

THE RÔLE OF THE ADRENAL GLANDS IN THE PLASMA AND URINARY  
ELECTROLYTE CHANGES DURING MODERATE AND SEVERE ANOXIA

by

Raymond Franklin Kline

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## INTRODUCTION

The scientific literature of the ancient and medieval world contains almost no reference to the physiological symptoms of oxygen lack. This absence of information may be due to the fact that the degree of anoxia experienced during mountain climbing was not severe enough to cause observable effects. Mount Etna, the only high mountain ascended, has an altitude of 3,310 meters, while the passes used through other mountains ranged between 1,500 and 2,700 meters. As the symptoms of oxygen deficiency under such conditions are very mild, only a few of the travelers were affected. In such cases the symptoms may be mistaken for fatigue.

The book, "La Pression Barometrique" by Paul Bert (1), contains an extensive review of the modern growth of knowledge concerning the effect of oxygen lack. Much of the following history is based on this review and references to the cited observations may be found in its bibliography. The first chapter of this book, as translated by Hitchcock and Hitchcock (2), is titled "Mountain Journeys" and contains the description of no less than one hundred and seventy-eight such trips during the years 1519 to 1841. Due to the fact that the observations made on the physiological effects of oxygen lack were the same in many of these accounts, only those that contained some new observation have been selected for this introduction. "Principles and Practice of Aviation Medicine" by Armstrong (3) and "Physiology in Aviation" by Gemmill (4) were also used as sources of information.

It was not until the conquest of Mexico and Peru, during military expeditions across the Cordilleras, that definite discomforts

from altitude were observed. The Jesuit father Acosta, in 1590, was the first to note physiological symptoms from breathing air at high altitudes. He described a condition of vomiting, dizziness, and hemorrhage from the nose and mouth.

Robert Boyle in 1670, using a pneumatic bell, showed that young animals were able to resist anoxic conditions better than older animals of the same species. He also noted acclimatization in repeated exposures.

In 1736 three French Academicians, Bouguer, La Condamine and Godin, attempted to explain hemorrhage resulting from high altitudes on the basis of the decreased weight of the air. This was the first attempt to study and discuss symptoms of decompression scientifically. It was thought that the compression exerted by the weight of the air aided the vessels in retaining their blood. Thus the decreased pressure due to high altitudes was thought to result in distention, rupture, and the observed hemorrhage.

In 1760 Cigna experimented on sparrows with different degrees of evacuation in closed vessels and noted a sequence of respiratory movements which were at first shallow and rapid, then rapid and deep, then deep and slow, culminating in convulsions and death. D'Ulloa, in 1780, observed that the members of his party who were in the best physical condition were able to tolerate the altitudes attained with least discomfort.

The invention (1783) and use of balloons added materially to the knowledge already gained concerning the physiological effects of oxygen deficiency. This discovery enabled the scientist to study the effects of high altitudes without the complicating influence of muscular

fatigue. On ascension, the investigators noted the various symptoms that had been observed during the sojourns on the mountains. In addition they described a state of indifference, a condition which, we now know, should be viewed with alarm, for it immediately precedes the loss of consciousness. Various observers noted further that this condition was closely followed by loss of ability to read the barometer, paralysis of the arms and legs, loss of vision, and finally loss of consciousness.

In 1831 Meyers, A German traveler, noticed an increase in heart and respiratory rates at high altitudes but claimed that neither was accelerated if one kept perfectly quiet. Charles Guilbert in 1860 also described such changes in respiration and heart rates, and stressed the fact that the rates rose as the altitude was increased. He further described a process of acclimatization by which physiological symptoms such as headaches, nausea and vomiting disappeared in twelve to twenty-four hours, while some weeks were required for the restoration of respiratory and heart rates to near normal conditions.

In 1869 Lortet studied the physiological changes due to decreased barometric pressure with precision instruments which showed that in the human body there resulted serious disturbances of circulation and respiration even before any discomfort was experienced. Lortet also observed that, even while resting, the pulse remained between 90 and 108 per minute as compared to a basal rate of 64 per minute.

The first extensive scientific study of anoxia was made by Paul Bert (1). From 1869 to 1878 he attempted by experimentation to test critically all the theories and hypotheses set forth to explain physiological changes observed on exposure to anoxia. For these tests he used birds, mammals and human beings as test objects. The experi-

ments were carried out in closed vessels ranging in size from one sufficient to hold a sparrow to one which a human could enter. He noted that at pressures under one atmosphere each species had a certain level to which oxygen tension could be lowered before death resulted, and that this range was very narrow. He stressed the idea that oxygen tension was the factor concerned in anoxia or mountain sickness and that the barometric pressure had little or no effect except to decrease the tension. He found that anoxia had the same effect on respiration as he had observed in experiments on asphyxia. Bert observed that during anoxia the heart rate increased very rapidly, following the general trend of the respiration. The expansion of intestinal gases, which had been claimed by previous workers, was substantiated. Convulsions, the result of lowered barometric pressure, were believed by Bert to be a violent reaction of the spinal cord due to over stimulation by deprivation of oxygen. Slow changes in pressure did not produce this phenomenon. Sugar was found in the urine of animals kept for several hours at low barometric pressure and a rise in sugar in the blood was seen during short exposures. If, however, the exposure was prolonged for a sufficient length of time, the sugar of the blood returned to normal. A great difference in resistance to decreased pressure was noted among the different types of animals. Birds were found to be the least resistant, with cats almost as susceptible, while cold-blooded animals could stand extremely low pressures. Bert set forth the theory that the phenomenon of acclimatization was due either to a chemical modification of the hemoglobin or to an increase in the number of red cells. It was not until 1880 that Vialt made careful counts of the number of red corpuscles per unit of blood and showed that they increased at high altitudes. In

1891 Muntz observed that the percentage of iron in the blood was increased. Bert believed that in his experiments he proved that anoxia was caused by the decreased partial pressure of oxygen in the inspired air and not by the decreased barometric pressure per se.

Bert's theory that diminished partial pressure of oxygen in the lungs was the cause of mountain sickness was challenged by Mosso. In 1898 he set forth the acapnia theory (lack of carbon dioxide) as the cause of mountain sickness. Longstaff (1906) also opposed Bert, believing that the symptoms were due to a combination of physical exertion and poor diet.

In 1925 Barcroft (4) published observations which disproved the claim of Mosso and showed that Longstaff's view was a partial explanation of mountain sickness, since exertion increases the oxygen demands of the body. He found that oxygen lack alone would cause mountain sickness, thus confirming Bert's theory. He demonstrated that the oxygen passage through the lung epithelium can be explained by diffusion, and is not due to a secretory mechanism as claimed by Haldane (5). Barcroft also found that acclimatization was due to an increase in the number of red cells and in their contained hemoglobin, caused by the increased activity of the bone marrow.

Very little interest was shown in the study of anoxia after the work of Baul Bert until World War I. The increasing use of heavier-than-air craft during this conflict stimulated the study of the physiological effects of low barometric pressures. On January 19, 1918, a Medical Research Board was appointed whose first action was to establish a medical research laboratory. Its efforts were directed to the problems of oxygen want at high altitudes and other related problems. In

1920, because of lack of interest, this project was abandoned.

In May, 1919, a new section of the Air Service Medical Research Laboratory had been established. It was permanently settled in 1931 at Randolph Field in Texas. Most of our knowledge concerning the effects of altitude on the human organism has been gained from work completed at this field, such as the reaction of the cardio-vascular system under the stress and strain of oxygen deficiency.

It was not until World War II, when ever increasing heights were attained in aviation, that an extensive interest was taken in the various physiological effects of exposure to low barometric pressures. Due to the impetus of this emergency and to the Army and Navy contracts given to numerous laboratories over the country, the literature concerning anoxia has become tremendous and is beyond the scope of this paper to review. In spite of the amount of work that has been done, there remain many unsolved problems and many new ones will arise.

In reviewing the foregoing literature the writer was impressed by the dearth of material related to electrolyte concentrations in the blood under anoxic conditions. There seemed to be a complete lack of such information until the mid-thirties of the present century, at which time a few isolated values were presented. Even World War II did not produce a single comprehensive study of this aspect of the effect of oxygen lack. Therefore, in view of this deficiency, an effort will be made in this paper to correlate electrolyte changes in the blood and urine with various degrees of anoxia, and to investigate the role played by the kidney and the adrenal glands in these observed shifts.

## METHODS

In the experiments now to be described cats were used, generally without anesthesia, but in some cases lightly barbitalized, using dial with urethane solution (Giba). Each cat to be anesthetized was given an initial injection of 0.50 cc. of dial per kg. of body weight, followed by succeeding intraperitoneal injections of 0.1 cc. of the solution. An interval of 15 to 20 minutes was allowed between injections. This procedure was continued until only a slight muscular movement resulted when the animal was stimulated by cutting the abdominal wall.

