOD; the scatter of the values was wide, even though the averaged data suggests a tendency toward such a relationship. It can be pointed out that in patients whose arterial blood HbO_2 percentage was depressed only slightly (above 87%), the hyperventilation was moderated (Table 4).

TABLE 5

Comparison of Basal Metabolism with Respiratory Minute Volume

Отклоненіе об- ста в % от нормы от нормы 1	Общее чи- сло боль- ных 2	3 Минутный объем дыхания в %, к норме					
		100 % и ниже 4	от 101 до 120 % 5	от 121 до 150 % 6	от 151 до 200 % 7	от 201 % и выше 8	
Ниже -21 9	5	1	2	—	2	—	
От -10 до -20 10	10	2	6	1	—	1	
Норма +10 11	53	7	10	20	15	1	
От +10 до +20 12	16	1	3	5	5	2	
От +21 и выше 13	16	—	1	5	6	4	
Всего 14	100	11	22	31	28	6	

1) Basal metabolism in % of deviation from norm; 2) total number of patients; 3) respiratory minute volume in % of norm; 4) 100% and below; 5) from 101 to 120%; 6) from 121 to 150%; 7) from 151 to 200%; 8) from 201% up; 9) below -21; 10) from -10 to -20; 11) norm + [sic] 10; 12) from +10 to +20; 13) from +21 up; 14) total.

Nor did we establish a direct relationship between the deviations of basal metabolism from normal and the increase in MOD. It can only be noted that a sharp increase in MOD was observed in patients with elevated metabolism, and only in isolated cases when the metabolism was depressed (Table 5).

The measurements presented showed that the vital capacity in these patients was within normal limits with reference both to age (after Shalkov) and to 1 square meter of body surface (after West and Kal'treyder); the residual-air index, which was measured in some of the patients (after Morza) was also found to be within the range of the age norm for healthy children. Mixing of the helium and settling at constant concentration required 1.5-2 min, which indicates uniform miscibility of the gases in the lungs and uniform pulmonary ventilation. It follows from this that despite chronic hyperventilation, there are no emphysematous changes in the lungs of these patients.

A bronchial-resistance test on the pneumotachograph indicated that the bronchial resistance was about the same at 24-64 mm H₂O during in-

spiration and 30-70 mm H₂O during expiration at a respiratory flow rate of 0.5 liter/sec in the group of patients with blue defects and in the same group of patients without cyanosis. These figures are somewhat higher than those observed in healthy individuals. It is known, however, that in small children the bronchial resistance is many times that in adults, since [sic; so that?] the the figures obtained attest only to age-connected changes in the bronchial resistance.

In children with congenital defects of the Fallot's tetrad type, the electrical activity of the respiratory muscles at rest was, as a rule, elevated markedly; intensified activity was manifest in only some of the adolescent and adult patients, and then to a lesser degree. As we know, the electrical activity of the respiratory muscles may be regarded as an index to effective impulsion coming from the respiratory center. In this case, amplification of excitation in the respiratory center may, as we have already noted, result from arterial hypoxia. The intensified electrical activity, which attests to the constant excitation of the respiratory center, indicates at the same time an increase in the amount of work done by the respiratory musculature. The latter would apparently result in increased consumption of O₂ by the respiratory muscles. Under the conditions of grave chronic hypoxemia, the increased consumption of O₂ by the respiratory musculature and the myocardium, whose work is also made heavier in this disease, further strains the oxygen balance of the organism. From this point of view we can understand the increase in basal metabolism that we observed so frequently. At the same time, and as we have already noted, half of the patients showed metabolism within normal limits, while only a small fraction of them showed a marked increase in basal metabolism. If we take into consideration the fact that in these patients the quantity of O₂ expended by the respiratory and cardiac musculature is in excess of

the norm, then a depression of metabolism in the remaining organs and tissues would appear to be a frequent occurrence.

Thus, for chronic arterial hypoxemia, which differs sharply in its origin from the forms ordinarily encountered (respiratory insufficiency, mountain hypoxemia), persistent hyperventilation is characteristic, just as it is for the common forms of hypoxic hypoxia. The distinguishing feature is the fact that the hyperventilation arises from early childhood and is maintained for the entire life. Although the O_2 consumption corresponds formally in most cases to the basal-metabolism norms (taking weight and height into account), the requirements of all organs and tissues are not fully covered. The opportunities to increase the supply of oxygen in these patients are sharply compromised by the increase in hypoxemia under load, which limits the capacity for muscular activity.

Such constant oxygen starvation and limitation of muscular activity have particularly severe effects in the growing organism, retarding the processes of its development.

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[Transliterated Symbols]

- 386 $K_{O_2} = K_I O_2 =$ koefitsient ispol'zovaniya $O_2 = O_2$ utiliza-
tion coefficient
- 386 $\Delta K = DK =$ dykhatel'nyy koefitsient = respiratory coefficient
- 387 $\text{ЖЕЛ} = \text{ZhYeL} =$ zhiznennaya yemkost' legkikh = vital capacity
(of lungs)
- 387 $\text{ВНИИМО} = \text{VNIIMiO} =$ Vsesoyuznyy nauchno-issledovatel'skiy
institut meditsinskogo instrumentariya i oborudovaniya =
All-Union Scientific Research Institute for Medical In-
strumentation and Equipment

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**МОД - MOD - minutnyy ob"yem dykhaniya - respiratory minute
volume**

CERTAIN ADAPTIVE REACTIONS OF THE ORGANISM IN HYPOXIC STATES
IN HYPERTONIA PATIENTS

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(Kiev)

The development of hypertonia is accompanied by progressively aggravating oxygen insufficiency, a phenomenon noted by both workers in the clinics and experimental researchers.

In the combined adaptation of the organism to mounting hypoxia, great importance is ascribed to the blood system, which provides for transportation of oxygen from the alveolar air to the tissues and carbon dioxide from the tissues to the alveolar air.

One of the indices to the blood's respiratory function is its oxygen capacity. The normal proportions between the oxygen capacity of the blood and its hemoglobin content, which were established by Hufner and according to which 1 g of hemoglobin combines with 1.34 ml of oxygen, are subject to considerable fluctuations under the conditions of the living organism. It has been established by the work of many investigators (A.A. Tregubov, A.G. Ginetsinskiy, Ye.K. Zhukov, G.G. Gazenko and T.I. Abramson, A.M. Charnyy et al.) that the oxygen capacity is not a constant, but varies under both physiological and pathological conditions. A.A. Tregubov found a hemoglobin-oxygen capacity of 1.31-1.34 ml in healthy humans. G.G. Gazenko and T.I. Abramson indicate wider variations: 1.17-1.7 ml of oxygen. The maximum volume of oxygen that can be bound to 1 g of hemoglobin has not yet been exactly established for man.

A distinct drop in hemoglobin-oxygen capacity was detected by A.A.

Tregubov in lobar pneumonia, cancerous cachexia and erythremia, while a mild and unsteady decrease is noted in circulatory insufficiency, the severe forms of sugar diabetes, azotemic uremia and pernicious anemia.

M.I. Zolotareva-Kostomarova and N.G. Stepanov detected fluctuations in the hemoglobin-oxygen capacity (both increases and decreases) in patients suffering from myocardial infarct, while K.M. Malenkova noted similar changes in hypertonia patients.

According to the data of the above authors, the variability of the hemoglobin-oxygen capacity may depend on many factors: changes in the medium surrounding the erythrocyte, the presence of toxic substances in the blood and the appearance of "inactive" hemoglobin products (A.A. Tregubov), as well as changes in the erythrocyte itself.

Without going into the pathogenetic details of the disturbance to the functional properties of hemoglobin, it is important to note the general conviction among researchers that the variability of the hemoglobin's capacity for oxygen in the direction of an increase is one of the compensatory adaptive reactions that the organism calls upon under the conditions of oxygen insufficiency.

In studying the respiratory function of the blood in hypertonia patients, we have drawn attention to the frequent noncorrespondence between the oxygen capacity of the blood and the amount of hemoglobin present, and also to changes in the hemoglobin-oxygen-capacity index in one and the same patient, as well as between patients in different stages of the disease. Taking these observations into account, together with the literature data set forth above, we conducted a number of complementary investigations, juxtaposing the data obtained from the oxygen capacity of hemoglobin with the distinctive features of the erythrocyte population of the blood in these same patients.

Observations were conducted on 140 hypertonia patients under the

conditions of the Hospital Therapy Clinic of the Kiev Medical Institute, based on the Lenin Regional Hospital; of these, according to the classification of N.D. Strazhesko, 42 persons were in stage I, 79 in stage II and 19 in stage III. The following quantities were studied in these patients: gas composition of the blood, hemoglobin content, erythrocyte count, diameter, volume and thickness of erythrocytes, and number of reticulocytes; this was followed by calculation of the oxygen index to hemoglobin capacity (after A.A. Tregubov).

Studies of the patients' blood-gas composition showed varying degrees of oxygen insufficiency in the organism, with a tendency to aggravate as the disease progressed from stage to stage.

In patients in stage I of the illness (42 individuals), the index of hemoglobin-oxygen capacity varied from 1.32 to 1.76, exceeding 1.4 ml of oxygen in the majority of persons examined (72%). Significant lack of correspondence between the amount of hemoglobin and its oxygen capacity was observed in many patients. Thus, in patients S., the erythrocyte count was 5,890,000 in 1 mm³, the hemoglobin content was 108%, and the oxygen capacity of the blood was 23.8% by volume, with the oxygen capacity index at 1.37 ml. In patient G., the erythrocyte count was 4,750,000, the hemoglobin content 90%, the oxygen capacity of the blood 22.8% by volume, and the hemoglobin-oxygen capacity index 1.57 ml of oxygen. Similar variations were observed in other patients.

Patients were observed to show normal erythrocyte contents, with the color index approaching unity (0.9-1.0). The variation curves of erythrocyte diameter were within normal limits. In the erythrocyte formula (according to R.G. Tsibulevskaya), macrocytosis was diffusely manifest in some of the patients together with normal average figures for the diameter, volume and thickness of the erythrocytes.

In patients in stage II of the disease (79 persons), the oxygen capacity of the blood was increased in the overwhelming majority of cases. The hemoglobin-oxygen capacity index varied: in the predominant

majority of patients, it was in the range from 1.4-1.7 ml of oxygen, from 1.3 to 1.4 in 25% of cases, and depressed in 10% of patients, from 1.21 to 1.23 ml of oxygen.

As was the case with patients in stage I of the disease, some of the patients showed lack of correspondence between the amount of hemoglobin and its oxygen capacity. Thus, in patient K., the erythrocyte count was 4,500,000, the hemoglobin at 92%, the blood-oxygen capacity at 22.5% by volume, and the hemoglobin-oxygen capacity index at 1.52 ml. The examinations were repeated a week later: the erythrocyte count was 4,680,000, hemoglobin 96%, blood-oxygen capacity 23.1% by volume and hemoglobin-oxygen capacity 1.5 ml. After still another week, the figures were: erythrocytes 5,050,000, hemoglobin 104%, blood-oxygen capacity 24.3% by volume and hemoglobin-oxygen capacity 1.4 ml.

As will be seen from these data, the hemoglobin-oxygen index decreased in parallel with an increase in the amount of hemoglobin and rising oxygen capacity of the blood. In this case, consequently, the increase in blood-oxygen capacity was achieved at the expense of increasing the amount of hemoglobin, rather than its oxygen capacity.

In patient R., dynamic studies at intervals of 7-10 days showed the following:

Er - 4,200,000, Hb - 80%, blood oxygen capacity - 19.8% by volume,
Hb oxygen capacity - 1.55 ml

Er - 4,640,000, Hb - 92%, blood oxygen capacity - 21.8% by volume,
Hb oxygen capacity - 1.47 ml

Er - 4,000,000, Hb - 78%, blood oxygen capacity - 19% by volume,
Hb oxygen capacity - 1.52 ml

As will be seen from the data given above, a drop in the oxygen capacity of the hemoglobin accompanied the increase in its amount, and the subsequent drop in the amount of hemoglobin was accompanied by a rise in its oxygen capacity. The changes in the oxygen capacity of the

blood followed the changes in the amount of hemoglobin. Similar changes were registered in other patients as well.

As regards the red blood, it was possible in some cases to detect mild degrees of both erythrocytosis and erythropenia against a background of more frequent normal erythrocyte counts. While the average erythrocyte diameter remained unchanged, the variation curve and erythrocyte formula showed certain shifts in the direction of macrocytosis in many of the patients. Periodic reticulocyte shifts were observed.

In the patients in stage III of the disease (19 individuals), observations of normal or only slightly decreased hemoglobin content were attended by a distinct drop in the blood oxygen capacity and in the hemoglobin oxygen index. In four patients, the oxygen capacity index of the hemoglobin varied in the range from 1.3-1.4 ml of oxygen, but as their condition progressively deteriorated, these indices fell off considerably. In some of the patients, we also observed periodic rises in the indices, but basically the hemoglobin-oxygen capacity indices were uniformly depressed.

In patient B., the hemoglobin-oxygen index varied with the state of the patient, although the amount of hemoglobin remained practically stable:

10 March 1962: Hb - 64%; Hb oxygen index - 1.28 ml

20 March 1962: Hb - 66%; Hb oxygen index - 1.32 ml of oxygen.

One day before the death of patient V., the hemoglobin-oxygen capacity index was at 0.92 ml of oxygen. Both anemia and mild erythrocytosis were observed as regards the red blood. The color index was at the upper limit of the normal range. The variational curve of erythrocyte diameters was shifted to the right in most patients. The erythrocyte formula showed manifest macrocytosis. The average volume and thickness of the erythrocytes were also increased somewhat. No essential

changes were noted as regards the reticulocyte population.

On comparing the changes in erythrocyte pattern as observed in patients in different stages of the disease with the changes in the gas composition of the blood and, in particular, with the hemoglobin-oxygen capacity indices in these same patients, and, further, taking the clinical picture into account, we were able to establish that as the hyper-tonia develops and oxygen insufficiency is aggravated, the morphological features of the erythrocytes and the functional properties of the hemoglobin underwent changes.

In stage I of the disease, these changes were rather vague in nature. However, periodic increases in the total erythrocyte and reticulocyte count, as well as the number of erythrocytes approaching the macrocyte state and the distinct tendency toward increased hemoglobin oxygen capacity in stage I and II patients already reflect compensatory stress on the blood's respiratory function as difficulties arise in oxygen exchange.

It is interesting to note that increases in oxygen capacity in stage I and II patients were not always accompanied by an increase in the hemoglobin-oxygen index, but that the reverse was observed quite frequently. In these cases, the concurrently increasing erythrocyte count and hemoglobin content reflected a variety of the blood's compensatory mechanisms, which are assuring the organism its required oxygen budget.

In patients in stage III of the disease, the hemoglobin-oxygen indices also dropped substantially together with the decrease in the oxygen capacity of the blood. The morphological peculiarities also become more evident in the erythrocyte population of the blood. In most of the patients studied during this phase of the disease, an increase in erythrocyte diameter was accompanied by increases in their volume and

thickness as well. If it is remembered that the basic and most important function of the blood - the dissociation of oxyhemoglobin - is performed at the surface of the erythrocytes, we cannot but recognize, in this increase in erythrocyte surface area with the development of hypertonia and the passage from stage to stage, a significant compensatory mechanism whose direction is to support metabolic processes in the organism under the conditions of progressing oxygen insufficiency.

In patients in stage III of the disease, distinct macrocytosis and moderate erythrocytosis are observed in company with an anemic state; microcytes have appeared, and this has given rise to more pronounced anisocytosis. Juxtaposing these data to the blood-gas-composition indices for these patients, which indicate developing tissue hypoxia and functional inadequacy of the hemoglobin, we are struck with the idea that these changes no longer indicate simply an adaptive stress imposed on the blood, but also exhaustion of its capabilities under the conditions of disturbed tissue metabolism in patients in stage III of the disease.

From the above we may conclude that the variability observed in the indices of hemoglobin-oxygen capacity and the variation of the erythrocyte composition of the blood represent compensatory mechanisms of the organism, mechanisms that arise in different combinations at different stages of the organism's adaptation to oxygen insufficiency in hypertonia.

CHARACTERISTICS OF HYPOXIC-DYSTONIC SHIFTS IN THE DIAGNOSIS OF
ENDOCARDITIDES AND THEIR IMPORTANCE FOR THERAPEUTIC PRACTICE

G.Ya. Danish

(Kiev)

In endocarditis patients, the damage to the endocardium is compounded by damage to the vascular system with its abundant endothelial apparatus. In occasional cases, these vascular disorders move into the foreground, while the injury to the endocardium recedes, as it were, into the general pattern of the disease. As we know, the factor of sensitization plays the leading role in the pathogenesis of endocarditis. In studying the clinical varieties of endocarditis, we have an attempt to investigate their relationship to focal infection as the most important factor in sensitization, to determine the injury to the vascular system as a manifestation of sensitization with the available clinical-laboratory techniques, and to examine the respiratory function of the blood and the extent of the hypoxic shifts.

In examining the patients, the general clinical investigations were accompanied by capillaroscopy, measurement of arterial pressure in the orthostatic position, electrocardiography, and gas analysis of the blood, using the Sechenov-Van-slyke apparatus. We investigated 34 patients with different forms of endocarditis. According to N.D. Strazhesko's classification, the patients were distributed as follows: acute and subacute benign endocarditides, 4; chronic endocarditides with indeterminate course, 5; chronic benign endocarditides without disturbances to blood circulation or in the initial stage of blood-circu-

lation disturbance, 25. The data of the study are assembled in Table 1.

Thus, foci of infection were detected in the form of chronic tonsillitis in 23 patients, in hepatocholecystitis in 6 patients, and in caries, sinusitis and the like in 6 other patients. Some of the patients had two and more infection foci. The clinical manifestations of one of the infection foci were taken into account preferentially for these patients. In some cases, this was hepatocholecystitis and maxillary sinusitis; dental caries and chronic hepatitis, and tonsillitis, although the most distinct changes were most frequently encountered in the tonsillar apparatus. Thus, the infection was not monofocal, and in such patients the second focus must be regarded as an additional factor in sensitization.

TABLE 1
Clinical Laboratory Data on Endocarditis Patients

1	2	3			7	8	9	ЭКГ ¹⁰		13	14	15		18	19
		Очаги инфекции	4	5				6	11			12	16		
Характер заболевания	Количество обследованных больных	Тонзиллиты	Гепатохолециститы	Прочие	Артериальная гипоксемия	Венозная гипоксемия	Тканевая гипоксия	Изменение зуб. д. 7	Смещение интервала ST	Синдром типа стенокардии	Изменение пульсового давления	Нарушение проницаемости	Нарушение капиллярного тонуса	Альбинурия	Гематурия
20 Острые и доброкачественные эндокардиты	4	3	—	1	—	—	1	4	3	1	1	4	4	2	1
21 Хронические эндокардиты с неопределенным течением	5	2	2	—	2	3	—	2	3	1	2	4	4	3	2
22 Хронические доброкачественные эндокардиты	25	18	3	5	3	5	2	15	11	13	8	18	12	8	4
23 Итого	34	23	5	6	5	8	3	21	17	15	11	26	20	13	7

1) Nature of disease; 2) number of patients studied; 3) foci of infection; 4) tonsillitis; 5) hepatocholecystitis; 6) other; 7) arterial hypoxemia; 8) venous hypoxemia; 9) tissue hypoxia; 10) EKG; 11) change in T-wave; 12) shift of ST interval; 13) syndrome of stenocardia type; 14) change in pulsepressure; 15) capillaroscopy; 16) disturbed permeability; 17) disturbed capillary tone; 18) albuminuria; 19) hematuria; 20) acute and benign endocarditides; 21) chronic endocarditides with indeterminate course; 22) chronic benign endocarditides; 23) total.

Some of the patients could not indicate the exact date at which the disease had begun, since its manifestations had appeared when the peripheral blood circulation was already interfered with or had been noticed accidentally. Other patients associated the onset of the illness with an attack of angina, with the "grippe," with a rapidly developed syndrome of acute polyarthrititis or arthralgia. The subsequent course of the disease, and its relapses in particular, although associated in most cases with the peculiarities of the focal infection, occasionally occurred after overfatigue, chilling or surgical intervention. Thus, in patient Ts-k, a relapse occurred after commissurotomy, and so severely that decompensation phenomena arose.

Together with complaints of palpitation and irregularity of the heartbeat and shortness of breath, some of the patients placed particular emphasis on pain of a squeezing and crushing type in the region of the heart, with irradiation under the left shoulder blade and into the left arm, particularly after physical exertion and at night. It was not possible to establish a dependence of the stenocardia-type syndrome on the form of the endocarditis, but nevertheless chronic sufferers and patients with aortomitral damage frequently presented such complaints.

The pathogenesis of the coronary-insufficiency syndrome is complex; damage to the vascular connective-tissue structures, vascular dystonia and hypoxic shifts are substantial factors here together with others (F.Ya. Primak, G.M. Povolotskaya, Ya.S. Leshinskaya and others).

The complaints described above, which would incline us to assume damage to the coronary vessels, were confirmed by EKG data. Thus, in 21 patients, the T-wave was modified, and in 15 the ST interval was shifted; this may be regarded as a manifestation of myocardial hypoxia, a disturbance to the permeability and tone of its vessels. A disturbance in vascular tone was indicated by data from measurements of ar-

terial pressure, particularly in the orthostatic position, when the pulse pressure dropped for six to ten minutes from 50 to 20, while the oscillatory index was halved. On capillaroscopy of the nailfold, 20 patients showed disturbances to capillary tonus in the form of tortuosity, constriction, aneurismatic protuberances and occasionally even paresis. The permeability disturbance could be judged from the turbidity of the basic background in the field of view, which sometimes rendered it impossible to distinguish the shape of the capillaries. Together with pronounced pericapillary edematization, escape of erythrocytes outside the capillary stream, with formation of extravasates, was observed in occasional cases. Urinalysis also indicated an elevated permeability of the capillaries, witness albuminuria (13 patients) and hematuria (7 patients) ranging from traces to distinct degrees, but most often of the microhematuric type. The above manifestations in the endocarditis patients suggest injury to vessels in various organs. As an example, let us present a brief extract of a case history.

Patient S-sh, 25 years old, Case History No. 3933. On 25 February 1962 was delivered by ambulance to 1st Surgical Division of the Hospital Named for the October Revolution from the treatment division of one of the regional hospitals around Kiev, with complaints of sharp pains in the upper abdomen, shortness of breath, palpitation of the heart, and a high temperature. He regards himself as having been ill since 1952, when he first suffered shortness of breath after a spell of acute polyarthritis. In February 1962, after an attack of angina, his temperature rose to 39° C and all his joints became acutely painful; the joints swelled and the patient was admitted to his neighborhood therapeutic ward where his state gradually improved. On 24 February 1962, his temperature rose to 38° C, the pain in the joints again intensified, a rash of the erythema annularis type appeared, together with sharp pains

in the abdomen, bloody stool, and urine the color of meat washings. This state recurred on 2-3 March, and the patient was transferred to the 1st therapeutic division with the following diagnosis: exacerbation of chronic endomyocarditis, polyarthrititis; mitral insufficiency, stenosis of the left venous orifice, diffuse vasculitis. On 20 March, the patient developed an acute attack of pain in the region of the heart, accompanied by a sensation of suffocation. The attack was cut short by administration of cardiac vasodilators and prescription of oxygen.

Blood analysis of 26 February 1962: erythrocyte count 5,350,000, hemoglobin 103%, leucocytes 25,400, stabnuclear 13, segmented 77, lymphocytes 6, monocytes 4, ROE [erythrocyte sedimentation test] 4 mm. On 10 March 1962: erythrocytes 4,090,000, hemoglobin 66%, leucocytes 4600, eosinophils 2, stabnuclear 3, segmented 61, lymphocytes 31, monocytes 4, ROE 11 mm.

Urinalysis: Albuminuria 3.3%, hematuria 40-60 slightly modified and leached-out erythrocytes in the field of view.

Arterial pressure: 90/50-100/60 mm Hg.

Capillaroscopy: Severe turbidity in the field, so pronounced that it was impossible to make out the size of the capillary. The field background was reddish-pink in color.

12 March 1962. EKG. Sinusoidal rhythm, pulse 108 per min, PQ 0.20, QRS 0.08, QT 0.32, distinct Q in derivations II-III and CR₄. ST_{I,II, CR_{4,6}} descended under isoelectric line. T_I + 1, T_{II} + 2, T_{CR₄} + 2, T_{CR₆} + 3.

28 March 1962. Sinusoidal rhythm, pulse 84 in 1 min, PQ 0.17, QRS 0.07, QT 0.32, Q in I-II > 2. ST_{I, II, CR_{4,6}} descended below isoelectric line. T_I + 1, T_{II} + 2, T_{III} + 3, T_{CR₄} + 4.

12 March. Blood gases. Arterial blood: oxygen content 16.06% by volume, CO₂ 48.78% by volume. Venous blood: oxygen content 6.47% by

volume, CO_2 54.97% by volume. Arterial venous difference in oxygen 9.59% by volume. Venosarterial difference in CO_2 6.9% by volume. Oxygen capacity 17.5. Percentage saturation of arterial blood 91, of venous blood 37.

The damage to the vascular structures in this patient, with the sharply pronounced disturbance to permeability and dystonia can be accounted for in terms of arterial hypoxemia (16.06% by volume, lower limit of normal range), and by venous hypoxemia, which is undoubtedly reflected in the vascular endothelium and endocardium and may serve as an explanation for the variety of clinical manifestations observed in this patient. Among the 34 endocarditis patients, we ran blood-gas composition analyses on 22 (see Table 2).

Investigations of the oxygen and carbon dioxide contents in the arterial and venous blood of 22 patients out of the total number observed brought out changes in the gas composition of the blood in a majority of them. These deviations could be detected in both acute and chronic forms of endocarditis. However, a particularly interesting point is the decrease in the arteriovenous oxygen difference. Thus, in patient S-ts, who was suffering from acute endocarditis, we noted a decrease in the arteriovenous oxygen difference to below 4% by volume, with an elevated oxygen content of 14.8% in venous blood, an observation suggesting that the utilization of oxygen by the organism's tissues had deteriorated.

In two chronic endocarditis patients in which the course of the disorder was indeterminate, we detected arterial hypoxemia, while venous hypoxemia was found in three. Among the 25 patients with chronic benign endocarditis, we studied the blood gas composition in 17. In this group, arterial hypoxemia was detected in three patients, venous hypoxemia in five and tissue hypoxemia in two.

TABLE 2
Blood Gases in Endocarditis Patients

1 Case No.	2 Surname	3 No. analysis											12 No. analysis in hospital																						
		4 Arterial blood			5 Venous blood			8 Arterial-venous difference in pO ₂		9 Venous-arterial difference in pO ₂		10 Oxygen saturation		11 Percent ventilation		4 Arterial blood			5 Venous blood			8 Arterial-venous difference in pO ₂		9 Venous-arterial difference in pO ₂		10 Oxygen saturation		11 Percent ventilation							
6 pO ₂	7 pCO ₂	8 pH	9 pO ₂	10 pCO ₂	11 pH	12 pO ₂	13 pCO ₂	14 pH	15 pO ₂	16 pCO ₂	17 pH	18 pO ₂	19 pCO ₂	20 pH	21 pO ₂	22 pCO ₂	23 pH	24 pO ₂	25 pCO ₂	26 pH	27 pO ₂	28 pCO ₂	29 pH	30 pO ₂	31 pCO ₂	32 pH	33 pO ₂	34 pCO ₂	35 pH						
23	Сва	18.7	43.7	14.8	53.4	3.9	9.7	16.7	23.6	94/86	22.3	44.1	12.9	47.4	6.3	5.0	18.7	23.3	95/85	22.3	44.1	12.9	47.4	6.3	5.0	18.7	23.3	95/85	22.3	44.1	12.9	47.4	6.3	5.0	
15	Г-а	18.1	33.5	14.2	47.6	4.9	14.4	21.0	30.4	90/67	19.5	35.7	9.7	49.7	9.8	14.0	18.1	35.7	90/67	19.5	35.7	9.7	49.7	9.8	14.0	18.1	35.7	90/67	19.5	35.7	9.7	49.7	9.8	14.0	
16	Г-а	16.8	37.0	9.5	57.2	7.3	20.2	19.3	17.0	87/49	-	-	-	-	-	-	16.8	38.9	94/72	16.8	38.9	9.0	49.5	7.8	10.6	16.0	38.9	94/72	16.8	38.9	9.0	49.5	7.8	10.6	
18	К-а	18.7	38.1	9.7	43.1	7.0	11.0	18.7	23.6	94/84	-	-	-	-	-	-	18.7	38.1	94/84	-	-	-	-	-	-	18.7	38.1	94/84	-	-	-	-	-	-	
19	Г-а	17.7	34.0	9.8	44.9	13.9	10.9	24.2	24.2	98/40	16.8	38.9	9.0	49.5	7.8	10.6	17.7	34.0	98/40	16.8	38.9	9.0	49.5	7.8	10.6	17.7	34.0	98/40	16.8	38.9	9.0	49.5	7.8	10.6	
20	Ш-а	16.0	49.2	14.6	54.5	1.4	5.3	17.0	17.0	94/72	-	-	-	-	-	-	16.0	49.2	94/72	-	-	-	-	-	-	16.0	49.2	94/72	-	-	-	-	-	-	
22	В-а	23.4	34.9	13.6	51.3	8.8	16.4	23.6	30.4	95/86	22.3	44.1	12.9	47.4	9.4	3.0	23.4	34.9	95/86	22.3	44.1	12.9	47.4	9.4	3.0	23.4	34.9	95/86	22.3	44.1	12.9	47.4	9.4	3.0	
23	С-а	18.2	40.3	13.3	46.5	4.9	6.2	20.4	20.4	90/65	23.2	37.8	12.4	52.9	10.8	15.1	18.2	40.3	90/65	23.2	37.8	12.4	52.9	10.8	15.1	18.2	40.3	90/65	23.2	37.8	12.4	52.9	10.8	15.1	
24	К-а	18.7	40.1	6.1	48.4	6.6	8.3	18.1	21.6	95/80	20.8	39.8	14.3	50.3	6.5	10.5	24	К-а	18.7	40.1	6.1	48.4	6.6	8.3	18.1	21.6	95/80	20.8	39.8	14.3	50.3	6.5	10.5		
25	С-а	20.9	44.9	6.6	45.9	12.3	11.0	19.8	21.6	95/86	20.4	42.8	15.8	57.9	4.6	9.7	25	С-а	20.9	44.9	6.6	45.9	12.3	11.0	19.8	21.6	95/86	20.4	42.8	15.8	57.9	4.6	9.7		
26	С-а	18.1	50.0	11.6	53.9	7.5	3.9	20.9	20.9	91/57	19.3	46.9	7.6	61.1	13.3	14.2	26	С-а	18.1	50.0	11.6	53.9	7.5	3.9	20.9	20.9	91/57	19.3	46.9	7.6	61.1	13.3	14.2		
27	Г-а	22.2	41.0	7.9	47.0	14.3	6.0	20.9	20.7	95/86	19.9	48.4	13.7	50.9	6.2	2.5	27	Г-а	22.2	41.0	7.9	47.0	14.3	6.0	20.9	20.7	95/86	19.9	48.4	13.7	50.9	6.2	2.5		
28	В-а	18.7	41.8	6.0	42.5	13.7	1.0	21.0	21.0	90/67	19.5	37.7	9.7	49.7	9.8	14.0	28	В-а	18.7	41.8	6.0	42.5	13.7	1.0	21.0	21.0	90/67	19.5	37.7	9.7	49.7	9.8	14.0		
29	В-а	19.1	33.2	14.2	47.6	4.9	14.4	21.0	18.4	89/60	-	-	-	-	-	-	29	В-а	19.1	33.2	14.2	47.6	4.9	14.4	21.0	18.4	89/60	-	-	-	-	-	-	-	-
30	В-а	18.4	36.2	11.2	52.9	5.2	17.7	18.4	22.5	87/67	19.9	45.5	8.8	56.1	11.1	12.1	30	В-а	18.4	36.2	11.2	52.9	5.2	17.7	18.4	22.5	87/67	19.9	45.5	8.8	56.1	11.1	12.1		
31	В-а	18.4	46.7	15.2	56.1	4.4	11.6	22.5	21.1	89/65	-	-	-	-	-	-	31	В-а	18.4	46.7	15.2	56.1	4.4	11.6	22.5	21.1	89/65	-	-	-	-	-	-	-	-
32	С-а	18.9	44.7	6.4	46.8	8.1	2.1	21.1	21.1	91/57	15.1	43.1	9.1	49.0	6.0	5.9	32	С-а	18.9	44.7	6.4	46.8	8.1	2.1	21.1	21.1	91/57	15.1	43.1	9.1	49.0	6.0	5.9		
33	С-а	18.0	44.7	6.4	46.8	9.6	6.2	21.7	21.7	94/57	-	-	-	-	-	-	33	С-а	18.0	44.7	6.4	46.8	9.6	6.2	21.7	21.7	94/57	-	-	-	-	-	-	-	-
34	С-а	20.5	48.7	12.4	53.2	6.1	4.5	21.7	21.7	94/57	19.1	42.1	10.1	43.7	9.0	1.6	34	С-а	20.5	48.7	12.4	53.2	6.1	4.5	21.7	21.7	94/57	19.1	42.1	10.1	43.7	9.0	1.6		
35	В-а	18.4	43.2	9.6	46.3	6.8	2.1	17.6	17.6	93/64	19.3	42.4	8.2	51.6	11.1	9.2	35	В-а	18.4	43.2	9.6	46.3	6.8	2.1	17.6	17.6	93/64	19.3	42.4	8.2	51.6	11.1	9.2		
36	В-а	17.1	38.9	11.5	42.9	5.5	6.0	18.1	18.1	94/64	19.9	38.9	10.1	44.1	9.5	5.2	36	В-а	17.1	38.9	11.5	42.9	5.5	6.0	18.1	18.1	94/64	19.9	38.9	10.1	44.1	9.5	5.2		
37	В-а	17.6	38.6	15.2	51.3	2.4	14.7	18.4	18.4	95/62	19.9	46.4	12.4	57.6	7.5	9.1	37	В-а	17.6	38.6	15.2	51.3	2.4	14.7	18.4	18.4	95/62	19.9	46.4	12.4	57.6	7.5	9.1		

1) Patient's surname; 2) diagnosis; 3) before treatment; 4) arterial blood; 5) venous blood; 6) O₂ content in % by volume; 7) CO₂ content in % by volume; 8) arteriovenous O₂ difference; 9) venoarterial CO₂ difference; 10) oxygen capacity; 11) percentage saturation of arterial/venous blood; 12) after treatment with oxygen and medications; 13) S-tsa; 14) acute benign endocarditis; 15) G-ye; 16) T-ch; 17) chronic endocarditis with indeterminate course; 18) K-k; 19) G-n; 20) Sh-ya; 21) chronic benign endocarditis; 22) B-v; 23) S-zh; 24) K-y; 25) F-ko; 26) S-n; 27) P-k; 28) Sh-ko; 29) K-uk; 30) P-va; 31) B-n; 32) S-ko; 33) S-sh; 34) V-va; 35) M-v; 36) Ya-na; 37) M-ko.

G.M. Povoitskaya, who links hypoxia to an intensification of the oxydative processes, makes reference to the occurrence of subacute hypoxia in patients suffering from chronic benign endocarditis.

The observed cases of arterial hyperoxia (4 cases) may be regarded as a compensatory amplification of the blood's respiratory function, and the low arteriovenous oxygen difference (below 4% by volume) may be taken as testimony to the presence of a kind of anaerobic type of metabolism. This is also suggested by the high content of oxygen in the venous blood, which sometimes reaches 15-15% by volume.

The capillary damage detected in capillaroscopy, the manifest albuminuria and hematuria and the clear-cut syndrome of coronary insufficiency (stenocardia syndrome) oblige us to give special attention to the peripheral vessels. Functional changes in these vessels and their inadequacy are indicated not only by the signs of vascular dystonia and capillaritis, but also by prominent signs of sometimes arterial and sometimes venous hypoxemia.

The variability observed in the manifestations of hypoxemia, and the way in which its symptoms are aggravated under unfavorable conditions, oblige us to reexamine the question of exacerbation of a focal infection delivering bacteria and toxic products into the general bloodstream. Even V.K. Vysokovich (collected works, Moscow, 1954) showed in his paper "On the Etiology of Acute Endocarditides" that the presence of bacteria in the blood is not by itself sufficient for the development of endocarditis; some further irritation of the endocardium is also necessary. In our opinion, this factor might be found in increasing symptoms not only of hypoxemia, but of tissue hypoxia as well.

In endocarditis patients, therefore, hypoxic-dystonic shifts may play an important role in the pathogenesis, sometimes advancing into the foreground in the clinical manifestation of the disease.

Application of a well-thought-out medication program in combination with oxygen therapy should be regarded as pathogenetic therapy whose object is to counteract the hypoxia by activating oxidation-reduction processes. This complex treatment has frequently resulted in normalization of capillary permeability, restoration of vascular tone, normalization of the EKG and elimination of the hypoxic shifts.

OXYGEN DEFICIENCY IN MITRAL DISEASE

B. A. Manyako

(Kiev)

Investigation of gaseous interchange in man during physical work permits an objective and rather precise evaluation of the functional state of the cardiopulmonary complex. This is done primarily by studying the oxygen deficit, a term first introduced into physiology by A V

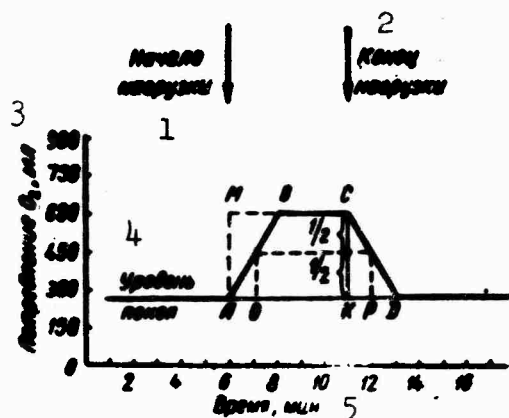


Diagram of dynamics of oxygen deficit, after A. Hill. Explanation in text 1) Beginning of stress; 2) end of stress; 3) O_2 consumption, ml; 4) resting level; 5) time, min.

Hill, who used it to refer to the amount by which the oxygen consumption during the period after cessation of work exceeds the resting level (see figure, KCD).

In circulatory insufficiency against a background of cardiac failure the magnitude of the oxygen deficit is governed by the circulatory disturbances, although the compensatory reserves of the external respiratory apparatus are considerably greater and completely unutilized (N.D. Strazheskiy and A.G. Dembo). In such cases the limit of the body's capacity for physical work is determined by the functional reserves of the cardiovascular system.

This report is intended as a description of the results of a study of elimination of oxygen deficiency in patients suffering from mitral disease with stenosis predominating during the performance of physical

work. The patients were examined during preparation for operative intervention in connection with constriction of the left auriculoventricular opening.

TABLE 1
Dynamics of Elimination of Oxygen Deficit as a Function of Stage of Disease

1 Stage of disease	2 Number of patients	3 Distribution of patients with respect to time (in min) required to eliminate oxygen deficit					6 Number of patients
		4 less than	5 more than	6 less than	7 more than	8 less than	
II	6	1	3	1	1	1	
III	10	—	1	4	5	5	
IV	12	—	2	2	8	8	
Score Sum- mation	28	1	6	7	14		

1) Stage of disease; 2) number of patients; 3) distribution of patients with respect to time (in min) required to eliminate oxygen deficit; 4) less than; 5) more than; 6) number of patients; 7) total number of patients.

We examined 28 individuals, 7 males and 21 females. They were distributed as follows with respect to age: 7 were from 16 to 25 years old, 9 were from 26 to 35, 12 were from 36 to 45, and 1 was older than 45. These patients included 6 individuals in the 2nd stage of decompensation, according to A. N. Bakulev's classification, while 10 were in the 3rd stage and 12 were in the 4th stage. We investigated no patients in the 5th stage, since even minimal physical stress is contraindicated for them.

The investigation was conducted under basal-metabolism-measurement conditions with F. Belau's apparatus, after the patient was preliminarily familiarized with experimental setup and allowed a practice session on the day before the experiment. We used two stresses: a) a power of 40-60 watts for patients in the 1st, 2nd, and 3rd stages of the disease; b) a power of 20-30 watts for patients in the 3rd and, primarily, 4th stages. We employed the following three tests to evaluate the extent of the oxygen deficiency, i.e., the magnitude of the oxygen deficit.

F. Belau's oxygen-deficit index, for the so-called "Erholungs Quotient" (rest quotient), expresses the ratio of the excess oxygen consumption above the resting level during work to the oxygen deficit (see figure, ratio ABCK/DCK).

The recovery period (in minutes) corresponds to the elapsed time from the beginning of the rest period until the oxygen consumption drops to its resting level, i.e., the time required to eliminate the oxygen deficit (see figure, KD).

Berg's half-value time (in minutes) is the sum of the adaptation and recovery half-periods, which characterize the temporal relationships of the compensatory adaptive reactions. The adaptation half-period corresponds to the time required for the oxygen consumption during the initial period of work to reach half its maximum value (see figure, AO). The recovery half-period is related to the restitution period and refers to the time required for the maximum oxygen-consumption level to be halved (see figure, KP).

We compared the data obtained with hemodynamic indices, the venous pressure and flow rate (ether and magnesium times). The tables show the dynamics of these indices as a function of the stage of the disease.

As may be seen from Table 1, only seven of the 28 patients could eliminate their oxygen deficit within 4 min, the other 21 exhibiting recovery periods lasting more than 4-5 min. While five of the six individuals in the 2nd stage of the disease eliminated their oxygen deficits within 5 min, only one taking longer, 5 of the ten patients in the 3rd stage required more than 5 minutes to cope with their oxygen deficits and only four of the 12 patients in the 4th stage eliminated their deficits within 5 min, the other eight accomplishing this over periods longer than 5 min. Thus, in mitral disease the recovery period increases steadily as the circulatory insufficiency progresses.

In considering the data in Table 2 our attention is struck by the fact that Belau's oxygen-deficit index decreases regularly and steadily as the circulatory disturbances become more severe. This reflects an increase in the oxygen deficit as mitral disease progresses.

TABLE 2

Comparison of F. Balau's Oxygen-Deficit index with Certain Tests of External Respiration and Hemodynamics

Показатели 1	2 Степень митрального стеноза (по классификации А. Н. Бакулева)					
	II		III		IV	
	Пределы колебаний 3	Среднее значение 4	Пределы колебаний	Среднее значение	Пределы колебаний	Среднее значение
5 Показатель кислородного долга по Ф. Валу:						
6 в абсолютных величинах	3,10—2,17	2,80	3,02—1,87	2,35	1,90—0,95	1,45
7 в % к должной величине	107—69	85,7	116—47	78,5	68—32	50,4
8 Время полузначения по Бергу (в мин.)	2,10—2,95	2,53	1,85—4,10	2,71	3,35—5,00	3,19
9 Восстановительный период (в мин.)	2,90—6,00	4,00	3,00—5,80	4,80	3,60—7,30	5,55
10 Венозное давление (в мм вод. ст.)	32—100	61,5	40—124	66,3	55—140	97,8
11 Скорость кровотока (в сек.): магнетальное время	12—19	14,5	12—25	15	7—19	15,8
12 эфирное время	4—7	5,3	5—14	9,3	5—15	9,6

1) Index; 2) state of mitral stenosis (according to A.N. Bakulev's classification); 3) limits of variation; 4) mean value; 5) F. Balau's oxygen-deficit index; 6) absolute values; 7) % of proper value; 8) Berg's half-value time (in min); 9) recovery period (in min); 10) venous pressure (in mm H₂O); 11) blood-flow rate (in sec); 12) magnesium time; 13) ether time.

The temporal oxygen-deficit indices also deteriorate in accordance with the stage of the disease. Thus, the recovery period and Berg's half-value time are markedly prolonged. This may indicate both an increase in the oxygen deficit and depletion of the compensatory reserves for its elimination. The temporal indices were found to be prolonged in certain patients with a normal Balau's oxygen-deficit index; this gives us grounds for assuming that the former are more sensitive in such cases and may reveal the disruption of gaseous interchange during earlier phases of the disease.

By comparing the oxygen-deficiency indices with the hemodynamic indices we can correlate the changes in the latter with the development

of the disease. In addition to clinical differentiation of the patients (in accordance with A.N. Bakulev's classification), this confirms the irregularity of the dynamics of the indices which we studied in mitral stenosis patients, using F. Belau's method and apparatus. When the data obtained were processed by the statistics of variation they were found to be statistically reliable. Analysis of the actual oxygen-consumption graph is of interest.

In a practically healthy individual (L., case history No. 252) the oxygen-consumption curve rises sharply under stress, i.e., the oxygen-consumption level reaches its maximum within the normal interval for the given stress (during the 2nd minute in the case in question); the curve then forms a smooth "steady state" plateau. The oxygen deficiency is relatively small, i.e., the major portion of the oxygen demand is satisfied during the actual period of work. On cessation of the stress the curve drops sharply to the resting level, the oxygen deficit being small.

The pattern of oxygen consumption under stress is entirely different for a patient with mitral stenosis in the 3rd stage (T-na, case history No. 2134); the curve rises very slowly and obliquely and reaches its maximum after the working period ends. A state of dynamic equilibrium is not reached and the oxygen deficiency is great. The oxygen consumption during the first five minutes of rest exceeds that during the five-minute stress period. The maximum oxygen-consumption level is appreciably reduced.

The third curve represents a patient suffering from combined mitral failure with stenosis not predominant (T-ko case history No. 2248). Our attention is struck by the high oxygen-consumption level. The curve rises rapidly and steeply under stress, but there is no "steady state" plateau.

CONCLUSIONS

1. Use of F. Belau's apparatus broadens our opportunities for clinical study of gaseous interchange.
2. Belau's oxygen-deficit index decreases markedly and the recovery period and Berg's half-value time increase steadily after the development of circulatory insufficiency in mitral disease. These indices are an objective test for evaluation of the functional state of the cardiopulmonary complex.
3. Investigation of the oxygen deficit by spirographic study of gaseous interchange under physical stress may be used for differential diagnosis of cardiac failure.

OXYGEN DEFICIENCY AS AN INDEX OF HYPOXIA DURING THE EARLY STAGES
OF HYPERTONIA

D. A. Nuzhnyy

(Kiev)

A disruption of gaseous interchange is one of the characteristics of the pathogenesis of hypertonia. In some of the patients in the first stage of hypertonia whom they examined F. Ya. Primak, A. G. Dembo, N. S. Zanozdra, V. P. Bezuglyy, and other authors have obtained data which indicate a certain decrease in external-respiration indices; this decrease frequently is manifested in arterial and venous hypoxemia, a change in basal metabolism, and an increase in tissue oxygen demand.

However, the oxygen deficiency of patients in the early stage of hypertonia, which cannot always be detected by ordinary methods, has not been sufficiently well investigated. Despite the laboriousness of such research, V. P. Bezuglyy and N. S. Zanozdra used physical stresses and a slightly modified Douglas-Holden apparatus to detect late elimination of oxygen deficiency. These authors did not have the facilities for making a continuous gas analysis and consequently conducted such analysis only at discrete, rather long intervals during the investigation.

Considering the importance of and lack of research on this problem, we devoted ourselves to an investigation of the oxygen deficiency in patients with first-stage hypertonia, using an improved gas-analysis apparatus. We employed the Belau apparatus, in which the chemical principles of prior equipment are superceded by electrophysical principles,

which insures highly dynamic observations and continuous recording of oxygen consumption and carbon dioxide elimination in the exhaled air.

It is well known that one of the methods for functional evaluation of the circulatory and respiratory apparatus is investigation of gaseous interchange and the manner in which it varies under stress (N. D. Strazhesko, V. Kh. Vasilenko, N. A. Kurshakov, V. R. Murashko, Khrbst, Eppinger, Lindkhard, Krog, et al.).

As the physical stress we used Belau's single-step test (20 ascents and descents per minute for 5 minutes, with a step height of 20 cm).

We examined 95 persons: 20 healthy individuals (the control group) and 75 first-stage hypertonia patients (according to the classification of the Ministry of Health USSR). Of the healthy individuals 16 were males and 4 females; 62 of the patients were males and 13 females. Both groups were uniform with respect to age.

The examination of the Belau apparatus was conducted on an empty stomach, after the subject was made to remain in a horizontal position for no less than 45 minutes. The investigation was conducted with the subject in a sitting position and a stress period of 5 minutes. The subject then remaining seated until his oxygen deficiency was completely eliminated (5-15 minutes).

The following indices were used to evaluate the extent of the oxygen deficiency: time required to eliminate oxygen deficiency (TEOD), Belau's recovery coefficient (RC), Berg's adaptation half-value (AHV), the onset time of maximum oxygen consumption under stress (OTMOC), and the onset time of the decrease in maximum oxygen consumption during the recovery period (TDMOC).

The following data were obtained for the healthy individuals: time required to eliminate oxygen deficiency - 2.1-3.6 minutes (up to 4 minutes according to Belau's data), recovery coefficient - 2.46-4.20 (2.5-3.6 according to Belau), adaptation half-value - 1.91-2.70 minutes (2.13-2.41 minutes according to Belau), onset time of maximum oxygen consumption under stress - 2.1-3.5 minutes, and onset time of de-

crease in maximum oxygen consumption during recovery period - 0-0.35 minutes.

Repeated examination of healthy persons over a period of two years convinced us of the consistency of the aforementioned tests. We compared the data obtained in examining the 75 first-stage hypertonia patients and the 20 healthy individuals with the normal values which we obtained and the data cited by F. Belau (see table).

As may be seen from the table, the time required to eliminate the oxygen deficiency was normal in 19 of the healthy persons and longer than 4 minutes in one. Of the 75 patients 21 eliminated their oxygen deficiencies within the normal interval, while 54 (or more than 2/3 of the total number) required more than 4-6-8 minutes, certain of them even taking until the 13th minute, well into the recovery period.

A very important index for appraising oxygen deficiency is the recovery coefficient. It expresses the ratio of the excess oxygen consumption during the stress period to the oxygen consumption during the rest period. Normal RC values were noted in 18 of the 20 healthy individuals, this index being slightly below normal in the other two. Of the 75 patients examined only 19 exhibited normal values, 56 yielding depressed indices

The adaptation half-value (the sum of the adaptation half-period under stress and the recovery half-period, which characterize the temporal relationships of the adaptive reactions) were normal in 17 of the healthy individuals, being slightly elevated in three. Normal values were obtained for 28 of the patients, while 47 exhibited considerably elevated values.

The onset time of maximum oxygen consumption under stress, which reflects the rapidity with which adaptive mechanisms are activated and the extent of acclimatization to stress, proved normal in 16 of the 20

Results of Investigation of Oxygen Deficiency in 20 Healthy Individuals and 75 Patients

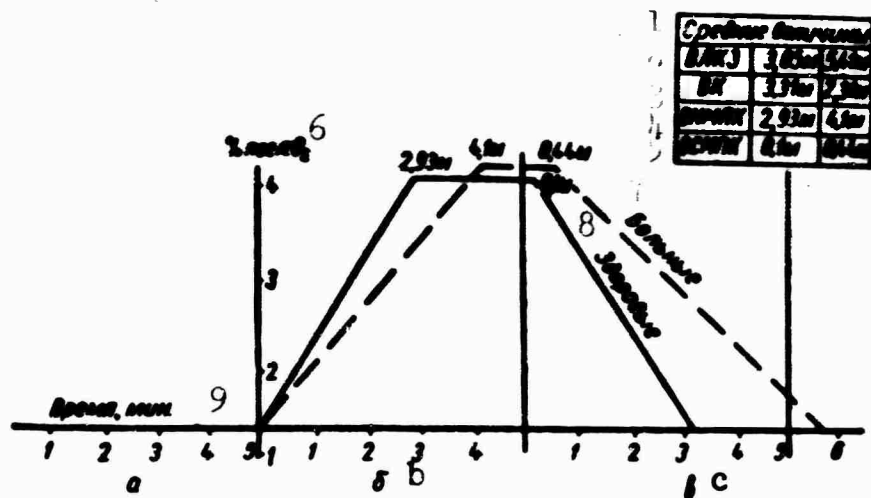
Пациенты первой стадии гипертонии 1	Значения и колебания 2	Здоровые 3	Пациенты первой стадии гипертонии 4
Количество обследованных 5	—	20	75
Время ликвидации кислородной задолженности 6	2,1—4 4—13 мин. 11	19 1	21 54
Восстановительный коэффициент 7	2,5—3,6 или 2,5 12	18 2	19 56
Полувалочный приспособления 8	2,13—2,41 больше 2,41 мин. 13	17 3	29 47
Время начала максимального поглощения кислорода при нагрузке 9	2,1—3,5 3,5—5,5—6 мин.	16 4	30 45
Время начала снижения максимального поглощения кислорода в восстановительном периоде 10	0—0,2 0,2—1 мин.	17 3	29 46

1) Oxygen-deficiency indices; 2) values and range of variation; 3) healthy individuals; 4) first-stage hypertonia patients; 5) number of subjects; 6) time required for elimination of oxygen deficiency; 7) recovery coefficient; 8) adaptation half-value; 9) onset time of maximum oxygen consumption under stress; 10) onset time of decrease in maximum oxygen consumption during recovery period; 11) min; 12) less than; 13) more than.

healthy individuals and in 30 of the patients. This index was retarded in 45 patients; the onset time of maximum oxygen consumption occurred later than 3.5 minutes and even extended into the beginning of the recovery period in certain patients.

The onset time of the decrease in maximum consumption after cessation of stress differed in the healthy individuals and the first-stage hypertonia patients: in the healthy individuals approximately 0.1 minute was required for the onset of the decrease in maximum oxygen consumption after physical stress, while a considerably longer period (0.44 min) was necessary in the patients.

For ease of visualization we will give a graph of the oxygen-con-



Graph of oxygen consumption in healthy individuals and first-stage hypertonia patients. a) In resting state; b) under stress; c) during rest. The mean values in the first column are for the healthy individuals and those in the second column are for the patients. 1) Mean values; 2) TEOD; 3) RC; 4) OTMOC; 5) TDMOC; 6) % O₂ consumption; 7) patients; 8) healthy individuals; 9) time, min.

sumption curves under stress and during the recovery period for healthy individuals and first-stage hypertonia patients. Mean values of the following oxygen-deficiency indices are utilized: TEOD, RC, OTMOC, and TDMOC (see figure).

In analyzing the oxygen-consumption graph for the healthy individuals it may be noted that the increase in oxygen consumption under stress occurs rather rapidly and that the consumption reaches its maximum after an average of 2.93 min from the beginning of the functional test. Beginning on cessation of the stress or 0.1 min thereafter the oxygen-consumption maximum decreases until the oxygen deficiency is completely eliminated, which requires an average of 3.05 minutes. This indicates that the healthy organism reacts well to the increased oxygen demand during physical stress, the oxygen deficit being rapidly eliminated over a brief recovery period.

Oxygen consumption under stress is slower in first-stage hypertonia patients than in healthy individuals, the maximum consumption being reached at 4.1 min. The maximum oxygen consumption remains high into

the first few minutes of rest and then gradually decreases, the oxygen deficiency being eliminated far later than in healthy individuals.

The adaptive reactions of the cardiovascular and pulmonary systems apparently react less completely to the demands made on the organism and supply oxygen later in first-stage hypertonia patients than in healthy persons. Thus, the oxygen deficiency and the late elimination of this deficiency exhibited by patients in the early stages of hypertonia may indicate the existence of hypoxia in the organism. The use of physical stress and Belau's apparatus reveals these hypoxic shifts in a larger number of patients than do ordinary methods.

It must be assumed that the number of first-stage hypertonia patients in whom hypoxic shifts occur is considerably greater than was previously supposed and that hypoxia occupies an important place in the pathogenesis of hypertonia. Rational measures intended to prevent oxygen deficiency serve as pathogenetic therapy in the early stage of hypertonia.

MECHANISMS OF THE DEVELOPMENT OF HYPOXIA IN CARDIOVASCULAR
DISEASES

V. D. Mel'nichenko

(Kiev)

Hypoxia may develop in the organism under the action of many external and internal factors. It accompanies the majority of pathological processes and morbid conditions.

Disruptions of pulmonary diffusion processes play a large role in studying the pathogenetic mechanisms underlying the development of the oxygen-deficiency syndrome. The functional properties of the lungs as organs of gaseous interchange result from certain of their structural characteristics: the lung is an organ in which the specifically functioning component of the parenchyma is a vascular-capillary system. All other components of the pulmonary tissue serve only to supplement the basic functional unit - the pulmonary alveolus. Polikar is quite correct that the lung of a mature individual is a vascular-capillary organ whose functional unit is the alveolus. The alveolar wall serves as a barrier between the alveolar air and the blood, its condition being one of the factors governing normal gaseous interchange in pulmonary ventilation. Disturbance of this barrier cannot but affect external respiration and lead to the development of pathological conditions in the pulmonary tissue and of the oxygen-deficiency syndrome. This problem received little attention in the literature until recently.

That portion of the alveolar septum which lies in the gas-diffusion path during arterialization of the blood must be assumed to be the

morphological substrate of the alveolar-capillary barrier. In an adult under normal conditions the membrane-like septum, which consists primarily of noncellular structures, is 0.3 to 2 microns thick (according to the data of Polikar, Khayyek, et al.). It contains a very thin protoplasmic layer of alveolar epithelium approximately 0.2 micron thick, situated on the basal membrane and the capillary wall. The septal tissue contains a network of argentophil fibers, intertwining capillaries, and a few elastic fibrils.

Khayyek believes that the alveolar-capillary membrane is a soft elastic gelatinous mass in vivo. It is understandable that any pathological process which results in a decrease in the permeability of this membrane considerably reduces the penetration of oxygen from the alveolar air into the blood. It must be emphasized that in such cases the alveolar-capillary gradient increases primarily with respect to oxygen. The content of carbon dioxide, which diffuses substantially more easily, may remain normal or even be somewhat reduced because of dyspnea.

In 1951 Austrian and MacClement suggested introduction of the term "alveolar-capillary blocking" to characterize the pathological state of pulmonary ventilation in which the alveolar-capillary membrane is considerably thickened as a result of pathological processes in the lungs.

The alveolar-capillary blocking syndrome, which is distinguished by characteristic clinical symptoms, has no single etiology. Causitive factors may include the so-called primary or primitive interstitial pulmonary scleroses: Hamman-Rich's disease, the chronic diffuse fibrosis described by Scadding, and the pulmonary elastofibrosis with plasma-cell reaction discovered by Walford and L. Kaplan.

It must be noted that the first two forms differ only in the rapidity with which their symptoms develop; many of their characteristics are pathologoanatomically similar and the literature consequently con-

tains no uniform opinion on the wisdom of differentiating these two diseases. While Sors, Bour-DuClerc, and others believe it possible to differentiate them, Vanek, Bruye et al., and others speak only of different clinical forms of Hamman-Rich's disease.

In addition to these (so to speak) primary pulmonary scleroses the alveolar-capillary blocking syndrome may also include a large group of pneumopathiae involved in a whole series of general diseases: certain infectious conditions, miliary carcinomatosis and tuberculosis, all pneumoconoses (especially berylliosis and asbestosis), reticulosis, collagenosis, damage to the lungs resulting from radiotherapy and roentgenotherapy, and browninduration of the lungs in congestion. In certain of these cases the disease affects primarily the lungs (pneumoconioses, pulmonary x-ray fibroses), while in others there is only a local manifestation of a general disease. The pathologohistological changes which occur in all forms of the alveolar-capillary blocking syndrome have common traits and are characterized by thickening of the septal tissue and development of fibrous tissue in the septum; this is occasionally accompanied by appearance of excess elastic fibrils, simultaneous degeneration of these structures, and changes in the morphology of the alveolar epithelium. The development of fibrous tissue in the alveolar septa must be assumed to be the basic process. It must be supposed that the changes in epithelial morphology, which involve the appearance of layers of characteristic cubic cells lining the inside wall of the alveolus, develop secondarily, as a result of cessation of gaseous interchange in the alveolus. The dependence of the morphology of the alveolar epithelium on the state of the septal tissue was pointed out in the older works of V.G. Garshin. L.M. Shabad, and many others.

Vik-Dyupon and his colleagues cite still another factor which influences oxygen-diffusion processes, a factor associated with the ob-

struction created in the alveolus itself when its lumen contains hyalin membranes which fit tightly against the alveolar wall. Hyalin membranes are encountered rather frequently in the lungs, but their pathogenesis is not known. Rosen and Castelman believe that their appearance results from a protein disturbance which they call "alveolar proteinosis."

In summarizing the data in the literature it must be noted that the predominant role of disruption of pulmonary diffusion processes is of very great clinical importance as the basis of hypoxia, although it unfortunately does not always receive proper attention. This factor is of especially great significance in cardiovascular diseases involving chronic circulatory disturbances.

Congestive phenomena may of themselves cause the development of tissue hypoxia. Congestive phenomena in the pulmonary circulatory system are of special importance in cardiac affections, since there is not a single organ whose functioning does not depend on that of both the heart and the lungs, the latter being, as we have already point out, essentially a vascular-capillary organ whose parenchyma is a capillary system. This is also the reason why patients with cardiovascular affections do not always die of actual cardiac damage, but frequently of the sequelae of the circulatory disturbance which occurs in the lungs when the alveolar-capillary blocking syndrome develops.

We have been occupied for a number of years in studying the changes which occur in the lungs in cardiac diseases and have detected a number of unusual changes in the noncellular structures which permit more precise determination of the character of the process which takes place in the pulmonary tissue. It must be pointed out that pulmonary pathology is distinguished by extreme diversity. The reactive reserves of the pulmonary tissue are very great. This results from the fact that in addition to gaseous interchange the lungs of cardiac patients exhi-

bit quite marked protective and barrier functions, these being necessary to impede the various foreign detrimental agents which enter them with the inhaled air.



Fig. 1. Thickened alveolar septa consist of a large number of dilated capillaries running in different directions. The capillary walls are consolidated. Silver staining by Fuji's method.

already been sufficiently well studied (A.I. Abrikosov, F.Ye. Ageychenko, N.A. Krayevskiy, N.A. Maksimovich, Tseyelen, Tanaka, Klinge, Shyurman, and many others).

Study of the noncellular structures of the lungs enables us to get a clearer idea of the changes in the capillary membranes and connective-tissue structures in the alveolar septa and to determine the pathogenetic links of the morphological substrate of alveolar-capillary blocking.

As is well known, in cardiac diseases accompanied by pulmonary

In cardiovascular diseases involving chronic pulmonary circulatory disturbance and active rheumatism all the necessary conditions are created for the development of a pulmonary pathological process which ultimately leads to the development of alveolar-capillary blocking.

On the basis of reports that the noncellular structures must be assigned the basic role in permeability and diffusion (Arnold, Chambers, Smirnova-Zamkova, Mogil'nitskiy, and many others), we turned our primary attention to this component of the pulmonary tissue, especially since the cellular reactions of the lungs in pulmonary congestion have

congestion one observes consolidation of the pulmonary tissue and development of brown induration, the latter being detected microscopically as thickening of the septal tissue.

REPRODUCIBLE



Fig. 2. Development of fibrous tissue in alveolar septa. Dilated thin-walled capillaries filled with blood may be seen at the boundary of the alveolar lumen. Hematoxylin-eosin.

It may clearly be seen from our material that thickening of the alveolar septum is not itself sufficient grounds for speaking of the existence of alveolar-capillary blocking. When such sections are silver-impregnated or treated by other methods to show the condition of the noncellular structures (periodate staining by Schiff's method, hematoxylin staining by Mallory's method) it is found that in a number of cases this septal thickening consists of a large number of dilated capillaries running in different directions, their walls lying directly against the alveolar lumen (Fig. 1). We naturally cannot speak of alveolar-capillary blocking in such cases.

We have never seen alveolar epithelium in the form of cubic cells located near the alveolar walls in these instances.

In other cases the tissue of the alveolar septum consisted of a large number of connective-tissue fibers among which capillary lumens could be seen only rarely. The capillaries lay at a great distance from the alveolar lumen. Groups or layers of cubic alveolar-epithelial cells were usually arrayed along the wall of the lumen in these cases. We maintain that only such manifestations of the pathological process in the alveolar septa can be designated as the morphological substrate of

alveolar-capillary blocking.

In a number of cases the thickened alveolar septum consisted of individual connective-tissue fibers, the capillaries running at random through the septal tissue. In such seemingly far-reaching fibroses intertwined tangles of capillaries filled with blood can frequently be seen along the edge of the septum bordering on the alveolar lumen. The walls of such capillaries are thin and their lumens are greatly dilated (Figs. 2 and 3). Similar tangles of capillaries may occasionally be seen even in the walls of the bronchioles. There are indications in the works of Polikar, Khayyek, and others that the anastomoses between the pulmonary and bronchial arteries are exposed when the lungs are congested and the pulmonary blood pressure is elevated. Considering this, it may be supposed that the bronchial capillaries described above may function in gaseous interchange.

Three processes may thus be distinguished in the changes which we have described in the lungs in cardiovascular diseases.

1. Dilatation and multiplication of the alveolar capillaries; in this case we must take into account the fact that not all of the alveolar capillaries are exposed under normal conditions of gaseous interchange. According to Polikar, the compensatory reserves of the alveolar capillaries are so great that if all the capillary loops of the alveolar septum are exposed they can dilatate to four-five times their ordinary size and reach the width of the alveolar lumen.

2. The development of connective tissue in the septal tissue must in all probability be attributed to manifestations of an allergic inflammatory process developing in the presence of the chronioseptic process characteristic of rheumocarditis. It is this process which is apparently basic to the development of alveolar-capillary blocking.

3. Compensatory hyperplasia of the capillary network at the sur-

alveolar-capillary blocking.

In a number of cases the thickened alveolar septum consisted of individual connective-tissue fibers, the capillaries running at random through the septal tissue. In such seemingly far-reaching fibroses intertwined tangles of capillaries filled with blood can frequently be seen along the edge of the septum bordering on the alveolar lumen. The walls of such capillaries are thin and their lumens are greatly dilated (Figs. 2 and 3). Similar tangles of capillaries may occasionally be seen even in the walls of the bronchioles. There are indications in the works of Polikar, Khayyek, and others that the anastomoses between the pulmonary and bronchial arteries are exposed when the lungs are congested and the pulmonary blood pressure is elevated. Considering this, it may be supposed that the bronchial capillaries described above may function in gaseous interchange.

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REPRODUCIBLE



Fig. 3. Development of fibrous tissue in the alveolar septa. The same process on silver impregnation. The septal tissue consists of argentophil fibrils. Capillary loops may be seen at the boundary with the alveolar lumen.

face of the fibrous filaments where the septal tissue comes into contact with the alveolar air.

The conjunction of these processes creates a rather variegated pattern of changes in the pulmonary tissues. The extent of alveolar-capillary blocking differs in accordance with whether the capillary-multiplication processes characteristic of congestive phenomena or the inflammatory reaction which develops in the septa is dominant.

We may thus assume that the intensity of the hypoxic phenomena associated with disruption of oxygen diffusion in the lungs depends to a greater extent on the development of the chronic inflammatory process in the tissues of the alve-

olar septa and the appearance of numerous connective-tissue fibers in them than on the congestive phenomena; when the latter are present there are actual reserves for compensating the process, these taking the form of dilatation of a considerable number of capillary loops.

However, it would be incorrect to assert that the congestive phenomena have no influence whatsoever on the condition of the alveolar-capillary membrane. In far-reaching cases of congestion severe consolidation of the argentophil membranes of the alveolar capillaries develops, this being accompanied by marked symptoms of polysaccharide polymerization and further collagenization of the capillary membranes, which leads to a considerable decrease in the permeability of the mem-

branes and a deterioration of oxygen diffusion.

In addition to all these changes in the alveolar septa during the development of alveolar-capillary blocking we cannot fail to take into account the vascular changes, the productive thrombovasculitis described in our previous works, which indirectly affect the state of pulmonary circulation and alveolar-capillary permeability.

THE DISRUPTION OF CARBON DIOXIDE INTERCHANGE IN CHRONIC HYPOXIA,
ITS PATHOGENESIS AND MODES OF TREATMENT

S.N. Sorinson

(Gor'kiy)

The relationship between O_2 and CO_2 interchange was established in the investigations of I.M. Sechenov, L.F. Verigo, K. Bor, and J. Haldane. Nevertheless, sufficient account has not been taken of it. In clinical practice O_2 deficiency is paid extraordinary attention in hypoxic conditions; the disruption of CO_2 interchange which develop in hypoxia are frequently underestimated. This leads to a somewhat one-sided and occasionally unwise procedure for setting up therapeutic measures.

This report is devoted to an analysis of the disruptions of CO_2 interchange which occur in chronic hypoxia of pulmonary etiology. It is based on the results of examination of 264 patients with pneumosclerosis involving 2nd- and 3rd-degree respiratory insufficiency. Together with the clinical data, the fact that these patients were suffering from oxygen starvation was confirmed by establishment of arterial hypoxemia, using direct gas analysis in a Van Slyke apparatus.

The disruption of CO_2 interchange was revealed on determination of the CO_2 content of the arterial blood. The mean arterial CO_2 content for healthy subjects was $44.4 \pm 1.2\%$ by volume, the range of variation being $40.0-47.1\%$ by volume. The majority of the patients examined (162 of 264) exhibited hypercapnia. The mean CO_2 content of the arterial blood was $50.8 \pm 7.5\%$ by volume. The CO_2 content frequently (in 20 pa-

tients) reached 64.0-75.0% by volume.

Similar results were obtained on investigation of the alveolar air. The alveolar $p\text{CO}_2$ for the control group (22 individuals) was 40.1 ± 2.88 mm Hg. The alveolar $p\text{CO}_2$ was greater than 43.0 in the majority of the patients (66 of 105) and reached 55.0-70.0 mm Hg in many (32).

Analysis of the causes of this accumulation of CO_2 was of definite interest. It is customarily assumed in the foreign literature that CO_2 interchange is disrupted only in the terminal stage of respiratory insufficiency, during the development of pulmonary hypoventilation. This corresponds to agonal respiratory insufficiency in Rossi's terminology. According to our data, CO_2 elimination is disrupted at an earlier stage. Thus, the CO_2 content of the arterial blood exceeded 48% by volume in half (98 of 189) of the patients with second-stage respiratory insufficiency. The minute respiratory volume not only failed to decrease, but usually increased, averaging 10.4 ± 2.3 liters/min. The ventilation equivalent reached 3.50 ± 0.46 (as against 2.35 ± 0.34 in the healthy individuals). Pulmonary hypoventilation consequently was not the cause of the CO_2 accumulation.

The results obtained enabled us to recognize that it is not so much a decrease in as a nonuniformity of pulmonary ventilation which is important in this respect. In conducting oxyhemometric investigations on the patients we discovered a considerable rise in the "saturation time." On shifting to inhalation of oxygen the maximum stable arterial-oxygenation level was reached only after an average of 8.1 min (309 observations), as against 2.7 min for the healthy individuals. The nonuniformity of alveolar ventilation was also indicated by an increase in the "mixing time" - a retardation of the rate at which nitrogen was washed from the alveolar air (L.N. Chernova's data). In the majority of the patients the alveolar nitrogen concentration exceeded 1.5% after

inhalation of pure oxygen for seven minutes, while in the healthy individuals this concentration averaged $0.84 \pm 0.46\%$. This corresponded to the increase in residual air (mean norm of $26.2 \pm 4.7\%$ of the total pulmonary capacity) established for the majority of the patients (106 of 129).

The insufficient CO_2 liberation might to some extent have been promoted by the difficulty of CO_2 diffusion through the fibrotically altered alveolar membrane. This was indicated by a comparative analysis of the results of investigations on different groups of patients. The CO_2 accumulation proved to be especially substantial in diffuse toxic pneumosclerosis. The majority of the patients in this group (44 of 78) exhibited marked hypercapnia (52.0% by volume or higher) and their mean CO_2 content reached $52.3 \pm 6.1\%$ by volume. Marked hypercapnia was observed considerably more rarely (in 63 of 186 patients) in other types of pneumosclerosis (pneumoconioses and postpneumonic pneumosclerosis), the mean arterial CO_2 level amounting to $48.5 \pm 6.9\%$ by volume ($p > 0.01$). These relationships reflected a rather marked decrease in pulmonary diffusion capacity and development of so-called "alveolar-capillary blocking," which have been shown to occur in diffuse pneumoscleroses of toxic etiology (Komro, Forster, DuBois, et al.).

In explaining the causes of the CO_2 accumulation we were also forced to take into account the characteristics of respiratory regulation under conditions of chronic hypoxia. An attenuation of the patients' reaction to inhalation of CO_2 was noted in our observations, this being in accord with the data of L.L. Shik and other authors (Donald and Christy, Chernyak and Snaydl, Alexander and Pauli). The investigations were conducted during respiration in a closed system, the CO_2 concentration being gradually raised to 5-6%. Under these conditions the increase in pulmonary ventilation in the patients (137) averaged

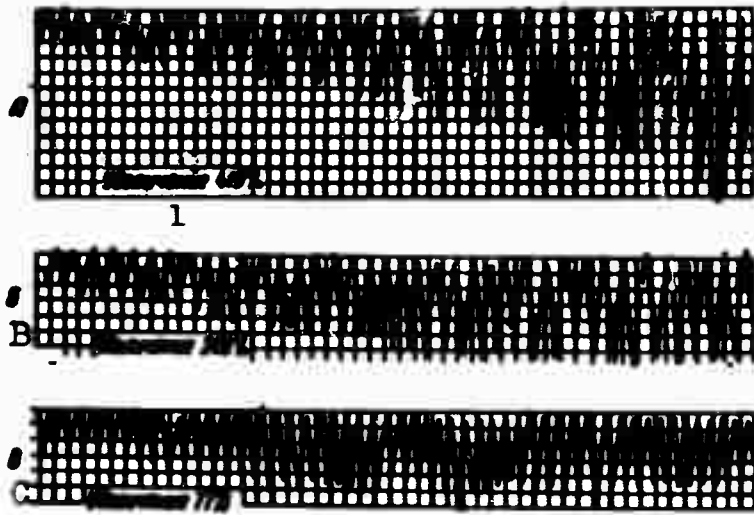


Fig. 1. Changes in spirogram during respiration in a closed system with a gradually increasing CO_2 content. A) O-v, 24 years old, healthy; B) patient B-a, 53 years old, 2nd-group invalid, previously a sand-blasting technician. Diagnosis of 2nd-degree silicosis with marked pulmonary emphysema and chronic asthmoid bronchitis. 3rd-degree respiratory insufficiency. 2nd-degree circulatory insufficiency; C) patient B, 50 years old, 3rd-group invalid, blacksmith. Diagnosis of chronic asthmoid bronchitis and pulmonary emphysema. 2nd-degree respiratory insufficiency. The time is shown along the abscissa (2 mm = 1 sec) and the depth of respiration along the ordinate (1 mm = 50 ml); both are scaled in mm. 1) Increase.

$53.0 \pm 27.3\%$ of the initial level, as against $102.7 \pm 34.8\%$ in the healthy individuals ($p > 0.01$). The results obtained are illustrated by the spirograms shown in Fig. 1. These data enabled us to assume that the indogenous CO_2 accumulation did not produce an adequate intensification of respiration in the patients and that this to a considerable extent promoted stabilization of the hypercapnia.

Statements have recently appeared in the foreign literature regarding the favorable influence of hypercapnia in chronic respiratory insufficiency. A high CO_2 level in the material blood and alveolar air is considered as an "adaptation mechanism" which facilitates CO_2 elimination at a lower respiration pressure (Barach, Riley, Richards, and Nauls). We cannot agree with this hypothesis. The danger of CO_2 accumulation was convincingly demonstrated in the works of P.M. Al'bitskiy. Numerous data have established that CO_2 accumulation depresses higher nervous activity (N.I. Krasnogorskiy, V.N. Zvorykin), promotes the de-

velopment of pulmonary hypertension (Turner, Fokon, Curran), increases the cerebrospinal pressure (Westlake and Key, Simpson), and inhibits diuresis (Braze and Jilmen, Feldt).

