UNCLASSIFIED

AD 268 226

Reproduced
by the

ARMED SERVICES TECHNICAL INFORMATION AGENCY
ARLINGTON HALL STATION
ARLINGTON 12, VIRGINIA

UNCLASSIFIED

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

268 226
268 226
757750
(1)
ASTIA FILE COPY

INFLUENCE OF ALTITUDE CHANGES ON INTESTINAL IRON ABSORPTION

61-107

SCHOOL OF AEROSPACE MEDICINE
USAF AEROSPACE MEDICAL CENTER (ATC)
BROOKS AIR FORCE BASE, TEXAS

ASTIA
DEC 28 1961

INFLUENCE OF ALTITUDE CHANGES ON INTESTINAL IRON ABSORPTION

CÉSAR REYNAFARJE
JOSÉ RAMOS

Institute of Andean Biology and the Department of Pathological Physiology
Faculty of Medicine, University of San Marcos
Lima, Peru

61-107

SCHOOL OF AEROSPACE MEDICINE
USAF AEROSPACE MEDICAL CENTER (ATC)
BROOKS AIR FORCE BASE, TEXAS

September 1961

7758-59682

INFLUENCE OF ALTITUDE CHANGES ON INTESTINAL IRON ABSORPTION

The mechanisms regulating intestinal iron absorption are still not very well known. It has been suggested that hypoxemia, acting on the intestinal mucosa, plays an important role in this phenomenon (1). On the other hand, it has been found that an increase in the absorption of this metal occurs when there is a greater demand due to hyperactivity of erythropoiesis, while a decrease occurs when there is a depression in the red blood cell formation (2). These observations suggested the applicability of performing iron absorption studies during changes of altitude, both in subjects taken from sea level to an altitude of 14,900 feet and in natives of that altitude taken to sea level. Such changes cause variations in oxygenation and, consequently, in the rate of red cell production (3).

MATERIAL AND METHODS

Eighty-two healthy adult men were studied. They were divided into fourteen groups, each of which was investigated under different conditions of altitude, as described later. Most of the groups consisted of 5 subjects each.

The iron was given orally as ferrous sulfate, tagged with Fe^{59} (4). The amount of the salt administered in most of the experiments was calculated to make a 100 mg. dose of metallic iron, which was equivalent to 1.5 to 1.8 mg./kg. of body weight. This relatively high dose was selected because it allowed less individual variation in the amount absorbed than would dosage at lower levels. In two groups, however, smaller quantities were administered (that is, 30 mg. of metallic iron, equivalent to 0.40 to 0.50 mg./kg. of body weight). In all cases the iron was taken by subjects in a fasting state. Eight days later, consecutive blood samples were taken until a maximum of radioactivity was obtained. A scintillation counter was used to measure radioactivity in the red blood cells. In ten of the groups, the percentage of iron absorbed by the subjects was calculated on the basis of the maximum amount of labeled iron appearing in RBC. In the four other groups the fraction eliminated was studied in addition to that appearing in the red cells. To determine the amount of unabsorbed iron, stools were carefully collected for 8 to 10 days. According to the technic of Bothwell et al. (2), the entire stool sample of each subject was treated with 5 liters of sulfuric acid for 10 days with periodic stirring. At the end of that time the mixture was strongly agitated, a 2 cc. sample removed, and the radioactivity measured. The uniformity of the counts obtained in two or three samples from the same subject indicated that there had been an even distribution of iron in the mixture.

Received for publication on 9 June 1961.

RESULTS

Absorption after ascent to 14,900 feet

The data obtained in three groups of subjects taken from sea level to Morococha (14,900 feet) are presented in table I and figure 1. Subjects of the three groups were given iron 2 days, 8 days, and 30 days, respectively, after their arrival. Results were compared with those obtained at sea level on a group of 15 subjects born at sea level. Each subject was given a dose of 100 mg. iron. The percentage of absorption was calculated on the basis of the

TABLE I

Intestinal iron absorption in sea level subjects after ascent to high altitude (percentage of 100 mg. dose)

	At Lima (sea level)	After ascent to Morococha (14,900 feet)—		
		2 days	8 days	30 days
Fe appearing in RBC (mean ±S.D.)	3.6 ±1.27	14.3 ±3.78	16.3 ±2.34	7.2 ±3.10
Fe reaching circulating plasma* but not RBC	0.5	0	0	0.4
Total	4.2	14.3	16.3	7.6
Fe uptake for Hb synthesis*	86/100	100/100	100/100	95/100
Hemoglobin (gm. %)	15.1	15.9	16.2	17.2
Number of subjects studied	15	10	5	5

*Estimated on basis of previous studies.