The decompression or altitude chamber was a modified autoclave of 88 liters capacity. The low barometric pressures were obtained by withdrawal of air from this chamber. This withdrawal was accomplished by two Cenco Hyvac Air pumps and a converted refrigerator compressor which worked at a maximum capacity at all times. The tank was also provided with an opening through which outside air was forced into the chamber by the prevailing external barometric pressure during evacuation. It was by regulation of this "leak" that the desired simulated altitudes were obtained and maintained. The time required to reach the desired altitudes varied between 3 and 12 minutes. Figure 1 shows the relationship between the rate of flow into, and the quantity of air (measured STP) present in, the tank at all altitudes used in the following experiments. The figure also shows the time required for a quantity already present to enter the chamber at each altitude. Up to 45,000 feet this time is less than 2 minutes. The simulated altitudes quoted were obtained

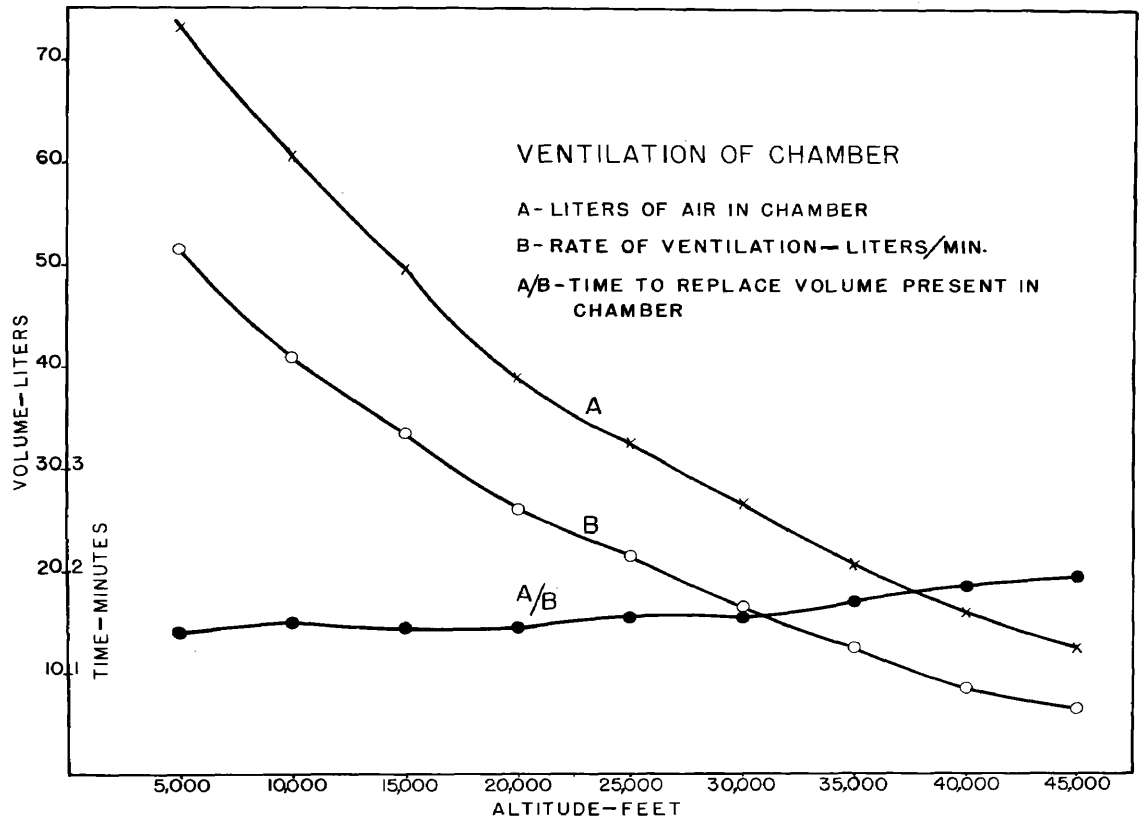


Figure 1



from the altitude-pressure table based on the United States standard atmosphere presented by Armstrong (2). In all experiments the local barometric pressures were converted to standard pressures by adjustment of the altitude scale.

The chamber temperature varied between 22.5° and 23.0° C. The value during any one experimental run did not vary more than 1.0° C. from that observed during the corresponding control run.

The respiratory rate was determined visually by means of a window in the chamber. Blood samples (4 to 5 cc.) were procured from the left heart by cardiac punctures. Urine was obtained by cannulation of the bladder and was collected under oil. The sodium and potassium values of the urine and plasma were determined by means of a Perkin-Elmer Flame Photometer. The plasma chloride values were ascertained by the method of Van Slyke and Sendroy (6).

Bilateral adrenalectomy or nephrectomy was performed in a one stage operation by the route of the midline incision. The operation involving the removal of the kidneys and the adrenal glands in the same animal was also performed in one operation by the same route. Denervation of the adrenal medulla was accomplished by the removal of the whole adrenal gland on the right side and the celiac ganglion on the left side. The operation was performed in the same manner as in the preceding operations except for the use of ether anesthesia instead of dial.

In order to evaluate comparatively the responses to anoxia resulting from exposure to 36,000 feet, 40,000 feet and altitudes above 40,000 feet, a certain criterion was adopted which was indicative of respiratory failure. This was the complete disappearance of respiration for 15 seconds. In all experiments, when this point was reached, the

animal was quickly returned to the initial barometric pressures. It was thus possible to make control and experimental runs on each cat.

## RESULTS

Control Experiments. In order to ascertain to what extent the resulting effects were due to the handling of the animal and the removal of blood for analyses, a series of unanesthetized cats was subjected to the same conditions as the experimental animals, except for exposure to lowered barometric pressure. Examination of table 1 shows that no change resulted in the plasma sodium and potassium levels and there was only a very slight fall in the hematocrit value.

Effect of 28,000 Feet (247 mm. Hg) Simulated Altitude. This condition will hereafter be referred to as "moderate anoxia." As shown in table 2, exposure to such an altitude for a 3 hour period, resulted in a marked decrease in plasma potassium from the control level of 15.9 mg.% to a level of 11.8 mg.%. In all animals the hematocrit increased. In two (#19 and #35) the increases were large, 16.1 per cent and 34.2 per cent, respectively. In the other 12 animals the increases were small, averaging 3.3 per cent only. In contrast to the prominent changes in potassium, no significant change was observed in the plasma sodium concentration. The animals were well able to withstand the moderate anoxic condition, showing no outward signs of physiological distress except for a slight initial rise in respiratory rate. They appeared perfectly normal on removal from the chamber after the exposure.

Effect of Severe Anoxia. In order to see if the physiological changes observed in the preceding exposure to anoxia could be accentuated, a series of unanesthetized animals was exposed to progressively lowered

TABLE 1

Effect of Handling and Cardiac Puncture on Hematocrit  
and Plasma Sodium and Potassium Values

Cat No.	Initial			After Manipulation		
	Hem. %	K mg%	Na mg%	Hem. %	K mg%	Na mg%
5	29.2	16.3	331	28.3	16.8	329
7	31.8	14.8	340	31.0	15.2	335
15	25.9	18.8	320	24.0	18.4	320
16	30.3	18.8	329	29.9	18.4	320
19	29.5	16.8	315	28.5	15.8	311
21	31.1	15.8	311	30.3	16.8	311
25	32.4	16.9	329	31.3	16.1	335
26	30.0	17.4	304	28.9	18.0	304
27	33.6	16.1	333	37.4	16.3	329
28	31.8	16.8	315	29.5	16.4	311
29	23.9	15.8	338	22.5	15.2	329
35	32.8	17.6	311	31.8	17.0	304
Av.	30.6	16.8	323	29.5	16.7	320

TABLE 2

Hematocrit and Plasma Sodium and Potassium Values  
Following a 3-Hour Exposure to 28,000 Feet

Cat No.	Initial			After Exposure		
	Hem. %	K mg%	Na mg%	Hem. %	K mg%	Na mg%
5	25.0	17.2	340	27.1	10.8	329
7	32.2	15.6	340	33.2	10.8	352
15	25.6	15.2	350	26.0	11.2	350
16	37.0	15.6	340	37.8	12.4	322
19	32.8	14.8	350	38.1	11.6	350
21	33.2	16.2	342	34.7	11.3	336
25	31.8	17.6	331	33.0	12.4	331
26	29.1	18.3	322	32.3	13.2	331
27	43.0	16.8	329	43.5	11.2	320
28	42.8	15.8	344	43.9	15.4	340
29	33.2	13.6	354	33.8	11.6	330
30	41.0	15.4	354	43.0	11.6	315
33	39.0	13.6	334	42.2	11.8	322
35	36.9	16.4	322	49.5	10.0	315
Av.	34.5	15.9	339	36.9	11.8	332
Percent change				+7.0	-25.8	-2.1

barometric pressures until respiratory failure resulted. This occurred at an average altitude of 42,500 feet, which was reached in from 5 to 8 minutes.

