PHYSIOLOGICAL COMPENSATORY MECHANISMS AT ALTITUDE

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Since the early days of Robert Boyle's studies of the effects of altitude by means of his vacuum pump in 1660 and those of Paul Bert's investigations of the effects of decreased barometric pressure in 1878, various workers have been attracted to this field of research, notable among them being Barcroft and Haldane. Later during the Himalayan expeditions, it became clear that climbing of Mount Everest called forth physiological adjustments in the human body which are of great interest for the practical bearing they have upon the success or failure of the venture. "It came to be realised that the climbing of the mountain is almost as much a physiological problem as a mountaineering feat". To-day, it can be said that medical and physiological research have contributed heavily towards the attainment of main objectives in studies of human factors in high altitude - high velocity flying simultaneously as man forges ahead in his quest to conquer the atmosphere (Table 1) Operational committments of our armed forces during the last four years has made studies of effects of altitude on the human body of very great importance to us.

There are several variables at high altitude which, in a measure, may influence physiological processes. Schneider (1921) has listed these as follows: (1) lowered atmospheric pressure; (2) lowered partial pressure of oxygen; (3) temperature; (4) humidity; (5) increased intensity of sunshine; and (6) electrical conditions. The most important of these factors is lowered partial pressure of oxygen and although it is possible that some of the other factors may influence physiological processes yet it is considered that presumably they play less important roles. *Hence in this paper the effects of anoxia on the human body have been dealt with.

Generally, four factors are recognised to determine the response of an organism under low oxygen: (1) suddenness of the production of oxygen want; (2) its degree of severity; (3) its duration and (4) physical condition of the body. It can be seen that the problem is essentially the same from the point of view of the Air Force as it is from that of the Army, although in the former first two factors need most immediate consideration while in the latter, factors (3) and (4) play a more important part in the case of a soldier who climbs the mountain slowly and to a much lesser height, but with a higher expenditure of energy due to heavy exertion during ascent. In the Armed Forces, during high altitude operations, it is obviously important for the authority to be able to foresee the capabilities and the limits of efficiency of men under his comand. As these limits may be rightly considered to have been imposed on them by the lack of acclimatisation during rapid ascent and inadequate haematological response to pure anoxic anoxia, and as it is obvious that the phenomena of respiratory and haematological responses are important features during the process of acclimatisation to reduced partial pressure of oxygen, so only these aspects of the changes met at high altitudes have been discussed here.

Atmosphere and Respiration.

The surface of the earth is surrounded by a layer of air, the composition of which remains the same upto about 53,000 feet or 10 miles. The layer upto this height is called the Troposphere. The causes of uniform composition of the air are the currents and eddies of air which arise from the uneven warming of the earth's surface. This vertical mixing of the air ceases about 53,000 feet and here the Stratosphere begins. This boundary between the Troposphere and the Stratosphere is said to lie lower near the poles and higher near the equator owing to the greater effect of the sun. Stratosphere is the layer above 10 miles and is thought to be about 500 miles thick. It has been subdivided into (1) Ozone layer; (2) Lower heaviside layer; (3) Heaviside layer; (4) Appleton layer, as shown in Fig. 1. The knowledge about the physical variables of the atmosphere is important because although for practical purposes to-day, the upper limits of aviation may be considered as round about 50,000 feet, with the present rapid advances in aircraft design, this may soon be superseded as stratosphere flying has its undoubted advantages, such as better engine performance, aerial superiority, smaller variations in temperature, absence of moisture and the high altitude jet - stream.

