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ACUTE MOUNTAIN SICKNESS; THE EFFECT OF AMMONIUM CHLORIDE¹

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Our knowledge of the etiology of mountain sickness has not advanced very much since Paul Bert's fundamental observations (1), and little has been added to the understanding of its mechanism.

Detailed descriptions of the symptoms of mountain sickness have been given by those who have studied it, from Acosta in 1569 (2) to Monge et al. in 1928 (3) (Douglas, Haldane et al. (4), Barcroft et al. (5)). Although opinion on the fundamental cause of this disturbance is unanimous, there is disagreement as to the manner in which the organism endeavors to prevent the appearance of mountain sickness. Since this paper deals only with the disturbances produced as a consequence of rapid ascents to high altitudes, it will not discuss either Haldane's secretion theory, which has been shown to be incorrect by the Chilean studies of Dill, Christensen and Edwards (6), or Barcroft's claim (5) that the oxygen dissociation curve of hemoglobin deviates to the left, shown to be incorrect by Keys, Hall and Barron (7) and by Hall (8) on the same expedition.² By most observers the following have been considered processes of adaptation to high altitude: 1, a rise in the arterial oxygen pressure; 2, a fall in alveolar CO₂ pressure and a corresponding rise in alveolar oxygen pressure; 3, an increase in the per cent and total amount of the hemoglobin of the blood; 4, an acceleration of the blood flow. Some of these processes will be discussed in the light of our experience during an automobile trip from Lima (160 meters) to Ticlio (4740 meters).³

PROCEDURE

On the day preceding the trip to Ticlio, six men (three medical students and three male nurses) of the twelve who made up the party took 15 grams each of NH₄Cl in three 5-gram doses before breakfast, lunch, and dinner. On the following day, between 6:10 a.m. and 7:50 a.m., samples of alveolar air, taken at the end of normal expiration, and 50 cc. of arterial blood were obtained from each of these six individuals. The party started from Lima in three automobiles at 8:15 a.m., and after two halts (one in San Mateo (3200 meters) for one hour and another in Casapalca (4140 meters) for one and one-half hours) arrived at Ticlio at 4:15 p.m. Upon their arrival the party had to walk about 200 meters to the engineer's house, where, after a rest of half an hour, arterial blood and alveolar air were taken from all but two members of the party. (Details concerning the individual reactions of the members of the party to the ascent are given at the end of this paper.)

Arterial oxygen saturation

Since hemoglobin has been considered the main factor of oxygen transport in mammals, all investigators have given to its degree of oxygen saturation a rôle of prime importance in the causation of mountain sickness. Since there was no experimental evidence for this claim (no analysis of arterial blood having been performed), "cyanosis" and "blueness of the lips" were given as proof for their contention.

¹ We wish to acknowledge our gratitude to Mr. Harold Kingsmill, General Manager of the Cerro de Pasco Mining Company, for providing facilities for the trip from Lima to Ticlio.

² These authors give details of financial support and itinerary of the "International High Altitude Expedition."

³ For rapidity of ascent from sea level to great alti-

tudes few places in the world can compare with the Lima-Ticlio region. It is for this reason peculiarly suited to the study of acute mountain sickness. This investigation is really an outcome of conversation on the Panama-Callao voyage with Dr. Crane, Chief Surgeon for the Cerro de Pasco Mining Company. His experiences make him a preeminent authority on the subject of acute mountain sickness.

TABLE I

Arterial oxygen saturation in acute mountain sickness. Arterial blood taken in Lima (160 meters) in the morning, before the trip, and in Ticio (4740 meters) in the afternoon of the same day

Name	Lima		Ticio		Condition
	HbO ₂ content	HbO ₂ saturation	HbO ₂ content	HbO ₂ saturation	
	<i>mM. per liter</i>	<i>per cent</i>	<i>mM. per liter</i>	<i>per cent</i>	
Sandoval.....	9.54	92.0	7.67	74.6	Ill. Mountain sickness
Aldazabar.....	9.71	92.6	7.49	70.3	Ill. Mountain sickness
Prieto.....			8.24	81.7	Ill. Mountain sickness
Cordova.....	8.24	92.7	6.44	72.9	Good
Tincopa.....	9.24	91.6	8.12	78.7	Good
Guzman.....	8.04	93.7	6.48	73.8	Good
A. Barron.....			6.17	65.4	Good
Hurtado.....			8.07	75.3	Good
E. S. G. Barron			8.05	73.3	Good
Average O ₂ saturations in Ticio:					
With mountain sickness.....				75.5	
In good condition.....				73.2	
Average O ₂ saturation at Montt (4710 meters)—acclimatized members of the Chilean Expedition.....				78.0	