The acid-alkali equilibrium is easily disrupted under the conditions which obtain in persistent hypercapnia. Our observations, just as the investigations of other authors, showed that there is a considerable increase in the arterial alkali reserve, to 60.0-70.0% by volume or more, while uncompensated gas acidosis occasionally develops, the pH dropping below 7.38.

All this led to an urgent demand for the development of therapeutic measures intended to prevent CO₂ accumulation in patients with chronic respiratory insufficiency. We studied the value of diacarb, ephedrine, and respiratory exercises in this respect.

Diacarb, which inhibits renal carbonic anhydrase, proved to be most effective. The decrease produced in the CO₂ content of the arterial blood and alveolar air when it was administered was more constant (occurring in 69 of 91 observations) and more marked. It was shown that the effect of diacarb results primarily from a considerable intensification of CO₂ elimination in the urine (by a factor of five) caused by suppression of tubule resorption of bicarbonates. Respiratory elimination of CO₂ was also somewhat increased in some patients under the influence of diacarb (according to the data obtained in investigations conducted in a closed system, using a AOOV apparatus).

Ephedrine and respiratory exercises also caused a regular decrease in hypercapnia. Employment of these measures (in 400 patients) produced a considerable improvement in bronchial passability, as could be seen from increases in the volume and rate of maximum forced exhalation, maximum pulmonary ventilation, maximum utilization of respiratory volume, and index of air-flow rate (our data and those of L.N. Postni-

kova and T.B. Kurando). The nonuniformity of alveolar ventilation ("saturation time" and "mixing time") decreased, which also promoted better CO₂ liberation. The CO₂ content of the exhaled air increased by an average of $13.4 \pm 6.63\%$ of its initial level after administration of ephedrine.

Oxygen therapy in chronic hypoxia presents special difficulties. It entails a considerable disruption of CO₂ interchange, as well as a disturbance of CO₂ transport resulting from the decrease in the CO₂ capacity of the oxygenated blood (Hazell's phenomenon). According to the data of Rossi, Barach, Wilson, and Schiller, the arterial CO₂ level reaches 90-100-110% by volume in this group of patients during oxygen inhalation. The additional CO₂ accumulation created prevents development of the protective reactions which act to prevent hyperoxia. For example, it has been established that when O₂ is supplied under a pressure of 3.5 atm the pO₂ of the blood flowing from the brain is 76 mm Hg, which is a result of the decrease in cerebral circulation. Under the same experimental conditions, but with 2% CO₂ added the pO₂ of the cerebral blood reaches 100 mm Hg, as a result of the substantial increase in cerebral circulation volume (K. Lambertsen, K. Schmidt et al.).

In the foreign literature we found descriptions of 150 cases of severe oxygen intoxication, frequently lethal, which developed during oxygen therapy in patients with chronic respiratory insufficiency. Composite analysis of these cases showed their dependence on a decrease in the threshold to the toxic action of oxygen, a decrease caused by CO₂ accumulation. It has been noted that the so-called negative or side effect of oxygen, which has recently attracted the attention of Soviet authors (N.S. Molchanov, N.A. Kurshakov, A.G. Dembo, and S.N. Scrinson), also results to a considerable extent from a disruption of CO₂ elimination.

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Fig. 2. Changes in CO₂ content of arterial blood during different periods of two-hour inhalation in oxygen tent. 1) Before inhalation; 2) after 1 hour; 3) after 2 hours.

These data indicated the inadmissibility of using carbogen and made it necessary to develop an oxygen-therapy method for chronic hypoxia which would not lead to any considerable CO₂ accumulation. Our observations showed that the extent of the increase in CO₂ concentration is a direct function of the concentration of the inhaled O₂ and the duration of inhalation (Fig. 2).

We concluded that noncontinuous and rigidly dosed oxygen therapy was best for this group of patients, in contrast to Dotrband's well-known requirement of copious and continuous oxygen supply. The method developed* provides for oxygen inhalation in conjunction with therapeutic measures which promote CO₂ elimination (diacarb, drugs with a bronchiolytic action - ephedrine, euphyllin, et al., respiratory exercises).

This method enabled us to achieve persistent favorable results in therapy and to avoid completely the development of complications. The arterial CO₂ content decreased in the majority of the patients (99 of

170) after this course of therapy and, when systematic repeated courses were given over an extended period, remained at a normal level (our observations lasted up to 10 years).

All the material presented above confirms that there are considerable disturbances of CO₂ interchange in chronic hypoxia of pulmonary etiology. Elimination of these disturbances should be one of the important aspects of treating this group of patients.

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S.N. Sorinson, Prakticheskiye rekomendatsii po ratsional'nomu provedeniye kislородnoy terapii pri khronicheskikh zabolevaniyakh legikh [Practical Recommendations for the Rational Conduct of Oxygen Therapy in Chronic Pulmonary Diseases], Gor'kiy, 1960.

CHANGE IN EXTERNAL RESPIRATION AND BLOOD ALKALI RESERVES AS AN INDEX OF
HYPOXIA IN BRONCHIAL ASTHMA PATIENTS

A.I. Dayuba

(Kiev)

It is well known that functional disturbance of the external respiratory apparatus affects oxydation-reduction processes in the organism.

In the work described herein we attempted to show the extent to which functional disruption of the external respiratory apparatus influences qualitative oxygen utilization by the tissues of the organism.

We examined 72 bronchial asthma patients with altered external respiratory functioning. A study was made of general clinical data: indices of external respiratory functioning (minute respiratory volume, pulmonary vital capacity, maximum ventilation, and forced pulmonary vital capacity, all as percentages of their normal levels, as well as frequency and depth of respiration), indices of the gas-transport function of the blood (oxygen capacity of the blood, arterial-venous oxygen difference, carbon dioxide content of the venous and arterial blood, venous-arterial carbon dioxide difference, percentage oxygen saturation of arterial and venous blood, and percentage tissue oxygen utilization), lactic and pyruvic acid content of the blood, and blood alkali reserves. These special indices were studied by the methods customarily employed in the clinic of the Department of Internal-Disease Propedeutics of the Kiev Medical Institute.

Clinical and laboratory examination of our patients established the basic diagnoses: paroxysmal or chronic bronchial asthma in the exacerbation period. During the examinations the patients displayed acute or chronic asthmatic conditions. An inflammatory process localized predominantly in the respiratory organs was detected in almost all of them.

third, a total of 17.

The transport of gases, lactic acid, and pyruvic acid and the blood alkali reserves were thoroughly studied (two or three times) in all the patients. We considered the following to be material signs of respiratory insufficiency: excess ventilation (manifested clinically as dyspnea), oxygen deficiency (hypoxia), i.e., a drop in the level of oxidative processes or an anoxybiotic change in them, and the presence of incomplete-oxidation products in the circulating blood. Qualitatively insufficient oxygen exchange and the appearance of insufficiency oxidized substances is believed to be a general symptom of hypoxia of various etiologies.

All our patients exhibited a disruption of ventilation (Table 1); this was manifested in the fact that the minute respiratory volume was from 127 to 240% above normal in some patients (8), while in the others (9), who displaced a normal minute respiratory volume (most frequently in first-degree pulmonary insufficiency), the disruption of ventilation took the form of an increase in respiration rate (a decrease in one patient) and a decrease or tendency toward a decrease in depth of respiration. In those cases where the respiration rate was normal or reduced there was a clear increase in the depth of respiration.

In all the patients the functional capacity of the respiratory surface of the lungs, i.e., the pulmonary vital capacity, was altered (which indicates an elevated residual volume) and the indices of bronchial possibility (forced pulmonary vital capacity) were reduced, obviously as a result of an allergic-infectious condition in the bronchial passages and subsequent mucosal edema, bronchial spasms, and occlusion of the bronchial mucosa, which promote the development of hypoxia.

A disruption of ventilation in the external respiratory apparatus, taking the form of an increase in minute respiratory volume or an abnor-

mal ratio of the constituent indices of the minute respiratory volume (an increase in respiration rate coupled with a decrease or a tendency toward a decrease in depth of respiration), was one of the characteristics of our patients' condition.

In studying the transport of gases, lactic acid, and pyruvic acid and the blood alkali reserves we established (Table 2) that the oxygen capacity of the blood was elevated (occasionally to 24% by volume) in 10 of the 13 patients examined, because of an increase in the erythrocyte and hemoglobin counts; however, the most common cause (in 7 patients) was obviously qualitative change in the hemoglobin, since no increase was observed in the erythrocyte and hemoglobin counts in this case. The individuals with an increased oxygen capacity also exhibited an elevated oxygen content in the arterial blood (arterial hyperoxemia), which may be considered as a compensatory reaction induced by oxygen starvation, since the percentage oxygen saturation of the blood was reduced in the majority of cases. The reduced percentage tissue oxygen utilization frequently encountered (in 10 of 13 patients) confirms the existence of tissue hypoxia in these cases. The hypoxic condition of our patients is also indicated by the elevated pyruvic and lactic acid contents in the blood. Almost all the patients thus displaced hypoxia.

As may be seen from the material presented above, our patient's illness was based on a pathological process affecting mainly the respiratory organs and causing a preferential disruption of external respiration and subsequent development of a hypoxic condition. This hypoxia, itself a consequence of a disruption of external respiration, causes a further disturbance, as may be seen in the physicochemical regulation of the acid-alkali equilibrium of the organism by the blood, which is associated with the presence of a bicarbonate buffer. Determination of the alkali reserves revealed an increase (alkalosis) in 5 patients and a de-

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TABLE 2

Distribution of Bronchial Asthma Patients in Accordance with Data Characterizing the Transport of Gases, Lactic Acid, and Pruvic Acid and Blood Alkali Reserves as a Function of Degree of Pulmonary Insufficiency

1 Параметры	2 Степень легочной недостаточности												7 Общее число обследованных больных
	I				II				III				
	3 Уровень	4 Норма	5 Понижен	6 Всего	3 Уровень	4 Норма	5 Понижен	6 Всего	3 Уровень	4 Норма	5 Понижен	6 Всего	
8 Количество больных													
9 (скорость движения крови (магnezия))	—	1	—	1	—	4	—	4	—	—	—	—	5
10 Количество эритроцитов крови	—	3	1	4	2	1	4	7	1	1	—	2	13
11 Гемоглобин крови	—	—	4	4	1	3	4	8	—	2	—	2	14
12 Кислородная емкость крови	2	2	—	4	7	—	1	8	1	—	—	1	13
13 Кислород артериальной крови	2	1	—	3	6	—	2	8	1	1	—	2	14
14 Кислород венозной крови	—	4	—	4	5	1	2	8	1	—	1	2	11
15 Артерио-венозная разница по кислороду	1	2	—	3	1	2	5	8	—	1	1	2	13
16 Процент утилизации кислорода	1	—	2	3	2	—	6	8	1	—	1	2	13
17 Насыщение артериальной крови кислородом	1	—	2	3	2	2	4	8	—	—	2	2	13
18 Насыщение венозной крови кислородом	1	1	1	3	5	—	3	8	—	—	2	2	13
19 Углекислый газ артериальной крови	—	2	1	3	6	—	2	8	2	—	—	2	13
20 Углекислый газ венозной крови	—	2	1	3	4	3	1	8	2	—	—	2	13
21 Венозно-артериальная разница по углекислоте	1	1	1	3	2	1	5	8	1	—	1	2	13
22 Молочная кислота	4	—	3	7	7	1	—	8	1	1	—	2	17
23 Пировиноградная кислота	5	—	—	5	7	—	—	7	1	—	—	1	13
24 Щелочные резервы крови	2	1	4	7	2	—	6	8	1	—	1	2	17

1) Index; 2) degree of pulmonary insufficiency; 3) elevated; 4) normal; 5) reduced; 6) total; 7) total number of patients examined; 8) number of patients; 9) blood-flow rate (magnesium); 10) erythrocyte count; 11) hemoglobin count; 12) oxygen capacity; 13) oxygen content of arterial blood; 14) oxygen content of venous blood; 15) arterial-venous oxygen difference; 16) percentage oxygen utilization; 17) oxygen saturation of arterial blood; 18) oxygen saturation of venous blood; 19) carbon dioxide content of arterial blood; 20) carbon dioxide content of venous blood; 21) venous-arterial carbon dioxide difference; 22) lactic acid; 23) pyruvic acid; 24) blood alkali reserves.

crease (acidosis) in 10.

When there is an increased quantity of insufficiently oxidized products we consider alkalosis to be a compensatory reaction caused by acidosis in the presence of intensified carbon dioxide elimination; however, this condition is disadvantageous for the organism, since it hinders HbCO_2 dissociation in the blood of the pulmonary capillaries and HbO_2 dissociation in the capillaries of the systematic circulatory system. We cannot exclude the possibility that the function of hemoglobin in gas transfer is blocked in this case.

The decrease in alkali reserves in the remainder of the patients resulted from bonding of the alkali metals of the bicarbonates to the acids of the unorthodox products (B.M. Shershevskiy, L.M. Georgiyevskiy, and D.N. Ferdman). Either an increase or a decrease in alkali reserves may thus be considered as a symptom of hypoxia.

As an illustration of all the material which we have presented, we reproduce below case history No. 2070.

Patient T-a N.I., 50 years of age, invalided by disease. Admitted 27 January 1961 in an asthmatic condition. Had been ill since April 1960. After recovery from a cold choking fits suddenly appeared against a background of emotional factors. The patient was treated without results as an ambulatory patient. She had suffered from typhoid, pulmonary tuberculosis at 17, and inflammation of the lungs and was subject to frequent cold-like conditions accompanied by elevated temperature, after which the choking fits were intensified and could be eliminated by theophedrine, ephedrine, and atropine. Except for the seizures, her condition was only moderately serious. In a sitting position, her pulse was 90 and rhythmic, and her respiration rate was 24, her blood pressure was 130/90 mm Hg, she displaced dyspnea, a slight-grey color, puffiness of the face, and acrocyanosis, the boundaries of the heart were displaced to the left, and the heart tones were muffled. The second tone was accentuated in the pulmonary artery, the lungs gave off a bandbox sound, and her breathing was harsh with many dry sibilant rales.

Blood analysis: erythrocytes - 4,690,000, Hb - 74% by Sahli's

method, leucocytes - 5300, basophils - 1, eosinophils - 10, stabnuclear elements - 2, segmentonuclear elements - 55, lymphocytes - 15, monocytes - 7, sedimentation rate - 12, globulins - 6.28 mg-%.

Diagnosis: exacerbation of paroxysmal bronchial asthma, second-degree pulmonary emphysema, pneumosclerosis, chronic rhinitis, first-degree external respiratory insufficiency, and toxic myocarditis.

Investigation of external respiration yielded the following data: respiration rate - 24, depth of respiration - 344 ml, minute respiratory volume - 127% of normal, pulmonary vital capacity - 59% of normal, maximum pulmonary ventilation - 130% of normal, forced pulmonary vital capacity - 43% of vital capacity, pulmonary CO₂ elimination - 67.4% of normal.

Investigation of the gas composition of the blood before treatment showed: oxygen capacity - 25.35% by volume, oxygen content of arterial blood - 22.94% by volume, oxygen content of venous blood - 13.52% by volume, arterial-venous oxygen difference - 9.42% by volume, percentage oxygen utilization - 41.1%, oxygen saturation of arterial blood - 90%, oxygen saturation of venous blood - 53%, carbon dioxide content of arterial blood - 36.49% by volume, carbon dioxide content of venous blood - 44.84% by volume, and venous-arterial CO₂ difference - 8.35% by volume. The lactic acid content was 16.2 mg-%, the pyruvic acid content 18.2 mg-%, and the alkali reserves 56.6% by volume.

Clinical improvement began after treatment, the indices enumerated moving back toward normal.

A similar pattern was observed in a number of other patients. The presence of both a disruption of external respiration and a number of other symptoms indicating a disturbance of the respiratory function of the blood, coupled with other signs of hypoxia, thus required a definite gradation of individual therapy. However, we attempted to base our treatment on the principle of desensitization of the organism together with administration of antispasmodics, conjoining the latter with cardiovascular and anti-inflammatory drugs in a number of cases. In individual instances we administered a 2-4% sodium bicarbonate solution, depending on the extent of alkalosis; this yielded satisfactory results.

CONCLUSIONS

1. A disruption of pulmonary ventilation and of the acid-alkali equilibrium of the blood must be considered a symptom of hypoxia.
2. Our patients' hypoxic condition is apparently the result of organic damage (frequently of an allergic-infectious character) to the external respiratory apparatus; this promotes the development of hypoxia, which in turn intensifies the alteration of external respiration. However, we cannot exclude the possibility that it is caused by a conjunction of local hypoxic manifestations in the pulmonary circulatory system, which may lead to subsequent disturbances of circulation and of the hematorespiratory barrier, although a peculiar closed circuit (the damage-induced disruption of external respiration, the hypoxia, and the intensified disruption of the structure and function of the external respiratory apparatus) is more frequently formed.
3. Organic damage to the lungs and the associated disturbance of pulmonary functioning is only a partial cause of hypoxia, since the external respiratory apparatus has a high adaptive capacity with regard to mechanically pathological changes which hinder ventilation.
4. Changes in the acid-alkali equilibrium of the internal medium may also be of great importance in the development of hypoxia; when such changes occur the hemoglobin cannot release CO_2 and pick up O_2 in the pulmonary capillaries, nor can it deliver O_2 to the tissues and remove CO_2 from them, a situation observed, e.g., in alkalosis.
5. It may be assumed that disadvantageous changes in the oxygen-alkali equilibrium of the internal medium may be corrected by drug therapy and appropriate diet, thus breaking the pathogenetic circle and making it possible for the organically damaged external respiratory apparatus to make fuller use of its great compensatory reserves.

OXYGEN STARVATION IN PATHOLOGICAL CONDITIONS OF THE LIVER

V.P. Bezuglyy

(Kiev)

The disruption of carbohydrate, protein, pigment, water-salt, and other types of metabolism which occurs in diseases of the liver, especially Botkin's disease, has not been studied with sufficient thoroughness. Little research has been done on gaseous interchange and the oxygen supply to the organism in hepatic diseases.

Snell (1935) investigated the gas composition of the blood in four patients with infectious jaundice and found that the oxygen saturation of the arterial blood dropped from 92.4 to 87.3%.

I.M. Turovets and I.G. Tonkonogly later investigated the gas composition of the blood in 14 patients with various hepatic diseases. These patients exhibited venous hypoxemia and an elevated arterial-venous oxygen difference.

The fact that the organism's oxygen supply is disrupted in Botkin's disease is indirectly indicated by data on the changes which occur in oxidation-reduction processes. Thus, an increase in the oxygen content of the urine (Schwartz), accumulation of oxidized glutathione in the blood (Kamenetskiy), a decrease in the oxidation of purine compounds to lactic acid (Andryushechkina and Nikolayeva), a drop in the rate of oxidative phosphorylation (Yakusheva), a disruption of carbohydrate metabolism in the muscles and signs of glycolysis (Mikhnev), and an attenuation of fatty-acid oxidation (Zabolctnyy et al.) are observed in the presence of this disease.

Clinically, patients with Botkin's disease, especially those with the severe form, exhibit marked cyanosis of the ears, lips, tip of the nose, chin, hands, etc., when coupled with complaints such as severe general weakness, susceptibility to rapid fatigue, loss of working capacity, etc. All this to some extent indicates the occurrence of hypoxia in this disease. In this connection we set ourselves the task of studying the oxygen supply to the organism in Botkin's disease. An investigation of the respiratory function of the blood was conducted for this purpose. The term "respiratory function of the blood" is used to refer to the mechanism by which oxygen is transported from the lungs to the tissues and carbon dioxide is transported from the tissues to the lungs. In order to study this function we investigated the gas composition of the arterial and venous blood, the oxyhemoglobin dissociation curves, and the carbonic acid fixation curves, taking hemodynamics into account.

We investigated the gas composition of the blood in a Sechenov-van Slyke apparatus. The gas composition of the arterial and venous blood was studied in 108 Botkin's disease patients, in 43 of whom the investigation was made under dynamic conditions, i.e., at the height of the illness and during the recovery period. The most characteristic peculiarity of the gas composition in Botkin's disease is a drop in the oxygen saturation of the arterial blood. Thus, the percentage oxygen saturation was below normal (less than 92%) in 88 of the 108 patients, which indicated arterial hypoxemia. It must be noted that the drop in the oxygen saturation of the arterial blood was a direct function of the severity of the disease in the majority of cases.

The oxygen content of the venous blood decreased markedly (to below 12% by volume). This index was depressed in 80 of the 108 patients. Indications of venous hypoxemia were consequently present in the overwhelm-

ing majority of the patients. This was also indicated by an increase in indices such as the arterial-venous oxygen difference (which was greater than 8% by volume in 72 of the 108 patients) and percentage tissue oxygen utilization which was greater than 35% in 76 patients). The majority of patients consequently exhibited symptoms of arterial and venous hypoxemia.

The carbon dioxide content of both the arterial and venous blood tended to decrease (this index was reduced in half the patients).

The percentage oxygen saturation of the arterial blood rose to normal during the recovery period in the majority (39 of 43) of the patients investigated under dynamic conditions. The oxygen content of the venous blood increased in a considerable number of these patients (in 22 of 43), remained unaltered in 6, and decreased in 15. The carbon dioxide content of the arterial and venous blood rose in half the patients during the recovery period. The arterial-venous oxygen difference and the percentage tissue oxygen utilization tended to normalize in a majority (22 of 43) of the patients (see Table).

The arterial hypoxemia was thus eliminated in the majority of the patients during the recovery period; the venous hypoxemia was also eliminated in many. However, the mechanism by which the arterial and venous hypoxemia developed remained unclear. In this connection we set ourselves the task of studying the oxyhemoglobin dissociation curves as a basic index of the respiratory function of blood, directly indicating the presence or absence of hypoxia.

We found no reports of research on the respiratory function of the blood in acute virous hepatitis -- Botkin's disease -- in either the Soviet or foreign literature. We know of only one work in this area (Kis and Snell), in which the authors studied the oxyhemoglobin dissociation curves in cirrhosis of the liver. They found that these patients exhibi-

Gas Composition of the Blood in Botkin's Disease

1 Фами- лия боль- ного	2 Артериаль- ная кровь		3 Венозная кровь		5 Арте- риаль- но-ве- нозная разни- ца O ₂	6 Про- цент исполь- зован- ной O ₂ тка- ней	7 Про- цент насы- щения артери- альной крови O ₂	8 Em- кость O ₂ об. %	9 Били- рубин mg%
	4 Содержание, об. %								
	O ₂	CO ₂	O ₂	CO ₂					
З-ик	18,81	43,4	4,65	52,1	14,1	65,2	87,4	21,0	399,6
10	21,1	46,7	8,28	56,6	12,8	60,7	95,8	22,0	51,2
Кр-ев	20,5	42,7	7,28	55,2	13,2	64,5	85,2	23,7	307,2
11	21,2	45,7	5,76	59,8	15,5	72,9	95,4	22,1	38,4
Ф-ев	17,3	38,1	10,20	47,1	7,1	40,8	86,6	17,3	102,4
12	18,4	44,4	12,30	47,3	6,2	33,2	94,9	18,4	—
К-ик	16,7	42,2	8,88	52,4	10,1	47,0	90,6	18,4	409,6
13	16,5	46,4	9,35	54,0	7,1	43,4	97,1	16,9	304,8
Му-я	17,8	39,4	4,41	51,9	13,4	75,2	84,9	21,0	409,6
14	19,3	41,3	7,47	48,6	11,8	61,3	97,4	19,3	25,6
М-ая	18,1	46,6	12,60	47,6	5,6	30,6	91,4	19,8	11,6
15	17,9	49,7	18,70	50,2	1,23	6,8	94,7	18,9	1,0
П-ик	16,3	40,9	8,0	44,1	8,3	50,9	89,0	18,3	7,2
16	20,8	48,1	11,90	53,5	8,7	42,0	94,3	21,8	0,5
На-ко	19,8	41,2	7,62	49,5	12,2	61,6	89,9	22,0	399,3
17	22,8	45,4	12,50	52,9	10,3	45,0	95,8	23,8	46,9
Но-ик	18,6	44,2	9,33	48,7	9,3	49,9	81,7	22,8	614,4
18	17,4	50,8	13,30	55,6	4,2	23,9	92,2	18,9	19,3
Д-ев	21,2	46,6	6,61	54,8	14,6	68,8	93,4	22,7	102,4
19	18,0	40,0	5,12	44,7	12,8	71,6	84,1	21,4	409,6

20

(ухва-
тание)

1) Patient's surname; 2) arterial blood; 3) venous blood; 4) content, % by volume; 5) arterial-venous O₂ difference; 6) percentage tissue O₂ utilization; 7) percentage O₂ saturation of arterial blood; 8) O₂ capacity of blood, % by volume; 9) bilirubin, mg-%; 10) Z-ik; 11) Kr-jev; 12) F-na; 13) K-shch; 14) Mu-ya; 15) M-aya; 16) P-ik; 17) Na-ko; 18) No-ik; 19) D-yey; 20) exacerbation.

ted insufficient saturation of the arterial blood and attributed this to a decrease in the affinity of hemoglobin for oxygen, since the dissociation curve dropped markedly and was displaced to the right.

We studied the oxyhemoglobin dissociation curves for 30 patients with Botkin's disease. In 20 of them the curves were displaced or tended to be displaced downward and to the right during the height of the illness (see the dissociation curve for patient Fet-va, Fig. 1). The curves were within normal limits for 9 patients and only one curve was displaced upward and to the left.

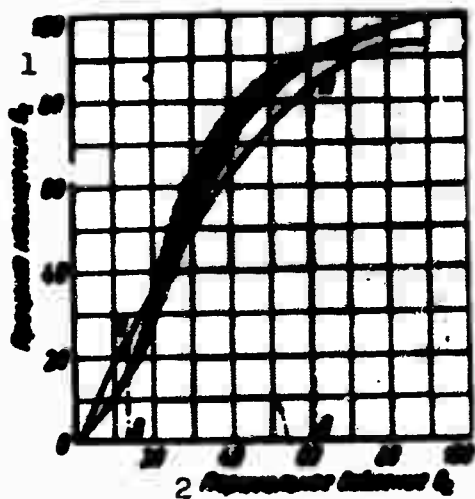


Fig. 1. Oxyhemoglobin dissociation curve for patient Fet-va. 1) Percentage O_2 saturation; 2) partial O_2 pressure.

The oxyhemoglobin dissociation curves were consequently displaced downward and to the right in the majority of the patients. This displacement was more marked in those patients with the moderately severe and severe forms of the disease. When the illness took a mild course the dissociation curves frequently remained within normal limits. This displacement of the oxyhemoglobin dissociation curves downward

and to the right in Botkin's disease indicates a decrease in the affinity of the hemoglobin for oxygen, caused primarily by manifestations of intoxication.

Toxic substances (phenols) are formed in the intestine during the decomposition of proteins; these pass into the liver and are converted into nontoxic conjugate (phenol-sulphur and phenol-glucuronate) compounds. 80 to 90% of the phenols are excreted in the urine as fixed phenols. When the barrier function of the liver is disrupted the quantity of fixed phenols in the urine decreases and the quantity of free phenols increases (Schwartz).

The disruption of the hepatic detoxification function which occurs in Botkin's disease is consequently one of the causes of the intoxication. The latter may also arise from a virus infection and the concomitant disturbance of oxidative processes. All this could naturally have been reflected in the oxyhemoglobin dissociation curves and have led to a decrease in the affinity of the hemoglobin for oxygen and thus to insufficient oxygen saturation of the arterial blood. It is possible that the latter phenomenon also promoted disruption of the permeability of

the pulmonary capillaries. The oxyhemoglobin dissociation curves reflect the dependence of the oxygen saturation of the blood on the partial oxygen pressure (pO_2).

In 16 of the 30 Botkin's disease patients examined, the partial oxygen pressure of the arterial blood (pO_2) was clearly reduced, i.e., was below 70 mm Hg. In addition, in 7 patients pO_2 displayed a tendency to decrease and was at the lower limit of the normal range, i.e., between 70 and 80 mm Hg. This index was within the normal limits (80-90 mm Hg) in only 7 patients. The pO_2 of the arterial blood was thus reduced or manifested a tendency to decrease in the majority of the patients examined; this is a direct indication of the existence of arterial hypoxemia in Botkin's disease.

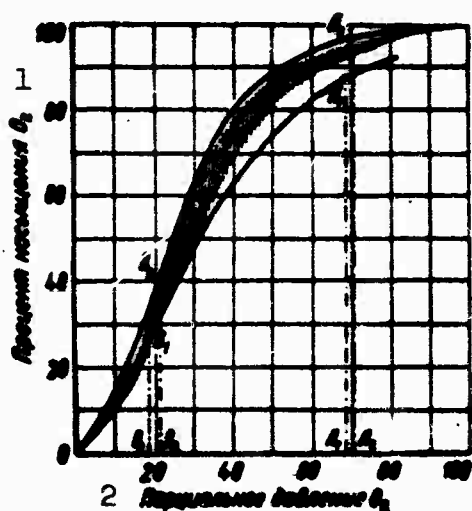


Fig. 2. Oxyhemoglobin dissociation curve for patient Fed-va. 1) Percentage O_2 saturation; 2) partial O_2 pressure.

The partial oxygen pressure in the venous blood was less than 30 mm Hg in 16 of the 30 patients examined. The pO_2 of the venous blood was between 30 and 40 mm Hg, i.e., at the lower limit of the normal range, in 11 patients and within the normal range (40 mm Hg) in 3.

The pO_2 of the venous blood was consequently reduced or exhibited a clear tendency to decrease in an overwhelming majority of the Botkin's disease patients.

This decrease in the pO_2 of the venous blood not only confirms the existence of venous hypoxemia, but is also a direct indication that tissue hypoxia occurs in Botkin's disease.

During the period of clinical recovery and decreasing jaundice, the oxyhemoglobin dissociation curves were displaced upward and to the left in 5 of 9 subjects, i.e., were on the way to normalization. Displacement of

the dissociation curves in this direction indicates an increase in the affinity of the hemoglobin for oxygen, again confirming that the oxygen saturation of the arterial blood is a function of the affinity of the hemoglobin for oxygen (see the dynamics of the oxyhemoglobin dissociation curves for patient Fed-va, Fig. 2).

In two patients in whom the disease took a mild course the oxyhemoglobin dissociation curves lay within the normal range and retained a normal shape until recovery. In 2 patients the dissociation curves lay within the normal range at the beginning of the illness and were displaced downward and to the right at recovery; however, the oxygen saturation and partial oxygen pressure of the arterial blood were elevated in both patients.

It is very important that the pO_2 of the arterial blood increased appreciably in almost all the patients (7 of 8) during the recovery period, this being conjoined with an increase in the percentage oxygen saturation; the pO_2 of the venous blood exhibited a tendency to decrease at clinical recovery in the majority of the patients (6 of 8).

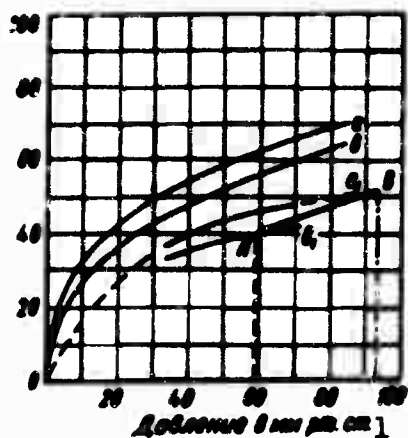


Fig. 3. CO_2 fixation curves for patient Ly-ko during the height of Botkin's disease. a) Reduction of blood; b) oxidation of blood. 1) Pressure, in mm Hg.

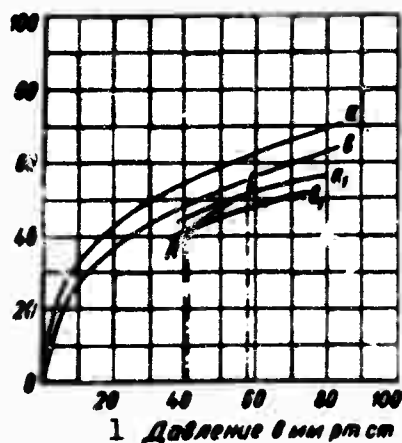


Fig. 4. CO_2 fixation curves for patient Ly-ko during the recovery period. a) Reduction of blood; b) oxidation of blood. 1) Pressure, in mm Hg.

The manner in which the diametrically opposed process -- the transport of carbon dioxide from the tissues to the lungs -- is effected in Botkin's disease remained unclear. In order to elucidate this problem, we studied the carbon dioxide fixation curves. We found no data in the literature regarding research on the carbon dioxide fixation curves in Botkin's disease. We studied these curves in 26 patients. In almost all of them the curves were considerably below normal at the height of the illness. The more severe the course of the disease and the more intensive the jaundice, the lower were the curves located. The partial carbon dioxide pressure in the arterial and venous blood was appreciably elevated in almost all the patients, which indicates disturbance of the blood's ability to fix, transport, and release carbon dioxide. In addition, the increase in the pO_2 of the venous blood indicates a rise in the partial CO_2 pressure in the tissues (see the CO_2 fixation curve for patient Ly-ko, Fig. 3).

The carbon dioxide fixation curves were displaced upward, toward normalization, during the recovery period. Our attention is struck by the decrease in the pO_2 of both the venous and arterial blood, which indicates a drop in the partial carbon dioxide pressure in the tissues and lungs (see the CO_2 fixation curve for patient Ly-ko, Fig. 4).

CONCLUSIONS

1. Changes in the gas composition of the blood, oxyhemoglobin dissociation, and a carbon dioxide fixation occur in acute virus hepatitis (Botkin's disease).

2. The following changes are observed in the gas composition of the blood: a decrease in the oxygen saturation of the arterial blood, a drop in the oxygen content of the venous blood, an increase in the arterial-venous oxygen difference, and a rise in oxygen utilization in the arterial venous blood. All this indicates the existence of arterial and ven-

ous hypoxemia.

3. The oxyhemoglobin dissociation curves are displaced downward and to the right at the height of the illness, which indicates a decrease in the affinity of the hemoglobin for oxygen. There is also a drop in the partial oxygen pressure of both the arterial and venous blood, which points to a disruption of oxygen transport and to the existence of tissue oxygen starvation (hypoxia).

The hypoxic manifestations which occur in Botkin's disease, resulting from infectious (virus) intoxication and a disruption of hepatic functioning, are an important pathogenetic factor, which may be transformed from sequelae to a positive agent with a negative influence on the damaged liver and the organism as a whole. It is possible that the disruption of oxygen supply to the tissues, including the damaged liver, plays a rather important role in the development of complications such as hepatargia and chronic hepatitis.

4. In addition to an increase in the percentage oxygen saturation of the arterial blood, the oxyhemoglobin dissociation curves tended to normalize during the recovery period. The partial oxygen pressure of the arterial blood rose, which indicated elimination of the arterial hypoxemia. The partial oxygen pressure of the venous blood increased in a majority of the patients. This latter indicates that the tissue hypoxia was not eliminated in the majority of the patients during the period when the jaundice was moderating.

5. Another component of the respiratory function of the blood, carbon dioxide transport, is also disrupted in Botkin's disease. This is indicated by the downward displacement of the carbon dioxide fixation curves and the increase in partial carbon dioxide pressure in both the arterial and venous blood. This points to a disruption of carbon dioxide transport and an accumulation of this gas in the tissues.

6. The presence of tissue oxygen starvation during both the height of Botkin's disease and the recovery period makes it necessary to take all possible measures to prevent hypoxia. Here we refer primarily to oxygen-tent therapy and gastrointestinal or subcutaneous administration of oxygen, a strict bed-rest regime being observed. Indirect methods of preventing hypoxia include administration of all drugs which act to eliminate the intoxication.

THE HORMONAL FACTOR AND ADAPTATION TO HYPOXIA IN TERMINAL CONDITIONS*

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(Novosibirsk)

Hypoxia is one of the most important pathological factors (V.V. Pashutin, N.N. Sirotinin, I.R. Petrov, A.M. Charnyy, et al.). In this connection more and more attention is being devoted to adaptation to hypoxia (N.N. Sirotinin, G.Ye. Vladimirov, A.N. Sokolov, N.V. Lauer, A.Z. Kolshinskaya, Barcroft, van Lir, et al.).

The principal subject of our study was adaptation to hypoxia. It is naturally impossible to deny the great importance of adaptation to a decrease in the partial oxygen pressure of the inhaled air or to insufficient pulmonary ventilation. However, as is well known, conditions under which other forms of hypoxia (hemic, circulatory, and tissue) dominate may arise in pathological states. This makes it important to study adaptation to endogenous forms of hypoxia, especially tissue hypoxia.

Hypoxia always appears as a component in terminal conditions, especially at the onset of clinical death, when it reaches its practical limit. It persists for an extended period after complex treatment has been administered to save the patient's life and restoration of vital functions has begun, being most marked before the diencephalon resumes functioning, over an interval of almost an hour after independent respiration is restored (V.A. Negovskiy). Rapid restoration of vital functions is nevertheless observed during this period. This phenomenon naturally indicates the existence of hypoxia-adaptive factors during the early stage of restoration of vital functions after terminal conditions.

In addition to its theoretical interest, elucidation of these factors is of definite practical importance in treating terminal conditions.

TABLE 1
Effect of Cortisone on Arterial Pressure in Revived Animals

1 Одновременное ка- тионизированную кровь	2 Число опытов	3 Артериальное давление					
		4 исход- ное (в мм рт. ст.)	5 после окисления (% к исходному)				
			6 макси- мум подъема	7 через 15 минут после первого вдоха	8 среднее, M	9 квадратиче- ская откло- нение, σ	10 средняя ошибка, m
12 После введе- ния кортизона	12	125	111	89	±23,2	±8,3	2,5
13 Обычное (кон- троль)	58	144	85	66	±13,7	±3,5	

1) Revival with cationated blood; 2) number of experiments; 3) arterial pressure; 4) initial (in mm Hg); 5) after revival (% of initial); 6) maximum rise; 7) 15 minutes after first breath; 8) mean, M; 9) mean square deviation, σ ; 10) mean error, m; 11) differential error, t; 12) after administration of cortisone; 13) normal (control).

As is well known, oxygen starvation causes a complex range of biochemical changes in the tissues, including liberation of a number of active products of altered protein metabolism (histamine and others). On the basis of the works of A.A. Bogomol'ts, Selye, et al., it may be assumed that one of the measures evolved for protecting against hypoxia will be associated with mobilization of corticoids, which specifically activate histaminase and themselves inactive excess histamine.

The investigations conducted showed that administration of adrenal hormones stimulates restoration of vital functions during certain stages of revival. Thus, in revival with the aid of cationated blood injected into an artery preliminary cortisone injections ensured a higher arterial pressure at the time when ocular reflexes reappeared (Table 1).

As may be seen from Table 1, the influence of cortisone on the arterial pressure of the revived animals was statistically reliable. It has been demonstrated that the results produced by the action of anti-

histamines (suprastine) in normalizing vital functions in animals revived by arterial injection of heparinated blood is equally reliable (Table 2).

Injection of corticoids and antihistamines thus had a favorable influence on adaptation to hypoxia in terminal conditions. This required further analysis. It seemed wise to employ a superficially contrasting variant – an experimentally induced deficiency in adrenal hormone secretion – for this purpose. One possible method of inducing such a deficiency is preliminary bilateral epinephrectomy in cats.

Table 2
Effect of Suprastine on Arterial Pressure in Revived Animals

1 Условия оживления	2 Число опытов	3 Артериальное давление					9 дифференциальная ошибка, t
		4 исходное (в мм рт. ст.)	5 через 1 час после оживления (% к исходному)		6 среднее, M	7 среднее квадратическое отклонение, σ	
10 После введения супрастина	10	130	83	±11,4	±3,65	2,6	
11 Обезьяны (контроль)	10	136	70	±8,8	±2,85		

1) Revival conditions; 2) number of experiments; 3) arterial pressure; 4) initial (in mm Hg); 5) 1 hour after revival (% of initial); 6) mean, M; 7) mean square deviation, σ; 8) mean error, m; 9) differential error, t; 10) after injection of suprastine; 11) normal (control).

The influence of epinephrectomy on the dynamics of revival after lethal exsanguination seemed paradoxical. Removal of the adrenal glands clearly promoted respiration of a number of vital functions: an initial increase in arterial pressure, prevention of cardiac fibrillation in revival with cationated blood, etc. However, most important was the fact that respiration was restored twice as rapidly in the revived epinephrectomized animals (after 3 min 50 sec, as against 6 min 30 sec – min in the control). We might have created the impression that administration of corticoids and epinephrectomy facilitate revival, but this means that they promote adaptation to hypoxia.

In this light attention was attracted by the difference in the effects which appear when the time factor is taken into account. Administration of corticoids has almost no effect on the dynamics of the initial stages of the recovery period, but acts later, after reflexes reappear; inversely, epinephrectomy stimulates restoration of respiration immediately before reflexes reappear and later, when diencephalic functioning is restored, leads to progressive hypotension, an intensification of oxygen starvation, and death an average of an hour and a half after revival.

We must take into account the fact that adaptation to hypoxia is based on peculiar changes in metabolism during the different periods of revival. During the initial period the oxidase system of respiratory enzymes is disrupted, the oxygen available to the blood is poorly utilized, tissue hypoxia develops, and anaerobic glycolysis becomes the basic energy source (V.A. Negovskiy, M.S. Gayevskaya, et al.). It is clear that we cannot discuss the stimulating influence of epinephrectomy during this period of revival without taking into account the interendocrine relationships of the adrenal glands, particularly the system formed by insulin and the counterinsulin hormones (S.M. Leytes, V.S. Il'in, G.I. Kassil', Cory, Woods, Hacter, et al.).

As is well known, epinephrectomy leads to a relative predominance of insulin. However, such a shift in the equilibrium of the insulin-counterinsulin system may be achieved without disrupting corticoid secretion, with the aid of insulin stress. The experiments which we conducted (20 experiments on cats) showed that subcutaneous injection of insulin (1-2 units/kg) affects the subsequent reaction to blood-letting and revival. The fact that the symptoms of stimulation of the early recover period observed in epinephrectomized animals proved to be even more marked after preliminary injection of insulin was extremely important. It was shown

that the stimulating effect of insulin is temporary in character: when the diencephalon resumes function it is succeeded by hypotension and hypoglycemia and the animal soon dies. Additional administration of cortisone (3 injections in a dose of 50 mg/kg) eliminates the stimulating effect of insulin on the dynamics of the early recovery period.

It is characteristic that in half our experiments involving experimental insulin deficiency (alloxan diabetes in rabbits) we were totally unable to restore respiration on revival after lethal exsanguination. In those experiments where respiration was restored it usually appeared later than in the control experiments.

Adaptation to hypoxia during the initial period of restoration of vital functions is thus governed primarily by the hormonal effect of insulin. However, the action of this adaptation mechanism is brief: under ordinary revival conditions it is succeeded by the developing predominance of corticoids after reflexes appear. This is understandable if we take into account the fact that corticoids promote normalization of oxidative processes (D.Ye. Al'pern et al., Basilo, Barron, Levy, and others). However, when severe tissue hypoxia dominates (during the initial stage of revival) adaptation results from an intensification of phylogenetically older aspects of metabolism, particularly anaerobic glycolysis, which may be stimulated by insulin, as was shown in the works of V.P. Nemissarenko, Marrac, Lynn, et al. All this characterizes adaptation to hypoxia in terminal conditions as a complex dynamic process.

Experimental administration of hormonal and chemotherapeutic preparations has proved to have a marked positive influence on the dynamics of restoration of vital functions. We are naturally faced with the problem of how far we can intensify the adaptive reactions of the organism itself. In this connection we investigated the influence of brief, pre-

Primarily induced hypotension (and thus hypoxia) on lethal exsanguination and subsequent restoration of vital functions. We induced hypotension in cats by intravenous injection of arfonad (0.4-0.6 ml, 1:100). It was found that the compensating hypertension produced has a favorable effect on the dynamics of revival after lethal exsanguination. Respiration was normalized more rapidly and arterial pressure was higher (Table 3).

TABLE 3
Effect of Arfonad on Arterial Pressure in Revived Animals

1 Условия оживления	2 Число опытов	3 Артериальное давление				
		4 через час после оживления (% к исходному)				
		5 исход- ное (в мм рт. ст.)	6 среднее, M	7 квадрати- ное откло- нение, σ	8 средняя ошибка, m	9 ошибка разности, t
10 После введения арфона- да	10	134	85	±11,8	±4,8	2,7
11 Обычное (контроль)	10	136	70	±8,8	±2,85	

1) Revival conditions; 2) number of experiments; 3) arterial pressure; 4) 1 hour after revival (% of initial); 5) initial (in mm Hg); 6) mean, M; 7) mean square deviation, σ; 8) mean error, m; 9) differential error, t; 10) after injection of arfonad; 11) normal (control).

Brief preliminary arfonad hypertension consequently promoted natural adaptation reactions to hypoxia in the terminal condition. An increase in resistance to hypoxia may also result from a pathological process characterized by hypoxia. In experiments conducted (in conjunction with M.I. Kitayev) we showed that resistance to hypoxia increases as the torpid stage of burn or electric shock becomes more severe (200 white mice). This phenomenon develops in stages: there is a phase of elevated sensitivity to hypoxia during the erectile period. Anesthesia prevents a build-up of resistance to hypoxia in shock, although itself increasing this resistance under ordinary conditions.

To sum up, we may state that adaptation to hypoxia is one of the components of the pathological process which occurs in terminal condi-

tions of various types.

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*Based on data obtained by the author and his colleagues -
N.S. Gvlimova, M.G. Kolpakov, V.I. Ladygin, M.G. Polyak, T.
G. Razumova, and G.S. Yakobson.

THE DURATION OF CLINICAL DEATH

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(Yerevan)

The problem of revival is part of the general problem of longevity which faces theoretical and practical medicine.

As a result of work primarily of Soviet scientists (Andreyev, Negovskiy, Chechulin, Bryukhonenko, Yankovskiy, Petrov, Sirotinin, Asratyan, Ionkin, and others), the problem of revivification has been raised from the level of mythology to become a pressing problem of modern medicine. It has shifted from the laboratory into the clinic.

Many data have now been amassed on the changes which occur in various functions of the organism in terminal conditions and subsequent revival. The Department of Pathophysiology of the Yerevan Medical Institute has for a number of years studied the functions of the gastrointestinal organs (Sarkisyan, 1958), the bile-producing function of the liver, the protective-adaptive reactions of the organism (Sarkisyan, Khachatryan, and Barkhudaryan, 1958, 1960), the changes which occur in the neurohumors 20 - histamine and acetylcholine - and the activity of the hemolytic enzymes which split them - histaminase and cholinesterase (Sarkisyan and Zakharyan, 1962), and the morphological composition of the peripheral blood and bone marrow (Sarkisyan and Atadzhanyan, 1962) both in terminal conditions and after revival.

We subsequently study the extent to which metabolic processes are disrupted and restored in the brain tissue in terminal conditions and after subsequent revival. Investigations conducted to study the absorp-

tion of glucose and pyruvate and the liberation of lactate by brain and muscle tissue (A.A. Sarkisyan, G.S. Khachatryan, and S.A. Khachatryan, 1962) clarified the extent to which the metabolic processes which form the basis for the functional activity of the brain and the functions of other organs (muscles, liver, stomach, salivary glands, etc.) are disrupted and restored.

The method which we employed, taking blood from the carotid artery and the posterior facial vein after transection of the other branches of the external jugular vein, made it possible to sample the blood flowing from the vein in a chronic experiment under dynamic conditions without disrupting the cerebral structures and thus to follow the changes in the levels of the components of cerebral carbohydrate metabolism in the conditions mentioned above. These investigations showed that the glucose absorption and lactate elimination of the brain are sharply elevated in the agonal state. The oxygen saturation of the blood from the posterior facial vein was reduced by a factor of only three from that observed under anesthesia. These data strikingly demonstrate that metabolic processes pass from the oxidative to the glycolytic mode during the agonal state which precedes clinical death. When vital functions are restored the brain absorbs glucose to a greater extent than under the initial anesthesia, but to a lesser extent than during the agonal period. The oxygen saturation of the blood flowing from the brain approximates its normal background level after 5-10 minutes. When the vital functions of the brain are restored oxidative carbohydrate decomposition thus prevails in its tissues. Our investigations of catalase and carbonic anhydrase activity in dogs in terminal conditions and after revival (Sarkisyan and Khactryan, 1962) point to a suppression of oxidation-reduction processes and respiratory metabolism.

We also noted a change in the quantity of mineral substances and

microelements in the venous and arterial blood in dogs during the agonal stage and after revival (Sarkisyan, Aydinyan, and Silavoryan, 1962). It was found that a new equilibrium state is produced during the agonal period and that restoration of the normal state begins during the first few hours after revival.

All the data cited above indicate that a substantial disruption of metabolic processes occurs in the organism (particularly the brain tissue) in hypoxia, it is observed both in terminal conditions and after restoration of vital functions.

The data which we obtained and those yielded by investigations of other authors shed some light on the problem of whether clinical death (by exsanguination) has a limiting duration of 5-6 minutes or whether it can be prolonged under certain conditions.

The question of the duration of clinical death has attracted and continues to attract a great deal of attention from many scientists (Negovskiy, Bryukhonenko, Yankovskiy, Asratyan, and others), since it is of extremely great theoretical and practical importance.

According to the data of S.S. Bryukhonenko, clinical death lasts 10-12 minutes. However, certain authors did not accept the interesting data which he obtained, since his experiments were conducted on puppies, which withstand oxygen starvation better, and consequently were not applicable to mature dogs.

According to the data of E.A. Asratyan, clinical death may last 20 minutes or even longer in dogs. His investigations are of great importance, since they reveal a number of regularities in the terminal condition. However, his research method was unusual, clinical death being induced by anemization of the brain (by elevated pressure).

According to the data of V.A. Negovskiy, clinical death lasts 5-6 min. This author induced clinical death by exsanguination, which is im-

portant in the practical respect.

The literature contains reports of revival of humans after 5-6 min of clinical death. However, restoration of vital functions occurred only as far as the "cortical level" in these cases, i.e., the functions of the cerebral cortex were not restored at all. The problem of the duration of clinical death thus remains a subject of dispute.

There are data in the literature which indicate that acclimatization to hypoxia reduces the percentage mortality among animals subjected to action of ionizing radiation (Orbeli et al.). Great interest also inheres in the observations of the N.N. Sirotinin, who conclusively demonstrated that acclimatization to high-altitude conditions is of value in treating various diseases (schizophrenia, epileptoid seizures, etc.) and in preventing premature aging.

The data cited above led us to believe that it might be possible to prolong clinical death if the subjects were preliminarily acclimated to hypoxia.

The experiments were conducted on mature dogs kept at high altitudes for 1-3 years (at the "Aragats" station, 3200-3500 m above sea level). In order to compare the duration of clinical death control experiments were performed on healthy dogs kept in the city of Yerevan (920-950 m above sea level). The meteorological conditions which obtain at the "Aragats" station are shown in the Table.

Clinical death was induced by exsanguination from the femoral artery and revival was carried out by the complex method developed by V.A. Negovski. The dogs' general behavior and body temperature were monitored before and after revival; we also investigated the morphological pattern of the peripheral blood (erythrocyte and leucocyte counts, hemoglobin percentage, and leucocyte formula) and (oxyhemometrically) the oxygen saturation of blood taken from large saphenous vein. After

revival we recorded the animals' respiration, blood pressure, and cardiac activity.

TABLE

Comparative Monthly Meteorological Data for the "Aragats" Station

1											
Месяцы											
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
2 Средняя месячная температура воздуха											
-11,2	-10,8	-10,6	-5,6	0,4	3,6	7,0	7,6	5,5	1,0	-5,6	
3 Абсолютный максимум температуры воздуха											
-2,5	-2,9	-0,1	3,4	8,6	12,2	16,0	16,5	14,2	9,3	3,5	
4 Абсолютный минимум температуры воздуха											
-26,4	-24,2	-20,8	-12,6	-9,6	-4,1	-0,5	-1,7	-2,7	-7,0	-16,9	
5 Абсолютная влажность воздуха											
2,3	2,3	2,2	3,7	5,2	6,2	7,6	7,0	5,4	4,8	3,3	
6 Относительная влажность воздуха (в %)											
66	82	78	90	80	78	77	68	61	74	77	
7 Среднемесячное давление воздуха											
680,1	679,0	676,9	680,5	686,8	686,3	686,7	686,1	690,2	692,8	686,5	
8											

- 1) Month; 2) mean monthly temperature; 3) absolute maximum temperature; 4) absolute minimum temperature; 5) absolute moisture content of air; 6) relative humidity (in %); 7) mean monthly air pressure; 8) atm.

The results of the experiments showed that dogs kept at an altitude of 920-950 m above sea level can be revived after clinical death lasting 6 min. Dogs kept at an altitude of 3200-3500 m can be completely revived after clinical death lasting 10-12 min. No complications were observed after revival in these dogs and the clinical pattern during the post revival period was similar to that observed after clinical death lasting 5-6 min. No differences in the morphological pattern of the peripheral blood or the oxygen saturation of the blood were noted between the experimental and control dogs.

The data which we obtained give us reason to assume that animals adapt to the reduced partial oxygen pressure at altitudes of 3200-3500 m above sea level. As is well known, a number of adaptive reactions develop in the organism under hypoxic conditions: pulmonary ventilation and the respiratory surface of the lungs increase, there are a number of hemodynamic shifts, dissociation of oxyhemoglobin into oxygen and hemoglobin is intensified, the tissues absorb more oxygen from the blood reaching them, and, in this connection, there is a reorganization of metabolism, anaerobic decomposition coming to predominate (I. R. Petrov). If the organism is subjected to oxygen starvation for an extended period (at the "Aragats" station in the case in question) the adaptability of the organism to the action of oxygen deficiency obviously increases. As a result, the functioning of the neurohumoral organisms which mobilize the organism's reserves gradually improves. The central nervous system, particularly the cortex, also adapts to hypoxia under these conditions. This observation is especially important in explaining the data which we obtained on the comparative ease with which hypoxia-adapted dogs withstand clinical death lasting 10-12 minutes.

OXYGEN DEFICIENCY IN BURN INTOXICATION

Ye.V. Gubler

(Leningrad)

The immediate cause of burn intoxication is the uncompensated loss of a considerable quantity of skin (T.Ya. Ar'yev, 1961). This in turn leads to a number of severe disturbances of the internal organisms. Local and general oxygen deficiency (OD) plays a rather large role in the mechanism of both the loss of skin and the affection of the internal organs.

Many works mention development of OD in burn shock. Engel (1952), Buchner (1956), Altman (1955), and Algover and Zigris (1957) indicated the presence of OD during subsequent periods of burn intoxication. The thorough experimental and clinical investigations conducted by G.V. Derviz and V.N. Smidovich (1955, 1958) conclusively demonstrated the existence of OD in severe burn intoxication.

Little research has been done on either the causes or the importance of oxygen deficiency in burn intoxication and its role is not taken sufficiently into account in treating the sequelae of severe burns.

Indices of OD in burn intoxication. As indices of OD in burn intoxication we may employ the accumulation of pyruvic, lactic, and other organic acids in the blood and their elimination in the urine (G.F. Milyushkevich, 1951; G.V. Derviz and V.N. Smidovich, 1955, 1958; V.N. Smidovich, 1957, 1959, 1962; Algover and Zigris, 1957).

G.V. Derviz and V.N. Smidovich (1955, 1958) suggested that the extent of the oxygen deficiency be evaluated from the acid-formation coef-

efficient of the urine, i.e., from the ratio of the total quantity of organic acids to the total quantity of nitrogen present in the urine. It was shown (V.N. Smidovich, 1957, 1962) that in man this coefficient increases in direct proportion to the severity of burn intoxication.

We studied Derviz and Smidovich's acid-formation coefficient in 13 patients, the lactic acid content of the blood in 14 patients, and Uhlenbruck's oxygen deficit in 10 patients. The latter index was not materially elevated in a single one of the 24 determinations made: it was not sufficiently sensitive for detection of OD in burn intoxication. The lactic acid content of the blood increased regularly only during the first two days after infliction of severe burns. According to G.V. Derviz and V.N. Smidovich (1958) this OD index is inconclusive, since it depends on muscular activity rather than solely on the extent of the OD. The acid-formation coefficient was elevated in 7 of the 16 determinations, the increase corresponding well to the severity of the patient's clinical condition.

An indirect indication of postburn oxygen deficiency in humans is excess pulmonary ventilation not corresponding to the basal metabolism level (E.P. Zimina). It develops as a result of an acceleration of respiration and leads only to excess ventilation of the dead air space rather than to excess alveolar ventilation.

In experiments on rabbits (which were resting when the blood samples were taken) the lactic acid content of the blood increased regularly after infection of severe burns over 20% of the body area, reaching its maximum 7-13 days after trauma. According to the data obtained in G.S. Fenster's experiments on rats, a Uhlenbruck's oxygen deficit was observed between the 2nd and 14th days after infliction of severe burns over 15-18% of the body area in 40-50% of all cases; this deficit gradually disappeared as the burns healed.

There is thus no doubt that OD occurs in burn intoxication. In humans acid-formation coefficient of the urine proved to be the most sensitive and reliable of the post burn OD indices which we checked. In experiments on animals we were able to detect to detect postburn OD by other methods as well.

Causes of general OD in burn intoxication. One of the causes of the OD which occurs during burn shock is the noncorrespondence between the high oxygen requirement and the disrupted oxygen supply to the tissues. Thus, in five cases we were able to determine basal metabolism in patients with burn shock accompanied by a drop in arterial pressure. In four cases basal metabolism was elevated by 10-35% and in only one case was it reduced, by 37% (Ye.V. Gubler and E.P. Zimina, 1962). L.L. Shik (1945), G.V. Derviz (1949), and M.G. Danilov (1950) noted a rise in basal metabolism in traumatic shock.

An additional source of the OD which occurs in burn intoxication may apparently be the burns frequently infected on the respiratory passages in fires and when clothing is ignited. V.N. Khrebtovich's carefully conducted experiments failed to confirm the hypothesis of Morits (1945) and others regarding the frequent development of edema of the glottal region following inflection of burns on the respiratory passages. It was also found that experimental flame burns of the respiratory passages in cats lead to affection of the lungs, in the form of edema and atelectasis, and to the development of arterial hypoxemia. The oxygen saturation of the blood decreased by 7-54% during the day after infliction of the burns.

As Coup's investigations (1951) and the data obtained in our laboratory (E.P. Zimina, 1960; Ye.V. Gubler and E.P. Zimina, 1962) showed, basal metabolism remains substantially elevated during the second, infectious-toxic period of burn intoxication, which lasts up to 1-1.5

months. This is apparently associated with the fact that high fever, excess pulmonary ventilation, and intensified metabolic processes are observed during this period. Tissue hypoxia develops against this background (G.V. Derviz and V.N. Smidovich, 1958). The known correspondence between oxygen demand and oxygen supply consequently persists during this period. Rapid development of anemia, resulting from destruction of erythrocytes at the instant of trauma, may also cause oxygen deficiency at this time (R.L. Ginsburg and N.N. Priorov, 1959).

Severe burn intoxication is frequently complicated by pneumonia. According to the data of V.M. Pinchuk, pneumonia was observed in the majority of fatalities during all periods of burn intoxication except the first two days. Massive pneumonia is apparently an additional source of OD.

The discrepancy between oxygen demand and oxygen supply evidently becomes greater when a hyperthermal reaction (body temperature above 39°) develops; such a reaction was observed in 40% of patients with burns over 10% or more of their body area. Death occurred far more frequently among middle-aged and elderly persons when their temperatures rose above 39° than when it did not. Hyperthermia was often observed on the day before death (Ye.V. Gubler, V.M. Pinchuk, V.I. Skorik, 1962).

The discrepancy between oxygen demand and supply may apparently increase during the postoperative period in surgical treatment of extensive burns. Arts and Rice (1957) and Middleton and Wolfson (1958) called attention to the postoperative cyanosis which develops in burn patients. As V.I. Skorik's observations showed, body temperature may drop by $2-3.5^{\circ}$ during autoplasty in emaciated patients with extensive burns. External heating of patients during the postoperative period, when hemodynamics are frequently disrupted, may lead to an intensification of basal metabolism and development of cyanosis (Middleton and Wolfson,

1958).

Causes of local tissue hypoxia in burn intoxication. The principal cause of the tissue hypoxia which occurs in the vicinity of a burn is apparently the damage inflicted on the oxidative enzymes when they are heated. However, as N.I. Kochetygov's experiments showed, it is very difficult to heat tissue and still maintain its circulation. It is possible that the damage to the erythrocytes and their loss of elasticity, which plays an important role in the development of capillary stasis (S.P. Botkin, 1859; Ye.V. Gubler, 1951), is one of the causes of the stasis which occurs in burns.

The reversibility of stasis depends to a large extent on free inflow and outflow of blood. Venous plethora is frequently observed in the vicinity of burn (V.M. Pinchuk), evidently being associated with elevated intratissue pressure. The latter may be caused by: a) contraction of the skin when burned (V.I. Skorik); b) tissue edema, which spreads far beyond the affected region; c) external pressure on the burned areas. Tissue edema is especially marked when the burn penetrates into the subcutaneous cellular tissue, as may be seen from the results obtained in statistical analysis of data on hemoconcentration in burn patients (Ye. V. Gubler, 1962).

Necrotic processes are often observed in the internal organs, especially the stomach and intestine, after severe burns; as is well known, these are characteristic of the general adaptation syndrome (Selye, 1951, 1960). In burn cases these affections are apparently based on various vascular disturbances (V.M. Pinchuk). They may result from prolonged compensatory spasm of the precapillary sphincters in compensated or uncompensated shock (Lebori and Ugenar, 1954).

Very characteristic in this respect was the 12-year-old female patient from Tashkent admitted to the Thermal Injury Clinic of the Mill-

ary-Medical Order of Lenin Academy imeni S.M. Kirov in a state of shock. She required three days after trauma to come out of shock. However, after 10 days she developed gastric hemorrhaging, which required an emergency operation. Two perforating duodenal ulcers were detected during surgery. The operation was successful, but the patient died after one week as a result of an unfavorable postoperative course conjoined with the severe general condition produced by the burn intoxication.

Local tissue hypoxia may be observed in kidneys, the damage to which, according to Algover and Zigris (1957), frequently has a hypoxic mechanism. In addition to complex and insufficiently studied vascular disturbances, this renal hypoxia based on "renal glaucoma" - a sharp increase in the pressure beneath the renal capsule conjoined with edema; the development of this phenomenon is explained by the fact that of the fluid resorbed in the renal tubules because of damage to them enters the renal interstitial tissue (M.S. Vovsi, 1961). The venous outflow of blood is disrupted and renal hypoxia develops. Local and general oxygen deficiency thus undoubtedly occur in severe burn intoxication and frequently play a material role in its development.

Effect of additional OD and oxygen therapy in burn intoxication.

Considering all the material presented above, one might conclude that the capacity to withstand additional oxygen deficiency induced against a background of burn intoxication by other factors must be reduced. However, it was found that this is not always so.

In V.I. Skorik's experiments on cats it was established that hour-long hypertonia involving a decrease in arterial pressure to 40 mm Hg, induced by blood-letting (with subsequent reinjection of the blood taken), is withstood just as well by burned animals on the day after trauma as by control animals. The survival time of the burned animals did not decrease after the blood-letting. The capacity to withstand such

hypertonia gradually decreased during subsequent periods of burn intoxication.

In experiments on rats G.S. Fenster discovered that 3-hour exposure to a rarefied atmosphere corresponding to an "altitude" of 5-6 km was not only well withstood by burned animals for a period of 10 days, but reduced their mortality from burn intoxication during the following days: 19% of the rats exposed to the rarefied atmosphere died of their burns, while the mortality among the control animals with the same burns reached 50%.

Oxygen therapy, which we administered during the first few hours after inflicting extremely severe burns on 20 rats, using pure oxygen under a pressure of 2.3-2.7 atm abs for three hours, did not cause the animals to survive any longer than the controls. The majority of the rats died during the therapy.

Pure-oxygen therapy, which may be effective even in tissue hypoxia (V.S. Shapot and G.M. Prus, 1958), yielded no clear positive or negative clinical results. 12 patients were given pure-oxygen inhalations for one hour twice daily over a period of 16-53 days, primarily during the infectious-toxic period of burn intoxication.

These effects of additional oxygen deficiency and oxygen therapy in burn intoxication may be explained by the fact that the detrimental action of hypoxia and the positive effect of burn therapy are somehow masked by the simultaneously developing toxic effect of oxygen and the correspondingly favorable action of hypoxia. This effect is theoretically admissible for burn intoxication, by analogy with radiation sickness.

Oxygen deficiency is undoubtedly of very substantial pathogenetic importance in burn intoxication and this problem requires further research.

INCREASING THE RESISTANCE OF ANIMALS TO THE TOXIC ACTION
OF EXCESS OXYGEN BY ACCLIMATIZATION TO HYPOXIA

A.G. Zhironkin

(Leningrad)

In making an extended study of the action of elevated oxygen pressure on the organism, we encountered data which indicated that hypoxic conditions play some role in the mechanism of this effect. Thus, in a number of experiments a decrease in resistance to hypoxia was observed in persons shifted to breathing air after prolonged breathing of oxygen under elevated pressure (A.G. Zhironkin, 1955).

We found confirmatory data in the literature. For example, Dickens (1940, 1946), Stedy et al. (1945), Haggard (1946), Mann and Quastel (1946), Z.S. Gershenovich et al. (1949), A.F. Panin (1960) and others observed a depression of metabolism and of the activity of the respiratory enzyme systems under high oxygen pressure.

At the same time, it was found that preliminary injection of certain metabolites, vitamins, and respiratory enzymes has a favorable influence on the course of oxygen poisoning (Massar, 1945; Z.S. Gershenovich et al., 1952; L.I. Grachev, 1954; A.G. Zhironkin, 1955; et al.).

These data gave us grounds for advancing the hypothesis that oxygen starvation develops in the oxygen-poisoned organism, arising in the same manner as tissue hypoxia, as a result of blocking of the respiratory enzyme system by the excess oxygen, which hinders assimilation of oxygen by the cells and its utilization for oxidation-reduction processes.

Taking the above material into account and calling attention to Z.I. Barbashova's data (1958, 1960) on the increase which acclimatization to altitude produces in the resistance of animals to the toxic action of the tissue poison hydrocyanic acid, we conducted several series of experiments to determine the extent of resistance to the action of high oxygen pressure after acclimatization to hypoxia. The results of these experiments constitute the subject of this report.

METHOD

Acclimatization to hypoxia was carried on mice, guinea pigs, and cats. The mice and guinea pigs underwent systematic (every other day) "ascents" to an altitude of 6000 m for 4.5 hours in an altitude chamber. There were three variants of the acclimatization: the mice were subjected to 25 "ascents" in the chamber and the guinea pigs to 13 and 30 "ascents." On the third and fourth days after acclimatization ended, the animals were exposed to oxygen compressed to 4.5-6 atm abs.

Unacclimatized control animals were placed in the high-pressure chamber together with the "acclimatized" mice and guinea pigs. In the experiments on cats data obtained for the same animals before acclimatization to hypoxia were used as the control. The time for which the animals remained under elevated oxygen pressure was determined by the onset of convulsive seizures in the experiments on guinea pigs and cats. The mice remained in compressed oxygen for 40 minutes.

The resistance of the guinea pigs to compressed oxygen was determined from the time required for the first symptoms of oxygen poisoning (local and general convulsive seizures) to appear and the rate at which their rectal temperature was normalized; the latter was measured with a maximum thermometer and, in some experiments, with thermocouple junctions.

In the experiments on mice the animals' capacity to withstand oxygen starvation was determined from the time required for convulsive seizures to set in and for terminal respiration to appear in the first mouse of each of the groups, which consisted of 4-6 mice. We also noted the total number of mice in each group which exhibited seizures and the number of terminal mice at the end of the experiment. We calculated the mortality over one day after the exposure to oxygen.

The cats were "acclimated" to hypoxia by reducing the oxygen con-

tent under normal atmospheric pressure. For this purpose a cat was placed in a small air-filled glass chamber with a volume of 3 liters. The chamber was hermetically sealed and the carbon dioxide released was absorbed by granulated sodium hydroxide in a small gauze bag on the bottom of the chamber. As oxygen was required air instead was passed into the chamber from a spirometer. The oxygen content in the chamber was thus gradually reduced and the animal developed a progressive hypoxemia. The air inside the chamber contained 5-7% oxygen and 1-1.5% carbon dioxide at the end of acclimatization. The animal was removed from the chamber when marked symptoms of oxygen appeared. The time for which the cat remained in the chamber usually amounted to one to one and one-half hours. All these hypoxia experiments were conducted once in one variant and four times in the other on each cat.

One and one-half hours after the single and one day after the four-fold hypoxia experiments the cats were placed in a chamber under high oxygen pressure. The cats' resistance to oxygen poisoning was determined from the time required for general convulsions to appear. We repeatedly determined the onset time of convulsions in control experiments in order to exclude the adaptive influences of the compressed oxygen. During the hypoxia experiment we calculated the oxygen demand for some of the animals.

The data obtained in the experiments on cats were subjected to statistical processing by Wilkinson's nonparametric pair-comparison test (Siegel, 1957). We used a total of 64 mice, 14 guinea pigs and 57 cats.

EXPERIMENTAL RESULTS

Our investigations showed that preliminary acclimatization of mice and guinea pigs to "altitude" increased their resistance to the action of high oxygen pressures with respect to that exhibited by unacclimated control animals (Table 1).

It may be seen from the data in the table that twice as long was required for convulsions to set in in the acclimated mice as in the control animals. The number of convulsive seizures occurring in the acclimated mice during the first 10 minutes in compressed oxygen "terminal" acclimated animals at the end of the experiment were also lower than in

TABLE 1

Oxygen Poisoning Indices in White Mice after Preliminary Acclimatization to Altitude

Группы животных	Количество мышей в группе	Время наступления судорог		Количество судорожных припадков в группе за 10 минут опыта	Количество мышей	
		судорог (в мин.)	терминального дыхания (в мин.)		с терминальным дыханием и потерей опыта (в %)	погибших через сутки после опыта (в %)
1	2	4	5	6	8	9
Контрольные 10.	37	2,8	24,0	10,8	46,0	70,3
Тренированные 11.	27	5,6	33,6	3,6	22,2	59,2

1) Groups of animals; 2) number of mice in group; 3) onset time; 4) convulsions (in min); 5) terminal respiration (in min); 6) number of convulsive seizures in group after 10 minutes of experiment; 7) number of mice; 8) with terminal respiration at end of experiment (in %); 9) dying within one day after experiment (in %); 10) control; 11) acclimated.

TABLE 2

Oxygen Poisoning Indices in Guinea Pigs as a Function of Acclimatization Altitude

Группы животных	Количество животных в группе	Число животных, у которых были судороги		Средняя величина латентного периода до наступления судорог (в мин.)	Среднее время восстановления ректальной температуры после декомпрессии (в мин.)
		4 локальные	5 общие		
1	2	3	4	6	7
Контрольные 8.	9	9	6	39,3	94,6
Тренированные 9.	9	1	2	50,5	19,3

1) Groups of animals; 2) number of animals in group; 3) number of animals exhibiting convulsions; 4) local; 5) general; 6) mean duration of latent period before onset of convulsions (in min); 7) mean time required for normalization of rectal temperature after decompression (in min); 8) control; 9) acclimated.

the control groups. The least marked effect was in the mortality of the mice after the experiment.

A clear positive effect was obtained in the experiments involving acclimatization of guinea pigs to altitude. While local convulsions developed in compressed oxygen in all the control guinea pigs, only one of the altitude-acclimated animals exhibited such seizures. General convulsions set in later in the "acclimated" animals than in the control guinea pigs and the rectal temperature of the former was normalized more

rapidly (Table 2).

TABLE 3

Time Required for Appearance of Oxygen Convulsions in Cats as a Function of Preliminary Hypoxia

Time after hypoxia (min)	Number of cats in group	Latent period before onset of convulsions (in min)		Statistical reliability (p)
		before hypoxia	after hypoxia	
Case . . . 7 . . .	8	6.74	14.8	0.01
Group . . . 8 . . .	19	8.7	20.7	0.01

1) Number of exposures to hypoxia; 2) number of cats in group; 3) latent period before onset of convulsions (in min); 4) before hypoxia; 5) after hypoxia; 6) statistical reliability, by Wilkinson's method; 7) one; 8) four.

The data obtained confirm our hypothesis regarding the possibility of increasing resistance to the toxic action of compressed oxygen by prolonged acclimatization to hypoxia.

In the experiments on cats involving fourfold and even single acclimatization to hypoxia we also established that there was a protective effect with respect to oxygen poisoning. It was found that both single acclimatization conducted one and one-half hours before the oxygen experiment and four-fold acclimatization markedly (by a factor of somewhat more than two) retarded the onset of convulsions in comparison with the control experiments (Table 3).

Special interest inheres in the experiments involving four-fold acclimatization, since the favorable effect persisted for 24 hours after acclimatization ended.

One of the important compensatory mechanisms which occurs under the toxic action of oxygen is apparently a depression of metabolic processes. In this connection we attempted to establish a relationship between resistance to high oxygen pressure and oxygen demand. It was found that convulsions set in earlier at an oxygen pressure of 6 atm in cats

with a high oxygen demand. Thus, convulsions began an average of 13.4 min in cats requiring 200 to 300 cm³ of oxygen (per kg of body weight) over 30 min, while cats requiring 400-500 cm³ of oxygen exhibited convulsions after 5 min (Table 4).

Acclimatization to hypoxia affected both the oxygen demand and the time required for convulsions to set in (Table 5). The increase in the latent period of convulsions which occurs in cats under high oxygen pressure after acclimatization to hypoxia may consequently be attributed partially to the reorganization of metabolic processes which occur as a result of repeated hypoxia.

TABLE 4

Time Required for Onset of Oxygen Convulsions
in Cats with Different Oxygen Demands

Группы животных по потреблению O ₂	1	Количество кошек в группе	Уровень потребления кислорода за 30 минут на 1 кг веса (в см ³)		Средний латентный период судорог (в мин.)
			3	4	
Низкий уровень	5	5	270	300	13.4
Средний уровень	6	6	300	400	10.6
Высокий уровень	7	7	400	500	7.5

1) Animals grouped in accordance with O₂ demand; 2) number of cats in group; 3) oxygen demand per kg of body weight over 30 min (in cm³); 4) mean latent period of convulsions (in min); 5) low level; 6) moderate level); 7) high level.

TABLE 5

Time Required for Onset of Oxygen Convulsions
in Cats with Different Oxygen Demands as a
Function of Acclimatization to Hypoxia

Группы животных по потреблению кислорода	1	Количество кошек в группе	3 Потребление кислорода за 30 минут на 1 кг веса (в см ³)		6 Латентный период (в мин.)	
			4 в начале тренировки	5 в конце тренировки	7 до тренировки	8 после тренировки
9 Средний уровень	6	6	328.5	256.4	10.6	30.6
10 Высокий уровень	5	5	425.6	348.1	7.42	16.5

1) Animals grouped in accordance with oxygen demand; 2) number of cats in group; 3) oxygen demand per kg of body weight over 30 min (in cm³); 4) at beginning of acclimatization; 5) at end of acclimatization; 6) latent

period (in min); 7) before acclimatization; 8) after acclimatization; 9) moderate level; 10) high level.

DISCUSSION OF EXPERIMENTAL RESULTS

The results obtained in our experiments clearly indicate that it is possible to increase resistance to the action of compressed oxygen by acclimatization to hypoxia. This increase in resistance is apparently based on the tissue adaptative and reorganization of metabolic processes which occur during acclimatization.