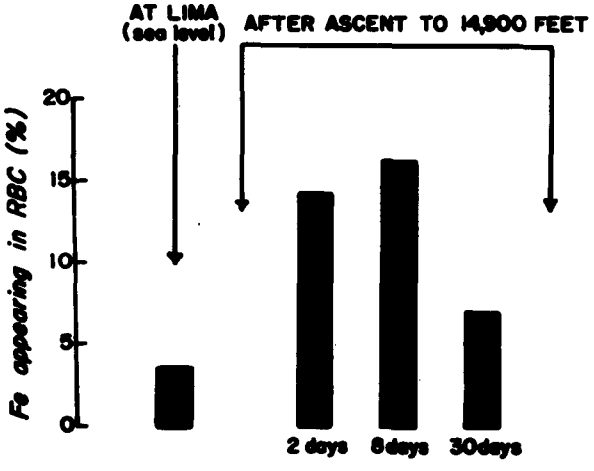

FIGURE 1

Iron absorption in sea level subjects after ascent to 14,900 feet.

amount of iron that appeared in the red cells, as mentioned before, but a correction factor was added for that fraction of the absorbed iron that presumably had entered the circulating plasma but did not appear in the red cells. This factor was applied on the basis of previous studies of intravenous iron uptake carried out in subjects under the same conditions of exposure to high altitude. By this correction we have replaced the double isotope method described by Saylor and Finch (5), which is used for the same purpose in cases in which the intravenous uptake of iron is unknown.

In the group of 15 sea level subjects studied under normal conditions of oxygen tension, the average amount of absorbed iron that appeared in the red cells was 3.6 percent, with a standard deviation of ±1.27. This figure represents 86 percent of the absorbed iron that reached the circulating plasma, of which the total was estimated to be 4.2 percent.

Two days after ascending to 14,900 feet, a group of 10 subjects showed a much greater absorption of iron, as reflected by the appearance of 14.3 ±3.8 percent in the erythrocytes. In the group studied after 8 days the absorption was even higher (16.3 ±2.3 percent). In both groups it was assumed that all absorbed iron was used in the production of red cells in accordance with previous investigations in which we have demonstrated that the total amount of iron available in the circulating

TABLE II

Intestinal iron absorption in high altitude subjects after descent from high altitude to sea level (percentage of 100 mg. dose)

	At Morococha (14,900 ft.)	After descent to sea level—				
		2 days	8 days	22 days	2 months	16 months
Fe appearing in RBC (mean ±S.D.)	4.80 ±1.20	1.48 ± .57	1.25 ± .38	0.75 ± .16	2.70 ±1.1	3.10 ± .86
Fe reaching circulating plasma but not RBC	0.40	0.98	0.86	0.50	0.44	0.50
Total	5.20	2.46	2.11	1.25	3.14	3.60
Fe uptake for Hb synthesis*	92/100	60/100	60/100	60/100	86/100	86/100
Hemoglobin (gm. %)	20.1	19.0	18.4	14.1	13.8	13.8
Number of subjects studied	8	4	5	5	5	5

*Estimated on basis of previous studies.

plasma was utilized for hemoglobin synthesis during this early stage of adaptation to high altitude (3, 4). A tendency for iron absorption to return to normal was observed in the 5 subjects studied 30 days after arrival at high altitude. An average of 7.2 ±3.10 percent of iron appeared in the red blood cells in this group, and it was assumed that this represented 95 percent of the 7.6 percent of iron which reached the plasma.

Absorption after descent from high altitude

This study was performed in five groups of natives of Morococha (14,900 feet), who were observed at 2 days, 1 week, 3 weeks, 2 months, and 16 months after descent to sea level. Baseline values were taken from a study of Morococha natives carried out at that place. The iron dose was 100 mg.

It can be seen in table II and in figure 2 that the mean value for absorbed iron appearing in the red cells of 8 altitude natives studied in their place of origin was 4.8 ±1.2 percent, which when corrected becomes 5.2 percent. This value is slightly higher than but not significantly different from values obtained in sea level subjects studied under conditions of normal oxygenation.