Examination of table 3 shows that instead of a further decrease in the plasma potassium level, a very significant rise was obtained from an average control value of 17.2 mg.% to an average terminal value of 25.4 mg.%, or an increase of 48 per cent. No significant changes were noted in plasma sodium or chloride concentrations.

As stated in the preceding section, the physiological effects of a simulated altitude of 28,000 feet on unanesthetized cats were mild, but as the level of 30,000 feet to 35,000 feet was reached, there developed a marked degree of restlessness and uneasiness with more rapid rate of respiration. A further decrease in barometric pressure led to extreme hyperventilation, salivation, dilated pupils, followed by convulsions, accompanied by symptoms similar to those found in cases of decerebrate rigidity. These convulsions were followed by a state of coma with deep, slow, infrequent respiration, a condition which was quickly followed by respiratory failure. These observations are in direct agreement with those reported by Oster, Toman and Smith (7). The cats were then quickly returned to normal conditions and blood samples were taken at once from the heart for analyses. The animals recovered in every case.

Effect of 36,000 Feet (170 mm. Hg). It seemed advisable to investigate the electrolyte changes at an altitude approximately midway between the barometric pressures of the moderate and of the severe exposures already described. A series of 4 unanesthetized animals was exposed to an altitude of 36,000 feet until respiratory failure resulted.

TABLE 3

## Plasma Electrolyte Changes After Exposure to Severe Anoxia

Cat No.	Initial			Altitude Attained feet	After Exposure		
	K mg%	Na mg%	Cl mg%		K mg%	Na mg%	Cl mg%
5	14.4	354	432	38,000	20.0	354	436
7	17.2	359	449	43,000	28.8	359	457
15	16.8	363	439	45,000	26.0	354	444
16	18.2	373	447	44,000	29.4	354	447
19	15.6	380	437	43,000	22.8	373	442
21	16.4	373	443	43,000	23.2	354	445
25	18.0	373	446	44,000	26.6	373	447
26	17.2	363	442	41,000	23.4	354	445
27	18.4	377	461	39,000	26.6	373	464
28	17.4	363	444	43,000	24.8	363	444
29	17.4	377	452	44,000	25.2	368	459
35	19.4	373	452	42,000	28.0	354	458
Av.	17.2	369	445	42,416	25.4	361	449
Percent change					+47.7	-2.2	+0.9

In 3 other animals, cessation of respiration did not result after an exposure to the same altitude for 30 minutes. The altitude was therefore increased to 40,000 feet (141 mm. Hg), and the animals were maintained at that level until respiratory failure. This occurred within 5 minutes, on average.

The electrolyte changes due to these exposures are tabulated in tables 4 and 5. The average increase in plasma potassium in tables 4 and 5 combined was 34 per cent as compared to the increase of 48 per cent (table 3) in the case of the severe exposure (Av. 42,500 feet). On closer analysis of the tabulated results, it is evident that in the case of the 3 cats which were exposed to the simulated altitude of 40,000 feet the average percentage increase in plasma potassium was 49 per cent, which is comparable to that obtained at 42,500 feet (table 3). The remaining 4 animals, while exhibiting the same physiological symptoms of respiratory failure, had an increase of only 20 per cent in plasma potassium. Thus it seems that, so far as plasma potassium changes are concerned, the severity of the oxygen deprivation is more important than the length of the exposure. The data also show that respiratory failure is not closely related to the terminal potassium ion concentration. As in all the preceding experiments, no significant changes were noted in the plasma sodium and chloride levels.

Effect of 28,000 Feet (247 mm. Hg) Followed by Altitudes Above 40,000 Feet. To determine if the potassium changes exerted by exposure to 28,000 feet were transient in character and if the potassium level could be influenced readily in either direction, a group of cats was subjected to a simulated altitude of 28,000 feet for 3 hours. The potassium

TABLE 4

## Plasma Electrolyte Changes after Exposure to 36,000 Feet

Cat No.	Initial			Exposure Duration min.	After Exposure		
	K mg%	Na mg%	Cl mg%		K mg%	Na mg%	Cl mg%
15	17.0	320	445	30.0	18.8	321	441
28	18.8	321	440	21.7	22.4	321	435
39	15.2	331	446	27.0	19.7	349	433
40	17.6	317	447	9.5	21.6	331	440
Av.	17.2	322	445	22.1	20.6	331	437
Percent change					+19.6	+2.8	-1.8

TABLE 5

## Plasma Electrolyte Changes after Exposure to 36,000 Feet, and then to 40,000 Feet

Cat No.	Initial			Altitude Attained feet	Exposure Duration min.	After Exposure		
	K mg%	Na mg%	Cl mg%			K mg%	Na mg%	Cl mg%
16	16.6	342	437	36,000	30.0	24.0	342	433
				40,000	4.5			
19	17.0	331	441	36,000	30.0	23.4	334	435
				40,000	5.0			
35	16.4	321	457	36,000	30.0	27.4	329	449
				40,000	6.0			
Av.	16.7	331	445			24.9	335	439
Percent change						+49.0	+1.2	-1.3

levels at the end of the first 90 minutes were determined by taking a blood sample after quick return to atmospheric pressure. Exposure to 28,000 feet immediately followed and this altitude was maintained for the rest of the 3 hour period. A second return to atmospheric pressure permitted another blood sampling, after which the chamber was evacuated for the third time, to cause severe anoxia at altitudes above 40,000 feet. A terminal blood sample was thus obtained. The average plasma potassium values were 17.5 per cent less than the controls after 90 minutes at 28,000 feet (table 7), 25 per cent less after 180 minutes at the same altitude, and 58 per cent greater after exposure to severe anoxia (table 6).

The Effect of Exposure to 28,000 Feet for 6 Hours on the Plasma Potassium. Four animals were exposed to 28,000 feet for 6 hours. The terminal potassium values were 21 per cent less than the controls (table 8). The value does not differ significantly from that observed at the end of 3 hours exposure.

The Effect of Cortico-Adrenal Extract on the Plasma Potassium Following Exposure to Moderate and Severe Anoxia. The effects of priming the animals with the hormone of the adrenal cortex before exposure to anoxic conditions were then investigated. 2.5 cc. of aqueous cortico-adrenal extract (cortin) were injected into the hearts of 4 normal animals, and at the end of 30 minutes they were exposed to 28,000 feet for 90 minutes. Blood samples were taken at the end of the exposures. The cats were immediately returned to the chamber and elevated to an altitude which resulted in respiratory failure. The results, as tabulated in table 9, show a decrease in plasma potassium of 25 per cent as compared



TABLE 6

Plasma Electrolyte Changes after 180 Minute Exposure to 28,000 Feet,  
and then to Severe Anoxia

Cat No.	Initial		After Exposure to 28,000 feet		Altitude attained feet	After Exposure to severe anoxia	
	K	Na	K	Na		K	Na
	mg%	mg%	mg%	mg%		mg%	mg%
15	19.2	315	10.4	373	48,000	22.4	334
16	12.4	363	10.6	363	53,000	18.0	322
42	14.8	312	10.6	334	53,000	26.6	315
43	12.4	361	9.6	361	54,000	20.0	322
44	11.8	340	10.0	331	50,000	19.6	320
45	12.8	361	10.2	342	49,000	20.4	328
46	11.2	340	10.2	340	54,000	27.4	315
47	14.8	341	10.4	347	53,000	18.4	331
Av.	13.7	340	10.3	349	51,750	21.6	323
Percent change			-25.0	+2.9		+58.0	-5.0

TABLE 7

Plasma Electrolyte Changes after 90 Minute Exposure  
to 28,000 Feet

Cat No.	Initial		After Exposure	
	K mg%	Na mg%	K mg%	Na mg%
15	19.2	315	17.8	373
16	12.4	363	10.8	370
42	14.8	312	10.4	334
43	12.4	361	9.6	361
44	11.8	340	10.4	361
45	12.8	361	10.4	361
46	11.2	340	10.6	340
47	14.8	341	10.4	340
Av.	13.7	340	11.3	353
Percent change			-18.0	+3.8

TABLE 8

Hematocrit and Plasma Potassium Changes  
after 6 Hour Exposure to 28,000 Feet

Cat No.	Initial		After Exposure	
	K mg%	Hem. %	K mg%	Hem. %
100	17.3	44	14.0	50
101	16.4	36	14.0	40
102	15.7	37	12.1	43
103	16.3	37	13.2	40
Av.	16.4	39	13.3	43
Percent change			-21.3	+10.3

TABLE 9

Effect of Cortin on the Plasma Potassium Values after  
90 Minute Exposure to 28,000 Feet, and then to Severe Anoxia

Cat No.	Initial	After Exposure	After Exposure to	
	K	to 28,000 feet	severe anoxia	
	K	K	Altitude	K
	mg%	mg%	attained	mg%
			feet	
105	17.2	12.3	51,000	21.9
106	16.2	12.6	52,000	23.3
107	16.6	12.4	49,000	23.6
108	15.4	11.8	54,500	25.2
Av.	16.4	12.3	51,625	23.5
Percent change		-25.0		+43.3

to an 18 per cent decrease observed in table 7.