This is indicated by the changes in alkali-acid equilibrium (G.Ye. Vladimirov et al., 1937, 1940), the increase in reduced glutathione (I. R. Petrov, 1952), and the intensification of respiratory enzyme activity in tissue-element energetics (Z.I. Barbasheva, 1952, 1960) which result from acclimatization to altitude.

It seems to us that adaptation to hypoxia is simultaneously adaptation to hyperoxia, since both processes are based on an adaptation mechanism at the cellular level.

The effect of acclimatization to hypoxia is confirmed by data obtained on acclimatibility to high oxygen pressure by repeated exposure to such pressure (A.G. Zhironkin, 1955).

This fact also indicates the common character of the effect of hypoxia and hyperoxia and creates two possible hypotheses regarding the role of acclimatization to hypoxia in the mechanisms of adaptation to the toxic effect of oxygen. On the one hand, it may be assumed that the mechanisms of altitude adaptation are nonspecific, involving cellular adaptation to many detrimental factors. On the other hand, it may be assumed that tissue hyperoxia is based on "hyperoxic hypoxia" and that the effect of acclimatization to hypoxia is specific, acting to produce adaptation to various forms of hypoxia, including the hyperoxic form. We are inclined to believe that the second hypothesis is closer to the truth,

but further research will show how correct it is.

CONCLUSIONS

1. We have established that it is possible to increase resistance to the toxic action of high oxygen pressures by preliminary acclimatization to oxygen deficiency.

2. Both single and repeated acclimatization to hypoxia have a protective effect with regard to the toxic action of oxygen.

3. We discovered a correlation in cats between oxygen demand and the onset time of oxygen convulsions.

ROLE OF OXYGEN IN REDUCING THE UNFAVORABLE EFFECT OF
ELEVATED CARBON DIOXIDE CONCENTRATIONS OF THE
ORGANISM

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In a number of cases professional activity involves a prolonged stay in an environment with an elevated carbon dioxide content.

The effect of high carbon dioxide concentrations on animals has been studied in comparatively great detail by many authors (P.M. Albitskiy, 1911; I.I. Golodov, 1946; V.P. Zargyadskiy, 1946, et al.). I. I. Golodov showed that elevated oxygen concentrations in the inhaled air reduce the toxic effect of high carbon dioxide concentrations on the organism. Our investigations of the influence of prolonged exposure to elevated carbon dioxide concentrations on animals revealed a depression of metabolic processes, which took the form of a decrease in oxygen demand and a suppression and inhibition of the activity of the respiratory enzymes cytochrome oxidase, succinic dehydrogenase, etc. This gave us grounds for studying the possibility of utilizing elevated oxygen concentrations to reduce the unfavorable effect of elevated carbon dioxide contents when animals are kept for a prolonged period under altered environmental conditions.

METHOD

We conducted four series of experiments on 56 rabbits. In two series we investigated the influence of a prolonged stay in an atmosphere

with an elevated carbon dioxide content and in an environment with elevated carbon dioxide and oxygen contents. We paid special attention to elucidating the characteristics of the aftereffect. When the gas composition of the environment is normalized two other series of experiments were conducted to study the reactivity to overloads of animals subjected to prolonged exposure to altered environmental conditions. In these experiments the carbon dioxide content was 3-5% and the oxygen content 32-35%. The animals were kept in the chamber for 5 and 10 hours.

The rabbits' frequency and depth of respiration, their reaction to sound stimuli (evaluated from the change in their breathing), an EKG at the second standard lead, and an EEG of the motor zone of the cortex were recorded before and after their stay in the chamber. We also determined rectal temperature. The aftereffect period was investigated over 1.5 hr.

During the rabbits' stay in the chamber we followed their respiration rate and observed their reactions to various types of stimuli. In order to trace the dynamics of the changes in respiration, cardiac activity, and cerebral bioelectric activity we conducted a series of experiments in which rabbits inhaled appropriate gas mixtures through a mask and systematically recorded all the aforementioned indices.

In investigating reactivity in the third and fourth series of experiments the rabbits were subjected to transverse overloads in the back-chest direction. The overloads varied from 5 to 7 G, with a maximum action time of 60 sec. Each rabbit was subjected to overload twice, on the day before it was placed in the chamber and 15 minutes after it was removed from the chamber.

EXPERIMENTAL RESULTS

The results of the experiments showed that the functional shifts in the organism during the aftereffect period were less marked when the animals were kept for a prolonged period in an environment with elevated carbon dioxide (3-5%) and oxygen contents (up to 35%) than when they were kept for the same length of time in an environment with an elevated carbon dioxide content and a normal oxygen concentration (21%).

Shifting the animals from an environment containing 3-5% carbon dioxide and 21% oxygen to normal atmospheric air was accompanied by an afteref-

fect, which took the form of a sharp drop in motor activity and suppression of reactions to sound stimuli. The aftereffect period lasted approximately 1.5 hours. When the animals were kept in an environment containing 3-5% CO₂ and 35% O₂ the aftereffect period was only half as long, motor activity was depressed to a considerably lesser extent, and reactions to sound stimuli were very marked, even greater than in the initial state in a number of cases. The table presents data on the changes in respiration and heart rates in animals kept in altered gaseous media of varying composition.

It may be seen from the table that a greater retardation of respiration occurred when the animals breathed a gas mixture with elevated CO₂ and O₂ contents than when the CO₂ content was elevated and the O₂ content was normal. However, an elevated O₂ content causes a more marked acceleration of respiration at the beginning of the aftereffect and a more rapid reversion of respiration to its initial state; one hour after the animal is removed from the chamber the respiration rate drops below its initial level. After breathing a gas mixture with an elevated CO₂ content and a normal O₂ content for one hour the heart rate was retarded in comparison with the initial state, while when the O₂ content of the gaseous mixture was raised to 35% it was slightly elevated.

Changes (in %) in Respiration and Heart Rates in Rabbits in the Presence of an Altered Gaseous Environment and During the Aftereffect (the Respiration and Heart Rates in Normal Atmospheric Air Are Taken as 100%)

1 Состав газовой среды	2 Частота дыхания				Частота сердечных сокращений через час после пребывания в камере
	при пребывании в камере		в последствии		
	3 в начале	4 в конце	5 сразу	6 через час	
CO ₂ (3-5 %) O ₂ (21 %)	88.4	71.0	105.8	111.6	97.3
CO ₂ (3-5 %) O ₂ (32-35 %)	80.1	60.9	128.8	89.7	105.2

1) Composition of gaseous environment; 2) respiration rate; 3) during stay in chamber; 4) at beginning; 5) at end; 6) during aftereffect; 7) immediate; 8) after 1 hour; 9) heart rate 1 hour after removal from chamber.

In the EKG an elevated carbon dioxide content caused a decrease in the voltage of the R wave and depression of the R and T waves. Conversely, when both the oxygen and carbon dioxide contents of the gaseous medium were elevated there was an increase in the voltage of the R and T waves. The EKG rapidly reverted to normal during the aftereffect.

Being kept in an environment with an elevated carbon dioxide content affected the animals' body temperature, which usually dropped 0.5-1.5° from its initial level. The situation was entirely different in an atmosphere with an elevated oxygen content. In the majority of these experiments the rabbits' body temperature increased 0.5-1.3°. It remained unaltered in certain experiments and occasionally decreased slightly.

Substantial changes were noted in the cerebral bioelectric activity of animals breathing the aforementioned gas mixtures. An elevated carbon dioxide content and a normal oxygen content caused initial acceleration of the β -waves, this being followed by the appearance of slow high-voltage waves. In the majority of the experiments the EEG retained this character after the rabbits were removed from the chamber. The EEG was normalized slowly, over a period of 45-70 minutes. When the oxygen content of the atmosphere was also elevated the changes in the EEG were very slight. The only noticeable phenomenon was a slight acceleration of the β -rhythm. Shifting the animals to an ordinary atmosphere frequently caused rather substantial changes in the EEG pattern.

However, all the aforementioned changes in the physiological functions studied became considerably more marked when the animals were subjected to overloads during the aftereffect period. In the initial state

maximum overload caused retardation of cardiac activity and respiration and acceleration of the β -potentials in the EEG. All these indices were normalized within 2-5 minutes after the centrifuge was stopped.

The rabbits subjected to overload after being kept for 5-10 hours in an atmosphere with an CO_2 content exhibited a more severe inhibition of respiration and cardiac activity, changes indicating a disturbance of myocardial excitability and conductivity (twinning of the P and T waves, depression of the S wave, and prolongation of the P-Q interval) and a sharp increase in the tonus of the vagus nerve (bradycardia passing into a sinoauricular block) appearing in the EKG; the EEG was depressed and became areactive with respect to sound stimuli. Rather serious remote sequelae were also observed; these included myocardial failure, myocardial infarct, and paresis of the hind legs and indicated that the prolonged exposure to elevated carbon dioxide concentrations caused considerable changes in the reactivity of the organism. Biochemical investigations conducted after the rabbits had been kept in this atmosphere for many days revealed a depression of oxidative-enzyme activity.

When the oxygen content of the gaseous environment was raised and the carbon dioxide content was kept at the same level (3-5%) the animals' capacity to withstand overload (as evaluated from the changes in respiration, pulse rate, and the EKG and EEG) differed relatively little from that observed in the initial state. The retardation of respiration and pulse rate on application of maximum overload was essentially the same; the changes in the EEG were slight (some drop in the voltage of the P, R, and T waves and respiratory arrhythmia) and the normal pattern was restored 2-3 minutes after the centrifuge was stopped. Slow high-voltage waves appeared in the EEG. Normalization of the pattern began after five-seven minutes. Overload caused prolonged depression of the encephalogram only in isolated experiments.

The experimental data cited above indicate that serious functional shifts occur in the organism, especially in the central nervous system, when an animal is kept in a gaseous medium containing from 3 to 5% carbon dioxide for 5-10 hours. As our investigations on humans showed, substantial functional shifts in the central nervous system and the analyzers, which cause a loss of working capacity, are also observed at lower CO₂ concentrations (1.2-2%) on longer exposure (1961). All this forces us to seek means of reducing the unfavorable effect of elevated carbon dioxide concentrations on animals and on humans who must remain for extended periods in altered environments. For this purpose we utilized elevated (to 35%) oxygen concentrations.

The experimental results cited above indicate that there is a considerable decrease in the unfavorable effect of elevated carbon dioxide concentrations and a curtailment of the aftereffect period when the oxygen content of the inhaled air is raised to 35%. We refrained from employing higher oxygen concentrations to provide maximum protection against the possible toxic action of the oxygen itself on the organism. Special emphasis must be placed on the fact that an elevated oxygen content in the inhaled air increases the resistance of the organism to other factors, particularly transverse excess-G stresses; this resistance is considerably reduced when a gas mixture containing 3-5% CO₂ and 21% O₂ is breathed.

The mechanisms by which elevated oxygen concentrations reduce the unfavorable effect of hypercapnia require more thorough investigation. Taking into account Al'bitskiy's hypothesis of the antagonism between carbon dioxide and oxygen in the organism, it may be assumed that oxygen in rather high concentrations activates the metabolic processes depressed under the influence of hypercapnia.

OXYGEN CONSUMPTION AND CARBON DIOXIDE ELIMINATION IN
RESPIRATION UNDER EXCESS PRESSURE

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The functional shifts which occur in the organism during inhalation of pressurized oxygen through a mask are to some extent due to the development of hypocapnia as a result of hyperventilation. This is also confirmed by the decrease in the partial carbon dioxide pressure in the alveolar air (N.A. Agadzhanian, M.I. Vakar, et al., 1961; A.G. Kuznetsov, 1957; and many others). However, it has been found that the same functional shifts are observed under these respiration conditions in cases where pulmonary ventilation fails to increase or even decreases. In our subjects pulmonary ventilation usually increased after 10 minutes of breathing oxygen under a pressure of 300 mm H₂O through a mask and remained at this elevated level, especially after the pressure was relieved (during the first few minutes). Investigations (conducted by Krog) showed that oxygen consumption was less during the first five minutes after the pressure in the mask was relieved and greater during the following five minutes. It remained somewhat below the initial level in both cases, averaging 582 ml per min, as against 602 ml per min initially. In experiments on two dogs the oxygen consumption during the first five minutes after the pressure was relieved averaged 378 ml per min in one and 145 ml per min in the other; during the following five minutes it averaged 484 and 195 ml per min respectively. An increase in oxygen consumption over the initial level was also detected in isolated

experiments, but no relationship was noted between this increase and the corresponding shifts in pulmonary ventilation. Moreover, if the subject's functional state was altered by a prolonged stay in an atmosphere with a 2% carbon dioxide content subsequent respiration under elevated pressure caused an increase in pulmonary ventilation and a further decrease in oxygen consumption (which averaged 315-345 ml per min).

Oxygen Consumption and Carbon Dioxide Elimination during Respiration Under Excess Pressure

1 Минута опыта	2 Минутный объем дыхания, л/мин	3 Поглощение кислорода		5 Выделение углекислоты	
		%	4 мл/мин	%	мл/мин
6 (рассчитано по составу выдыхаемого воздуха)					
7 Исходное положение	7,7	4,9	377	2,6	277
8 При избыточном давлении равном 300 мм вод. ст.					
Первая	10,5	4,5	168	2,2	125
Вторая	8,7	3,3			
11 После сброса давления					
Первая	10,5	4,5	477	3,2	336
Шестая	6,7	5,0	335	3,6	244
13 Такой же опыт был повторен с дыханием в замкнутую систему, но без поглощения углекислоты выдыхаемого воздуха					
Исходное положение	8,8	4,8	422	3,9	343
14 При избыточном давлении в маске, равном 300 мм вод. ст.					
Вторая	3,0	5,1	153	2,7	81
Шестая	3,0	4,1	112	2,3	69
Десятая	7,5	5,1	362	2,9	217
После сброса давления					
Вторая	10,5	4,9	514	3,8	400
Самая	13,7	4,6	630	4,0	548

Note: The residual air contained 16.8% by volume oxygen and 3.1% by volume carbon dioxide after the experiments. The subject's capacity to withstand the respiration conditions decreased.

1) Minute of experiment; 2) minute respiratory volume, l/min; 3) oxygen consumption; 4) ml/min; 5) carbon dioxide elimination; 6) calculated from the composition of the exhaled air; 7) initial; 8) under excess pressure of 300 mm H₂O; 9) first; 10) second; 11) after relieving pres-

sure; 12) sixth; 13) the same experiment was repeated with respiration in a closed system, but without absorption of carbon dioxide from the exhaled air; 14) with a mask overpressure of 300 mm H₂O; 15) tenth; 16) seventh.

When overpressure was employed in the mask the changes in gaseous interchange were determined by investigating the oxygen and carbon dioxide contents in the exhaled air, ordinary air being supplied to the mask. Under these respiration conditions the changes in pulmonary gaseous interchange were distinguished by certain quantitative deviations, but there was an increase in the oxygen content and a decrease in the carbon dioxide content of the exhaled air no matter when the sample was taken.

Let us now present the data obtained in our investigation of subject V. (see table).

This version of the experiment involving respiration in a closed system was set up in such fashion as to exclude any loss of carbon dioxide from the monitored system. In both versions of the experiment carbon dioxide elimination and oxygen consumption decreased when overpressure was applied at the mask (when ventilation increased there was a corresponding decrease in the carbon dioxide content of the exhaled air). Both carbon dioxide elimination and oxygen consumption began to increase rapidly after the pressure in the mask was relieved.

The data thus obtained for animals differ little from the aforementioned results of our experiments on humans, but the pressure in the mask proved to have a more severe effect on the animals and the changes in their gaseous interchange were greater in extent. In a number of cases only traces of carbon dioxide were detected in the exhaled air. The oxygen content of the exhaled air accordingly varied little.

These experiments create the impression that the disruptions of gaseous interchange which occur under such respiration conditions are

based not on changes in pulmonary ventilation, but on the gaseous interchange conditions in the lungs, circulation in the vessels of the pulmonary circulatory system being disrupted and the quantity of circulating blood in the organism being reduced as a result of marked venous congestion. It is noteworthy that the oxygen consumption during application of overpressure at the mask and after this pressure is relieved is correlated with the pressure, oscillatory amplitude, and frequency of the pulse. Chernyakov (1960) has also noted that the blood-flow rate and oxygen saturation of the blood depend on the pulse rate under these conditions.

That gaseous interchange depends on the blood supplied to the lungs has also been found in direct observations made through an artificial "window" in the thoracic wall, through which it may be seen that the lungs are anemized (decolorized) when the pressure in the mask is increased; after the pressure is relieved, when the venous congestion rapidly breaks down, the lungs become hyperemic and distended. This is apparently associated with a deterioration of pulmonary gaseous interchange at the beginning of the recovery period, after the pressure in the lungs is relieved.

The changes which occur in the gas composition of the blood when the pulmonary pressure is elevated are frequently evaluated from the oxyhemometric changes, which show that there is a decrease in the oxygen saturation of the arterial blood. Blagoverov and Saradzheva (1960) and others turned their attention to the discrepancy between the oxygen saturation and carbon dioxide content of the arterial blood and the content of these gases in the alveolar air (the oxygen content of the latter is high, while its carbon dioxide content is very low). Using Van Slyke's method, we observed an increase in the oxygen saturation of the arterial blood (to 21.6% by volume) in dogs after increasing the

mask pressure (although this was not noted in all the subjects). Conversely, the oxygen saturation of the venous blood was sharply depressed throughout the entire experiment. After 15 minutes the arterial-venous oxygen difference was almost twice its initial value. The carbon dioxide content of the venous blood varied little, but that of the arterial blood had dropped by 6% by volume after 15 minutes. As a result, the venous-arterial carbon dioxide difference increased in the same manner as the oxygen difference. These differences still persisted 4 minutes after the pressure in the mask was relieved. Blagoverov and Saradzheva also obtained contradictory results for the changes in the gas composition of the blood in half their subjects. We noted similar discrepancies in animals whose respiration was for various reasons complicated by asphyxia. It is well-known that such complications are frequently observed in experiments on humans.

Oxygen consumption and carbon dioxide elimination thus decrease under mask overpressure. An oxygen deficiency develops even at sea level or on inhalation of pure oxygen, regardless of the changes in pulmonary ventilation. It is caused by an elevated intrapulmonary pressure, which produces a decrease in the circulating blood volume, a drop in the blood-flow rate, and development of venous congestion. The hypoxia observed in this case results from insufficiency of oxidative processes (oxygen starvation). Hyperventilation may intensify hypocapnia, but in this case the oxygen and carbon dioxide contents of the alveolar air do not correspond to those of the blood.

After the pressure in the mask is relieved compensation, restoration, and oxygen absorption are somewhat hampered by the pulmonary hyperemia and distension which develop during the rapid breakdown of the venous congestion.

IONIC SHIFTS IN THE ORGANISM OF THE HUMAN AND ANIMALS DURING
HYPOXIC PHENOMENA OF VARIOUS ORIGINS (SUBNORMAL BAROMETRIC
PRESSURE, ACCELERATION, VIBRATION)

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(Moscow)

Numerous investigations have been devoted to the problem of the influence of hypoxia on the human organism. This problem has become most acute during recent years in connection with the development of aviation and space physiology. Study of the intimate mechanisms of regulation and compensation of the organism's functions, including the shifts in ionic equilibrium in the various biological media of the organism, is of major interest in this broad-scope problem.

The first studies devoted to this problem date from the '30's. Thus, in 1935, E. S. Sundstrem and G. Zhirogosints noted an increase in the potassium concentration of the blood plasma and a decrease in sodium concentration in experiments performed on animals under the conditions of hypobaric-chamber "ascents" to "altitudes" of the order of 3000-8000 m with exposure times ranging from three hours to two months. The extent of this shift was related in a certain way to the altitude of the ascent and the duration of the disturbance. Similar data were obtained in a study by Sundstrem and Mikhaelis (1942).

In an experimental study completed in S. A. Kapienskiy's laboratory on humans and animals (rats, rabbits, dogs) under the conditions of hypobaric-chamber "ascents" to "altitudes" of 5500-7000 m with various exposure times, I. I. Gorelov (1938) failed to note any substantial

shifts in the organism's ionic equilibrium. Only on ascents to altitudes greater than 9000 m did the author succeed in observing a considerable rise in potassium concentration and a minor decrease in the sodium concentration of the blood plasma.

Undertaking a study of acid-base equilibrium in the human organism under the conditions of subnormal barometric pressure, I.I. Dedyulin (1940) noted a certain increase in the potassium concentration of the blood plasma after sojourns in the hypobaric chamber at an "altitude" of 6000 m lasting 6 and 24 hours (from 17.2-23.4 mg% in the initial state to 18.5-27.1 mg% after six hours of exposure and to 17.8-29.8 mg% after 24 hours' exposure)

In a study performed on rabbits, M.I. Belogorskiy (1947) observed no shifts in the potassium and sodium concentrations in the blood plasma after hypobaric-chamber "ascents" by animals to "altitudes" of the order of 4000-6000 m with exposure times of 6-8 hours.

In a study made in 1955, Pratt, Smith and Ferguson noted in experiments on rats that after the animals had spent 30 minutes at altitudes of 8, 9, 10 and 11.7 thousand meters, the plasma potassium concentration has dropped to 8.2-22%, respectively, while it increases by 51% on "ascent" to an "altitude" of 13.3 thousand meters. In adrenalectomized animals, these shifts were smoothed out considerably in some cases, and this enabled the authors to confirm an essential point in the relationship between mineral metabolism and adrenal function.

In view of the urgency of study of the organism's ionic-equilibrium shifts for understanding of certain mechanisms in the regulation and compensation of functions in hypoxia, and also in view of certain contradictions in the literature data on this question, it appeared to us expedient to investigate the potassium-sodium equilibrium in the human organism in various forms of hypoxia under the conditions of aero-

nautical and space flight.

The present communication sets forth data from a number of our investigations, in which the plasma-photometry method was used to determine the concentrations of sodium and potassium ions in various fluid media of the organism (blood plasma, urine and saliva) under subnormal barometric pressure and the effects of acceleration and vibration. It is our view that an element of hypoxia is present in one form or another in all of these disturbances, which are inherent to the problems of contemporary aviation and astronautics.

Five specimens of urine (taken before the "ascent" and every 40-50 minutes thereafter) from humans "taken up" in a hypobaric chamber to "altitudes" of 5000 m (30 minutes) and 6000 m (15 minutes) were analyzed. Saliva was collected by means of a Leshli capsule: before the "ascent," during the first 15 minutes of the stay at "altitude," during the subsequent 15 minutes of the stay at "altitude" and after the "descent to the ground" (two specimens with a 10-minute interval) (A.S. Barber and E.V. Yakovleva, 1962). A total of 26 persons were studied in "ascents" to 5000 m. All of them showed good tolerance to this disturbance.

The nature of the shifts that appeared in the sodium and potassium concentrations in the urine is shown in Table 1 for this group of individuals. As will be seen from the table, distinct shifts in the proportions of the components under study have intervened after the thirty-minute sojourn at the "altitude" of 5000 m. The sodium concentration shows a tendency to diminish, and that of potassium to increase, although these shifts are still absent in the first specimen taken after the disturbance, and appear quite clearly only in the second portion. The changes in the Na/K ratio are clearest here. As concerns the ionic shifts in the saliva, a distinct rise in the concentrations of potassium and sodium is noted during the first 15 minutes of the sojourn "at altitude." During the next 15 minutes, the sodium and potassium concen-

trations decrease. However, the potassium concentration remained above the initial level. It is seen from the next two specimens taken that in the first twenty minutes after the "ascent," the potassium concentration showed a tendency to return to the initial level, while the sodium concentration still remained subnormal during this period (Table 2).

TABLE 1

Summary Data on Change in Concentrations of Potassium and Sodium in Urine After 30-minute Stay at "Altitude" of 5000 m

No. spec-imen	1	2	3	Na/K
1	487.7	183.9	2.8	2.8
2	—	—	—	—
3	482.6	177.1	2.8	2.8
4	473.9	222.0	2.3	2.3
5	432.0	208.0	2.3	2.3
6	481.4	202.9	2.3	2.3

1) Specimen No.; 2) sodium concentration (in mg%); 3) potassium concentration (in mg%); 4) disturbance.

TABLE 2

Ionic Shifts in Saliva of Test Subject K-v during "Ascent" to "Altitude" of 5000 m

No. spec-imen	1	2	3	Na/K
1	27.9	143.0	0.19	0.19
2	31.9	173.0	0.18	0.18
3	12.1	151.0	0.08	0.08
4	20.1	192.0	0.12	0.12
5	12.1	120.0	0.10	0.10

1) Specimen No.; 2) sodium concentration (in mg%); 3) potassium concentration (in mg%).

A group of 24 persons was studied in ascents to 6000 m; of these, 18 showed good tolerance for the disturbance, while the six others showed lower-than-normal stability to this degree of hypoxia. Clinically, this lower stability manifested in palor, hyperhidrosis, a drop in arterial pressure and a slackening of the pulse, and in one case these phenomena were accompanied by temporary loss of consciousness. It should be noted that all individuals "taken up" in the hypobaric chamber to an "altitude" of 6000 m had been "lifted" to an "altitude" of 5000 m two to four days previously.

Summary data on the changes in the concentrations of the substances being investigated in individuals with good tolerance for this disturbance are presented in Table 3. As will be seen from Table 3, this "ascent" did not produce substantial shifts in the proportions of the components being studied. Thus, the

Na/K ratio remained close to the initial value. As concerns the changes

that took place in persons with lower tolerance for this type of disturbance, a distinct shift toward lower sodium concentration and higher potassium concentration was noted in these individuals. Thus, the Na/K concentration ratio dropped from 3.2 in the first sample to 1.7 in the third.

TABLE 3

Summary Data on Changes in Potassium and Sodium Concentrations in the Urine after 15-minute Sojourn at "altitude" of 6000 m, in Individuals with Good Tolerance for this disturbance

№ образца	Концентрация натрия (в мг %)	Концентрация калия (в мг %)	Na/K
1	2	3	
1	518,8	226,1	2,7
Во время	—	—	—
смены			
2	493,4	205,7	2,5
3	485,2	200,7	2,6
4	489,3	196,7	2,7
5	482,1	203,5	2,6

1) Sample No.; 2) sodium concentration (in mg%); 3) potassium concentration (in mg%); 4) disturbance.

Thus, hypoxia induced by "ascents" in the hypobaric chamber is accompanied by ionic shifts in the direction of higher potassium ion concentration and lower sodium ion concentration. Repeated "ascents" even to higher "altitude" are accompanied by shifts smaller than the primary ones, something that we can, in all probability, attribute to adaptation phenomena, and only in cases of low tolerance did these shifts also remain distinctly manifest in disturbances subsequent to the first.

The ionic shifts accompanying acceleration were studied in experiments on animals (rats) and humans. Four series of experiments were performed on the animals, with an acceleration of 10g applied for 1 minute. The acceleration acted in the tail-to-head direction in the first series, in the head-to-tail direction in the second, and in the dorsal-ventral direction in the third, while in the fourth series of experiments the same magnitude of acceleration, directed along the tail-to-head axis, was studied as a repeatedly applied factor (4 times a day for a month). The ionic proportions were determined in the blood plasma, which was collected after decapitation performed immediately after the centrifuge was stopped.

The typical ionic equilibrium shifts, taking the direction of increased potassium ion concentration and decreased sodium ion concentra-

tion, were observed. These shifts were noted most distinctly in those experiments in which the blood supply to the brain had been disturbed to the greatest degree, that is to say, with the accelerations directed along the tail-to-head and head-to-tail axis. In the case of multiple applications of the acceleration, a certain graduation was observed in the development of this reaction. Thus, after 20-30 applications, when certain adaptation phenomena came into evidence, the severity of the ionic shifts was lower. Subsequently, these shifts again intensified, coincidentally with a breakdown of adaptation, which was judged from a complex of symptoms (Barer, 1958).

The other studies were made with 43 persons (Barer and Yakovleva, 1960). The subjects were given repeated doses of acceleration directed along the spinal axis, 3g for 30 sec, 5g for 30 sec, 6g for 30 sec and 7g for 30 sec, with intervals of 5-10 minutes. In most cases, the potassium and sodium concentrations were determined in the urine, and less often in the saliva. The urine was collected by portions with 40-50-minute intervals. The first four samples were collected before the disturbance and the last four after the disturbance. The saliva was collected by the same method as used in the hypobaric-chamber "ascents," in four portions: before the disturbance, during the time of the 3- and 5-g acceleration disturbances, during the 6- and 7-g disturbances and after the experiment had been completed.

Distinct changes in the proportions of sodium and potassium ions were observed in all cases. The concentration of potassium ions increased in the urine and the saliva, while the sodium ion concentration decreased, with the shift most distinct in individuals with low tolerance to this disturbance, manifesting in the usual visual disturbances and sometimes even in loss of consciousness (Tables 3 and 4).

The investigation of the ionic shifts in humans subject to vibra-

TABLE 4

Change in Concentration of Sodium and Potassium in Urine of Humans with good Tolerance of Acceleration

№ пробы	1	2	3	№/К
	Концентрация натрия (в мг%)	Концентрация калия (в мг%)		
1	446,1	177,5		2,86
2	428,2	178,6		2,66
3	463,9	186,1		2,68
4	463,0	194,7		2,54
Водянистость 4	—	—		—
5	468,5	199,1		2,55
6	420,9	216,0		2,23
7	438,0	242,7		2,19
8	427,2	188,1		2,45

1) Specimen No.; 2) sodium concentration (in mg%); 3) potassium concentration (in mg%); 4) disturbance.

TABLE 5

Change in Concentrations of Sodium and Potassium in Urine of Individuals with low Tolerance for Acceleration

№ пробы	1	2	3	№/К
	Концентрация натрия (в мг%)	Концентрация калия (в мг%)		
1	511,9	181,6		3,29
2	564,9	140,1		4,28
3	582,3	209,4		3,25
4	503,2	211,5		2,80
Водянистость	—	—		—
5	502,1	198,1		2,80
6	419,0	248,3		1,88
7	477,5	263,8		2,26
8	466,8	218,3		2,23

1) Specimen No.; 2) sodium concentration (in mg%); 3) potassium concentration (in mg%); 4) disturbance.

tion disturbances (10 cycles at an amplitude of 0.8 mm for 45 minutes and 60 cycles at an amplitude of 0.4 mm for 45 minutes) was also made with the urine and the saliva, with the saliva collected before, after and during the disturbance.

A total of 15 persons (men) participated in the experiments. The clearest shifts in the direction of increased potassium concentration and decreased sodium concentration were observed precisely in the saliva. No essential differences were to be noted in the concentration changes of the subject substances during the vibration disturbances at the different frequencies (Table 5).

It is seen from the studies performed that all three types of disturbance - "ascent" in the hypobaric chamber, acceleration and vibration - are accompanied by shifts of the same type in the proportions of sodium and potassium ions in the human and animal organism.

In our opinion, these features in common to the response reactions of the organism when disturbed by various stressors can

also be accounted for by the fact that oxygen starvation of vitally important organs, and primarily of the brain, were observed in all three cases. Only in the hypobaric-chamber "ascents" did this take the form

of hypoxic hypoxia; in the case of the acceleration disturbances, it was hypoxia of the circulatory type, and in the vibration disturbances it was obviously of the mixed type, with contributions both from hemodynamic derangements of the reactions and from disturbances to the processes by which the tissues assimilate oxygen. Also to be remembered is the fact that changes in the sodium and potassium ion concentrations in the intertissue fluid depend primarily on the permeability of the cell membranes to these ions.

RESISTANCE OF RATS TO HYPOXIA IN ACUTE RADIATION SICKNESS

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(Leningrad)

The action of various forms of hypoxia on irradiated animals has been studied in a number of works. In the majority of cases the authors were interested in hypoxia as a factor influencing the course and outcome of the radiation affection (Bychkovskaya, Strelin, Shiffer, 1956; Blagovestova et al., 1957; Berokonskiy, 1959; et al.). Research in this direction naturally paid little attention to the reaction of irradiated animals to hypoxia. There are only a few works devoted to this problem.

Smis and Smis (1955) detected an increase in resistance to hypoxia in mice irradiated in doses of 325 and 700 r. Konstantinov (1955) showed that resistance to hypoxia is elevated one-two days before death in mice irradiated in a dose of 1000 r. Newsom and Kimeldorf (1954) established that the survival rate among rats kept for four hours in a pressure chamber at an "altitude" of the order of 8000 m or more rises considerably on the first-third day after irradiation in doses of 500-600 r. This effect was less marked at lower "altitudes." The authors believe that this increase in survival rate results primarily from starvation, since severe anorexia is observed in irradiated animals during this period. They showed that rats starved for 72 hours are almost as resistant to hypoxia as irradiated animals. However, the authors did not advance any hypotheses regarding the causes of the increase in resistance to hypoxia which occurs on the day after irradiation.

The characteristics of the reaction of the irradiated organism to

hypoxia thus requires further study. This problem is of great interest, since, firstly, the action of hypoxia may be employed as a functional test which enables us to elucidate certain aspects of the pathogenesis of radiation sickness and, secondly, information on the sensitivity of irradiated animals to oxygen deficiency is of undoubted practical interest.

In this connection the principle task of the work described herein was investigation of the changes which occur in the resistance of white rats to hypoxia throughout the entire course of acute radiation sickness and an attempt to clarify certain of the pathophysiological mechanisms underlying them. We studied the survival times of rats kept in a pressure chamber at various "altitudes." We also measured the animals' body temperature and determined their gaseous interchange while breathing atmospheric air and in hypoxia.

METHOD

Male white rats of the Wistar strain weighing 200-250 g were subjected to whole-body x-irradiation in a dose of 750 r (on a RUM-11 apparatus at 190 kv and 20 ma, with a 0.5 Cu + 0.5 Al filter and a dose rate of 8.3 r/min). Individual groups of rats were "taken up" in a pressure chamber immediately after irradiation and after 3, 6, 12, 24, 48, 72, and 96 hours. An "ascent" to a pressure of 140 mm Hg (an "altitude" of approximately 12,000 m) was carried out over five minutes, with five 30-second halts. The "ascent" was discontinued on reaching a pressure of 140 mm Hg and determination of the animals' survival time at this "altitude" (to an accuracy of within 15 sec) began at that point. The rats were judged dead when their respiratory movements ceased. Two or three irradiated rats and the same number of control animals were taken up together. The rats' weight and rectal temperature were determined before the "ascent."

Gaseous interchange was investigated by two methods. The ordinary chamber method involving analysis of the air in a Holden apparatus was employed to determine the oxygen consumption rate in breathing atmospheric air. For this purpose we measured the gaseous interchange of

the same rat for a period of three days before irradiation and then at the same intervals at which we determined survival rate (0, 3, 6, 12, 24, 48, 72, and 96 hours) after irradiation. Kalabukov's method (1951) involving automatic oxygen supply was used to determine gaseous interchange in breathing a gas mixture with a reduced oxygen content. For this purpose 12 or 72 hours after irradiation the experimental and control rats were placed in a special gaseous interchange chamber and their oxygen consumption in breathing atmospheric air was determined. The air in the chamber was then replaced by a gas mixture containing 7-7.8% oxygen, which corresponds to a pressure of the order of 250-280 mm Hg or an "altitude" of approximately 8000 m, for 1-1.5 minutes.

A total of 211 control and 241 irradiated rats were used in our work.

EXPERIMENTAL RESULTS

At the dose which we employed the rats exhibited marked gastrointestinal disturbances three days after irradiation; approximately 80 hours after irradiation the rats began to die en masse, so that no more than 25-30% of the irradiated animals survived to the end of the fourth day.

Table 1 shows data on the change in the resistance of rats to hypoxia at various intervals after irradiation. These results were processed by the sieve method, which made it possible to determine both the mean time for which the animals survived in the pressure chamber and another, more indicative quantity - the time required for 50% of the animals to die.

It may be seen from the table that no material reliable difference in resistance to hypoxia was noted between the control and irradiated rats immediately after irradiation or three hours later. However, the animals' resistance to hypoxia was found to be elevated six hours after irradiation. The time required for 50% of the subjects to die was prolonged to approximately the same extent 6, 12, 24, and 48 hours after irradiation. The most substantial increase in resistance to hypoxia was

TABLE 1.

Survival Rate Among Rats in Pressure Chamber at a pressure of 140 mm Hg

1	2	3								
		0	3	6	12	24	48	72	96	
4	125	26	14	24	20	20	15	27	23	
5										
6		4'30"	7'45"	1'35"	6'35"	11'45"	11'0"	11'45"	19'30"	5'30"
		1'30"	1'15"	1'45"	6'45"	6'30"	7'30"	5'45"	14'00"	4'30"

1) Index; 2) control; 3) time after irradiation (hours); 4) number of animals; 5) mean survival time (minutes and seconds); 6) time required for 50% of rats to die (minutes and seconds).

observed 72 hours after irradiation, when the symptoms of radiation sickness were already rather marked. Finally, at the last of the intervals which we investigated, 96 hours after irradiation, resistance was considerably reduced in comparison with the preceding interval, 72 hours, although the surviving rats proved to be more resistant to hypoxia than the control animals.

Systematic measurement of the rectal temperatures of all the experimental rats during the course of the radiation sickness showed that no reliable changes in temperature occur during the first 48 hours after irradiation. Rectal temperature was depressed by an average of 3.9° 72 hours after irradiation. This gave us grounds for assuming that the increase in resistance to hypoxia, at least that observed 72 hours after irradiation, is caused by a drop in the intensity of metabolic processes. The first step in analyzing the results obtained was consequently to study the rate of gaseous interchange in rats during acute radiation sickness.

The data available on this problem in the literature are quite

TABLE 2

Oxygen Consumption of Rats During Acute Radiation Sickness

Показатели 1	Контр- роль 2	3 Время после облучения (часы)							
		0	3	6	12	36	48	72	96
4 Количество животных . . .	36	12	10	10	12	12	12	12	10
5 Потребление O ₂ (в мл/г/час)	1,68	1,57	1,54	1,38	1,60	1,58	1,63	1,54*	1,82
6 Потребление O ₂ (в мл/час на крысу) . . .	392	333	292	256	332	336	301*	295*	298*

Note: The asterisks indicate values which differ reliably from those for the control ($P < 0.05$).

1) Index; 2) control; 3) time after irradiation (hours); 4) number of animals; 5) O₂ consumption (in ml/g/hr); 6) O₂ consumption (in ml/hr per rat).

contradictory. Certain authors (Kirkhner et al., 1949; Mole, 1953) detected a rise in the rate of O₂ consumption after irradiation, while others (Smis et al., 1952; Smis, Thiry, et al., 1951) did not observe any material changes; a drop in the rate of O₂ consumption occurred only in those cases where there was substantial starvation. Novak (1958) showed that gaseous interchange in the adaptation phase does not change during the first day after irradiation in doses of more than 400 r, but is then depressed, reaching its maximum on the third day after irradiation.

We determined the rate of O₂ consumption in breathing atmospheric air at all the aforementioned intervals after irradiation in a dose of 750 r (Table 2).

As may be seen from Table 2, the O₂ consumption in ml/hr per unit body weight varies little during radiation sickness. The only exception is a slight but reliable drop in the consumption rate 72 hours after irradiation. However, animals occasionally lose substantial amounts of weight during this period, primarily because of loss of water and de-

pletion of the lipid depots rather than at the expense of metabolically active tissues (Krayevskiy, 1957). We consequently felt it proper to determine both the rate of oxygen consumption per unit weight and the oxygen consumption of the entire organism per unit time. With the results expressed in this manner it may be seen that the O₂ consumption remains near the control level through the first two days of radiation sickness and that the rate of gaseous interchange begins a statistically reliable drop 48 hours after irradiation.

TABLE 3

O₂ Consumption of Control and Irradiated Rats with Normal and Reduced Oxygen contents in the Inhaled Air

Группа 1	Количество крыс 2	Потребление O ₂ (в мл/г/час) 3			7 Потребление O ₂ (в мл/г на крысу)		
		Воздух 4	Гипо- ксия 5	% сни- жения 6	Воздух	Гипо- ксия	% сни- жения
Контроль 8	21	1,74	1,26	28	410	276	33
12 часов после облучения 9	7	1,58	1,26	25	390	296	24
72 часа после облучения 10	11	1,20	0,66	45	278	170	39

1) Group; 2) number of rats; 3) O₂ consumption (in ml/g/hr); 4) air; 5) hypoxia; 6) % decrease; 7) O₂ consumption (in ml/g per rat); 8) control; 9) 12 hours after irradiation; 10) 72 hours after irradiation.

In the next series of experiments we determined the oxygen consumption of irradiated rats under hypoxic conditions. In setting up these experiments we proceeded from the assumption that the increased resistance of irradiated rats to oxygen deficiency results not so much from a drop in the initial metabolic level as from the greater decrease which occurs under hypoxic conditions. The correctness of this assumption is shown by, e.g., the work of Wexler (1959), who detected a more rapid and severe drop in body temperature in irradiated animals under hypothermic conditions.

The results of this series of experiments are shown in Table 3. These data confirm those of the preceding series: gaseous interchange

in breathing atmospheric air is not altered with respect to the control 12 hours after irradiation, but is depressed after 72 hours.

It may be seen from Table 3 that the absolute level of gaseous interchange under hypoxic conditions is considerably lower 72 hours after irradiation than in unirradiated rats for 12 hours after irradiation. It must be noted that there is no difference in gaseous interchange between the latter two groups either under hypoxic conditions or at normal oxygen tension.

DISCUSSION OF EXPERIMENTAL RESULTS

The data which we obtained thus lead us to assume that the mechanism underlying the increase in resistance to hypoxia differs in various stages of radiation sickness. At longer intervals after irradiation, 72 and possibly 48 hours, this increase in resistance apparently results from a depression of metabolism accompanied by a slight hypothermia, in all probability caused by starvation and a number of other factors. Here it is important to note that, in addition to the reduced initial gaseous interchange level, animals in this stage of radiation sickness exhibit a more marked depression of gaseous interchange under hypoxic conditions. As a result, the absolute O_2 consumption under hypoxic conditions is considerably lower for this group of rats than for the other groups. At the same time, as is well known, as the metabolic rate decreases the resistance of the organism to hypoxia increases, a phenomenon caused by a whole series of factors (Opits and Schneider, 1950; et al.). Resistance to hypoxia differs little from that of the control animals 96 hours after irradiation, although the metabolic rate remains low. This is probably explained by the severe disruption of all basic vital functions characteristic of the terminal stage of radiation sickness.

The increase in resistance to hypoxia which occurs during the ear-

Earlier stages of radiation sickness (6-24 hours) is apparently not due to a change in metabolic rate under either normal or hypoxic conditions, but results from other factors; further research is required to clarify the nature of these factors.

CURRENT CONCEPTS OF THE REORGANIZATION OF CELL CHEMISM DURING
ACCLIMATIZATION TO HYPOXIA

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The work of Soviet physiologists and biochemists occupies an important place in research on the mechanisms of acclimatization to hypoxia. Unfortunately, their interest in this problem has diminished considerably in recent years. However, it is quite impossible to consider this question to be completely exhausted. Even if nothing essentially new can be found in determining the changes in pulmonary ventilation, cardiac functioning, general hemodynamics, or the morphological composition of the blood in animals during acclimatization, there is still a broad field of activity in research on the reactions at the tissue or cellular level. The adaptive reactions which develop in the cells are a no less important factor in the general adaptation syndrome than the functional changes; the data on these reactions are still fragmentary and frequently contradictory.

Without fear of exaggeration we may state that many Soviet investigators clearly place too little importance on this aspect of the problem. In discussing the mechanisms of acclimatization to hypoxia a number of works discourse in detail on the great importance of the intensification of the functioning of the pulmonary respiration, blood, and circulatory systems and somewhere at the end, incidentally, note that these mechanisms are some sort of adaptation reactions in the tissues. These processes are not enumerated and there is no indication of their

significance.

This report is intended to characterize the current state of the problem of cellular adaptation and especially to show that the adaptive changes in the tissues involve a wide of metabolic processes and that these changes have a general biological character in a number of cases, since they are observed not only in acclimatization to hypoxia, but also in adaptation to other "stressors" (the action of changes in the temperature and chemical composition of the surrounding medium, certain drugs, repeated muscular exercise, etc.).

There is now no doubt that acclimatization to hypoxia increases the general or nonspecific resistance of man and animals. The organism becomes more resistant to both oxygen deficiency and the action of a number of other unfavorable environmental factors. Thus, Levy (1932) detected a high resistance to strychnine poisoning in hypoxia-acclimated mice. Berry et al. (1955) also noted an increased resistance to virus infection in such animals. The use of repeated "ascents" in a pressure chamber as stimulatory therapy was recommended in the works of N. V. Balanina (1947) and V. V. Turanov (1949). We (Barbashova, 1955, 1956) and other investigators (Mikhaylov, 1956; Vasil'yev, 1958; Belokonskiy, 1959; et al.) showed that prolonged acclimatization to hypoxia increases the resistance of the organism to ionizing radiation. I. R. Petrov and his colleagues came to the same conclusions regarding overheating, overcooling, anemia, and thermal burns (Petrov, 1960; Gubler and Fenster, 1960; et al.).

There is no question that the nonspecific resistance of an organism acclimated to oxygen deficiency is complex in nature. It may be caused by an intensification of the functioning of the respiratory, cardiovascular, and hematogenic systems, but reorganizations of the physicochemical properties of the tissue structures, which change the

resistance of the cellular elements to alteration, may be of no less importance.

What is the substance of the change in tissue chemism? The experimental data which have been amassed indicate primarily a change in cellular respiratory metabolism. The basic results obtained by a number of investigators, including us, reduce to the following. Cell metabolism may be altered in two essentially opposite directions. On the one hand, the reactions which ensure maintenance of oxidative processes at a sufficiently high level are stimulated and, on the other hand, the anaerobic modes of energy liberation are activated, which may compensate for the restriction of oxidative metabolism.

Thus, it is well known that various tissues of hypoxia-acclimated animals may exhibit an increase in myoglobin content and activity, in ascorbic acid, glutathione, yellow enzyme, and cytochrome C content, and in cytochrome oxidase, succinoxidase, succinic dehydrogenase, cyclophorase, histaminase, carbonic anhydrase, catalase, globinoxidase, adenosine triphosphatase, etc., activity. As a result of these changes the tissues become capable of maintaining a sufficiently high oxidative metabolism rate despite a drop in the partial oxygen pressure of the capillary blood. In the direct experimentation described in our prior works (Barbashova, 1952) we established that oxygen utilization increases in the tissues of hypoxia-acclimated animals in the presence of oxygen deficiency.

At the same time, we demonstrated that there is an intensification of anaerobic glycolysis in the tissues, which is especially marked in the cells of the grey matter of the brain, these being extremely sensitive to oxygen deficiency (Barbashova, 1952, 1958). Tissue adaptation may also be effected by restriction of oxygen consumption, as was detected in Duquors' experiments (1961). In this case the author also

noted a decrease in the activity of certain oxidative enzymes (e.g., cytochrome oxidase) and, conversely, an increase in the activity of aldolase, which, as is well known, plays an important role in anaerobic glycolysis and glycogenolysis. It is interesting that adenosine triphosphatase activity may be intensified and the content of energy-rich phosphates - creatine phosphate and adenosine triphosphate - increased in a number of tissues during acclimatization to hypoxia (Tappan et al., 1957).

This activation of oxidative-metabolism enzyme systems and stimulation of anaerobic processes undoubtedly increases tissue resistance to environmental change, which in some manner causes a disruption of cell respiration. However, a nonspecific increase in resistance is observed in the tissues of hypoxia-acclimated animals in addition to the change in respiratory metabolism. This was first demonstrated by A. G. Ginetsinskiy in a work conducted jointly with us (Barbashova and Ginetsinskiy, 1956). Using Nasonov's vital staining method, we found that the muscles of acclimated mice and rats sorb less neutral dye when exposed to alterative agents than those of control animals. Taking into account the fact that the intensity with which tissues are stained is a criterion of the extent of the paranecrotic changes occurring in them, we concluded that the tissues of acclimated animals are more resistant than those of unacclimated animals. This increasing resistance had a nonspecific character, since the tissues acquired a higher resistance both to the action of agents which inhibit oxidative metabolism (e.g., cyanides or anaerobiosis) and to ethyl alcohol, which denatures cell proteins, as well as to high caffeine concentrations.

Valle-Imenez (1954) obtained similar results in studying the histophysiological properties of the reticuloendothelial system in hypoxia-acclimated rabbits. This author detected a decrease in the sorption of

Congo red and an increase in the activity of the reticuloendothelial system, the latter taking the specific form of a rise in its resistance to viruses.

It is very interesting that all cellular elements, including the nuclear apparatus, exhibit an increase in nonspecific resistance during acclimatization to hypoxia. This is evidenced by the results of the work of V.P. Paribok et al. (1959. X-irradiating normal and hypoxia-acclimated mice, the authors found that the nuclear structures, particularly the chromosomal apparatus, of the latter were more resistant. It turned out that at equal x-irradiation dose rates a number of pathological disturbances during various stages of mitosis (in the corneal epithelium) were considerably less in extent in the acclimated animals than in the control animals.

We may get some idea of the nature of the nonspecific resistance of cells and tissues from the theory of paranecrosis developed by D.N. Nasonov and V.Ya. Aleksandrov (1940). According to this theory, exposure to an injurious agent causes denaturation of the cell proteins. It may be assumed that during a prolonged stay under hypoxic conditions some sort of changes occur in the cell proteins, increasing their physicochemical "strength." In this case we use the term "strength" to refer to the sum of the properties which retard the development of paranecrotic, or denaturing changes. These concepts impelled us to investigate certain of the physicochemical properties of the tissues of hypoxia-acclimated animals.

In order to determine the general physicochemical properties of the tissues we and Yu.Ye. Moskalenko (1961) measured the electrical conductivity and dielectric permeability of muscle tissue in the low radiofrequency range. The experiments were conducted in vivo. The data obtained enabled us to construct curves for the dielectric losses (Fig.

1).

As may be seen from Fig. 1, the maximum of the dielectric loss curves for the femoral muscles of acclimated rats is considerably displaced toward lower radiofrequencies (800-900 cps) in comparison with that for the muscles of the control animals (1150-1300 cps). It is well known that the change in conductivity and dielectric permeability of live tissues in the low radiofrequency range is closely associated with a change in the structure of the living matter at the macromolecular level. Although it is still difficult to say precisely what was altered in the structure of the muscle tissue, the fact that the electrical parameters of the muscle tissue shifted indicates that it acquired some new properties.

The results of this work and Nasonov and Aleksandrov's main investigation of the role of cell proteins in the tissue reactions to alternative agents led us to turn our attention to studying the properties of tissue proteins. We first studied the proteins of muscle tissue, since it was in the skeletal musculature that we established the changes in nonspecific resistance and electrical characteristics.

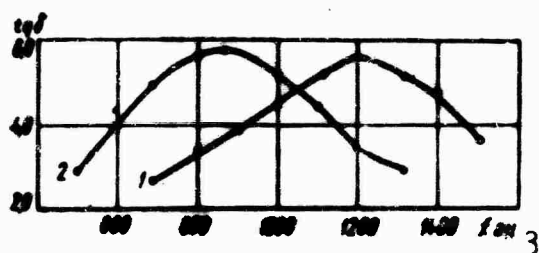


Fig. 1. Dielectric losses of rat muscle tissue as a function of frequency. 1) Control animals; 2) acclimated animals; 3) cps.

In work conducted jointly with G. A. Skul'skaya (1962) we studied the physicochemical properties of muscle contractile proteins, more precisely the viscosity of actomyosin in various concentrations. These experiments showed that the viscid properties of

actomyosin vary identically on dilution in acclimated and control animals. The actual viscosity values are also identical at equal protein concentrations. This means that acclimatization does not cause any change in the size or configuration of the protein molecule. It would

scarcely follow to expect severe changes in the structure of the protein molecule, which has been fixed by the entire course of evolutionary development. The situation is different with respect to changes in the properties of the protein molecules and their activity in interacting with one another and with other biologically active cellular substances. Our further experiments showed that certain properties of actomyosin actually undergo marked changes. The interaction between actomyosin and ATP proved to be nonuniform in character. In our work with Skul'skaya we determined the change in viscosity of the actomyosin of the skeletal musculature under the action of ATP. It is well known that addition of ATP sharply reduces the viscosity of actomyosin, since the actomyosin complex dissociates into actin and myosin. After a certain interval the complex is restored and the viscosity of the protein rises to its initial level. It may be seen from Fig. 2 that the change in actomyosin viscosity on addition of ATP differs in control and hypoxia-acclimated rats. The rate at which actomyosin is restored after dissociation is considerably higher in the acclimated animals than in the control. This means that the chemical properties of the contractile proteins of the skeletal musculature are altered during acclimatization. The proteins become more active. It is on this basis that the phenomenon proceeds, although it is still unclear, and we are occupied in determining its causes.

The change in the tissue content and activity of certain enzymes and biologically active substances and the concomitant changes in oxidative metabolism, electrical characteristics of muscle tissue, and interaction of muscle actomyosin with ATP comprise our basic present knowledge of the reorganization of tissue or cellular chemism in hypoxia-acclimated animals. It is very important that all this bears directly on understanding the nature of tissue resistance. However, to con-

firm this we must make a direct comparison between the resistance of the tissue and its biochemical composition and physicochemical properties. The attention of physiologists, biochemists, and biophysicists must be drawn to solution of this problem.

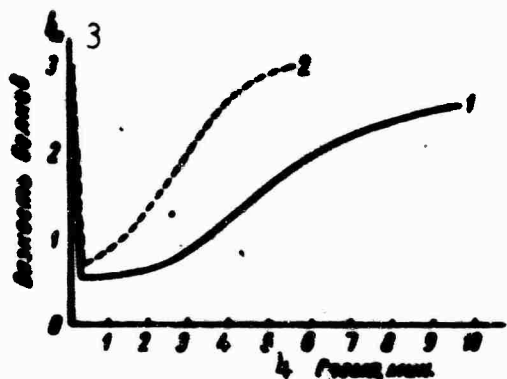


Fig. 2. Change in the viscosity of the proteins of the actomyosin complex under the influence of ATP in control (1) and hypoxia-acclimated (2) rats. 3) Protein viscosity; 4) time, min.

Despite the fragmentary character of the available data on tissue or cellular adaptation and the absence of any precise concept of the dynamics and relationships of the individual adaptive reactions, we may assume it to be beyond doubt that cellular adaptation, which involves the basic processes of cell metabolism, is an extremely important factor in the general adaptation syndrome.

It is also quite important that similar changes in cell chemism occur during adaptation to stressors other than hypoxia. This is indicated by the data obtained in studying the thermal adaptation mechanisms of the muscles of poikilotherms and homotherms, adaptation to an altered environmental salt content in poikilotherms, the mechanisms of muscle accommodation, etc. The similarity of adaptive reactions at the cellular level under the action of various stressors to a considerable extent explains why the increase in the resistance of tissues or the entire organism under the action of one stressor is also a positive factor under the action of another stressor. The nonspecificity of this increase in resistance may consequently be attributed to the fact that it is based on adaptive reactions of general biological significance. The similarity of the adaptive reactions of different animals gives us grounds for assuming that the mechanisms of cellular or tissue adapta-

tion have been laid down in phylogenesis throughout the entire course of evolution and are utilized by the organism when it encounters extreme conditions.

The existence of nonspecific resistance is of great theoretical and practical importance. It gives us a basis for the development of measures to increase man's resistance to the action of unfavorable environmental and industrial conditions, infectious diseases, etc.

The problem of resistance has not been studied to an extent consistent with its vital importance. It is to be hoped that the joint efforts of researchers in various fields will furnish new data which will enable us to gain a deeper understanding of the nature of adaptation.

PHYSIOLOGICAL AND BIOCHEMICAL MECHANISMS OF ADAPTATION
TO HIGH MOUNTAIN CONDITIONS

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Adaptation to high-mountain conditions, just as to any other conditions, is effected by changes in the entire organism rather than by particular changes in a given organ. However, adaptation to any conditions presupposes the existence of primary factors specific for the environmental conditions in question. Under high-mountain conditions the primary factor is undoubtedly the reduced partial oxygen pressure.

It is naturally to be expected that animals which live at high altitudes, being continuously adapted to a reduced partial oxygen pressure, would have characteristics not present in lowland animals.

The complexity of the problem lies in the fact that among the animals which live at high altitudes are both aboriginal forms, which always live there, and lowland animals which come to the mountains for a limited time. Specifically, in various regions of the Soviet Union employing the migratory system of animal raising certain species of animals (sheep, goats, and cows) are driven to high pastures located at altitudes of 3000-4000 m, where they remain for several weeks or months. These animals include varieties whose native habitat is the foothills (Gissar and Kirgiz sheep, etc.) and varieties brought into the foothills for purposes of acclimatization.

We are faced with the problem of what forms of adaptation to high-mountain conditions occur in naturally mountain-dwelling animals, ani-

mals which periodically move into mountainous regions, and lowland animals first brought into such regions. It would seem that the most natural course of investigation consists in first making a detailed study of true mountain-dwelling animals. The morphological and physiological-biochemical characteristics of this group of animals would be valuable in enabling us to solve the problem of the adaptation mechanisms of various animals coming under high-altitude conditions.

TABLE 1

Животные 1	2 Эритроциты, млн.	3 Гематокрит, %	4 Кислородная емкость крови, об. %	5 Гемоглобин		8 Объем эритроци- тов, μ^3	Коли- чество гемогло- бина в эритроци- тах, г	Кон- центра- ция ге- могло- бина в эритроци- тах, %
				6 по кисл. мет.	7 по Цейсу			
11 Лама	12,5	34,0	26,2	19,5	17,9	28,1	14,9	53,0
12 Лама	12,4	32,3	21,7	16,2	16,5	26,0	13,6	51,1
12 Сибирский козел	27,0	40,1	22,2	—	16,6	20,0	—	41,4
13 Козел	28,5	38,4	23,3	—	17,4	15,0	6,8	45,3
14 Урвал	4,0	46,0	24,5	18,1	18,5	32,8	13,2	40,2
15 Муфлон	12,2	41,8	—	—	16,6	34,2	13,6	40,8
16 Архар	13,7	44,0	—	—	18,4	32,1	—	41,8
17 Гиссарская овца	8,3	29,0	13,0	9,7	10,1	35,0	12,1	34,8
18 Дагестанская горная овца	8,9	28,3	—	—	10,3	—	—	—

1) Animals; 2) erythrocytes, millions; 3) hematocrit, %; 4) oxygen capacity of blood, % by volume; 5) hemoglobin; 6) from oxygen capacity; 7) by Zeiss' method; 8) erythrocyte volume, μ^3 ; 9) quantity of hemoglobin in erythrocytes, γ ; 10) hemoglobin concentration in erythrocytes, %; 11) llama; 12) Siberian goat; 13) goat; 14) urial; 15) mouflon; 16) central-Asian sheep; 17) Gissar sheep; 18) Dagestan mountain sheep.

TABLE 2

Животные 1	2 Сред- ний вес, кг	3 Эрит- роци- ты, млн.	4 Гематокрит, %	5 Гемоглобин, г %	6 Кровь, % к весу тела	7 Гемогло- бин, г/кг ве- са	8 Автор и год опубли- кования данных
9 Советский ме- ринос	56,4	8,9	30,3	10,4	7,0	8,6	14 Коржув и др., 1957
10 Прекос	62,1	9,9	33,2	11,3	7,6	8,4	« « « «
11 Гиссарская ов- ца	65,2	10,9	35,4	11,3	7,6	8,6	15 « « « «
12 Архар	60,0	14,0	44,1	18,2	10,8	18,6	Булатова, 1953
13 Урвал	30,0	—	45,0	18,6	9,6	17,0	« «

1) Animals; 2) mean weight, kg; 3) erythrocytes, millions; 4) hematocrit, %; 5) hemoglobin, g-%; 6) blood, % of body weight; 7) hemoglobin, g/kg of body weight; 8) author and year in which data were published; 9) Soviet merino; 10) prekos; 11) Gissar sheep; 12) Central-Asian sheep; 13) urial; 14) Korzhuyev et al., 1957; 15) Bulatova, 1953.

However, and not strangely, little research has been done in this

direction on the true mountain-dwelling animals. Despite the existence of monographs devoted to the biology of mountain-dwelling animals (Severtsov 1873; Nasonov, 1913; Tsalkin, 1951), we are still unclear as to which morphological characteristics provide for specific adaptation to high-altitude conditions or, more precisely, to the reduced partial oxygen pressure.

There are only fragmentary data on the physiological-biochemical characteristics of the blood of mountain-dwelling animals such as the llama (Hall et al., 1936; Bulatova, 1953), the Central-Asian sheep, and the Ibex (Bulatova, 1953). All these animals are characterized by a very hemoglobin concentration in the blood (Table 1).

The total quantity of blood in the bodies of mountain-dwelling animals reaches 11% of their body weight (Bulatova, 1953), while in lowland domestic sheep it averages 7-8% of the body weight (Table 2). The amount of hemoglobin in the blood of mountain-dwelling animals is approximately twice that in the blood of related lowland domestic animals. We must take into account the fact that, in addition to the hemoglobin of the blood, there is muscle hemoglobin, whose concentration is higher in the muscles of mountain-dwelling animals than in those of domestic animals (Verbolovich, 1961); it is also higher in the muscles of animals raised in the mountains than in those of lowland animals (Table 3). Similar data were obtained for dogs raised in the mountains and at sea level (Khurtado et al., 1937).

The fact that the ascent of lowland animals into the mountains leads to a considerable increase in the hemoglobin content and erythrocyte count of the blood merits attention (Table 4).

In all cases there are thus marked differences between lowland and mountain-dwelling animals with respect to the level of the oxygen-transporting components of the red blood and the concentration of muscle

TABLE 3

Животные 1	2 Концентрация (в мг на 100 г сырого мяса мышц)						
	Сердечная мышца 3	Диафрагма 4	Жевательные мышцы 5	Двуглавая мышца бедра 6	Икроножные мышцы 7	Двуглавая мышца плеча 8	Длинный в мышце спины 9
10 Козерог	867,0	1057,0	831,0	397,0	721,0	556,0	625,4
11 Козел	466,4	592,0	479,2	496,2	463,7	501,3	374,3

1) Animals; 2) concentration (in mg per 100 g of dry muscle); 3) myocardium; 4) diaphragm; 5) masseters; 6) biceps femoris; 7) gastrocnemius; 8) biceps brachii; 9) longissimus dorsi; 10) Ibex; 11) goat.

TABLE 4

Условия исследования 1	2		
	Эритроциты, млн. 2	Гематокрит, % 3	Гемоглобин, г-% 4
5 На уровне моря	4,1	22,8	8,4
6 На летних пастбищах (2300 м над уровнем моря)	5,4	29,5	10,5

1) Conditions of investigation; 2) erythrocytes, millions; 3) hematocrit, %; 4) hemoglobin, g-%; 5) at sea level; 6) in summer pastures (2300 m above sea level).

hemoglobin. The erythrocytes and hemoglobin of the blood and muscles are thus an important factor in adaptation to high-altitude conditions.

There is, however, a view which holds that a certain group of animals periodically taken into the mountains (Gissar and Kirgiz sheep) does not exhibit an intensification of the activity of

the organs which provide the organism with oxygen, but rather a stable depression of tissue oxidative processes. We were able to cite considerations to refute this treatment (Korzhujev, 1959) and can now add only that it is very improbable that, having such powerful structures as the bone marrow and body musculature, which constitute half or more of the body weight and are the foci of hemoglobin synthesis, the organism would resort to other forms of adaptation, neglecting the available mechanisms, on being subjected to a reduced partial oxygen pressure.

As for the problem of the morphological characteristics of mountain-dwelling animals, we noted that they do not exhibit any specific structures characteristic of mountain conditions. However, there is no doubt that there must be a change in the structure of the organism in connection with adaptation to a reduced partial oxygen pressure and

this change occurs in the organs which supply oxygen. Prime among these structures are the skeleton and musculature, which are high-intensity foci of hemoglobin synthesis, since mechanisms which ensure the necessary level of oxidative processes must be available when the partial oxygen pressure is reduced. We can evaluate the intensity of the hemopoietic function only from the weight of the skeleton, which constitutes approximately 17% of the body weight of the Central-Asian sheep. We may draw an analogy with the reindeer, an excellent runner, in which the weight of the skeleton constitutes approximately 13% of the body weight, while the bone marrow accounts for approximately 45% of the weight of the skeleton (Korzhuyev and Nikol'skaya, 1960). If we take into account the fact that the bone marrow also accounts for 45% of the skeletal weight of the Central-Asian sheep, it amounts to approximately 7.6% of its body weight - a very substantial fraction, since in lowland animals such as the guinea pig and rabbit the bone marrow comprises 1.5-3.0% of the body weight. We must also consider that Central-Asian sheep have horns, which may reach very large size. The core of the horn is a bony formation.

Morphologists hold no unanimous opinion regarding the biological causes of the intensive horn development in Central-Asian sheep. It has been hypothesized that these highly developed horns are necessary for jumping crevasses. However, there are well-grounded data to indicate that the sheep do not make such jumps, since they live on mountain plateaus. It is impossible to regard this peculiarity as a secondary sexual characteristic, since it has also been established that intensive horn growth occurs only in sheep living at high altitudes, in contrast to those living in the foothills (Tsalkin, 1951).

We are forced to the conclusion that the highly developed horns of Central-Asian sheep and Ibexes serves as an adaptation to high-altitude

conditions, since an important constituent of the horn is the core, massive bony formations containing bone marrow, i.e., the horn is an additional focus of hemoglobin synthesis.

Highly developed horns are one of the forms of adaptation to high-mountain conditions. However, llamas, which are also excellently adapted to high-altitude conditions, lack horns. It is apparent that they have other adaptation mechanisms. It is well known that llama hemoglobin has a very high affinity for oxygen. It is also known that the camel's lungs are highly developed, constituting approximately 3.5% of its body weight. Only the seal has such lungs. In Central-Asian sheep the lungs constitute 2.5% of the body weight, while in domestic sheep they comprise 1.25% of the body weight for the Soviet merino and 1.75% of the body weight for Gissar sheep.

Study of the morphological and physiological-chemical characteristics of various animals enables us to discover the specific mechanisms by which they adapt to high-altitude conditions. We must know these characteristics in order to find a successful solution to the problem of acclimatization to high-mountain conditions.

INVESTIGATION OF OXIDATIVE METABOLISM ENZYMES (SUCCINOXIDASE AND
CYTOCHROME OXIDASE) IN THE CEREBRAL CORTEX AND MYELENCEPHALON
IN HYPOXIA-ACCLIMATED RATS

Ye. Yu. Chenykayeva

(Leningrad)

We have published data on the acclimatization of white rats to oxygen deficiency in a series of works (Kreps et al., 1956, 1956a, and 1956b).

It was found that keeping several generations of rats under a reduced oxygen concentration (10.5% in the ambient medium) increased their capacity to withstand acute oxygen starvation; in our opinion, this indicates that acclimatization occurred. A number of changes could be observed in the animals' physiological and biochemical systems. Certain of them, affecting the respiratory and blood systems, set in rapidly. They were observed in the first (parent) generation of acclimated rats and were maintained in the next three generations examined. The shifts in gaseous interchange, which were manifested in an ability to maintain a normal level in an environment with a reduced oxygen tension, set in later and were detected in rats of the third and fourth generations. The biochemical changes, which affected tissue oxidative processes, apparently set in substantially later.

In our earlier examinations of all three generations the myoglobin and cytochrome C contents of the muscle tissue of the heart, diaphragm, and extremities remained within normal limits. The activity of the cytochrome oxidase - cytochrome system in the heart, diaphragm, and brain

in the acclimated animals did not differ materially from that in the control animals. On the basis of these data we advanced the view that the reorganization in the tissue systems is more complex and time-consuming than the processes which develop during the first stage of acclimation, affecting primarily the physiological systems and being similar in character to adaptation. True acclimatization, which is associated with profound biochemical tissue reorganizations, is a prolonged multistage process and can be detected only in later generations of hypoxia-acclimated animals. This work has continued and we now have available the fifteenth, sixteenth, and seventeenth generations of hypoxia-acclimated rats.

This report presents the results of an investigation of the activity of two oxidative enzymes, cytochrome oxidase and succinoxidase, in the cerebral cortex and myelencephalon in rats of the fourteenth-seventeenth generations.

In contrast to our prior experiments, in which we used the manometric method, in the work described herein we employed the spectrophotometric method to determine cytochrome oxidase activity. This method has been described by Hess and Pope (1953) and Pope et al. (1956) as an ultramicroscopic method, but under our conditions it was simply a microscopic method and enabled us to make determinations in 0.5-1.0 mg of moist tissue. The cytochrome oxidase activity was determined from the rate at which reduced cytochrome C was oxidized by enzyme extracted from the tissue homogenate.

The succinoxidase system was determined by the tetrazole method, from the reduction of a tetrazole-neotetrazole salt, which is reduced from the uncolored to the colored state (formazine) in the presence of a succinate and succinoxidase.

DETERMINATION OF CYTOCHROME OXIDASE

As a rule, we simultaneously investigated two rats, one control and one acclimated, in each experiment. The animals were killed by decapitation. The brain was quickly removed, placed on ice, and cleaned

of blood and membranes. The cortex was excised and a 30-40 mg weighed portion was pulverized in a chilled mortar in 0.75% sodium deoxycholate, 1 mg of tissue being used for every 0.02 ml of deoxycholate. The homogenate was centrifuged at 5000 rpm for 10 minutes and the clear supernatant was drawn off for determination.

The same method was followed for the myelencephalon: we always used tissue fragments from the level of the rhomboid fossa. The determination was made on a SF-4 spectrophotometer at a wavelength of 550 millimicrons (the α -absorption band of reduced cytochrome C). The cytochrome solution contained $2.5 \cdot 10^{-5}$ M of reduced cytochrome C in a 0.05 M phosphate buffer at pH 7.4. The cytochrome was completely reduced by adding sodium hydrosulfite to a final concentration of 0.001 M. The excess hydrosulfite was removed by shaking the test tube for several minutes. Two milliliters of the reduced cytochrome solution was poured into the spectrophotometer tube (the thickness of the layer in the tube was 1 cm), a first reading of the optical density D was taken, and extract containing 0.5-1.0 mg of moist tissue was added to the tube. After the tissue was added we began to make readings every 15 sec for 2-3 min. The rate at which absorption decreased, which characterized the rate at which the reduced cytochrome was oxidized, served as the criterion of enzyme activity. The activity of the cytochrome oxidase may be expressed as the change in optical density per minute per unit tissue weight. Our calculations were made for the first 30 seconds of enzyme action, i.e., in that segment of the curve where the rate of decrease in absorption was a linear function of enzyme activity. This rate also depends on the ratio of enzyme to cytochrome in the sample. Under our experimental conditions (at a cytochrome concentration of $2.5 \cdot 10^{-5}$ M in 2 ml of solution) the quantity of tissue added could not exceed 0.5 mg for the cortex, in which cytochrome oxidase activity is greater, and 1 mg for the myelencephalon (Fig. 1).

Figure 1 shows the change in optical density per minute as a function of the quantity of tissue in the sample. When the cytochrome C concentration in the sample was increased to $3.7 \cdot 10^{-5}$ M the direct proportionality for the cortex was maintained in the vicinity of 0.75 mg of tissue. Figure 2 presents curves for the cortex and myelencephalon representing the change in optical density with time at two tissue con-

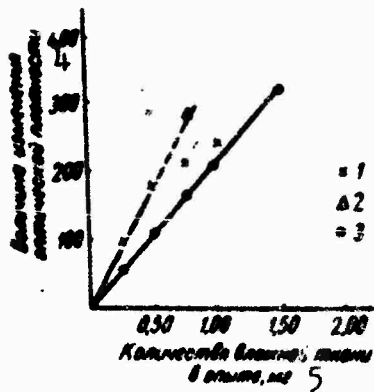


Fig. 1. Change in optical density D as a function of quantity of tissue in sample. 1) Cortex; 2) cortex, in experiment with cytochrome concentration of $3.7 \cdot 10^{-5}$ M; 3) myelencephalon; 4) change in optical density; 5) quantity of moist tissue employed in experiment, mg.

centrations in the sample (calculated per mg of moist tissue). As may be seen from Fig. 2, the resulting curve is linear for the myelencephalon over the first 60 sec with 0.5 mg of tissue and over the first 30 sec with 1.2 mg of tissue. For the cortex this linear function persisted for only 45 sec with 0.5 mg of tissue, the reaction going almost to completion within the first 15 sec with 1.2 mg of tissue. We used these data as the basis for our further experiments and made our calculations for the first 30 sec.

Cytochrome oxidase activity in the myelencephalon was investigated in 23 experiments on acclimated rats and an equal number on control animals. For the cortex we conducted 15 experiments on acclimated rats and 17 on control animals. The results obtained

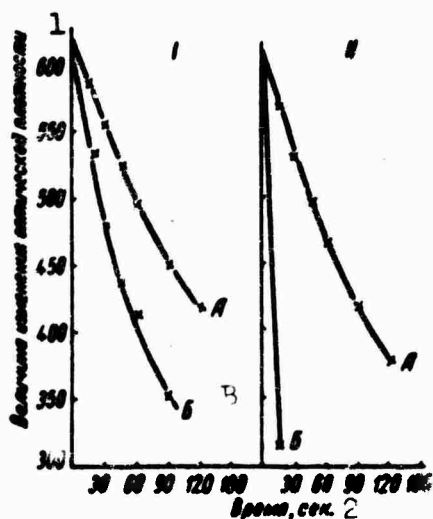


Fig. 2. Change in optical density D with time at two tissue concentrations in sample. I) Myelencephalon; II) cortex; A) 0.5 mg of moist tissue; B) 1.2 mg of moist tissue. 1) Change in optical density; 2) time, sec.

are shown in Fig. 3, where the cytochrome oxidase activity is expressed as the change in optical density D per min per mg of dry tissue.

As may be seen from Fig. 3, cytochrome oxidase activity in the myelencephalon was higher in the acclimated rats than in the control animals. The mean enzyme activity in the experiments on the control rats was 0.216, while that for the acclimated animals was 0.286. Statistical processing of the data demonstrated this difference to have a reliability of 0.999. We were unable to detect any

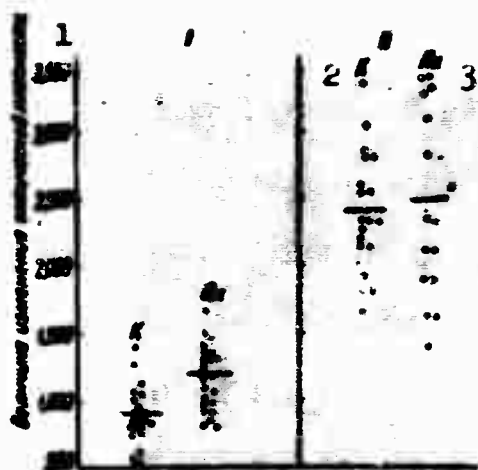


Fig. 3. Cytochrome oxidase activity expressed as the change in optical density per min per mg of dry tissue. The dots represent individual experiments and the horizontal lines the arithmetic means. I) Myelencephalon; II) cerebral cortex. 1) Change in optical density; 2) control animals; 3) hypoxia-acclimated animals.

reliable differences in the experiments on the cortex.

DETERMINATION OF SUCCINOXIDASE

Succinoxidase activity was determined in cortical and myelencephallic homogenates by Wattenberg and Long's modification (1960) of Shelton and Rice's method (1957).