In Table I are given the oxygen saturation and content of the arterial blood of the members of the party, as taken in Lima and in Ticio. The average oxygen saturation of the individuals with mountain sickness was 75.5 per cent, while that of the individuals who did not feel any ill effects at this altitude was 73.2 per cent. Prieto, with an arterial oxygen saturation of 81.7 per cent, was ill; while A. Barron, with an oxygen saturation of 65.4 per cent, was well. Similar results were found earlier in Chile. In Montt, at 4710 meters, only 30 meters lower than Ticio, Dill, with an arterial oxygen saturation of 71.6 per cent, was working with normal efficiency; while Hall, with an oxygen saturation of 83.2 per cent, had a mild case of mountain sickness (headache, lack of appetite, nausea).

Hemoglobin concentration

Barcroft (9), in his excellent studies on the physiology of the spleen, considers this organ as one of the main storehouses or depots for blood, adding as others the liver, lungs, and subpapillary vessels of the skin. The rôle of the spleen as a blood reservoir which the organism may utilize in case of need seems to vary in the different animal species. For example, while the dog's spleen, according to Barcroft, raises by its contraction during exercise the oxygen capacity of the blood,

such a rise does not occur in man (Dill, Talbott and Edwards (10)). It could be argued that during the ascent to high altitudes, before there is an increase in hemoglobin formation these blood reservoirs throw into the general circulation their reserve red cells, thus increasing the oxygen capacity of the blood. In Table II is given the oxygen capacity (a more reliable figure than the red cell count) of those members of the party whose arterial blood was obtained at both places, Lima and Ticio. There was essentially no difference between the average arterial oxygen capacity in Lima, 9.68 mM. per liter, and that in Ticio, 9.76 mM. per liter. Although there was a slightly higher average increase in the oxygen capacity of those who felt no ill symptoms than of those who suffered mountain sickness, the difference is too small to deserve attention. We may therefore conclude that these "blood stores" play no important function in the rapid adjustments of the organism to high altitudes. For comparison we have added the oxygen capacity of the acclimatized members of the Chilean Expedition after a gradual ascent to Montt, practically the same altitude as Ticio. Here the increase in hemoglobin concentration is evident.

TABLE II

Arterial oxygen capacity soon after an ascent to high altitudes (Ticio, 4740 meters)

Name	Oxygen capacity		Condition in Ticio
	In Lima	In Ticio	
	<i>mM. per liter</i>	<i>mM. per liter</i>	
Sandoval.....	10.37	10.25	Ill. Mountain sickness
Cordova.....	8.90	8.82	Good
Aldazabar.....	10.48	10.65	Ill. Mountain sickness
Tincopa.....	10.10	10.30	Good
Guzman.....	8.58	8.77	Good
Average.....	9.68	9.76	
Ill, mountain sickness.....	10.42	10.45	
In good condition..	9.19	9.30	
	Boston (sea level)	Montt (4710 meters)	
Members of the Chilean Expedition.....	8.84	10.72	

*Pressure of oxygen in alveolar air.
Effect of NH_4Cl*

A rise in the pressure of oxygen in the alveolar air, accomplished by an increase in the total ventilation, has been considered as one of the mechanisms of adaptation. Furthermore, Haldane and Priestley (11) state that "the diminution in available alkali seems to be much more important" for the process of adaptation to high altitudes. They then add, "Possibly this part of acclimatization might be greatly hastened by the administration of NH_4Cl " (11, p. 317). If an increase in the pressure of oxygen of the alveolar air may prevent mountain sickness, Haldane's suggestion seemed reasonable. Greene, during the expedition to Mount Kamet (12), took small doses of NH_4Cl (0.45 gram three times daily) and thought that the effect was beneficial. Later, Douglas, Greene and Kergin (13) compared the general condition and capacity to do muscular work of one subject at a pressure of 347 mm. Hg in a steel chamber with and without the administration of NH_4Cl . With NH_4Cl the subject showed a lower alveolar CO_2 pressure and a higher oxygen pressure, a lessened degree of cyanosis, a slower pulse rate, and a greater ability to perform muscular work than in experiments in which no NH_4Cl had been taken. According to Fölling (14) the increase in alveolar ventilation after ingestion of NH_4Cl over a two-day period is not proportionate to the decrease in alkaline reserve, the result being an uncompensated acidosis.