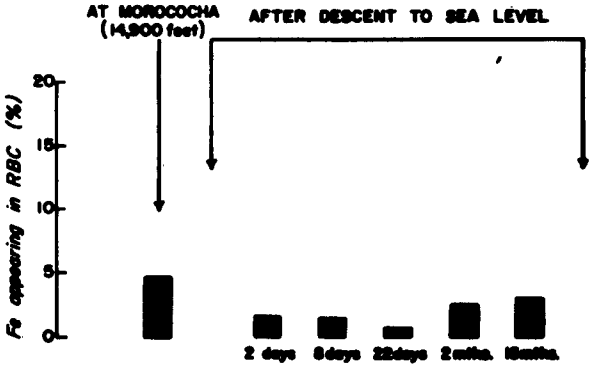

FIGURE 2

Iron absorption in high altitude natives after descent to sea level.

Regarding the natives of high altitude brought down to sea level, it can be seen that in the group of subjects studied 2 days after their arrival there was considerable decrease in iron absorption. The mean value for the

TABLE III

Comparative study of iron absorption in newcomers from altitude between values obtained at sea level and 2 weeks after return to high altitude (percentage of Fe appearing in RBC)

Subject	Sea level	High altitude
1	0.71	0.69
2	1.10	1.30
3	1.39	1.20
4	1.80	1.70
Mean	1.25	1.22

iron appearing in the red cells was 1.48 ±0.57 percent in this group. The decrease was slightly more marked in the 8-day group, 1.25 ±0.38 percent, and reached a minimum of 0.75 ±0.16 percent in the group studied 3 weeks after leaving high altitude. When the correction factor for the observed iron reaching the circulating plasma but not appearing in the red blood cells is added, the values (given above) became 2.46, 2.11, and 1.25 percent, respectively, which represent an increment of 40 percent over the former values. In the group studied 2 months after arrival at sea level there was a tendency toward a recovery of normal iron absorption (2.7 ±1.1 percent) and the 16-month group had returned nearly to normal with a mean of 3.6 percent when corrected for iron not appearing in the red cells.

Effect of erythropoietic stimulation after iron absorption

In the group of native subjects studied 2 days after their arrival at sea level from high altitude it was noted, as indicated, that only a small percentage of labeled iron appeared in the red cells. The possibility that this might actually be only a small part of the total iron absorbed was investigated in the group on the basis that the fraction not incorporated in the cells might form a reserve ("labile pool") that could be used in later demands of the bone marrow as it has been described in cases of pernicious anemia (6). For this purpose these subjects were exposed to further erythropoietic stimulation by being returned to high altitude immediately after they had reached maximum radioactivity in red cells at sea level (11 days). Two weeks after their return to altitude, and without further administration of iron, blood samples were taken in which no additional labeled iron was found. Table III shows the percentages of radioactivity in blood samples before and after the return of the subjects to high altitude.

Recovery of iron in feces

In a first series of experiments 10 students born at sea level were studied—5 after being taken to Morococha (14,900 feet) and 5 at sea level. Thirty mg. of labeled iron as ferrous sulfate were given to each one. This small dose was used in order to obtain a greater percentage uptake, thus permitting better analysis of the difference between the amount of iron appearing in the red cells and that eliminated in the feces. The subjects studied at altitude took the iron 3 days after their arrival.

Individual data are presented in table IV. The average value of iron recovered in feces of the group studied at high altitude was 78.1 ±5.6 percent, and in the group studied at sea level it was 91.6 ±2.6 percent. Absorbed iron appearing in the red cells plus that which was assumed to have reached the circulating plasma, but not incorporated into hemoglobin, averaged 19.6 ±6.9 percent in the group observed at high altitude and 5.8 ± 3.0 percent in the group studied at sea level. The total of the iron recovered in the feces plus the amount of iron absorbed in the blood had a mean value of 97.7 percent at high altitude and 98.4 percent at sea level.

The second series of studies of elimination of nonabsorbed iron was carried out in a group of 4 natives of high altitude 8 days after their arrival at Lima (sea level). For comparative purposes, observations of the same type were made on 5 subjects native to the sea level environment and studied there. In both groups, 100 mg. of iron were administered as ferrous sulfate. The average value for iron recovered in feces was 96.0 ± 2.4 percent in the natives of altitude brought down to sea

TABLE IV

Percentage of iron uptake and fecal elimination of nonabsorbed iron at sea level and 3 days after arrival at Morococha (after dose of 30 mg.)