The homogenates were prepared under refrigeration by manual pulverization of tissue in an agate mortar, using 2 mg of tissue per 0.001 ml of 0.05 M phosphate buffer at pH 7.4. The homogenate was added for incubation to a solution with the following composition: 0.11 M NaCl, 0.003 M KCl, 0.001 M Mg₂SO₄, 0.03 M Na₂HPO₄, 0.05 M sodium succinate, and 0.5 mg of

tetrazole-neotetrazole per ml of solution. From 5 to 40 mg of moist tissue was added to 2 ml of the incubation mixture. Incubation lasted 1 hr, 30 min at 37°. At the end of the incubation period the reaction was halted by adding 0.05 ml of 30% trichloroacetic acid. The tetrazole, which accepts hydrogen during the oxidation of succinate, was reduced and converted to the colored state (formazine); the quantity of formazine characterizes the activity of the enzymatic reaction, which may be expressed in micrograms of formazine formed per hr per mg of dry tissue. The formazine was extracted with a mixture of tetrachlorethylene and alcohol (1:3) and the extract was subjected to photometry on a SF-4 apparatus at a wavelength of 540 millimicrons.

The results of these experiments are shown in Fig. 4. Succinoxidase activity was higher in the cortex than in the myelencephalon. However, we were unable to note any difference in enzyme activity between the control and acclimated rats in either the cortex or the myelencephalon.

DISCUSSION OF EXPERIMENTAL RESULTS

In our previous investigations, which were conducted on earlier (the first and second) generations of acclimated rats, we detected no marked shifts in cytochrome oxidase and cytochrome-system activity in



Fig. 4. Succinoxidase activity expressed as micrograms of formazine formed per hr per mg of dry tissue. The figures at the left indicate micrograms of formazine, the dots represent individual experiments, and the horizontal lines designate the arithmetic means. I) Myelencephalon; II) cortex. 1) Micrograms of formazine; 2) control animals; 3) hypoxia-acclimated animals.

either the myocardium or the brain. In the third and fourth generations we even noted a slight decrease in the activity of this system when it was investigated in atmospheric air. However, with a low oxygen tension the cytochrome system of the brain and heart proved to be capable of maintaining a higher level of activity than in the control animals. The acclimated rats of the third and fourth generations also exhibited a slight intensification of anaerobic glycolysis in the brain tissue.

It thus seemed to us that the third and fourth generations displayed two types of changes in the tissue biochemical systems of the brain - a tendency toward intensified anaerobic glycolysis and an alteration of the properties of the cytochrome system, the latter taking the form of greater efficiency under new (hypoxic) environmental conditions. The hemoglobin content, erythrocyte count, and carbonic anhydrase activity of the blood remained at a high level in these generations. The higher survival rate among the acclimated rats under condi-

tions of maximal hypoxia resulted from the aggregate of all these factors.

Comparison of the data which we obtained in studying the fourteenth-seventeenth generations with those yielded by our experiments on the first-fourth generations confirms the repeatedly advanced hypothesis that the focus of the acclimatization processes shifts to the tissue systems in later generations. Thus, the blood hemoglobin content in the rats of the fourteenth-seventeenth generations did not differ as markedly from that in the control animals as in the early generations. In the latter case the difference was of the order of 40%, while in the later generations it did not exceed 20%.

We also noted a decrease in the difference in hemoglobin content during true acclimatization in the inhabitants of high-mountain villages in Tsey (Marzhibinskaya, Kreps, Fetisenko, Chenykayeva, and Shmatova, 1956). It was found that the blood of those villagers who had always lived under high-altitude conditions contained less hemoglobin than the blood of those villagers who had stayed in low-lying areas for extended periods (three-four years) and recently returned to their native village. Mountain climbers staying at the alpine camp exhibited the same pattern as residents of Tsey recently returned from the lowlands; after 20 days in camp the increase in their hemoglobin count reached 25%, while the hemoglobin count of the residents who had always lived under high-mountain conditions exceeded that for lowland residents by 7%.

From a comparison of the data cited above we may conclude that the data which we obtained in our experiments on later generations of acclimated rats indicate that they exhibit a higher degree of acclimatization, this being manifested in the fact that the cytochrome system becomes more active in the central nervous system, at the stage in question primarily in the myelencephalic structures most closely associated

with respiration; this also explains the higher survival rate among these animals under conditions of maximal hypoxia. The most profound tissue reorganization of biochemical systems is put off until the last stage of the change in the blood system (hemoglobin and carbonic anhydrase).

It is puzzling that there are no changes in succinoxidase activity, this enzyme being, just as cytochrome oxidase, one of the links in the general oxidation cycle.

RATE OF LIPID AND CARBOHYDRATE RENEWAL IN THE BRAIN AND LIVER IN HYPOXIA

M.I. Prokhorova, L.S. Romanova, and G.P. Sokolova
(Leningrad)

A characteristic which distinguishes the brain from other organs is its maintenance of a high metabolic level with a relatively constant content of plastic energy-containing substances. This is observed both at rest and in various functional states. However, the brain is exceptionally sensitive to oxygen deficiency; we consequently undertook a study of the characteristics of lipid and carbohydrate metabolism in the brain and liver in hypoxia.

METHOD

The experiments were conducted on mature white rats. Hypoxia was induced by formation of methemoglobin; sodium nitrite was used as the methemoglobin-forming agent. The nitrite was injected subcutaneously in a dose of 15-20 mg per 100 g of body weight. The experiment lasted 45 min after the NaNO_2 injection. Approximately 40-50% methemoglobin was formed in the blood during this time and the animals developed the characteristic symptoms of hypoxia.

The total lipid content was determined by Folch, Ascoli, Lis, Mich, and LaBaron's method (1951). This method was also used to determine the specific activity of the total lipid fraction.

The cholesterol content of the brain and liver was determined by a colorimetric method based on the Lieberman-Burkhard color reaction. The principle of the Windhaus method, which consists in the formation of cholesterol-digitonide, was used to measure specific cholesterol activity (Prokhorova and Tupikova, 1959). We obtained pure cerebrosides and determined their specific activity by the procedure developed by Taranova (1962) from the methods of Azmen (1953) and Radin, Lavin, and

Braun (1955). We employed Svennerholm's modification (1956) of Klenk's method (1942) to isolate the gangliosides from the cerebral tissue. The glycogen content of the brain was determined by Kerr's method, while that of the liver was determined by Pfluger's method. The same methods were used to measure specific glycogen activity (Prokhorova and Tupikova, 1959; Prokhorova, Brodskaya, and Sokolova, 1957). The glucose content of the brain and liver was determined by Fujita and Iwataka's method.

TABLE 1

Change in Total Lipid, Cholesterol, Glycogen, and Glucose contents of Brain and Liver in Hypoxia

Органы 1	Условия работы 2	Общая фракция липидов (%) 3	Холестерин (в мг%) 4	Гликоген (в мг%) 5	Глюкоза (в мг%) 6
Мозг 7	Норма 9	9,2	—	74	50
	Гипоксия 10	9,2	—	51	47
Печень 8	Норма	5,5	239	2100	222
	Гипоксия	4,7	205	490	239

1) Organ; 2) working conditions; 3) total lipids (in %); 4) cholesterol (in mg-%); 5) glycogen (in mg-%); 6) glucose (in mg-%); 7) brain; 8) liver; 9) normal; 10) hypoxia.

The rate of total lipid, cholesterol, and cerebroside metabolism was determined from the rate at which radioactive acetic acid administered in a dose of 30 μ C per 100 g of body weight was incorporated into these fractions, while that of ganglioside and glycogen metabolism was determined from the rate of glucose incorporation. Since glycogen is synthesized from glucose considerably more intensively than gangliosides, we administered 5 μ C of glucose to study glycogen metabolism and 25 μ C to study ganglioside metabolism. Exposure to the radioactive substance lasted 1 hour. The specific activities of all the components investigated were expressed in pulses/min per mg of carbon (specific activity is henceforth abbreviated SA and relative specific activity RSA).

In order to evaluate the radioactivity level in the cerebral and hepatic tissues we measured the specific carbon activity of brain and liver homogenates in all the experiments (Prokhorova and Tupikova, 1959).

We did not investigate cholesterol metabolism in the brain, since its rate is extremely low in mature animals. The experimental data obtained were subjected to statistical processing.

EXPERIMENTAL RESULTS

The data obtained, which characterize the changes in the contents of the components investigated, are shown in Table 1.

As may be seen from Table 1, the total lipid content of the brain did not change in hypoxia. There was a drop in the total lipid and cholesterol contents of the liver (statistically reliable). The glucose content of the brain and liver remained virtually normal, the changes observed not being statistically reliable. The glycogen content varied most markedly in hypoxia. It decreased by an average of 25-30% in the brain. An especially sharp drop in glycogen content was observed in the liver in hypoxia; while it normally averaged 2100 mg-%, in the presence of oxygen deficiency it dropped to 490 mg-%.

TABLE 2

Influence of Hypoxia on Specific Activity of Homogenate and Individual Lipid Fractions in the Brain and Liver

Орган 1	Радиоактивные вещества 2	Условия опыта 3	Количество опытов 4	5 Пульс (мин/мг углерода)				
				Гомогенат 6	Общая фракция липидов 7	Церебро-сиды 8	Ганглиозиды 9	Холестерин 10
Мозг 11	Ацетат 13	Норма 15	6	196±7	140±7	54±2	—	—
	Глюкоза 14		16	47±3	37±3	15±1,4	—	—
	Гликоген 14		8	124±10	13±1,3	—	174±24	—
Печень 12	Ацетат 13	Норма 15	10	234±10	25±2	—	170±20	—
	Гликоген 14		8	142±9	249±19	—	—	1033±86
		Гипоксия 16	8	158±21	162±2	—	—	545±101

1) Organ; 2) radioactive substances; 3) experimental conditions; 4) number of experiments; 5) pulses/min/mg of carbon; 6) homogenate; 7) total lipids; 8) cerebroside; 9) ganglioside; 10) cholesterol; 11) brain; 12) liver; 13) acetate; 14) glucose; 15) normal; 16) hypoxia.

As is well known, quantitative changes do not always reflect the rate of metabolism of the substances under investigation, since their decomposition and synthesis are usually in dynamic equilibrium. A change in the content of the components under study results from predominance

of the anabolic or catabolic processes occurring in the organism: in the first case the metabolite content is elevated, while in the second it is reduced. The rate of renewal of the components under investigation may be established by the radioactive-tracer method. As was already noted, we used acetate and glucose containing radioactive carbon, C^{14} , for this purpose. Table 2 shows the specific activity of the carbon of the individual lipid fractions and homogenates in the brain and liver under normal conditions and in hypoxia.

It may be seen from Table 2 that the SA of the brain homogenate dropped sharply (from 196 to 47 pulses/min/mg) in the hypoxic animals on administration of acetate; the SA of the total lipids and cerebro-sides also decreased. Conversely, on administration of glucose the SA of the brain homogenate increased from 124 to 234 pulses/min/mg, which indicates retarded glucose utilization in hypoxia. The SA of the total lipid fraction increased, while the ganglioside radioactivity level was unaltered.

The SA of the liver homogenate remained at approximately the same level under normal conditions and in hypoxia. At the same time, the SA of the total lipid fraction decreased from 249 to 162 pulses/min/mg; cholesterol SA dropped especially sharply, from 1033 to 545 pulses/min/mg. Since the radioactivity level in the brain and liver changed, we determined the relative specific activity (RSA) in order to get a more adequate representation of the rate of renewal.

The RSA is the ratio of the SA of the C in the substances under investigation to the SA of the C in the homogenate.

In our experiments the SA of the homogenate carbon was arbitrarily assumed to be one. Data on the RSAs of the individual lipid fractions under normal conditions and in hypoxia are given in Fig. 1.

As may be seen from Fig. 1, the RSA of the total cerebral lipids

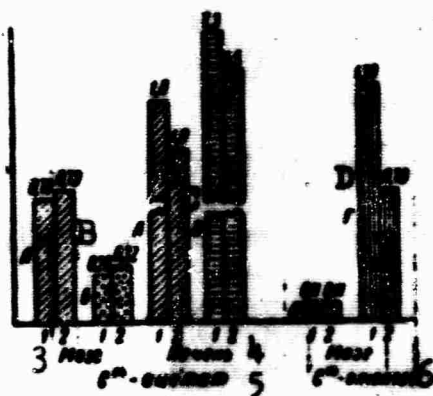


Fig. 1. Relative specific activity of cerebral and hepatic lipid fractions under normal conditions and in hypoxia. 1) Normal; 2) in hypoxia; A) Total lipids; B) cerebro-sides; C) cholesterol; D) gangliosides. 3) brain; 4) liver; 5) acetate; 6) glucose.

in hypoxia did not vary noticeably on administration of acetate or glucose; the RSA of the cerebro-sides also remained essentially unaltered. There was a marked drop in ganglioside RSA, from 1.39 to 0.78, which indicates retarded ganglioside synthesis in hypoxia.

The RSA of the total hepatic lipids decreased from 1.8 to 1.0; the cholesterol RSA dropped especially sharply, from the normal 7.3 to 3.5. These data indicate a marked decrease in the rate of renewal of total lipids and cholesterol

in the liver in hypoxia. Table gives the results of investigation of the SA of cerebral and hepatic carbohydrates under normal conditions

TABLE 3

Influence of Hypoxia on Specific Activity of Homogenates and Glycogen in the Brain and Liver (after Administration of C^{14} -glucose)

Орган	Условия опыта	Число опытов	Мин/мин/мг углеводов		Мин/мин/г ткани	
			Гомогенат	Гликоген	Гомогенат	Гликоген
Мозг 8	Нормал 10	8	11±3	417±92	1375	136
	Гипоксия 11	7	12±3	255±71	1509	57
Печень 9	Нормал	7	14±4	45±12	1960	416
	Гипоксия	10	16±3	20±8	2340	43

1) Organ; 2) experimental conditions; 3) number of experiments; 4) pulses/min/mg of carbon; 5) homogenate; 6) glycogen; 7) pulses/min/g of tissue; 8) brain; 9) liver; 10) normal; 11) hypoxia.

and in hypoxia.

As may be seen from the data in Table 3, the SA of the cerebral and hepatic homogenates remained essentially unaltered. At the same time, the SA of the cerebral and hepatic glycogen decreased markedly. The most obvious change in the rate of glycogen renewal in hypoxia was

detected in determining glycogen radioactivity per g of tissue. We took into account both the SA of the substance under investigation and its content in making this calculation. In the case in question, i.e., under conditions of hypoxia, the radioactivity of the cerebral glycogen per g of tissue decreased by an average factor of almost 2.5 (from 136 to 57 pulses/min/mg). The radioactivity of the hepatic glycogen was reduced still further, by a factor of nearly 10 (from 416 to 43 pulses/min/mg). These data indicate a sharp retardation of glycogen synthesis in the brain and liver in hypoxia, as is also confirmed by determination of the glycogen RSA and the percentage radioactive carbon content of the cerebral and hepatic glycogen. The corresponding data are given in Fig. 2. The total carbon radioactivity in the homogenate of the tissues under investigation was taken as 100%.

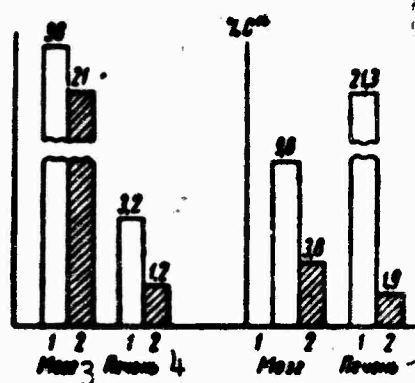


Fig. 2. Radioactivity of cerebral and hepatic glycogen under normal conditions and in hypoxia. 1) Normal; 2) in hypoxia; 3) brain; 4) liver.

As may be seen, the cerebral glycogen was metabolized at a greater rate than the hepatic glycogen or, especially, the lipid components (Fig. 1). On comparison of the RSAs of the individual fractions with the RSA of the cerebral glycogen it is found that the latter is renewed approximately 50-100 times as rapidly as the former.

It may also be seen from the data in Fig. 2 that the RSA of the cerebral glycogen was 38 under normal conditions, but decreased to 21 in hypoxia. The RSA of the hepatic glycogen was 3.2, but was reduced to 1.2 in the presence of oxygen deficiency. The cerebral glycogen contained an average of 9.8% of the total radioactive carbon of the cerebral homogenate under conditions, the C^{14} content decreasing to 3.8% in hypoxia. An even more marked change was

observed in the liver: under normal conditions the hepatic glycogen accounted for 21.3% of the total C^{14} in the hepatic homogenate, while in the presence of oxygen deficiency it comprised only 1.9%. All this indicates a severe retardation of glycogen synthesis in the brain and especially in the liver in the presence of oxygen deficiency. Energy resources are consequently greatly reduced in hypoxia and this leads to a severe deterioration of the animal's condition.

CONCLUSIONS

1. The content and rate of renewal of the total cerebral lipids and the rate of cerebroside renewal remained unchanged in hypoxia. The rate of ganglioside renewal from glucose was almost halved in hypoxia.

2. A substantial decrease in the total lipid and cholesterol contents of the liver was noted in the presence of oxygen deficiency. The rate at which these compounds were renewed was even more markedly altered. The relative specific activity of the total lipid fraction and cholesterol was reduced by a factor of 1.8-2.2.

3. The glycogen content of the brain decreased by an average of 25-30% in hypoxia, while that of the liver was reduced by a factor of four. The rate of glycogen renewal was also sharply altered. The relative specific activity of the cerebral glycogen decreased by a factor of 1.8, while that of the hepatic glycogen was reduced by a factor of approximately 2.6. Accordingly, the radioactivity of the cerebral glycogen per g of tissue decreased by a factor of 2.6 and that of the hepatic glycogen decreased by a factor of almost 11.

OXYGEN-FIXING PROPERTIES OF BLOOD HEMOGLOBIN DURING ACCLIMATIZATION OF
THE ORGANISM TO CHRONIC HYPOXIA

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During acclimatization to chronic oxygen starvation a whole series of changes intended to compensate for this condition occur in all the systems of the organism. More specifically, the changes in the circulatory system include an increase in the erythrocyte and hemoglobin counts of the blood and an increase in the quantity of blood in the brain.

There is a difference of opinion regarding the possibility of a change in hemoglobin properties, i.e., a change in the respiratory function of the blood under the influence of hypoxia during acclimatization. One of the basic qualitative indices of hemoglobin is the shape and position of the oxyhemoglobin dissociation curve. Certain authors (Dill, 1931; Hall, Dill and Barron, 1936; Barbashova, 1941; Barbashova and Genetinskiy, 1942; et al.) did not detect any changes in the oxyhemoglobin dissociation curves during acclimatization to chronic oxygen starvation. Other authors (Barcroft, Kemis, Roberts, and Mathison, 1911-1912; Khurtado, 1959; et al.) found that the oxyhemoglobin dissociation curve was displaced to the right. Still others (Slonim et al., 1959, and others) detected a shift to the left in the dissociation curve. Charnyy, et al., (1946) found that when dogs were subjected to repeated "ascents" to an "altitude" of 5000 m the curve acquired a very marked S-shape (it was displaced to the right in the vicinity of the lower in-

flection and to the left in the vicinity of the upper inflection). Ol'-nyanskaya et al. (1946) showed that when sheep are acclimatized to an altitude of 4000 m the oxyhemoglobin dissociation curve is displaced to the left in the charging segment and to the right in the discharging segment.

The work described herein was intended as a study of the whole-blood oxyhemoglobin dissociation curves of white rats during acclimatization to chronic oxygen starvation over a number of generations (from the first to the thirteenth, inclusive).

For this purpose we placed the rats in a "hypoxic" gas-flow chamber with a capacity of 10 m³. A mixture of nitrogen (89.5%) and oxygen (10.5%) was supplied to the chamber under normal atmospheric pressure. The carbon dioxide and moisture which accumulated in the chamber were absorbed by soda lime and silica gel. The air in the chamber was agitated by a fan and the oxygen and carbon dioxide contents were checked periodically. A "hypoxic" regime was maintained in the chamber for 12 hours a day and the chamber door was left open for the remaining 12 hours.

The rats spent their entire lives and reproduced in this chamber. The control rats and multiplied under normal atmospheric conditions. The "hypoxic" and control rats were from the same source and were kept on the same diet. The investigation was conducted on mature male and female rats 6-15 months old. Each experiment was performed on "hypoxic" and control animals of the same sex, age, and weight.

A new method, cell oxyhemometry, was employed to obtain the oxyhemoglobin dissociation curves. The percentage oxygen saturation of the blood, i.e., the percentage HbO₂, was determined within 2 min with this method, as compared with 1-1.5 hr for the van Slyke apparatus; only 0.4 ml of blood was required for analysis.

In order to construct each oxyhemoglobin dissociation curve, i.e., the curve showing the percentage HbO₂ as a function of partial oxygen pressure, we determined eight points. Consequently, blood was taken simultaneously from two rats of the same litter and sex for each experiment (involving parallel investigations).

In all the experiments the saturators containing the blood were

filled with the same eight gas mixtures, which were prepared beforehand in tanks under high pressure. All eight mixtures contained the same percentage of carbon dioxide (5.3%), i.e., its partial pressure was 40.3 mm Hg at a total pressure of 760 mm Hg. The oxygen contents of the mixtures were 2.4, 4.4, 5.2, 6.3, 8.3, 10.5, 11.6, and 13.4%; the corresponding partial oxygen pressures at a total pressure of 760 mm Hg were 18.2, 33.4, 39.5, 47.9, 63.1, 79.8, 88.7, and 101.8 mm Hg.

We investigated nine whole-blood oxyhemoglobin dissociation curves for the "hypoxic" rats of the first generation. These rats were placed in the "hypoxic" chamber at an age of 2-2.5 months and remained there for 12-13 months. Not a single one of these curves differed from the curve for the control rats.

Of the ten dissociation curves obtained for the "hypoxic" rats of the second generation, i.e., rats which had been born in the "hypoxic" chamber and spent their entire lives in it, two were displaced with respect to the curves for the control animals. One curve was shifted to the right in the vicinity of the lower inflection and the other was shifted to the left in the vicinity of the upper inflection and to the right in the vicinity of the lower inflection (Fig. 1).

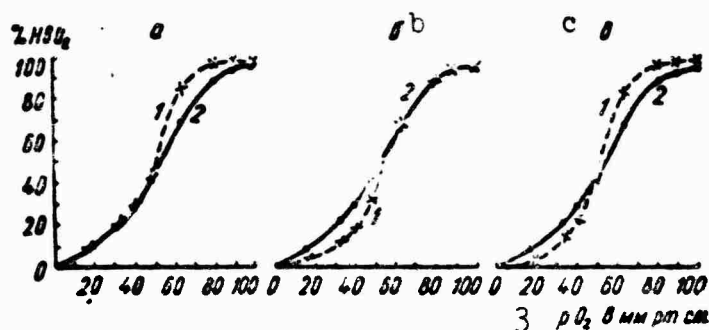


Fig. 1. Examples of whole-blood oxyhemoglobin dissociation curves for "hypoxic" rats (1), which differ from those for control rats (2). a) Shifted to the left in the vicinity of the upper inflection; b) shifted to the right in the vicinity of the lower inflection; c) shifted to the left in the vicinity of the upper inflection and to the right in the vicinity of the lower inflection. 3) pO_2 , in mm Hg.

Of the ten oxyhemoglobin dissociation curves investigated for the

"hypoxic" rats of the third generation three did not correspond to those of the control rats; two were displaced to the left in the vicinity of the upper inflection and one was displaced to the right in the vicinity of the lower inflection.

Of the 14 dissociation curves obtained for "hypoxic" rats of the tenth-eleventh generations eight were displaced with respect to those of the control animals: the upper segments of five were shifted to the left, the lower segments of two were shifted to the right, and one exhibited an upper segment displaced to the left and a lower segment displaced to the right.

Of the seven curves obtained for "hypoxic" rats of the twelfth generation four were displaced with respect to the curves for the control rats: three were shifted to the left in the vicinity of the upper inflection and one was shifted to the right in the vicinity of the lower inflection.

Finally, of the 11 oxyhemoglobin dissociation curves investigated for "hypoxic" rats of the thirteenth generation six were shifted with respect to those for the controls: the upper segments of three were displaced to the left, the lower segments of two were shifted to the right, and one exhibited an upper segment displaced to the left and a lower segment displaced to the right.

Thus, more of the oxyhemoglobin dissociation curves failed to correspond to those of the control animals for the "hypoxic" rats of later generations (tenth-thirteenth) than for those of earlier generations (second-third). Of the 32 dissociation curves obtained for the tenth-thirteenth generations of rats acclimated to chronic oxygen starvation, or 56%, were displaced; of the 20 curves for "hypoxic" rats of the second-third generations only five or 25%, differed from those for the control rats.

GRAPHIC ART

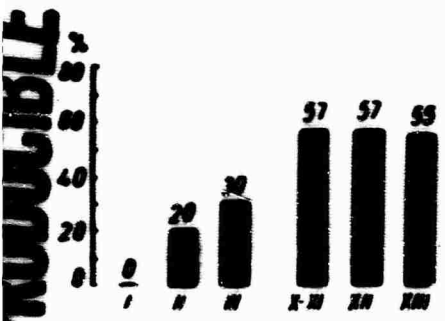


Fig. 2. Number of whole-blood oxyhemoglobin dissociation curves for "hypoxic" rats differing from the dissociation curves for control rats (in %). The figures above the bars indicate the percentage of the curves for the "hypoxic" rats differing from those for the control rats; the figures beneath the columns indicate the generations of "hypoxic" rats.

Consequently, according to our data, a shift is observed in the oxyhemoglobin dissociation curves of all rats subjected to chronic oxygen starvation. Some regularity may be noted in the frequency with which the configuration of the dissociation curves is altered. The increase in the percentage of displaced curves is a function of the number of generations subjected to chronic oxygen starvation.

Thus, in "hypoxic" rats of the first generation there were no displaced oxyhemoglobin dissociation curves at all, in rats of the second generation the number of displaced curves constituted 20% of the total number of curves, in rats of the third generation this

figure was 30%, in rats of the tenth-eleventh generations it was 57%, in rats of the twelfth generation it was 57% as well, and in rats of the thirteenth generation it was 55% (Fig. 2).

It must be noted that the oxyhemoglobin dissociation curves for the "hypoxic" rats (regardless of generation) were most frequently displaced to the left in the vicinity of the upper inflection (according to our data, in 57% of all cases), were less frequently shifted to the right in the vicinity of the lower inflection (in 30% of all cases), and were even more rarely displaced to the left in the vicinity of the upper inflection and to the right in the vicinity of the lower inflection (in 13% of all cases).

All the changes which we detected in the position of the S-shaped oxyhemoglobin dissociation curve are a manifestation of acclimatization

of the organism to chronic hypoxia, i.e., adaptation directed at preventing tissue oxygen starvation.

In order for hemoglobin to efficiently carry out the transfer of oxygen from the lungs to the tissues it is necessary that it be completely oxidized at the oxygen tension present in the lungs and that the oxygen which it fixes be released without delay in the tissue capillaries. The oxyhemoglobin dissociation curves characterize the respiratory function of the blood and give us some notion of the affinity of the hemoglobin for oxygen. The oxyhemoglobin dissociation curves for the "hypoxic" rats, which were shifted to the left in the vicinity of the upper inflection or to the right in the vicinity of the lower inflection with respect to the curves for the control rats, thus characterize the organism's ability to exist more efficiently under hypoxic conditions.

A displacement of the dissociation curve to the left in the vicinity of the upper inflection indicates an increase in the capacity of the hemoglobin for oxygen absorption in this region, i.e., at a comparatively high partial oxygen pressure.

This is favorable to an organism living under hypoxic conditions, since the arterial blood can be saturated with more oxygen at a lower partial oxygen pressure in the inhaled air than is ordinarily the case. As a result, the arterial-venous oxygen difference increases and the tissues receive more oxygen.

A displacement of the dissociation curve to the right in the vicinity of the lower inflection indicates a decrease in the affinity of the hemoglobin for oxygen at lower partial oxygen pressures. The tissues may receive more oxygen from the blood in this case, since oxyhemoglobin dissociation begins at a higher oxygen tension in the tissues. All of the shifts which we observed in the oxyhemoglobin dissociation curves

are consequently beneficial to an organism living under conditions of oxygen starvation.

Finally, we may conclude that a change in the oxygen-fixing properties of hemoglobin may occur during prolonged acclimatization of a number of generations of rats to hypoxic conditions; this change begins with the second generation and is one of the organism's protective measures for combating oxygen starvation.

COUPLED ION EXCHANGE OF POTASSIUM AND SODIUM SALTS
BETWEEN HUMAN ERYTHROCYTES AND BLOOD PLASMA AT
VARIOUS PARTIAL OXYGEN PRESSURES

I.M. Dedyulin
(Leningrad)

Our data clarify the mechanism of the regulatory increase which occurs in the potassium content of human blood serum at high altitudes, a phenomenon unexplained for the past 25 years. We will discuss the ion-exchange adsorption of potassium and sodium chlorides by amino acids. Amino acids are found in the adsorbed state on the surface of erythrocytes (Abdergalden, 1923; B.I. Abarskiy, 1925) and are amphoteric capable of fixing both positively charged potassium and sodium ions and negatively charged chlorine ions. We will also explain the preferential adsorption of potassium ions in the pulmonary circulatory system and sodium ions in the systemic circulatory system. The conversion of hemoglobin to oxyhemoglobin in the lungs and the possibility of hydrochloric acid formation accounts for the liberation of potassium from erythrocytes and its adsorption by the amino acids on the erythrocyte surface.

The entry of a large quantity of carbon dioxide into the blood plasma in the capillaries of the systemic circulatory system leads to intensive formation of carbonic acid, "which competes successfully for sodium"; this results in the formation of hydrochloric acid. The latter dislodges potassium ions from the erythrocyte surface and they then enter the erythrocytes in the form of potassium chlorides. Sodium ions

are preferentially adsorbed on the erythrocyte surface. This process is well balanced under uniform conditions at altitudes of 4250, 5300, and 5096 m, because of the intensive "washing of carbon dioxide" from the blood in the pulmonary circulatory system, and the development of gas alkalosis is not completely compensated in the capillaries of the systemic circulatory system. This leads to an increase in potassium concentration in the blood serum.

The increases which we detected in potassium content on storing a blood clot under refrigeration only confirm the adsorption mechanism of the increase in potassium content observed in human blood serum at high altitudes.

The arguments advanced above support the sorption theory of cell permeability (D.N. Nasonov, V.Ya. Aleksandrov, and A.S. Troshin), strike a blow at the "sodium pump" theory, confirming its incorrectness, and permit us to advance the alternative hypothesis that buffer systems composed of hemoglobin and oxyhemoglobin are the basic systems involved in regulating exchange of minerals between erythrocytes and blood plasma.

DATA ON HYPOXIA AND ACCLIMATIZATION

L. G. Pilatova

Frunze

The current state of the theory of acclimatization does not permit us to postulate any single acclimatization mechanism for all organisms and for various cases of oxygen deficiency.

Investigations which we conducted over a number of years in Kirgiz indicated that substantial differences in physiological functions occur under the conditions of the Tyan'-Shan' mountain system in comparison with other mountainous regions.

These differences consist primarily in a marked persistent decrease in energy consumption in both humans and animals. The mechanism of this decrease is not clear. However, there is reason to believe that a considerable change (depression) occurs in the functional state of the thyroid gland under these conditions (M. K. Akhunbayev et al., 1955).

The decrease in thyroid functioning which occurs under the conditions of Kirgiz may have an adaptive character. It is well known that cessation of thyroid functioning causes an increase in the organism's resistance to altitude (P. N. Veselkin, 1942; M. Ye. Vasilenko, 1955; our data, 1955) by depressing metabolism and apparently by reducing the sensitivity of the cerebral cortex to hypoxia, since the thyroid hormone is a specific cortical stimulant. A decrease in cortical sensitivity may also cause the cortex to become more stable to the action of stimuli picked up by many receptors.

A physiological paradox may be observed under experimental condi-

tions when the erythrocyte and hemoglobin counts decrease by 40-50% (as a result of blood-letting) and the organism's resistance to altitude not only fails to decrease, but even increases. This increase is apparently caused (L.G. Filatova and E. Abdikasheva, 1961) by a substantial reduction in gaseous interchange after blood-letting (Fig. 1).

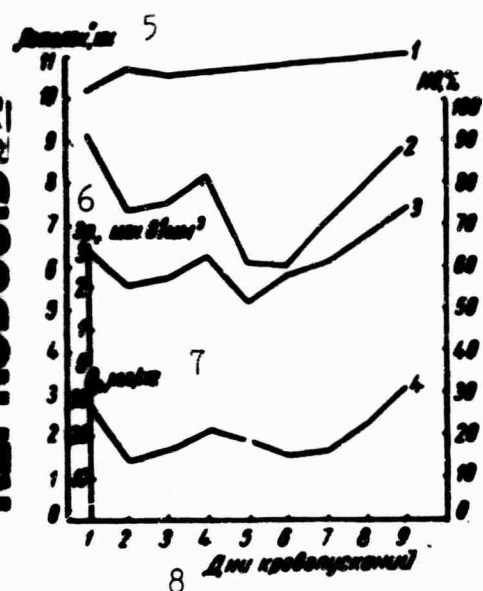


Fig. 1. "Ceilings" of tame doves after blood-letting. 1) "Ceilings" (in km); 2) hemoglobin (in %, by Sahli's method); 3) erythrocyte count (in millions per mm³); 4) gaseous interchange (ml/kg of oxygen per min); 5) ceilings, km; 6) erythrocytes, millions per mm³; 7) O₂, ml/kg; 8) days of blood-letting.

Adaptation to hypoxia by a depression of gaseous interchange was observed not only in animals and humans acclimatized in Kirgiz, but also on disruption of normal oxygen supply (Fig. 2, experiments on curled hedgehogs).

The data cited, which are examples of adaptation to hypoxia by metabolic depression and thyroid hypofunctioning, may represent a general mechanism employed when the struggle for oxygen (in the light of Z.I. Barbashova's data, 1960) cannot be completely won. In this case the organism may resort to glycolytic metabolism to satisfy its energy requirements. This ability of tissue to

adapt to normal functioning in the presence of severe oxygen deficiency (in ischemia) was demonstrated in our experiments involving application of a tourniquet to a limb. Here we can also obviously assume that anaerobic glycolytic decomposition takes part in the prolonged maintenance of the capacity for muscular work.

According to our data, the reduction in basal metabolism in humans and animals at altitudes of 760-2500 m in Kirgiz was accompanied by depression of a number of other physiological functions - circulatory,

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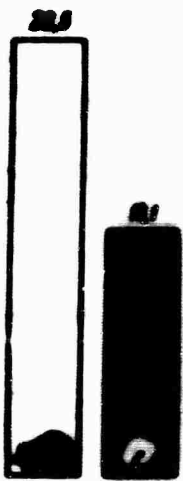


Fig. 2. Gaseous inter-change in hedgehogs in the uncurled and curled positions (ml/kg of oxygen per min).

cardiovascular, and respiratory (N. F. Pisarenko, A. D. Taranukhina, N. D. Zaytseva, and others).

However, an altitude of 3000-3500 m above sea level causes an intensification of physiological functions; this indicates the stimulating action of this altitude and the inability of the organism to compensate for the oxygen deficiency by the mechanisms which it employs for this purpose at 760-2500 m. Additional compensatory mechanisms must be activated or those already in action must be reinforced (A. D. Slonim et al., 1949; L. G. Filatova, 1957).

The exteroceptors and cerebrum play an important role in adaptation to hypoxia. Our investigations (E. Tokobayev, L. Tokmergenova, G. Shmidt, and E. Shelukhina) showed that

Disengagement of the Visual Receptor in White Mice by 20% lye and 2% and 0.5% Dicaïne and Stimulation by Intermittent Illumination

I «Потолки» (в км)									
2 Контрольные животные		4 Подопытные животные							
3 I подъем	II подъем	5 20%-ная щелочь		8 2%-ная дикаин		9 0,5%-ный дикаин		10 Прерывистое освещение	
		6 норма	7 выключение	норма	выключение	норма	выключение	норма	11 освещение
9,5	9,5	8,2	10,0	9,4	10,6	8,0	7,7	9,6	8,0
0,5	10,5	8,7	11,0	9,8	10,3	10,3	9,2	9,3	7,9
9,6	9,5	10,4	9,5	10,3	9,8	9,4	9,7	8,8	8,8
6,3	6,4	6,7	7,5	9,6	9,7	9,6	8,7	10,0	9,2
8,7	8,7	9,5	10,6	10,0	11,0	9,0	8,7	9,9	9,5
9,7	9,7	9,6	10,8	9,2	10,2	—	—	10,2	8,4
8,8	9,0	8,7	9,2	9,7	10,4	—	—	9,8	9,6
7,7	7,5	8,5	9,2	9,5	10,2	—	—	—	—
12 8,3	8,5	8,7	9,2	9,5	10,3	—	—	—	—
9,8	9,6	7,5	9,0	—	—	—	—	—	—
В среднем 6,9	8,9	8,5	9,7	9,7	10,4	9,4	8,5	9,8	8,8

1) "Ceilings" (in km); 2) control animals; 3) ascent; 4) experimental animals; 5) 20% lye; 6) normal; 7) disengagement; 8) 2% dicaïne; 9) 0.5% dicaïne; 10) intermittent illumination; 11) illumination; 12) average.

stimulation or disengagement of the exteroceptors (visual, auditory, or olfactory) substantially alters resistance to hypoxia, with respect to

both convulsions and respiratory arrest. It was established that the baroreceptors, which are located in the nasal and aural cavities, take an active part in adaptation to hypoxia and that their disengagement considerably increases the resistance of the organism to acute altitude-induced hypoxia. On the basis of the data in the literature and our own investigations it was demonstrated that extirpation of the cerebrum or its disengagement by anesthetization or in hibernation substantially raises resistance to altitude. Conversely, stimulation of the cerebrum reduces the ability of the organism to withstand hypoxia (see table).

The sensitivity of the cerebral cortex and its state at any given moment (inhibition or excitation) thus play an important role in the resistance of the organism to altitude. This may apparently govern individual differences in resistance to altitude and, possibly, those among species as well.

Since it is quite impossible to consider the influence of reduced barometric pressure independently of the action of other physical factors on the organism (temperature and its fluctuations, humidity, organic- and mineral-nutrition conditions, the influence of radiations of varying character and intensity), we have every reason to speak of the specificity of individual mountain systems.

This specificity is also manifested in the different acclimatization reactions which develop against the background of the decrease in barometric pressure common to all mountain systems. It must be assumed that the alteration of the thyroid gland and the changes in all other functions in the humans and animals examined represent a unique norm characteristic of the conditions of Kingiz.

If we hold to this view, it is obviously necessary to introduce corrections in comparing morphophysiological investigations conducted under local conditions with general standards in order to determine the

limits of the incipient pathological process in characterizing the general state of the organism.

From the data cited and the analysis made of them we must draw the general conclusion that the theory of acclimatization to altitude cannot neglect the physiological state induced by the physicogeographic substrate on which the organism lives and develops.

The unusual character of Tyan'-Shan' also explains the peculiarities which we noted in acclimatization to altitude.

MECHANISMS EMPLOYED BY THE ORGANISM TO ADAPT TO HIGH-
ALTITUDE CONDITIONS

B. T. Tupusbekov

(Frunze)

The literature contains a great many works devoted to the influence of high-mountain conditions on the organism; these elucidate the role of hemopoiesis, hemodynamics, and external respiration and demonstrate the importance of the higher divisions of the central nervous system and the endocrine glands.

However, despite the existence of these works the intimate mechanisms of acclimatization to high altitudes have still not been discovered. There is no widely accepted definitive view regarding the specific classification of the mechanisms by which humans and animals adapt to the altered conditions of mountainous terrain. Many researchers occupied with this problem give very diverse definitions, frequently contradictory; for the most part these definitions fail to characterize correctly the adaptive mechanisms underlying acclimatization.

Under high-mountain conditions the organism lives in an environment where, in addition to the ordinary physiological stimuli, it is acted upon by unusual stimuli of varying character, prime among which is oxygen deficiency. In this connection physiologists have developed pressure chambers and research methods involving gases to mimic high-altitude conditions, particularly hypoxia. These investigations continue to increase in number.

It must be noted that while a constant environment with a reduced

oxygen content is set up over a short time under model conditions, in pressure chambers, the following factors vary over a definite period under high-mountain conditions: barometric pressure and the related partial oxygen pressure, ambient temperature, the flow rate, moisture content, and degree of ionization of the air, the electrical properties of the soil, the intensity of the ultraviolet and infrared radiation, etc. The high-mountain climate thus differs qualitatively and quantitatively from pressure-chamber conditions, being the aggregate of non-specific and specific factors under whose influence diverse functional and morphological changes occur in the organism.

The terms "high-mountain acclimatization" and "pressure-chamber and gas" or "altitude" adaptation (adaptation to hypoxia) have come to be employed as though they were absolutely identical and many authors equate them. All the reactions observed in the organism under the influence of high-mountain and pressure-chamber conditions are lumped together under the general term "acclimatization to hypoxia." Thus, "acclimatization to hypoxia" is taken to mean the mobilization of the reserve capacities of the organism in order to ensure its oxygen supply, regardless of whether this occurs in the mountains or in a pressure chamber.

It seems to us that "acclimatization to hypoxia" as such is not present, the process which actually occurs being adaptation to hypoxia. In this case the organism undergoes a temporary and transient reorganization of physiological functions with no change in morphology. This view is supported in the works of N.N. Sirotinin (1940, 1957), P.V. Yegorov, (1936, 1941), and D.Ye. Rozenblyum (1943).

In the opinion of P.A. Appolonov and V.G. Mirolyubov (1938), V.V. Strel'tsov (1938, 1942, 1947), and D.Ye. Rozenblyum (1943), the only adaptation which occurs in the hypoxia created in pressure chambers or

in breathing appropriate gas mixtures is to the pressure-chamber "altitude" and not to a high-mountain climate. We consequently feel it useful to differentiate the adaptive reactions which occur during a prolonged stay in the mountains from those which develop under the brief acute action of the pressure-chamber "altitude."

The word "adaptation" is the most suitable to describe the changes which develop during brief exposure to acute hypoxia, indicating adjustment of the organism to a new stimulus.

The expression "acclimatization to hypoxia" is consequently unsuitable both from the terminological standpoint and because it does not sufficiently well reflect the nature of adaptation to high-altitude conditions. It severely restricts the biological significance of acclimatization and causes confusion in describing the intimate mechanisms of acclimatization to high-mountain conditions and adaptation to pressure-chamber "altitudes." We believe it incorrect to employ the term "acclimatization" to characterize the changes which occur in the organism during brief oxygen starvation, as E. I. Barbashova, and A. G. Ginetsinskiy (1942), B. B. Koyranskiy (1960), and other Soviet and foreign authors have done.

Our objection to the improper use of the expression "acclimatization to hypoxia" is thus not a fight for terminological precision, but an attempt to demonstrate the inadequacy of a widely held view which inaccurately explains the nature of biological acclimatization.

It must be noted that not all the changes which occur in the organism under the influence of high-altitude or pressure-chamber conditions are acclimational in character. These changes are frequently no more than an inevitable consequence of the influence of extreme conditions and have an adaptive rather than an acclimational character. Only those functional and morphological changes developing under the influ-

ence of a new environment which are genetically transmitted and promote the normal development of the organism may be termed acclimational.

We do not deny that the use of pressure chambers in investigating the action of low barometric pressures is justified. They are known to have greatly furthered the study of vital activity during high-altitude flights and in mountain climbing. Pressure-chamber investigations were the starting point for the theoretical solution of problems of oxygen starvation and "altitude" adaptation.

If we consider acclimatization to mountain conditions to be completely separate from "altitude" adaptation, the essential element in the former is adjustment to the bioclimate (the biological conditions of the environment), i.e., the establishment of a positive symbiosis with various animals, the plant world, and the social and economic conditions of the geographical region and climatological zone in question.

Acclimatization to mountain conditions occurs during prolonged stays in mountainous regions. It is characterized by relatively persistent changes in a number of physiological functions and a stable morphological reorganization of individual systems. However, these functional and structural changes do not alter the individual's general type, but make humans and animals equal members of a new natural community, ensuring life and, especially, reproduction.

The fact that under the conditions of a given geographic area humans or animals must have a broad capacity to alter their way of life and acquire different habits to meet climatological and ecological conditions and environmental requirements is of great importance. In other words, acclimatization revolves about four basic factors: climatological, ecological (living conditions), biological, and social. The latter is of definitive importance for humans.

We thus recognize acclimatization to mountain conditions to be bi-

ologically broader, essentially the combination of two parameters similar in character but opposite in significance - adaptive excitation (Ye.I. Bakin) and active adaptation (N.N. Sirogin).

As our investigations showed, during the first 2-12 days for which animals are in mountainous country adaptive excitation develops in response to the integral action of climatological factors on the organism. It is characterized by an increase in arterial pressure, acceleration of the heart and respiration rates, a decrease in the threshold of the chemoreceptors and mechanoreceptors of the principal vascular reflexogenic zones, a reduction in the threshold of electrical excitability of the peripheral nerve trunks, an intensification of the arterial-pressure and respiratory reflex reactions, an increase in the tonus of the sympathetic nervous system, and a decrease in the tonus of the parasympathetic nervous system.

During the period of adaptive excitation the organism passes out of danger as a result of emergency mobilization of its autonomic reserve capacities, creating the necessary conditions for maintenance of a relatively constant internal environment. Through changes in the functional state of its hemodynamics and respiration, the parameters of adaptive excitation, the organism actively restores its disrupted homeostasis for "free living." The duration of adaptive excitation depends on the animal's individual characteristics and the adaptive-protective reactions begin to fade gradually away only after 5-14 days.

Since the functional organization of adaptation is one of the most important conditions of the evolutionary process, the preferentially sympathetic innervation of the cardiovascular and respiratory systems during the initial stages of adaptation must be evaluated on the basis of general biological criteria or laws, as must be the subsequent transition to a new functional level and the concomitant attenuation of sym-

pathetic and intensification of parasympathetic innervation.

This approach to the observed phenomena was taken first by L.A. Orbeli and then by Kh.S. Koshtoyants and D.A. Biryukov. In the opinion of these authors, the discovery of the functional characteristics of different organs and structures with different developmental histories, having different "ages" with regard to the evolutionary history of the animal in question, is of great biological interest.

Adaptive excitation develops in any highly organized organism under the influence of the unusual conditions of mountainous terrain and is part of the evolutionary process. During adaptive excitation optimum conditions are created by mobilization of the functional reserves of hemopoiesis and the cardiovascular system, and the organism which has the greatest potential capacities and makes the best use of its functional resources is the best adapted to the unusual conditions which obtain in mountain country.

It must be noted that when the organism has set in action hemopoiesis, hemodynamics, and respiration through the appropriate neural devices under the influence of the extremal stimuli of mountain conditions any additional stimulus (electrical or mechanical stimulation of efferent nerves, frequent repeated stimulation of the chemoreceptors and mechanoreceptors of the carotid sinus) causes inverse arterial-pressure and respiratory reactions. The development of pathological forms of respiration and Traube-Hering waves is frequently noted. A lethal outcome involving a progressive drop in arterial pressure is often observed. Intracardiac adrenaline injections almost never restore cardiac activity.

Of course, no highly organized organism can remain in a state of adaptive excitation, since this leads to severe depletion of the organism's reserve capacities and death from the disruption of homeostasis.

The organism's reaction consequently does not stop at adaptive excitation, but passes on to a second phase - active adaptation. As we noted above, this second phase differs greatly from the first and is characterized by an increase in the threshold of the chemoreceptors and mechanoreceptors of the principal vascular reflexogenic zones, a rise in the threshold of electrical excitability of the nerve trunks, and an adequate reaction of the cardiovascular and respiratory systems, the latter taking the form of reversion of arterial pressure and heart and respiration rates to the values normal for lowland and acclimated animals.

Adaptation, which is characterized by inhibition and equilibration of physiological functions, ultimately leads to stable restoration of homeostasis.

In Hill's opinion, adaptation to an agent with a prolonged action is a "constant increase in threshold," while according to Edwards it is a "cessation of the excitatory action of a persistent stimulus," according to A.A. Ukhtomskiy (1937) it is a "self-limitation of the activity which has begun in the substrate" with respect to the resting period after excitation, and according to D.G. Kvasov (1952) it is an "increase in resistance."

On the basis of our study of the functional state of hemodynamics and respiration we may thus conclude that the autonomic functions of the organism undergo a two-phase change, first increasing and then decreasing, under the integral action of climatological factors under mountain conditions. This two-phase change in hemodynamic and respiratory indices may be considered as a mechanism which ensures a definite adaptive relationship between the organism and the special external conditions which obtain in mountainous terrain. Adaptation protects the organism from substantial stresses, expanding its "protective-adaptive

self-regulatory" capacities and increasing its resistance to the extreme factors of the mountain climate.

Analyzing the physiological and morphological data obtained by the workers of our laboratory (L.A. Bryantseva and A.T. Tynybekov) in a systematic study of permanent and newly-arrived residents of mountain country, we may conclude that acclimatization begins after adaptation. Its characteristic symptoms are a slight acceleration of respiration, bradycardia, a retardation of blood-flow rate, vagotonicity of the functioning of the autonomic nervous system, enlargement of the thoracic cavity, etc.

The data of Barcroft et al., K.M. Bykov, and E.E. Martinson indicate that similar changes are one of the forms of adaptation to prolonged stays in the mountains.

These functional and morphological changes, developing during prolonged stays in mountainous areas, serve to best adapt the organism to the unusual factors involved in mountain conditions. Assimilating the external conditions, the organism is altered for the further full development of its offspring (T.D. Lysenko). This is quite understandable, since useful traits are genetically reinforced and nonuseful traits discarded during evolution (I.V. Michirin).

CONCLUSIONS

1. Adaptive excitation is the starting point for adaptation and acclimatization. It is an adequate reflection in the organism of the external factors of mountain conditions and a result of the transformation of external to internal.

2. The second stage, which is closely associated with the first, is active adaptation. During this stage of adjustment the specific and nonspecific stimuli of mountain conditions are generalized and differentiated and the functions of the entire organism undergo an adequate

reorganization.

3. The third stage, which is closely associated with the second, is acclimatization. During this phase the functions and structures, forms and mechanisms of dynamic adaptation develop and are perfected, useful traits and properties being transmitted genetically. Acclimatization considerably increases the plasticity and mutability of the vital functions of animals and man under the action of altered environmental conditions, making them equal members of a new natural community.

DATA ON ACCLIMATIZATION TO THE MOUNTAIN COUNTRY OF
KIRGIZ

M.M. Mirrakhimov

(Frunze)

The influence of the mountain climate on the functional state of the organism has been studied for a comparatively long time and very important data, which shed light on the mechanism of acclimatization, have been amassed in this connection (N.N. Sirotinin et al., Ye.M. Kreps et al., G.Ye. Vladimirov et al., M.Ye. Vol'skiy, O.N. Pavlova, Tsunts, Levi, Mosso, Barcroft, Khurtado, Monge, and others). It has been discovered that moving to a mountainous area is accompanied by changes of a compensatory character intended to aid in the "fight for oxygen" (Z.I. Barbashova). In essence, these shifts consist in an intensification of the functions of the circulatory, respiratory, and hematopoietic organs and the nervous system, changes in the alkali-acid equilibrium, etc. It has been found that, in addition to these functional changes, there is an alteration of tissue enzymatic processes, this ultimately ensuring better blood supply to the tissues. It is noteworthy that there is a change in blood distribution under conditions of oxygen starvation; this takes the form primarily of an increase in blood supply to the vitally important organs, especially the brain (M. Ye. Marshak, V.I. Voytkevich, et al.).

Observations have shown that the reaction of the organism to a stay in mountainous terrain depends not only on the decrease in barometric pressure, but also on the peculiarities of other climatological

factors of the area. This creates a situation in which each mountain region is distinguished by its own specific characteristics and these determine the unique reactions of the organism to the conditions which obtain therein (K.M. Bykov, A.D. Slonim). It has been demonstrated that the reactions of the circulatory, hematopoietic, and respiratory organs are less marked under the conditions of the mountains of Kirgiz than in the mountain climate of the Caucasus (A.D. Slonim, G.P. Konradi, M.Ye. Vol'skiy, et al.). A.G. Ginetsinskiy and Z.I. Barbashova detected this peculiarity somewhat earlier in the sheep of Pamir. These investigations served as the basis for further attempts to determine the characteristics of the reaction of the organism under various mountain climatogeographical conditions.

Work on problems of mountain physiology has been done and is being done primarily in this direction, which is of both theoretical and practical importance. In addition, the characteristics of the physiological functions of mountain residence and new arrivals not yet acclimatized have still not been conclusively determined. K.M. Bykov was correct when he wrote in 1933: "we still know very little regarding the physiological conditions, morphological peculiarities, and neuropsychological reactions of the inhabitants of our mountain regions. This matter requires further study, so that we can draw up a correct daily regime and a rational working regime for mountain areas." Considerable work has been done in this respect both in the Soviet Union and abroad (K.M. Bykov, A.D. Slonim, G.P. Konradi, A.G. Ginetsinskiy, Z.I. Barbashova, M.Ye. Vol'skiy, M.P. Redlikh, M.M. Mirrakhimov, N.I. Averina, L.G. Filatova, O.N. Pavlova, A.P. Zhukov et al., V.S. Asatiani, Monge, A. Khurtado, and others). Study of this aspect of mountain physiology is of great practical importance in connection with the development of agriculture and industry in mountain regions.

Kirgiz, a mountainous area, occupies a special place among the republics of the Soviet Union. In addition to low barometric pressure, the characteristics of high mountain areas include dry air, intense solar radiation, and a rather high ambient air temperature.* These climatological characteristics apparently cause acclimatization to the mountain conditions of Kirgiz to have somewhat of an unusual character.

Among the first to study the influence of the mountain climate of Kirgiz on the human organism were N.N. Sirotinin and his assistants. Only a few reports on this problem have appeared in the literature in recent times. In our republic mountain physiology has been the subject of especially intensive work on the part of A.D. Slonim, M.Ye. Vol'skiy, G.P. Konradi, and their colleagues over the past two decades.

This article presents data which we (A.I. Arakcheyev, L.A. Preobrazhenskaya, A.D. Dzhaylobayev, T.D. Davletbekov, Z.I. Khasanova, and R.P. Malofiyevskaya) have amassed over the past ten years. Determination of the characteristics of the physiological functions of acclimated mountain residents occupied a special place in our investigations; in addition, during the past three years we turned our attention to the influence of brief stays at high altitudes on the human organism.

Reactions of the human organism to brief stays at high altitudes.

In conjunction with L.A. Preobrazhenskaya and Z.I. Khasanova we studied the reactions of the organism to brief stays at moderate altitudes (Anan'yevo - 1750 m) and at high altitudes (Kogondu-Kiya - 3300 m).

On examining 16 persons 22-26 years of age in Frunze and after 3, 15, and 30 days at an altitude of 1750 m we were unable to detect any statistically reliable change in pulse rate, arterial or venous pressure, or blood-flow rate. As regards the erythrocyte and hemoglobin counts, after three days at this altitude there was a moderate decrease in hemoglobin content (from 82 to 78 units), but after 15 and 30 days

it exhibited a statistically reliable increase of 7 or 8 units. The erythrocyte count had risen by an average of 270,000 after three days and by an average of 386,000 after 15 and 30 days, figures which were not statistically reliable. These data indicate that moving to a moderately high mountain region is not accompanied by an intensification of circulatory functioning or an increase in erythrocyte count, the only phenomenon observed being a slight increase in hemoglobin count from the 15th day onward. In contrast to the mountain country of Kirgiz, marked compensatory changes in the circulatory and hematopoietic systems are observed at approximately the same altitudes in the Caucasus (M.M. Efendi-Zade, S.M. Bedalova, S.A. Ali-Zade, Ye.V. Ivanova and N. P. Patrik, R.A. Mikayelyan, G.A. Nargizyan, Beridze, et al.). Investigation of capillary permeability and stability by the Konchalovskiy, McClure-Aldrich, and histamine-wheal tests revealed no regular changes in the majority of cases. An increase in the number of hemorrhages in Konchalovskiy's test was noted in 22.2% of all cases after three days at the altitude in question.

The reactions of the organism to a stay at the 3300 m altitude of Tyan'-Shan' were investigated in 43 persons of approximately the same age. Three sets of observations were made, in Frunze and on the 4th-5th and 10th-11th days at the altitude in question. The respiration and pulse rates were regularly elevated, the systolic and diastolic pressures were reduced, and the time for which the breath could be held was curtailed (Stange's test). The red-blood indices were also elevated (see table).

The data cited are in agreement with the indications in the literature. In contrast to the reaction of the circulatory apparatus in the Alps, under our conditions a stay at high altitude in the Caucasus causes a decrease rather than an increase in arterial pressure. As may

be seen from the table, the most marked changes are detected after 10-11 days at high altitude. The Konchalovskiy and Nesterov tests showed the subjects to exhibit a regular decrease in capillary stability and an increase in capillary permeability.

Summarizing our data on the influence of brief stays in the mountain country of Kirgiz, we may state that the adaptive changes which occur under the conditions of Tyan'-Shan' develop at a considerably greater altitude than in other mountain regions.

Influence of prolonged stays at high altitudes on the human organism. The necessity of investigating the functional state of the organism during prolonged stays at high altitudes is dictated by the fact that many persons settle, live, and work for years in mountain regions. At the same time, investigation of the natives of mountain regions may shed some light on the characteristics of the physiological functions of residents of mountainous terrain. Comparison of the results of investigations of newly-arrived and native residents may promote more correct determination of the time required for complete acclimatization.

Over a period of many years we investigated circulatory functioning in more than 1500 mountain residents, approximately one-third of whom were natives, while the remainder were settlers who had lived in mountain country for from 6 months to 10 years or more. The majority of the subjects were 20-40 years of age. Arterial pressure was investigated in more than 8000 residents of Frunze (780 m above sea level), approximately 6000 residents of Przheval'ska (1750-1800 m), and approximately 2000 residents of Naryn (2020 m). In addition, we were interested in the functioning of the autonomic nervous system and, during the past three years, in gaseous interchange, the indices of the peripheral blood, and alkali-acid equilibrium. Since we are unable to give any comparatively complete description of the data amassed, we will present

Change in Certain Physiological Indices Under the Influence of Brief Stays at an Altitude of 3300 m

Показатели	2 г. Фрунзе				3 На высоте							
	На 4-5-й день		4		5		На 10-11-й день					
	M	$\sigma \pm$	m \pm	P <	M	$\sigma \pm$	m \pm	P <				
6 Число дыханий (в 1 мин.)	20	2,2	0,3	0,001	25	3,2	0,5	0,001	27	2,8	0,4	0,001
7 Пульс	76	6,9	1,0	0,001	89	6,9	1,0	0,001	93	7,8	1,1	0,001
8 Систольное артер. давление	118	11	1,6	0,05	109	9,4	1,4	0,05	103	10	1,5	0,001
9 Диастолическое артер. давление	77	7,7	1,1	0,05	72	9,1	1,3	0,05	66	7,7	1,1	0,001
10 Проба Штанге (в 1 сек.)	33	13	1,9	0,001	25	8	1,2	0,001	25	9,8	1,4	0,001
11 Количество эритроцитов (в 1 мм ³)	3 865 000	517 000	81 000	0,001	4 427 000	512 000	76 000	0,001	5 395 000	62 900	93 000	0,001
12 Количество гемоглобина (в ед.)	79	7,5	1,1	0,001	93	6,00	0,9	0,001	104	5,6	0,8	0,001

Note: M designates the arithmetic mean, σ the mean square deviation, m the error in the arithmetic mean, and P the reliability criterion for the difference from the initial data.

1) Index; 2) Frunze; 3) at altitude in question; 4) after 4-5 days; 5) after 10-11 days; 6) number of breaths (per min); 7) pulse rate; 8) systolic arterial pressure; 9) diastolic arterial pressure; 10) Stange's test (in sec); 11) erythrocyte count (per mm³); 12) hemoglobin count (in units).

only the overall results of our investigations.

In studying the functioning of the circulatory apparatus we detected no tachycardia on measurement of the pulse rates of mountain residents, a phenomenon which has been observed in persons moving into mountainous regions. On the contrary, approximately half the mountain residents exhibited bradycardia (less than 60 beats per minute) or a tendency to it (61-64 beats per minute). Persons living on the shore of Lake Issyuk-Kul' displayed bradycardia more frequently than residents of Naryn. Attention was called to this fact, which has been confirmed by the comparatively large amount of data which we amassed, by M.P. Redlikh in 1946 and by A.D. Slonim and G.P. Konradi somewhat earlier. L.G. Filatova, who made her observations a bit later, obtained approximately the same results. There is thus every reason to believe that relative bradycardia is a reaction characteristic of mountain residents of Kirgiz living at altitudes of up to 2000 m.

Arterial pressure (especially systolic pressure) proved to be somewhat lower than the values established for Moscow (Ye.P. Fedorova et al.) and Leningrad (Z.M. Volynskiy et al.). That a moderately marked, predominantly systolic hypertonia occurs has been confirmed by the investigations of A.D. Slonim, G.P. Konradi, M.P. Redlikh, M.A. Aliyeva, L.G. Filatova, and others. In contrast to the systolic and diastolic pressure, the mean dynamic pressure exhibited no marked deviations from normal.

The blood-flow rate was reduced in both the pulmonary and systemic circulatory systems. Comparison with the corresponding data for residents of Frunze revealed a statistically reliable difference. This retardation of blood flow was more marked in persons living on the shore of Lake Issyuk-Kul' than in residents of Naryn.

One of the basic hemodynamic factors, minute cardiac volume, was

found to be within normal limits or somewhat elevated in the majority of cases when investigated by the acetylene method in persons living at altitudes of 1650 and 2020 m.

Nailbed capillariscopy revealed a decrease in the number of capillary loops and in their lumen size in the overwhelming majority of the persons examined. The blood flow in the capillaries was quite frequently retarded.

Application of a measured physical stress to mountain residence and evaluations of pulse rate and arterial pressure in some and vital capacity in others usually revealed no pathological reaction of the cardiovascular system.

We and L.A. Preobrazhenskaya, but primarily the latter, have amassed considerable data (based on examinations of more than 1800 persons by various methods - the Lendis, Nesterov, Konchalovski, histamine-wheel, and McClure-Aldrich tests) characterizing capillary permeability and stability in residents of Frunze, the shore of Lake Issyk-Kul', and Noryn. Statistical processing and comparison of the results showed that persons who live at high and moderate altitudes have somewhat more permeable and fragile peripheral capillaries. In order to exclude the possible influence of vitamin deficiency or elevated hyaluronidase activity in some of the mountain residents L.A. Preobrazhenskaya investigated the serum ascorbic acid and hyaluronic acid contents. Her observations showed that there were no deviations from normal. On this basis we may consider the elevated capillary permeability to be a characteristic peculiarity of persons who live at high altitudes. It is curious that special investigations conducted on animals brought from Frunze to an altitude of 1800 m revealed an elevated pulmonary-capillary permeability (as evaluated from the state of the argyrophilic matter) and increased engorgement of these capillaries with blood after 6-18 months.

Study of the functioning of the cardiovascular system in persons living at moderate and high altitudes thus revealed relative bradycardia, arterial (primarily systolic) hypotonia, a rise in venous pressure, an increase in capillary permeability, a decrease in lumen size, a drop in the number of nailbed capillaries, a normal or slightly elevated minute volume, and a normal circulatory reaction to measured stress. Considering that these characteristics are observed in a comparatively large number of healthy individuals and have been confirmed by the investigations of other authors, we are correct in holding them to be regular for residents of the mountain country of Kirgiz and regarding them as normal for the conditions in question.

The regularities described above enable us to state that the human organism "develops" the "norms" most suitable to specific conditions during adaptation to high altitudes. This hypothesis is in accord with the opinion of many authors occupied with mountain physiology (O.N. Pavlova, Dekhtyar, and others). In essence, if the functional activity of the organism were always maintained at a high level, as is the case at the beginning of stays under high-mountain conditions, or corresponded to the "norms" for persons living at sea level, we could hardly expect the performance of relatively heavy physical labor to be possible for many years under mountain conditions.

As our investigations have shown, in residents of the Kirgiz mountain country the functioning of the cardiovascular system is at a lower level under resting conditions and naturally does not require the energy consumption which occurs at sea level. It seems to us that this is a suitable functional state for the cardiovascular system, since the organism has available great reserves which can be mobilized when necessary. Some increase in capillary permeability is obviously also useful under these conditions, as it can improve the exchange of substances

between the blood and the tissues. However, such an increase in capillary permeability may apparently have undesirable consequences in pathological conditions. The comparatively high permeability of the pulmonary capillaries evidently explains the fact that pneumonia takes a more severe course under high-mountains, as was observed by N.T. Tsishnatti, P.P. Shilov, and others.

Investigations of basal metabolism by Holden's gas-analysis method, which we conducted jointly with A.D. Dzhaylcbayev, also yielded curious results. Studying gaseous interchange in 127 residents of Rybach'ye (1650 m) and 120 residents of Naryn, we established that there was a marked decrease in basal metabolism in more than half the subjects. Our data are in complete accord with the results which A.D. Slonim, G.P. Conradi, L.G. Filatova obtained in investigations of residents of the mountain country of Kirgiz.

It would seem that the uniformity of the results obtained by many authors enables us to draw the indisputable conclusion that residents of moderately high areas of Kirgiz exhibit a low gaseous-interchange level. What is the mechanism underlying this depression of gaseous interchange? An intensification or depression of metabolism is customarily associated with the functional state of the thyroid gland. We assume that thyroid functioning was somewhat reduced in residents of the moderately high mountain country of Kirgiz. The special investigations of S. Turmanbetov, which were devoted to a morphological characterization of the thyroid glands of sheep in regions of endemic goiter in northern Kirgiz, also speak in favor of this hypothesis. Histological examination of the thyroid glands of these animals showed them to be hypofunctional. The rather low functional activity of the circulatory apparatus observed among residents of the mountains of Kirgiz would seem to be partially attributable to a moderate thyroid hypofunctioning.

However, this hypothesis requires further verification by special investigation, research which we have planned for the near future. The usefulness of thyroid hypofunctioning under high-altitude conditions is also indicated by the investigations of N.N. Sirotinin, M.Ye. Vasilenko, Ye.F. Kolomiyets, Granshan, et al.

The results of a study of autonomic functioning with the aid of spatial reflexes and the ocular-cardiac, Chermak and adrenaline-histamine tests are also in agreement with this hypothesis. Our investigations also revealed a vagotonicity of autonomic functioning in the overwhelming majority of mountain residents.

The peripheral blood was investigated in 100 residents of Frunze, 128 residents of Rybach'ye, and 235 residents of Naryn. Statistical processing and comparison of the results of these investigations showed that the erythrocyte count is approximately the same in all three groups, although it was somewhat elevated (to an extent not statistically reliable) in the mountain residents. The hemoglobin content of the blood proved to be somewhat higher in the residents of Rybach'ye and Naryn (to a statistically reliable extent).

Our data thus indicate that a stay in the moderately high mountain, of Kirgiz is accompanied by an increase in hemoglobin content and maintenance of a normal erythrocyte count. In this respect our data are not in complete agreement with the results obtained by A.D. Slonim, G.P. Konradi, and L.G. Filatova, who concluded that the hemoglobin content of the blood does not increase at moderate altitudes in Kirgiz.

Finally, we were interested in the acid-alkali equilibrium. According to G.V. Derviz, the content of insufficiently oxidized products in the blood should increase in the presence of oxygen deficiency. In order to detect symptoms of oxygen deficiency we investigated the reserve alkalinity, free oxygen, glutathione, and carbonic anhydrase of the ven-

ous blood in more than 250 residents of Frunze, Rybach'ye, and Naryn. These investigations did not reveal any acidotic change.

Thus, a prolonged stay under the high-mountain conditions of Kirgiz (Tyan'-Shan') is accompanied by reorganization of individual functions of the organism, especially the cardiovascular system; this results in more rational and economic oxygen utilization. This type of reaction includes depression of gaseous interchange, an increase in hemoglobin content with a normal erythrocyte count, retardation of pulse rate, a moderate drop in arterial pressure, a decrease in blood-flow rate, an increase in venous pressure, a rise in capillary permeability, intensified filling of the lungs with blood, parasympathetic innervation of autonomic functions, etc. The basic hemodynamic index - minute cardiac volume - remains normal under these conditions, as does the mean arterial pressure.

Comparing the results of our observations, we may state that the human organism does not react in the same manner to brief and prolonged stays under high-altitude conditions and that adaptation consequently involves different mechanisms in these few cases.

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The temperature in the mountainous regions of Kirgiz is higher than that at corresponding altitudes in the Caucasus or the Alps.

CHANGES IN THE NERVOUS SYSTEM AT AN ALTITUDE OF 2000 m

L.M. Telcharov, N. Nikolev, and St. Chernayev

(Plovdiv, Bulgarian People's Republic)

Research on the functioning of the nervous system at mountain altitudes was already being conducted in the last century (Conway, 1894; Mosso, 1899). These investigations were continued in greater detail on scientific expeditions in the Alps (Stern, 1926; Abdergalden, London, et al., 1927; Levy, 1932) and the Himalayas (Finch, 1925; Kingston and Barcroft, 1927; Kant, 1954). In these instances primary attention was devoted to the functioning of the autonomic nervous system. Investigations to study higher nervous activity at the altitudes reached in the Caucasus (approximately 5000 m) were first undertaken in the thirties, by N.N. Sirotinin and his colleagues (Yu.N. Popov, 1931; A. Z. Kolchinskaya, 1949, 1952; V.V. Turanov, 1952). Of considerable interest are the investigations of higher nervous activity conducted in a study of mountain sickness made in the Alps and Balkans in 1937.

While at mountain altitudes above 4000 m the drop in atmospheric pressure is the principal factor governing physiological changes, it also plays some part at altitudes of up to 3000 m, especially in persons making their first ascent. The role of the central nervous system in the vascular disturbances which occur at high altitudes is well known (Mateyev, 1949). In certain persons, particularly those who have long lived at these altitudes, pathological functional disturbances frequently develop as conditioned reflexes, possibly as a result of the unpleasant sensations associated with certain atmospheric and topograph-

ic conditions.

At the end of the winter of 1961 we organized an expedition to the Karsto region of the Pirin Mountains in order to investigate the state of the central nervous system, especially higher nervous activity and its relationship to the autonomic nervous system. The subjects (students) remained at an altitude of 2000 m (in the mountain hut "Yavorov"), where they were daily exposed to the severe mountain climate (snow and wind) during not particularly fatiguing climbs.

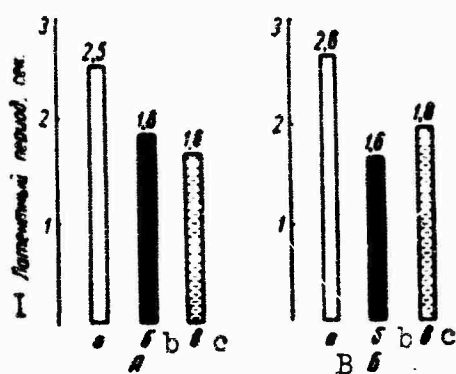


Fig. 1. Diagram A. Change in duration of latent period during investigation of higher nervous activity in an associative experiment (in seconds). a) Mean latent period of responses of all subjects before ascent; b) the same, during stay in mountain hut; c) the same, after return to Plovdiv. Diagram B. Subject K.S., 34 years of age. a) Mean latent period of subject's responses before ascent; b) during stay in hut; c) on return to Plovdiv. I) Latent period, sec.

METHOD

Higher nervous activity was investigated in an associative experiment in 27 subjects (19 males and 8 females 19-35 years of age). In this experiment the subject was given 20 words to which he had to respond. In the second and third investigations five or ten new words were added as a control. The autonomic nervous system was investigated from the indices of dermal neurovascular reactivity, by mediophoresis with adrenaline and acetylcholine. The results of the first investigations, which were conducted in Plovdiv, were used as the initial data. The indices of respiration (vital pulmonary capacity, limits of respiration as determined with a Hermanssen spirometer, and respiratory impulse) characterized the respiratory function of the lungs. Examinations were made before and after the expedition. Higher nervous activity, dermal neurovascular reactivity, and vital pulmonary capacity were studied during the stay at the mountain hut "Yavorov."

EXPERIMENTAL RESULTS AND DISCUSSION

Higher nervous activity. The associative experiment showed that the latent period (LP) of the response to the listed words varied from

1.8 to 3.4 sec in certain individuals before the expedition; the mean LP or all the investigations was 2.5 sec. During the stay in the hut the LP varied from 1.35 to 3.36 sec in certain subjects, the mean being 1.8 sec. On returning to Plovdiv the LP ranged from 1.16 to 1.71 sec, with a mean of 1.6 sec (diagram A, Fig.1).

Scrutinization of the individual results shows that, despite the fact that the mean LP was shorter in all the subjects after returning to Plovdiv than at the hut "Yavorov," in certain persons (9) the LP was somewhat prolonged after their return. We can use the figures in diagram B (Fig. 1) as an example. In another group (15 individuals) the LP was reduced (diagram C, Fig. 2) and in a third group (3 persons) it remained unchanged. No qualitative changes were detected in the character of the responses.

Dermal neurovascular reactivity. Diagram D (Fig. 2) shows the results of an investigation of adrenergic dermovascular reactivity (AddVR). Before the expedition 14 of the subjects reacted to adrenaline in a dilution of $1 \cdot 10^{-7}$, 6 reacted to a dilution of $1 \cdot 10^{-9}$, and 6 reacted to a dilution of $1 \cdot 10^{-11}$. The mean adrenaline dilution to which the subjects reacted was $1 \cdot 10^{-8.4}$ (unshaded bar). During their stay in the hut the subjects reacted to adrenaline: 5 persons reacted to a dilution of $1 \cdot 10^{-7}$, 4 to a dilution of $1 \cdot 10^{-9}$, 9 to a dilution of $1 \cdot 10^{-11}$, and 8 to a dilution of $1 \cdot 10^{-13}$. The solid column represents the mean value for all the reactions ($1 \cdot 10^{-10.5}$). After returning to Plovdiv 13 persons reacted to an adrenal dilution of $1 \cdot 10^{-7}$, 6 to a dilution of $1 \cdot 10^{-9}$, 4 to a dilution of $1 \cdot 10^{-11}$, 1 to a dilution of $1 \cdot 10^{-13}$, and two to a dilution of $1 \cdot 10^{-1.5}$. The mean for all the reactions was $1 \cdot 10^{8.9}$ (shaded bar).

Examination of the data obtained shows that there were no changes whatsoever in AddVR in 5 persons, while in 8 reactivity increased mark-

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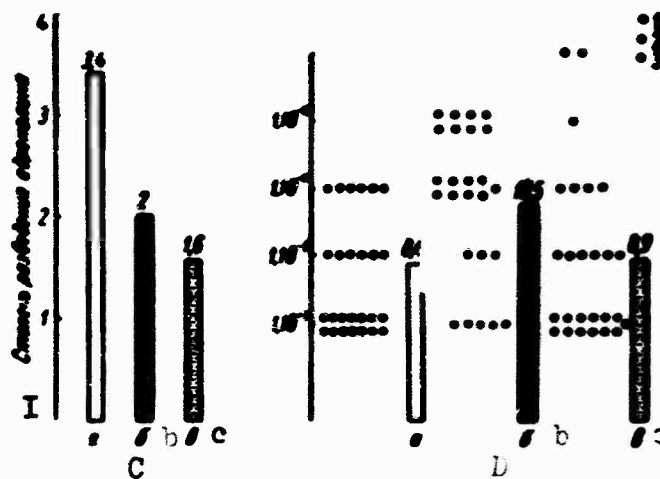


Fig. 2. Diagram C. Subject S.N.D., 20 years of age. The key is the same as in Fig. 1. Diagram D. Dermovascular reactivity to adrenaline. 1) Values for different persons investigated before ascent to hut; 2) during stay in hut; 3) on returning to Plovdiv; a) Mean intensity of reaction adrenaline before ascent; b) during stay in hut; c) after returning to Plovdiv; I) adrenaline dilution.

edly only while they were at the hut "Yavorov," then reverting to its initial value; in 5 individuals reactivity increased at the hut and dropped below its initial value on returning to Plovdiv. In one case it was established that reactivity increased after returning to the city, while in 3 persons reactivity was elevated at the hut and remained unchanged after returning to Plovdiv. Only two persons exhibited a decrease in reactivity at the hut, which was followed by a reversion to the initial value on returning to the city.