The fact that there is no relation, *down to certain limits*, between the arterial oxygen saturation and mountain sickness raises strong doubts as to the usefulness of NH_4Cl in preventing mountain sickness. Furthermore, the uncompensated acidosis produced by the drug in displacing the oxygen dissociation curve to the right would tend to neutralize the effect of the increased oxygen pressure in the blood.

Notwithstanding these considerations, a practical test seemed worth while. This test was performed in Peru. Of the 12 members who made up the party, 6 took NH_4Cl in the doses stated under "Procedure."

Proof that this method of administering NH_4Cl resulted in a significant decrease in alkaline reserve and in alveolar ventilation over the critical

TABLE III

Effects of NH_4Cl on blood and alveolar ventilation on normal subjects at sea level

5 grams were ingested after each meal on the first day. Blood was drawn on the morning of the first day and 24 and 30 hours later. The results for the 3 specimens are in chronological order for each individual.

Subject	Alveolar air		Equilibrated oxygenated blood			Calculated arterial pH _s	Total CO_2 of oxygenated blood, when $\text{pCO}_2 = 40$ mm.
	pCO_2	pO_2	pCO_2	Total CO_2	HbO_2		
	mm. Hg	mm. Hg	mm. Hg	m.eq.	mM.		m.eq.
Dill.....	41.8	106	42.3	22.5	8.29	7.38	22.1
	38.3	110	42.1	18.7	8.38	7.33	18.3
	39.7	106	42.4	20.8	8.71	7.36	20.3
Forbes....	42.6	96	42.0	21.5	9.09	7.36	20.7
	40.2	103	40.9	18.2	8.80	7.30	18.0
	40.3	98	38.3	17.9	8.69	7.30	18.1
Edwards..	41.6	99	41.5	21.0	9.30	7.36	20.6
	38.0	103	39.6	17.2	9.58	7.30	17.2
	35.9	105	38.8	17.2	9.71	7.32	17.4
Keys.....	42.1	101	41.7	21.7	9.00	7.37	21.3
	38.8	107	38.4	17.4	8.90	7.30	17.7
	40.3	98	39.7	18.9	8.84	7.33	19.0
F. Con-solazio..	39.3	103	43.4	20.7	9.48	7.37	20.2
	34.5	109	37.4	16.3	9.71	7.32	17.0
			39.0	18.7	9.53		18.9
Daly.....	42.4	97	43.9	21.5	8.49	7.35	20.4
	35.2	120	37.7	16.7	9.26	7.32	17.3
			41.0	18.9	9.08		18.8
Mean values..	41.6	100	42.5	21.5	8.94	7.37	20.9
	37.5	109	39.4	17.4	9.10	7.31	17.6
	39.0	102	39.9	18.7	9.09	7.33	18.7

period was obtained after our return to Boston. Six subjects were given the same quantity at the same rate. Studies were made of the alveolar air and properties of the blood in the morning before beginning ingestion, the following morning, and the following afternoon. The results are shown in Table III. For comparison, the level of the CO_2 curve of oxygenated blood of fully acclimatized men at various altitudes is shown in Table IV. It appears that the reduction in available alkali accomplished in 24 hours by the administration of NH_4Cl is approximately equal to that established by normal men after gradual (but incomplete) acclimatization to an altitude of about 5000 meters. Therefore, if alkaline reserve is closely related to mountain sickness, as has been claimed, one would expect significant benefits

TABLE IV
CO₂ of oxygenated blood at pCO₂ = 40 mm.
Results in m.eq. per liter

Name	Sea level	Chuqui 2810 meters	Ollagüe 3660 meters	Montt 4710 meters	Quilcha 5340 meters	Punta 6140 meters
Members of expedition						
Forbes.....	22.4	19.4	17.6	19.3	17.3	16.2
Talbott.....	21.9	19.2	18.8	18.8	17.7	16.0
Dill.....	22.2	20.7		19.8	18.7	15.2*
Barron.....	20.9	19.2	18.9	18.7	19.2	15.1
Edwards.....	21.5	18.4		18.4	16.9	13.8*
Christensen....	21.6	19.1	21.6	19.9	18.5	
Keys.....	22.3	18.2	19.4	17.4	17.2	15.7
McFarland....	21.7	19.1		18.3	17.6	16.5
Hall.....	20.4	18.8		18.0	17.1	17.1
Matthews.....		19.2		19.3	17.5	16.8
Average...	21.7	19.1	19.2	18.8	17.8	16.2
Residents						
Bastias.....					16.2	
Heredia.....					14.8	
Campos.....					14.8	
Martinez.....			18.0			
Alcaino.....					17.4	
Troncoso.....					15.0	
Alcio.....					15.6	
Fritz.....					15.3	
Carrasco.....			18.3			
Average...					15.9	

* After NH₄Cl ingestion. Not included in the average.

from the administration of NH₄Cl as it was carried out in Peru.