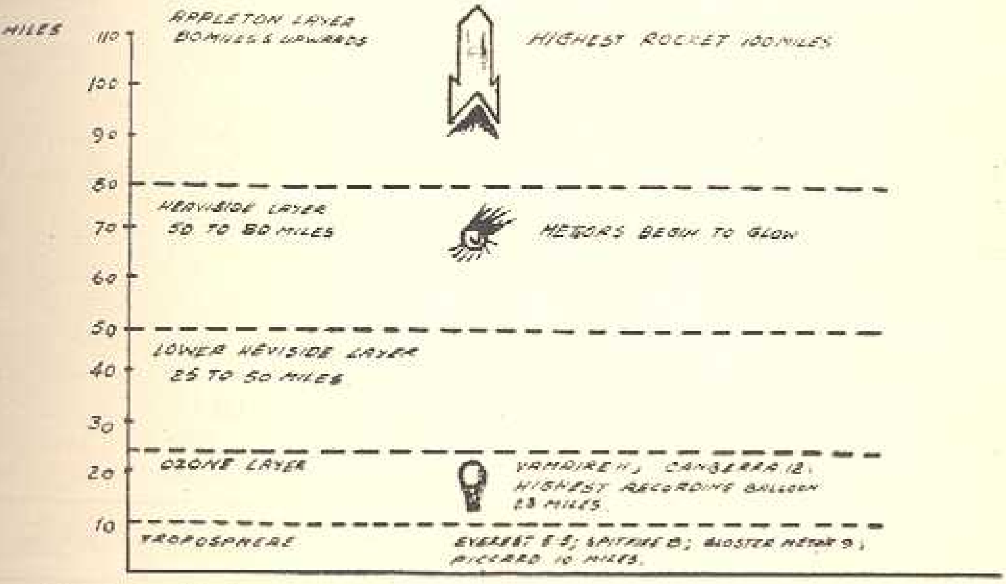

Fig. 1 In this diagram of the atmosphere, stratosphere is everything higher than about 10 miles. (Modified from the Defence Science Organisation).

Since air has mass it also has weight and the air at normal density in the neighbourhood of the earth is only one-eightieth of the weight of water. The layers of air near the earth's surface are pressed upon by those above and thus at high altitude we would expect this pressure to be less and in practice this has been found to be true. It is evident, the higher the altitude lower the pressure and that there is a definite relationship between the two. As can be seen from Table 2 pressure difference between zero and 1000 feet altitude amounts to 27 mm. Hg. while at higher altitude it is less. Hence the altitude pressure curve is not a straight line but as we ascend, each 1000 feet of altitude involves a progressively lesser drop in pressure.

In the consideration of atmospheric air it must be remembered that here the law of partial pressures apply and that the partial pressure of oxygen in a gas mixture is its contribution to the total pressure. Table 2 shows that the partial pressure of oxygen at different altitude will at all times amount to about one-fifth of the total pressure obtained. While oxygen is the only constituent of the atmospheric air utilised by the body, the other gases present are not of much importance, except of course CO2, as they are dissolved in the blood just as they are dissolved in any other fluid exposed to the air, and are inspired and expired in equal amounts and unchanged.

	Above Sea Level Feet	Miles
Constellation airliner can fly at	25,000	4.8
Highest mountain in the world (Mt. Everest)	29,141	5.5
Highest summit climbed by man (Mt. Everest)	29,141	5.5
Boeing Stratocruisers can fly at	30,000	5.7
Average height of high cloud formation	33,000	6.2
Stratosphere begins (over Poles)	37,000	7.0
Spitfires on weather patrols fly at	40,500	7.7
Gloster Meteor (ceiling)	49,000	9.2
Balloon-Prof. Piccard's record	54,540	10.3
Stratosphere begins (over Equator)	58,000	11.0
Altitude record in Vampire fighter (1948)	59,446	11.2
Altitude record in Canberra bomber (1953)	63,668	12.0
Balloon—U.S.S.R. record	72,176	13.7
Balloon—U.S.A. Record	72,395	13.7
Altitude record—Unofficial, in a sky rocket (1953)	83,235	15.7
Balloon—record for weather recording	121,440	23.0
Meteors (shooting stars) begin to glow	370,000	70.0
Record altitude of Rocket	528,000	100.0

Table 1. A Table Of Heights. (Modified from the Defence Science Organisation)

In order to appreciate fully the factors which have to be considered, there must be a clear understanding of the gaseous exchange taking place in the body. Respiration is the interchange of gases between the body tissues and the air and depends to a large extent on the partial pressure of these gases and in this respect they obey Dalton's Law. The physical process of exchange of gases between the alveolar air and mixed venous blood depends on (1) Difference of tension of the gases present in the two (2) Permeability of the membrane (3) Solubility of the gases (4) Elastic tissue of the alveoli and (5) Density of the gases. The velocity of gaseous exchange can be expressed as follows:-

$$\text{Velocity of exchange} = \frac{\text{Pressure difference X Solubility}}{\text{Density of the gas}}$$
$$\text{X} \quad \frac{0.139 \text{ X area of the lung surface}}{\text{thickness of the membrane}}$$

As far as the process of respiration is concerned we are primarily interested in the composition of alveolar air whose oxygen tension is 103 mm. Hg. But the alveolar air is always completely saturated with water vapour at body temperature and this exerts its own partial pressure of 47 mm. Hg. This figure has to be subtracted from the total pressure in the lungs before the partial pressures of the alveolar gases can be accurately assessed. For this vapour pressure, it should be noted that, for a given decrease in atmospheric pressure with height, the change in the percentage composition of the alveolar air is not constant and that the vapour pressure itself (and of course the CO_2 pressure of 40 mm. Hg.) remains constant through very great variations of barometric pressure, thereby affecting the ratio of other gases in the lungs. On the venous blood side, at normal atmosphere pressure, oxygen partial pressure is only 40 mm. Hg. and the CO_2 pressure is 46 mm. Hg. The simple diffusion of the two gases through the membrane tries to establish a pressure equilibrium, passing from a high pressure to a low pressure zone, and thus oxygen passes inwards towards the blood and C02 diffuses outwards towards the lungs.