Electrolyte Changes in the Urine on Exposure to 28,000 Feet.

It seemed pertinent at this point to investigate the possibility that the loss of potassium from the blood was due to increased elimination of this ion by the kidneys. With this in mind, a group of barbitalized cats were subjected first to a control period of 3 hours at existing barometric pressures. The urine was collected continuously by cannulation of the bladder. Blood samples were taken by cardiac puncture at the end of the period. Immediately following this control period the animals were exposed to a lowered barometric pressure equivalent to an altitude of 28,000 feet and maintained at this level for 3 hours. Urine was collected continuously and blood samples were acquired in the same manner as during the control period. The period of exposure was divided into two equal parts, so that at the end of each 90 minute period the animals were quickly returned to atmospheric pressure, blood samples were taken and the urine was removed for measurement and analysis. The results obtained were <sup>seen</sup> to be highly significant, as shown in table 10. Polyuria was definitely present, as shown by the 93 per cent increase in urine flow during the first exposure period as well as the 46 per cent increase during the second exposure. Equally striking was the increase in total potassium and sodium of the urine (60 per cent and 100 per cent, respectively) as a result of the first exposure. The total potassium excreted during the second period was, however, the same as had been observed in the control period, while the total sodium excreted, although lower than during the first 90 minute period, still was 69 per cent above the normal.

TABLE 10

Urine Electrolyte and Volume Changes After Exposure to 23,000 Feet

Cat No.	Initial			After 90 Minute Exposure			After 180 Minute Exposure		
	Total K mg/hr	Total Na mg/hr	Volume cc/hr	Total K mg/hr	Total Na mg/hr	Volume cc/hr	Total K mg/hr	Total Na mg/hr	Volume cc/hr
15	6.9	16.7	1.7	21.1	24.5	5.1	7.2	11.1	1.7
16	19.1	7.2	4.3	12.3	47.2	7.7	7.7	32.4	4.0
42	16.6	3.4	2.5	46.2	25.9	5.2	24.3	31.8	6.1
43	20.7	14.3	2.9	27.1	29.8	4.5	19.7	10.8	2.6
44	8.6	4.4	2.1	14.8	17.6	4.9	22.3	22.3	6.7
45	9.2	38.1	5.0	17.1	33.4	7.1	11.4	45.9	6.0
46	11.9	3.3	1.2	14.4	7.7	3.3	10.7	6.8	3.2
47	20.7	13.9	3.0	29.9	17.6	5.4	20.4	9.8	2.8
Av.	14.3	12.7	2.8	22.9	25.4	5.4	15.5	21.4	4.1
Percent change				+60.1	+100	+92.9	+8.4	+68.5	+46.4

### Effect of Moderate and Severe Anoxia on Blood Electrolytes

Following Nephrectomy. In order further to study the rôle of the kidney in the electrolyte changes observed in the blood, a series of cats was nephrectomized under dial. They were exposed to a simulated altitude of 28,000 feet for 90 minutes, followed by exposure to severe anoxia (Av. 48,167 feet). Blood samples were taken at the end of each exposure. Table 11 shows that at the altitude of 28,000 feet there was a decrease of 19 per cent in plasma potassium, approximately the same as in the normal animals of table 7, and no significant change in sodium levels. However, the potassium value after exposure to higher altitudes, resulting in respiratory failure, increased 80 per cent, an increase well above any increase procured in preceding experiments of this type. No significant change was noted in the sodium level. Both the plasma sodium and potassium values returned to normal at the end of one hour at normal barometric pressure.

Effect of Exposure to 28,000 Feet on the Potassium Content of the Erythrocyte. The loss of potassium from the plasma on exposure to 28,000 feet was thought to be due to increased excretion by the kidney until the same decrease in plasma potassium was noted after nephrectomy. As the concentration of potassium in the erythrocyte of the cat is only 6 m.eq./l., and since the red cell is somewhat permeable to potassium ions, it was believed pertinent to explore the possibility that this was the storage place of the potassium lost from the plasma. Therefore, a small series of cats was subjected to 28,000 feet for 90 minutes, and blood samples were taken from the heart before and immediately after the exposures. The red cells of the heparinized blood were separated as

TABLE 11

Effect of Nephrectomy on Plasma Electrolytes after 90 Minute Exposure to 28,000 Feet, and then to Severe Anoxia

Cat No.	Initial		After Exposure to 28,000 feet		After Exposure to severe anoxia		
	K	Na	K	Na	Altitude attained feet	K	Na
	mg%	mg%	mg%	mg%		mg%	mg%
48	16.4	350	10.4	341	52,000	32.4	322
49	16.4	358	12.0	358	52,000	30.4	348
51	14.0	368	12.4	361	45,000	29.2	352
52	15.6	382	12.4	382	50,000	20.0	368
54	12.4	409	11.8	409	45,000	18.8	393
56	12.8	340	12.0	347	45,000	27.2	340
Av.	14.6	368	11.9	366	48,167	26.3	354
Percent change			-18.5	-0.5		+80.1	-3.8

quickly as possible from the plasma by centrifugation and placed in distilled water, in the proportion of one part of cells to four parts of distilled water. After hemolysis, the resulting ghosts were separated by centrifugation and the solution was analyzed for potassium. The results are set forth in table 12, which shows, as has been observed in preceding experiments, a decrease in plasma potassium of 26 per cent, but no significant change in the intracellular potassium.

Effect of Adrenalectomy on Electrolyte Balance during Anoxia.

The influence of the adrenal cortex on the electrolyte levels in the normal body has been well established. It seemed logical at this point to see to what extent the adrenal gland is involved in the observed electrolyte changes under the stress of low barometric pressures. An attempt was made in the beginning to remove the adrenals the day before the experiment, but it was found that the animals so treated were only able to tolerate a simulated altitude of 28,000 feet for a short time. The average survival time for the 3 animals was only 14 minutes, but, as shown in table 13, the potassium level in the plasma was increased on the average by 78 per cent while that of the sodium was increased by only 5.2 per cent. It also may be noted that the rate of urine flow during the whole experiment was very low, being on the average only 0.28 cc. during one hour at normal barometric pressures, and that a condition of extreme oliguria resulted upon exposure to 28,000 feet, with no measurable flow.

As a result of this experience, a series of barbitalized cats was adrenalectomized and the bladders were cannulated in one operation, on the morning of the experiment. These animals were well able to

TABLE 12

Effect of 90 Minute Exposure to 28,000 Feet  
on the Potassium Content of the Erythrocyte

Cat No.	Initial		After Exposure to 28,000 feet	
	Plasma	Cell	Plasma	Cell
	K mg%	K mg%	K mg%	K mg%
61	13.6	23.6	12.0	24.0
62	14.8	16.4	10.2	16.4
63	14.4	14.8	9.2	13.6
Av.	14.3	18.3	10.5	18.0
Percent change			-26.6	-1.6

TABLE 13

Effect of Adrenalectomy on Plasma Electrolytes and  
Urine Volume After Exposure to 28,000 Feet,  
24 Hours After Operation

Cat No.	Initial			Exposure duration min.	After Exposure to 28,000 feet		
	Serum		Urine vol. cc/hr		Serum		Urine vol. cc/hr
	K mg%	Na mg%			K mg%	Na mg%	
7	14.0	340	0.33	14	29.6	350	0
15	15.2	353	0.33	18	24.6	370	0
21	14.4	398	0.17	11	23.2	428	0
Av.	14.5	364	0.28	14	25.8	383	0
Percent change					+78.0	+5.2	-100



tolerate exposures to 28,000 feet for 90 minutes and their degree of tolerance to very high altitudes was approximately the same as had been observed in unoperated animals. The potassium values of the plasma, as shown in table 14, decreased only 3 per cent during the exposure to 28,000 feet. They rose by only 13 per cent upon exposure to very severe anoxia (Av. 45,400 feet). The sodium level remained practically unchanged during the moderate anoxia, but decreased at the high altitudes by 4 per cent.

The significant changes in urine volume and electrolytes may be found in table 15. The control values compare favorably with those of normal cats (table 10), but after exposure the urine volume decreased by 49 per cent, while total sodium and potassium values fell by 67 per cent and 39 per cent, respectively. Such changes diverge widely from results obtained in unoperated animals exposed to 28,000 feet for similar periods of time.