In Table V are given the alveolar pO₂ and pCO₂ of the members of the party from whom reliable samples were obtained. There was an increase in the alveolar pO₂ of those who took NH₄Cl, and the average pO₂ was higher (49.6 mm. Hg) than those of Hurtado (45.0) and Barron (47.0), both thoroughly acclimatized to high altitudes. In spite of this increase in the pO₂ of the alveolar air, of the 6 subjects who took NH₄Cl, one, Montoya, became critically ill at 4140 meters, and 2 more became ill in Ticlio; i.e., half of those who had taken NH₄Cl had mountain sickness. Of the other 6 members, who had not taken NH₄Cl, 2 had mountain sickness, one in Ticlio and the other on his way down. It should be emphasized that the three subjects who had taken NH₄Cl and had mountain sickness had been in high altitudes previously with no ill effects. The gastric disturbances frequently produced by

the drug might have accelerated the onset of the symptoms.

DISCUSSION

Although there is general agreement with Paul Bert's contention that the fundamental cause of mountain sickness is oxygen want, its mechanism is still obscure. In fact, Redfield's statement in 1922 (15) that in mountain sickness "each case is an individual story and up to the present no one has been able to predict who will and who will not be affected," as well as Loewy's remarks (16) made ten years later that "ihre Aetiologie jedoch ist durch neuste Beobachtungen eher dunkler geworden als aufgehehlt," may still be repeated.

The alveolar air and the arterial oxygen saturations which we determined in subjects suffering from mountain sickness have revealed only that in rapid ascents up to 4700 meters the development of mountain sickness has no simple dependence on the arterial oxygen saturation and the alveolar oxygen pressure. Haldane's suggestion that diminution in the alkaline reserve by NH₄Cl ingestion might hasten acclimatization is not borne out; our experience indicates that NH₄Cl offers a handicap rather than an advantage.

Since mountain sickness may be due to diminished oxygen utilization by certain tissues, in particular by the central nervous system, the factors concerned with the maintenance of a suitable oxygen supply to the tissues may be stated. These factors are essentially two: the *vascular oxygen transport system* (blood hemoglobin), whose efficiency is regulated by the arterial oxygen capacity and saturation and by the alveolar pO₂; and the

TABLE V
Alveolar air in Lima and Ticlio

Name	Lima, barometric pressure 752 mm. Hg		Ticlio, barometric pressure 432 (4740 meters)			
	pO ₂	pCO ₂	pO ₂	pCO ₂	NH ₄ Cl	Physical condition
Sandoval..	105.9	33.6	53.9	23.9	Yes	Ill. Mountain sickness
Cordova..	103.0	36.6	49.8	26.9	Yes	Good
Aldazabar.	104.0	35.6	50.9	24.8	Yes	Ill. Mountain sickness
Montaya..	103.9	34.9			Yes	Ill. Mountain sickness (Left in Casapalca)
Tincopa...	102.2	37.1	49.5	26.4	Yes	Good
Guzman...	100.0	38.0	44.1	30.1	Yes	Good
Prieto....					None	Ill. Mountain sickness
A. Barron.					None	Good
Hurtado..			45.0	29.7	None	Good
E. S. G. Barron..			47.0	28.3	None	Good