Altitude (feet)	Inches of Hg.	mm. of Hg.	oC.	Decrease	Oxygen Partial pr. (mm. of Hg.)	Equivalent oxygen percentage
0	29.921	760.0	15	0	159.2	20.96
1,000	28.86	733	13	-2	153.6	20.18
2,000	27.82	706.6	11	4	148.1	19.46
3,000	26.81	681	9	6	142.7	18.76
4,000	25.84	656.4	7	8	137.5	18.07
5,000	24.89	632.4	5	10	132.5	17.41
6,000	23.98	609	3	-12	127.6	16.77
7,000	23.09	586.4	1	-14	122.9	16.15
8,000	22.22	564.4	-1	-16	118.2	15.54
9,000	21.38	543.2	-3	-18	113.8	14.96
10,000	20.58	522.6	-5	-20	109.5	14.39
11,000	19.79	502.6	7	-22	105.3	13.84
12,000	19.03	483.2	9	-24	101.2	13.31
13,000	18.29	464.6	-11	-26	97.3	12.79
14,000	17.57	446.4	13	-28	93.5	12.29
15,000	16.88	428.8	-15	-30	90.5	11.81
16,000	16.21	411.8	-17	-32	86.3	11.34
17,000	15.56	395.4	-19	-34	82.8	10.89
18,000	14.94	379.4	-21	-36	79.5	10.45
19,000	14.33	364	-23	-38	76.2	10.02
20,000	13.75	349.2	-25	-40	73.1	9.61

Table 2—Altitude - pressure - temperature table to which is added the oxygen partial pressure and equivalent oxygen percentage. (modified from "Physiological aspect of flying." July 25, 1941, War Dept.)

Respiratory Changes.

During an ascent to altitude, as the partial pressure of oxygen decreases, haemoglobin becomes less and less oxygenated and the body cells do not receive their normal supply. There are however, compensatory mechanisms which come into play. When anoxia is induced, the lack of oxygen acts as a stimulus to the respiratory centre in the medulla. This stimulus though relatively weak, increases pulmonary ventilation. Increase in lung ventilation washes an excessive amount of carbon dioxide out of the system and thus equilibrium is established. As CO_2 content again reaches normal level, pulmonary ventilation is again stimulated by the oxygen lack and these alternating episodes continue to occur until a new rate of lung ventilation is attained, which is higher than normal and results in a slight increase in the alveolar oxygen. Secondly, the circulatory system tries to secure a compensatory response to anoxia by increasing circulating rate, supplying oxygen to the tissues more rapidly. Initially, pulse rate may increase and blood pressure rises, while later an increase in pulse pressure may take place. For reasons not understood, circulation resumes its normal state, after a period of exposure, which may be due to excessive washing out of carbon dioxide or a normal response to strain. When the above happens, alkali passes out of the blood to a corresponding extent The final compensatory modification of gaseous exchange is known as the "Bohr Effect". When CO_2 tension of the blood is below normal or blood pH is increased, haemoglobin has a greater affinity for oxygen and becomes more highly saturated. At the same time, blood holds tightly to its oxygen so that it is not given off readily to the tissues and a greater tissue anoxia results.

What has been described above are changes which result at very high altitude and which are the immediate results of exposure when the reserve Red blood cells are brought into play from the Spleen and Liver reservoir. But these changes do undoubtedly take place to a less degree during slow ascents to heights as in mountaineering expeditions. Although it is thought that mountain climbing does not effect respiration due to slow transformation processes, yet it is dependant on the period of acclimatisation. We (loc.cit) did not observe any change in rate or depth of respiration upto 10,000 feet, during resting conditions. At 12,000 the rates of 12 men were slightly increased to 22.4 per minute while at 13,000 feet it was 23.5 per minute. During sleep, physiological slowing of respiration was usually observed but no typical Cheyne-Stokes type was encountered although irregularity of rhythm was noted. Colder nights of course produced more slowing and rates of 14-16 per minute have been recorded. The type of respiration was considerably reduced.