At sea level					After arrival at Morococha				
Subject	Iron appearing in RBC	Fe reaching plasma but not RBC (estimated)	Iron eliminated in feces	Total iron	Subject	Iron appearing in RBC	Fe reaching plasma but not RBC (estimated)	Iron eliminated in feces	Total iron
1	2.1	0.4	96.3	98.8	1	15.7	0	83.2	98.9
2	7.0	1.3	88.2	96.5	2	15.3	0	83.5	98.8
3	7.0	1.3	90.2	98.5	3	23.4	0	75.4	98.8
4	10.2	1.7	90.7	102.6	4	12.1	0	79.8	91.9
5	2.7	0.5	92.6	95.8	5	31.3	0	68.6	99.9
Mean	5.8	1.0	91.6	98.4	Mean	19.6	0	78.1	97.7
S.D.	±3.0	—	±2.6	—	S.D.	±6.9	—	±5.6	—

TABLE V

Percentage of iron uptake and fecal elimination of nonabsorbed iron in high altitude natives 8 days after arrival at sea level compared with sea level normals (after dose of 100 mg.)

Normals at sea level					Morococha natives 8 days after arrival at Lima				
Subject	Iron appearing in RBC	Fe reaching plasma but not RBC (estimated)	Iron eliminated in feces	Total iron	Subject	Iron appearing in RBC	Fe reaching plasma but not RBC (estimated)	Iron eliminated in feces	Total iron
1	4.1	0.6	95.0	99.7	1	1.1	0.7	98.2	100.0
2	3.5	0.5	93.7	97.7	2	1.8	1.2	92.1	95.1
3	4.0	0.6	89.6	94.2	3	1.3	0.9	95.5	97.7
4	1.5	0.2	96.8	98.5	4	0.9	0.6	98.0	99.5
5	4.0	0.5	92.2	96.7					
Mean	3.4	.5	93.5	97.4	Mean	1.3	.8	96.0	98.1
S.D.	± .9	—	±2.7	—	S.D.	± .3	—	±2.4	—

level. Adding the absorbed iron found in blood (correction factor included) gives a total of 98.1 percent. In the group of sea level subjects studied in Lima, the iron found in feces was 93.5 ±2.7 percent; when the iron absorbed in blood (corrected) is added, the total is 97.4 percent. See table V.

It should be noted that in the four groups just described there were individual variations in the total amount of iron recovered in blood and feces. In most cases the total was below 100 percent of the given dose. Our findings are similar to those of Bothwell et al. (2), whose technic we used.

DISCUSSION

The observations presented here indicate that changes in altitude produce modifications in iron absorption. These variations are closely related to the demand for this element in connection with erythropoietic activity. Iron absorption was increased three to four times during early exposure to high altitude, a period during which a marked hyperactivity of the red blood cell precursors has been demonstrated (3). On the other hand, there was a decrease in iron absorption during descent from high altitudes, coincidental with a depression of bone marrow activity (3, 7); however, permanent residents of high altitude, in whom equilibrium of erythropoietic activity was demonstrated previously (3, 8, 9), did not show a significant difference in iron absorption as compared with people born and living at sea level. As for altitude effects, these observations suggest that intestinal absorption of iron is stimulated by variations in iron uptake by bone marrow and in production of red cells, rather than by oxygen saturation of the blood or oxygen pressure at the intestinal level. Only in this way can one explain the finding of no significant elevation or iron absorption in altitude natives studied in their own locality (14,900 feet) despite their arterial oxygen saturation of 80 percent. The close relationship between the level of red cell production and iron absorption suggests that the regulating mechanisms of iron absorption during altitude changes must take place in intimate relation to or through a mechanism similar to that controlling erythropoiesis, which is generally believed now not to be brought about by direct action of the changes in oxygen pressure or content on the erythropoietic tissues (9-14).

The fact of no increase in the appearance of previously administered labeled iron in the red cells of altitude residents recently brought to sea level and then returned to high altitude indicates that the iron absorbed in these subjects did not take part in the "labile pool" (15). In other words, all the absorbed iron went either for hemoglobin formation or for the fulfillment of other biologic needs.

The studies on fecal recovery of nonabsorbed iron tend to confirm the modification of normal iron absorption during changes in altitude. This modified iron absorption is interpreted on the basis of the quantity incorporated in red cells plus the small amount presumed to reach the circulation but not utilized in hemoglobin synthesis. It is necessary, however, to make individual analyses of these determinations. It has been seen that the total amount of iron in feces and blood (corrected) was in nearly all cases less than 100 percent of the given dose. In some subjects the amount of unrecovered iron was as high as 10 percent. This could be attributed to incomplete collection of feces, but assuming that collection was thorough, it may still be accounted for by the removal of the remaining fraction by the liver during primary passage through that organ by the portal circulation and its storage, probably in the form of hemosiderin, which is difficult to mobilize. This phenomenon may occur in subjects who have low iron reserves, but there may be some other unknown causes.