Dermovascular reactivity to acetylcholine (AcDVR). The results of our investigations are shown in diagram E (Fig. 3).

Before the ascent 14 persons reacted to an acetylcholine dilution of 1^{-2} and 12 reacted to a dilution of 1^{-3} . The mean for all the subjects, $1^{-2.4}$, is represented by the unshaded bar. We obtained the following results at the hut: 3 persons reacted to a dilution of 1^{-2} , 10 to a dilution of 1^{-3} , 8 to a dilution of 1^{-4} , and 6 to a dilution of 1^{-5} . The mean value, $1^{-3.3}$, is represented by the solid bar. After returning to the city we obtained the following data: 10 persons reacted

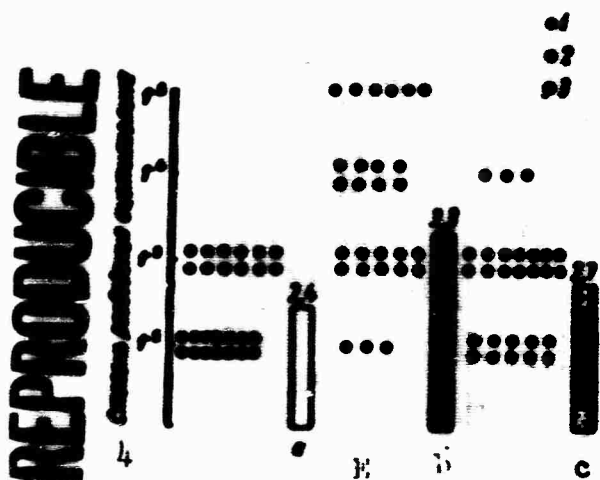


Fig. 3. Diagram E. Dermo-vascular reactivity to acetylcholine. Key the same as in Fig. 2, (diagram D), but for acetylcholine. 4) acetylcholine dilution.

increase persisted after returning to the city. In 2 persons the reaction was intensified in the mountains and reverted to its initial level on returning to the city. In one individual the reaction first increased after returning to the city and in another it was of the same intensity in the mountains as in the city, but dropped below its initial level on returning.

A general review of the data on mediophoretic reactions showed that the majority of the subjects (16 of a total of 27) responded with a simultaneous increase in reactivity to acetylcholine and adrenaline; there were no changes at all in three subjects and the remainder exhibited either an increase in one reaction and a decrease in the other or an increase in one and no change in the other.

Indices of respiration. The limits of respiration remained unchanged in 4 persons, decreased in 10, and increased in 10. Vital pulmonary capacity remained unchanged in 7 individuals, decreased in 5, and increased in 7. Respiratory impulse remained unchanged in 9 subjects, dropped in 7, and rose in 8.

Our investigations showed that a stay in the mountains at an alti-

to a dilution of 1^{-2} , 14 to a dilution of 1^{-3} , and 3 to a dilution of 1^{-4} . The mean value, $1^{-2.7}$, is represented by the shaded bar. Individual examination yielded the following results: there were no changes whatsoever in AcDVR in 6 persons, while in 8 individuals the reaction was intensified at the mountain hut and then reverted to its initial value. In 8 persons the reaction was intensified at the mountain hut and the

tude of 2000 m leads to functional reorganization of the organism. Cortical excitation develops, radiating to the autonomic centers and producing an increase in dermal neurovascular reactivity

We cannot state that these changes were detected only in persons coming to the mountains for the first time. They were also observed in tourists and mountain climbers. Conversely, some persons coming to the mountains for the first time failed to exhibit these changes. The facts cited confirm the conditioned-reflex character of the changes in persons of the first group and the role of a constitutional factor (e.g., the type of higher nervous activity) in persons of the second group.

It was also established that pulmonary functioning is very little affected at mountain altitudes. It is probable that there is every possibility of regulation (compensation and adaptation), which requires normal or intensified nervous functioning, at this altitude (2000 m). However, a prolonged intensification of nervous functioning may lead to depression and marked disruptions of regulation. Excitation of the nervous system during ascents of high mountains must consequently be considered a "reminder" of previous pathological functional disturbances.

VALUE OF OXYHEMOMETRIC DETERMINATION OF BLOOD-FLOW RATE
AND OXIDATION LEVEL IN APPRAISING ACCLIMATIZATION TO HIGH-
MOUNTAIN CONDITIONS:

A.M. Tyurin
(Leningrad)

The skiing competitions of the last Olympic Games were held at altitudes of 1500-2000 m above sea level.

Holding athletic competitions under mountain conditions imposes increased demands on the athlete's body and makes a definite impression on his training. In this connection the problem of acclimatization to mountain conditions acquires considerable importance and must be taken into account in training skiers for competition. This is made even more important by the fact that the topography of modern ski courses is complicated by exceptionally broken terrain. Ascents made under mountain conditions lead to the development of hypoxemia of an extent not ordinarily seen in races held at low altitudes. Consequently, in addition to ordinary acclimatization, the athletes must prepare themselves to perform intensive work under hypoxemic conditions during a comparatively brief stay in the mountains. All this requires thorough and careful medical study of athletes during training and competition.

In 1959-1960, as members of a group of physicians, biochemists, and physiologists, we examined members of the Soviet National Ski Team during their training for the VIII Winter Olympiad, which was carried out at Bakuiani (1700-2000 m above sea level) and Zlatoust. In evaluating acclimatization, in addition to wide employment of doctors' observa-

tions of pulse rate and arterial pressure and functional tests under stress, we used the oxyhemometric method to investigate the intensity of oxidative processes and one of the basic hemodynamic factors, blood-flow rate, both under basal-metabolism conditions and during the recovery period after training and competition.

The intensity of oxidative processes gives a relative characterization of basal metabolism (A.G. Dembo, 1959; S.B. Tikhvinskiy, 1960; A.A. Penkovich, 1960)] The majority of authors detected a rise in basal metabolism in healthy persons under high-altitude conditions (Byurzhi, 1900; Zhake and Shtekhelin, 1901; Tsunts et al., 1906; Levy, 1925; Willbrandt, 1938; N.N. Sircinin, 1939; G.Ye. Vladimirov et al., 1941; L.L. Shik, 1947 N.I. Tavastsherna, 1954; et al.). At the same time, the dynamics of the change in basal metabolism during the acclimatization period have not been sufficiently well studied.

The results of investigation of blood-flow rate under high-mountain conditions in healthy persons who are not athletes are contradictory; blood-flow rate has not been studied at all for athletes. This apparently results from the complexity of the method used to determine it, (Monkhe et al., 1955; M.M. Mirrakhimov, 1955, 1957; V.A. Breydo, 1957; et al.).

Blood-flow rate was determined by a previously described method, using a O-38 oxyhemometer and a portable PPO-1 oxyhemometer (A.M. Tyurin, 1960; A.G. Dembo and A.M. Tyurin, 1961). The intensity of the oxidative processes, which gives a relative characterization of basal metabolism, was determined from the duration of the AB phase of the exhalation breath-holding curve by a method developed in the laboratories of the Leningrad Scientific Research Institute for Physical Culture by A. A. Penkovich (1956-1960). The AB phase was recorded with a timer before the blood-flow rate was determined during the same exhalation breath-holding after a normal inhalation. The timer was started at the end of a deep exhalation and stopped when the oxygen saturation of the arter-

ial blood had dropped by 1%. The blood-flow rate was recorded with a second timer during the same breath-holding. All the investigations were conducted twice and the arithmetic mean of the two determinations was calculated; the permissible error between the determinations was not permitted to exceed ± 1 sec.

Determination of the blood-flow rate and intensity of oxidation was part of the general medical examination conducted immediately on arrival in the mountains and every four days during the month for which the athletes remained there (N.N. Yakovlev, B.A. Ashmarin, L.G. Leshkevich, A.M. Tyurin, and N.G. Fedorova, 1959).

A total of 65 athletes - Masters of Skiing - were examined, 49 being male and 16 female (34 at Bakuriani in January 1959, 41 at Zlataoust in November 1959, and 45 in Bakuriani in January 1960).

During their first two days in the mountains the athletes complained of malaise, poor sleep, and headaches. This was accompanied by a deterioration of reactions to a functional cardiovascular test (intensification of the pulse reaction to stress, appearance of cases of "zero," or minimal pressure, prolongation of recovery time, especially after running in place for three minutes, etc.) and an increase in the hemoglobin content of the blood. At the same time, the resting pulse rate and arterial pressure remained unchanged, as they did throughout the entire subsequent acclimatization period. During these first two days there was a clear increase in the intensity of oxidation and an acceleration of blood flow in the "lung-ear" segment of the vascular bed.

During the first three-eight days of acclimatization the athletes' training took the form of walks involving ascents to altitudes of 2500-2700 m. From the eighth-tenth day onward the speed and distance covered were gradually increased, the maximum distance covered rising from 0.5-1 to 8-10-15 km.

This increase in training stress from the eighth-tenth day of acclimatization onward is explained by the fact that the functional state

TABLE 1

Change in the Functional State of Skiers during Acclimatization to Mountain Conditions (Bakuriani, 1959)

1	2	3	4	5	6	7
Длительность пребывания в горах (в днях)	Частота пульса (в мин.)	Артериальное давление (в мм рт. ст.)	Содержание гемоглобина в крови (в %)	Фаза АТ (в сек.)	Скорость кровотока (в сек.)	Количество случаев задержанного восстановления работоспособности после тренировки (в %)
1-4	51	103/82	13,2	10,8	5,34	80
5-8	51	100/80	12,5	12,2	6,02	20
9-12	51	102/80	12,3	12,5	6,33	12
13-16	51	104/63	12,5	12,3	6,70	4
17-20	50	102/80	12,3	13,9	7,21	4
8 21 и больше	49	102/80	12,1	13,8	7,20	0

1) Length of stay in mountains (in days); 2) pulse rate (per min); 3) arterial pressure (mm Hg); 4) hemoglobin content of blood (g-%); 5) AB phase (sec); 6) blood-flow rate (sec); 7) number of cases of retarded restoration of working capacity after training (%); 8) 21 or more.

of the organism at this time approximated that observed at low altitude before coming to the mountains, the changes in the males and females being essentially the same. More precisely, the reaction to the functional cardiovascular test and the hemoglobin content of the blood were the same as at sea level. There was also a slight decrease in the intensity of oxidation, a drop in blood-flow rate, and a decrease in the number of cases of retarded recovery after training sessions in comparison with the first few days in the mountains (Table 1).

Analysis of the results of determination of blood-flow rate by the diffusion method enabled us to conclude that there were material differences in the athletes' blood-flow rates in accordance with the length of their stay in the mountains and that these differences could not be attributed to fortuitous factors. The diffusion ratios obtained in our analysis (3, 89) exceeded those listed in the standard tables (3, 21), for a probability of 0.99 with degrees of diffusion freedom of 5 (intergroup) and 103 (intragroup). Similar changes depending on time spent in the mountains were observed in analyzing the data on the in-

tensity of oxidation.

The oxyhemometric data on oxidation intensity and blood-flow rate were thus normalized after 15-17 days of acclimatization. Consequently, despite the fact that the pulse rate, arterial pressure and its reaction in the functional stress test, and the hemoglobin content of the blood were the same as at sea level on the eighth-tenth day of acclimatization, normalization of the oxyhemometric data began only after an average of 15-17 days in the mountains. All this indicates the importance of the indices which we studied for conclusive evaluation of acclimatization to high-mountain conditions and that a 15-17 day acclimatization period is not standard for all skiers. According to all our data, acclimatization begins after an average of eight days in the mountains for certain highly conditioned athletes. These acclimatization times for athletes training at 2000 m above sea level agree with those established in the investigations of other authors (A.D. Bernshteyn et al., 1957, et al.).

Despite the restoration of pulse rate and arterial pressure, direct investigation of the influence of competition on the changes in blood-flow rate and the AB phase made it possible to conclude that working capacity is not fully restored on the day after competition and that the training regime must be altered correspondingly. For example, on the morning before competition at 30 km athlete K-ov's pulse rate was 51, his arterial pressure was 115/75 mm Hg, his "lung-ear" blood-flow rate was 7.6 sec, and his AB phase lasted 12.7 sec; on the morning of the day after competition his pulse rate and arterial pressure had been restored, but there was an acceleration of blood flow (6.2 sec) and an intensification of oxidation (10.2 sec). The AB phase and blood-flow rate were restored only on the second day (13.2 and 7.5 sec).

The previously discovered fact (A.G. Dembo and A.M. Tyurin, 1961)

that blood flow is retarded in athletes as their conditioning improves has been completely confirmed under high-mountain conditions. In many highly skilled skiers - Honored Masters of Sport and Masters of Sport - blood-flow rate is retarded to 8.3-10.1 sec from the normal 5.5 sec during training acclimatization.

We are faced with the problem of whether or not to attribute the retardation of blood-flow rate which occurs under high-altitude conditions to the influence of the mountain climate on the cardiovascular system. This question is well taken, since M.M. Mirrakhimov (1955, 1957), Monkhe et al. (1955), and other authors found a retardation of blood flow to occur in mountain residents who did not participate in sports.

Our further investigations of the same athletes showed that in the majority of cases oxyhemometric indices during acclimatization were better during the principal training period of 1960 than during the preceding year or at the beginning of the principal training period in Zlatoust (Table 2).

The investigations which we conducted enable us to recommend the bloodless oxyhemometric method of determining blood-flow rate and oxidation intensity for establishing more precisely the periods required for athletes to become acclimated to mountain conditions. These investigations showed, firstly, that 15-17 days of active acclimatization are quite sufficient for all skiers and, secondly, that the blood-flow rate and oxidation intensity for athletes under mountain conditions do not differ materially after acclimatization from those for the same period of training at sea level. Observations of the recovery period after training and competition expand our concepts of the functional state of the organism and enable us to alter the training regime.

There is no doubt that bloodless, simple, convenient oxyhemometric

TABLE 2

Mean Blood-flow Rate and Oxidation-rate Indices
(AB phase of Breath-holding) in Skiers on the
1959-1960 Teams

1 Вид спорта	2 Показатели	3 с. Бакурiani, январь 1959 г.			5 г. Златоуст, ноябрь 1959 г.	7 с. Бакурiani, январь 1960 г.			
		4 Дни пребывания в горах				6	Дни пребывания в горах		
		9-12	13-16	17 и больше			9-12	13-16	17 и больше
8 Лыжные гонки	Фазы АБ ¹²	12,0	11,8	12,7	12,8	12,3	12,9	14,4	
9 (мужчины)	Скорость кровотока ¹³	6,8	6,5	7,0	7,4	7,4	7,2	8,0	
10 Лыжные гонки	Фазы АБ	14,0	13,6	13,7	12,5	11,7	13,8	13,8	
10 (женщины)	Скорость кровотока	5,7	5,9	6,3	5,5	6,1	6,1	6,3	
11 Классическое лыжное двоеборье	Фазы АБ	—	—	—	10,7	—	11,6	—	
	Скорость кровотока	—	—	—	6,5	—	7,4	—	

1) Type of sport; 2) index; 3) Bakuriani, January 1959; 4) length of stay in mountains, days; 5) 17 or more; 6) Zlatoust, November 1959; 7) Bakuriani, January 1960; 8) ski races; 9) males; 10) females; 11) classic two-part competition; 12) AB phase; 13) blood-flow rate.

investigations of oxidation intensity and as important a hemodynamic index as blood-flow rate should come to be as widely used as arterial-pressure measurement.

INFLUENCE OF HIGH-MOUNTAIN FACTORS ON THE REFLEX RELATIONSHIPS
BETWEEN RENAL AND SALIVARY ACTIVITY

B.Ye. Esipenko

(Kiev)

Despite the large number of investigations which have been devoted to studying the activity of organs and systems of the organism under high-mountain conditions, sufficient work has not been done on the problem of the influence of high-altitude factors on its regulatory systems. The works of Barcroft (1921, 1922), Kingston (1925), N.N. Sirotnin (1928, 1929, 1931, 1935, 1939), Yu.N. Popov (1930), V.A. Samtsov (1933), A.Z. Kolchinskiy (1952), and others indicate that there are substantial changes in the functioning of the central nervous system, especially psychic activity, when ascents are made to high altitudes. However, the literature available to us describes no investigations intended to study the central nervous system as the regulator of the activity of all the organs and systems of the organism under high-altitude conditions. The work which bears directly on this problem has been conducted under laboratory conditions, in acute experiments (E.Sh. Ayrapetyants and V.N. Zvorykin, 1952; T.V. Popova, 1952) or in experiments involving the breathing of a gas mixture with a reduced oxygen content (M.D. Chirkin, 1958).

In addition, study of the regulation of the functions of the organism and of the interrelated and interdependent activity of its organs and systems when it remains at high altitudes is of undoubted theoretical and practical interest.

We studied the reflex relationships of various organs (the kidneys and salivary glands) under mountain-climate conditions under different altitudes. This work was conducted during 1960 and 1961 at the mountain stations of the Institute of Physiology imeni A.A. Bogomol'ts of the Academy of Sciences UkSSR, which are located in the vicinity of Mount El'brus at altitudes of 2000 and 3200 m. We observed the diuretic function of the kidneys and the alimentary secretion of the salivary glands at different renal-activity levels in dogs with chronic fistulae of the parotid glands and stomach and ureters brought out to the skin. In order to intensify the diuretic function of the kidneys 500 ml of water at 36-38° C was infused through the gastric fistula. The urine was collected every 15 minutes and the saliva for two minutes every 15 minutes.

EXPERIMENTAL RESULTS

The experiments conducted in Kiev showed clear reflex relationships between renal and salivary activity in all four experimental dogs. The relationships between these organs in dogs, which we described previously (1954, 1956), take the form of a depression of alimentary salivary secretion during intensified renal activity. The results of the individual control experiments are shown in the table and in Fig. 1.

The data presented in the table indicate that the alimentary secretion of the parotid glands is reduced during intensified diuresis. Diuresis increases sharply 15-30 minutes after introduction of 500 ml of water into the stomach and remains at a high level for one hour (from 15 to 100 ml in the 15-minute samples). The saliva samples collected during this period are smaller and have a lower solid-residue content than samples collected against a background of depressed diuresis.

A different type of relationship between diuresis and saliva secretion was observed under high-mountain conditions. At an altitude of

Relationship of Renal and Salivary Activity Under aqueous Stress

Percentage	Время в минутах 2										
	15	30	45	60	75	90	105	120	135	150	165

3. Собака Норка, опыт от 27.VI 1960 г.

a	2,3	1,7	1,8	1,7	1,5	1,4	1,2	0,8	0,9	1,1	1,5
b	25,9	21,7	22,1	19,7	19,2	17,9	14,4	9,4	12,5	13,4	18,6
c	4,3	4,5	4,4	3,4	9,6	60,0	66,5	72,1	41,4	10,6	5,0
d	22	234	265	225	349	488	299	411	497	250	222

4. Собака Астра, опыт от 22.VI 1960 г.

a	1,7	1,7	1,5	1,5	1,3	1,1	0,9	1,1	1,3	1,3	1,5
b	15,1	15,1	15,9	14,5	19,9	9,8	10,6	10,0	10,4	11,2	13,6
c	2,3	3,0	2,5	3,6	7,0	42,4	70,2	53,0	18,5	5,3	5,2
d	231	299	255	331	490	305	442	641	438	240	400

5. Собака Пантера, опыт от 17.VI 1960 г.

a	1,15	1,2	1,2	1,2	1,2	1,1	1,0	0,9	1,1	1,1	1,25
b	12,2	12,1	9,8	11,8	10,7	11,0	9,1	9,0	10,7	9,1	11,5
c	8,8	8,0	7,0	11,0	4,5	25,0	44,7	65,5	47,9	30,5	21,3
d	215	191	161	273	123	300	264	314	369	305	366

6. Собака Пальма, опыт от 17.VI 1960 г.

a	1,6	1,5	1,3	1,7	1,4	1,4	1,2	1,3	1,35	1,6	1,6
b	16,0	15,9	13,8	19,9	14,7	14,6	12,6	14,0	14,0	16,6	16,8
c	14,0	11,0	5,5	4,0	13,0	47,0	75,0	61,0	50,0	19,0	7,0

Note: a) Quantity of saliva (in ml); b) solid residue of saliva (in mg); c) quantity of urine (in ml); d) solid residue of urine (in mg).

1) Index; 2) time in minutes; 3) dog Norka, experiment of 27 June 1960; 4) dog Astra, experiment of 22 June 1960; 5) dog Pantera, experiment of 17 June 1960; 6) dog Pal'ma, experiment of 17 June 1960.

2000 m (Terskol) the relationships between renal and salivary activity were unstable in character. During the first one or two days the experimental dogs exhibited renal-salivary relationships similar to those observed in the experiments in Kiev, i.e., there was a substantial depression of the alimentary secretion of the salivary glands during intensified renal activity (Fig. 1). Specifically, during this period the saliva-secretion level in the presence of intensive diuresis was 86% of that recorded during reduced diuresis in Pal'ma and 66% in Pantera. We

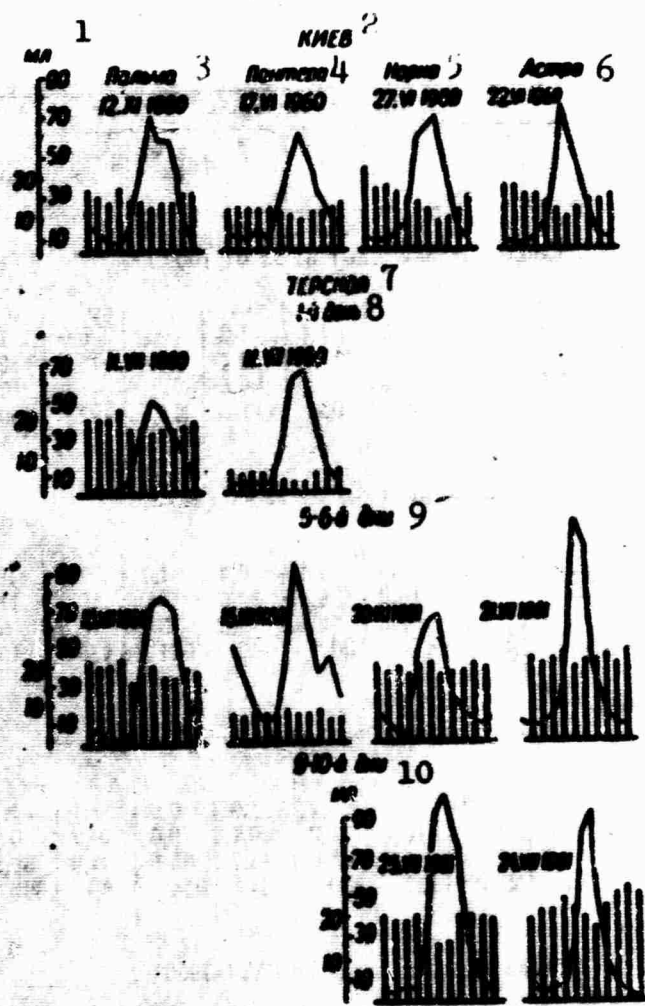


Fig. 1. Diuresis and saliva secretion in experiments involving aqueous stress in Kiev and on different days at an altitude of 2000 m. 1) ml; 2) Kiev; 3) Pal'ma; 4) Pantera; 5) Norka; 6) Astra; 7) Terskol; 8) 1st day; 9) 5th-6th day; 10) 9th-10th day.

subsequently observed no relationship between renal and salivary activity. Between the fourth and eighth days at 2000 m the saliva secretion level during intensive diuresis was the same as that observed before application of the aqueous stress, i.e., during comparatively low diuresis.

The relationships between renal and salivary activity were later (after 9-12 days) restored. In experiments conducted on the ninth day at 2000 m saliva secretion during intensive diuresis was 94% of its initial level, on the tenth day it was 91%, and on the eleventh day it was 85%, as against 88% under the conditions of Kiev.

After the experiments at 2000 m we conducted a series of experiments at 3200 m (Priyut 105). At this altitude the experimental dogs

exhibited essentially uniform salivary and renal activity, with no marked relationships between them, from the first to the last (12th) days. In a number of experiments the saliva secretion level during water-induced diuresis was only slightly (3-6%) less than that during ordinary diuresis, while in the remaining experiments it was the same (Fig. 2).

The data obtained in our experiments indicate that the character of the relationships between renal and salivary activity after application of aqueous stress under high-mountain conditions differs from that observed under lowland conditions, pointing to disruption and disappearance of these relationships. In contrast to the experiments at Terskol, at 3200 m we observed no restoration of the relationships between renal and salivary activity.

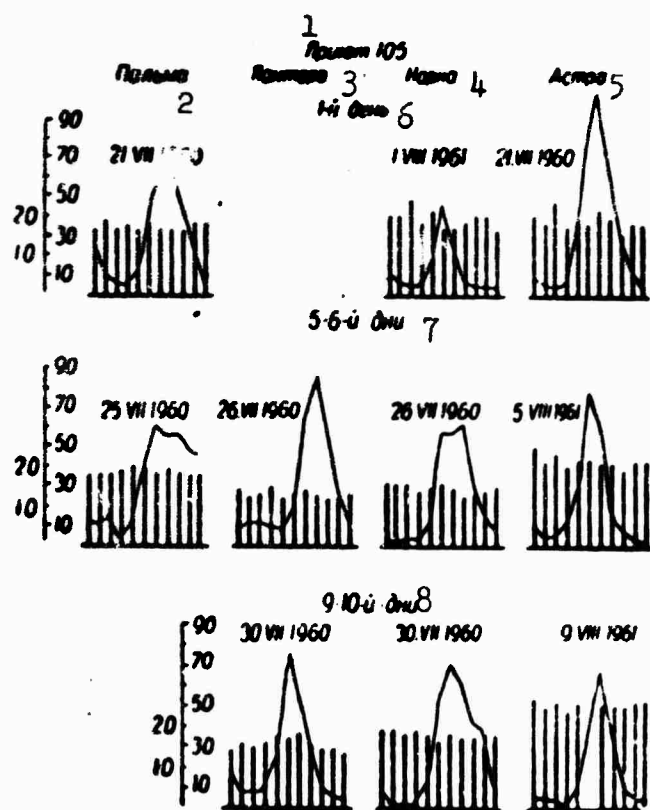


Fig. 2. Diuresis and saliva production in experiments involving aqueous stress on different days at 3200 m. 1) Priyut 105; 2) Pal'ma; 3) Pantera; 4) Norka; 5) Astra; 6) 1st day; 7) 5th-6th day; 8) 9th-10th day.

The results of these experiments enable us to assume that the relationships between the activities of these organs of the secretory and

digestive systems are disrupted as a result of the action of oxygen deficiency on the organism, primarily on the central nervous system. The correctness of this view is indicated by the works of E.Sh. Ayrapetyants and V.N. Zvorykin (1952), T.V. Popova (1952), and M.D. Chirkin (1958), in which it is demonstrated that the reflex relationships between the gastrointestinal tract on the one hand and blood pressure, cardiac activity, and respiration on the other are disrupted in the presence of oxygen deficiency caused by breathing a gas mixture with a low partial oxygen pressure or by administration of KCN. In addition, a substantial basis for this view is furnished by the data in the literature (Ye.M. Kreps and V.I. Voytkovich, 1955) on the decrease in the oxygen content of the blood which occurs on the second day at 2000 m and the restoration of the original indices which occurs on the seventh-eighth day. As was shown above, the dynamics of the relationships between renal and salivary activity at 2000 m coincide with the changes in the oxygen content of the blood at this altitude.

In the ascent to 3200 m and the subsequent 12-day stay at this altitude we did not detect the relationships between the change in renal activity after aqueous stress and the alimentary secretion of the salivary glands usual under lowland conditions. The data in the literature indicate that the organism requires a longer time to adapt to hypoxia at high altitudes.

All this gives us reason to assume that the reflex relationships between the kidneys and salivary glands are disrupted at high altitudes as a result of the action of oxygen deficiency on the central nervous system, particularly as a result of a change in the interaction of the nerve centers which regulate these relationships under the influence of hypoxia. On the basis of the data presented above we may draw the following conclusions:

1. The reflex relationships between the activities of various organs (the kidneys and salivary glands) are disrupted under high-mountain conditions.

2. The reflex relationship between the functions of these organs is restored when the organism adapts to the oxygen deficiency.

THE UROPOIETIC FUNCTION OF THE KIDNEYS UNDER THE CONDITIONS
OF THE HIGH MOUNTAINS

B. Ye. Yesipenko and A.P. Kostromina

(Kiev)

Although a considerable number of studies have been devoted to investigation of various functions of the organism under high-mountain conditions, the literature contains almost no information concerning the physiology of the kidneys under these conditions. This is difficult to explain when we consider the high importance, from both the theoretical and practical standpoints, of the influence exerted on the organism by the subnormal atmospheric pressure and other factors operating in the high mountains. Further, the essential role of the kidneys in maintaining homeostasis within the organism and the fact that the organism's internal medium is considerably influenced by high-mountain factors, confer particular importance upon this question. However, except for indirect observations made in the studies of P.M. Al'bitskiy (1884), Ye.A. Kartashevskiy (1906) and N.N. Sirotin'in, we have no data on kidney function under high-mountain conditions. A number of investigations by both foreign and [Soviet] authors, among which the monumental work of A. G. Kuznetsov (1955) is worthy of note, have been devoted to study of the influence exerted upon kidney function by such an important mountain factor as oxygen insufficiency. However, the conditions of the experiments (acute experiments, experiments with inspiration of gas mixtures with low oxygen content, hypobaric-chamber experiments, etc.) cannot be identified with the conditions obtaining in the high mountains,

simply in view of the short time spent by the animals at subnormal oxygen contents.

In the light of the above, it is our view that the data that we obtained in a study of the uropoietic function of the kidneys in dogs at various altitudes on the El'brus should offer a certain amount of interest.

METHOD

The work was done on dogs with the ureters diverted to the skin of the abdomen (after Pavlov-Tsitovich) and with gastric fistulas. The experiments were conducted in the morning hours (from 9-10 o'clock), before the dogs were fed.

The amount of urine was registered using graduated cylinders at 15-minute intervals over the course of two hours. In water-load experiments, the urine was collected over 45 minutes before administration of the water load and for two hours afterward. In addition to the quantity, the concentration of dense substances in the urine was determined by the reflectometry method (B.Ye. Yesipenko and M.S. Yaremenko, 1961). The water load was administered through the gastric fistula in an amount of 500 ml at a temperature of 36-38°C. The experiments were conducted at Kiev and in high-mountain regions of El'brus (Terskol, altitude 2000 m and Priyut 105, altitude 3200 m) during the 1960 and 1961 expeditions of the the A.A. Boromol'ts Physiology Institute of the Academy of Sciences of the Ukrainian SSR. The work was done on five dogs.

EXPERIMENTAL RESULTS

The experiments in which continuous (spontaneous) excretion of urine was observed indicated that in dogs, formation of urine under the conditions of the high mountains does not take place in the same way as under lowland conditions. At Kiev, uropoiesis was characterized by the following data in the experimental animals: for Norka, the level of uropoiesis averaged 4.3 ml every 15 minutes, the quantity of urine formed over the time of the experiment (2 hours) was 34.3 ml, and the concentration of dense substances was 7.2%. In the course of the experiment,

the level of uropoiesis was observed to diminish and the quantity of urine formed during the second hour of the experiment was 12% lower on the average than during the first hour. The percentage content of dense substances in the urine rose toward the end of the experiment. In Taksa, the uropoiesis level as 4.7 ml in 15 minutes, 37.8 ml of urine were formed over two hours, and the concentration of dense substances in it came to 6.77%. No decrease in the level of uropoiesis was observed in this animal during the course of the experiment, nor was there, in contrast to all of the other experimental dogs, any increase in the concentration of the urine toward the end of the experiment. In the case of Dzhina, 5.0 ml of urine were formed on the average every 15 minutes, 41.0 ml formed over the two-hour interval, and the concentration of dense substances in the urine was 6.68%. In this dog, we noted a more significant decrease in the level of uropoiesis in the course of the experiment: the quantity of urine that was formed during the second hour of the experiment was 34% smaller than during the first hour. The percentage content of dense substances in the urine increased.

Under mountain conditions at an altitude of 2000 m (Terskol), we observed an enhancement of the uropoietic function of the kidneys in all of the experimental dogs, together with a considerable decrease in the concentration of dense substances in the urine.

In Norka, the average quantity of urine in the 15-minute specimens came to 4.5 ml, while it was 35.8 ml over the two hours of the experiment. The percentage content of dense substances in the urine fell to 4.43% as compared with the Kiev experiments. For Taksa, the level of urine excretion at this altitude was 6.1 ml in 15 minutes, and 48.5 ml of urine formed over the course of the experiment. The concentration of dense substances dropped to 2.91%.

TABLE 1

Uropoiesis in Dogs under Lowland and Mountain Conditions

Собаки 1	2 Время (в мин.)									В сред- ном 3	За 2 часа 4
	15	30	45	60	75	90	105	120			
5 Киев											
6 Норка: мл	5,80	4,20	4,50	4,50	3,70	3,90	3,60	4,10	4,3	34,30	
8 Дзгина: мл	5,80	6,30	6,80	7,0	7,9	7,93	8,44	8,27	—	7,20	
9 Такса: мл	4,40	3,90	3,90	5,0	5,50	4,9	5,60	4,70	4,7	37,90	
%	7,33	7,76	7,55	6,83	6,42	6,82	6,06	6,06	—	6,77	
10 Терскол (высота 2000 м)											
6 Норка: мл	12,0	6,50	3,40	2,80	2,3	2,90	2,90	3,0	4,5	35,80	
8 Дзгина: мл	28,0	22,20	11,50	9,10	8,50	6,40	7,50	6,40	12,9	103,0	
9 Такса: мл	6,70	6,0	5,10	6,0	7,10	6,0	5,30	6,20	6,1	48,40	
%	2,92	2,84	2,76	3,01	2,93	2,97	2,95	2,85	—	2,91	
11 Приют 105 (высота 3200 м)											
6 Норка: мл	14,40	8,90	3,90	3,70	3,30	3,20	3,20	3,30	5,5	44,0	
8 Дзгина: мл	33,80	21,80	12,70	9,80	9,0	9,00	8,80	7,0	13,8	111,0	
9 Такса: мл	8,0	7,10	7,0	6,70	7,70	8,0	7,90	7,0	7,4	59,40	
%	2,86	2,80	2,86	2,98	2,96	2,88	2,92	3,01	—	2,91	

1) Dog; 2) time (in min); 3) average; 4) over 2 hours; 5) Kiev; 6) Norka; 7) ml; 8) Dzhina; 9) Taksa; 10) Terskol (altitude 2000 m); 11) Priyut 105 (altitude 3200 m).

The most significant rise in the uropoiesis level at the 2000-m altitude was observed for Dzhina. The quantity of urine in the 15-minute specimens rose for this animal from 5.2 ml (Kiev) to 12.9 ml, and an average of 103.0 ml was formed over the two two hours of the experiment. The percentage content of dense substances decreased to 2.4.

At the 2000-meter altitude, the dogs showed a more significant drop in the uropoiesis level than that observed at Kiev, together with a rise in the percentage content of dense substances in the urine toward the end of the experiment. As in the preceding series of experiments, Taksa was an exception; in this animal, uropoiesis remained at the same level over the entire course of the experiment.

REPRODUCIBLE

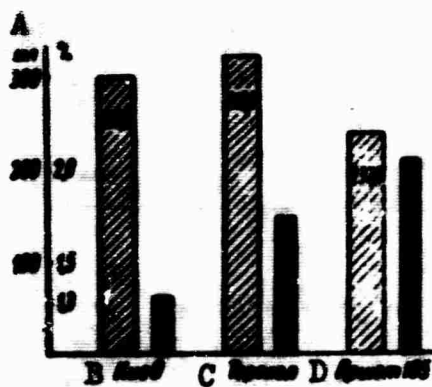


Fig. 1. Continuous (Spontaneous) formation of urine under lowland and mountain conditions (dog Norka, 1960 expedition). A) ml; B) Kiev; C) Terskol; D) Priyut 105.

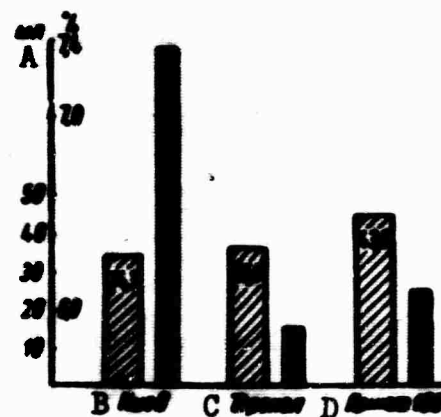


Fig. 2. Water diuresis under lowland and mountain conditions (dog Norka, 1961 expedition). A) ml; B) Kiev; C) Terskol; D) Priyut 105.

At the altitude of 3200 m (Priyut 105), the experimental animals showed an even higher level of the kidney uropoietic function. All animals secreted more urine at this altitude than they had at Kiev and Terskol; the percentage content of dense substances in the urine was higher than at Terskol and lower than at Kiev.

In Norka, the uropoietic function of the kidneys at the 3200-m altitude was characterized by the formation of 5.5 ml of urine over 15 minutes, and 43.8 ml over the two hours of the experiment. The concentration of dense substances in the urine was 6.09%; in Taksa, the corresponding figures were 7.4 ml, 59.5 ml and 3.11%; for Dzhina, they were 13.8 ml, 111 ml and 3.51%. The nature of uropoiesis in the experimental animals under lowland and mountain conditions is reflected in Table 1 and Fig. 1.

Changes of another type in the kidney uropoietic function were observed in the dogs under mountain conditions when they were administered a water load. At an altitude of 2000 m, the water diuresis that followed administration of 500 ml of water through the gastric fistula exceeded the quantity of urine excreted over two hours under the same experimental

TABLE 2

Water Diuresis in Dogs under Lowland and Mountain Conditions

1 Собака	2 Киев			3 Терскол			4 Приют 105		
	5 Количество мочи за 2 часа (в мл)	6 Плотные вещества (в %) (в мл)	7 Плотный остаток (в мг)	5 Количество мочи за 2 часа (в мл)	6 Плотные вещества (в %) (в мл)	7 Плотный остаток (в мг)	5 Количество мочи за 2 часа (в мл)	6 Плотные вещества (в %) (в мл)	7 Плотный остаток (в мг)
Норка 8. (экспедиция 1960 г.)	289,4	1,30	3976	356,3	1,08	3850	298,0	1,31	3912
Норка 9. (экспедиция 1961 г.)	299,2	1,31	3933	319,8	1,74	5561	237,8	2,04	4850
Астра 10. (экспедиция 1960 г.)	270,4	1,45	3920	364,7	1,46	5335	343,9	1,42	4902
Астра 11. (экспедиция 1961 г.)	305,3	1,49	4565	291,6	1,59	4643	210,5	2,78	4375
Пантера 12	240,5	1,47	3547	284,8	1,59	4530	225,3	1,74	3925

1) Dog; 2) Kiev; 3) Terskol; 4) Priyut 105; 5) quantity of urine in 2 hours (in ml); 6) dense substances (in %); 7) dense residue (in mg); 8) Norka (1960 expedition); 9) Norka (1961 expedition); 10) Astra (1960 expedition); 11) Astra (1961 expedition); 12) Pantera.

conditions at Kiev by an average of 15% in all dogs, and was accompanied by an increase in the concentration of dense substances in the urine. For example, while Astra had produced 270.4 ml of urine over two hours after a water load administration at Kiev, the uropoietic kidney function was characterized at the 2000-m altitude by formation of 364.7 ml of urine; the corresponding figures for Norka were 289.4 and 356.3 ml (1960) and 299.2-319.8 ml (1961 expedition), while Pantera produced 240.5 and 284.8 ml.

The concentration of dense substances in the urine was higher at an altitude of 2000 m, and the total quantity of these substances in the urine was naturally higher than at Kiev. Thus, for Norka the concentration of dense substances in the urine formed during the two hours after administration of the water load was 1.31% at Kiev, and the quantity of dense substances excreted with this urine was 3933 mg; at 2000 m, however, the concentration of dense substances excreted over two hours

was 5561 mg.

Thus, as will be seen from Table 2, uropoiesis in the dogs at an altitude of 2000 m differs from that under lowland conditions (Kiev) in having a higher rate and increased excretion of dense substances from the organism.

At the 3200-m altitude, the level of uropoiesis was, in all experimental dogs, approximately 15-20% lower than at the altitude of 2000 m, and somewhat lower than in Kiev in most of the experiments. For example, for Norka (1961 expedition) 238 ml of urine were formed at the 3200-m altitude during the two hours after administration of the water load, as against 320 ml at the 2000-m altitude and 299 ml at Kiev; the figures for Pontera were 225 ml at 3200 m, 285 ml at 2000 m and 240 ml at Kiev.

The concentration of dense substances in the total quantity of urine formed over two hours following administration of the water load at an altitude of 3200 m was, as a rule, the highest observed. Thus, for Astra (1961 expedition), the concentration of dense materials in the urine was 2.78% at the altitude of 3200 m, 1.59% at Terskol and 1.49% at Kiev. Similar results were obtained in the majority of experiments for all of the experimental dogs. Figure 2 permits comparison of the nature of the water diuresis under lowland and mountain conditions.

Summing up the results of the study, we can affirm that both the continuous (spontaneous) uropoiesis and water diuresis take different forms under lowland and mountain conditions. However, while the continuous excretion of urine increases progressively in the experimental dogs as they are brought to higher altitudes, the water diuresis shows an initial rise in the ascent (2000-m altitude), but subsequently, when the higher altitude is reached, its rate shows no substantial difference from the figures observed under lowland conditions. We observed quite another pattern in the changes of the dense-residue content in the urine

in continuous and water diuresis at the different altitudes. In this case, we observe a direct relationship between altitude of ascent and the concentration of the dense urine residue, with higher percentage contents of dense substances in the urine at higher altitudes. Determination of the dense-residue content of the urine in continuous urine excretion showed a substantial drop on ascent to an altitude of 2000 m, and, subsequently, on ascending to 3200 m, a rise in this index, although it falls far short of the percentage content of dense residue observed under the conditions of Kiev.

A study of the state of water metabolism in the experimental dogs under mountain conditions, which we made by determining the total quantity of water in the organism (antipyrine method) and determining the blood indicators (hemoglobin, dry blood serum residue, etc.) together with the weight of the dogs, indicated that a marked depression has occurred at 3200 m. As compared with control experiments run at Kiev, the dog organism contains a smaller amount of water with a higher percentage of dry substances in the blood serum under the conditions of the 3200-m altitude, despite the fact that water was not rationed. Thus, for Pantera, the total quantity of water in the organism dropped by 11% as a result of a 10-day sojourn at the 3200-m altitude. Similar data were obtained in experiments on Dzhina and Taksa.

No such dehydration of the organism was observed at the 2000-m altitude; on the contrary, there was even a certain amount of hydration as compared with the figures obtained in Kiev. These data are sufficient to account for the changes observed in the kidney hemopoietic function under mountain conditions, as follows: the progressive increase in spontaneous diuresis with the ascent into the mountains is necessary for excretion of salts from the organism, since their concentration has increased as a result of loss of water at 3200 m. Thus, the spontaneous

diuresis observed under mountain conditions may be regarded basically as a saline diuresis that maintains the organism's internal medium constant. The lower-level water diuresis observed at 3200 m is accounted for by the fact that a certain amount of the water taken in by the dogs is held in the organism because of a certain shortage in the organism at this altitude.

We may draw the following conclusions on the basis of the data obtained:

1. A relationship has been established between the uropoietic function of the kidneys and the altitude of ascent.

2. There is a direct relationship between the level of continuous (spontaneous) diuresis and the altitude to which the animals are taken. At the 2000-m altitude, the level of uropoiesis in the dogs was higher than under lowland conditions and lower than at the 3200-m altitude.

3. The water diuresis increases with the ascent to the 2000-m altitude and subsequently drops to the values observed at Kiev and even lower as the animal is brought up to 3200 m.

4. The concentration of dense substances in the urine with ascent to altitude increases, although the values in spontaneous diuresis are lower than under lowland conditions.

5. The change in the kidney uropoietic function is a consequence of the organism's water-balance dynamics under the conditions of the high mountains and has the purpose of holding the organism's internal medium constant.

NEUROHUMORAL SHIFTS IN THE BLOOD OF ANIMALS UNDER MOUNTAIN CONDITIONS

G.I. Kulik

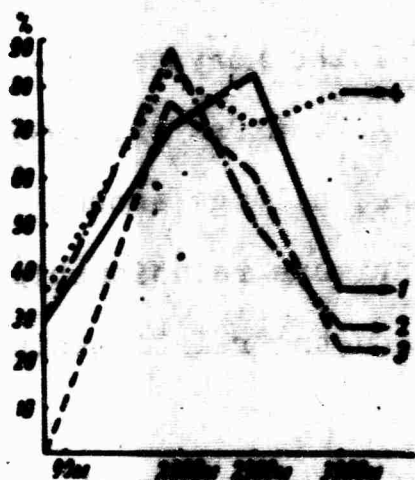
(Kiev)

It has been established by a number of investigators that in hypoxia developed either in an "ascent" in a hypobaric chamber or under mountain conditions we observe changes in the activity of the nervous system (N.N. Sirotinin, 1949; A.Z. Kolchinskaya, 1954; A.V. Lifshits, 1949; G.V. Altukhov, 1955, and others). At the present time, a large amount of material has been accumulated attesting to the intimate relationship between the functional state of the nervous system and the relationships among the neurohumoral substances in the blood.

The studies of W. Cannon (1936), K.M. Bykov (1937), I.P. Razenkov (1937), A.V. Kibyakov (1936), D.Ye. Al'pern (1944), Kh.S. Koshtoyanets (1950) and others have established that when the nervous system is excited, humoral substances accumulate in the blood and transmit the nervous excitation in the central and peripheral divisions of the nervous system.

Despite the large number of studies that have been devoted to changes in the central nervous system during hypoxia, the question as to neurohumoral shifts in the organism during oxygen insufficiency has been illuminated only to a very minor degree. References to the accumulation of biologically active substances in the blood during hypoxia can be found in D.Ye. Al'pern and Ye.N. Berger (1943) and in V.S. Raitses (1954). The latter author determined the content of biologically active substances in the blood during transitory hypoxia induced in animals by in-

spiration of air with a subnormal oxygen content. During the hypoxia, the blood of the animals had an exciting effect on an isolated frog heart and produced an increase in blood pressure in cats and dogs that had been sensitized with cocaine. Accumulation of acetylcholine was not observed in experiments run on the dorsal muscle of a leech. On the basis of the data obtained, the author suggests that biologically active substances of a sympathotropic type accumulate in the blood during short-term hypoxia.



Changes in inotropic activity of blood serum under conditions of hypoxia. 1) Dog Lera; 2) dog Zita; 3) dog Dzhek; 4) turkey.

Our observations toward study of neurohumoral shifts in the blood of the experimental animals were conducted under natural mountain-hypoxia conditions during an El'brus expedition of the Physiology Institute of the Academy of Sciences Ukrainian SSR headed by Acting Member of the Academy of Medical Sciences USSR N.N. Sirotinin. Various animals were used in the experiment (dogs, turkeys, geese).

To characterize the neurohumoral shifts, we determined the inotropic activity of the blood serum on a Straub-isolated frog heart and the blood cholinesterase by Scheiner's biological method. The studies were made under dynamic conditions at various altitudes above sea level; Kiev (96 m), Terskol (2000 m), Novyy Krugozor (2900 m) and Ledovaya baza (3900 m).

The experiments carried out indicated that the inotropic and cholinesterase activity of the blood undergoes phasic variations in hypoxia.

Thus, the inotropic activity of the animals' blood serum (Table 1) increases sharply on ascent to the 2000-m altitude and is maintained

at a rather high level at the 2900-m altitude. When the animals were taken up to Ledovaya baza (3900 m), the inotropic activity of the blood serum diminished (see Figure), and did so more distinctly in the dogs than in the birds.

The shifts in blood cholinesterase activity were of a similar nature (Table 2).

The most significant rise in blood cholinesterase activity was noted at an altitude of 2900 m. Thus, the cholinesterase activity rose by 20% ($P < 0.05$) in dogs brought up from the 2000-m altitude to 2900 m. During the subsequent ascent to Ledovaya baza (3900 m), the cholinesterase activity dropped by 17% ($P < 0.05$) as compared to the activity that it had shown at 2000 m, and by 30% with reference to the maximum cholinesterase activity, which had been observed at 2900 m of altitude. The decrease in cholinesterase activity at the 3900-m altitude was, like the inotropic activity, less sharply manifest in the birds than in the dogs.

Thus, the investigations carried out indicated that in hypoxia arising under mountain conditions, during an ascent up to 3900 m above sea level, we note two phases in the accumulation of neurohumoral substances in the blood. The first phase, that observed in the ascent to 2900 m of altitude, is accompanied by intensified accumulation of neurohumoral blood substances. The second phase, which accompanies ascent to 3900 m, is characterized by a decrease in the neurohumoral activity of the blood.

As has been shown by many authors (A.V. Lifshits, 1949; A.Z. Kolchinskaya, 1954; G.V. Altukhov, 1955; N.A. Agadzhanian, 1956; Mal'mezhak and Plan, 1951, and others), we note three phases of change during hypoxia in the activity of the central nervous system. The first, which corresponds to altitudes of 2000-3000 m, is characterized by an intensification of excitation processes in the central nervous system.

TABLE 1

Inotropic Activity of
Blood Serum at Various
Levels of Hypoxia

Животные	Инотропная активность (%)			
	Киев, 96 м	Тер- скол, 2000 м	Новый Круго- зор, 2900 м	Ледо- вая База, 3900 м
	3	4	5	6
7 Собаки:				
8 Лера	28	70	82	35
9 Джек	0	77	60	22
10 Зита	30	86	80	26
11 Чернушка	—	37	50	40
12 Цыган	—	84	100	80
13 Индюк № 45	30	88	33	70
14 Индюк № 5139	34	83	71	78
15 Гусь № 38	11	80	37	28
16 Гусь № 35	20	87	80	44

1) Animal; 2) inotropic activity (in %); 3) Kiev, 96 m; 4) Terskol, 2000 m; 5) Novyy Krugozor, 2900 m; 6) Ledovaya baza, 3900 m; 7) dogs; 8) Lera; 9) Dzhek; 10) Zita; 11) Chernushka; 12) Tsygan; 13) turkey No. 45; 14) turkey No. 5139; 15) goose No. 38; 16) goose No. 35.

TABLE 2

Cholinesterase Activity
of Blood at Various Lev-
els of Hypoxia

Животные	Холинэстеразная активность (в единицах Шейфера) 2			
	Киев, 96 м	Тер- скол, 2000 м	Новый Круго- зор, 2900 м	Ледо- вая База, 3900 м
	3	4	5	6
7 Собаки:				
8 Лера	1,65	2,0	2,0	—
9 Джек	2,25	2,50	2,86	2,0
10 Зита	2,20	2,12	2,60	1,60
11 Чернушка	—	2,22	3,0	2,0
12 Цыган	—	2,50	3,0	1,90
13 Индюк № 45	1,60	1,80	2,07	1,72
14 Индюк № 5139	1,56	2,40	2,20	1,78
15 Гусь № 38	0,80	0,70	1,03	1,0
16 Гусь № 35	0,63	0,75	0,95	0,70

1) Animal; 2) cholinesterase activity (in final units); 3) Kiev, 96 m; 4) Terskol, 2000 m; 5) Novyy Krugozor, 2900 m, 6) Ledovaya baza, 3900 m, 7) dogs; 8) Lera; 9) Dzhek; 10) Zita; 11) Chernushka; 12) Tsygan; 13) turkey No. 45; 14) turkey No. 5139; 15) goose No. 38; 16) goose No. 35.

At moderate degrees of hypoxia (3000-5000 m), we note a drop in functional activity in the brain and the development of protective inhibition. Finally, severe degrees of hypoxia (6000-7000 m) produce diffuse inhibition in the cortex and a hypnotic state.

On comparison of our observations of neurohumoral shifts in hypoxia with literature data on changes in the central nervous system, it is impossible not to note the rather strict correlation between these disturbances.

In all probability, the change in the functional state of the central nervous system results in shifts of the indices characterizing the neurohumoral activity of the blood. It is interesting that in birds, which are animals with a less highly differentiated nervous system,

these neurohumoral shifts are less distinct than they are in dogs.

CHANGES IN ARTERIAL PRESSURE, CARDIAC RHYTHM AND RESPIRATION WITH
NORMAL AND DEPRESSED FUNCTIONING OF THE THYROID GLAND
UNDER MOUNTAIN CONDITIONS

M.I. Imanaliev

(Frunze)

The adaptive reactions of the organism, and those of the cardiovascular system in particular, when unaccustomed mountain factors are in operation are most intimately related to the functional state of the endocrine glands, which, exerting their influence on the metabolism, affect the working conditions for all of the organism's organs and systems.

The importance of the thyroid gland in its various functional states for regulation of the hemodynamics and respiration under mountain conditions has been given almost no experimental study. The present paper is devoted to the problem of the state of the cardiovascular system and respiration in animals with normal and hypofunctioning of the thyroid gland under mountain conditions.

METHOD

The experimental animals were 88 dogs of both sexes. The experiments consisted of two series: a first, lowland (Frunze) series, in which 44 dogs were used, of which 20 were healthy and served in turn as a control for 24 dogs suffering from hyperthyroidism, while the second, mountain series employed 44 unadapted animals, of which 10 were healthy and 34 had thyroid hyperfunction.

The mountain series of experiments was performed at the highest point on Tyuya-Ashu (altitude 3200 m above sea level). Experimental thyroid insufficiency was induced by feeding the animals with 6-methyl-

thiouracil (6-MTU) in doses figured at the rate of 50 mg per 1 kg of live weight over 11-12 days. Animals that had been conditioned in this manner at Frunze were then transferred to the summit. The investigation was made under the conditions of acute experiment with weak thiopental narcosis. The thiopental was administered intraabdominally in a dose figured on the basis of 0.3 ml of the 10% solution per 1 kg of live weight. The arterial pressure was registered in the femoral artery with a damped mercury manometer, and respiration with a Marey capsule, which was connected to a pneumograph and secured to the animal's epigastric region.

RESULTS OF EXPERIMENTS

We judged the hypofunctioning of the thyroid gland on the basis of basal metabolism and the morphological changes in the gland.

TABLE 1

Comparative Indices of Arterial Pressure and Respiratory Frequency in Animals with Normal Functioning of the Thyroid Gland and Hypothyroidism under Lowland Conditions (town of Frunze)

Показатели вариационной статистики 1	2 Артериальное давление (в мм рт. ст.)		5 Дыхание (в мин.)	
	3 контроль	4 опыт	3 контроль	4 опыт
6 Среднее арифметическое и его станд. ошибки $M+m$	134±4,6	107±3,7	15±1,3	18±1,5
7 Среднеквадратическое отклонение, σ	22,9	16,5	6,3	6,8
8 Доверительные границы	124,5+143,5	99,3+114,7	12,3+17,7	14,1+21,1
9 Разность по M	27		3	
10 Средняя ошибка разности t при $P=0,05$	5,9 4,5		1,9 1,6	

1) Variational-statistics indicator; 2) arterial pressure (in mm Hg); 3) control; 4) experiment; 5) respiration (per minute); 6) arithmetic mean and its standard errors, $M + m$; 7) root mean square deviation, σ ; 8) confidence limits; 9) difference in M ; 10) mean error of difference t for $P = 0.05$.

Lowland series of experiments. Table 1 shows comparative data for the control (healthy) and experimental (thyroid hyperfunction) groups of dogs in terms of their arterial pressure, pulse and respiration in-

dices. The results obtained were evaluated by the method of variational statistics.

Table 1 does not present comparative data on the pulse rate, since we failed to establish a definite difference between the figures for the control and experimental groups of dogs. Thus, in the first group of dogs with thyroid hypofunction, no changes in the cardiac rhythm were observed under the conditions of acute experiment, while an insignificant slackening was noted in the second group.

TABLE 2

Comparative Data on Arterial Pressure, Pulse Frequency and Respiratory Frequency in Healthy Animals at Frunze and at the Summit

Показатели вариационной статистики	Артериальное давление (в мм рт. ст.)		Пuls (в мин.)		Дыхание (в мин.)	
	2	3	4	5	6	7
1	5	6	5	6	5	6
	Фрунзе	Тянь-Аншун	Фрунзе	Тянь-Аншун	Фрунзе	Тянь-Аншун
7 Среднее арифметическое и его станд. ошибки, $M \pm m$	134 ± 4,6	160 ± 4,1	141 ± 4,9	133 ± 2,8	15 ± 1,3	18 ± 1,5
8 Среднеквадратическое отклонение, σ	22,9	13	23,7	8,7	6,3	7,2
9 Доверительные границы	124,5+ 143,5	150,8+ 178,2	130,9+ 151,1	126,7+ 139,3	12,3+ 17,7	31,6+ 42,4
10 Разность по M	35		8		22	
11 Средняя ошибка разности t при $P=0,05$	6,1 5,7		6,3 1,2		2,7 8,1	

1) Variational-statistics indicator; 2) arterial pressure (in mm Hg); 3) pulse (per minute); 4) respiration (per minute); 5) Frunze; 6) Tyuya-Ashu; 7) arithmetic means and its standard deviation, $M + m$; 8) root mean square deviation, σ ; 9) confidence limits; 10) difference in M ; 11) mean error of difference t with $P = 0.05$.

It is evident from Table 1 that there is a definite difference between the control and experimental groups as regards the number of respiratory motions. While the number of respiratory motions averages 15 ± 1.3 per minute for the normal dogs, it is 18 ± 1.5 in the dogs with thyroid hypofunction, i.e., the respiration has quickened by 20% as compared with dogs of the control group. Further, the experimental dogs show more superficial respiration, with smaller-amplitude excursions of

the thoracoabdominal wall.

A sharp difference between the experimental and healthy groups of dogs was noted in the arterial pressure indices. The average level of arterial pressure in the 20 healthy dogs was 134 ± 4.6 mm Hg, while in the 24 dogs with depressed thyroid function it averaged 107 ± 3.7 mm Hg, i.e., was 25% lower. The results of statistical evaluation indicate that this difference is significant.

Having obtained preliminary data on the hemodynamic and respiratory state of the healthy and the dogs with thyroid hypofunction under the conditions of Frunze, we decided to repeat the experiments under mountain conditions.

High-mountain series of experiments on unadapted dogs. The data obtained at Frunze on the normal animals and animals with thyroid hypofunction, together with the data for the unadapted (normal) animals under mountain conditions, served as the control for this series of experiments.

As will be seen from Table 2, the normal animals respond to the combined operation of high-mountain factors with an adaptive increase in arterial pressure coupled with a simultaneous slackening of the cardiac tempo and a quickening of respiration. The arterial pressure rose by 26%, the cardiac tempo dropped by 6% and the respiratory frequency rose by 146% as compared with lowland animals. These changes were found to be significant on statistical evaluation.

A totally different picture was presented by the arterial pressure, cardiac tempo and respiration indices for dogs with experimental thyroid insufficiency when they were transferred into the mountains.

Table 3 presents comparative data obtained on the two groups of dogs with thyroid hypofunction - at Frunze and at the summit of Tyuya-Ashu.

TABLE 3

Comparative Data for Arterial Pressure, Pulse Frequency and Respiratory Frequency in Dogs with Thyroid Hypofunction under Lowland and Mountain Conditions

Параметры вариационной статистики 1	Артериальное давление (в мм рт. ст.) 2		Пульс (в мин.) 3		Дыхание (в мин.) 4	
	Фрунзе 5	Тюя-Ашу 6	Фрунзе 5	Тюя-Ашу 6	Фрунзе 5	Тюя-Ашу 6
7 Среднее арифметическое и его станд. откл. $M \pm m$	107 ± 3,7	100 ± 3,9	143 ± 5,7	149 ± 5,3	18 ± 1,5	22 ± 1,8
8 Среднеквадратичное отклонение, σ	16,5	23,1	23,6	30,8	6,8	10,6
9 Доверительные границы	99,8+ 114,2	92,4+ 107,6	131,1+ 154,9	139+150	14,9+21,1	18+26
10 Разность по M	7		6		4	
11 Средний ошибка разности	5,3		7,1		1	
1 при $P = 0,05$	1,3		0,8		1,9	

1) Variational-statistics indicator; 2) arterial pressure (in mm Hg); 3) pulse (per minute); 4) respiration (per minute); 5) Frunze; 6) Tyuya-Ashu; 7) arithmetic means and its standard deviation, $M + m$; 8) root mean square deviation, σ ; 9) confidence limits; 10) difference in M ; 11) mean error of difference t with $P = 0.05$.

As will be seen from Table 3, animals with thyroid hypofunction respond to the climatic factors of the high mountains with reactions on the part of the cardiovascular and respiratory systems that are weaker than those of intact animals. Thus, the average arterial pressure figure for the experimental animals under lowland conditions was 107 ± 3.7 mm Hg, while in the mountains it was 100 ± 3.7 mm Hg or 7 mm Hg lower. The cardiac rhythm and respiration were slightly accelerated.

On the basis of the results of the experiments conducted, we arrive at the conclusion that feeding the animals a thyroid-function blocking agent under lowland conditions results in a decrease in arterial pressure without any particular changes in cardiac activity, and in an insignificant quickening and amplitude decrease of the respiratory movements.

In contrast to the healthy group of dogs, animals with thyroid hyperfunction do not respond with an adaptive arterial pressure increase

to the complex disturbance presented by the mountain environment; on the contrary, they undergo a certain decrease in arterial pressure with a simultaneous insignificant quickening of the pulse and respiration.

As we know, the arterial pressure level depends on the systolic volume of the heart, the tone of the blood vessels, the total volume of circulating blood and the rate and depth of respiration. In its turn, each of these factors is subject to physiological fluctuations and depends on a whole series of conditions. For example, thyroid hypofunction, which gives rise to profound changes in the metabolism, influences the work of the cardiovascular and respiratory systems and determines their reactivity with respect to unusual factors in the environment. It is also known that pharmacological intervention with thyreostatic agents is not limited to the thyroid gland alone: working through the thyroid gland, it affects the functional state of the pituitary-adrenal system, which, in turn, finds its reflection in the level and responsiveness of arterial pressure and respiration. For this reason, we suggest that animals with thyroid hyperfunction, which have a metabolic level, do not experience oxygen starvation on transfer into the unaccustomed mountain environment, and do not require an increased oxygen supply to the tissues, with the result that they do not come under strain and do not mobilize the activity of the cardiovascular and respiratory systems. They have no need to do so, since the amount of oxygen available in the mountain environment fully covers the demands being made by the organism.

This position finds confirmations in the work of N.N. Sirotinin, K.M. Bykov, Cannon, M.M. Pavlov, A.D. Slonim, R.P. Ol'nyanskoy, Gell'gorn and others.

CONCLUSIONS

1. A drop in arterial pressure takes place in thyroid hypofunction under both lowland and mountain conditions.

2. Animals with thyroid hypofunction are less responsive to the operation of factors encountered in the mountains.

**INFLUENCE OF VITAMINS ON THE FUNCTIONAL STATE OF THE ADRENAL CORTEX IN
LOCAL INHABITANTS OF THE EASTERN PAMIR (ALTITUDE 3700 m ABOVE SEA LEVEL)**

V.M. Braginskiy and M.M. Mirzoyev

(Dushanbe)

The central nervous system (Petrov, Sirotinin) and the pituitary-adrenal system are major factors in the process of acclimatization to hypoxic conditions. Ye.V. Kolpakov and N.V. Lauer have shown that hypophysectomy results in an increased tolerance for hypoxia. Removal of the suprarenal glands sharply reduces the tolerance. Administration of adrenal-cortex extract increases stability against hypoxia not only in adrenalectomized animals, but also in intact specimens. In extreme hypoxia, the hyperfunctioning of the suprarenals may be so significant that the weight of the gland increases by 30-40% of the initial value. In protracted and acutely manifest hypoxia, this hypertrophy may be supplanted by atrophy. It has been established by a number of investigators that exhaustion of the adrenal cortex takes place only in the initial period, and then its activity returns to normal. G.L. Mednik, O.G. Lorents, B.M. Braginski and A.G. Glushchenko showed that this so-called "initial period" is rather long in duration. Over 50% of persons examined after living at altitudes of 3700-4300 m above sea level for 6 months to three years showed negative Thorn's tests.

The present communication presents data concerning the functioning state of the adrenal cortex in local inhabitants of Eastern Pamir who are residents at an altitude of 3700 m above sea level.

The urine was observed to contain 3 basic steroid groups, which may

be taken as characterizing the synthetic and secretory activity of the adrenal cortex, to wit: corticosteroids of the 17-hydroxycorticosterone type, modified; partly modified corticosteroids still retaining, however, the pregnane structure; and, finally, 17-ketosteroids, which represent conversion products of the suprarenal cortex androgenic function, corticosteroids and the androgenic hormones of the testicles.

In females, the 17-ketosteroids are formed almost completely from compounds synthesized by the adrenal glands, while in males 2/3 of them are formed at the expense of testicular steroids. As a consequence, determining the amount of 17-ketosteroids excreted with the urine gives a conception of the functional state of the adrenal cortex, if only an approximate one.

We determined the total content of 17-ketosteroids in the daily urine by the Uvarovskaya method (using the Zimmerman reaction with meta-dinitrobenzene). Since the daily variations in the excretion of 17-ketosteroids with the urine may be quite considerable in certain individuals, the arithmetic mean obtained from determinations of the 17-ketosteroids in the daily urine over a 3-day period was taken as the initial rate.

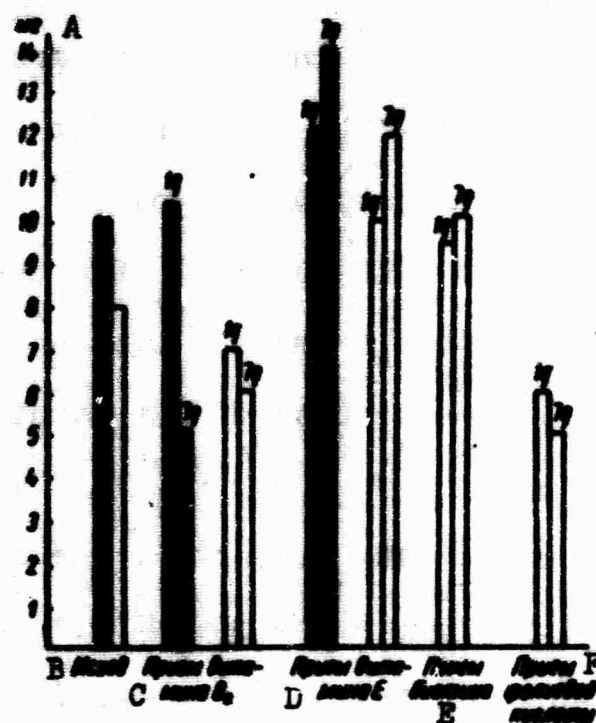
The subjects were 2 groups of people: the 1st group was composed of 30 practically healthy individuals living under the same conditions of work, domicile and diet (to exclude the influence of the later factors on the functional state of the suprarenal cortex) and in residence at an altitude of 1100 m above sea level. This group of individuals was the control group. The 2nd group was composed of 40 practically healthy individuals also under uniform conditions as enumerated above, but in permanent nontraveling residence at altitudes of 3700-4300 m above sea level. Since the excretion of 17-ketosteroids with the urine varies over the course of the year, these two groups of individuals were studied in August of 1960 and August of 1961. The age of individuals in the 1st group ranged from 20-22, and that of individuals in the 2nd group from 16-20 years, with only 4 persons aged 16. The literature contains references to maximum excretion of 17-ketosteroids with the urine at ages from 20-25 years.

Most authors agree that under normal conditions, 12-19 mg of 17-ketosteroids are excreted in the urine of males and 9-12 mg in that of females, although some of them state the norm for men as 4.3-14.2 mg and for women as 4.5-12.9 mg. Some authors place the norm for men at 8-14 mg and that for women at 5-10 mg. The difference would appear to be a function of age differences among the persons studied and the time of year (seasonal factor). The results of the studies that we made are shown in the figure.

As will be seen from the data presented, the average content of 17-ketosteroids in the daily urine was 10.1 ± 1.1 mg in individuals of the 1st group and 8.0 ± 0.4 mg in the 2nd group (statistically significant difference - P less than 0.001). The first group comprised 4 women, while the second included 3. No particular difference was noted in the ketosteroid excretion figures for these individuals (statistically insignificant difference).

Thus, among local inhabitants of Eastern Pamir, the daily excretion of 17-ketosteroids with the urine is 20% below the figure for the control group. If we take into account that the excretion of 17-ketosteroids with the urine rises in winter and that the temperature at the 3700 m altitude is lower in August than at the same time of year at 1100 m above sea level, then the difference in the amount of 17-ketosteroids excreted with the urine becomes more pronounced.

The depression of the suprarenal cortex functional state under the conditions of mountain hypoxia is similar to that observed in the hypoxia of patients with injury to the respiratory organs and with heart defects (Danilyak, Shul'tsev and others). Our data are also supported by the fact that the total cholesterol content in the blood of inhabitants of the Eastern Pamir is higher than that of the control. According to literature data, the latter may serve as an index to the decrease in



**GRAPHIC NOT
REPRODUCIBLE**

Influence of vitamins on excretion of 17-ketosteroids with the urine. Dark bars represent control group of individuals; open bars represent lifelong inhabitants of Eastern Pamir. A) mg; B) start; C) administration of vitamin B₂; D) administration of vitamin E; E) administration of biotin; F) administration of folic acid.

adrenal cortex function.

It was also regarded as interesting to study the influence of vitamins on the functional state of the cortex with the purpose of using them eventually to improve acclimatization. The literature data on this matter are sparse. There are references to the influence of vitamin C and pantothenic acid. It has been shown (Arutyunov and Yarusov, Klimov, Bakhus et al.) that in vitamin C deficiency there is at first observed an increase in the excretion of 17-ketosteroids with the urine as a result of corticosteroid decomposition, and that this is followed by a decrease in their excretion.

We administered large, but within the pharmacopoeia, doses of riboflavin - 50 mg per day taken internally - to groups 1 and 2. The data are presented in Figure 1. As will be seen from this figure, a single administration of riboflavin resulted in a small, statistically uncer-

tain (P greater than 0.1) increase in the excretion of 17-ketosteroids with the urine in the control group. Among the local inhabitants of Eastern Pamir, a single dose of riboflavin produced a statistically reliable (P less than 0.01) decrease in the excretion of these substances. Intake of riboflavin over 7 days sharply reduced the excretion of 17-ketosteroids with the urine. It is interesting to note that this dose of riboflavin did not affect the total amount of cholesterol in the blood. This may provide a certain justification for the statement that riboflavin does not depress the functioning of the adrenal glands, but reduces the amount of corticosteroids decomposed to 17-ketosteroids, as is also suggested by the decreased excretion of chlorides with the urine during riboflavin treatment - and effect that can be related to increased generation of aldosterone.

Vitamin E was administered internally in 100 mg doses. In both groups 1 and 2, single-shot and week-long intake of vitamin E produced a statistically reliable increase in the excretion of 17-ketosteroids with the urine (Fig. 1). Other investigators have also obtained similar results. A direct relationship between the administration of vitamin E and the functional state of the adrenal cortex is indicated. Vitamin E increases the excretion of 17-ketosteroids with the urine. It has been established that the degenerative changes that take place in the adrenal glands of animals under hypoxic conditions are reduced when the animals are given vitamin E.

Under the influence of 500 γ of biotin (taken internally each day), a (statistically reliable) increase in the excretion of 17-ketosteroids with the urine takes place, together with a decrease in the excretion of chlorides (see Figure), which suggests a stimulating effect of biotin on the functional state of the adrenal cortices.

We also administered folic acid. It was found that daily intake of

30 mg of folic acid (internally) resulted in a decrease in the amount of 17-ketosteroids excreted with the urine and an increase in the excretion of chlorides in local inhabitants of Eastern Pamir. Since there is a close functional relationship between folic acid and vitamin C (formation of folinic from folic acid takes place with participation of vitamin C), it can be assumed that folic acid binds part of the ascorbic acid and that the deficiency of the latter that one of us detected in local inhabitants of this mountainous area (Braginskiy, 1962) is aggravated, and that this is also manifested in depression of the adrenal cortex functional state.

Thus, large but pharmacologically admissible doses of riboflavin, vitamin E and biotin enhance the functional state of the adrenal cortex in local mountain inhabitants; intake of folic acid depresses the functional state of the suprarenal cortex.

INFLUENCE OF HYPOXIA UNDER MOUNTAIN CONDITIONS ON DOGS

WITH ECK-PAVLOV FISTULA

Ye.V. Kolpakov and N.M. Shumitskaya

(Kiev)

As we know, the liver plays the leading role in the physiology of the liquid part of the blood: it is the site of formation of the plasma proteins fibrinogen (Forster, Whipple, 1922), prothrombin (Smith, Warner, 1938), albumin and globulin (Kerr, Gurvits, Whipple, 1916; Kapran, 1937; Madden and Whipple, 1940; Lauer, Kolpakov, Roytrub (1961) and hemoglobin (Whipple, Robshayt-Robbins and Hawkins, 1945), as well as protein-type blood-coagulation plasma factors: convertin, proconvertin, accelerin, proaccelerin, and antihemophilia globulin (presented after the monograph of Belik and Khodorova, 1957).

The liver also takes a significant part in the formation of the formed elements of the blood, particularly in the embryonal stage and, according to certain sources (Mori, Takahashi, 1936; Hirayoke, Yanosuke, 1936; Mito Chuyo, 1937; Chernyaev, 1938; Kumode, 1960) even in the post-embryonal period, and also in the resorption of dead or exhausted blood corpuscles (Sirotinin, 1936; Erenshteyn and Lokner, 1959). The liver is also of enormous importance in hemodynamics (as a blood depot, etc.).

In the light of the above, it was felt interesting to study the manner in which the morphological composition of the peripheral blood varies in animals both under the conditions of liver-function disturbance and in connection with the over-all complex of disturbances that arise at this time in the activity of the organism (Domarus, 1908; Nassau,

1914; Gorev, 1937; Chernyaeva, 1938; Kolpakov, Lauer, Ozadovskaya, 1958).

An extremely interesting matter, and one that has been given almost no study (Chernyaeva, 1938) was found in the discovery of adaptive capabilities in the organisms of dogs with experimental hypoxic insufficiency, and, in particular, to the conditions of oxygen insufficiency, such as may be observed in one degree or another in the life of man as well, when he goes up into the mountains as a climber, a skier or simply as a tourist.

The literature is known to contain statements to the effect that persons suffering from liver disease are advised against staying in the mountains (Kollarits; Sirotinin, 1939, 1958), although the reason for the deterioration in the state of liver patients has not been clarified to this day.

METHOD

The Eck-Pavlov fistula was selected as a classical model for reproduction of liver insufficiency in the experiment. This model is not only of considerable theoretical interest for study of liver pathology under experimental conditions, but it is also of great importance in clarifying a whole series of problems related to the diagnosis and treatment of liver disease in man.

Data was collected at Kiev (initial data) and during two expeditions to El'brus organized by the A.A. Bogomolets Physiology Institute of the Academy of Sciences Ukrainian SSR in 1960 and 1961. The work extended over 2.5 years with the participation and under the supervision of Prof. Ye.V. Kolpakov, as well as that of Active Member of the Academy of Medical Sciences USSR N.N. Sirotinin.