Effect of Exposure to 28,000 Feet and High Altitudes on Plasma Electrolytes after Adrenalectomy-Nephrectomy. It seemed advisable to investigate the electrolyte changes which would result from exposing a series of adrenalectomized-nephrectomized animals to elevations of 28,000 feet and altitudes of such height that respiratory failure resulted. The belief that such a study would help to clarify the relation of the adrenal glands to the potassium changes observed was justified, as is illustrated by table 16. On exposure to 28,000 feet for 90 minutes, there resulted no significant change in plasma potassium, a result similar to that observed following adrenalectomy alone. On exposure to severe anoxia, however, an elevation of 33 per cent in potassium concentration resulted,

TABLE 14

Effect of Adrenalectomy on Plasma Electrolytes After 90 Minute Exposure to 28,000 Feet and then to Severe Anoxia, 2 Hours After Operation

Cat No.	Initial		After Exposure to 28,000 feet		Altitude attained feet	After Exposure to severe anoxia	
	K	Na	K	Na		K	Na
	mg%	mg%	mg%	mg%		mg%	mg%
50	16.0	358	17.6	358	49,000	16.0	358
53	14.0	361	12.4	361	45,000	16.4	361
55	10.8	361	10.2	361	43,000	14.8	361
57	11.8	382	11.6	361	44,000	14.0	361
58	14.4	352	13.2	340	49,000	19.4	322
59	13.2	361	12.6	361	43,000	14.8	340
60	12.6	361	12.4	352	45,000	14.4	322
Av.	13.3	362	12.9	356	45,429	15.7	346
Percent change			-3.0	-1.7		+18.0	-4.4

TABLE 15

Effect of Adrenalectomy on the Urine Electrolytes and Volume After 90 Minute Exposure to 28,000 Feet, 2 Hours After Operation

Cat No.	Initial			After Exposure		
	Total K	Total Na	Volume	Total K	Total Na	Volume
	mg/hr	mg/hr	cc/hr	mg/hr	mg/hr	cc/hr
50	11.7	2.8	1.2	11.8	1.1	0.9
53	15.7	34.8	7.0	8.4	8.3	2.7
55	20.4	31.4	4.9	9.6	9.6	2.6
57	17.5	7.2	2.7	13.4	5.2	2.8
58	13.0	9.1	4.0	8.3	6.1	2.1
59	15.8	2.2	2.0	7.3	1.0	0.8
60	12.0	18.2	4.1	5.2	3.9	1.4
Av.	15.1	15.1	3.7	9.1	5.0	1.9
Percent change				-39.7	-67.0	-48.6

TABLE 16

Effect of Adrenalectomy-Nephrectomy on Plasma Electrolytes  
after 90 Minute Exposure to 28,000 Feet, and then to Severe Anoxia

Cat No.	Initial		After Exposure to 28,000 feet		After Exposure to severe anoxia		
	K	Na	K	Na	Altitude attained	K	Na
	mg%	mg%	mg%	mg%	feet	mg%	mg%
70	14.8	405	18.8	361	42,000	14.8	405
71	17.6	352	16.4	352	47,000	21.0	340
73	12.4	417	12.0	391	44,000	17.6	370
74	12.0	428	12.4	391	47,000	22.2	405
75	13.0	428	12.6	405	45,000	17.2	370
Av.	14.0	406	14.4	380	45,000	18.6	378
Percent change			+2.8	-6.4		+32.9	-6.9

which was greater than that observed after adrenalectomy alone. This increase was not as great as that following nephrectomy alone and again suggests adrenal participation in the shifts. A decrease in plasma sodium was observed on exposure, both to 28,000 feet (6 per cent) and to high altitudes (7 per cent). The transient nature of the shifts in potassium was also noted, for at the end of one hour at control conditions the concentration of the cation had returned almost to the initial value.

Effect of Moderate and Severe Anoxia on Blood Electrolytes Following Splanchnicectomy. The effects of adrenalectomy on the potassium levels under anoxic conditions, as shown in the preceding section, necessitated the separation of the rôles played by the two component parts of the adrenal gland. The secretion of adrenalin was, therefore, eliminated in 4 cats by denervation of the adrenal medulla under ether anesthesia. The animals, 11 to 14 days later, were exposed to simulated altitudes of 28,000 feet for 90 minutes. They were then returned to normal conditions and blood samples were quickly taken. The animals were immediately replaced in the decompression chamber and subjected to severe anoxia at high altitudes. They were then again returned to initial barometric pressure and blood samples were taken. As a result of the exposure to 28,000 feet, the potassium content of the plasma decreased 14 per cent, which is nearly the same as the change noted in normal animals after 90 minutes at this altitude (table 7). The exposure to very high levels, however, resulted in an increase of only 11 per cent. There was no change in the hematocrit values as a result of either exposure. These results are tabulated in table 17.

Effect of Adrenalin Injections in Splanchnicectomized Animals on Blood Electrolytes Combined with Exposure to Severe Anoxia. The

TABLE 17

Effect of Splanchnicectomy on Plasma Potassium and Hematocrit Values after 90 Minute Exposure to 28,000 Feet, and then to Severe Anoxia

Cat No.	Initial		After Exposure to 28,000 feet		After Exposure to severe anoxia		
	K mg%	Hem. %	K mg%	Hem. %	Altitude attained feet	K mg%	Hem. %
S1	17.6	33	15.2	34	46,000	18.4	34
S2	15.2	34	12.8	36	47,000	18.8	36
S3	16.8	37	15.0	36	45,000	17.2	36
S4	15.6	40	13.4	38	48,000	18.0	37
Av.	16.3	36	14.1	36	46,500	18.1	36
Percent change			-13.5			+11.0	

splanchnicectomized animals, after 5 days of rest, were injected with 0.4 cc of 1:1,000 adrenalin, directly into the heart, and 5 minutes later were subjected to severe anoxia. Examination of table 13 will show an increase in hematocrit and plasma potassium of 11 per cent and 45 per cent, respectively. These <sup>potassium</sup> values vary little from those of normal animals exposed to like conditions, as shown in table 3.

Effect of Adrenalin on Plasma Potassium in Normal Animals. It seemed pertinent at this time to determine if it was possible to duplicate, by injections of adrenalin in normal animals, the plasma potassium increases observed in cats following exposure to severe anoxia. Three normal cats were injected with 0.4 cc. of 1:1,000 adrenalin and blood samples were taken at the end of 5 minutes. An increase of 67 per cent (table 19) is somewhat greater than the changes observed in the normal animal when subjected to severe anoxic conditions (table 3). Plasma potassium quickly falls, so that at the end of 10 minutes the value was only 29 per cent above the control level.

#### DISCUSSION

The literature contains relatively few references to electrolyte changes in the blood on exposure to anoxia. Such comments as exist refer to the blood changes as a side observation. There is no systematic study made at various altitudes. In the few papers available conflicting values are given for potassium levels in the blood. A decrease in the plasma potassium levels in dogs was reported by Ziegler (8) and McQuarrie, Ziegler and Hay (9), and in rats by Hoagland (10). In contrast, an increase in plasma potassium in rats was described by Darrow and Sarason (11) and a slight rise in rabbits by Thorn and his coworkers (12).

TABLE 18

Effect of Adrenalin (0.4 cc. 1:1000), Combined with Exposure to Severe Anoxia 5 Minutes Later, on Hematocrit and Plasma Potassium after Splanchnicectomy

Cat No.	Initial		Altitude attained feet	After Exposure to severe anoxia	
	K mg%	Hem. %		K mg%	Hem. %
S1	16.7	36	47,000	25.3	40
S2	14.9	36	46,000	21.3	41
S3	15.4	33	46,000	21.2	36
S4	16.3	35	47,000	23.6	39
Av.	15.8	35	46,500	22.9	39
Percent change				+45.0	+11.4

TABLE 19

Effect of Adrenalin (0.4 cc. 1:1000) on Plasma Potassium in Normal Animals

Cat No.	Initial K mg%	Time of injection	First Sample		Second Sample	
			Time	K mg%	Time	K mg%
1	17.2	9:12	9:17	28.8	9:22	26.6
2	15.6	9:16	9:21	26.6	9:26	19.0
3	16.7	7:30	7:35	27.1	7:40	18.2
Av.	16.5			27.5		21.3
Percent change				+67		+29

Lewis (13), using dogs and rats, found no significant change in plasma potassium levels. These differences may be based on two facts which are evident in table 20, a summary of the above references. First, there were variations in the degrees of oxygen lack and length of exposure used by these authors. Secondly, it has been known since the time of Paul Bert that there is a species difference in resistance to anoxia.

In the present work an effort was made to study the effects on the blood electrolytes of exposure to various degrees of low barometric pressure in one species, namely the cat, and to determine to what extent the hormones of the adrenal gland are concerned in the observed changes. The results obtained from exposures to 28,000 feet, 36,000 feet, 40,000 feet, and altitudes above 40,000 feet are set forth in tables 2, 4, 5 and 6. From these data one can readily see that the variations in the literature values for the blood potassium are probably in part due to differences in degree of oxygen lack. When cats were exposed to a simulated altitude of 28,000 feet for 3 hours, there resulted a decrease in plasma potassium of 26 per cent (table 2). When, however, the oxygen tension was reduced to a level simulating the altitude of 36,000 feet (average exposure time = 22 minutes), there was an increase of 20 per cent over the control values. At 40,000 feet, after a previous period of 30 minutes at 36,000 feet, there was an increase of 49 per cent. At altitudes above 40,000 feet, the increase was 48 per cent if reached quickly (table 3), whereas an increase of 58 per cent was observed if the cats were taken to higher altitudes after 3 hours at 28,000 feet (table 6).