Finally, it should be pointed out that the stimulation or depression of red cell production due to altitude changes offers a fertile field for studies on the mechanisms of iron absorption.

SUMMARY AND CONCLUSIONS

The absorption of iron in the form of ferrous sulfate has been studied in 82 subjects

and under various conditions of altitude exposure. From the observations made, the following conclusions can be deduced:

1. Intestinal absorption of iron increased during the first days of exposure to an altitude of 14,900 feet and reached a maximum at the end of a week. It was less marked 4 weeks later.

2. Iron absorption decreased in natives of high altitude brought down to sea level, reached a minimum in 3 weeks, and then returned to normal within 16 months.

3. Iron absorption was essentially the same in natives from high altitude as in sea level subjects when each was studied in his own locality. The slightly higher values in altitude subjects lacked statistical significance.

Studies on the recovery of iron in feces confirmed the changes that were interpreted on the basis of the amount of iron appearing in the red blood cells plus the iron that presumably reached the circulating plasma but was not used in red cell formation. The possible significance of failure in some cases to recover a small fraction of the total iron that was administered is discussed.

REFERENCES

1. Granick, S. Iron metabolism. Bull. N.Y. Acad. Med. 30:81-105 (1954).

2. Bothwell, T. H., G. Pirzio-Biroli, and C. A. Finch. Iron absorption. J. Lab. Clin. Med. 51:24-48 (1958).

3. Reynafarje, C., R. Lozano, and J. Valdivieso. The polycythemia of high altitudes: Iron metabolism and related aspects. Blood 14:433-455 (1959).

4. Moore, C. V., R. Dubach, V. Minnich, and H. K. Roberts. Absorption of ferrous and ferric radioactive iron by human subjects and by dogs. J. Clin. Invest. 23:755-767 (1944).

5. Saylor, L., and C. A. Finch. Determination of iron absorption using two isotopes of iron. Amer. J. Physiol. 172:372-376 (1953).

6. Dubach, R., S. T. E. Callender, and C. V. Moore. Studies in iron transportation and metabolism. VI. Absorption of radioactive iron in patients with fever and with anemias of varied etiology. Blood 3:526-540 (1948).

7. Huff, R. L., J. H. Lawrence, W. E. Siri, L. R. Wasserman, and T. G. Hennessy. Effects of changes in altitude on hematopoietic activity. Medicine 30:197-217 (1951).

8. Merino, C. F. Studies on blood formation and destruction in the polycythemia of high altitude. Blood 5:1-31 (1950).

9. Hurtado, A., C. F. Merino, and E. Delgado. Influence of anoxemia on the hemopoietic activity. A. M. A. Arch. Intern. Med. 75:284-326 (1945).

10. Carnot, P., and O. Deflandre. Sur l'activité hémopoïetique des différents organes au cours de la régénération du sang. Compt. rend. Acad. d. sc., Par. 143:432-435 (1906).

11. Stohlman, F., Jr., C. E. Rath, and J. C. Rose. Evidence for humoral regulation of erythropoiesis; studies on patient with polycythemia secondary to regional hypoxia. Blood 9:721-733 (1954).

12. Reissmann, K. R. Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia. Blood 5:372-380 (1950).

13. Gordon, A. S., S. J. Piliero, W. Kleinberg, and H. H. Freedman. A plasma extract with erythropoietic activity. Proc. Soc. Exp. Biol. Med. 86:255-258 (1954).

14. Merino, C. F. The plasma erythropoietic factor in the polycythemia of high altitudes: Preliminary report. USAF School of Aerospace Medicine Report 56-103, Nov. 1956.

15. Dubach, R., C. V. Moore, and V. Minnich. Studies in iron transportation and metabolism. V. Utilization of intravenously injected radioactive iron for hemoglobin synthesis, and an evaluation of the radioactive iron method for studying iron absorption. J. Lab. Clin. Med. 31:1201-1222 (1946).

16. Greenberg, G. R., and M. M. Wintrobe. A labile iron pool. J. Biol. Chem. 165:397-398 (1946).