It was the purpose of the present investigations to trace consistencies in the behavior and peripheral blood-picture changes in dogs

with Eck-Pavlov fistula in the dynamics of hepatic-insufficiency development of normal atmospheric pressure (at Kiev), and to ascertain the nature and qualitative features of the hypoxia-adaptation capabilities of control animals and those of the dogs with Eck-Pavlov fistula and liver insufficiency of variously long standing, both during stepwise acclimatization to the high-mountain climate (1961 expedition) and under the conditions of acute hypoxia without preliminary acclimatization of the animals in the mountains (1960 expedition).

The experiments were performed on 16 full-grown mongrel dogs, mostly females (14 females out of the 16), aged 1-3 years, and weighing 8-15 kg. In advance of the expedition (by 20 days to 27 months), 11 of the dogs were operated upon to produce the Eck-Pavlov fistula, while 5 served as a control. All of the experimental animals were kept on a milk and vegetable diet during the observation period.

The basic technique used in the study was hematological analysis of the peripheral blood. The animals were studied in accordance with a definite schedule: twice before the fistula was formed (initial data), and thereafter, beginning of the 21st day after the operation, monthly for 2-27 months right up to the start of the El'brus expedition.

In the 1960 expedition, all animals (2 control animals and 6 with fistulas) were taken, without any preliminary acclimatization to the mountain climate, for a truckride up to "Piket-105" at an altitude of 3500 m above sea level (oxygen partial pressure in the air 103 mm Hg), where they were examined on the second and tenth days.

In the 1961 expedition, all dogs (3 controls and 5 with fistulas) were examined during the process of stepwise adaptation to the mountain climate: and the second and seventh days of residence at Terskole on a spur of El'brus situated at an altitude of 2000 m above sea level (oxygen partial pressure in the air 124 mm Hg), on the fifth day of residence at Novyy Krugozor (altitude 3000 m above sea level, partial oxygen pressure in the air 110 mm Hg), on the fifth day of a stay at "Piket-105" (3500 m above sea level, oxygen partial pressure in the air 103 mm Hg) and on the fifth day of residence at Ledovaya baza (3700 m above sea level, oxygen partial pressure in the air 100 mm Hg).

After the return to Kiev, all of the dogs were examined once a

month at normal atmospheric pressure for four months with the object of ascertaining the persistence features of the mountain-climate acclimatization mechanisms in the control and experimental animals.

EXPERIMENTAL RESULTS

A progressive and distinctly manifest development of mechanisms for acclimatization to the mountain climate is observed in the control dogs during progressive acclimatization to this climate as the oxygen partial pressure in the inspired air diminishes, and as a result of increasing time of residence under the conditions of oxygen insufficiency. The percentage content of hemoglobin in the blood increases, the number of erythrocytes becomes significantly larger (reaching its maximum at Ledovaya baza at an altitude of 3700 m above sea level, on the 22nd day of the sojourn in the mountains); accordingly, we observe a progressive rise in the number of reticulocytes, with the appearance of an increased number of the younger maturing stages (III); the body weight of the animals also increases, indicating that they feel good. After the return to Kiev, the mechanisms of acclimatization to hypoxia persist for another two to three months.

With the development of oxygen starvation in the mountains, the dogs with fistulas did not tolerate hypoxia as well as the control animals. They responded with a minor increase in the hemoglobin percentage and erythrocyte count in the peripheral blood, which failed to reach or slightly exceeded the preexpedition figures, although the number of reticulocytes increased significantly, with younger maturing stages (II, III) appearing in the peripheral blood in increased numbers. The low color index, which did not even reach 0.6 in the experimental dogs as compared with a normal value of 0.7, indicates distinct erythrocyte hypochromia. This red-blood reaction to the mountains in the fistulated dog Pyatnashka cannot be accounted for by the poor condition of the animal

(a progressive increase in body weight (+9.8%) was observed to occur as a result of the animal's voracity, while the other four fistulated dogs taken with the expedition showed a distinct weight loss (by 12.5-32.1%) as compared with the preexpedition data (Fig. 1)).

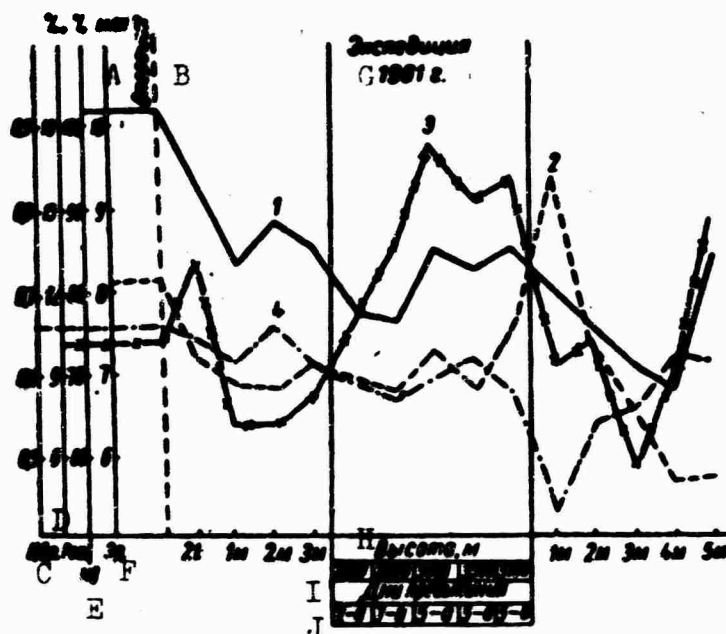


Fig. 1. Influence of stepwise acclimatization to the mountain climate on the red-blood indices of a dog with Eck-Pavlov fistula. (Pyatnashka, mongrel female, age 1 year, weight 15.5 kg). 1) Hemoglobin; 2) erythrocytes; 3) reticulocytes; 4) color index. A) Million; B) operation; C) color index; D) reticulocytes; E) hemoglobin; F) erythrocytes; G) 1961 expedition; H) altitude, m; I) days of sojourn; J) 2nd, 7th, 5th, 5th, 5th.

After the return to Kiev, the acquired red-blood acclimatization mechanisms were retained only for about one month, and then, immediately following a considerable increase in erythrocyte count concurrently with a progressive drop in the percentage hemoglobin content, we observed distinct erythrocyte hypochromia (color index 0.45), which gradually went over to a state of manifest hypochromic anemia.

In the 1960 expedition, on the tenth day in the mountains, control dogs subject to acute hypoxia (the altitude was 3500 m above sea level) without preliminary acclimatization to the mountain planet showed, after a slight decrease in the hemoglobin percentage and erythrocyte count on the second day of the stay in the mountains due to the abnormally high

fragility of the erythrocytes (Uzhanskiy, 1945), a rather significant development of mechanisms for acclimatization to the mountain climate (erythrocytes, hemoglobin, reticulocytes). The body weight of the dogs increased.

A month after the return to Kiev, however, both control dogs were observed not to maintain the acclimatization mechanisms on the high level for a very long time, as was recorded in the 1961 expedition; to the contrary, we observed a distinct drop in the percentage hemoglobin content, erythrocyte count, reticulocyte count and body weight, all of this indicating an unfavorable effect of acute hypoxia without preliminary acclimatization to the mountain climate, even for the organism of the control animals.

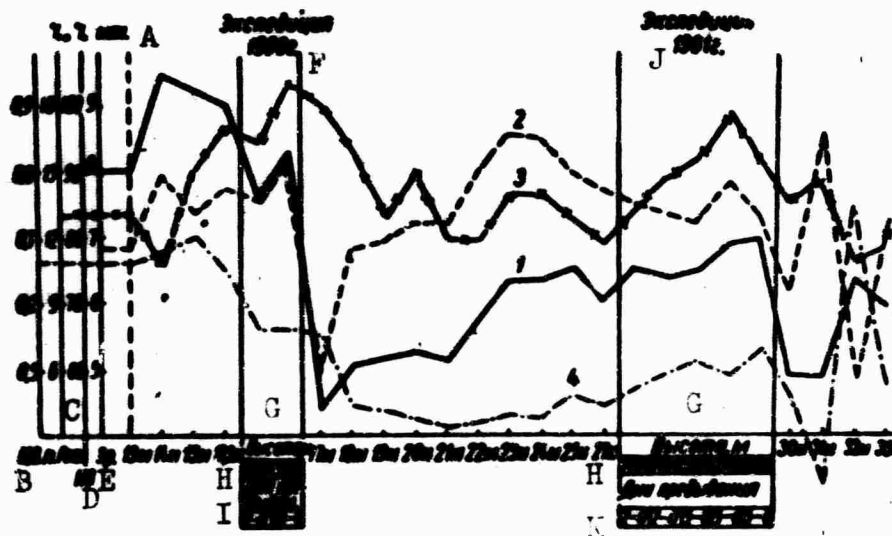


Fig. 2. Influence of acute hypoxia and stepwise acclimatization to the mountain climate on red-blood indices of dog with Eck-Pavlov fistula (Bel'chik, a mongrel male, aged 2.5 years, weight 10 kg). Legend same as in Fig. 1. A) Million; B) color index; C) reticulocytes; D) hemoglobin; E) erythrocytes; F) 1960 expedition; G) altitude; H) day of sojourn; I) 2nd, 10th; J) 1961 expedition; K) 2nd, 7th, 5th, 5th, 5th.

Under the conditions of acute hypoxia in the mountains, the dogs with direct Eck-Pavlov fistula showed poorer tolerance for oxygen starvation than did the control dogs (Bel'chik, Fig. 2). Basically, the red-blood reaction in these dogs was similar in nature, but the degree to which the hemoglobin content had fallen on the second day of the sojourn

in the mountains was much more evident than in the control dogs. The acclimatization mechanisms developed were also very feeble: the dog Bel'chik with his 16 months of post-operational "experience" responded to acute hypoxia with only a very slight increase in erythrocyte count and percentage hemoglobin content, and the latter was significantly lower than even the preexpedition level. Manifest hypochromia of the erythrocytes was noted (color index 0.56).

The peripheral blood of both the control and the experimental animals (but the latter to a much sharper degree) showed manifest changes in the erythrocytes and leucocyte formula under the conditions of acute hypoxia due to the organism's incipient acclimatization to the mountain climate: the blood of the post-surgical dogs showed a considerable retardation in the maturing of both erythrocytes and leucocytes, with the delay particularly distinct in the latter case. On the tenth day of the sojourn at this altitude, a significant nuclear shift to the left in the neutrophilic leucocytes (0.23-0.40 instead of the 0.1 for the control dogs) was observed in the fistulated dogs. Together with a sharp increase in the number of stabnuclear and immature neutrophilic leucocytes in the peripheral blood, occasional bone-marrow cells — metamyelocytes and even myelocytes — made their appearance.

The qualitative changes in the formed elements of the blood were also nonuniform: while regenerative changes predominated in the control dogs, they were also accompanied in the dogs with liver insufficiency by sharply manifest alterative changes in the blood cells (erythrocytes, neutrophilic leucocytes), and abortive forms of cell division among the lymphocytes and monocytes.

A month after the return to Kiev, both the control animals and, to an even greater degree, the fistulated dogs showed decreases in all of the red-blood indices and in body rate. During the ten months that fol-

lowed (Bel'chik), the dogs with liver insufficiency did indeed show a progressive, very slow rise in the hemoglobin and erythrocyte figures, but the distinct hypochromia of the erythrocytes (the color index was 0.42-0.47) indicated a clear disturbance to the hemoglobin-forming function of the liver in dogs with Eck-Favlov fistula.

CONCLUSIONS

1. Switching the liver out of the portal circulation by introducing a direct Eck-Pavlov fistula in dogs affects the activity of the entire organism to a certain degree at normal atmospheric pressure. This operation also has an influence on the morphological composition of the peripheral blood, resulting in the appearance of indistinct erythrocyte hypochromia with normal erythrocyte count and in degenerative leucocyte changes in most dogs within 2-13 months after the fistula has been introduced.

2. The nature and extent of the adaptive capabilities of the experimental dogs under the conditions of oxygen starvation depends both on the extent to which the oxygen partial pressure in the inspired air has been reduced as a consequence of an increase in altitude and prolonged residence under conditions of hypoxia and on the duration of the post-operational period.

3. The post surgical and control dogs showed differing response reactions under the conditions of hypoxia. Both under the conditions of progressive acclimatization to hypoxia and to an even greater degree in acute hypoxia, the experimental dogs suffered more severely than the control animals from the oxygen starvation, apparently because of a disturbance to the hemoglobin-forming function of the liver in these animals when they were moved to the mountains.

4. In dogs with liver insufficiency, the mechanisms of acclimatization to the mountain climate went into action more slowly than those of

the control animals, as indicated by the appearance of a larger number of immature erythrocytes in the blood, a more pronounced leftward shift in the neutrophilic leucocytes and insufficient formation of hemoglobin.

5. More distinct alterative changes in the erythrocytes and particularly among the leucocytes observed in the experimental dogs under the conditions of acute hypoxia (3500 m above sea level) are a result of intoxication by incompletely oxidized nitrogen-metabolism products due to disturbance to the antitoxic function of the liver, which is intensified in the mountains under the influence of secondary hypoxia resulting from inadequate production of hemoglobin.

6. The investigations that we made on dogs with direct Eck-Pavlov fistula under the conditions of hypoxia indicate significant participation of the liver in the hematogenetic processes and in the formation of hemoglobin.

CHANGE IN THE NUMBER OF EOSINOPHILS UNDER CONDITIONS
OF HIGH ALTITUDE

P.V. Beloshitskiy and Lo Sin'-Mao
(Kiev)

The eosinopenia reaction is widely used to determine the functional capacity of the hypophyseal-adrenal system. This indicator is one of the most prompt and constant, not only where ACTH is administered (the Thorn test), but also where the animal organism or the human being is subjected to various stresses. A stress of this magnitude and variety was represented in our experiments by the rarefied atmosphere of a pressure chamber, and by conditions of high altitude.

It should be noted that Z.I. Malkina (1931), Shteubli (1910, 1911), and Kraandiyk (1932) have already studied changes in the eosinophil content under mountain conditions. The above-mentioned authors did not, however, observe distinct fluctuations.

Recently, Frovli, Thorn and co-authors (1951), Koller and co-authors (1954), Bryuner and co-authors (1960), have observed a diminution in the number of eosinophils in the peripheral blood of human beings, in an instance where these people have ascended to a higher altitude. This eosinophil-number change clearly indicated intensified functioning of the adrenal cortices.

Armstrong and Kheym (1938), Dokhen (1942), Lengli and Klark (1942), Sandstrem and Michels (1942), Thorn and co-authors (1942), Gordon and co-authors (1943), Kheylmen (1944), Meydzhil and Marbarder (1955) have directed attention to the fact that there is an increase in the weight

of the adrenals of animals that have lived for extended periods of time under conditions of a rarefied atmosphere.

Evans (1934), Louis, Thorn and co-authors (1942), Darov and Sarason (1944) reported an activation of the adrenal cortices in the case of animals that have lived for extended periods under conditions of a rarefied atmosphere.

In the investigations that we have undertaken, we have used the eosinopenia reaction as the indicator of functional capacity of the adrenal cortices. The blood smears were stained with Khinkleman's solution; the count was conducted in a Goryayev-Fuchs-Rosenthal chamber. In addition, a count of the eosinophils in the smear was undertaken for control.

At first, experiments were conducted in a pressure chamber. Eosinophil and leucocyte counts were made for each of 12 guinea pigs, and the air pressure in the altitude chamber was reduced to 180 mm Hg, which resulted in the incidence of cramps; thereupon, the pressure was raised again to the normal. Eosinophil and leucocyte counts were made immediately after the experiment, and then after 4, 19, and 22 hours. Immediately after the experiment, in 10 instances, a 15% increase in the number of eosinophils was recorded, and a 24% increase in the number of leucocytes. After 4 hours, the number of eosinophils was down by 53% while the leucocyte determination indicated an 11% increase. After 18 hours, there was a 13% decrease in the number of eosinophils and a 4% increase in the number of leucocytes. After 22 hours the number of eosinophils was down 7%.

Investigations were also undertaken during expeditions to El'brus (1959, 1962), and were conducted under the leadership of N.N. Sirotinin, Active Member of the Academy of Medical Sciences of the USSR. What in particular was studied was the change in the eosinophil count as influenced by altitude, and the character of the Thorn test.

Shown in Table are the results of a count of the number of eosinophils in the peripheral blood of mice at various altitudes (1959). It was established that with an increasing altitude there was an ever

TABLE 1

Number of Eosinophils in the Blood of Mice at Various Altitudes (Expedition to El'brus, 1959)

Высота (в м)	1	Киев(58)	2000	2500	2900	3000
3 День пребывания на данной высоте		—	9. 10-а	2. 4-а	8. 10-а	14-а
4 Количество эозинофилов в 1 мм ³		210±26	172±26	63±10	111±37	175±7

1) Altitude (in meters); 2) Kiev (58); 3) day of habitation at the given altitude; 4) number of eosinophils in 1 mm³.

TABLE 2

Number of Eosinophils in the Blood of Human Beings at Various Altitudes (Expedition to El'brus, 1960)

1	2	3 Абсолютное количество эозинофилов в 1 мм ³															
		4 на высоте 2200 м		на высоте 2500 м													
Участник экспедиции	Киев (исходное количество)	5 День пребывания на данной высоте															
		3-а	3-б	3-в	7-а	7-б	10-а	10-б	3-а	4-а	5-а	3-а	7-а	10-а	3-а	4-а	
6 В. П.	300	100	100	125	100	25	50	100	25	25	—	25	25	25	50	100	25
7 М. В.	75	175	200	400	350	225	50	300	475	400	325	275	225	200	—	—	—
8 М. А.	400	375	350	400	350	275	175	425	300	250	125	250	225	300	—	—	—
9 Г. М.	150	75	75	175	100	50	50	25	25	—	25	50	25	—	—	25	—
10 В. Г.	300	—	25	125	50	—	150	100	100	25	25	75	100	125	50	50	25
11 Г. Э.	100	50	50	100	75	75	—	50	50	175	100	100	75	50	25	100	50
12 В. В.	375	300	225	150	125	100	100	75	125	75	50	275	200	200	175	125	50
13 Ф. В.	125	25	125	100	75	25	50	75	75	25	25	125	50	100	75	100	25
14 Д. Н.	200	175	200	150	150	125	125	50	25	25	25	—	25	25	—	100	—
15 К. Н.	250	150	175	225	200	150	100	125	—	—	—	150	150	25	—	—	—

1) Member of the expedition; 2) Kiev (initial number of eosinophils); 3) absolute number of eosinophils in 1 mm³; 4) at the altitude of 2200 meters; 5) day of habitation at the given altitude; 6) B.P.; 7) M.V.; 8) M.A.; 9) G.M.; 10) V.G.; 11) G.E.; 12) B.V.; 13) F.V.; 14) D.I.; 15) K.N.

greater manifestation of decrease in the number of eosinophils in the blood of the mice. Then, evidently as a result of an acclimatization phenomenon, the number of eosinophils gradually increased.

During the expedition to El'brus in 1960, eosinophil counts were made at various altitudes with human beings as subjects (Table 2). Here, 8 of the 10 subjects displayed a fifty percent reduction in their eosinophil counts when they had reached an altitude of only 2000 meters

above sea level. In the case of two subjects, there was no reduction to be observed in the number of eosinophils relative to the initial (Kiev) datum. During the expedition to El'brus in 1961, a significant reduction in the number of eosinophils was again revealed, moreover, in the case of every one of the twelve participants (Table 3).

TABLE 3

The Number of Eosinophils in the Blood of Human Beings at Various Altitudes (Expedition to El'brus, 1961)

1 Абсолютное количество эозинофилов в 1 мм ³						
2 Участник экспедиции	3 Киев (исходное количество)	4 на высоте 2000 м				
		5 День пребывания на данной высоте				
		2-й	7-й	2-й	7-й	2-й
Б. П. 6.	350	125	50	25	12,5	125
Ф. В. 7.	75	50	25	25	12,5	62,5
Д. Д. 8.	250	100	150	75	50	125
О. Г. 9.	175	125	75	50	25	125
П. С. 10.	200	150	150	50	75	37,5
Н. С. 11.	250	100	125	—	50	50
Д. В. 12.	150	50	50	50	25	25
Д. Л. 13.	450	325	275	270	150	137,5
Т. Х. 14.	250	175	275	225	175	270
О. К. 15.	225	50	50	25	12,5	25
Л. Г. 16.	325	100	25	12,5	25	112,5
С. Н. 17.	—	325	224	200	175	175

1) Absolute number of eosinophils in 1 mm³; 2) member of the expedition; 3) Kiev (initial number); 4) at the altitude of 2000 meters; 5) day of habitation at given altitude; 6) B.P.; 7) F.V.; 8) D.D.; 9) O.G.; 10) P.S.; 11) N.S.; 12) D.V.; 13) D.L.; 14) T.Kh.; 15) O.K.; 16) L.G.; 17) S.N.

Represented in Table 4 are the results of an eosinophil count made during the expedition to El'brus in 1961 on 23 white mice (the count being undertaken on the 4th day after reaching each of the successive altitude levels) and 15 guinea pigs (count made on the 2nd day after reaching each of the successive altitude levels).

During the expedition to El'brus in 1959, it was also demonstrated that after a 25-unit intramuscular ACTH administration, the eosinopenia reaction in the case of the mice was, with the increase in altitude, somewhat intensified on the 9th or 10th day of habitation at the 2000-meter altitude level and, on the 4th day at the 3500-meter level; all

tests of this series were positive (Table 5). However, the Thorn test, which was conducted with ten guinea pigs during the expedition to El'brus in 1960, on the second day at each successive altitude, revealed that upon administration of 2.5 units of ACTH the eosinopenia reaction becomes less intense with the increase in altitude. This, in Kiev the reduction in the eosinophil count was 77.6%, at the altitude of 2000 meters it was 71.4%, at the altitude of 3200 meters it was 62%, and at the altitude of 3500 meters it was 38.4%.

TABLE 4

Number of Eosinophils in the Blood of Mice and Guinea Pigs at Various Altitudes (Expedition to El'brus, 1961)

Высота (в м)	Среднее количество эозинофилов в 1 мм ³ крови у морских свинок	Примечание	Среднее количество эозинофилов в 1 мм ³ крови у белых мышей	Примечание
1	2	3	4	3
Киев (58)	617	6	227	8
2000	502	В двух случаях наблюдалось увеличение	72	В одном случае на всех высотах отмечалось увеличение
3700	383		Не считали	
4300	383	В двух случаях наблюдалось увеличение	18	

1) Altitude (in meters); 2) average number of eosinophils in 1 mm³ of blood in experiment with guinea pigs; 3) observation; 4) average number of eosinophils in 1 mm³ of blood in experiment with white mice; 5) Kiev (58); 6) in two instances an increase was observed; 7) not counted; 8) in one instance an increase was noted at every altitude.

TABLE 5

The Thorn Test with Mice Conducted at Various Altitudes (Expedition to El'brus, 1959)

Высота (в м)	58 м	2000 м	3200 м	3500 м	
1	2	4	5	6	
Дата пребывания на данной высоте	—	9, 10-8	4-8	8, 10-8	14-8
Число проб	44	15	10	10	5
Средний процент уменьшения эозинофилов после введения АКТГ	81 ± 2,1	94,2 ± 1,7	94 ± 1,1	87 ± 2,3	87,6

1) Altitude (in meters); 2) 58 meters; 3) day of habitation at given altitude; 4) 9th, 10th; 5) number of tests; 6) average percentage decrease in eosinophil number after ACTH administration.

CONCLUSIONS

1. Habitation under conditions of high altitude, or subjection to the rarefied air in a pressure chamber activate the hypophyseal-adrenal system. This effect is indicated by a fall in the absolute number of eosinophils in the peripheral blood.

2. On the second day of habitation under conditions of successively increasing altitude the administration of ACTH (the Thorn test) to animals results in an eosinopenia reaction which is weak in comparison with the control series of experiments. Then on the 4th, 9th and 10th days, apparently in conjunction with an incipient acclimatization phenomenon, the eosinopenia reaction becomes somewhat more intense.

CHANGES IN THE ERYTHROCYTE COUNT, PULSE RATE AND BLOOD
PRESSURE UPON AN ASCENT TO HIGHER ALTITUDE AFTER
PRIOR ACCLIMATIZATION TO HIGH ALTITUDE CONDITIONS

A.B. Zakharyan
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Along with shifts in a series of physiological functions of the organism during an ascent to and habitation under high altitude conditions, changes occur also with respect to the erythrocyte population. These latter changes represent the homeostatic reaction of the organism to new conditions, here basically to a lowered partial pressure of oxygen in the inspired air.

The objective of the present work was to clarify the question of how the number of erythrocytes and the percentage content of hemoglobin change when experimental subjects who have already undergone a prior acclimatization to high altitude conditions ascent to a still greater altitude. The work was conducted in Aragatz, a high-mountain locality. The investigation comprised the study of 76 healthy men, all in the 20-26-year-old age group. The experimental subjects had been living at an altitude of 3250 meters above sea level. The aggregate of 76 experimental subjects was divided into four groups, on the basis of length of residence at the 3250-meter level. The first group was composed of 21 men who had been living at the designated altitude for no longer than one month. The second group comprised 15 men whose period of habitation at the given altitude level was one to six months. The third group contained 17 men who had been living from six months to one year

at this altitude, and the fourth group included 23 men who had been living at the 3250-meter level for longer than one year. The ascent accomplished subsequently was from the altitude of 3250 meters to 3900 meters. The number of erythrocytes and the percentage content of hemoglobin were determined before this ascent was undertaken, then at the altitude of ascent, and again a day after the return to the 3250 meter level.

It was found that at the altitude of ascent, all groups experienced an increase in the number of erythrocytes as well as increase in the percentage content of hemoglobin. Upon comparing the changes in erythrocyte-number and hemoglobin-percentage shown by the various groups at the altitude of ascent, it was established that the first group had experienced the greatest change (erythrocyte-number increase by 500,000, hemoglobin percentage by 7%), and that the fourth group had experienced the least change (erythrocyte-number increase by 250,000, hemoglobin percentage by 3%). The number of erythrocytes and percentage content of hemoglobin were determined for each experimental subject one day after he had returned to the 3250-meter altitude level; in all groups studied, an insignificant reduction in the values of the specified indicators was noted, but in each case they exceeded the initial determination. Since the first group comprised individuals who were in only the initial stage of acclimatization, they showed the greatest changes in erythrocyte number upon ascent. Conversely, the fourth group, composed of individuals in the state of total acclimatization, showed the smallest changes on the part of the erythrocyte population. This permits us to conclude that acclimatization increases the organism's tolerance of hypoxia.

We made it our task to ascertain how the pulse rate and blood pressure might be affected upon further ascent as a function of the

length of habitation of the experimental subjects under conditions of high altitude. The investigation was conducted in Aragatz, a high-mountain locality. The altitude of 3250 meters above sea level served as point of departure, and from here an ascent to the 3900 meter altitude level was organized. The investigation comprised the study of 92 healthy men in the 20-25 year old age group. The experimental subjects were divided into four groups, and a man belonged to one group or another dependent on the length of time he had been living at the 3250 meter level. The first group comprised 25 men who had been living at the specified altitude for no longer than one month; the second group was composed of 26 men whose period of habitation at this altitude was one to six months; the third group contained 18 men who had been living from six months to one year at this altitude; and the fourth group was composed of 23 men who had been living at the specified altitude longer than one year. Pulse rate and blood pressure were checked 10-15 minutes, one hour, and then two hours after the ascent from the 3250 meter level to 3900 meters above sea level had been completed.

The experimental subjects of all four groups showed an acceleration of pulse rate after the ascent. After two hours at the 3900 meter altitude, examination revealed a pulse rate reduction; but it was still elevated in comparison with the initial data. However, experimental subjects comprising the first group experienced the greatest acceleration of pulse rate relative to the initial determination (by 36, 26, 22 beats per minute); and the smallest acceleration (by 19, 15, 10 beats per minute) was experienced by experimental subjects comprising the fourth group.

Let us now examine the nature of the changes in the average maximal and minimal blood pressure values, after the ascent. It is necessary to note that the experimental subjects of all groups experienced

an increase in both maximal and minimal blood pressure. Even here, however, it was found that the greatest increase was experienced by the men who comprised the first group, and the least by the members of the fourth group. For example, 10-15 minutes after the ascent the members of the first showed an average increase in the maximal blood pressure value by 22 mm Hg, and an increase in the minimal blood pressure value by 11 mm Hg. In the fourth group the maximal blood pressure value had increased on the average by 8 mm Hg, and the minimal blood pressure value by 5 mm Hg. One day after their return to the 3250 meter altitude level the blood pressure and pulse rate of all experimental subjects were checked; on the whole, these indicators had returned to their initial values.

On the basis of the observations that we have made, we may conclude that acclimatization to a high-mountain climate increases resistance to anoxia. This is indicated by the fact that the greatest hemodynamic changes were observed in individuals constituting a group that was in only the initial stage of acclimatization; whereas the experimental subjects constituting a group in the state of complete acclimatization experienced the smallest hemodynamic changes.

INFLUENCE OF THE MOUNTAIN CLIMATE OF THE EL'BRUS REGION ON THE EXTERNAL
(PULMONARY) RESPIRATORY FUNCTION IN BRONCHIAL ASTHMA PATIENTS

S.P. Mel'nichuk

(Pyatigorsk)

In 1957-1959, the Pyatigorsk Balneological Institute collaborated with the Physiology Institute of the Academy of Sciences Ukrainian SSR (staff headed by Prof. N.N. Sirotinin) conducted clinical-physiological observations on a group of patients suffering from bronchial asthma, who remained for a month at an altitude of 2200 m above sea level in the El'brus region. The clinical observations (S.A. Ul'yanova and A.A. Kochumyan) indicated that living in the mountains actually does have a favorable effect on bronchial-asthma patients: toward the end of a month's sojourn, 39 of 44 patients subject to the mountain climate showed an improvement in condition, the state of three showed no change, and only two were slightly worse. On the return to Kislovodsk from the expedition, most of the patients showed a temporary relative deterioration in clinical state, followed by a more stable and protracted improvement. For several months to a year and more thereafter, the bronchial asthma of most patients took a considerably easier course than it had in preceding years. Their ability to perform work improved noticeably, and a few of the men were practically restored to health.

When the patients were taken into the mountains in 1959, the basic problem posed was that of studying the influence of the mountain climate on the external (pulmonary) respiratory function. A group of 22 patients was selected for participation in the trip; they were inhabitants of

Kislovodsk (12 men and 10 women) ranging in age from 20-49 years with histories of bronchial asthma varying in length and gravity, but without concomitant disorders of the cardiovascular system.

The following basic indices of external respiration were determined: The vital capacity of the lungs, the volumes of augmentation, respiratory and reserve air, the number of respirations per minute, the pulmonary-ventilation minute volume, oxygen requirement, utilization coefficient of oxygen in the lungs, limit (maximum) of pulmonary ventilation, and the volume rate of forced expiration. The phases of the investigation were concurrent, with a single procedure employing a Knippina-Artynov spirographic instrument (1951), B.Ye. Votchal's pneumotachometer (1949), a breathing valve and a gas meter.

The actual values obtained for the indices (except for respiratory frequency) were expressed in percentages of the normal physiological values. The latter were calculated on an individual basis from the normal tabulated basal metabolism level, which was multiplied by the various conversion factors according to A. Antoni (1937), A.G. Dembo (1957), and others. The results of the investigations were given statistical processing with calculation of the arithmetic means (M), their errors (m) and the confidence coefficient of the difference t (Yu.L. Pomorskiy, 1929; L.S. Kaminskiy, 1959).

Before the ascent into the mountains, the external respiratory function was studied in these patients on a monthly schedule -- in April, May, June and July.

The results of the investigations are presented in Table 1.

The individual values of the external respiration indices are not stable in bronchial asthma patients, but vary over a relatively broad range; on the whole, however, they are considerably lower than the normal physiological level. Most severely depressed were the indicators that directly reflect the functional permeability of the bronchi and the elasticity of the lung tissue -- the rate of forced expiration and the pulmonary ventilation limit. These indices were also found to be the most unstable: the fluctuations in their level from the over-all averages amounted to ± 10 - $\pm 17\%$.

TABLE 1

State of External Respiratory Function Indicators in Bronchial Asthma Patients Before Ascent into Mountains, During April-July 1959

Показатели внешнего дыхания	Общие средние значения (M ± m)	Оптимальные (ближайшие к норме) значения
1	2	3
4 Жизненная емкость легких	79,4 ± 2,3	86,6
5 Дополнительный воздух, % ДЖЕЛ	42,5	—
6 Дыхательный воздух, % ДЖЕЛ	17,7	—
7 Резервный воздух	19,4	—
8 Частота в минуту	17,5 ± 0,4	15,3
9 Минутный объем легочной вентиляции	199,2 ± 4,5	184,1
10 Потребление кислорода	122,5 ± 1,0	118,4
11 Коэффициент использования кислорода в легких	64,3 ± 1,5	67,4
12 Предел легочной вентиляции	58,3 ± 3,0	75,0
13 Скорость форсирного выдоха	43,7 ± 2,7	53,3

1) External respiration index; 2) over-all average value (M + m); 3) optimum (nearest normal) value; 4) pulmonary vital capacity; 5) augmentation air, % of DZhYeL; 6) respiratory air, % of DZhYeL; 7) reserve air; 8) per-minute frequency; 9) pulmonary ventilation minute volume; 10) oxygen consumption; 11) oxygen utilization coefficient for lungs; 12) limit of pulmonary ventilation; 13) rate of forced expiration.

The external respiration was studied five times (every 5-6 days) during the sojourn in the mountains. The first study, which was made a day after ascent to an altitude of 2200 m, showed definite changes even in the status of the indicators of this function. These were of a dual nature (Table 2).

A significant increase in the pulmonary ventilation minute volume and the level of oxygen consumption, together with a slight decrease in the coefficient of its utilization in the lungs, suggested that the respiratory apparatus of the bronchial-asthma patients is performing under a manifest functional (ventilation) stress during the first few days of adaptation to the mountain climate. At the same time, the considerable increase in pulmonary vital capacity, pulmonary ventilation limit, and rate of forced expiration attested to a distinct improvement in the functional permeability of the bronchi and provided objective confirmation for the patients' statements to the effect that they were able to

TABLE 2

State of External Respiratory Function in Asthma Patients During First Few Days of Sojourn in Mountains

Показатели внешнего дыхания	1	Уровень показателей (M ± m)	2	Отличие от исходного уровня	3
4 Жизненная емкость легких		90,2		+10,8	
5 Минутный объем легочной вентиляции		264,4		+65,2	
6 Потребление кислорода		161,3		+38,8	
7 Коэффициент использования кислорода в легких		61,6		-2,7	
8 Предел легочной вентиляции		71,6		+13,3	
9 Скорость форсированного выдоха		52,6		+8,9	

1) External respiratory index; 2) level of index ($M + m$); 3) difference from initial level; 4) pulmonary vital capacity; 5) pulmonary ventilation minute volume; 6) oxygen consumption; 7) pulmonary oxygen utilization coefficient; 8) pulmonary ventilation limit; 9) rate of forced expiration.

breathe much better.

As the sojourn in the mountains wore on, the patients' external respiration indices varied about the level achieved during the first few days after the ascent. They usually dropped slightly during poor weather (drop in temperature, rain, fog), after the patients had over-exerted themselves physically or become psychological upset. The average level of the external respiration indices in the mountains was found to be much closer to normal than at Kislovodsk (Table 3).

As compared with the first few days of the stay in the mountains, the pulmonary ventilation minute volume dropped slightly, but it still remained above the level that had been observed at Kislovodsk. Also considerably above the Kislovodsk level was the consumption of oxygen. Consequently, a higher level of the oxidative processes in the patient's organism was maintained stably under the conditions of the mountain climate. The coefficient of oxygen utilization in the lungs was found higher than the initial level, despite the much lower atmospheric pressure (90-100 mm Hg lower than at Kislovodsk) and the corresponding decrease

TABLE 3

Average Values of External Respiratory Function Indicators in Asthma Patients During Sojourn in Mountains

Показатели внешнего дыхания	1	Уровень показателей (M ± m)	2	Отличие от исходного уровня	3
4 Жизненная емкость легких		93,8 ± 1,6		+14,4	
5 Дыхательный воздух		20,7 ± 0,4		+3,0	
6 Частота дыхания в минуту		16,0 ± 0,3		-1,5	
7 Минутный объем легочной вентиляции		223,5 ± 3,0		-24,3	
8 Потребление кислорода		151,2 ± 2,8		+26,7	
9 Коэффициент использования кислорода в легких		69,7 ± 0,2		+5,4	
10 Предел легочной вентиляции		77,9 ± 2,4		+19,6	
11 Скорость форсированного выдоха		55,8 ± 2,2		+12,1	

1) External respiratory index; 2) level of indices (M + m); 3) difference from initial level; 4) pulmonary vital capacity; 5) respiratory air; 6) respiratory frequency, per minute; 7) pulmonary ventilation minute volume; 8) oxygen consumption; 9) oxygen utilization coefficient for lungs; 10) pulmonary ventilation limit; 11) rate of forced expiration.

in the oxygen partial pressure of the inspired air. Thus, the assimilation of oxygen by the respiratory apparatus of the bronchial-asthma patients under the conditions of the mountain climate was, despite hypoxic hypoxia, accomplished with less functional (ventilation) stress than at lower altitudes.

It is also important to note the fact that the respiratory movements of the patients became much deeper and less frequent, constituting a kind of continuous natural "light" exercise (Turban and Spengler, 1906) and undoubtedly improved the alveolar ventilation (Kompo et al., 1961).

The pulmonary vital capacity, the pulmonary ventilation limit and the rate of forced expiration increased for the rest of the time in the mountain, both as compared with the initial level and as compared with the first few days of the mountain visit. The data obtained attest to a significant and objectively documented improvement in the functioning of the external (pulmonary) respiratory apparatus — the function most

seriously impaired in bronchial-asthma patients – under the conditions of the mountain climate.

In subsequent experiments carried out after the return from El'brus, we attempted to clarify the question as to the persistence and stability of the external- expiration improvement that had developed in the mountain climate. The indicators of this function were determined during the first two to four days after the return, and then 1, 4 and 8-10 months afterward.

TABLE 4

State of External Respiratory Indices in Asthma Patients During the First Few Days After the Return from El'brus

Показатели внешнего дыхания	1	Уровень показателей ($M \pm m$) ²	Отличие от уровня в горах ³	Отличие от исходного уровня ⁴
5 Жизненная емкость легких . . .		89,1	- 4,7	+ 9,7
6 Частота дыхания в минуту . . .		15,0	- 1,0	- 2,5
7 Минутный объем легочной вентиляции . . .		163,1	-60,4	-36,1
8 Потребление кислорода . . .		129,1	-22,1	+ 6,6
9 Коэффициент использования кислорода . . .		79,9	+10,2	+15,6
10 Предел легочной вентиляции . . .		65,8	-12,1	+ 7,5
11 Скорость форсированного выдоха . . .		60,8	+ 5,0	+17,1

1) External respiratory index; 2) level of indices ($M \pm m$); 3) difference from level in mountains; 4) difference from initial level; 5) pulmonary vital capacity; 6) respiratory frequency, per minute; 7) pulmonary ventilation minute volume; 8) oxygen consumption; 9) oxygen utilization coefficient; 10) pulmonary ventilation limit; 11) forced expiration rate.

As will be seen from Table 4, the state of the external respiration indices in the bronchial-asthma patients was much better during the first few days after the return than before the visit to the mountain region. The level of most of the indices, except for the pulmonary vital capacity and the ventilation limit, was found to be even better than it had been in the mountains.

The next study of external respiration, which was made a month later, coincided with the development of a temporary deterioration of

clinical state in most of the 18 patients examined at this time period. During this "negative phase" of the reacclimitization period, we also noted a drop in the external respiratory indices (on the average, to the initial values). Subsequently, however, when the period of temporary deterioration had passed and a relatively stable improvement of the patients' clinical state had set in, the external respiratory function indices again improved considerably. Thus, four months after the visit to the mountains (December 1959), despite the fact that it was winter, the average level of these indices was found to be much higher than prior to the El'brus expedition. The state of the external respiratory functions was found to be even better in the spring - in April-May 1960 - , i.e., 8 months after the ascent into the mountains and exactly one year after the first study of respiration in the patients (Table 5).

The optimum external respiration indices noted after the stay in the mountains were found to be closer to normal than the corresponding indices in the natural state.

TABLE 5

State of External Respiration Indices in
Bronchial Asthma Patients in April-May
1959 and 1960

Параметры внешнего дыхания	1	Средний уровень в апреле-мае 1959 г.	Средний уровень в апреле-мае 1960 г.
		2	3
4 Жизненная емкость легких		81,1	94,2
5 Минутный объем легочной вентиляции		196,0	174,8
6 Потребление кислорода		119,3	141,3
7 Коэффициент использования кислорода		62,2	77,2
8 Предел легочной вентиляции		64,4	72,4
9 Скорость форсированного выдоха		45,7	61,3

1) External respiratory index; 2) average level in April-May 1959; 3) average level in April-May 1960; 4) pulmonary vital capacity; 5) pulmonary ventilation minute volume; 6) oxygen consumption; 7) oxygen utilization coefficient; 8) pulmonary ventilation limit; 9) forced expiration rate.

An inference to be drawn from the above is that an improvement in the regulation of the external-respiratory apparatus, with a significant and protracted improvement in the indices of this function, plays an important role in the mechanism of the beneficial therapeutic effect of the mountain climate on bronchial-asthma patients. Thus, a sojourn under the conditions of a mountain climate may with justification be regarded not simply as a symptomatic and temporary method of treatment and prophylaxis for bronchial asthma, but a long-lasting one with a pathogenetic basis. The data of N.N. Sirotinin (1939, 1955) and his collaborators on the possibility and necessity of more extensive therapeutic and prophylactic utilization of the mountain climate have been confirmed on the example of bronchial asthma.

Subsequent investigations, and, in particular, study of the influence of longer and repeated stays in a mountain locality on bronchial-asthma patients and the search for ways to eliminate or alleviate the "negative phase" of the reacclimitization period are of considerable interest and should be continued.

Manu-
script
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No.

[Transliterated Symbol]

646 ДЖЕЛ = DZhYel = dolzhnaya zhiznennaya yemkost' legkikh =
normal pulmonary vital capacity

INFLUENCE OF THE MOUNTAIN CLIMATE ON THE COURSE OF BRONCHIAL ASTHMA

A.A. Kochum'yan

(Kislovodsk)

The therapeutic effect of the mountain climate on patients suffering from bronchial asthma attracted the attention of numerous investigators as long ago as the last century. However, this matter has to this day not been given an adequate clinical verification and pathogenetic basis, and remains one of the most neglected problems in the literature.

The Caucasus Mineral Waters Balneological Institute and the Kislovodsk Health Resort Polyclinic have carried out a joint program of observation of 22 bronchial asthma patients residing at Kislovodsk.

The study method consisted in observing the course of the illness, electrocardiographic study, fluoroscopy of the chest organs, clinical analysis of the blood and sputum, and measurements of arterial pressure, respiratory frequency and pulse.

The observations were made at three different altitudes: from March to July 1959 at Kislovodsk (altitude 800-850 m), and then from 13 July through 10 August 1959 at Terskol on a spur of the El'brus (altitude 2000 m) and at Novyy Krugozor (altitude 3000 m above sea level).

The patients were classified into two groups on the basis of clinical data: the first group consisted of 5 patients with so-called pure uncomplicated asthma, and the second group of 17 patients with secondary pulmonary emphysema and asthmatic bronchitis. There were 12 male patients and 10 females, with ages varying from 20 to 50 years.

The patients were distributed as follows on the basis of the length of time for which they had been ill:

less than 1 year	from 1 year to 5 years	from 6 to 10 years	from 11 to 15 years	from 16 to 20 years	over 20 years
1	2	4	7	6	2

Before the excursion to El'brus, two patients of the first group had been suffering attacks of suffocation 6-8 times a month, while daily attacks were observed in the other three. The pulse rate varied from 72-76 per minute, and the respiratory frequency from 16-21 per minute. The arterial pressure was within the range 100/70-120/80. The eosinophil count in one patient was normal (3%), while the other four showed abnormally high figures ranging from 4-12%.

In patients with complications in the form of pulmonary emphysema and asthmatic bronchitis, the clinical picture was characterized by the following data. Attacks were observed in two patients from 3 to 5 times a month, and 1-2 times a day in 6 patients. The suffocation attacks in these eight patients were more severe than in the patients of the first group. The other 9 of the 17 patients were in an asthmatic state that formed a background for attacks of bronchial asthma from 4 to 20 times a day.

Rales could be heard in the lungs of 14 patients of the second group. Coughing with sputum was observed in 9 persons. The frequency of the cardiac rhythm varied from 68-100 beats per minute, and the respiration frequency from 14 to 24 per minute. The arterial pressure ranged from 100/70-120/85 mm Hg.

In 15 patients of the same group, the eosinophil count was found to be abnormally high, varying from 5-14%; mild leucocytosis (9100-13,000) was noted in 6 patients. In chest fluoroscopy, signs of pulmonary emphysema were detected in 15 patients. On examination of the sputum of eight

patients, Charkot-Leyden crystals were not detected in a single case, while Curschmann's spirals were found in two patients.

The campsite to which the patients were taken was located in the village of Terskol between the valleys of the Terskol and Azau rivers. During our stay at the 2000-m altitude, the weather became relatively chilly and moderately damp, with frequent torrential rain storms. The air temperature in the morning and evening hours varied from +8 to +17°, and around midday from +16 to +25°. The atmospheric humidity ranged from 60-80% in the morning and 30-50% in the afternoon. The average atmospheric pressure was 589 mm (variations did not exceed 2 mm).

The condition of all first-group patients deteriorated during the first two days of the sojourn at Terskol: the attacks of suffocation became more frequent and more severe, and there was no improvement until the third to fourth day; the attacks ceased altogether in three patients, while in the other two they became less frequent and less severe than at Kislovodsk. The patients took a markedly smaller amount of medication. Two of them even refreshed themselves with cold water from a mountain stream. Under ordinary conditions, chilling would, as a rule, produce difficulty in breathing. All patients became more active and took long walks within a radius of three to five kilometers. During the first few days of the sojourn at El'brus, we noted that their pulse had quickened by 8-12 beats as compared with the corresponding index for Kislovodsk. The maximum arterial pressure increased by 10-20 mm and the minimum by 10 mm of Hg as compared with the initial data. Respiration was faster by two to five inspirations per minute. These changes in pulse, arterial pressure and respiration were apparently due to slight hypoxia as a result of the lower oxygen partial pressure.

In the second group, conditions deteriorated for five patients of the seventeen; the attacks of suffocation became more frequent and in-

creased in gravity during the first two days of the visit at Terskol. No significant shifts in the state of health took place in the other 12 individuals. Subsequently, the attacks stopped in four of the 17 patients. In the remaining 13, attacks of suffocation were observed more rarely and became less severe. Rales vanished in seven individuals, subsided in six, and remained unaffected only in one case. Coughing and elimination of sputum ceased in eight individuals, and were reduced in one.

During the first few days of the stay at Terskol, a quickening of the pulse by approximately 12-16 per minute and respiration by 1-3 per minute was observed in patients of the second group. The maximum arterial pressure rose on the average by 10-20 mm, and the minimum by 5 mm Hg.

After two weeks at Terskol, 12 individuals of the second group and two of the first group were transferred to Novyy Krugozor at an altitude of 3000 m above sea level (the camp was set up on a mountain slope bare of vegetation) and stayed there for six days. The mean air temperature in this region was $+6.9^{\circ}$. During the morning and evening hours it ranged from $+4$ to 6° , and did not exceed $+12^{\circ}$ in the afternoon. These low air temperatures were observed against a background of high humidity, giving the sensation of a raw, cold climate, and the atmospheric humidity approached saturation (100%) during the evening hours.

Analysis of the weather conditions at the 2000 and 3000 m altitudes during the time in which the patients were there showed that the weather pattern at Terskol was considerably milder than that at Novyy Krugozor. The atmospheric pressure here was considerably lower than at Terskol. The condition of two patients of the first group and 11 patients of the second group deteriorated at this altitude. In some patients, the attacks of suffocation that had disappeared at Terskol reappeared here,

while in others they became even more severe. We began to detect rales, and patients began to cough and bring up sputum. Due to their worsened condition, the patients were obliged to resort more frequently to the various spasmolytic agents and take them in larger doses.

Together with this, a number of symptoms of mountain sickness began to appear in the patients at Novyy Krugozor: headache, dizziness, ringing in the ears, lassitude, stumbling, foul moods and disturbed sleep. Almost all of the patients experienced acute exhaustion even on undertaking minor physical exertion. Only a single patient in the second group showed no worsening of condition on the change in altitude.

The deterioration of the patients' state during the six-day sojourn at Novyy Krugozor would apparently be accounted for by the fact that under the conditions of lower oxygen content in the atmosphere, hypoxia manifested to a more acute degree, so that the inadequacy of the adaptive reactions of the cardiovascular and respiratory systems stood revealed. Another no less important factor must be seen in the highly unfavorable weather conditions at Novyy Krugozor, where chilly temperatures accompanied by rain and fog persisted for the entire sojourn.

Storm van Leeuwen (1923) arrived at the conclusion that the improvement in the state of patients at high altitudes excludes the possibility of temperature, atmospheric pressure and humidity playing any essential part in the process, although these factors may from time to time have some importance.

Our observations are not in agreement with the statement of Storm van Leeuwen. The results of observations made on 14 patients taken up to the 3000-m altitude indicate that altitude is apparently the only factor without independent significance for the improvement in the patients. If this were not the case, our patients should have felt better at the altitude of 3000 m than at 2000 m, but this did not happen. It

must be concluded that the state of bronchial asthma patients improved with increasing altitude only up to a certain point. Further, favorable weather conditions are of great importance in this respect.

On the return to Terskol, 11 patients showed improvement, returning to the state prevailing prior to the ascent to 3000 m. Two others also improved, but did not become as well as they had been during the first sojourn at Terskol. And in 1 patient of the first group the deterioration that had begun at Novyy Krugozor persisted until the departure to Kislovodsk. The cardiac frequency indices, the number of respirations per minute and the arterial pressure amplitude diminished slightly as compared with the data from the first few days of the sojourn at Terskol and approached the initial values.

Comparing the data of laboratory examinations of the blood at the end of the mountain sojourn with the initial data, we noted a decrease in eosinophil and leucocyte count in all patients, those of both the first and second groups, in agreement with the results obtained by N. M. Schumitskoy and S.A. Ul'yanova (1959). A repetition of fluoroscopy produced the same results as before. In eight patients of the second group, the production of sputum had ceased during the sojourn in the mountains, and it had diminished in one patient.

Electrocardiographic tests were run on 17 patients of the second group. Signs of hypertrophy of the right ventricle were detected in five patients (high R wave in the right precordial lead and in standard derivations 2 and 3; downward shift of ST in standard leads 2 and 3).

Partial block of the right septal division of the bundle of His was established in three patients and block of the right septal division of the bundle of His in one patient. In five patients we observed a low ORS voltage in the standard leads, and, in the precordial leads,

a deep S and a deviation of the electrical axis to the right; three patients showed high P₂₋₃.

Dynamic changes in the EKG were observed in three patients. They were manifested in disappearance, in one patient, of the partial block of the bundle of His right septal division and in a considerable lowering of the T₂₋₃ wave; in the second patient, they took the form of a normal QRS-complex voltage (on the first EKG, the QRS voltage of this patient had been low). In the third patient, B., aged 50 years, the second EKG, taken at the end of the sojourn in the mountains, showed, in addition to the partial block of the right septal division of the bundle of His, which had been identified from the first EKG, a low T-wave in the V₄₋₅₋₆ derivation - apparently a sign of disturbance to the nutrition of the anterior and lateral walls of the left ventricle. It must be concluded that a latent coronary insufficiency had been brought out at the mountain location under the hypoxic conditions prevailing there.

In summarizing our observations, we must note that of the five patients of the first group, two began a considerable improvement manifested in total disappearance of the suffocation attacks. An improvement was noted in two further cases, i.e., a decrease in the number of attacks of bronchial asthma and a shortening of their duration. One patient showed deterioration associated, as described above, with the ascent to the 3000-meter altitude.

Among the patients of the second group, a considerable improvement was observed in three individuals, an improvement in 13, and a slight improvement in one patient, manifest in this case in a longer time between attacks and a decrease in the production of sputum. Thus, of the 12 patients who came under our observation, 5 showed a considerable improvement, 15 an improvement, one an insignificant improvement and one

a worsening of condition.

Analyzing the results obtained, we may conclude that the mechanism behind the therapeutic effect of the mountain climate on bronchial asthma patients consists, as correctly stated by Academician N.N. Sirotnin, of the complex effect of a number of causes.

Patients brought under the conditions of a rarefied atmosphere and the associated low oxygen partial pressure are in a state of mild hypoxia. This is indicated by the quickening of pulse and respiration observed in our patients together with a slight rise in arterial pressure - phenomena most distinct during the first few days of the stay in the mountains. In other words, a number of adaptive mechanisms regulating circulation and respiration have been stimulated.

The decrease in the eosinophil count in the blood of the patients indicates that the allergization of the asthma patient's organism has abated.

CONCLUSIONS

1. A mountain climate (altitude 2000 m) has a favorable influence on patients suffering from bronchial asthma.
2. A sojourn at a higher altitude (3000 m) causes a worsening of the course taken by the bronchial asthma as compared with the lower altitude (2000 m). There is a possibility, however, that this was a consequence of unfavorable weather conditions encountered during the sojourn at the 3000 m altitude.
3. Since medicine does not yet have at its disposal drastic means for the treatment of this serious disorder, and in view of the positive results obtained with the bronchial asthma patients under the conditions of the mountain climate, both as per our observations and the results of other authors, further study of this problem is necessary.

EXPERIENCE IN THE TREATMENT OF BRONCHIAL ASTHMA PATIENTS BY STEPWISE
ACCLIMATIZATION TO THE MOUNTAIN CLIMATE

S.A. Ul'yanova and N.M. Shumitskaya

(Pyatigorsk, Kiev)

It was noted as early as the end of the last century that inhabitants of mountainous regions very seldom suffer from bronchial asthma. In connection with this observation, a number of investigators have recommended use of the mountain climate for treatment of this disease.

The literature reflects studies devoted to the treatment of bronchial asthma by hypoxia, both in the hypobaric chamber (Sirotinin, 1940, 1941; Chikh-Val'ter, 1954; Kheken, 1955) and at mountain altitudes (Turban and Egger, 1906; Steubli, 1913; Storm van Leeuwen, 1923; Gottesfried, 1940; Gens, 1956; Fskomel, 1957; Sirotinin, 1958; Klod [Claude], 1958; Rozhe, Boduen and Mat'ye [Rogier, Baudouin, Mathieu], 1958).

While they noted the positive influence of the mountain climate on bronchial asthma patients, the above authors were nevertheless unable to account for this improvement altogether convincingly.

At the present time, most investigators embrace the allergic theory of the origin of bronchial asthma, according to which an increase in the sensitivity (sensitization) of the organism is regarded as the cause of bronchial asthma on frequent contact with certain substances (allergens). Various substances of both vegetable and animal origin may act as allergens of this type and produce attacks of suffocation: the pollen of flowers and grasses, irritating odors, various types of dust, the black dye "Ursol," wool and the sweat of domestic animals, etc.

The diagnosis of bronchial asthma and subsequent desensitization employ tests in which asthma attacks are provoked by inhalation of aerosols containing various allergens, intracutaneous tests, and skin-allergy tests (scarification method). The latter, as the least dangerous, are extensively used by foreign researchers.

The question as to the role of allergens in the course of bronchial asthma in the mountains has not as yet been given sufficient study.

The present paper presents results from a composite study conducted by staff members of the A.A. Bogomolets Physiology Institute of the Academy of Sciences Ukrainian SSR (Kiev) and staff members of the State Caucasus Mineral Waters Scientific Research Balneology Institute, devoted to research into the influence of prolonged residence in the mountains on the disorders of bronchial asthma patients.

The data was collected at Pyatigorsk-Kislovodsk (initial data) and during two expeditions to El'brus in 1957 and 1958. The work was carried out under the supervision of Academician of the Academy of Medical Sciences USSR N.N. Sirotinin.

BRIEF CHARACTERIZATION OF THE PATIENTS

Of the 24 bronchial asthma patients placed under observation, 11 were year-round inhabitants of Pyatigorsk, while 10 were residents of Kislovodsk. In the 1957 expedition, 13 individuals were treated, and of the 15 treated in 1958, four were return cases. The age of the patients varied from 19 to 52 years, with most of them in the 20-30-year age bracket. There were a majority of women among the patients (16 out of 24). Their occupations included plant engineers, a manicurist, a printing-house worker (female), a cook, a cabinet-maker, medical workers, animal husbandry specialists, a weaver, a veterinarian, etc. All those investigated had bronchial asthma in one or another degree of

severity and persistence (the latter ranging generally from 2 to 10 years). Some of the patients suffered from concomitant disorders in addition to the bronchial asthma (emphysema of the lungs, chronic bronchitis, stenocardia, hypertonia, atherosclerosis, etc.).

Among the causes that had preceded the appearance of bronchial asthma, the foremost position must be accorded to inflammatory processes in the upper respiratory tracts, together with psychic traumas and inspiration of various irritating substances.

Most of the patients (17 out of 24) had suffered frequent attacks of suffocation before the expedition. The asthma was taking a particularly grave course in eight patients. The attacks recurred every day, several times a day, and were severe and protracted in nature (lasting several hours apiece). It was necessary to resort to repeated injections of adrenaline to cure them. An asthmatic state was observed in two patients during the last week prior to the excursion.

We noted the following each day for all of the asthmatics: general condition, number and nature of attacks, body temperature, pulse and arterial pressure. Further, we followed the changes in the allergy skin tests on a dynamic basis, as well as the morphological state of the peripheral blood during the course of the ascent to altitudes of 2000 m (Terskol), 3000 m (Novyy Krugozor), 3500 m (Tik "105") and with increasing time of residence under the mountain conditions. Skin tests were set up four times with four groups of composite allergens made up separately and freshly each time from products of vegetable and animal origin by the method of Koch and Milford (1925) and Storm van Leeuwen (1927). The result of the reaction was read after 20 minutes and 24 and 48 hours had elapsed following application of the allergen. Skin tests with the same allergens were run on 16 healthy individuals as a control, and produced negative reactions in all cases.

TREATMENT OF PATIENTS AND ITS RESULTS

The basic therapeutic factor was climatic. Medication was used only during attacks. During the first 3-4 days, eight patients reported lassitude, indisposition, and headaches, apparently stemming from adaptation to the new conditions presented by the mountain climate. Toward the end of the first week, the condition of almost all patients had improved: the attacks began to appear with decreasing frequency and were shorter and milder. They were almost always cured by theophedrine or antasthman. The mood of the patients improved, and the "feeling that my chest is in a vice" disappeared. The patients breathed "with the full chest." As they put it, "now the air can get into my lungs freely." The patients were able to take hikes of 5-6 kilometers, something that would have been altogether impossible previously.

With the purpose of acclimatizing the patients to hypoxia by degrees, they were driven up to various altitudes on El'brus - to Novyy Krugozor (3000 m) and to Pik "105" (3500 m above sea level), where they stayed for two days in each case while the observations continued. It is necessary to note that at the 3000-3500 m altitude and even at Ledovaya baza (3900 m), to which some of the patients climbed under their own power, they felt better than they had at Terskol.

It was established as a result of the observations made on the patients that prolonged sojourns (30 days) in a mountainous locality at an altitude of 2000-3500 m above sea level has a favorable influence on the course of the disease. Improvements appeared in 14 patients: the frequency and sharpness of the attacks decreased and the bronchitis phenomena abated. A considerable improvement appeared in four patients (two of them did not suffer a single attack in the mountains, although the attacks had recurred daily at Kislovodsk). The asthmatic condition disappeared in two others, having lasted a week or more before the ex-

pedition. Mild attacks did occur in these patients, but they were quickly cured on administration of theophedrine, whereas it had been necessary at Kislovodsk to resort to adrenaline injections as often as 20 times a day.

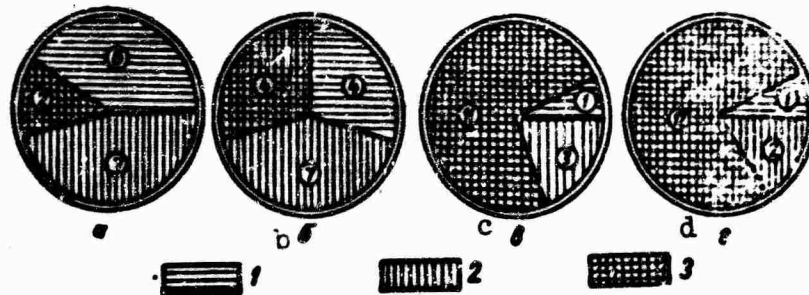


Fig. 1. Changes in skin allergy tests in bronchial asthma patients in the mountains, read 20 minutes after application of the allergen (15 individuals). a) Initial data; b) Terskol, 2000 m, second day; c) Terskol, tenth day; d) Novyy Krugozor, 3000 m, 19th day.

The stay in the mountains produced no marked improvement in three patients. This is obviously to be accounted for by the fact that one of them (female) had suffered an inflammation of the lungs, while in two others the general condition had deteriorated at the end of the expedition as a result of the rainy and cold weather. Only one (female) patient showed a deterioration in condition that was related to her age (51 years) and age-connected disorders (atherosclerosis of the blood vessels of the brain and of the coronary vessels).

Laboratory studies made on 22 patients (two patients were obliged to return to Pyatigorsk by the severity of the concomitant complaints) indicated that in those asthmatics for whom scarification tests run at Pyatigorsk-Kislovodsk before the expedition produced positive and slightly positive allergic results within 20 minutes to 24 hours after application of the allergens there was a decrease in the intensity of the allergic tests, usually with a progressive passage into the negative-

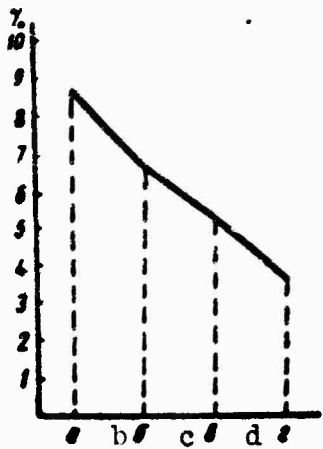


Fig. 2. Change in eosinophil count in blood of bronchial asthma patients in the mountains (average data). a) Initial data; b) Terskol, 2000 m, second day; c) Terskol, tenth day; d) Novyy Krugozor, 3000 m, 19th day.

reaction region (Fig. 1) as they were subsequently taken to increased altitudes and with increasing time of residence in the mountains.

Changes in the composition of the bronchial asthma patients' peripheral blood as a function of the extent of acclimatization to the mountain climate were also distinctly manifest. In most of them, with increasing altitude and increasing sojourn time in the mountains, we observed an increase in the erythrocyte and reticulocyte counts and the hemoglobin percentage. However, the content of the latter did not increase concurrently with the increase in erythrocyte count in all cases, and in some instances this resulted in a decrease in the color index. The number of reticulocytes had increased by a factor of 2.5-4.5 in the peripheral blood on the 19th day of the sojourn in the mountains at the 3000-m altitude, with a left shift in the reticulocyte formula.

As for the morphological composition of the white blood in the asthmatics during their stay in the mountains, it can be stated that the number of leucocytes varied insignificantly in these persons, although a certain left shift in the leucocyte formula was observed.

It must be emphasized that the increased eosinophil count (5-19%) in the blood of all the bronchial asthma patients observed before the expedition - a characteristic of this disorder - decreased progressively as the asthmatics remained in the mountains (Fig. 2) and reached a level considerably lower than the initial level.

Remove post-experimental observation of the patients indicated

that during the first few days after their return home, the suffocation attacks were renewed with the same force as before in some of the patients, but that this exacerbation did not last very long — from a few days to one month. During the following 1-3-6-12 months, some of the asthma patients felt considerably better than they had before the expedition, and others, while they did suffer attacks, experienced them considerably less frequently and found that they were milder.

Our data are in agreement with the observations of Steubli (1910), Ugralidze, and Sirotinin (1939) to the effect that another allergic disorder, rheumatism, is almost never encountered among the local mountain population, and that exacerbation of the rheumatism does not occur when rheumatics are taken to the mountains. According to Avetisyan (1957), treatment of rheumatic polyarthrititis at the mountain health resort Alma-Arasan (Tien-Shan mountains) at an altitude of 1800 m above sea level gives an improvement in 87% of cases. As noted by Chen' Tsza-peï (1959), the phenomenon of Artus is weaker in rabbits during their acclimatization to the mountain climate, an observation that is in agreement with our results.

CONCLUSIONS

1. Long (30-day) visits by bronchial asthma patients to a mountainous locality (altitudes of 2000-3500 m above sea level) has a favorable influence on the course taken by the disease. The asthma attacks become considerably less frequent and assume a milder nature, and bronchitis phenomena abate.

2. The improvement in the condition of most bronchial asthma patients in the mountains is to be accounted for by acclimatization of their organism to hypoxic conditions; this is indicated by the manifest stimulation of adaptation mechanisms: increase in erythrocyte count and hemoglobin content, increase in number of reticulocytes with left shift

of the formula.

3. A decrease in the allergic sensitization of the bronchial-asthma patient was established; this is indicated by weaker reactions to the skin patch tests, with a progressive change in most patients to negative results, and by the considerable decrease in the number of eosinophils in the peripheral blood, down to values considerably lower than the initial ones.

4. The problem studied is here is of definite practical importance, because, although the majority of investigators now accept the allergic theory of the origin of bronchial asthma, the problem of demonstrating the organism's sensitization in bronchial asthma and the change in the latter in the treatment process has not yet been given adequate study.

ON THE THERAPEUTIC PROPERTIES OF THE MOUNTAIN CLIMATE IN HYPERTONIA

M.A. Aliev

(Frunze)

As long as 25 years ago, N.N. Sirotinin, in his book "Zhittya na visotakh i khvorova visoti" [Life at High Altitude and Altitude Sickness], made reference to the beneficial effect of the mountain climate in hypertonia. Subsequently, several papers confirming this view of N. N. Sirotinin have made their appearance. Thus, S.I. Telyatnikov (1954) observed at one of the mountain health resorts of Kazakhstan (1300 m) that the arterial blood pressure of individuals suffering from hypertonia generally decreased during sojourns at the resort.

E. Efendiev, S.M. Bedalova and D.K. Akhundov (1959) published the results of their observations of hypertonics residing at the health resort Isti-Su (2200 m). According to these authors, the high-mountain climate had a hypotensive effect on the hypertonia.

Kirgizia is a mountainous country. It occupies the entire western half of the Tien-Shan mountain system and part of the Alay mountain range. Three-quarters of the entire land area of the republic is at elevations above 1500 m, and slightly less than half of it is at altitudes of 3000 m and higher. The climate of Kirgizia is characterized basically by three features: sharp continentality, aridity and vertical climatic zonality.

Utilization of the Kirgizian mountain climate for treatment purposes in hypertonia is not only of theoretical but also of practical significance that extends beyond the boundaries of our republic. Sub-

stantiation of the therapeutic effect of the mountain climate on hypertonia will open unimaginably broad prospects for the use of mountain health resorts in a number of republics (Kirgizia, Uzbekistan, Tadzhikistan, Georgia and Armenia). All of this provided impetus for the organization of six scientific expeditions made in 1955-1961 to localities in the high mountains of Kirgizia, in which over 100 hypertonic and healthy (subsequently operated upon in the mountains) animals to those high altitudes.

METHOD

The renal form of experimental hypertonia was produced in dogs by collapsing one or both kidneys with a rubber capsule. The arterial pressure was determined by auscultation on the carotid artery, which was diverted into a skin pouch. Pressodepressor tests were performed using such pharmacological agents as adrenaline and nitroglycerine, mazatone and aminazine. The cholinesterase activity of the blood serum was determined by a chemical technique.

RESULTS OF EXPERIMENTS

First to be ascertained experimentally was the influence of mountain climatic factors at various altitudes upon the manifestation of the renal form of hypertonia. Thus, under the conditions of an altitude of 1800 m above sea level, the appearance and development of hypertonia was distinctly retarded in all six of the dogs in which unilateral renal ischemia had been produced. The arterial pressure in these animals even remained in the range of physiological fluctuations a month after the operation: systolic/diastolic = $(3 + 5.6)/(5 \pm 3.7 \text{ mm})$; $p > 0.5$ and 0.25 .

At the town of Frunze, surgical intervention on the kidney had produced, within a month after the operation, a permanent increase in arterial pressure: $(+38 \pm 4.6 \text{ mm})/(+28 \pm 4.8 \text{ mm})$; $p > 0.001$, i.e., manifest hypertonia.

Factors in the mountain climate at 2700 m above sea level also have a delaying effect on the development of renal-hypertonia. Thus, unilateral ischemization of a kidney was not capable in any of the four dogs of causing disturbances to vascular tone, and hypertonia did not resolve itself out. A month after the operation, the average values of the abnormally high arterial pressure did not reach a level that might be taken as a criterion of the hypertonic state.

The retarding influence of the mountain climate on the appearance of hypertonia after unilateral and bilateral renal ischemization was verified at an altitude of 3200 m above sea level. Hypertonia did not develop in any of three dogs with one kidney collapsed, just as in the case of the 1800 and 2700-meter altitudes. Collapsing both kidneys in three dogs resulted in a stable increase in arterial pressure, i.e., hypertonia (180-200 mm Hg). In the town, unilateral renal ischemization had produced an arterial pressure increase to 180 mm, while the bilateral operation raised it to 250 mm Hg.

Thus, the mountain climate or even a complex of altitude factors has a retarding influence on hypertonia stemming from unilateral kidney damage. In bilateral kidney damage, hypertonia develops, as a rule, without any noticeable signs that it is being suppressed.

The delaying effect also extends to other forms of experimental hypertonia. Thus, at an altitude of 3500 m above sea level, the development of desoxycorticosterone (injections of DOK over 35 days) and renal-desoxycorticosterone (unilateral renal ischemization, injection of DOK) hypertonias is clearly retarded. It has also been established that the mountain climate has a therapeutic effect on renal hypertonia produced even before the ascent to high altitude.

Keeping four dogs with a mild form of hypertonia (ischemization of one kidney) at an altitude of 1800 m above sea level resulted in nor-

malization of their arterial pressure. Thus, on the fortieth day, the average values of the hypotensive effect in these animals were as follows: with respect to systolic pressure 44 ± 6.3 mm (with $p > 0.01$), and with respect to diastolic pressure 35 ± 7.5 mm Hg (with $p > 0.02$). In control dogs left in town, the pressure remained abnormally high.

Under the conditions of the 2700 m altitude, we verified the effectiveness of mountain climate therapy in a more severe form of renal hypertonia produced by ischemitizing both kidneys. It should be noted that a hypotensive effect was observed in this form of hypertonia only during the latter part of the sojourn (on the 39th to 69th days) at the 2700-m altitude. The average values of the arterial-pressure decrease in five dogs with hypertonia on the 55th day in the mountains (2700 m) were as follows: in systolic pressure 49 ± 15.8 mm and in diastolic pressure 46 ± 12.8 mm Hg (with $p > 0.02$).

Climate therapy of both forms of renal hypertonia (unilateral and bilateral renal ischemization) was tested under the conditions of a 3200-m altitude. Hypertonia produced by collapsing a single kidney (4 dogs) "was cured" considerably more quickly than its more severe form - that stemming from collapse of both kidneys (3 dogs). The average values of the hypotensive effect ($n = 7$) on the 68th day were 30 ± 8 mm (with $p > 0.01$) in systolic pressure and 23 ± 6 mm (with $p > 0.02$) in diastolic pressure. In the five control animals left behind in town, the pressure remained at the hypertonic level at all times.

Thus, the climate of the high mountains, which constitutes a complex of atmospheric factors (subnormal barometric pressure, intense sunlight, negative ionization of the air, moderate temperature, etc.) may be characterized by a therapeutic effect on hypertonia. We must, however, state the reservation that such effective climate therapy in the renal form of experimental hypertonia was found to be possible only

during the summer (July-August). As a rule, we observed relative increases in arterial pressure in previously "cured" dogs early in the onset of cooler weather in the mountains (September-October).

Our data indicated that invoking hypertonia of both kidneys into the pathogenetic chain results in the development of a hypertonic state even under the conditions of the mountain climate or, in other words, the mountain climate was found to be "powerless" before hypertonia developed by bilateral injury to the kidneys.

In view of this, we made it our task to provide effective preventive measures against renal hypertonia by reinforcing the "antihypertensive" effect of the mountain climate with certain hypotensive agents. Thus, a new problem arose: that of mountain climatic and pharmacological prevention of experimental renal hypertonia. Out of the battery of pharmacological agents we settled upon two preparations: aminazine and reserpine.

A number of authors have reported on the hypotensive property of aminazine (Kurvuaz'ye, Mayer et al., M.D. Mashkovskiy et al., I.P. Anokhina, V.N. Mentova and others). As concerns reserpine, however, it has now been acknowledged one of the best of the most powerful hypotensive agents (A.L. Myasnikov, V.V. Zakusov, M.D. Mashkovskiy, K.N. Zamyslova, Z.A. Il'ina, Vakil', Arnold, Dev, Mayer et al.).

The mountain base at which this series of experiments was set up was located at an altitude of 3500 m above sea level. A total of 11 dogs were experimented with. Four dogs received aminazine in a dose of 1 mg/kg per day between two operations (renal ischemization), and it was administered to four other dogs in the same dose after the bilateral operation. Three dogs served as a control.

Let us first dwell upon the results obtained from the first version of aminazine prophylaxis for renal hypertonia. Prescription of

aminazine between the two operations (for 14 days) delayed the appearance of hypertonia by 16-20 days, while it arose a week after the second operation in the control dogs. The second preventive variant (prescription of aminazine after two operations on the kidneys) proved less effective (in the sense of the delay before the appearance of hypertonia). However, even this variant of prophylaxis was found to be expedient in that it limited the possible pressor shifts.

Thus, the arterial pressure had risen by 83 ± 25 mm (systolic) and 66 ± 19 mm Hg (diastolic) ($p > 0.01$) as compared with the initial level in the control animals by the 45th day after collapse of the second kidney. On the other hand, in the experimental animals that had received aminazine after two operations, the pressor shifts at this time were only 34 ± 21 ($p > 0.5$) and 31 ± 15 ($p > 0.25$), respectively. In the dogs that received aminazine between operations, the pressor shifts were even smaller — 17 and 14 mm Hg ($p < 0.25$ and 0.5).

The combination of mountain climate therapy with medication (aminazine and reserpine) produces clear-cut results in any form of renal-hypertonia. Thus, prescription of aminazine at an altitude of 3500 m causes the arterial pressure to decrease sooner in the treated dogs than in the control dogs (M.A. Aliev). Nevertheless, aminazine therapy for hypertonia is less effective under mountain conditions than treatment with reserpine. It is sufficient to administer 0.08 mg of reserpine per day to cause total disappearance of the hypertonia within two weeks when it is produced by collapsing both kidneys (T.P. Kalmykova).

Parallel study of the neurohumoral shifts indicated that the favorable effect of the mountain factors is accompanied by functional shifts in the central vasoregulatory mechanisms. For example, when animals with hypertonia are kept under mountain conditions (2700-3500 m), the pressor reaction to adrenaline and mesatone is suppressed to a marked degree

and, conversely, the depressor reactions to nitroglycerine and amiazine are clearly enhanced.