Variations in plasma potassium concentrations were observed



TABLE 20

Summary of References Dealing with the Effect of Anoxia  
upon Plasma Potassium

Reference Number	Species	Altitude attained feet	Length of Exposure	Effect on plasma potassium
8	Dog	33,000	150 minutes	Decrease
9	Dog	33,000	150 minutes	Decrease
10	Rat	12,500	180 minutes	Decrease
11	Rat	20,000	1, 2 and 7 days	Increase
	Rat	25,000	1, 2 and 7 days	Increase
12	Rabbit	25,000	4 hours daily for 7 weeks	Increase
13	Dog	18,000	24 hours	No change
	Rat	18,000	24 hours	No change

when the time of exposure to 28,000 feet was increased. There resulted a 25 per cent decrease when the animals were exposed to this altitude for 180 minutes, as compared to an 18 per cent decrease when the time was reduced to 90 minutes. The failure to obtain an even greater decrease in potassium concentration when the time of exposure was increased to 360 minutes (table 8) may be due to the prolonged stimulation of the adrenal cortex, which may result in fatigue of this gland.

A summary of the plasma potassium changes observed in each animal at the various altitudes studied, as well as results obtained at various time intervals at 28,000 feet, is set forth in figure 2. This graphical representation enables the reader to discern visually how the potassium changes are related to varying degrees of oxygen lack.

A condition of polyuria resulted on exposure to 28,000 feet and there was an increase of 60 per cent in potassium excretion, as shown in table 10. The occurrence of polyuria during anoxia has been found by numerous investigators (13, 14, 15, 16, 17, 18), while other workers claim a condition of oliguria exists (19, 20, 21, 22, 23, 24, 25). Some of the latter group found a condition of polyuria in unanesthetized animals (21, 22, 23, 24), which may indicate that narcosis was deep in those animals where the condition of oliguria was noted. The animals used in the present study, when anesthetized, received only minimal quantities of dial.

In the present study, no significant changes were noted in the plasma sodium and chloride levels, an observation previously made by Lewis and his coworkers (13), Marshall, Thorn and Davenport (26), and Ziegler (8). Only at levels above 40,000 feet did plasma sodium decrease

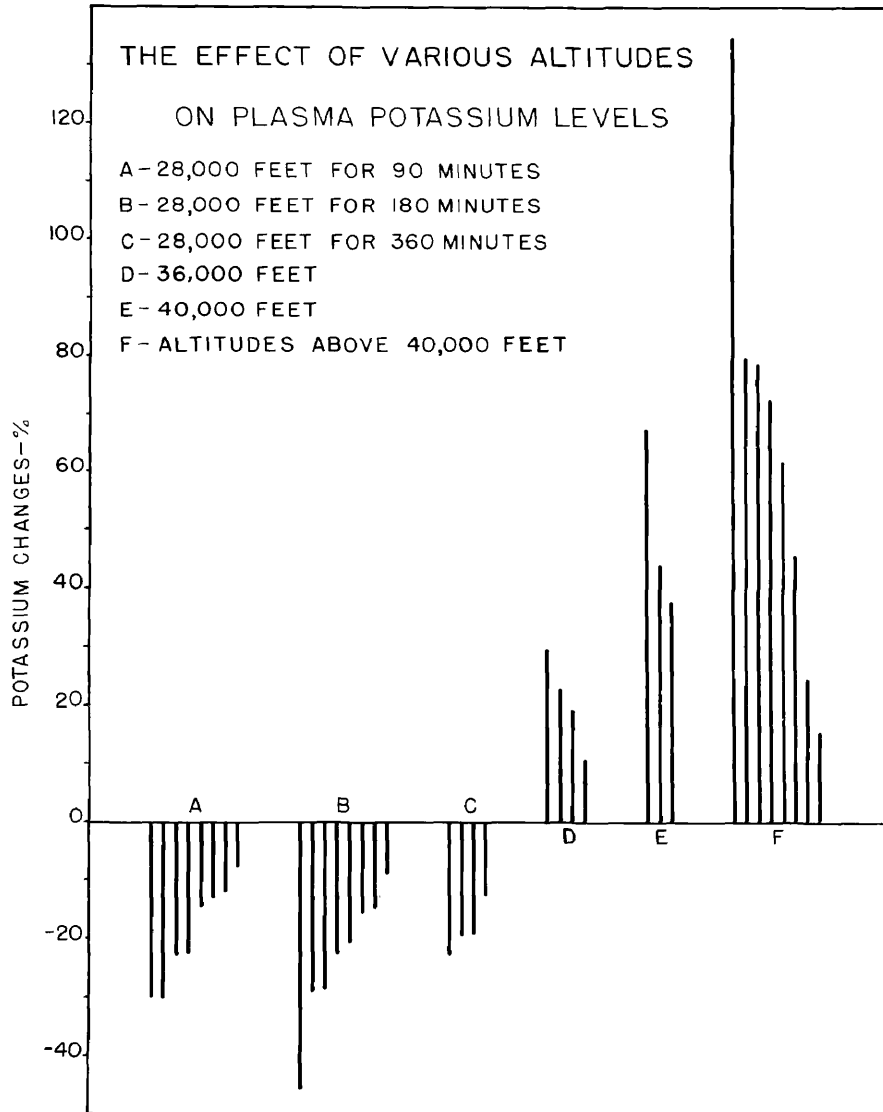


Figure 2

(5 per cent). This loss had been noted previously by Thorn and his co-workers (12).

The decrease in plasma potassium concomitant with the increase in potassium excretion on exposure to 23,000 feet suggested that the kidney is the avenue of escape for the potassium from the blood. When nephrectomized animals, however, were exposed to like conditions, and a comparable decrease in plasma potassium occurred, such a supposition was discarded.

The determination of the site of storage of the potassium that is lost from the plasma is beyond the scope of this paper, although one exploratory attempt was made. The concentration of potassium is low in the cat erythrocyte. According to Ponder (27, 28), potassium shifts are possible between the extracellular and the intracellular fluids. It therefore seemed possible that the erythrocyte might be a site of storage. It was found, however, that no significant change in the intracellular potassium of the erythrocyte resulted after exposure to 23,000 feet (table 12).

Evidence in the literature seems to point to the liver as a receiving depot for the potassium which disappears from the plasma under conditions of moderate oxygen lack. Evans (29), Langley and Clarke (30), and Lewis and his coworkers (13) have shown that there is a rise in liver glycogen following a short period of anoxia. In addition, Fenn (31) pointed out that the formation of glycogen in the liver must be accompanied by the deposition of potassium and water. Thus it may be that, during the 90, 180 and 360 minute exposures to 23,000 feet, the glycogen deposited is sufficient to account for the potassium loss from the plasma.

Numerous investigators have shown experimentally the importance of the adrenal cortex in regulating the potassium levels of the blood. The adrenal gland, therefore, may be instrumental in the potassium changes described in this paper. Many workers in the field of anoxia have shown that the adrenal cortex is activated by the stress of oxygen deficiency. Langley and Clarke (30), as well as Giragossintz and Sundstroem (32), showed that adrenalectomized animals require larger injections of cortico-adrenal extract for survival under anoxic conditions than at sea level. An increase in tolerance to lowered barometric pressure has been shown after injections of cortin by Britton and Kline (33), Li and Herring (34), Thorn and his coworkers (35), and an increase in size of the adrenal after repeated exposures was found by the last named workers, as well as by Armstrong and Heim and Silvette (36) (37). Darrow and Sarason (11) produced histological evidence of depletion of the adrenal cortex lipid as a result of anoxic anoxia. The present study further supports the view that the adrenals are activated by the stress of oxygen lack. The decrease in plasma potassium and the increase in total urine potassium (60 per cent) and volume (88 per cent) on exposure to 28,000 feet is a true picture of the action of cortin, as may be seen in the following references.

Various workers (38, 39, 40), basing their conclusions on the results obtained from the injection of cortin into normal animals, postulate that this hormone lowers the serum potassium by increasing the rate of excretion by the kidneys. Ingle and his coworkers (41) showed, however, that even after removal of the kidneys the administration of cortin caused the usual fall in serum potassium. Comparable results were ob-

tained in the present study by exposing nephrectomized cats to 28,000 feet for 90 minutes. A decrease in plasma potassium resulted which was of the same magnitude as that obtained in normal animals.

Further evidence was found for adrenal participation in plasma potassium regulation. When cats that had been adrenalectomized 2 hours previously were exposed to 28,000 feet for 90 minutes, there resulted an insignificant decrease of 3 per cent <sup>in</sup> plasma potassium, as well as a decrease in urine volume and total urinary potassium of 49 per cent and 39 per cent, respectively. Comparable results in plasma potassium changes were also observed in cats, following an operation involving both adrenalectomy and nephrectomy in the same animal.