Haematological Changes

As transmission of oxygen in the blood is done by the Red blood cells and to a very little extent (1%) to the plasma, blood can be considered to hold in general the key to the altitude problem.

Erythrocyte Count and Haemoglobin. When the tissues suffer from oxygen lack due to insufficient oxygen at their disposal, first compensation is achieved by creating conditions for increased oxygen absorption and increased oxygen capacity of blood. The increase of red blood cells with that of Haemoglobin content is considered to be the measure to counter balance the oxygen want. It has already been mentioned that reserve

Red blood cells are brought into play from the Spleen and Liver reservoir as the immediate result of more or less sudden exposure to very high altitude.

Although it has been shown by Armstrong & Heim that normal individual shows a general lowering of both Haemoglobin and cells and a rise in White cells during four hours exposures on three consecutive days to 12,000 feet in the Decompression Chamber, literature is full of findings of various investigators most of whom aver that, at least in case of mountain climbing there had been increase in the Red blood cells and Haemoglobin, and that this increase is a necessary feature in the process of acclimatisation to altitude. Barcroft has even found a correlation between altitude and rise in the Erythrocyte Count, as shown in Table 3. Fitzgerald has formulated the law that for every 100 mm. fall in the atmospheric pressure there is an average rise of 10 percent Haemoglobin. Although an enormous amount of data has been collected on Polycythaemia produced by high altitudes, nevertheless there is much individual variations, under different conditions. Eggers, for example, has reported RBC level of 7.2 millions and Haemoglobin of 111 percent at a low altitude of 7,567 feet. Shankaran and Rajagopal (1938) recorded 19.6 grammes percent of Haemoglobin in some British troops at 6,200 feet. But Ramalingaswamy and Venkatachalam (1950) did not find high values of Red cells and Haemoglobin of Indian civilians and soldiers at 7,500 feet. The author collaborating with Mookerjee (1951) and working with 50 unacclimatised Indian soldiers, found that the original Red cells count of 5.26 millions (S.D. 0.06) taken at base after a slight fall to 5.04 (S.D. 0.06) on arrival at 9,000 feet showed a significant rise to 5.70 millions (S.D. 0.07) on the 10th day. They however, failed to show a similar rise in Haemoglobin level. Table 4 shows the results obtained by different workers.

The factors producing Polycythaemia were naturally thought to be due either to a low barometric pressure or decreased oxygen tension. After animal experimentations by a number of workers it has been shown that blood changes due to high altitudes were due essentially to low partial pressure of oxygen and that Polycythaemia produced by high altitude is due to oxygen want and not to a diminished barometric pressure.

Size of Erythrocytes. From preceding paragraphs it would seem that increase in the number of RBC is the answer to the problem of anoxia. Smith et al (1924) reported that at an altitude of 11,000 feet, individual Red blood cells were slightly smaller although they were capable of holding the same amount of Haemoglobin. But from the report of other workers, it would seem that increase in Haemoglobin and quantitative changes in circulating RBCs are not the essential compensatory processes for adaptation to high altitude. For example, Emmons (1927) by experimenting with animals suggested that the volume of individual erythrocyte varies inversely with the total number found, a large corpuscular volume compensating for smaller number of cells. Ramalingaswamy etal. (loc. cit.) concluded that the haematological adjustment to a chronic anoxic stimulus does not involve primarily an increase in circulating Red blood cells and Haemoglobin. But it appears that an increase in the surface area of erythrocyte represent the basic compensatory mechanism involved in permanent adaptation to high altitude, although an increase in the number of erythrocytes and in Haemoglobin is frequently met with. Their figures which compare well with those obtained on Indian soldiers and civilians at 9,000 feet by Mookerjee & Ghose (loc. cit.) are shown in Table 5. In can be seen that values for packed cell volume and mean corpuscular volume are higher than can be expected in normal healthy adults in the plains. However, this point needs further study and clarification.

Altitude in thousands OF feet	Corpuscles, millions per cu.mm.
0.7	4.5
4.4	5.2
8.0	6.0
10.0	6.6
12.0	6.8
12.4	6.8
13.3	7.5
15.6	7.8
16.9	7.6
18.2	8.3

Table 3. After Barcroft taken fron Best & Taylor's "The Physiological Basis of Medical Practice", July 1950 Ed. P. 12. (Here the altitude in thousands of feet multiplied by 0.225 gives a figure which approximates the increase in red cell count, in millions per cubic millimetre, above that at sea level. In this instance the count at sea level was 4.25 millions.)