A decrease in the cholinesterase activity of the blood is a favorable biochemical shift in experimental hypertonia (Ye.A. Kakushkina, N.V. Il'chevich). Effective mountain climate and pharmaceutical treatment of renal hypertonia also reduces the cholinesterase activity of the blood serum.

Thus, N.N. Sirotinin was absolutely correct when he remarked at a 1955 conference on hypoxia: "We are still underestimating the prophylactic and therapeutic importance of the mountain climate."

Our experimental data, which were collected in the course of periodic expeditions (1955-1961) into mountainous regions of central Tien-Shan, as well as the data of N.V. Il'chevich and M.A. Kondratovich, who demonstrated the hypotensive influence of the El'brus mountain climate (1961), provide full confirmation for the above statement of N.N. Sirotinin and may be cited as experimental justification for practical use of mountain climate factors for the prevention and treatment of hypertonia.

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[Transliterated Symbol]

670

ДOK = DOK = dezoksikortikosteronovyy = desoxycorticosterone

DISTINCTIVE CHARACTERISTICS OF OXYGEN SUPPLY TO THE ORGANISM IN PATIENTS
WITH CARDIAC VALVE DEFECTS UNDER THE CONDITIONS OF THE MOUNTAIN CLIMATE

A.Yu. Tilis, M.M. Mirrakhimov and A.D. Dzhaylobayev

(Frunze)

There is a voluminous body of literature devoted to the problem of the influence of hypoxia, and, in particular, its hypoxic form, on the various functions of the organism. However, most authors have studied the influence of hypoxia on healthy individuals, and then chiefly under hypobaric-chamber conditions.

Adequate study has been devoted to the changes in the functioning of the cardiovascular and nervous systems (N.N. Sirotinin, N.V. Lauer, A.Z. Kolchinskaya, A.Grol'man, K. Vizinger, Garrison and Blelok et al.), the respiratory function (A.D. Slonim, O.N. Pavlova, A.I. Israel', S. Monge, A. Hurtado, Holden and Priestley et al.), and to changes on the part of the blood system and disturbances to certain other functions of the organism (P.I. Yegorov, G.Ye. Vladimirov, I.M. Dedyulin, Kh. Dal'-vig and others). All of these investigations are of extremely great importance in clarifying the mechanisms by virtue of which healthy individuals adapt to altered environmental conditions.

However, the literature contains very few studies planned to investigate the nature of the adaptive mechanisms that permit humans to live and work under the conditions of mountainous regions when they are suffering from one or another illness. Cardiovascular disease, in which precisely those systems that participate most directly in the process of acclimatization to the high mountains, is of particular interest.

According to R. Gerbst, who studied the influence of oxygen insufficiency on patients with cardiac insufficiency in the hypobaric chamber, and according to the data of P. Atland, B. Gigman and I. Roshe, who studied animals with aortal insufficiency, hypoxia causes the development of more distinct circulatory function disturbances, and does so with a higher oxygen content in the blood than in the case of healthy individuals.

Our investigations made it their objective to ascertain the nature of the organism's oxygen supply in patients with cardiac valve defects who had lived for a long time (since birth) in mountainous regions of Tien-Shan. A total of 64 patients were studied. Of these, 31 individuals were in Rybach'ye, which is situated at an altitude of 1650 m (atmospheric pressure 630 mm Hg), and 33 were at Naryn (2050 m) (atmospheric pressure 595 mm Hg). The patients were classified into five groups in accordance with the degree of circulatory insufficiency (after G.F. Lang).

The gas metabolism of all patients was studied by the Douglas-Holten method, with determination of the amount of oxygen absorbed by the organism in one minute, followed by appropriate calculations (through the heat equivalent of oxygen) to determine the basal metabolism. Further, in view of the existing relationship between the oxygen supply to the organism and hemodynamics, we also studied certain indices descriptive of the functioning of the cardiovascular system: arterial and venous pressure, blood stream rate (by the garlic and saccharine method, separately for the pulmonary and greater circulations), and the heart minute volume by the gas-analysis method after I.I. Khrenov. We juxtaposed the results with those of investigations conducted under the same conditions on healthy individuals (139 cases). We also had a so-called control group of heart patients whose gas metabolism and hemodynamics

were studied at Tashkent, which is situated in the foothill region of Tien-Shan.

According to L.A. Molchanov, the yearly average atmospheric pressure at Tashkent is 721 mm Hg. To exclude the additional effect of high temperature in the surrounding air, this group of patients, which comprised 27 individuals, was investigated during the winter at a bedroom temperature of 17-19°C.

Having studied the functioning of the circulatory system in heart patients under the conditions of the Tien-Shan foothills, we were able to establish a distinct relationship between the changes that made their appearance and the degree of circulatory insufficiency.

Thus, in patients with compensation effects and in circulatory insufficiency of degree I, we were unable to discern any substantial deviations of the hemodynamic indices studied from those of healthy persons. The values of the arterial and venous pressures, the blood stream rate and the heart minute volume remain within the so-called normal range. In other patients, as we pass from one degree of circulatory insufficiency to another, we note a progressive and consistent decrease in the blood stream rate and increases of acute disorganization of the blood supply, the blood stream time reaches its highest values (35-40 sec, averaging 33 sec).

The venous pressure varies in accordance with the gravity of the illness and the degree of cardiovascular insufficiency. In patients with degree IIA circulatory insufficiency, the venous pressure, although corresponding closely to the data observed in healthy individuals, is considerably in excess of the pressures obtained on patients of the preceding group. In the next group (degree IIB), the venous pressure reaches even higher values, fluctuating from 98 to 236 mm of water (averaging 170 mm of H₂O). The highest figures were obtained on patients with de-

gree III circulatory insufficiency (232 mm H₂O).

A more complete conception of the circulatory system's functional state was obtained in studying the heart minute volume. In our studies of patients with heart-valve defects, attention is drawn to the small amount of blood expelled by the heart each minute. As compared with the normal circulatory volume computed from I.I. Khrenov's tables, most of the heart patients have heart minute volumes reduced by 13-44%. In only two patients does this index vary within normal limits or slightly exceed them. Our data are in complete agreement with figures cited in the literature (G.F. Lang, A.A. Miller and M P. Kapost, Ye.G. Etinger and Ya.I. Mazel', N.M. Genin, Reyli et al.).

A considerable drop in heart minute volume indicates that the work of the cardiovascular system has become extremely difficult in the patients with cardiac valve defects. At the same time, even when the pathological process takes a very severe course in cardiac insufficiency, the amount of oxygen absorbed not only does not decrease, but frequently even increases as compared to the normal values (by 5-21%). This increase in the amount of absorbed oxygen would hardly satisfy the patient's oxygen requirement, since, according to V.Kh. Vasilenko, the phenomena observed in oxygen starvation of the organism make their appearance in circulatory insufficiency, even in the quiescent state. It must be acknowledged, however, that at a barometric pressure of 720 mm Hg the gas metabolism of the cardiac patients is found to be at the necessary level. This circumstance is characteristic for the conditions of the Tien-Shan foothills. As was indicated by our investigations (A. Yu. Tilis), such compensation is achieved at the expense of utilization of the blood system's reserves: the coefficient of oxygen utilization in the tissues rises, the arteriovenous oxygen-content difference increases, the dissociation of oxyhemoglobin is made easier; given high

oxygen capacity, delivery of the necessary amount of oxygen is made considerably easier as a result. Augmentation of breathing must be ascribed great importance in the regulation of the oxygen budget in patients with cardiac valve defects.

It was made clear that the respiratory minute volume in cardiac patients exceeds the necessary values by 38-74% under the foothills conditions. However, this amplification of pulmonary ventilation is of little effect, since the utilization coefficient of oxygen from the ventilated air settles at a very low level (27 instead of 38, as in healthy individuals).

As concerns the distinctive characteristics of the organism's oxygen supply and the state of its hemodynamics in circulatory insufficiency under mountain conditions, we succeeded in establishing a certain dependence of the changes that made their appearance upon the patients' histories of residence at various altitudes.

Thus, at the town of Rybach'ye (altitude 1650 m), the cardiac-valve patients showed a decrease in blood stream rate. With increasing severity of the pathological process, the slowdown of the bloodstream in the pulmonary and greater circulations becomes increasingly distinct (19.5 and 38 sec, respectively). A similar relationship was also revealed in patients in residence at Naryn (altitude 2050 m). With increasing altitude and with the consequent lowering of the oxygen content in the inspired air, however, the slowdown in the cardiac patients' bloodstream rate is noted even in the insipient forms of circulatory insufficiency and even in cases that we had regarded, on the basis of their clinical course, as compensated forms of the illness. This circumstance acquires the greater significance as a rather distinct tendency toward acceleration of the bloodstream was observed in healthy individuals with increasing altitude.

In view of the fact that a deceleration of the bloodstream rate, according to the testimony of F.G. Lang, N.D. Strakhesko, A.L. Myasnikov, B.Ye. Votchal and others, constitutes a highly sensitive indicator for the diagnosis of disorders of the cardiovascular system, it should be acknowledged that the inadequacy of circulatory function in patients with cardiac valve defects appears earlier with increasing altitude than under the conditions of the Tien-Shan foothills.

The same conclusion also follows from analysis of the venous-pressure figures. Thus, in the towns of Rybach'ye and Naryn, an increase in this indicator is noted even in the initial stages of disturbance to cardiovascular function (164-168 mm H₂O instead of the initial 128). Further, the following peculiarity comes to light: at Rybach'ye, the stagnation phenomena are more distinctly expressed at a given degree of circulatory insufficiency than they are under the conditions of the foothills. With increasing altitude (town of Naryn), the venous pressure remains abnormally high in the cardiac patients, but it is not possible to discern any consistent increase in this pressure in connection with increasing gravity of the pathological process. As follows from our investigations, irrespective of the degree of the circulatory insufficiency, the venous pressure remains at the 160-169-mm-of-water level in the patients at Naryn, while at Rybach'ye it increases consistently on passage from one degree of circulatory insufficiency to another (from 164 mm H₂O to 224 in degree III patients).

In the clinic, an increase in venous pressure is conventionally taken as one of the early signs of insipient circulatory insufficiency, and particularly of weakening of the right heart (V.A. Val'dman, A.L. Vilkovskiy, A.A. Vakar and others). In evaluating the venous pressure, however, it is also necessary to take into consideration the nature of the venous-tone change (G.A. Malov, N.N. Anichkov, et al.).

We may advance the hypothesis that the monotonic variation that we have noted in the venous pressure in our patients at Naryn and the absence of an increase in this index as cardiac decompensation advances are results of the development of venous hypotonia as a result of breathing rarified air.

It should be noted that under the conditions of the high mountains of Kirgiziya, vascular tone is, according to certain authors, subnormal (M.A. Aliyev, M.M. Mirrakhimov, et al.). In our investigations, this conclusion may also be drawn from analysis of the arterial-pressure indices. In particular, healthy individuals in the town of Rybach'ye and Naryn showed maximum arterial pressures of 109-112 mm Hg and minimum values of 69-70 mm Hg, or figures slightly below the generally accepted norms and the values obtained in the Tien-Shan foothills (117 mm Hg).

An important fact is that various fluctuations in arterial pressure are noted in cardiac-valve patients as a function of the altitude at which the examination is made. At the time of Rybach'ye, this index is somewhat higher than in healthy individuals and higher than in patients with the corresponding degrees of circulatory insufficiency examined in the Tien-Shan foothills (120-144 mm Hg). At the higher altitude (town of Naryn), the arterial pressure remained essentially at the level characteristic for individuals who live year-round under these conditions (111-128 mm Hg).

Thus, cardiac patients differ from healthy individuals in not showing a compensatory reaction on the part of vascular tone in response to the mountain climate. In all probability, the regulatory mechanisms in these patients have been completely exhausted or, even more probably, they are directed toward compensation of the basic distress.

In this connection, it is extremely important to find out how fully patients with cardiac valve defects are supplied with oxygen under the

conditions of a mountain locality. It was found that for a given degree of circulatory insufficiency, the gas-metabolism value varied differently depending on the altitude at which the patients were examined. On comparing the amount of oxygen actually absorbed with the "necessary amounts" we established that at the town of Rybach'ye (1650 m) the gas metabolism was 12-31% above normal. Only patients with the compensated form of cardiac valve defect absorb less oxygen than would correspond to the amounts necessary for them. In such patients, the gas metabolism deviates in the same direction as in healthy individuals (see Table). As the pathological process increases in gravity, the amount of oxygen absorbed per minute increases slightly, with the nature of the insipid changes showing the same tendency as was observed in the patients under the conditions of the Tien-Shan foothills.

Changes in Quantity of Absorbed Oxygen in Patients with Cardiac Valve Defects under the Conditions of the High Mountains and the Tien-Shan Foothills (in ml per 1 min)

1 Степень недостаточности кровообращения	2 Предгорье Тянь-Шаня			6 Высота 1650 м (г. Рыбачье)			7 Высота 2050 м (г. Нарын)		
	3 Должное	4 Фактическое	5 В % к должному	3 Должное	4 Фактическое	5 В % к должному	3 Должное	4 Фактическое	5 В % к должному
0	190	199	+ 5	211	174	- 18	201	177	- 12
I	195	214	+ 10	255	326	+ 19	192	181	- 6
8 IIА	210	228	+ 14	190	212	+ 12	196	178	- 10
IIБ	192	227	+ 18	182	209	+ 31	179	172	- 4
III	189	229	+ 21	187	219	+ 17	—	—	—
9 Здоровые	199	217	+ 9	208	191	- 9	204	198	- 3

1) Degree of circulatory insufficiency; 2) Tien-Shan foothills; 3) necessary; 4) actual; 5) in % of necessary; 6) altitude of 1650 m (town of Rybach'ye); 7) altitude of 2050 m (town of Naryn); 8) IIB; 9) healthy.

In contrast to the above, the gas metabolism is subnormal in patients at Naryn for all degrees of circulatory insufficiency; the patients absorb less oxygen than would correspond to their needs and, what is most important, less than patients in just as serious condition at the town of Rybach'ye (see Table). Consequently, starting at the alti-

tude of 2000 m, we may discern certain complications in the course of the fundamental pathological process and a greater degree of impediment to gas exchange than would be expected on the basis of the nature of the disorder itself. Changes in the basal metabolism also follow in accordance with the change in gas exchange: in the Tien-Shan foothills, this index exceeds the necessary values by 17-23% and at Rybach'ye by 12-14%, while at Naryn the basal metabolism is 9-15% below normal. It is highly indicative that the effectiveness of respiration declines markedly with increasing altitude. Thus, while the utilization coefficient of the oxygen from the ventilated air was 27 in patients with IIB circulatory insufficiency under the conditions of the Tien-Shan foothills, it drops to 25 at Rybach'ye and to only 22 at Naryn. This result testifies to considerably more difficulty in the diffusion of oxygen through the pulmonary membrane and reflects the degree of stagnation phenomena in the pulmonary circulation.

The significant decrease in the oxygen utilization coefficient in the cardiac patients in the mountains is accompanied by an increase in the respiratory minute volume (by 55-80%), something that would appear to be a function of the increase in the organism's oxygen supply, in addition to other factors. As we know, oxygen supply is supported by a complex of systems: external respiratory, circulatory and hematopoietic. As would follow from our studies in circulatory insufficiency, the external respiratory apparatus functions under the heaviest strain, but is of low effectiveness.

The circulatory function must be ascribed decisive importance in the oxygen budget. Under the conditions of the Tien-Shan foothills, however, our patients with cardiac valve defects had subnormal heart minute volumes. When this indicator was studied in patients in the towns of Rybach'ye and Naryn, we did not obtain unequivocal results: the heart

minute volume was depressed in some of the patients, but cases were observed in which it was higher than normal.

There is no doubt that this problem requires further elaboration and the use of other research methods. Of importance, however, is the fact that, when faced with oxygen shortage in the external atmosphere, patients with cardiac valve defects have at their disposal compensation mechanisms whose action supports gas exchange and the state of hemodynamics at the level that inevitably stems from the nature of the pathological process itself, continuing to do so up to a certain altitude. This limiting altitude is 2000 m. Beginning at this level, cardiac patients in all degrees of circulatory insufficiency show more distinct difficulty in supplying their organism with oxygen than is usually the case.

At an altitude of 1650 m, heart-valve patients with complete compensation and those in the initial forms of circulatory insufficiency show good adaptation to the environmental conditions, while a certain aggravation of the fundamental disorder is observed in degrees IIB and III. These results stake out the basic paths to be taken in treatment of heart-valve patients under mountain-climate conditions — first and foremost, along the lines of oxygen therapy.

ARTERIAL PRESSURE NORMS FOR NATIVE INHABITANTS OF THE
MOUNTAINOUS REGIONS OF KIRGIZIA

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(Frunze)

Kirgiziya is a mountainous country. Hence it is very important to study the mechanisms by which man becomes acclimatized to the high mountains. To this day, it remains unclear whether the physiological indices to the activity of the cardiovascular system in inhabitants of the high mountains correspond to the values found for lowland inhabitants. Hence it is necessary to make a large scale study of the population in mountainous regions of the republic (At-Bashin, Narin and the Arpa-Aksay pastureland of the Tien-Shan region, at altitudes of 2000-3500 m above sea level) with the object of establishing local arterial pressure norms.

Individuals of both sexes, aged 17 to 92 years, were studied. A total of 5344 practically healthy individuals were included in the study, including 2588 men and 2756 women. The arterial pressure was measured by the Korotkov method in the state of rest, after 10-15 minutes of relaxation. The cuff was applied to the right arm and the pressure measured in the sitting position until stable figures were reached.

In evaluating the data that we had collected, we were guided by the arterial-pressure norms published by A.L. Myasnikov, Ye.F. Fedorova (Moscow); V.M. Avakyan, G.O. Badalyan (Armenia), Z.M. Volynsk'iy et al. (Leningrad) and V.A. Khlyupin (Stavropol'). The material was given variational-statistical analysis (see Table).

It is evident from the Table that in the compact population groups the systolic pressure is 90-130 mm Hg in the 17-39-year age group. This arterial pressure level is observed in 94.7-95.8% of men and 95.7-98.4% of women.

Percentage Distribution of Various Values for Systolic and Diastolic Arterial Pressure in Practically Healthy Persons by Age Groups

1 Величина давления в мм рт. ст.	2 Возраст													
	17-19		20-24		25-29		30-39		40-49		50-59		60-70 и более	
	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины	4 Мужчины	5 Женщины
6 Систолическое давление														
70-79	—	0.5	0.2	0.3	0.2	—	—	0.2	—	—	—	—	—	—
80-89	2.2	2.9	1.9	3.5	0.7	0.9	0.6	2.1	0.4	2.0	0.9	1.8	0.7	0.5
90-99	8.0	14.3	9.2	7.1	5.7	12.4	6.5	11.6	6.5	6.5	4.2	5.0	2.6	3.0
100-110	49.8	59.1	48.7	51.0	43.0	51.3	44.0	49.0	40.1	44.5	37.0	32.0	27.0	21.0
111-120	25.5	16.7	30.5	28.5	35.0	27.0	31.0	26.0	27.0	25.4	25.4	28.0	25.1	25.3
121-130	11.5	5.9	7.2	8.7	12.1	8.6	13.2	9.3	20.1	15.0	20.0	21.0	25.0	25.5
131-140	2.6	0.5	3.1	1.3	3.3	0.7	4.7	2.0	5.2	7.0	11.7	9.8	12.6	22.3
141-150	—	—	—	—	—	—	—	—	0.7	—	0.9	3.2	7.2	6.7
M ± m	100 ± 0.8 12.3	100 ± 0.7 10.7	106 ± 0.5 12.7	105 ± 0.7 13.6	111 ± 0.6 11.9	109 ± 0.5 11.4	112 ± 0.5 12.9	110 ± 0.4 10.5	115 ± 0.8 12.7	114 ± 0.7 13.3	122 ± 0.9 14.0	117 ± 0.7 13.0	122 ± 0.9 14.9	128 ± 0.8 15.2
7 Диастолическое давление														
40-49	0.5	1.0	0.9	1.8	0.5	0.5	0.7	1.3	0.4	0.3	0.4	0.3	—	0.3
50-59	4.9	11.8	5.7	7.6	2.9	5.2	0.7	3.6	2.3	4.1	1.4	1.8	1.8	1.6
60-70	75.5	73.4	74.7	77.0	74.0	80.0	64.1	76.1	61.8	70.0	61.0	56.1	57.1	51.0
71-80	16.5	12.3	16.0	13.2	18.3	14.1	30.0	17.2	30.7	21.6	31.4	35.8	34.1	39.6
81-90	2.6	1.0	3.0	0.8	4.0	0.7	4.7	1.7	5.0	4.9	6.0	6.0	7.0	7.6
91-95	—	—	—	—	—	—	—	—	—	—	—	—	—	—
M ± m	66 ± 0.7 8.5	65 ± 0.7 9.3	70 ± 0.4 9.9	64 ± 0.4 8.6	68 ± 0.4 9.2	66 ± 0.4 8.3	70 ± 0.4 9.5	67 ± 0.4 8.8	70 ± 0.6 9.7	69 ± 0.6 8.6	72 ± 0.6 9.0	69 ± 0.5 9.9	71 ± 0.6 9.4	73 ± 0.5 9.0
8 Количество обследованных	225	233	474	394	454	418	640	695	264	339	236	335	275	372

1) Pressure value in mm Hg; 2) age; 3) (in years); 4) men; 5) women; 6) systolic pressure; 7) diastolic pressure; 8) number of persons examined.

In the 40-59-year age group, systolic pressures in the range from 90-140 mm Hg are encountered in 98.2-98.9% of men and 95-98% of women. For the group 60-70 years of age and over, systolic pressures in the range from 90-150 mm Hg were registered in 99.3% of men and 99.5% of women.

Thus, the lower boundary of systolic pressure is 90 mm Hg for all ages, while the upper boundary is 130 mm Hg for ages 17-39, 140 mm Hg for 40-59 years and 150 mm Hg for ages beyond 60 years.

Average systolic pressure values vary among the inhabitants of the mountainous regions of Kirgiziya from $M \pm m = 106 \pm 0.5$ - 122 ± 0.9 mm Hg in men and 105 ± 0.7 - 128 ± 0.8 mm Hg in women.

These data show a slight but consistent increase in the average systolic pressure value with increasing age in persons of each sex; the difference between men and women as regards systolic pressure level is insignificant.

The diastolic-pressure boundaries of the compact groups at ages 17-29 are 50-80 mm Hg. These values are encountered in 96.1-98.5% of men and in 97.4-98.8% of women. A diastolic pressure of 50 mm Hg may be regarded as the lower boundary of the norm, and 80 mm Hg as the upper boundary.

In the age groups from 30-39 years, the lower diastolic pressure boundary of the compact groups is 60 mm Hg and the upper boundary 80 mm Hg. Diastolic pressures within these limits were registered in 94% of men and 93.4% of women.

In later age groups (40-70 years), the boundaries of the diastolic pressure compact groups are 60-90 mm Hg, figures that are observed in 97.3-98.6% of men and in 95-98.3% of women.

Consequently, the normal diastolic pressure values at ages 17-29 lie between 50 and 80 mm Hg, for ages from 30-39 years between 60 and 80 mm Hg, and at age 40 and older between 60 and 90 mm Hg.

The average diastolic pressure values vary in the range $M \pm m = 60 \pm 0.7$ - 72 ± 0.6 mm Hg in men and in the range 65 ± 0.7 - 73 ± 0.5 mm Hg for women (see Table).

In the individuals whom we examined, pulse pressures of 35-60 mm Hg were noted in 85% of men and 85.5% of women; pressures below 35 mm Hg were found in 11% of men and 11.2% of women, and values higher than 60 mm Hg were observed in 4% of men and 3.3% of women. The pulse

pressure increases with increasing age irrespective of sex.

Thus, on comparison of data secured in this examination of the inhabitants of the Kirgizian mountains with the corresponding indices for inhabitants of lowland areas (Moscow and Leningrad), we may draw the following inferences: the arterial-pressure level, whether systolic or diastolic, is slightly lower in native inhabitants of the Kirgizian high mountains than in inhabitants of Leningrad and Moscow. These differences are observed particularly frequently at ages below 29 years; in older persons, both men and women, such a difference is not detected.

EXPERIMENTAL DATA ON THE EFFECT OF THE MOUNTAIN CLIMATE ON THE COURSE
OF ARTERIAL HYPERTONIA AND MYOCARDIAL INFARCT

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(Kiev)

In the mountains, the human organism is subjected to the action of a set of factors that produce changes in a number of physiological functions. The changes in blood pressure, pulse and respiration as an effect of ascents into the high mountains have been studied by many authors (Tret'yakov, Godden, Wiggers, Sirotinin, Bykov, Vereshchagin and Boldyrev, Minut-Sorokhtina, Gregg, Gadzhiev, and others), but the results of these researches have been somewhat contradictory. Thus, some authors noted a decrease in blood pressure during the sojourn in the mountains, while others reported that it increased, and so forth.

Most of the authors who observed a rise in the blood pressure level on ascent into the mountains regard it as one of the manifestations of a compensatory reaction on the part of the cardiovascular system to the drop in the oxygen partial pressure.

The question as to the influence of hypoxia on the cardiovascular systems of healthy animals has been the subject of numerous studies (Grin and Zhil'ber, Miki, Charnyy, Van-Lir, Lauer, Bukhalovskiy, and others).

Of considerably greater interest is experimental study of the various forms of pathology of the cardiovascular system under the conditions of hypoxia. Only occasional studies have been devoted to this problem (Smirnov, Miterev, Gurevich and Kvitnitskiy, and others), and

these have been conducted under laboratory conditions. In the recent literature, the only report known to us is that of Aliev, who studied the influence of the high mountains (1800-3200 m, Kirgiziya) on the development and course of experimental renal hypertonia. The author concludes that the higher the altitude, the slower is the development of hypertonia, and the more rapidly is the arterial pressure normalized in animals in which hypertonia has already developed.

The present study, which was carried out during an El'brus expedition of the A.A. Bogomolets Physiology Institute of the Academy of Sciences Ukrainian SSR, was devoted to study of the effect of the mountain climate on the dynamics of a number of indices to the functional state of the cardiovascular system in dogs with experimental renal hypertonia and experimental myocardial infarct. Control studies were also set up.

Renal hypertonia was produced by application of split silver rings to the renal arteries, and myocardial infarct by application of a ligature to the middle third of the descending branch of the left coronary artery. Both carotid arteries were diverted into skin pouches in all of the experimental dogs.

The animals were examined twice at Kiev: before the operation whose purpose was to produce the experimental pathology of the cardiovascular system and after it. Then the animals were examined four more times: at Terskol (2000 m above sea level) at Novyy Krugozor (3200 m), at Ledovaya baza (3900 m) and after the descent to camp at Terskol. The dogs were examined again a month after the return to Kiev.

The dynamics of the experimental animals' arterial blood pressure (maximum and minimum) pulse, respiration, reflex response to lowering of the pressure in the carotid sinus and electrocardiograms was studied.

Dynamic study of the respiratory frequency on the ascent to El'brus showed a consistent quickening without any distinctive features among the various groups of experimental animals. The heart rhythm also quickened in all animals (including the control group), but differently in different groups. The sharpest acceleration of cardiac rhythm with

smoothing of the sinus arrhythmia was noted in the dogs with experimental hypertonia. They showed distinct tachycardia even before arrival at Terskol, and its degree increased with the ascent to Novyy Krugozor and Ledovaya baza. Thus, the highest excitability of the extracardial nervous apparatus on ascent into the mountains was noted in experimental hypertonia. Analogous phenomena have been noted in the hypobaric chamber (Gurevich and Kvitnitskiy).

In the dogs with myocardial infarct (and in the control group), the arterial pressure showed little change with the ascent into the mountains, although a vague tendency to diminish was observed. This is in agreement with literature data on a lowering of the reflex excitability of the cardiovascular system after a major branch of a coronary artery has been tied off (Aronova, Kozak and Il'chevich, Frol'kis). Different results were obtained in studies of the dogs with experimental hypertonia. At Terskol, the arterial pressure of these animals had either increased slightly (within 10-15 mm) or not changed at all, but by the time of arrival at Novyy Krugozor, all dogs with arterial hypertonia showed a distinct drop in arterial pressure, by 20-40 mm Hg. This decrease was even more conspicuous at Ledovaya baza. At the same time, the sinocarotic reflex (Fig. 1) had increased considerably (by a factor of 1.5-2).

A comparison of the dynamic changes in arterial blood pressure and magnitude of sinocarotic reflexes during the development of experimental renal hypertonia has been made under laboratory conditions by N.N. Gorev and his co-workers. It was established here that during the first few months of the development of hypertonia, the blood pressure level and excitability level of the vasomotor center, the latter judged on the basis of the strength of unconditioned vascular reflexes, increase concurrently. Only in the fourth to fifth month of the development of

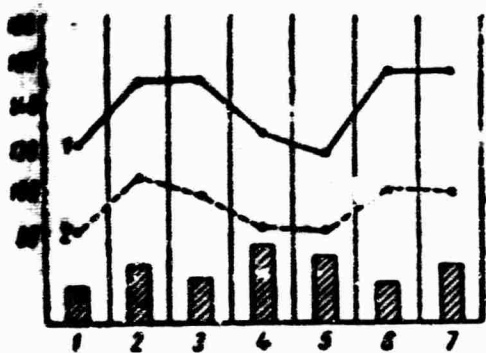


Fig. 1. The dog Pal'ma. Renal hypertonia. Dynamics of arterial pressure in mm Hg and magnitude of sinus reflex. 1) Before operation; 2) after operation; 3) at altitude of 2000 m; 4) at altitude of 3200 m; 5) at altitude of 2900 m; 7) at Kiev. 1) Maximum pressure; 2) minimum pressure. The bars indicate the magnitude of the sinus reflex.

hypertonia do we observe divergence between these indices. While the excitability of the vasomotor center diminishes, the blood pressure level continues to rise. This divergence is accounted for by the fact that by the fourth to fifth month of the development of hypertonia, the renal pressor factor is permanently "engaged," and this is responsible for the subsequent rise in blood pressure.

In our experiments on dogs with renal hypertonia, it was possible to perceive that with increasing altitude, the blood pressure level is lowered, while the excitability of the vasomotor center, which is determined by the strength of the sinocarotic reflex, increases. These data cannot be related to the time point in the development of hypertonia, since the experiments were performed on animals with hypertonia of two months' standing, and, of course, the changes observed were totally different from those manifested under laboratory conditions.

The rise in the excitability of the central nervous apparatus regulating vascular tone as the experimental animals are brought up to higher altitudes suggests that the drop in blood pressure level observed here cannot be accounted for simply in terms of changes in the functional state of the central nervous system. An increase in the excitability of the vasomotor center in the animals with renal hypertonia should have promoted a rise in blood pressure and not the contrary. Hence, it is more probable that a certain role is taken by peripheral

mechanisms responsible for a drop in arterial pressure in the animals with renal hypertonia under the conditions of the high mountains.

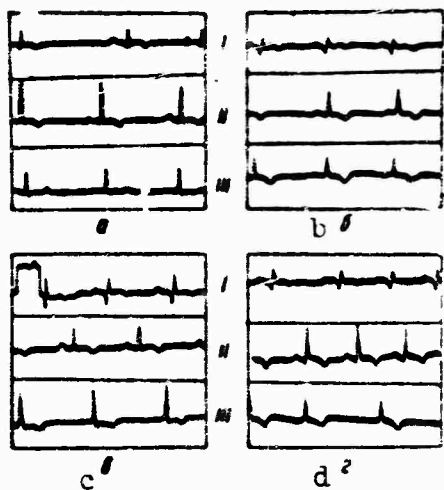


Fig. 2. Electrocardiogram of the dog Al'ma. Experimental insufficiency of coronary circulation. a) EKG recorded at Kiev; b) at Terskol; c) at Novyy Krugozor; d) at Ledovaya baza. I, II, III) derivations.

isoline in derivation III) and the appearance of deep negative T_{2-3} waves, phenomena apparently connected to focal ischemia of the myocardium in the posterior wall of the heart against a background of insufficiency of the coronary collateral circulation that has arisen (Fig. 2).

On the ascent into the mountains, the dogs with experimental hypertonia also exhibited (highly variable) manifest dynamism in the elements of the EKG, with sinus tachycardia developing particularly sharply and consistently with increasing altitude. Thus, at Terskol, the dog Pal'ma, which was afflicted with the renal form of hypertonia, showed a negative phase of the T-wave in derivations I and II. When the dog was taken up to Novyy Krugozor, we noted that all waves went positive, while at Ledovaya baza, together with the acute tachycardia, we observed that the T_{2-3} waves had again gone negative with a sharply positive

The dynamics of the EKG indices in the experimental animals is also of definite interest. Particularly sharp shifts were noted in animals with experimental pathology of the cardiovascular system, and in particular in those with coronary disease (the dogs Al'ma and Tarzan).

Thus, even at Terskol, the dog Al'ma showed a discordant type of change in the EKG waves in the classical leads; on the ascent to Novyy Krugozor and Ledovaya baza, we note dynamic shifts in the S-T interval (below the level of the

11.

Thus, myocardial hypoxemic changes of a diffuse or focal nature arise in animals with experimental myocardial infarct and experimental renal hypertonia with ascent to altitude in the mountains. Here we observe a lower excitability of the heart, but a more distinctly manifest focal pathology in the dogs with coronary insufficiency as compared with the "hypertonic" dogs.

In summary, it may be noted that the mountain climate has distinct and variegated effects on the functional state of the cardiovascular system, particularly when the latter is in pathological states.

This problem is of considerable practical and theoretical interest and is no doubt worthy of further study.

CHANGES IN CERTAIN INDICES OF THE CARDIOVASCULAR SYSTEM AND RESPIRATION
UNDER MOUNTAIN CONDITIONS

(A Comparative Study in Schizophrenia Patients and Healthy Persons)

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(Gor'kiy, Kiev)

Over the past several years, the laboratory headed by N.N. Sirotin-in has established, in experiments in the hypobaric chamber and at high altitudes, that schizophrenia patients have excellent tolerance for oxygen insufficiency (A.Z. Kolchinzkaya and S.D. Rasin, 1952). Many patients showed a permanent improvement after a sojourn in a mountainous locality. These observations provided impetus for a broad-scale, comprehensive study of the changes that develop in the physiological and psychic functions of schizophrenia patients under mountain conditions.

The task of the present study was to compare the changes in the indices to the state of the cardiovascular and respiratory systems of schizophrenics and healthy individuals at various altitudes. The changes in respiration and blood circulation that appear quickly when the oxygen partial pressure is lowered are well known from the literature on the mountain climate. We felt it would be expedient to ascertain whether the nature and degree of manifestation of similar shifts in schizophrenics are the same as those observed in healthy individuals. The study was performed by one of the teams of the 1954 composite El'brus expedition undertaken by the A.A. Bogomolets Physiology Institute of the Academy of Sciences of the Ukrainian SSR.

METHOD

The following quantities were determined: pulse, blood pressure (on left and right arms), pulmonary vital capacity, and the maximum force of the airstream on inspiration and expiration (from data of pneumotachometry after B.Ye. Votchal); electrocardiograms were recorded (in the three standard leads). Also studied was the reaction to light physical exertion (12 situps in one minute). The reaction to exertion was taken into account in terms of the pulse, blood pressure and electrocardiogram changes. The indices were determined immediately after exertion and during the recovery period.

Examinations were made four times: in the area of Terskol (2000 m above sea level) immediately after arrival and again four to five days later; at El'brus Novyy Krugozor (3000 m) on the second to third day after the ascent; and at Priyut Eleven (4200 m) on the second day after the ascent. Further, some of the studies were repeated in the area of Terskol after the descent. The examinations were made during the afternoon hours, usually just before the evening meal.

A total of 7 schizophrenics and 16 normal individuals were studied. The patient group was composed of men aged 16-34 years. All had been diagnosed as schizophrenics at a psychiatric retreat (Kiev). The standing of the disease varied from 1 year 4 months to eight years. The group of healthy individuals consisted of ten men and six women ranging in age from 20 to 54 years. There were no abnormalities in the cardiovascular systems and respiratory organs of any of the subjects, whether schizophrenic or normal.

RESULTS OF INVESTIGATIONS

1. In most of the patients, whether healthy or schizophrenic, the pulse changes were characterized by acceleration. In the patient group, the tachycardia was found to be more distinct and occurred more frequently than among the healthy individuals. Thus, at the first examination, the pulse was above 90 per minute in all of the schizophrenics, ranging as high as 132 beats per minute. During the same period, the pulse rates of the comparison group did not exceed 100 per minute and were above 90 in only half of the subjects. On the repeated examination

at Terskol, a decrease in the tachycardia was noted in both groups. As before, however, the pulse rate was comparatively higher among the schizophrenics. With increasing altitude, there was another acceleration of the pulse, particularly at the 4200-meter level. In the examination at Priyut Eleven, the schizophrenia patients were again observed to have the most rapid pulses (Table 1).

2. Increases in blood pressure were observed considerably less often than quickening of the pulse. The shifts in the maximum pressure were considerably more distinct as compared with the changes in minimum pressure. The blood pressures of the schizophrenics were observed to rise less often than those of the healthy individuals. At all altitudes, the maximum and minimum blood pressure figures were found to be lower more often in the schizophrenics. The pulse pressure showed a certain tendency to rise in the follow-up examinations. The fluctuations of pulse pressure were approximately the same in both groups. The difference in the blood-pressure indices as measured on the right and left arms was within the normal range (not over 10 mm Hg) in the normal individuals and in the schizophrenia patients. In four schizophrenia patients, a minor asymmetry of the blood pressure (5-10 mm) was observed on the first examination, and disappeared at the second and reappeared in subsequent examinations at altitudes of 3000 and 4200 m (see Table 1).

3. Signs of myocardial ischemia were detected in the electrocardiographic examination. The more frequent deviations were a shift in the S-T interval and a decrease or inversion of the T-wave, more frequently in derivation III. Less often, we noted a decrease in the R-wave and the appearance of a high T-wave. No particular differences were noted in the electrocardiogram changes in the healthy persons and the schizophrenia patients. The frequency and extent of the electrocardiographic

shifts increased with increasing altitude. The largest changes were noted when the curves were registered at an altitude of 4200 m. At this level, the electrocardiogram remained normal only in two healthy individuals and a single patient out of the total number of subjects. After the descent to Terskol, the electrocardiogram returned to normal in the majority of subjects.

4. The reaction to physical exertion was manifested in a quickening of the pulse, a rise in blood pressure, and the appearance or aggravation of electrocardiographic shifts. The changes were at maximum immediately after exertion and then gradually smoothed out. On the first examination, the extent to which the pulse was accelerated after exertion amounted to 5-30% of the initial figure. At higher altitudes, performance of the same work frequently caused a quickening of the pulse by 40, 50 and 60%. The changes in blood pressure after exertion were less strongly manifest. The maximum pressure usually rose by 3-11% of the initial figure. The minimum pressure frequently showed no change at all on performance of work. In the cases in which the minimum pressure rose, the increment after exertion was 6-17% of the initial value. In three subjects from the healthy group, we observed a paradoxical reaction to exertion in the form of a slight decrease in the minimum pressure, and a slackening of the pulse in one case. No increase was observed in the blood-pressure changes after exertion as the altitude was increased. Restoration of the initial pulse and blood-pressure levels was usually complete 2-3 minutes after stopping work, and less often after 4-5 minutes.

The electrocardiographic changes following exertion were characterized by the appearance or increase of signs of myocardial ischemia (shift of the ST interval, flattening or inversion of the T-wave, drop in R-wave, appearance of a high T-wave). The frequency and sharpness of

the electrocardiographic changes were functions of altitude. The greatest changes following exertion were noted in the electrocardiographic tests at the level of Priyut Eleven. At this altitude, exertion resulted in disturbances to the cardiac rhythm in addition to the ischemic shifts. In the subject B., a healthy young woman of 26 years, a distinct sinus arrhythmia appeared after exertion. In the case of the patient T., male, 20 years old, the electrocardiogram taken after exertion registered ventricular extrasystoles. After the descent to Terskol, performance of physical work produced no changes on the electrocardiogram in most cases.

The reaction to physical exertion was of the same type in both of the subject groups. The schizophrenia patients frequently showed a less distinct reaction than the normal individuals. The amount by which the pulse quickened was often smaller, shifts of the maximum pressure were more frequently absent, and the paradoxical reaction to exertion was not observed. The nature and frequency of the electrocardiographic changes after exertion were identical in the two groups.

5. The pulmonary vital capacity underwent no changes. In almost all of the subjects, healthy individuals and schizophrenia patients alike, the spirometry results were in conformity with the norms. With increasing altitude, the pulmonary vital capacity either remained unchanged or showed minor fluctuations, either increasing or decreasing.

The pneumotachometry data present a certain amount of interest to the extent that we have been unable to find any literature indications regarding the maximum force of the air stream under mountain conditions. According to our data, the maximum air stream force on expiration is normally 4-8 liters/sec, while that on inspiration is 3-6 liters/sec. The force of expiration always exceeds that of inspiration, with the result that the coefficient expressing this ratio is always greater

100. Frequency and Blood Pressure Level in Healthy Individuals and Schizophrenia Patients at Various Altitudes on El'brus

Фамилия	Пол	Возраст, лет	2000 м (I)				2500 м (II)				3000 м				3500 м				3800 м (3)			
			Пульс		Кровяное давление		Пульс		Кровяное давление		Пульс		Кровяное давление		Пульс		Кровяное давление		Пульс		Кровяное давление	
			по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе	по-топ	по-группе
Группа больных																						
Ш-76	М.	23	104	140	95 55	100 80	-	-	-	-	88	120	100 60	105 60	104	120	90 55	100 60	95	95	100 75	100 95
Т-6	М.	20	96	132	90 50	100 50	80	100	120 70	120 75	88	112	120 65	125 70	112	140	90 60	110 60	84	96	95 70	100 75
Ш-6	М.	26	132	180	90 60	110 60	84	112	120 65	130 70	84	120	120 85	125 85	-	-	-	-	-	-	-	-
Ф-6	М.	29	92	108	100 70	110 70	88	84	135 90	140 90	88	102	110 70	120 70	80	96	110 70	120 70	84	90	110 80	115 85
У-6	М.	16	98	120	95 65	100 65	98	124	90 60	110 70	88	112	90 60	110 65	108	120	75 55	90 60	84	114	85 60	85 60
Л-6	М.	34	114	130	90 60	100 60	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Л-8	М.	21	96	112	110 70	130 65	96	124	120 80	130 80	96	104	120 80	125 80	104	120	115 65	125 80	84	108	105 70	105 80
Группа здоровых																						
Л-8	М.	20	86	72	100 60	140 80	85	84	120 70	125 70	68	90	130 80	130 80	56	90	110 60	120 70	60	72	100 75	110 80
Л-8	М.	44	92	120	140 80	150 80	84	96	145 80	150 90	84	108	130 80	135 80	92	114	120 70	125 80	96	114	115 90	125 95
Л-6	Ж.	36	88	102	100 60	105 60	76	104	120 80	130 80	76	104	120 80	135 80	72	108	100 60	110 65	66	120	95 70	105 65
А-8	М.	46	100	120	120 80	160 90	92	140	145 90	160 90	100	120	140 85	160 90	100	120	150 100	160 100	96	120	130 110	135 110
Д-8	М.	28	88	100	120 80	135 50	76	102	120 80	130 80	72	96	120 80	120 80	92	108	110 70	115 80	-	-	-	-
Л-6	М.	20	88	102	110 55	110 60	80	76	120 75	130 80	76	120	110 75	120 80	90	92	95 60	100 65	72	114	95 65	110 60
Л-6	Ж.	26	92	100	110 70	120 60	84	120	125 80	130 80	80	108	130 80	130 80	96	120	120 70	120 75	75	84	120 95	125 100
Б-6	Ж.	26	96	120	100 60	120 70	88	120	115 70	140 90	92	116	120 80	140 80	80	120	110 70	120 80	72	120	100 75	100 60
Д-8	М.	36	92	120	110 65	130 70	-	-	-	-	76	108	135 96	140 100	92	120	110 75	120 85	72	96	135 85	135 85
Б-6	Ж.	26	-	-	-	-	80	120	110 70	125 75	64	96	115 80	120 80	-	-	-	-	-	-	-	-
Т-6	Ж.	32	-	-	-	-	66	76	90 60	110 70	92	120	120 70	125 75	-	-	-	-	-	-	-	-
В-6	М.	31	-	-	-	-	88	80	100 60	110 70	76	102	115 75	120 80	-	-	-	-	-	-	-	-
М-6	М.	25	96	108	95 60	100 70	80	102	120 80	130 80	76	90	120 80	135 90	68	96	110 80	115 80	76	80	130 80	140 80
С-8	М.	35	76	84	95 70	95 70	66	96	100 70	105 80	78	96	105 80	110 85	72	96	100 75	100 70	-	-	-	-
С-8	М.	54	-	-	-	-	76	96	120 90	125 80	80	96	120 90	125 80	84	102	145 95	160 95	-	-	120 80	120 80
В-6	Ж.	32	92	111	110 80	120 80	64	102	115 80	130 80	92	114	120 80	130 80	82	114	120 80	125 80	84	114	125 75	120 80

1) Name; 2) sex; 3) age, years; 4) pulse; 5) at rest; 6) after exertion; 7) blood pressure; 8) patient group; 9) Sh-t'; 10) male; 11) T-o; 12) Sh-a; 13) F-v; 14) U-v; 15) P-v; 16) P-y; 17) normal group; 18) L-n; 19) D-n; 20) L-a; 21) female; 22) A-n; 23) O-y; 24) T-o; 25) D-a; 26) B-a; 27) R-y; 28) B-a; 29) T-a; 30) V-o; 31) M-v; 32) S-n; 33) S-n; 34) V-ch.

TABLE 2

Pneumotachography Data and Vital Capacities of Healthy Individuals and Schizophrenia Patients at Various Altitudes on El'brus

Фамилия	Пол	Возраст, годы	2000 м (Л)				2000 м (Ж)				2000 м				2000 м				Жизненная емкость легких		
			Жизненная емкость легких	выдох	вдох	коэффициент	Жизненная емкость легких	выдох	вдох	коэффициент	Жизненная емкость легких	выдох	вдох	коэффициент	Жизненная емкость легких	выдох	вдох	коэффициент			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
9 Группа: больных																					
Ш-т'	М.	23	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Т-о	М.	20	3200	5,0	3,0	1,66	3000	5,0	2,5	2,0	3200	5,0	3,0	1,66	3000	—	—	—	—	—	
Ш-а	М.	26	4000	5,5	2,5	2,20	3000	5,0	2,5	2,0	3500	4,5	2,5	1,80	—	4,0	2,5	—	1,60	2200	
Ф-в	М.	29	3500	6,5	4,0	1,62	3200	5,0	4,0	1,25	3300	5,0	4,0	1,25	3500	5,0	4,0	—	1,25	4000	
У-в	М.	16	2000	3,0	2,0	1,50	2000	3,5	3,0	1,17	2300	3,5	3,0	1,17	2500	4,0	3,5	—	1,14	2400	
П-а	М.	34	4000	5,5	3,5	1,57	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
П-а	М.	21	3000	4,5	2,5	1,80	2800	4,0	2,5	1,6	3200	4,5	2,5	1,8	3100	4,5	2,5	—	1,8	2500	
18 Группа: здоровых																					
Л-н	М.	20	4900	7,5	4,0	1,87	4000	7,0	2,5	2,8	4500	7,5	4,5	1,67	4400	7,0	4,0	—	1,75	4700	
Л-н	М.	44	3500	4,5	4,5	1,0	3400	4,5	4,5	1,0	3400	4,0	4,0	1,0	3400	4,0	4,0	—	1,0	3500	
Л-н	М.	36	2800	3,5	2,5	1,4	2600	3,5	2,0	1,75	2700	4,0	2,5	1,6	2600	3,5	2,7	—	1,29	3000	
Л-н	Ж.	46	4800	4,0	4,0	1,0	4200	4,0	4,0	1,0	4500	3,8	4,5	0,83	4500	4,0	4,5	—	0,89	4400	
О-а	М.	28	5500	7,0	6,0	1,16	5200	6,5	6,0	1,08	5300	6,5	6,5	1,0	5300	6,0	6,0	—	1,0	—	
Т-о	М.	20	4500	6,0	5,0	1,2	4300	5,5	4,0	1,37	4500	5,5	4,5	1,22	4300	5,5	5,0	—	1,1	4500	
Д-а	Ж.	26	2800	4,5	3,0	1,5	2700	4,3	3,0	1,43	2900	4,5	3,5	1,29	2600	4,0	3,5	—	1,14	2700	
Б-а	Ж.	28	4000	5,5	4,0	1,37	3700	5,0	3,7	1,35	3900	5,0	4,0	1,25	3700	5,0	4,0	—	1,25	4000	
Р-у	М.	36	4100	4,5	3,5	1,29	—	—	—	—	4000	5,0	4,5	1,11	3800	4,5	4,0	—	1,12	4100	
Б-а	Ж.	26	—	—	—	—	4000	5,0	3,3	1,54	4000	5,0	4,0	1,25	—	—	—	—	—	—	
Т-о	Ж.	32	—	—	—	—	4000	5,0	4,0	1,25	3500	5,0	4,5	1,22	—	—	—	—	—	—	
В-о	М.	31	—	—	—	—	4000	7,0	4,0	1,75	4000	6,5	4,5	1,44	—	—	—	—	—	—	
М-в	М.	25	3400	5,0	3,0	1,66	3400	4,5	3,0	1,5	3500	4,5	3,5	1,28	3500	4,0	3,5	—	1,14	3500	
С-н	М.	35	4000	5,5	4,0	1,37	3800	5,5	3,7	1,49	3900	5,5	3,7	1,49	4000	5,0	3,5	—	1,41	—	
С-н	М.	54	—	—	—	—	3400	4,5	3,5	1,28	3000	4,3	3,0	1,42	3000	4,0	3,5	—	1,14	3000	
В-ч	Ж.	32	3500	4,0	2,2	1,81	3300	4,0	2,2	1,81	3500	4,5	2,5	1,8	3500	4,5	2,5	—	1,8	2600	

1) Name; 2) sex; 3) age, years; 4) vital capacity; 5) pneumotachometry; 6) expiration; 7) inspiration; 8) coefficient; 9) patient group; 10) Sh-t'; 11) male; 12) T-o; 13) Sh-a; 14) F-v; 15) U-v; 16) P-v; 17) P-y; 18) normal group; 19) L-n; 20) D-k; 21) L-a; 22) female; 23) A-n; 24) O-y; 25) T-o; 26) D-a; 27) B-a; 28) R-y; 29) B-a; 30) T-a; 31) V-o; 32) M-v; 33) S-n; 34) S-n; 35) V-ch.

than unity.

In the majority of subjects, both healthy and schizophrenic, the pneumotachometry indices were found to be normal. In the first examination, a slight decrease in the expiration force was noted in three per-

sons (of whom one was a patient) and a drop in inspiration force in five (two healthy individuals and three patients). In almost all of the test subjects, the expiration force was greater than the inspiration force. Only in two persons was the expiration/inspiration coefficient equal to unity.

With increasing altitude, the normal group showed some change in the expiration-to-inspiration force ratio. In half of the subjects, the inspiration pneumotachometry increased slightly, by 0.5-1.0 liter. The expiration force either remained the same or diminished slightly. The value of the expiration/inspiration coefficient was reduced accordingly.

We suppose that the appearance of absolute and relative increases in inspiration force at high altitudes reflect a change in respiratory regulation due to increasing oxygen deficiency.

In the group of schizophrenia patients, the dynamics of the pneumotachometry data had no particular distinction. The analogous change in the relationship between inspiration and expiration force with increasing altitude was not observed (Table 2).

CONCLUSION

The results of this study made it possible to discern certain peculiarities in the reaction of schizophrenia patients under high-mountain conditions as compared with that of healthy individuals. The general nature and trend of the shifts in the indices studied were of the same type in both groups and in agreement with literature data (N.N. Sirotinin, van-Lir, Levi and others). Some differences can be detected in the frequency and conspicuousness of the changes. In the group of schizophrenia patients, the shifts were observed somewhat more seldom and were less significant than those in the group of healthy individuals. This applies to the blood-pressure indices, both maximum and minimum but particularly the latter, and came to light in analysis of the

pneumotachometry data in comparative study of the reactions to physical exertion.

The changes in the physiological functions in the mountain locale reflect a definite readjustment of the organism, shifts in the regulatory mechanisms to conform to the changed conditions of the environment. The decrease in the oxygen content of the surrounding air results in a change in gas-metabolism regulation, and specifically in higher respiratory and circulatory stress. Our observations were on a modest scale. Nevertheless, we gain the definite impression that a sojourn in a mountain locality causes a smaller readjustment on the part of the organism in schizophrenia patients. In any event, the shifts in the indices studied were moderated in the schizophrenia patients under identical conditions, at identical times and under identical living conditions. Particular attention is drawn to the weaker reaction of the schizophrenics to physical exertion, since this index is in a sense the most general, integral and indicative of the organism's reactivity.

The exception in our observations was the more distinct quickening of the pulse in the schizophrenics. It must be remembered, however, that schizophrenia patients show characteristic instability of the pulse rate and tachycardia not associated with external causes even under ordinary conditions at low altitude.

On the whole, the observations conducted may be regarded as additional confirmation of the high tolerance of schizophrenia patients to oxygen insufficiency under the conditions of a mountainous locality (2000-3000 and 4200 m).

THERAPEUTIC VALUE OF THE HIGH MOUNTAIN SOJOURN
IN CERTAIN PSYCHIC DISORDERS

N.V. Kantorovich

(Frunze)

Under the conditions of the high mountains, as a consequence of hypoxia and certain other accessory factors, changes occur in oxidation-reduction processes in the brain, the internal secretory functions of the glands, and the course of psychic processes in healthy individuals. The symptoms of the "mountain sickness" that arises under these conditions and the phenomena of acclimatization have been quite thoroughly studied for healthy individuals. In the pathogenesis of psychic disorders, and in the mechanisms of active-therapy techniques for these disorders, considerable importance is also attributed to changes in oxygen metabolism and endocrine and nervous regulation. Hence, arises the theoretical possibility of using prolonged mountain hypoxia as directed therapy applied to the course of certain mental illnesses. The process of change in the altitude of habitation, mountain sickness, acclimatization and deacclimatization give rise to a kind of "massage," in which new, as yet uncrystallized pathological nerve connections may vanish as a result of normalization and regulation of the oxidation-reduction and endocrine processes.

In 1952-1954, N.N. Sirotinin and V.P. Protopopov conducted such studies on mental patients (schizophrenics in almost all cases), who were transported up into the El'brus region. The preliminary results were evaluated as positive. Subsequently, however, "the method of treat-

ing schizophrenia patients by transfer to the high mountains has shown inadequate effectiveness" (V.P. Protopopov). Further, similar positive results were obtained on placing schizophrenia patients under sanatorium conditions in a lowland locale. As a result, the question as to the salutary effect of the high mountains on psychic disorders has remained unclear.

In 1960 and 1961, the Psychiatry Department of the Kirgiz Medical Institute and the Regional Medicine Institute of the Kirgiz Academy of Sciences organized temporary psychiatric retreats at the Torugart high pass in the Tien-Shan region, at an altitude of 3540 m above sea level and 520 km by highway from the town of Frunze. The retreat functioned during July and August of both years, with each patient staying there for 3-6 weeks. A total of 74 patients were transferred, including 40 with schizophrenia, 12 with various forms of depression and involution psychosis, 8 in the manic phase of manic-depressive psychosis, 7 with epilepsy, and so forth.

Residence in the high mountains produced its most striking effect in the manic phase of manic-depressive psychosis and in psychomotor excitation in general. In all 8 patients in the manic phase it was cured rapidly and to total remission. The symptoms of almost all patients with psychomotor excitation of other origins also vanished. In balance, however, no positive effect was obtained during depression. Nor was there any improvement in the condition of patients with stupor and substupor. A transitory and in general rather doubtful effect was noted for epilepsy.

Of 40 schizophrenia patients, 23 had been ill with the disorder for less than one year, and the rest for more than a year. Total remissions and significant improvements were noted in 17, improvements in 9, and no improvement or deterioration in 14. The best results were obtain-

ed in the hallucinatory paranoid form (11 total remissions and significant improvements among 18 patients). Excellent results were also obtained in the catatonic form (4 complete and partial remissions out of 6 patients). The therapeutic effect on the simple form was not as good (3 remissions among 7 patients). No remissions were obtained in the hebophrenic form, but improvements were noted; there was no positive effect in the hypochondriac form (2 patients). As with other methods of treating schizophrenia, the best results were obtained in patients with a short history of the disorder or with a remittent tendency.

There was not sufficient time for comprehensive judgments as to the duration of the therapeutic results obtained, but we have catamneses ranging from 5.5 to 18 months for 28 of the schizophrenia patients. The condition of the patients was evaluated as follows in the catamnetic follow-up: total remission and practical cures in 14 patients, minor improvement and no change in 10, and 4 cases of relapse.

At the altitude of 3540 m, some of the patients showed distinct symptoms of mountain sickness, while in other patients these symptoms appeared less sharply or not at all. The therapeutic effect made itself felt chiefly in patients who had had a comparatively difficult time in the primary acclimatization. On the other hand, patients who had showed no subjective response to the change in altitude frequently also failed to show any positive changes in their state of mental health. Basically, however, in those cases where it did occur the positive effect developed quite quickly, during the first few days of the sojourn in the high mountains, which would correspond to the primary acclimatization phase. In the action of the mountain climate on the course of the mountain climate on the course of the psychic disorders we can distinguish between the effect on the course of the pathological process as a whole and the symptomatic effects. Particularly distinct among the latter

were the elimination of excitation and hallucinations. The rapid relief from the psychomotor excitation made it almost unnecessary to use aminazine or other pharmaceuticals for this purpose at Torugart. No less conspicuous was the relief from auditory and other hallucinations. In several patients, a supplementary hike up to an altitude 600 m higher, i.e., to 4000 m, relieved excitation and hallucinations strikingly and completely. In some cases, these symptoms did not return, while other cases required repeated trips up, on which the excitation and hallucinations would again disappear. Incidentally, these observations do not speak in favor of the inhibition theory of hallucination.

As a rule, the patients did not receive any medication while at Torugart, although the effect of single doses of medications under high-mountain conditions was studied for special purposes in a number of patients. It was found that the saporific effect of aminazine is considerably enhanced. Insulin has several times the effect observed under lowland conditions. Even small insulin doses, of the order of 20-30 units, can produce shock.

Needless to say, we regard hypoxia as the basic factor influencing the course of psychic disorders at Torugart. However, hypoxia is not the sole cause of the changes in the mental condition of the patients. We may not omit secondary factors from consideration. These are, first and foremost, physical exertion - hikes, mountain climbing and manual labor in the fresh air. The change in regimen, stereotype and situation may have a certain significance, although it would hardly be essential. The influence of other climatic and geographic factors apart from altitude and hypoxia, the effect of radiation, etc. remains unaccounted for.

As will be evident from the above, our data disagree essentially with those of N.N. Sirotinin and V.P. Protopopov. It would appear to us that this is to be accounted for primarily by the varying states of

the patients. For example, we observed the most pronounced therapeutic effect in patients with psychomotor excitation and in the manic phase of manic-depressive psychosis, while there were apparently no such patients on the expeditions led by N.N. Sirotinin and V.P. Protopopov. As concerns the schizophrenia patients, we apparently had a larger number of recent and acute cases.

ON THE RESULTS OF TREATING SCHIZOPHRENIA PATIENTS BY RESIDENCE IN THE
HIGH MOUNTAINS DURING 1961

A.I. Durandina

(Frunze)

The 1960 expedition of the Psychiatry Department of the Kirgiz Medical Institute to Torugart (V.A. Rozhnov, V.I. Rybkina and K.O. Osmonalnev) obtained positive preliminary results as regards the influence of the mountain climate on the course of certain mental illnesses, including schizophrenia. In a program of further study of the influence of the high mountains on the course of mental illnesses, the Kirgiz Medical Institute sent a second expedition into the Tien-Shan mountains in 1961. For this purpose, a group of schizophrenia patients was taken out to Torugart, at an altitude of 3540 m above sea level, where they spent 19-48 days.

The influence of the mountain climate was combined with physical exertion and sunburn. Almost daily hikes were prescribed for the patients, during which they traveled 6-12 km over even terrain or climbed to altitudes of 3800-4200 m above sea level in the mountains, where they stayed three to six hours. Each patient made 8-11 climbs. Much attention was given sports and individual participation. The patients were kept occupied with light athletics and played volleyball. Morning calisthenics were made compulsory for all of them. Each day (by turns) 5-6 patients were kept busy with manual tasks.

We conducted observations on 21 schizophrenia patients ranging in age from 19 to 35 years (17 men and 4 women). This group comprised both

individuals with disorders of recent onset (16), within the preceding 2-8 months, and patients with recidive histories of illness (5). The patients were classified into the following groups on the basis of the forms taken by the illness: a) 12 with the hallucinatory-paranoid form, of whom 8 had short histories and 4 had had relapses; b) 2 paranoids; c) 3 hebephrenics; d) 2 catatonics, one of recent onset and one with a recidive history.

Figures Indicating Favorable Effect of High Mountains on Schizophrenia Patients

Формы шизофрении	1	2	3		Результаты				
			Период пребывания в условиях высокогорья		Ремиссия I	Ремиссия II	Ремиссия III	Ремиссия IV	Безперемены
			от 23 до 27 дней	50 дней					
12 Галлюциноз - параноидная	12	9	3	4	3	—	3	2	
13 Параноидная	2	2	—	2	—	—	—	—	
14 Гебефреническая	3	3	—	—	—	—	2	1	
15 Простая	2	1	1	1	—	—	—	1	
16 Кататоническая	2	1	1	1	—	—	—	1	
	21	16	5	8	3	—	5	5	

1) Form of schizophrenia; 2) number of patients; 3) time of sojourn under mountain conditions; 4) from 23 to 27 days; 5) 50 days; 6) results; 7) remission I; 8) remission II; 9) remission III; 10) remission IV; 11) no change; 12) hallucinatory-paranoid; 13) paranoid; 14) hebephrenic; 15) simple; 16) catatonic.

The visit by the schizophrenia patients to the mountain locale in Tien-Shan had a favorable effect on them. Remissions occurred in 11 patients (remission I in 7 and remission II in 4), of whom 8 were recent cases of schizophrenia. Remissions I and II also occurred in patients with relapses of hallucinatory-paranoid schizophrenia. Minor improvement occurred in 5 patients (3 hallucinatory paranoids and 2 with the hebephrenic forms). No change in the pathological state occurred in 5 patients (2 hallucinatory paranoids, 1 catatonic, 2 simple cases and 1 hebephrenic) under the conditions of the high mountains (see Table).

As we know, a complex adaptive readjustment of the organism and its

accommodation to the subnormal oxygen partial pressure take place in response to hypoxia and other factors operating in the mountains. Obviously, changes in the functional state of the central nervous system and readjustment of the metabolism and activity of the endocrine glands are at the bottom of the therapeutic effect of the high mountains on schizophrenia. Hikes, mountain climbing, athletics and manual labor intensified the hypoxia and the readjustment of the organism's functional systems, thereby enhancing the therapeutic effect. This viewpoint finds confirmation in the fact that excellent results were obtained in those patients who adhered strictly to the high-mountain regimen. In patients to whom the regimen of the high-mountain retreat could not be applied, we noted only insignificant shifts in the direction of improvement or no changes at all.

The changes in the psychotic symptomatic picture of schizophrenia under the conditions of the high mountains intervened most frequently in the period between the third and tenth days (11 patients), and less often in the period between the 15th and 27th days (5 patients). In some patients, a 23-28-day stay in the mountains produced no changes in the nature of the illness (5 patients). It had not been possible to apply the regimen of the mountain retreat fully to these individuals. Three of them did not go mountain-climbing once and did not participate in the hikes or in the manual labor. Two of this group participated only in the climbing expeditions. Once up there, they frequently showed exacerbation of their psychotic symptoms. The patients experienced a flood of delirious ideas and their behavior became more foolish. The usual state, that prevailing prior to the mountain-climbing excursion, returned when they came back down.

Our observations indicate that psychotic symptoms change in all forms of schizophrenia under the conditions of the high mountains.

Hallucinatory-paranoid and paranoiac forms. We observed 14 patients afflicted with the hallucinatory-paranoid and paranoiac forms. The clinical picture showed the symptoms typical for schizophrenia before they were taken up into the mountains. We present a case history of the disorder by way of illustration.

Male, 22 years of age. Childhood growth and development healthy. Seventh-grade education. Worked as a locksmith. Nervous breakdown in June of 1961. Periodically, he would hear voices, slept fitfully at night, and was afraid of something vague and undefined. Somewhat later, he began to fear various screams, knocking sounds and voices. From time to time, a voice would warn the patient as follows: "Soon the starts will come flying and turn you into stone." He reported to the militia with the unreasonable request that they test his blood. Was admitted to a clinic for treatment on 2 July 1961. Physical conformation correct, nutrition excellent. Heart: clean sounds, AD [arterial pressure] 120/70, pulse 76 beats per minute. Lungs: vesicular respiration. Abdomen soft, liver and spleen not enlarged. Configuration of pupils normal, pupil reaction to light quick to convergence and accommodation excellent. Tongue medial; arm, knee and Achilles tendon reflexes quick. No pathological reflexes were produced. No disturbance to coordination.

Patient is oriented in time and space, and understands that he is at a psychiatric retreat. Experienced olfactory, auditory and visual hallucinations; believed that a powerful gas was seeping into the room, heard voices demanding that he change his religion. He had a vision of himself with half a torso. Emotionally, he was severely distraught and experiencing powerful dread. Gave voice to delusions of persecution, violence and poisoning. He believed that dynamite had been planted under the building and would be exploded by the bribed watchman, killing everybody. He was of the belief that the moon and stars were falling. Even at home, he had noted how the sun and moon were coming down and felt their effects on him. "Rays hit me in the forehead, I became very dizzy, my body went over to my brother and a worm crawled across my body." There is a danger that everything will be set fire by the moon and stars and will burn up. The patient is afraid to sleep at night and has an impulse to stand at the window. On several occasions, he jumped out of bed and ran out into the street, staying there until he was carried back.

He tried to cut an electrical wire, which he felt was about to be used to detonate the dynamite. He believed that he was being poisoned by substances sprinkled onto his food. He frequently refused to eat. In addition to the delirious experiences, his thinking was marked by discontinuity and incoherence: "Rays are hitting my head. Where did I jump? And there went an airplane, flying along beside me. Did I fall or didn't I? Many have tears in their eyes." The patient's behavior was extremely foolish, with outbursts of rage and excitement.

During the first few days of his stay in the mountains, we observed tachycardia, the pulse reaching 100-108 beats per minute; there was also a slight facial cyanosis. The patient succeeded in undertaking the entire regimen of the mountain retreat. He made 11 hikes up into the mountains to altitudes of 3800-4200 m above sea level. During the intervals between climbs, he would go hiking, became sunburned, participated in individual activity, played volleyball and did chores.

Extracts from daily record. On 12-13 July (after 8 days' residence in the mountains), he quieted down and his behavior became more orderly. The pathological subjective experiences lost their previous force. He does not volunteer information on these experiences. He regards his ideas of persecution and the downfall of the moon and stars as foolish, but thinks, as before, that his body has gone over to his brother. He expresses his ideas clearly. He is active, socializes with the patients, participates in the work and hikes. Subsequently, his condition improved progressively, although on some days he would give halting expression to delusions of poisoning and was afraid of being transformed into a baboon. Became incoherent. On going up into the mountains, he always behaved properly, his mood was considerably better, and the picture reverted to the earlier morbid experiences.

Was discharged as cured on 5 August. Ambulatory treatment with maintenances of aminazine was recommended.

The state of the patients changes considerably under the mountain conditions even during the first 10 days or within two to three weeks after arrival. The emotional state improves markedly. The fears, incoherence, irritability and tendency to fly into a rage subside. Spirits seem to be lifted somewhat. The behavior of the patients becomes more socially acceptable; they begin to show interest in their surroundings.

While it had not been possible to put the patients to work previously, they now begin to participate of their own accord in the athletic games, hikes, labor and individual activity. Simultaneously, the hallucinatory experiences and delusions gradually lose their urgency. The thought processes become orderly. In the associative experiment, we note a considerable improvement in the associations on the 12th day of the sojourn in the mountains, particularly among the patients that were cured or showed an improvement in condition. Toward the end of the mountain sojourn, the subordinate associations vanish or the number is reduced sharply in those patients who were showing positive effects. The latent period remains long, averaging 2.3 sec. During the adaptive-readjustment process (during the first 15 days of the sojourn in the mountains), changes arise in higher nervous activity, with normalization or improvement of the basic nervous processes in many cases. The pathological symptoms gradually go away under the conditions of the mountains. They undulate after an improvement has set in, now vanishing and now reappearing. With the passage of time, the patients' condition shows progressive improvement. Additional climbs up into the mountains to altitudes of 3800-4200 m have a particularly favorable effect on the patients. During these climbs, the influence of hypoxia and other mountain factors is enhanced. As a result, euphoria becomes stronger. The patients become more active. On the climbs into the mountains, they cover distance vigorously, converse brightly during the rest periods, ask questions, discuss the events of their lives and books that they have read. As a rule, the hallucinations and delusions become less urgent during these climbs. The patients do not discuss their illness voluntarily, tending to avoid conversations on this topic. Hallucinations frequently disappear during the climbs. On the descent, however, they return, but each time with less force. Certain patients showed aggravation of the morbid symptoms.

They experienced torrents of hallucinations and delusions. On descent, the acuteness of the morbid subjective experiences had spent itself. With the course of time, these symptoms diminished sharply or even vanished. In some patients, psychotic symptoms vanished during the mountain sojourn within 2 to 3 weeks. In others, however, only a minor improvement had been accomplished by this time. Subsequently, the condition of the patients improved progressively and the psychotic symptoms were relieved within four to seven weeks. As a result of the visit to the mountains, nine individuals among the patients with the hallucinatory-paranoid and paranoiac forms had I and II remissions. Only some improvement was observed in three patients. No change at all occurred in the course of the illness in two cases.

Although mountain observations of patients with other forms of schizophrenia are spotty, it is nevertheless of interest to examine the therapeutic results obtained in these forms.

Hebephrenic form. Three patients with this form came under our observation. The psychic state in this form improved by the fifth to tenth day of the sojourn in the high mountains. The patients begin to think more correctly, their behavior becomes orderly, and the motor derangements subside. The mood remains euphoric. The symptoms of hebephrenia exhibited by two patients subsided in the mountains. In one individual of this group, there was only a transitory improvement, which lasted three to ten days. The observational data suggest the necessity of longer sojourns in the high mountains, since the shifts in condition indicate an enhancement of reactivity and, consequently, a possibility of considerable improvement in condition or cure.

Simple form. We observed two patients with the simple forms; one of these was going through a second flare-up of schizophrenia. The mountain climate was observed to have a favorable effect on 1 patient; it had

none on the other. Changes in the psychotic symptoms of this form were noted on the ninth day of the patient's mountain sojourn. By this time, the active psychotic symptoms taking the form of unproductive thinking, depersonalization and psychomotor inhibition had abated significantly. The patient's mood was better. The psychotic symptoms flared up again at intervals afterward. With the passage of time, however, the patient's state improved progressively and a remission I had intervened by the 48th day of the visit to the mountains.

Catatonic form. Two patients with this form were observed in a state of acute psychomotor inhibition, with occasional periods of stupor. A positive effect was noted in one patient, while the other showed no response at all. The change in the psychotic symptoms was observed on the ninth day. The patient's state of inhibition had abated, and he was participating actively in the work, although inadequacies would appear occasionally in the emotional sphere and in behavior. The psychotic symptoms had vanished after 48 days. During the four months that followed, she was healthy and able to work, but then suffered a relapse of the illness.

We made catamnetic follow-ups on 28 schizophrenia patients over 6-18 months after treatment in the mountains in 1960 and 1961. It was found that 9 out of 10 patients who had had I and II remissions continued healthy and able to work.

Of four patients with repeated flare-ups of the illness after I and II remissions, relapses had occurred in three 2-9 months after the mountain sojourn. All five of the patients in whom only minor shifts in the direction of improvement had occurred during the mountain visit were subsequently treated with amnazine (4) and insulin (1) during the period after the stay in the mountains. Three of them showed excellent remissions as a result of the treatment. It is impossible to deny the pos-

itive effect of the mountains on the course of the disorder in these cases. It would appear that the readjustment of the functional systems that takes place in the high mountains increases the reactivity of the organism and renders it more susceptible to therapy. In patients in whom no improvement had been observed in the mountains, it was not possible to achieve helpful results even by subsequent treatment with active techniques.

CONCLUSIONS

1. Placing schizophrenic patients under the conditions of the high Tien-Shan mountains has a favorable effect on the course of all forms of this disorder. The mountain climate has its most striking effect on the hallucinatory-paranoid form of schizophrenia. Poorer results are obtained with the simple, hebephrenic and catatonic forms.

2. The improvement in mental state occurs most often between the third and tenth days. The psychotic symptoms vanish completely or diminish conspicuously during the period from two or three to four to seven weeks. This duration of the mountain sojourn is not optimal and requires further refinement.

3. To evaluate the effectiveness of the mountain treatment, the associative experiment can be used together with clinical observation. The associations are improved or normalized when the mountain climate is effective.

4. Our observations reaffirm that the Tien-Shan mountains can be used for purposes of therapy in schizophrenia.

**COURSE OF PSYCHOMOTOR EXCITATION AND MANIC DEPRESSIVE PSYCHOSIS UNDER
THE CONDITIONS OF THE HIGH MOUNTAINS**

V.A. Rozhnov

(Frunze)

Psychomotor disturbance is one of the gravest symptoms of mental disease. In the state of psychomotor excitation, patients are exhausted very quickly, lose weight and may commit acts dangerous both to themselves and to those around them. In spite of the considerable number of papers that have been devoted to psychomotor excitation, the pathogenesis and etiology of this state and methods of dealing with it are still far from adequately developed. Study of psychomotor excitation is a pressing problem for psychiatry.

I.P. Pavlov believed that "subcortical turbulence" arises in psychomotor excitation and gets out of control of the cortex, and that the interaction of the cortex and subcortex is disturbed due to diffuse cortical inhibition.

Psychomotor excitation arises in many mental illnesses and may proceed with various degrees of manifestation and take various forms. In July and August of 1960 and 1961, the Psychiatry Department of the Kirgiz medical institute took 17 patients into the region of the Torugart high pass in the Tien-Shan region (altitude 3540 m), all of them in a state of psychomotor excitation, with eight patients suffering from manic-depressive psychosis in the manic phase, eight from schizophrenia with catatonic-paranoid and hallucinatory-paranoid disturbances and one patient suffering from hashish psychosis with distinct motor and speech

disturbance.

Of particular interest are our observations of the patients with manic depressive psychosis in whom the psychomotor disturbance vanished on the first to third day of the stay in the mountains. In those cases in which the manic patients still retained their psychomotor disturbance during the first two days of the sojourn at 3540 m, the motor and speech disturbances vanished immediately when they were taken up to an altitude of 4200-4500 m and then brought back down.

In the schizophrenic patients, the psychomotor disturbance had disappeared by the third to thirteenth day of the mountain sojourn. In three patients with the catatonic-paranoid syndrome, the disturbance disappeared on the third to fifth day, and in five patients with the hallucinatory-paranoid form, on the fifth to thirteenth day; in these, the psychomotor excitation gradually abated, while in the patients with the catatonic-paranoid syndrome it was relieved dramatically.