In order to evaluate visually the role of the adrenal cortex in the plasma potassium changes observed on exposure to 28,000 feet for 90 minutes, such changes are presented graphically in figure 3. This graph clearly shows the importance of the adrenal cortex in the decrease in plasma potassium noted under such conditions.

When normal and nephrectomized animals, previously held at 28,000 feet, were exposed to altitudes above 40,000 feet, there resulted increases in plasma potassium of 58 per cent and 80 per cent, respectively. When adrenalectomized animals were similarly exposed, there was an increase of only 18 per cent in plasma potassium. Such observations suggest that the adrenal gland plays a dual rôle in plasma potassium regulation. The cortex may act to reduce potassium values during stress, whereas the medulla operates to increase them. The actual blood levels at any altitude may be the result of the interplay of these two factors.

A considerable literature supports this conception. The large

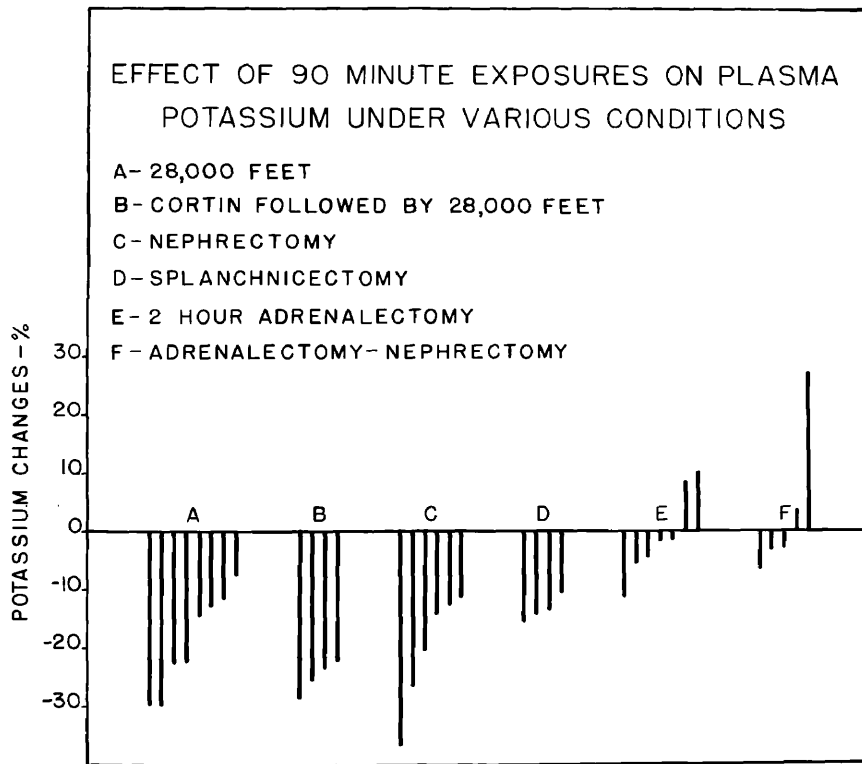


Figure 3

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changes observed in the potassium levels following exposure to severe anoxia are similar to the increases observed from stimulation of the adrenal medulla or injections of adrenalin. Brewer, Larson and Schroeder (42) and D'Silva (43, 44, 45) postulated from experimental data that the injection of adrenalin, by its effect on the liver, liberates potassium into the blood. Houssay and his coworkers (46) showed that in asphyxia the rise in potassium is dependent upon the presence of the liver and presumably, therefore, <sup>the</sup> adrenal participates in this reaction. The rôle of the adrenal medulla is clearly demonstrated by the present anoxic studies on animals, in which the medullary part of the adrenal gland had been denervated. The plasma potassium of such animals increased only 11 per cent on exposure to very severe anoxic conditions, a value far below any that had been obtained from the exposure of normal animals to like conditions. These same animals, however, when injected with adrenalin and exposed to comparable altitudes, showed increased plasma potassium values of the same magnitude as had been observed in normal cats. Furthermore, the injection of adrenalin into normal animals, not exposed to lowered barometric pressures, resulted in increases in plasma potassium as great as any that had been obtained under the stress of low barometric pressure. Thus it seems that the adrenal medulla liberates adrenalin in sufficient quantities to affect the electrolytes of the blood only under conditions which call for unusual effort on the part of the body to combat stress, such as severe anoxia.

Figure 4 is a graphical summary of plasma potassium changes obtained on exposure to severe anoxia under various experimental conditions. This graph plainly shows the rôle of the adrenal medulla in the



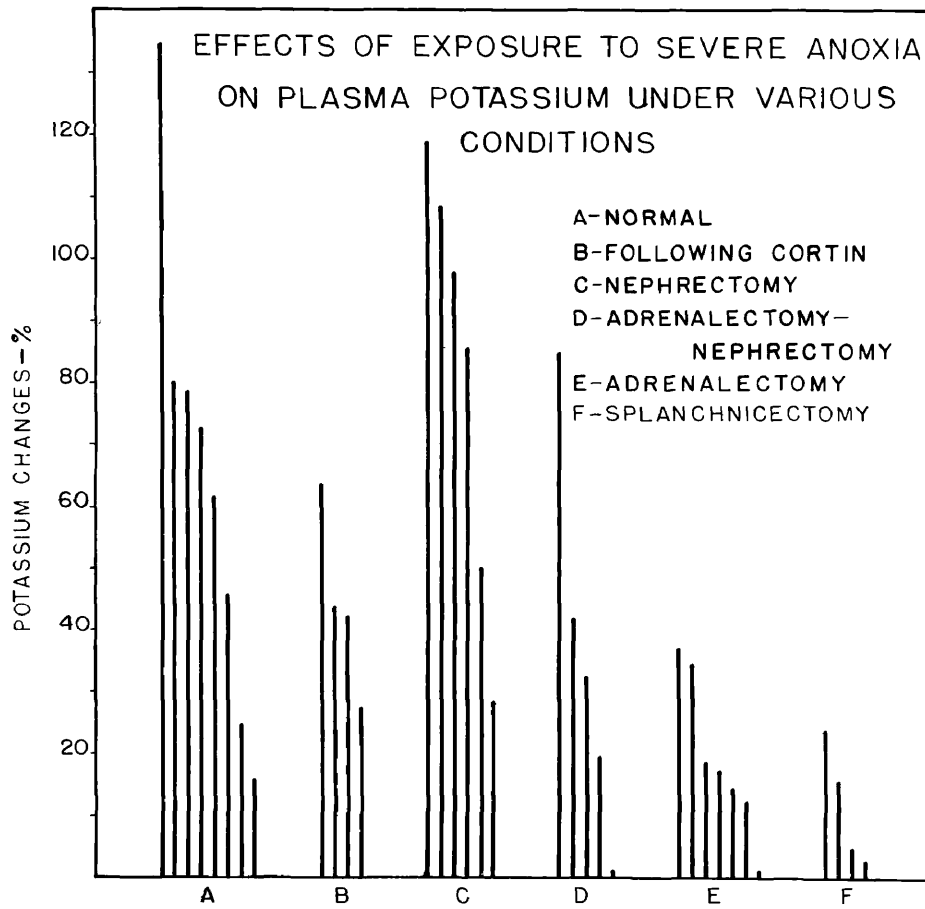


Figure 4

increases noted on exposure to altitudes above 40,000 feet.

It would appear, therefore, that at some altitude between 28,000 feet and 36,000 feet such a stress condition develops in the cat. Furthermore, it seems that at the lower altitudes, that is 28,000 feet or less, the adrenal cortex is dominant while at higher altitudes, above 28,000 feet, the adrenal medulla is activated and assumes control. Such a conception explains the further increases in the plasma potassium values as due to greater liberation of adrenalin under conditions of increased stress, as the altitude is raised to 40,000 feet or to higher levels. It is not possible to determine from the results of this study whether adrenalin is liberated at the altitudes of 28,000 feet. It may be postulated, however, that, if adrenalin is secreted at such an altitude, it is in such minute quantities that its effects are overshadowed by those of the cortico-adrenal extract. The results obtained from the exposure of splanchnicectomized animals to 28,000 feet for 90 minutes, where an average decrease of 14 per cent in plasma potassium was obtained, seemed to indicate that adrenalin is not liberated in significant amounts at such an altitude (table 17). If the adrenal medulla were activated at 28,000 feet, its removal from the system should result in a decrease in potassium greater than that observed in normal animals. No such decrease was observed and the postulation of little or no secretion of adrenalin is supported.

The celerity of the plasma potassium changes on exposure to severe anoxia is most striking. A period of from 6 to 12 minutes was taken to attain simulated altitudes which resulted in respiratory failure. In this relatively short space of time increases as high as 69 per cent in plasma potassium were obtained. The similarity of such rapid changes

to those resulting from the injection of adrenalin provides further evidence of adrenal medulla involvement under the stress of severe anoxia.