tissue oxygen transport system (myoglobin and part of the cytochrome complex), whose efficiency is regulated by the blood flow, the state of the capillaries, etc. The studies of Monge, Encinas, Hurtado and Heraud (3) and of Hurtado (17) on the dwellers of the high Andes, and those of the Chilean expedition, have shown that normal life is possible with an arterial oxygen saturation as low as 70 per cent. These studies suggest that undue importance has been given to the vascular oxygen transport system. Since mountain sickness may occur when the vascular oxygen transport system is still within normal limits, it is suggested that the tissue oxygen transport system plays an important rôle in determining the appearance of mountain sickness, because it contains and transports the molecular oxygen which will be immediately utilized by the oxidizing enzymes, i.e., the enzymes concerned with cellular respiration. Little is known of the properties of this system. However, Theorell's brilliant contribution (18) has shown that the oxygen dissociation constant of horse myoglobin at pH 7.46 is 3.26 mm. O_2 ; i.e., the myoglobin, at equal hydrogen ion concentration and temperature, has six times as great an affinity for oxygen as horse hemoglobin has; and Millikan reports (19) that myoglobin combines with oxygen several times as fast as hemoglobin. This relation between the affinity for oxygen (as expressed by the dissociation constants) and the rate of combination in these two systems is of great physiological importance. The same relation between free energy and rates of reaction has been found by Barron (20) to exist in a number of oxidation processes of biological importance. The existence of cytochrome in the heart, liver, and brain of mammals has been reported by Cohen and Elvehjem (21). In sudden ruptures of equilibrium conditions (mountain sickness) this relation might influence the rate of diffusion of oxygen from the vascular oxygen transport system to the tissue oxygen transport system. Other factors which probably take part in the regulation of oxygen passage from the vascular system to the tissue transport system are an increased blood flow, as reported by Grollman (22), and dilatation of the capillaries.

CONCLUSIONS

The appearance of acute mountain sickness is not closely dependent upon the degree of arterial oxygen saturation and the alveolar air oxygen pressure, down to certain limits. Acute mountain sickness is not prevented by diminishing the alkaline reserve of the blood, as shown by the failure of ammonium chloride to prevent it in a rapid ascent from sea level to 4740 meters. The tissue oxygen transport system (myoglobin and part of the cytochrome complex) probably plays an important rôle in mountain sickness.

PROTOCOLS OF THE EXPERIMENTS

Members of the party who developed acute mountain sickness on the trip to Ticlio

Number 1. Montoya. Nurse, 26 years. Born in Arequipa (2280 meters). Had passed through Ticlio before with no ill effects. On arrival at Casapalca (4140 meters) he became extremely ill. He was very pale, felt chills and such severe dizziness that he could not walk, vomited, and had to be taken to the hospital on a stretcher. No samples of blood or alveolar air were taken. At the hospital he was given oxygen, and at 9:00 p.m., when we returned to Casapalca, he was feeling better and returned with us to Lima. He had taken NH_4Cl , which he felt sure was the cause of his illness.

Number 2. Sandoval. Student, 24 years. Born in Huari (3160 meters). Had crossed the Andes on horseback at heights of 4800 meters several times with no ill effects. On arriving at Ticlio he felt very cold, was extremely pale, complained of dizziness and nausea, and finally vomited. After resting in bed he felt better. He had taken NH_4Cl and felt certain that it made him ill.

Number 3. Aldazabar. Nurse, 25 years. Born in Lima. Had been repeatedly at high altitudes. In Ticlio he felt extremely cold, had nausea, headache, dizziness, ringing in the ears. He was continuously shivering, so that samples of alveolar air could not be taken. He had taken NH_4Cl .

Number 4. Prieto. Student, 24 years. Born in Arequipa. Had never been in altitudes higher than Arequipa. From San Mateo on he felt headache and dizziness. In Casapalca he began to

feel weak. At Ticlio, while walking to the engineer's house, he felt still weaker. At the house, he felt dizzy and faint; had nausea, vomiting, chills, extreme pallor, headache, and ringing of the ears. He was put to bed. His pulse was 88, rhythmic and vigorous. During the return to Lima, he began to feel ill again, at about 2100 meters, and vomited copiously. This was his first ascent to so high an altitude. He had taken no NH_4Cl .

Number 5. A. G. Barron. Member of the faculty in the Medical School of Lima, 33 years. Born in Huari. Extremely susceptible to mountain sickness. One week previously he had come by car along this road and had had to stop in Matucana (2370 meters) because of headache and dyspnea. He had had mountain sickness when passing through Ticlio by train on two previous occasions. In Ticlio he was feeling dyspneic and had tachycardia (pulse 128). On the way down, at about 2700 meters, he felt headache and nausea, and vomited. No blood sample could be taken. He had taken no NH_4Cl .

The other members of the party felt no ill symptoms; nor did the three drivers. Edwards, Hurtado and E. S. G. Barron worked steadily in Ticlio from 4:45 p.m. to 8:30 p.m., taking the blood and air samples. Edwards and Barron had recently been in the Chilean Andes, and Hurtado goes through Ticlio every other week to Morococha (4500 meters).

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