The basic symptom in the patient K., who was suffering from the catatonic-paranoid syndrome of schizophrenia, was manifest psychomotor disturbance. He spouted spontaneous gibberish at all times, shrieking occasional words: "I ran all the way over to Narzan to tell Anna that I love her and my underwear needs washing. My cap isn't Indian - they don't wear such caps. The water doesn't taste very good. Ach! Ach! Stones! stones! Here is a lake. The geese are flying, but there aren't any sparrows... ." The patient was irascible, rancorous, torn by conflicts; he whistled, cursed cynically, and screamed. He was forever trying to run off somewhere. He did not respond to instructions and requests. On the ninth day of his sojourn at the high-mountain camp, after hiking to Narzan (which was 4 km away) and climbing up to 4400 m, he quieted down, became more contained, proper and quiet. The psychomotor disturbance had vanished. The condition and behavior of the patient had

undergone a sharp change; he was, as it were, transfigured. He entered willingly into the work activities, began to play at draughts, chess and volleyball. He participated in individual activity. He sang lyrical songs willingly. Our observation of patients with psychomotor disorder in the mountain camp indicated that the mountain climate is a powerful factor against motor and speech excitation.

The manic-depressive psychosis is still a disorder with inadequately understood etiology and pathogenesis. It is characterized by periodically emerging manic and depressive phases with lucid intervals between them. Each individual phase usually lasts for four to six months. Varying combinations of phases and the frequency of their repetition determine the gravity of the illness. The manic-depressive psychosis has been studied by S.A. Barannikova, M.F. Bordanova, P. Dmitrov, S. P. Pavlov, B.Ya. Pervomayskiy, I.A. Polishchuk, V.P. Protopopov, F.I. Sluchevskiy, L.I. Spivak, A.N. Timofeyeva, T.Ya. Khvilivitskiy and others.

In the pathophysiology of manic-depressive psychosis, I.P. Pavlov attributed great importance to the predominance of excitation processes in the cortex and the absence of relaxation periods alternating with the active state. I.I. Pavlov noted that in manic-depressive psychosis there is a tendency toward acute and abrupt excitation of the cortex and subcortex. V.P. Protopopov found a number of humoral, somatic, metabolic and vegetative changes in patients with manic-depressive psychosis. The basal metabolism changes, and the contents of glycogen and adrenaline in the blood are abnormally high. The fact that exceptional importance is attributed to changes in metabolism in manic-depressive psychosis suggested to us that it might be expedient to take a group of such patients up into the mountains.

We conducted observations on eight patients suffering from manic-

depressive psychosis (manic phase) at an altitude of 3540 m above sea level. The condition and behavior of all patients changed very soon after arrival in the mountain region. The patients withstood the trip from Frunze to the destination (522 km) very well, despite the fact that it was necessary to cross four elevations at altitudes of around 4000 m along the way.

Distinct acclimatization phenomena were observed in seven patients, but they continued only for one to two days. The patients had severe headaches, which intensified considerably on bending over and doing physical work. They complained of weakness, general lassitude, fatigue and weakness in the knees. "I feel as though I had been doing hard labor for a very long time, had not slept for many days and had eaten something that did not agree with me," - such was the patient Zvon's evaluation of the way she felt. All patients experienced nausea, vomiting, and dizziness, and fine movements lost their precision; they tottered in walking and became troublesome. They experienced difficulty even in performing simple motor tasks. Tachycardia (pulse rate 102-110 beats per minute, with increased filling and stress) and shortness of breath were noted. All of these effects vanished on the second day of the sojourn in the mountains. In the patient Ibr., no external signs of acclimatization arose, possibly because this patient had previously gone out to high alpine meadows six years in a row (altitudes 2000-2600 m above sea level), stayed there for two to four months out of each year and had apparently developed stable neurohumoral protective mechanisms that alleviated the morbid phenomena that usually accompany arrival in the high mountains.

A complete cure (in six cases) or considerable improvement (in two cases) amounting almost to total cure took place in all patients during the first 2-13 days of the stay in the mountains. The great importance

of these encouraging results becomes even clearer in the light of the fact that our patients included individuals in whom the disorder was of 7, 14 and 17 years' standing and had taken a highly unfavorable course.

The patient Vak., 47 years of age, has been suffering from manic-depressive psychosis since 1943. Both the manic and depressive phases had been observed in this individual, but the manic outbursts were more frequent. The disorder had proceeded without lucid intervals for the last 13 years. During the first two days in the mountains, acclimatization phenomena were observed (headache, nausea, vomiting, tachycardia, shortness of breath, general tiredness and weakness in the knees, shambling gait, chest pains, troubled sleep) and the hypomanic syndrome was in evidence. The patient became acquainted very quickly with all of the local residents, was convinced that he had to explore the neighborhood within a radius of 5 km, and tried to stay in the mountains, at Chetyr-Kul' Lake and other nearby lakes. He sang, swore dreadfully, exhibited himself and was hypersexual. He talked a great deal and demanded that everyone obey him. He slept two to three hours a day. He stayed in motion at all times. On the third day of the sojourn in the mountains, the verbal and motor excitation abated, but all the other symptoms remained without change. On 14 July (on the seventh day of the sojourn at the mountain camp), the patient went on a climb to the crest of the Tuz-Bel' (White Ridge) range. He remained for five hours at the altitude of 43-4400 m. After descending and returning to camp, he experienced very great fatigue and weakness. He complained of headache and nausea. Vomiting was observed. He asked to be put to bed, lay down and fell asleep quickly. This was the first time he had slept during the day; in the evening he was quiet, in contact with his surroundings, and polite. The speech and motor hyperactivity vanished completely. The patient was

completely reborn as a healthy individual "it is as though all the weight had dropped from my shoulders, everything was bothering me has gone someplace else. I don't want to do everything backwards the way I used to. I am in a new state of mind. I feel very good and relaxed. I want to get rested and gather my strength and then go back to work," said the patient. No subsequent pathological symptoms were observed. He entered willingly into any work process (carrying water, sawing and splitting wood, policing the camp area, assisting other patients), entered into the gymnastics and morning calisthenics, and participated willingly in the games and hikes. On returning home, he was employed as the manager of a movie theater (he had been unemployed for the previous 15 years, with the status of an invalid of the first or second group). This case clearly demonstrates the occurrence of significant positive shifts in the pathological symptom picture in a patient with extremely severe course of the manic-depressive psychosis. Others among our patients were cured or showed considerable improvement (nearly to normality).

The manic-depressive patients spent from 8 to 42 days (on the average 21 days) in the high mountains. Some patients could have been discharged even much earlier. Thus, a sojourn in the high mountains has excellent therapeutic results in treatment of the manic phase of manic-depressive psychosis.

ON THE ROLE OF THE HYPOXIC FACTOR IN THE DEVELOPMENT AND
COURSE OF EXPERIMENTAL EPILEPTIC SEIZURES

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(Kiev)

A large number of papers by [Soviet] and foreign clinicians and physiologists have been devoted to study of the epilepsy problem, which is one of the most important in contemporary clinical and experimental medicine.

The most serious and severe manifestation of epilepsy is the convulsive epileptic seizure, to which investigators have given special attention. The mechanisms by which the convulsive seizures arise and develop has been studied for the most part on experimental animals. Needless to say, the experimental epileptiform seizure cannot fully reproduce the entire many-faceted picture of epilepsy as an illness in which the seizure is only one of its manifestations, even though it is the principal one. Nevertheless, experimental simulation of epilepsy in animals makes it possible to clarify a number of important aspects of this disorder.

Most of the authors regard epileptic seizures as due to a disturbance in the reciprocal relationships between the cortex and subcortex. M.Ya. Sereyskiy (1945) and many other investigators regard biochemical shifts as the proximate cause of the attack - accumulation of ammonia, increase in the content of residual nitrogen, globulin fractions, changes in carbohydrate metabolism, etc. I.Uzunov (1956, 1957), I.A. Slivko (1948), S.K. Kapran (1936) and others take the position that

the prime factor in the development of epileptic seizures is changes in the tone of the blood vessels of the brain, which disturb the physiological state of neurodynamic processes. Other authors relate the organism's abnormal tendency toward convulsive reactions to oxygen insufficiency. In particular, it has been shown in the papers of N.D. Yer-shov (1937) and Ye.V. Maystrakh (1949) that the enhancement of the organism's convulsion reaction at subnormal barometric pressure is characterized principally by anoxemia of the brain and a disturbance of acid-base balance in the direction of alkalosis. I.I. Fedorov (1958) concludes that the mechanism by which the convulsive process develops is based on a transitory spasm of vessels, with the result that the brain's supply of nutritive substances, and oxygen in particular, is disturbed. T.P. Yakimova (1955) concludes on the basis of completed research that the central inhibition observed in the convulsive attacks results in a decrease in the organism's oxygen supply.

THE PRESENT INVESTIGATIONS

We have made an attempt at at least partial study of the role of hypoxia in the genesis of convulsive seizures. Since the oxygen balance of the organism is supported by the respiratory and circulatory systems and by the ability of cells to absorb oxygen, we decided to investigate the functional state of these systems during seizures.

convulsive seizures were induced in dogs and rats by intravenous injections of an ether solution of camphor, cardiazole and coramine. Respiration was registered on the dogs during the convulsive seizures, and both respiration and blood pressure were traced during acute experiments. Respiration was registered on a kymograph using a special drum placed upon the animal's rib cage and connected to a Marey's capsule.

In the dogs, the epileptiform attack began with motor disturbance of brief duration, restlessness, and occasional spasmodic twitches. No substantial changes in respiration were observed during this period.

This was followed by development of the most severe tonic phase of the attack with acute opisthotonos and cyanosis. Respiration was suspended during the same period and remained so to the end of the panic phase (Fig. 1). The cessation of respiration is of particular interest, since the organism has a particularly low tolerance for it. Most investigators have advanced the opinion that this suspension reflects both tonic contraction of the respiratory musculature and inhibition of the respiratory center. During the clonic phase, which follows on the heels of the tonic phase, respiration becomes intermittent and without pattern; when the clonic spasms are over, we note a considerable quickening and deepening of respiration (Fig. 1). The respiratory movements gradually return to normal.

In the next series of experiments on previously "sinusotomized" dogs, we studied gas analyses of the blood made by the Van Slyke method. The blood for the analyses was taken simultaneously from the sagittal sinus of the brain and from the femoral artery; samples were drawn before the spasms, at the height of the seizure (in the tonic phase) and at various intervals of time after the seizure.

Basically, we were interested in data on the amount of oxygen in the blood, since this index can, to some degree, be used to characterize the state of the brain's oxygen supply. The following data were obtained from the analyses that we conducted: in all arterial blood analyses made at the height of the seizure, the quantity of oxygen was subnormal (down from a normal value of 20-22% by volume to 16-18% by volume). The content of oxygen in the venous ("sinus") blood taken during this same period was found to be elevated (from a normal value of 12-14% by volume to 17-18% by volume). During the seizure, therefore, the content of oxygen in the "sinus" blood approaches the oxygen content of the arterial blood; the arterial venous oxygen difference is down sharp-

ly during the seizure - to 3-0.7% by volume (the normal figures are 6-9% by volume.

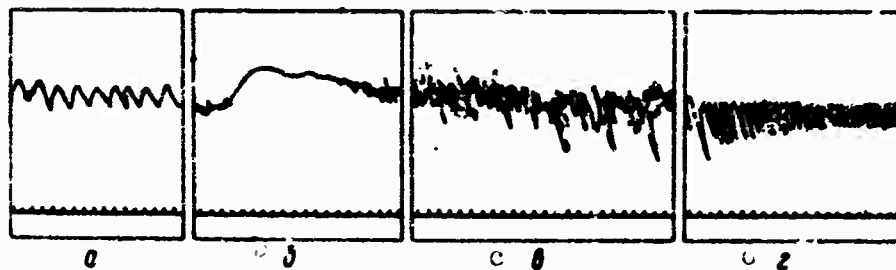


Fig. 1. Changes in respiration in dog during convulsive seizure. a) Normal respiration; b) cessation of respiration during tonic phase; c) respiration in clonic convulsions; d) respiration after seizure. Time marker 2 sec.

A study of the bloodstream rate (by the cytitone and bubble methods) indicated that the circulation is accelerated significantly during the seizure and retarded afterward. When the convulsive seizure is over, the quantity of oxygen in the arterial and venous blood returns to normal, and the arterial venous difference with respect to oxygen rises.

The studies made indicate that during the tonic phase of a convulsive seizure, the flow of blood to the brain is obviously reduced, since stoppage of respiration, a decrease in the oxygen content of the arterial blood and a simultaneous rise in this content in the "sinus" blood and a sharp drop in the arterial venous oxygen difference are observed.

We also felt it was in order to study the problem of oxygen absorption by the brain tissues during a convulsive seizure. Very few papers have been devoted to this problem. Most detailed are the researches of K.I. Pogodayev and his co-workers (1959), who studied the tissue respiration in various divisions of the brain in the various phases of electrospasm seizures.

We performed the experiments on rats. Seizures were induced with camphor in ether solution, cardiazole and coramine. The animal was briskly decapitated during the tonic or clonic phase of the seizure. The membranes and blood were removed from the cerebral hemispheres, which had been put on ice. The brain tissues were then homogenized. The

respiration of the tissue homogenate was determined by the conventional Warburg technique in an atmosphere of pure oxygen at a temperature of $38 \pm 0.01^{\circ}$. The amount of oxygen taken was expressed by the conventional coefficient QO_2 , which is equal to the number of cubic millimeters of oxygen taken up in 1 hour by 1 mg of tissue, converted to dry weight.

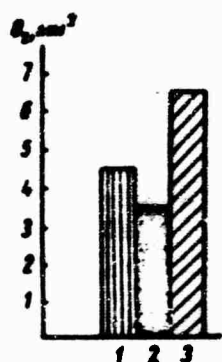


Fig. 2. Average values of oxygen uptake by tissue of rat cerebral hemispheres in camphor-induced convulsive seizures. 1) Control; 2) tonic phase of attack; 3) clonic convulsions.

The data that we obtained on the camphor-attack example are shown in Fig. 2.

The cerebral-hemisphere tissue-respiration figure determined under normal conditions (control animals) varied in the range from 4-5 mm³ of oxygen (QO_2). Since the respiration of brains removed during the single tonic phase of the attack showed no differences from the normal figures, it was decided to increase the doses of epileptogenic agents to produce multiple convulsive attacks. The tissue respiration of cerebral hemispheres taken during multiple tonic phases showed a consistent decrease ($QO_2 = 3.8-3.5$ mm³ of O_2). The rate of tissue respiration of cerebral hemispheres isolated during the period of clonic spasms was up in all cases

($QO_2 = 6-7$ mm³ of O_2).

Thus, during the tonic phase of the convulsive seizure we observed a decrease in the rate of tissue respiration of the cerebral hemispheres, in agreement with the data of K.I. Pogodayev.

In a series of acute and clonic experiments, we investigated the dynamics of changes in the brain oxygen tension of dogs during seizures. The determinations were made by the polarographic method on animals with electrodes implanted in their brains. It was found that a consistent change takes place in the brain's oxygen tension during the seizure. As a rule, stoppage of respiration and tonic stressing of the musculature are accompanied by a sharp drop in the oxygen tension curve



Fig. 3. Changes in dog brain oxygen tension during convulsive attack. 1) 50 sec.

(Fig. 3). Resumption and amplification of breathing result in a considerable rise in the brain oxygen tension. The data obtained also confirm the inadequacy of the brain's oxygen supply during the convulsive seizures.

The experiments performed on the dogs and rats confirmed the hypothesis that the brain's oxygen supply is depressed during experimental convulsive states. Using this as a point of departure, we decided to investigate the influence of adaptation and acclimatization to hypoxia on the nature and course of experimental convulsive seizures.

Rats of the same age and weight were selected for each series of experiments. The optimum dose of camphor solution, that which produces epileptic seizures of medium severity on intravenous injection, was determined. The experiments were conducted under hypobaric-chamber conditions. After preliminary acclimatization, the animals were left at an "altitude" of 8000 m for 54 hours. At the end of this time, the rats were taken from the hypobaric chamber and the camphor solution was administered to them.

It was found that not a single one of the rats could be brought to a seizure, even when doses in excess of the optimum were administered. Investigations in the high mountains were conducted to refine these data: the animals were kept at an altitude of 3400 m on El'brus for eight days. After this, some of the rats were given the camphor solution, but they showed no response to it. Even on the seventh to eighth days, counted from the day of descent from the mountains, it was impossible to induce spasms in the rats in response to administration of increased

doses of the epileptogenic.

Thus, the data from the experiments on rats confirm the hypothesis that the hypoxic factor is important in the pathogenesis of convulsive seizures. In particular, adaptation to hypoxia resulted in an increase in the animals' tolerance to the epileptogenic factor.

CONCLUSIONS

1. Respiration and blood pressure vary considerably during convulsive seizures. In the tonic phase, a sharp increase takes place in blood pressure and respiration stops.

2. At the peak of the attack, the content of oxygen in the arterial blood is down and that in the venous (sinus) blood is up. The arterial venous oxygen difference is sharply reduced.

3. At the height of the attack, during the tonic phase, the rate of oxygen uptake by the tissues of the cerebral hemispheres is depressed.

4. The oxygen tension in the brain drops at the height of the seizure.

5. Adaptation and acclimatization to hypoxia results in increased tolerance to an epileptogenic factor.

ON THE SIGNIFICANCE OF HYPOXIA IN THE MECHANISM OF INSULIN
THERAPY AS APPLIED TO SCHIZOPHRENIA PATIENTS

Ya.M. Britvan and I.A. Mizrukhin

(Vinnitsa)

A large number of research efforts notwithstanding, the mechanism by which insulin has its effect in treatment of schizophrenics remains inadequately studied. At the same time, insulin therapy is still one of the most effective methods for active treatment of schizophrenia. To this day, the question as to the importance of the variable depth of the insulin-induced comatose state in the effectiveness of the treatment has not been definitely resolved.

M.Ya. Sereyskiy (1950) indicates that a factor of particular importance in the insulin mechanism is its stimulating effect on the diencephalon and midbrain. Ye.A. Popov (1950) concludes that what is basic to the mechanism involved in active treatment methods for schizophrenia is their effect on diencephalic centers that govern the adjustment of the vegetative nervous system.

The cortico-subcortical mechanism of the action of insulin has emerged with steadily increasing clarity as a result of electrophysiological researches of recent years. It was shown by the observations of S.I. Subbornik and P.I. Shpilberg (1948) that in the development of insulin hypoglycemia induced for the purpose of treatment in schizophrenia patients, slow, high electroencephalogram waves are registered, and we sometimes observe the disappearance of biocurrents from the brain cortex. Intravenous injection of glucose restores the previous rhythms

at once.

Working in Ya.P. Frumkin's clinic, G.L. Voronkov (1955) observed amplification of the alpha-waves in schizophrenia patients in the initial stage of insulin hypoglycemia; in more profound hypoglycemia (soporose and comatose states), delta waves predominate in the electroencephalogram. The appearance of convulsions is accompanied by high-amplitude waves. Following relief of the comatose state, a depression of the brain cortex electrical activity is observed for some time. Ye.T. Danilenko (1958) obtained virtually similar results. She showed that during insulin hypoglycemia, we observe, together with deepening of the vein-cortex inhibition, inhibition of subcortical divisions that regulate unconditioned vascular reflexes.

It should be noted that great importance came to be attributed to oxygen starvation of the brain in the insulin mechanism even during the first few years after it had been introduced into the treatment of schizophrenia. Meyer, Harris, Blelok and Horwitz (1938) and others concluded that a depression of the oxidative processes in the brain and oxygen starvation of that organ formed the basis for the therapeutic effect of insulin on schizophrenics. Gel'gorn (1938) stressed the importance of the retardation of cranial circulation in the mechanism by which insulin acts. He drew analogies between the symptoms of hypoxia that appear and the phenomena observed on inspiration of oxygen-deficient gas mixtures. Damechek and Mayerson (1935) noted excessive oxidation of blood taken from the cubital and jugular veins during the development process of insulin hypoglycemia.

As was shown by the experimental studies of V.P. Komissarenko (1949), phenomena of reduced glucose consumption by the brain and hypoxia of cellular elements in the brain tissue are responsible for insulin convulsions and coma.

It is worthy of note that schizophrenics show effects of brain oxygen starvation even in their usual state, prior to the administration of insulin. M.Ya. Sereyskiy (1957) emphasized in a discussion of the pathogenesis of schizophrenia that one of the most convincing theories is that of tissue hypoxia in the brain. The hypnoid phases in the activity of the brain and its functional impairment stand in direct relationship to oxygen starvation.

N.N. Sirotinin (1954) suggested that therapeutic value might be found in aggravation of the brain oxygen starvation already present in schizophrenia patients - something that might be achieved by means other than the administration of insulin in large doses. Attempts were made at first to treat schizophrenics by oxygen starvation induced under hypobaric-chamber conditions. Studies in this direction were conducted by S.D. Rasin and A.Z. Kolchinskaya (1952) on patients in V.P. Protopopov's clinic. They noted a high tolerance on the part of the central nervous system to oxygen shortage in the inspired air and a low arterial venous oxygen difference, suggesting a decrease in the amount of oxygen being used by the brain. N.N. Sirotinin considers that it will be expedient to use such high degrees of oxygen starvation of the brain as are observed in insulin shock for treating patients in cataton-ic stupor.

The helpful influence of prolonged sojourns by schizophrenia patients, particularly when the history of the illness is short, under the conditions of the high mountains has been studied in recent years (V.P. Protopopov and N.N. Sirotinin, 1954).

Our research has indicated that suppression of respiration takes place in schizophrenia patients during the development of the comatose state induced for therapeutic purposes by large doses of insulin. It might be suggested that, in addition to oxygen starvation of the brain,

arterial hypoxemia stemming from the respiratory insufficiency also plays a role in the mechanism of insulin therapy. To verify the hypothesis advanced here, we undertook investigations to ascertain the level of oxygen saturation of the arterial blood during the development of insulin coma in schizophrenia patients.

The method of continuous cathodic oxyhemometry was used to investigate the oxygen saturation of the arterial blood with simultaneous continuous kymographic registration of respiration. As the insulin coma developed, we checked the blood sugar level, blood pressure and pulse rate. Our attention was drawn to the clinical symptoms of depth of coma. O.P. Girich and L.I. Rabina participated in the investigations. It is necessary to note that the oxyhemometry technique is being used in increasing volume in medical practice. Many reports are being published on changes in the oxygen saturation of the arterial blood during surgery of the lungs and heart and in patients in therapeutic, obstetric-gynecological and other clinics.

We have encountered only two papers reporting on the use of oxyhemometry in clinical psychiatry. One of these, by Z.R. Tyushkevich (1957) was devoted to the variation of the arterial blood oxygen saturation during insulin therapy of schizophrenia, while the other, by B.V. Ryazantsev (1957), was compiled on the basis of research material on schizophrenia patients, generally with the apathetic syndrome, under the conditions of functional stress. It was noted in the latter work that when a patient is switched from breathing pure oxygen to atmospheric air, the arterial blood becomes saturated to 90-98%. In our studies, the oxygen saturation of the blood was 94-96% before the administration of insulin.

We examined 16 patients with paranoid and catatonic forms of schizophrenia. The patients exhibited varying degrees of the comatose

state. The study was made on the state of manifest or profound coma in 10 patients, on the precomatose state in 4 and in a state of psychomotor excitation lasting several hours but not terminating in coma in 2 patients. We followed the suggestions of N.K. Bogolepov (1950) in defining the depth of the comatose state.

The results of our observations indicate that a considerable drop in the oxygen saturation of the arterial blood is to be observed in all patients as insulin hypoglycemia becomes more acute and the comatose state develops. A slight lowering of the oxygen saturation of the blood is noted as soon as 20-30 min after administration of the insulin. The subsequent decrease takes place gradually and reaches its maximum in the comatose state. A decline in the oxygen saturation level of the blood was noted also in 2 patients in whom prolonged psychomotor excitation did not terminate in coma. In one of these, the oxygen saturation of the blood had dropped from 95 to 80% 1 hour 50 minutes after administration of 84 units of insulin, and it was down to 74% after 2 hours 30 minutes. In the other patient [both females - Trans.], the maximum decrease in the oxygen saturation of the arterial blood following administration of 112 units of insulin occurred after 3 hours 25 minutes at 82%.

It should be noted that the precomatose state was distinguished by a smaller decrease in the oxygen saturation of the blood than was the comatose state. Strict parallelism between the depth of the comatose state, the degree of hypoglycemia and the extent to which the blood oxygen saturation has been reduced was observed only in some of the patients. The dynamic aspect of the reciprocal relationships involved in the changes in the patients' clinical state, extent of hypoglycemia and arterial hypoxemia as the comatose state develops following administration of insulin may be seen from the examples presented below.

In the patient S. [female], profound coma was accompanied by a drop in blood sugar to 30 mg-% with a decrease in the oxygen saturation of the arterial blood to 84%. In patient N. [male], the precomatose state had developed 3 hours after administration of 75 units of insulin. The blood sugar came to 40 mg-%, while the oxygen saturation of the blood was 74%. In patient G. [female], a state of drowsiness and persistent stupefaction was developing 2 hours 15 minutes after administration of 108 units of insulin. The oxygen saturation of the arterial blood dropped to 78%, and a further decrease to 70% was observed 15 minutes later. Coma intervened soon thereafter, and was accompanied by convulsive seizures. The patient could be brought out of the comatose state only after 12 hours. During the entire period of profound coma, no further decrease in the oxygen saturation of the arterial blood was observed.

Prior to administration of insulin, the patient G-va [female] had a blood-sugar content of 103 mg-% and a 96% oxygen saturation of the arterial blood. Then, 30 minutes after subcutaneous injection of 32 units of insulin, the oxygen saturation of the blood was 94%; it was 92% after 1 hour, 90% after 2 hours and 88% after 3 hours. When 3 hours and 20 minutes had elapsed since administration of the insulin, distinct coma arose; at this point, the blood sugar was 35 mg-% and the oxygen saturation of the arterial blood was 88%. Prior to the injection of insulin, the patient P-ich [female] had a blood sugar of 115 mg-% and 94% oxygen saturation of the arterial blood. When 30 minutes had elapsed following subcutaneous administration of 116 units of insulin, the oxygen saturation of the blood was 92%; at 2 hours the figures were 82% with 45 mg-% of sugar, and deep coma intervened after 3 hours 30 minutes. The blood oxygen saturation was 60% and the sugar content 32 mg-%. The oxyhemometry data of this patient are shown in Fig. 1.

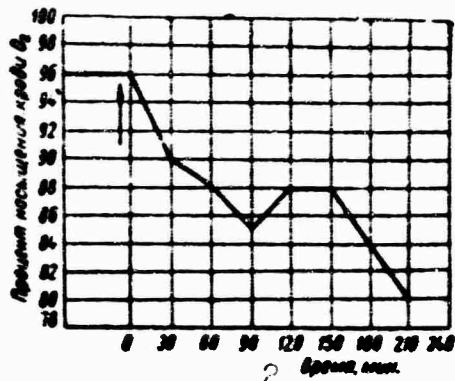


Fig. 1. Oxygen saturation of arterial in patient P-ch during the development of insulin coma. The arrow marks administration of 116 units of insulin. 1) Percentage saturation of blood with O_2 ; 2) time, minutes.

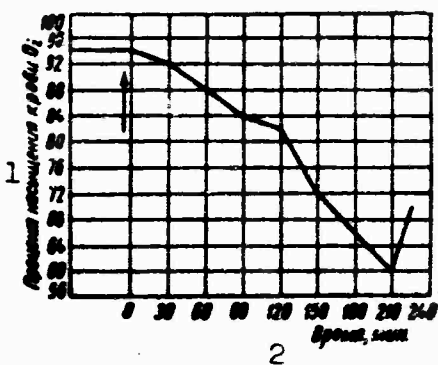


Fig. 2. Oxygen saturation of arterial blood in patient G-k during development of insulin coma. The arrow marks the administration of 38 units of insulin. 1) Percentage saturation of blood with O_2 ; 2) time, minutes.

In the patient G-k [female], the blood sugar was 107 mg-% and the oxygen saturation of the arterial blood 96% prior to the administration of insulin. The oxygen saturation of the blood had dropped to 90% 30 minutes after subcutaneous administration of 38 units of insulin, to 88% after 2 hours and to 84% after 3 hours. The precomatose state was observed after 3 hours 30 minutes, with the blood sugar at 45 mg-% and the blood oxygen saturation at 80%. The oxyhemometry data for this patient are shown in Fig. 2.

Tests were made on a number of patients after they had come out of the comatose state. Restoration of the blood-sugar level took place very rapidly, but while the oxygen saturation of the arterial blood showed a significant rise during the first 10 minutes following the administration of glucose, it did not reach the initial figures during 30 minutes of observation.

In most of the patients that we examined, respiration was progressively suppressed during the development of hypoglycemia and the comatose state. In the initial phase of insulin hypoglycemia, we usually noted a decrease in the amplitude of respiration with a quickening of its rhythm. Undulating variations in amplitude occurred frequently. In patients with psychomotor excitation and manifest vegetative derangements, considerable variability of the res-

piratory rhythm and amplitude was observed in the period prior to the onset of coma. Sometimes the rhythm was thrown into total disorder, with excitation periods alternating with temporary suspensions of respiration. As stupefaction deepened, however, the periods of uniform respiration became longer and longer at decreased amplitude.

The respiratory rhythm usually became more uniform at onset of the distinctly comatose state, with nonuniform amplitude values in different patients and a somewhat accelerated rhythm. The impression formed was that the pneumogram was approaching normal. Not once did we observe the typical chain-stokes respiration or any severe derangements of the terminal type (prolonged apneusis, Kussmaul's rhythm, continuous "gasping").

Emergence of the patients from the comatose state after intravenous administration of glucose was accompanied by disordered respiratory rhythm, periods of deep breathing alternating with highly superficial respiration. Arrhythmia of respiration vanished completely.

Our data on the changes in blood pressure and pulse frequency following administration of insulin differ little from those described in the literature (Kirillov, 1948, and others). An increase in pulse pressure at the expense of a drop in diastolic pressure, together with a quickening of cardiac rhythm, must be regarded as most characteristic for insulin hypoglycemia in schizophrenics. In the patients studied, we noted that a relatively high maximum arterial pressure was maintained on onset of coma.

Thus, the results of our investigations indicate that in schizophrenia patients, a progressive decrease in the oxygen saturation of the arterial blood takes place during the development of insulin hypoglycemia and the comatose state. The decrease begins a short time after administration of large doses of insulin. During the time of hypoglycem-

ic excitation and vegetative disturbances, the oxygen saturation of the arterial blood continues to diminish and reaches its maximum [sic] in the pre- and comatose states.

The level of arterial blood oxygen saturation diminishes to different degrees in the comatose state in different patients. In many patients, a considerable decrease coincides with suppression and distinct derangement of respiration. However, a decrease in the oxygen saturation of the blood can be observed together with uniform, deep and quickened respiration. This can be accounted for by considerable vasomotor disturbances and redistribution of the blood in the organs, with changes in the relationship between the ventilation and blood supply to the lungs as a result of the insulin intoxication.

As has been shown by the studies of M.Ye. Marshak (1953), the arterial blood oxygen saturation depends not only on the degree of pulmonary ventilation, but also on the reciprocal relationship between the ventilation and blood supply of the lungs, and sometimes even that of individual zones of the lungs. M.Ye. Marshak invokes changes in the functional interrelationships between ventilation and blood supply to the lungs to account for the considerable drop in the percentage oxygen saturation of the arterial blood during muscular work in unconditioned persons. The effect of muscle load on the oxygen saturation of the arterial blood under normal and hypoxic conditions was investigated by V.I. Voytkevich (1955). She came to the conclusion that the arterial blood oxygen saturation depends on the ability of the organism to intensify its respiration and blood circulation and on the extent of the correlation between the respiratory and circulatory changes. Experimental studies on animals to determine the various ways in which changes in the arterial blood oxygen saturation depend on the type of respiration were published in 1956 by Al'bers, Brendel' and Yuzinger.

L.A. Ballonov and A.Ye. Lichko (1958) indicate that in schizophrenia patients, the variety of respiratory reactions increases with advancing insulin hypoglycemia, manifesting at times in the form of acute excitation, at other times in prolonged suspension; arrhythmia and alternation of periods of frequent with slackened respiration are noted at times, with the amplitudes nonuniform.

P.M. Kazakov (1957) observed considerable variability in respiration of schizophrenia patients prior to the onset of the comatose state. He stresses the more uniform nature of the respiration as the coma sets in. Literature data concerning changes in respiration during insulin hypoglycemia in schizophrenics still remain sparse, as was noted as long ago as 1939 by L.P. Molukalo.

The results of our investigations permit the conclusion that, together with oxygen starvation of the brain, arterial hypoxemia is also a factor in the mechanism of insulin-coma therapy. It may be assumed that general tissue-hypoxia also arises during insulin intoxication. The experimental studies of S.G. Genes (1957) indicated that when we administer large doses of insulin we are observing its direct action upon the organism's organs and tissues.

As concerns the intermediate links in the mechanism of the therapeutic effect of insulin coma, it appears that particular importance must be ascribed to the profound inhibition of the central nervous system that arises under the influence of hypoxia and stimulates recovery processes. In conclusion, we must point out the necessity of adoption of the continuous cathodic oxyhemometry technique on a broader scale in psychiatric practice.

DYSOXIA AS A CONDITION DISTINCT FROM HYPOXIA*

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(Moscow)

We should like to introduce clarity into certain problems concerning hypoxia, as well as into a broad range of states frequently associated with it, in which oxidative metabolism processes are disturbed. The fact is that in my everyday work with experimental pathophysiologists and clinical medicine specialists, I frequently encounter a strong feeling of dissatisfaction in processing data and occasionally I am obliged to resort to long-winded explanations to develop proper understanding.

As we know, the following terms are in widespread use at the present time: oxygen insufficiency, an extremely broad term denoting "some sort of unwell condition" of the organism connected with oxygen; oxygen starvation, a concept making reference to a deficiency of oxygen; and hypoxia - perhaps the most satisfactory, crisp and expressive term, but still a rather vague one. Do we not employ this last term too often? After all, as some people understand it, hypoxia occurs in almost any pathological state.

I should like to emphasize that by its etymology, the term hypoxia should connote something associated either with low concentration, or with decreased quantity, or with quantitatively inadequate utilization of oxygen. But this term has no content as regards the quality of the oxidative process itself. The latter may be qualitatively altered or unaltered as compared with the normal process. In all probability, it

will be affected if there is a significant shortage of oxygen, but this is not absolutely necessary.

At the same time, we have, in our study of pathology, accumulated data indicating not so much a change in the amount of oxygen being used as the qualitative nature of this consumption, i.e., the nature of intracellular oxidative processes. Let us present some of the facts that we have derived.

First, a few words on the methodological approach that we have used. Usually, the consumption of oxygen is determined in studies of the respiration of isolated tissues by the Warburg method, quite often concurrently with an investigation of anaerobic glycolysis, although it must be noted that there is little linking these two processes. In a departure from this design of the experiments, we have made an effort at more purposive study of the oxidation process. Using the Warburg with the tissues incubated in an oxygen atmosphere, we determined the gas metabolism of the tissues, i.e., not only the consumption of O_2 , but also the CO_2 evolved. Further, the total quantity of organic acids formed and, sometimes also the specific quantity of pyruvic acid, were determined in the cell suspension before incubation and at the end of incubation. Thus, we obtained a conception as to the quantity of both one of the initial products (oxygen) and the principal final product (carbon dioxide) of the oxidative process. Calculating the respiratory coefficient, we drew inferences as to the completeness of the combustion process and the extent to which the oxygen remains bound in intermediate stages of the oxidation. These data were supplemented by direct determination of the intermediate metabolic products in the form of the total organic acids.

In 1955, working with A.G. Stepanenko, we studied the gas metabolism of a bone-marrow suspension after it had been denervated. One of

the rear extremities of a cat was denervated. For this purpose, a segment 1-2 cm long was resected from the femoral and sciatic nerves, and the nerve plexuses running along the femoral artery were destroyed by moistening them with tincture of iodine. The other rear extremity was left alone. Also included in the experiment were animals one of whose rear extremities had been cut across, but without damage to the nerves (surgical traumatic injury to the extremities). The animals were sacrificed 5-10 days later. Suspensions of bone marrow were prepared in buffer-phosphate-salt solution from the marrow of the femora and tibiae.

It was found that nothing unusual could be detected as regards the amount of O_2 absorbed by the "denervated" bone-marrow suspension; some decrease in the uptake of O_2 as compared with the controls may be accounted for by the edema observed in the denervated bone marrow and, consequently, the decreased amount of dry active matter in it.

The most interesting observation in these experiments was the fact that a decrease in the amount of CO_2 excreted takes place out of proportionality to the O_2 figure, so that the respiratory coefficient of the "denervated" bone-marrow suspension turned out to be slight (by 0.1-0.2 unit) but consistently lower as compared to the "respiratory coefficient" of the "control" bone-marrow suspension (Table 1). That this effect is not accidental is indicated by the following. After surgical trauma (without denervation), we observed only insignificant differences, not exceeding the errors of the method used, in the respiratory coefficients of the bone marrow of the two extremities.

Subsequently, again working with A.G. Stepanenko, we studied gas metabolism and organic acid formation during incubation of guinea pig liver pulp from animals that had perished or been sacrificed during anaphylactic shock. Control determinations were made with liver from sensitized animals sacrificed by air embolism or by asphyxia, since

TABLE 1

Respiratory Coefficient (CO_2/O_2) in the Respiration of an Isolated Bone-marrow Suspension

1 5 дней после денервации				2 10 дней после денервации			
3 Коэффициент			Различия 7	3 Коэффициент			Различия 7
4 № опыта	5 контроль	6 денервированный		4 № опыта	5 контроль	6 денервированный	
V	0,72	0,58	-0,14	IV	0,78	0,71	-0,07
VII	0,77	0,74	-0,03	VI	0,82	0,81	-0,01
IX	0,80	0,76	-0,04	VIII	0,82	0,76	-0,06
XI	0,70	0,67	-0,03	X	0,70	0,55	-0,15
XIII	0,74	0,67	-0,07	XII	0,77	0,68	-0,09
XIV	0,77	0,68	-0,09	XVI	0,75	0,67	-0,08
XV	0,68	0,62	-0,06				

8 10 дней после операционной травмы			
3 Коэффициент			Различия 7
4 № опыта	5 контроль	6 травмированный	
XVII	0,82	0,81	-0,01
XVIII	0,79	0,80	+0,01

1) 5 days after denervation; 2) 10 days after denervation; 3) extremity; 4) experiment No.; 5) control; 6) denervated; 7) difference; 8) traumatized.

there is a body of opinion to the effect that asphyxia is a factor of no little importance in the pathogenesis of anaphylactic shock in guinea pigs.

It is evident from Table 2 that the absorption of O_2 for "shock" liver tissue was equal to that under normal conditions, both in the experiment and in the control. The figures vary within the same limits and have the closely similar averages of 205, 212, and 221 μl ; on the other hand, the excretion of CO_2 by the "shock" tissue is down sharply, at 88 μl instead of the normal 159 μl , i.e., it has been almost halved. As a result, the respiratory coefficient of the "shock" liver tissue is exceptionally low: it fluctuates in the range from 0.37-0.50, averaging only 0.42 instead of the normal 0.76.

The following interesting and consistently observed phenomena must

TABLE 2

Oxygen Absorption and Carbon Dioxide Excretion
During Incubation of Guinea Pig Liver Tissue
Pulp

Показатели 1	№ по журналу 2	Дни сен- сibilиза- ции 3	Поглоще- ние кисло- рода (в мл) 4	Выделение углекис- лоты (в мл) 5	Дыхатель- ный коэф- фициент 6
Норма (сенсibilизирован- ные животные) 7	8	16	231	180	0,77
	9	24	170	131	0,77
	10	14	215	162	0,75
	8 Среднее		205	159	0,76
Анафилактический шок 9	6	14	184	78	0,42
	7	16	237	70	0,37
	11	14	185	79	0,42
	15	24	230	115	0,50
	17	26	212	88	0,41
	20	15	222	98	0,44
	8 Среднее		212	88	0,42
Асфиксия (сенсibilизиро- ванные животные) 10	22	17	249	195	0,79
	23	19	215	152	0,71
	24	18	201	145	0,72
	8 Среднее		221	164	0,74

1) Indicator; 2) bookkeeping No.; 3) days of sensitization; 4) absorption of oxygen (in mm³); 5) excretion of carbon dioxide (in mm³); 6) respiratory coefficient; 7) normal (sensitized animals); 8) average; 9) anaphylactic shock; 10) asphyxia (sensitized animals).

be noted in connection with the organic acids. While a decrease in the total quantity of organic acids by 1-2 mg-eq, and decrease in the amount of pyruvic acid by 1 mg-% take place in normal liver tissue during incubation (i.e., the organic acids are subject to oxidative "clean-up" during incubation in the oxygen atmosphere), the quantity of these substances increases by as much in the "shock" tissue. It may be assumed that the "shock" tissue has lost its ability to oxidize organic acids rapidly even in an oxygen atmosphere (or its ability to break them up in other ways).

But how can we characterize the state of the cells that is observed in the two cases described: as more acute in anaphylactic shock

and of lower level when the bone marrow is denervated? Formally, I used to interpret it as a kind of histotoxic hypoxia with disturbance to oxidative processes, but without a quantitative change in oxygen consumption. This, however, was clearly against logic, since there was no oxygen starvation in these cases: the cell suspension was in an oxygen atmosphere and was taking up a normal amount of oxygen. There was only a disturbance to the oxidative processes with formation of incompletely oxidized substances.

This naturally brings to mind the terms used to denote changes in oxidative processes. As we know, a disturbance of the oxidation process throughout the entire organism with an elevated O/N coefficient in the urine was given the name dysoxidative carbonuria by Bikel' and Kaufman-Kosel. Then Perel'man (1947) described dysoxidative processes. Later, at a conference on the problem of "Oxygen Insufficiency in the Organism" (Kiev, 1947), I expressed my feeling that a special group of dysoxidative states be singled out from among the states of histotoxic hypoxia, and followed up with my proposal to a session of the biochemistry section of the Society of Physiologists, Biochemists and Pharmacologists (Moscow, 1953). Over 10 years have passed since then, and the facts that have been accumulated have not only failed to refute the propositions advanced at that time, but, to the contrary, have convinced me of the necessity of distinguishing the fully justified term dysoxia in parallel to hypoxia.

I propose the use of this term to connote pathological states in which a change in the oxidative metabolic process of the cells takes place without quantitative disturbance to oxygen uptake and without any hindrance to this uptake. It is possible to conceive of a state in which the activity of the cytochromic systems remains normal, but there is lack of harmony among the enzymatic processes, and oxidative and

other processes that normally follow smoothly one after the other become disjointed; in particular, it would appear that the splitting off of CO_2 (decarboxylation) is disturbed. Needless to say, far from everything is absolutely clear in this area, and study of the essential nature and mechanism of the disturbances to the oxidative processes is an interesting problem for biochemical research.

It appears that cases occur in which changes in the intermediate processes are accompanied by accumulation of intermediate substances even without a change in the character of the respiratory coefficient.

We had occasion to investigate, together with A.G. Stepanenko and O.D. Romanova, the gas metabolism of pathological leucocytes obtained from the blood of leukemia patients. As will be seen from Fig. 1, the gas metabolism of these leucocytes was abnormally high as compared with that of normal ones. The excretion of carbon dioxide was also at a high level, with an even greater abnormality than that observed for oxygen. The respiratory coefficient was found to be unusually high; it averaged 1.06 as compared with 0.87 for the control (i.e., the gas metabolism of normal leucocytes). Thus, it is as though oxidation were proceeding conspicuously, but nevertheless on investigation of the organic acids it was found that after incubation, the leucocytes of leukemia patients show an increase in organic acids, while in normal cells the organic acids are, as usual, lower (Fig. 2).

It might be assumed that fats formed in the leucocytes of the leukemia patients at the expense of carbohydrates, while at the same time organic acids accumulated as a result of some process yet unidentified. This observation, which should under no circumstances be referred to as hypoxia, may be called "dysoxia."

Up to this point, we have been discussing respiration of cells in an oxygen atmosphere in in vitro experiments, but it will be understood

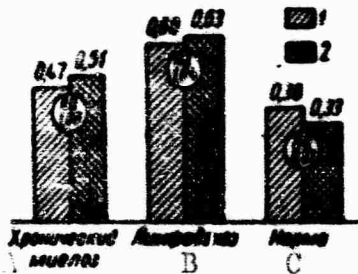


Fig. 1. Gas Metabolism of leucocytes (in μl of gas per 10^6 leucocytes). 1) O_2 uptake; 2) CO_2 excretion. The respiratory coefficient is shown in the circles. A) Chronic myelosis; B) lymphadenosis; C) normal.



Fig. 2. Organ acids in leucocytes before and after incubation (in mg-%). 1) Before incubation; 2) after incubation. A) Chronic myelosis; B) lymphadenosis; C) increase; D) by +2.2; E) by +1.1; F) normal; G) decrease by 0.3.

that the same also applies to the organism as a whole. Here again, also in contradistinction to hypoxia, behind which there is no oxygen insufficiency, are definitely distinguishable.

Summing up, we can make the following statement. There has been nothing particularly new in the questions that I have raised. Reports on dysoxidative carbonuria, dysoxidative processes and dysoxidative states have long been appearing in the literature. However, taking advantage of the present conference, I have again resolved to draw attention to this problem, proposing that a clear boundary be drawn between hypoxia and dysoxia. It seems to me that progress in the field of biochemistry and experimental technique is now at a level such that study of the difficult but interesting matter of disturbances to oxidative and other metabolic processes of the tissues can be advanced rapidly and fruitfully.

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ON THE PROBLEM OF CLASSIFYING DEGREES OF HYPOXIC STATES*

A.Z. Kolchinskaya

(Kiev)

Despite the fact that an enormous number of experimental and clinical investigations have been devoted to the problem of hypoxia, there is no consistent terminology for definition of the degree of a hypoxic state. To this day, various authors are using arbitrary selected terms ("nonacute hypoxia," "hypoxia of low degree," "hypoxia of moderate degree," "acute hypoxia," "anoxia," and the like), without connoting by these terms any conceptions with rigorous scientific sense defined by definite parameters.

The absence of a consistent terminology is accounted for by the fact that there is as yet no satisfactory and generally accepted classification of the degrees of hypoxic states. The urgent necessity of working out such a classification is demanded not only by the rigors of experiment, but also by the requirements of the clinic, which is forever encountering hypoxia in various disorders and forms of surgical intervention, and by those of medical support for the mining industry, aviation, astronautics, etc., where precise and timely diagnosis of the degree of a hypoxic state can provide safety in work at high altitudes and flight safety.

In defining oxygen insufficiency, the terms "hypoxia" - reduced quantity of oxygen - and "anoxia" - absence of oxygen - are often used synonymously. Thus, Van Lir one of the foremost specialists on hypoxia, uses the term "anoxia" to signify all imaginable varieties of hypoxic

state. To most authors, on the other hand, "hypoxia" is a term referring to a state of oxygen insufficiency, while "anoxia" refers to the extreme degrees of oxygen starvation.

Wiggers (1941) proposed that the term "hypoxia" be applied to states that develop when the oxygen content of the inspired air is reduced to 12%. States that develop when the oxygen content in the inspired air is further lowered to 7-6%, when acute cardiac insufficiency manifests itself, he prefers to call "critical anoxia." The classification of Wiggers, in which the basic indices are the percentage contents of oxygen in the inspired air and the change in the frequency of heart contractions, has not come into widespread use, since, first of all, the percentage content of oxygen in the inspired air can be used only as an orientative criterion of degree of hypoxia, since at a given oxygen partial pressure in the air, the degree of hypoxemia, the oxygen saturation of the arterial-blood hemoglobin and the content of oxygen in it may vary; the state of the organism and the oxygen uptake by the tissues may also be different. Further, even so important an index of the organism's state as the change in pulse frequency, which Wiggers takes as a basic criterion, cannot be considered dependable when taken in isolation, particularly in hypoxia of subacute manifestation.

The most widely known classification of hypoxic-state degrees is that proposed by Henderson (1933). This author, and later Van Slyke (1935), juxtaposed the indices characterizing the composition of the inspired gas mixture (oxygen partial pressure in the inspired air, altitude in thousands of meters above sea level) with the percentage oxygen saturation of the arterial hemoglobin, the oxygen partial pressure in the arterial blood and certain other subjective and clinical indices.

Distinguishing four degrees of acute hypoxic hypoxia, the authors assign to the first degree hypoxia that arises on inspiring air with

$pO_2 = 120-90$ mm Hg (altitude below 4870 m), when the arterial hemoglobin is 89-85% saturated with oxygen and the pO_2 of the arterial blood is 60-45 mm Hg. The accompanying clinical symptoms are headache, general weakness, a decline in the functions of the central nervous system, disturbances to muscular coordination, and quickening of the pulse and respiration.

The second stage of hypoxia arises when the pO_2 in the inspired air has dropped to 70 mm Hg (altitudes up to 7550 m), when the arterial hemoglobin is 87-74% saturated and the pO_2 in the arterial blood = 55-40 mm Hg. Clinically, we note precoma or postcoma in such cases - states approaching loss of consciousness. Phenomena observed include a weakening of the critical faculty, emotional instability, a shambling gait, muscular efforts producing cardiac weakness, and insensitivity to cuts and bruises.

The third degree of hypoxia in this classification sets in when the pO_2 of the inspired air has dropped to 45 mm Hg (10,500 m); here, the oxygen saturation of the arterial hemoglobin may drop to 33% and the pO_2 of the arterial blood to 40-20 mm Hg. Clinically, we observed loss of consciousness, cerebral coma with "a fixed glassy stare." The organism can be brought out of this state by administration of oxygen.

The fourth degree of hypoxia takes over when the pO_2 of the arterial blood is below 20 mm Hg (altitudes exceeding 10,500 m). The comatose state is observed; respiration is extremely sluggish. Cessation of respiration culminates in death.

In our opinion, an essential defect in this classification is the fact that it does not accord the initial degrees of hypoxia the attention that they merit. According to this classification, the first degree of hypoxia would encompass too broad a range of physiological states developing in the organism as the pO_2 is lowered to 120-90 mm Hg.

Further, this classification does not give adequate consideration to the objective indices to changes in the organism's physiological functions; the basic attention is devoted to the partial pressure of the oxygen in the arterial blood and the oxygen saturation of the arterial hemoglobin - extremely important indices, but not the only ones that decide the state of the organism.

In recent years, there has appeared a tendency to classify degrees of hypoxia in terms of individual physiological indices and their complexes of symptoms, which are amenable to automatic registration and can provide objective information on the severity of the hypoxic state. Thus, Noel' (1950) proposed that stages in hypoxia be distinguished on the basis of the corresponding electroencephalogram changes. Noel' regarded the appearance of slow fluctuations at a frequency of six per second and slower as a symptom of hypoxia representing a threat to the pilot. As we know, however, the electroencephalogram may be of importance in the diagnosis only of an uncompensated hypoxic state. Even in the development of the fourth stage of hypoxia, orientation to the electroencephalogram may lead us to erroneous conclusions, since in some cases depression of the biocurrents may occur even after respiration has stopped.

Included in the present collection is a paper by V.B. Malkin, in which is proposed that the severity of hypoxic states be determined automatically on the basis of simultaneous registration of such indices to the physiological functions as the electroencephalogram, electrocardiogram, respiratory movements, arterial pressure and the oxygen saturation of the arterial blood, with the information being fed to an automatic device that would signal the degree of the hypoxic state. Here V.B. Malkin proposes that four stages of hypoxia be distinguished.

The first would be the stage of stable adaptation, when the devel-

Stages of Acute Hypoxic Hypoxia

Симптом	Субъективные ощущения	Изменения в состоянии сознания	Изменения в состоянии дыхания	Изменения в состоянии кровообращения	Изменения в состоянии нервной системы	Изменения в состоянии органов чувств	Изменения в состоянии сердечно-сосудистой системы	Изменения в состоянии желудочно-кишечного тракта	Изменения в состоянии мочеполовой системы	Изменения в состоянии кожи	Изменения в состоянии зрения	Изменения в состоянии слуха	Изменения в состоянии обоняния	Изменения в состоянии вкуса	Изменения в состоянии осязания	Изменения в состоянии мышечной системы	Изменения в состоянии костно-суставной системы	Изменения в состоянии иммунной системы	Изменения в состоянии эндокринной системы	Изменения в состоянии репродуктивной системы	Изменения в состоянии старения																																																																			
I. Сильная гипоксия	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
II. Умеренная гипоксия	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100												
III. Слабая гипоксия	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100																								
IV. Крайняя гипоксия	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100																																			
V. Терминальная гипоксия	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100																																												

1) Stage; 2) subjective sensations and behavior; 3) changes in higher nervous activity; 4) electrical activity of brain cortex; 5) respiration; 6) pulse rate; 7) EKG; 8) percentage O₂ saturation of arterial blood hemoglobin; 9) A - V in O₂; 10) O₂ uptake; 11) content of CO₂ in the arterial blood; 12) approximate altitudes at which the state in question is observed; 13) 1. Latent hypoxia; 14) slightly euphoric mood, no changes in the way the subject feels. Motions more rapid, gestures slightly exaggerated; 15) slight disturbance to internal inhibition; fine differentiations are disinhibited, while coarser differentiations are not disturbed. Strength of conditioned reflexes increases, with shorter latent period. The subject talks faster. Fine coordination of movements is disturbed; 16) no noticeable changes on EKG; 17) respiratory frequency in supine position at complete rest may either not change

at all or change insignificantly. The MOD [respiratory minute volume] increases. The MOD increase may reach 4-50%; 18) either shows no change or rises insignificantly (3-10%); 19) no marked changes. R-R cycle may be shortened; 20) 94-89; 21) within normal limits; 22) either does not change or increases insignificantly; 23) within normal limits; 24) 1-3 thousand meters in the hypobaric chamber; 1-2 thousand meters in the mountains (in the first few days of a sojourn); 25) II. Compensated hypoxia; 26) a feeling of heaviness in the head and the entire body arises. The subject may experience headache, nausea, accelerated beating of the heart. Mental and physical work requires effort. Motions slowed down; 27) strength of conditioned reflexes decreases, and latent period becomes longer. All forms of internal inhibition are disturbed, and coarse differentiations are disinhibited. Hypnoid phasic states are observed. The rate of speech slows down, and we note a deterioration in the quality of the speech reactions, difficulty in forming new verbal associations; 28) quickening of the electrical oscillations may be observed, with an increase in their amplitude; 29) respiration may become more frequent; the MOD increases by (approximately) 20-80%; 30) increases by 6-30%; 31) the P and T waves are flattened out and the R-wave subsides, but may increase in some cases. R-R becomes shorter due to a decrease in the T-P interval; 32) 88-70; 33) decreases, usually due to a relatively small drop in the oxygen saturation of the venous-blood hemoglobin; 34) increases as compared with normal values; 35) decreases; 36) 4-5 thousand meters in the hypobaric chamber; 3-4 thousand meters in the mountains; 37) III. Distinct hypoxia, with decompensation setting in (with stressed activity of the reflex compensatory mechanisms); 38) headache, nausea, presyncopic state with pallor, perhaps twitching of the eyelids and facial muscles; 39) deepening of phasic hypnoid states. Predominance of diffuse inhibition; 40) the changes in the EEG are most pronounced. The voltage of the biocurrents diminishes and the rhythm becomes slower and more distinct, as is observed in a faint; spindle-shaped volleys may be observed. Slow oscillations appear; 41) the MOD increases by a factor of two or more, and respiration quickens markedly in most subjects; 42) quickening exceeds 30% of initial norm; 43) the EKG becomes lower in voltage, with only the amplitude of the T-wave increasing. R diminishes, and changes in the duration of the P-Q and Q-T intervals may be observed; 44) 70-40; 45) increases; 46) distinct hypoxia; 47) 5.5-7 thousand meters in the hypobaric chambers; 4.5-6 thousand meters in the mountains; 48) IV. Uncompensated hypoxia (with disturbance to the activity of reflex adaptive mechanisms); 49) loss of consciousness, convulsions, involuntary micturition and defecation possible; 50) the MOD is lower than in the preceding stage, but may, in some cases, remain higher than at normal atmospheric pressure. Respiration of the periodic type may be observed; 51) pulse slackens as compared with previous stage; 52) increase in duration of R-R cycle, prolongation of P-Q and Q-T, further decrease in EKG voltage, disappearance of P, appearance of a high T or transition of T to the negative, appearance of an S-T shifted in either direction from the isoline; 53) below 40; 54) reduced; 55) has decreased as compared with the previous stage, but may nevertheless remain above the normal level; 56) 8-9 thousand meters in the hypobaric chamber; 57) terminal hypoxia; 58) agonal state; 59) sharp deceleration of respiration to 3-2-1 per minute, total cessation of breathing possible; 60) sinus rhythm; 61) decline in cardiac activity. High, sharp-peaked T; 62) below 20; 63) reduced; 64) considerably lower than under normal conditions; 65) 10-11 thousand m in the altitude chamber.

opment of adaptive respiratory and circulatory reactions is still capable of maintaining the functional state of the central nervous system at an adequately high level. According to V.B. Malkin, this stage covers the states in which the oxygen saturation of the arterial blood may drop below 85 and even reach 60%.

The second is the stage of uncompensated oxygen deficiency, when the oxygen saturation of the arterial blood drops below 60%.

The third is the stage of profound derangement in the activity of the central nervous system, total loss of the ability to perform work due to loss of consciousness, the appearance of clinical convulsions and other severe disturbances, a quickening of respiration to a level above 30-35 per minute or suspension of respiration for longer than 25-30 seconds, and a more than fourfold increase in the energy of the electroencephalogram low-frequency spectrum.

The fourth is the stage of disturbances to respiration and circulation that pose a threat to life, suspension of respiration, drop in blood pressure, depression of biocurrents.

Something of unquestionable value in the author's suggestion is his desire to find an automatic method for determining the degree of hypoxia - a technique based on taking account of changes in a set of physiological indices amenable to objective registration. However, the actual classification submitted by V.B. Malkin can hardly be regarded as a happy one. First of all, the first stage of hypoxia according to V.B. Malkin covers a wide variety of states of the organism in which the oxygen saturation of the arterial blood drops to 60%, thus embracing two of the periods distinguished by Henderson and Van Slyke. Essentially, this classification fails to give a conception of varying degrees in the compensated hypoxic state. Moreover, taking the initial stages of hypoxia and its development into consideration may be of

V.B. Malkin again combines different states of the organism under his second stage of hypoxia. Basically, he ascribes importance only to those indices that attest to a condition already threatening the life of the organism, indices that are so obvious that they do not require complex instrumentation to register them.

In this classification, the third and fourth stages of hypoxia are essentially statements of preterminal states.

As will be seen from the literature data presented above, very little attention has thus far been devoted in classifications of degrees of acute hypoxic hypoxia to early changes in the functioning of the brain's higher divisions, and, in particular, to changes in higher nervous activity; also, virtually ignored are early changes in the vegetative functions - respiration, cardiac activity, and the like. On attentive study of these indices, however, it becomes obvious that the gravity of a hypoxic state may be judged quite objectively from the ensemble of these changes, taking into account the indices of arterial and venous hypoxemia (percentage saturation of the arterial and venous hemoglobin, content of oxygen in the arterial and venous blood) and the oxygen uptake by the organism as a whole.

Taking into account changes in the functions of the central nervous system, respiration, cardiac activity and humoral shifts in hypoxia, we have proposed that the following stages be distinguished in the hypoxic state: the stage of latent hypoxia, the stage of compensated hypoxia, the stage of manifest hypoxia with onset of decompensation, the stage of uncompensated hypoxia and the terminal stage.

In the first stage, an amplification of external respiration compensates the organism for the shortage of oxygen in the inspired air. An effect of the subnormal oxygen partial pressure on the organism can

be detected only by special objective tests, since it is almost imperceptible subjectively; the oxygen saturation of the arterial blood drops insignificantly, to 94-89%.

In the second stage, amplification of the external respiration, taken alone, is no longer sufficient; other mechanisms - primarily an increase in the blood supply to vitally important organs - also participate in compensating the oxygen deficit. The tissues still receive O_2 in considerable quantities even in manifest hypoxemia. In this stage, the hypoxia is perceived not only objectively (marked disturbances appear in higher nervous activity, the EEG and EKG change, and so forth), but subjectively as well, since the ability to work diminishes and the subject begins to feel poorly. The O_2 saturation of the arterial blood drops to 88-70%.

In the third stage, despite the stressed activity of the numerous reflex mechanisms, tissue hypoxia begins to appear. Decompensation with total loss of ability to perform work sets in. The presyncopic state is observed. The O_2 saturation of the arterial blood drops below 70% (as far as 40%).

In the fourth stage, the activity of such adaptive mechanisms as the amplification of external respiration and circulation is disturbed and the subject loses consciousness. Here the O_2 saturation of the arterial blood is below 40%.

The fifth terminal stage is the agonal state.

The most essential changes in the physiological functions in acute hypoxic hypoxia are indicated, as related to our viewpoint, in the attached table (see foldout).

It goes without saying that the table submitted here is, like others, schematic and incomplete. We believe, however, that it may serve as the foundation upon which a more perfect characterization of the de-

degrees of acute hypoxic states may be built (we are concerned here primarily with hypoxic hypoxia in middle-aged persons).

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[Transliterated Symbol]

754 МОИ = MOD = minutnyy ob"Yem dykhaniya = respiratory minute
volume

FUNDAMENTALS FOR AUTOMATIC DIAGNOSIS OF THE HYPOXIC STATE*

V.B. Malkin

(Moscow)

The experience that has been accumulated in many years of study of acute oxygen starvation arising in animals and man on "ascents" in the hypobaric chamber and under surface conditions on inspiration of oxygen-deficient gas mixtures has made it possible to approach the solution of a new problem -- the development of a medical program for a diagnostic machine that automatically signals the development of hypoxic hypoxia and determines the gravity of the hypoxic state.

To design a diagnostic machine that will determine the presence and depth of oxygen insufficiency, it is first necessary to evaluate the various indices (electroencephalogram, electrocardiogram, blood pressure, respiration, oxygen saturation of arterial blood, and so forth) that can be used for diagnostic purposes. Here, the object of the investigation determines to a major degree the manner in which the corresponding physiological information will be processed.

The polygraphic method of registering the basic physiological functions, with simultaneous quantitative determination of some of the most significant physiological shifts, has been a methodological approach that meets the basic research requirements.

This methodological approach enables us to compare hypoxic shifts in various functional systems and isolate complexes of symptoms that characterize qualitative changes in the physiological state, i.e., to establish the various stages in oxygen starvation.

Analysis of examinations made on 318 persons in whom acute oxygen starvation developed indicated that as a rule, and despite the fact that consistent changes in the functional states of the basic physiological systems are observed during the development of hypoxic hypoxia, none of the indices characterizing the activity of the circulatory, respiratory or central nervous systems can, by itself, be used for diagnosis of the depth of acute oxygen starvation.

It should be noted that the various indices are not all of the same value for diagnosis of the hypoxic state. It can, for example, be shown that the electroencephalogram, which enables us to follow hypoxic changes in the bioelectric activity of the brain, is of exceptionally great importance in determining the depth of oxygen insufficiency. However, even this index, when evaluated in isolation, is found inadequate in many cases for evaluation of the hypoxic state.

The results of the investigation made provide a basis for the assumption that in setting up the physiological algorithm, it will be most expedient to single out symptom complexes, i.e., to combine hypoxic changes in various physiological systems into groups such as will characterize essential changes in the physiological state. Here it is important to submit symptom complexes that characterize the depth of oxygen starvation. In this connection, it has become necessary to provide at least a schematic description of the various stages in acute oxygen starvation.

We propose to distinguish four stages in the development of acute hypoxic hypoxia.

I. Stage of stable adaptation. In this stage of hypoxia, the development of adaptive reactions on the part of respiration and blood circulation is still sufficient to maintain the functional state of the central nervous system on an adequately high level. There is no essen-

tial decrease here in the ability of the individual to perform work.

II. Stage of inadequate effectiveness of the adaptive reactions, which may be characterized as the stage of uncompensated oxygen insufficiency. As regards the nature of changes in the physiological functions, this stage manifests in two forms: either in derangement of the adaptive reactions - disturbances to the circulatory regulation (acute bradycardia, drop in arterial pressure, and so forth), or in disturbances to the activity of the central nervous system in spite of a manifest augmentation of the circulatory and respiratory functions - disturbances that are reflected on the electroencephalogram (EEG) in the form of a slackening of its rhythm.

Timely diagnosis of this stage in hypoxia is of great practical importance, since the ability to perform work diminishes markedly when it develops, as can be judged from disturbances to the coordination of fine motor habits - illegibility of handwriting, a considerable drop in the quantity and quality of work done, failing of the memory, and so forth. A highly important point is the fact that consciousness is still adequately preserved in this stage of hypoxia, so that the oxygen-shortage signal can find a sensible response.

III. The stage of profound derangements to the activity of the central nervous system can be defined as the third stage in the development of acute hypoxic hypoxia. Total loss of ability to work resulting from loss of consciousness; the appearance of clonic convulsions and other severe disturbances characterize this stage.

A timely signal warning of the onset of the third stage in hypoxia is of great importance if assistance is to be rendered quickly, for example, by switching on an emergency oxygen supply. As a rule, restoration of normal breathing conditions results in rapid disappearance of the hypoxic disorders and restoration of ability to perform work.

Research studies made on various species of animals have made it possible to distinguish a fourth stage - the stage of respiratory and circulatory disturbances that pose a threat to life.

The proposed breakdown of acute hypoxic hypoxia into four stages is only one of the possible schemes and thus has certain disadvantages. For the purposes of diagnosis, however, it appears to us to be quite justified.

The manifestation of these stages in acute hypoxic hypoxia depends on the extent to which the oxygen partial pressure in the inspired air has diminished, i.e., on the rate of development of the hypoxic state. When the oxygen partial pressure in the inspired air drops rapidly and by a considerable amount, there is no first stage, and the manifestations of the second and third stages occupy very short spans of time. This is of great importance for the diagnosis, since 10-15 sec are required to establish it.

Precise and timely diagnosis of the uncompensated hypoxic state is of particularly great importance in ensuring the safety of high-altitude aviation, since the basic problem is protecting the crew from the development of acute oxygen starvation, which impairs ability to perform work.

The development of a medical program for an automatic hypoxia warning system required not only thorough study of experimental data available in the literature, but also necessitated conducting new research using the polygraphic method in combination with quantitative determination of some of the most important physiological shifts.

In performing this work, we made an effort to accumulate a sufficiently large volume of factual material, that is, enough to yield statistically dependable results. To prevent spurious actuation of the warning device, it was necessary to take account of individual differences

in the reactions of the various experimental individuals. The basic condition that the program (physiological algorithm) of the device's operation had to meet is that no symptom complex characterizing the development of the uncompensated hypoxic state may correspond to a complex of symptoms symbolizing a normal physiological state. Here, the functional shifts in the stage of compensated hypoxia can also be identified provisionally as normal. In this connection, it becomes reasonable to introduce the concept of stress-norm, i.e., that functional "stress" that does not yet reflect the development of a pathological state.

It should be noted here, however, that this is a new problem, since the concept of the "norm" has generally been associated up to now with the conditions of physiological rest.

In writing up the warning system's operating program, it is necessary to evaluate each physiological parameter characterizing the hypoxic state not only qualitatively, but also quantitatively to the greatest possible extent.

Since evaluation of changes in physiological parameters is basic to the construction of the logic chart for the signal-device program, it will be worthwhile to dwell briefly on this aspect of the problem.

The hypoxic state was diagnosed on the basis of analysis of the electroencephalogram, electrocardiogram, respiratory movements, arterial blood pressure and the oxygen saturation of the arterial blood.

OXYGEN SATURATION OF ARTERIAL BLOOD

Following practical adoption of the photometric method for determining the oxygen saturation of the arterial blood (oxyhemometry), certain investigators (Opits, Shtrugkhol'd and others, have been inclined to feel that this research method could be used successfully to diagnose the hypoxic state. This viewpoint is based on the fact that there

is rigorous correspondence between the extent to which the oxygenation of the arterial blood has fallen off and the gravity of the hypoxic state.

Experience gained in "high-altitude ascents" in the hypobaric chamber has made it possible to establish a definite parallelism between the decrease in oxygen saturation of the arterial blood and the altitude of ascent. Significant individual differences in the blood oxygen saturation have been detected. Thus, the oxygen saturation varied from 83-60% in different individuals taken up to an altitude of 5000 m. With increasing altitude, this difference became smaller, and at 7000 m, the oxygen saturation of the arterial blood was varying from 72 to 55%.

The occurrence of significant individual variations in the oxygen saturation of the arterial blood makes it difficult to evaluate this indicator for diagnostic purposes. Most essential, however, is the fact that it is not possible to establish strict dependence between the gravity of the hypoxic state and the decrease in the arterial blood oxygen content. Occasional cases occur here of individuals with abnormally high sensitivity to hypocapnia, when profound disturbances to circulation and the activity of the central nervous system arise against a background of relatively high blood oxygen saturation (85-80%). In some studies, however, it has been noted that a considerable decrease in the oxygenation of the blood (to 65-60%) is still not accompanied by the development of a serious hypoxic state.

Thus, we may draw the conclusion that a decrease in the oxygen saturation of the arterial blood indicates the development of hypoxic hypoxia, but it does not, as a rule, justify an inference as to the gravity of oxygen starvation. Only on a very sharp drop (to 60% and below) can it be stated with certainty that an uncompensated hypoxic

state is developing in these cases.

In view of the above, we have introduced two values of the change in the oxygen saturation of the arterial blood into the diagnostic symptom complex (the machine program): a decrease in saturation to 85% and below and a decrease to 60% and below.

RESPIRATION

The results of the respiration study permitted us the conclusion that when an uncompensated hypoxic state develops in a healthy individual (this includes cases in which consciousness is lost), the changes in the rhythm, frequency and depth of the respiratory movements do not follow a consistent pattern. The assertions of certain authors to the effect that derangement of the regular respiratory rhythm ("periodic" respiration) indicates that the test subject has a low tolerance for hypoxia were not confirmed in our investigations.

The results of experiments on animals indicate that certain changes in respiration - the development of hypoxic apnoea and terminal respiration - are of great importance for diagnosis of severe hypoxic states that represent a threat to life. Hence parameters characterizing only the depth of the respiratory disturbance have been introduced into the diagnostic complexes: suspension of respiration by more than 25-30 sec and an increase in the respiratory frequency to higher than 30-35 per minute.

BLOOD CIRCULATION

Changes in blood circulation during the development of acute oxygen starvation are of great diagnostic importance.

While characteristic changes appear on the electrocardiograms of patients suffering from cardiovascular diseases as acute oxygen starvation develops: a shift in the S-T interval to a position below the isoelectric line, T-wave inversion, and so forth, all forming a basis for

Judgements as to the severity of the disease (Levi, Gol'din and others), these EKG changes do not, as a rule, occur in practically healthy individuals. In such people, the most characteristic changes are the development of sinus tachycardia, flattening of the T-waves and a subsidence of the R_1 and R_2 waves. However, there is no strict correlation between the extent to which these changes are manifested and the gravity of the hypoxic state. Consequently, they cannot be used for diagnostic purposes.

As indicated by our experience and certain literature data (Shneyder, Titel', and others), the dynamics of the changes in cardiac rhythm are of essential importance for diagnosis of the uncompensated hypoxic state. A considerable and abrupt drop in the frequency of cardiac contractions is of diagnostic importance because it precedes, or coincides in time with, the development of the uncompensated hypoxic state. In evaluating the physiological essence of this symptom, it should be noted that it reflects functional shifts in the nervous apparatus regulating the cardiac activity, and not hypoxic changes in the myocardium itself.

In diagnosis of the 4th stage of hypoxia - that of states posing a threat to life - such profound changes in the EKG as polytopic ventricular extrasystoly, fibrillation of the ventricles, and various degrees of inhibition of cardiac activity (syncope) are of great importance. These disturbances to cardiac activity may be introduced into the appropriate diagnostic symptom complexes.

BLOOD PRESSURE

The absence of a dependable method for continuous determination of arterial pressure in the human makes it extremely difficult to use this highly important circulatory index for diagnostic purposes. According to our proposal, periodic determination of blood pressure must be ac-

completed when certain shifts arise in the pulse frequency. According to data from the investigations of Yegorov and Aleksandrov, Shneyder et al., and our own observations, the development of an uncompensated hypoxic state is, as a rule, indicated by a decrease in pulse pressure as a result of a rise in the diastolic pressure while the systolic pressure either remains the same or diminishes, as well as by a 10-15 mm Hg or larger decrease in the systolic pressure, or by a simultaneous drop in both the systolic and diastolic values. It must be borne in mind that hypertension and, first and foremost, a considerable rise in the systolic pressure occur frequently in acute oxygen starvation during the period in which compensation is still sufficiently complete, and therefore have no special diagnostic significance.

THE ELECTROENCEPHALOGRAM

In 1949, in following up a proposal by Kornmueller, Noel' recommended that certain changes in the electroencephalogram - the appearance of slow fluctuations at frequencies of 6 per second and lower - be used aboard aircraft to signal the development of hypoxia to a level dangerous for the crew.

The attempt to use the EEG as a fundamental and self-sufficient index for judgements as to the gravity of the hypoxic state was based on the results of studies by Berger, Davis, Davis and Thompson, Kornmueller et al., Beygel', Haarstich, Pal'me and others, which established a rigorous relationship between the gravity of the hypoxic state and the left shift on the EEG, i.e., the appearance of slow fluctuations on the EEG. As a result, Noel' even proposed (1950) a new classification in which the stages of hypoxia were identified in correspondence to shifts on the EEG.

Our investigations indicate that, despite the great importance of the EEG changes in diagnosis of the uncompensated hypoxic state, the

EEG are found to be inadequate for diagnosis in a number of cases with primary disturbances to the regulation of blood circulation, so that they cannot be used as the sole index characterizing the severity of acute oxygen starvation.

In development of the 4th stage of hypoxia, orientation to the EEG alone may lead to erroneous conclusions, since the depression of the biocurrents occurs in some cases even after respiration has ceased, being one of the indicators of a grave hypoxic state. We have observed this in experiments on animals in which acute oxygen starvation was induced at various levels of narcosis. Consequently, not even the state of narcosis can be judged in all cases from the pattern of the brain's bioelectric activity.

These observations are not in agreement with conclusions drawn by certain investigators who proposed the use of electroencephalography for control of the depth of narcosis (Bickford, 1956, and others). It should be noted that this position has been the target of serious criticism in clinical anesthesiology as well (Schneider, Yefuni).

Our data indicate that diagnostic importance resides in the redistribution of energy in a certain region of the electroencephalographic spectrum - an increase in the amount of energy in the low-frequency region. As the observations indicate, a relatively constant energy level is observed in the Θ - and Δ -rhythms of practically healthy persons under normal conditions. Studies in which analyses of electroencephalograms were performed during the development of acute oxygen starvation with integration of the energy of various parts of the spectrum (using integrators with V.V. Kozhevnikov's discrete system and continuous accumulation) indicated that as a rule, an energy increase in the low-frequency spectrum (2-8 cycles) by a factor larger than two coincides in time with the development of the 2nd stage of the hypoxic state, and

an increase by more than 4 times to the third stage.

Depression of the biocurrents - a sharp drop in energy - manifests, as a rule, in the 4th stage of the hypoxic state. Hence we included the two degrees of energy increase in the low-frequency spectrum and depression of the biocurrents in the diagnostic symptom complexes.

In developing the medical program for the automatic hypoxia-warning system, the logical difficulties connected with writing up the diagnostic symptom complexes are compounded by technical difficulties of no lesser import. They stem from the inadequate reliability of the performance obtained from certain biosensors (blood pressure) and the possible appearance of various artefacts, which may result in spurious triggering of the warning device.

Despite these difficulties, however, there is reason to believe that the problem of automatic diagnosis of changes in physiological state that endanger working performance and threaten life - a problem of importance for physiology and clinical medicine - will find its solution in the near future.

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