However, following adrenalectomy, splanchnicectomy and adrenalectomy-nephrectomy, increases in plasma potassium (18, 11 and 33 per cent, respectively) resulted when the animals were exposed to levels producing respiratory failure. These increases, according to Moon (47), may be attributed to changes in the permeability of tissue cells, particularly in the muscles, due to damage by lack of oxygen. Thus it seems that at the altitudes of 40,000 feet and above the large increases in plasma potassium are due not only to the secretion of adrenalin, but also to permeability changes. The 33 per cent increase in plasma potassium is quite high and it is impossible to explain such a concentration entirely by increase in permeability. Therefore some other factor seems to be involved, the mechanism of which is not known at this time.

#### SUMMARY

The evidence obtained in this study indicates that under anoxic conditions the plasma potassium levels are determined by the degree of oxygen lack. On exposure to 28,000 feet (moderate anoxia) for 90 minutes there resulted an average decrease in plasma potassium of 18 per cent. An average decrease of 25 per cent in plasma potassium concentration was obtained when the time of exposure to an altitude of 28,000 feet was increased to 180 minutes. Exposure to this altitude for 360 minutes, however, resulted in an average decrease of only 21 per cent. Fatigue of the cortex of the adrenal gland is postulated as the cause of this lower value. When, however, animals were exposed to simulated altitudes of

36,000 feet, 40,000 feet and levels above 40,000 feet (severe anoxia), there resulted average increases of 20 per cent, 49 per cent and 48 per cent, respectively, as compared to control values. Somewhat greater increases (Av. 53 per cent) were observed if severe anoxia was imposed after a previous period at 28,000 feet. Each animal served as its own control.

The kidney is not the avenue of escape of the potassium from the plasma, since plasma potassium decreases by 13.5 per cent on exposure to 28,000 feet after nephrectomy. Nor are the erythrocytes a storage site for the potassium lost from the plasma. A review of the literature suggests the liver as a possible depot.

Definite evidence of polyuria in barbitalized cats was obtained during a 90 minute and a 130 minute exposure to 28,000 feet, as shown by the 93 per cent and the 46 per cent increases in urine volume, respectively. Adrenal involvement is indicated by the decrease in urine excretion (49 per cent) when cats were exposed to 28,000 feet for 90 minutes, beginning 2 hours after adrenalectomy.

Further studies have demonstrated the involvement of the adrenal gland in the electrolyte changes noted. They show an antagonistic action between the medullary and the cortical divisions of the gland. The results obtained indicate that the adrenal cortex exercises dominant control at moderate altitudes. Thus, after a 90 minute exposure to moderate anoxia, its hormones cause a decrease in plasma potassium of 13 per cent of normal, and of 19 per cent and 14 per cent in nephrectomized and splanchnicectomized animals, respectively. The influence of the adrenal medulla predominates at higher altitudes, causing large as well as rapid

increases in plasma potassium values, similar to those caused by the injection of adrenalin.

An increase in the permeability of tissue cells to potassium is postulated as an additional factor involved in the high plasma potassium values at altitudes above 40,000 feet, to explain the smaller increases still observed after adrenalectomy or splanchnicectomy.

#### LITERATURE CITED

- (1) Bert, Paul. Barometric Pressure. Translation by Hitchcock. College Book Company, Columbus, Ohio, 1943.
- (2) Armstrong, H. G. Principles and Practice of Aviation Medicine. Williams and Wilkins, Baltimore, 1939.
- (3) Gemmill, Charles L. Physiology in Aviation. Charles C. Thomas, Springfield, 1943.
- (4) Barcroft, J. The Respiratory Function of the Blood. Book II, 2nd edition, Cambridge, 1928.
- (5) Haldane, J. S., and J. G. Priestly. Respiration. Yale University Press, 1935.
- (6) Peters, John P., and Donald D. Van Slyke. Quantitative Clinical Chemistry. Volume II, Methods. Williams and Wilkins, Baltimore, 1932.
- (7) Oster, Robert H., J. E. P. Toman and Dietrich C. Smith. Am. J. Physiol. 141: 410, 1944.
- (8) Ziegler, Mildred R. Proc. Soc. Exper. Biol. and Med. 43: 165, 1940.
- (9) Mcquarrie, Irvine, M. R. Ziegler and L. J. Hay. Endocrinology 30: 898, 1942.
- (10) Hoagland, Hudson. J. Av. Med. 18: 450, 1947.
- (11) Darrow, Daniel C., and Ernest Sarason. J. Clin. Invest. 23: 11, 1944.
- (12) Thorn, George W., Benjamin F. Jones, Roger A. Lewis, Ellis R. Mitchell and George F. Koepf. Am. J. Physiol. 137: 606, 1942.
- (13) Lewis, Roger A., George W. Thorn, George F. Koepf and Samuel S. Dorrance. J. Clin. Invest. 21: 33, 1942.
- (14) Swann, Howard G., and W. Doyne Collings. J. Av. Med. 14: 114, 1943.
- (15) Silvette, Herbert. Am. J. Physiol. 140: 374, 1943.
- (16) Burrill, Marie W., Smith Freeman and A. C. Ivy. J. Biol. Chem. 157: 297, 1945.
- (17) Stickney, J. Clifford, David W. Northrup and Edward J. Van Liere. Am. J. Physiol. 147: 616, 1946.
- (18) Van Middlesworth, L., R. L. Banner, F. Lawson and E. M. Cox. Proc. Soc. Exper. Biol. and Med. 69: 288, 1948.

- (19) Adolph, Edward F. *Am. J. Physiol.* 108: 177, 1934.
- (20) McConce, R. A. *The Lancet* 2: 370, 1935.
- (21) Toth, L. A. *Am. J. Physiol.* 113: 131, 1935.
- (22) Toth, L. A. *Am. J. Physiol.* 119: 127, 1937.
- (23) Van Liere, E. J., H. S. Parker, G. R. Crisler and J. E. Hall. *Proc. Soc. Exper. Biol. and Med.* 33: 479, 1936.
- (24) Toth, Louis A. *Am. J. Physiol.* 129: 532, 1940.
- (25) Malmejac, J. *J. Av. Med.* 15: 167, 1944.
- (26) Marshall, Clinton Jr., George W. Thorn and Virginia D. Davenport. *Bull. Johns Hopkins Hosp.* 79: 70, 1946.
- (27) Ponder, Eric. *Hemolysis and Related Phenomena.* Grune and Stratton, New York, 1948.
- (28) Ponder, Eric. *J. Gen. Physiol.* 33: 745, 1950.
- (29) Evans, G. *Am. J. Physiol.* 114: 297, 1935.
- (30) Langley, L. L., and R. W. Clarke. *Yale J. Biol. Med.* 14: 529, 1942.
- (31) Penn, W. C. *J. Biol. Chem.* 123: 297, 1939.
- (32) Giragossintz, George, and E. S. Sunstroem. *Proc. Soc. Exper. Biol. and Med.* 36: 432, 1937.
- (33) Britton, S. W., and R. F. Kline. *Am. J. Physiol.* 145: 190, 1945.
- (34) Li, C. H., and V. V. Herring. *Am. J. Physiol.* 143: 548, 1945.
- (35) Thorn, G. W., M. Clinton Jr., B. M. Davis and R. A. Lewis. *Endocrinology* 36: 381, 1945.
- (36) Armstrong, Harry G., and J. W. Heim. *J. Av. Med.* 9: 92, 1938.
- (37) Silvette, Herbert. *Proc. Soc. Exper. Biol. and Med.* 51: 199, 1942.
- (38) Hartman, F. A., L. Lewis and G. Toby. *Science* 36: 129, 1937.
- (39) Thorn, G. W., H. R. Garbutt, F. A. Hitchcock and F. A. Hartman. *Proc. Soc. Exper. Biol. and Med.* 35: 247, 1936.
- (40) Thorn, G. W., R. P. Howard and K. Emerson Jr. *J. Clin. Invest.* 18: 449, 1939.
- (41) Ingle, D. J., H. W. Nilson and E. C. Kendall. *Am. J. Physiol.* 118: 302, 1937.

- (42) Brewer, G., P. S. Larson and A. R. Schroeder. Am. J. Physiol. 126: 708, 1939.
- (43) D'Silva, John L. J. Physiol. 82: 393, 1934.
- (44) D'Silva, John L. J. Physiol. 87: 181, 1936.
- (45) D'Silva, John L. J. Physiol. 90: 303, 1937.
- (46) Houssay, B. A., A. D. Marenzi and R. Gerschman. Compt. rend. Soc. de Biol. 124: 382, 383, 384, 1937.
- (47) Moon, Virgil H. Shock—Dynamics, Occurrence and Management. Lea and Febiger, Philadelphia, 1942.