Reticulocytes. The normal count of 50,000 reticulocytes in a cubic millimetre of blood and constituting 1 to 1½ percent of the erythrocytes, is generally thought to increase as a result of exposure to altitude and Barcroft has shown that there was an increased amount of red bone marrow in six Peruvian natives. Experimentally, 6 to 14 percent increase of reticulocytes has been shown to occur in guinea pigs kept at simulated altitude of 18,000 feet for a fortnight.

Blood Platelets Although relatively little work has been done on this problem the concensus of opinion is that there is an increase of the platelet count and figures as high as 340,000 per cubic millimetre have been reported at an altitude of 6,000 feet. The cause is not known, but it might be due to the stimulating effect of anoxia on the production of megakaryocytes.

Observers	Altitude (in feet)	RBC., (mm.per cu.mm	Haemoglobin (average)
Kuending, Loewy & co-workers	5,200	6.50	130% Sahli
Eggers	6,000	7.00	—
Sankaran & Rajagopal	6,200	—	19.65 gms. %
Ramalingaswamy & Venkatachalam	7,500	5.38	15.87 gms. %
Eggers	7,567	7.52	111% Sahli
Mookerjee & Ghose	9,000	5.70	14.8 gms. %
Viault	14,667	8.00	—
Hingstron	14,667	7.09	—
Barcroft	15,000	7.00	
Hurtado	16,667	6.66	15.93 gm %

Table 4. Modified from E. J. Vanlier's "Anoxia, its effect on the body" (Chicago University Press, 1943) p 34.

Leucocytes. The total count, it has generally been thought, is not affected as a result of reduced barometric pressure or partial pressure of oxygen, although there may be a relative increase in the number of large lymphocytes at the expense of polymorphonuclear cells. Recently Mayer, Severs and Beatty (1935) have shown by subjecting guinea-pigs to 15,000 feet for 42 hours and rats to 15,000, 20,000 and 25,000 feet for a week, that there is a temporary leucocytosis followed by leukopenia. The former effect they attribute to the emptying of reservoirs of cells in the spleen and liver and lungs and the latter to a functional depression of the bone-marrow and the lymph nodes.

Blood Viscosity. Increase of blood viscosity from the normal value of 5.1 (limits 4.7 to 5.9) to 8.6 (5.2 to 15.2) has been reported. Brandage (1934-35) showed that an increase of red cells by one third increases the viscosity by three times. But Dill (1938) rightly points out that if the resistance to flow within the body is relatively proportional to the increase of red cells, work of the heart at altitude would be out of proportion to any advantage gained by the increased number of red cells. It has been proved by other workers that the contention of Dill that increase in number of red cells produced by anoxia does not throw an extraordinary burden on the circulatory system, is true. It has been shown that the plasma moves slowly along the periphery in the arterioles, but that there is an axial flow of red blood cells. When blood enters the capillary bed, admittedly the resistance to flow in a capillary must be approximately proportional to the number of red cells, some of the capillaries which are shown by Krogh (1929) to lie dormant may open up so that a large factor of safety is provided and the extra burden on the circulatory system avoided.

	Observers		
	Ramalingaswamy & Venkatachalam	Mookerjee & Ghose	
Types of subject.	Mixed	Troops	Civilians (porters)
No. of subject.	100	31	8
OBSERVATIONS			
Red cells, mills. per cu. mm.	5.32	5.40	5.23
Haemoglobin, gms. percent.	15.86	14.22	13.10
Packed cell volume, percent	49.27	49.80	53.30
M.C.V., Cubic microns	92.27	92.20	101.80
MCH, micro-micro-gms.	29.69	26.50	25.10
MCHC, percent.	32.25	28.30	24.60

Table 5. Haematological Picture of Indian Soldiers and Civilians (Modified from Ind. Jour. Med. Res. 39, 4, October 1951-Mookerjee & Ghose)

Blood Specific Gravity. Specific gravity of blood which is normally 1.055 is increased to 1.067 due to increase in the number of Red cells and blood platelets.

Fragility of Erythrocytes. The resistance of red cells to hypotonic sodium chloride solution is increased due perhaps to preponderance of young blood cells formed as a result of anoxic stimulus.

Coagulation Time of Blood. Due to increase in the number of blood platelets (vide supra) the coagulation time is decreased. But if cold is associated with altitudes as is found during mountaineering expeditions, there may be an increase due perhaps to the depression of enzymic processes responsible for coagulation.

Summary

1. Physical aspects governing respiratory gaseous exchange have been discussed. Importance of partial pressure of oxygen vis-a-vis respiration has been stressed.
2. Compensatory mechanisms which follow the onset of hyperventilation at altitude have been described.
3. Haematological changes met at altitude have been presented in detail.

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