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# Anemia and Erythropoietin in Space Flights

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**Since the very early manned missions in space, a state of anemia associated with reduced erythropoietin levels and reduced plasma volume was disclosed. The reduction in red blood cell mass is driven by a process of selective hemolysis, which has been named *neocytolysis*. This phenomenon also occurs in people living at a high altitude who descend rapidly to sea level. The origin of the signal leading to destruction of newly produced red blood cells probably is located in central circulation, but the operating mechanism is unknown. The importance of plasma cell volume reduction in the genesis of a lower red cell mass also is supported by the inverse correlation seen at moderate altitude. People arriving at moderate altitude have increased erythropoietin concentration that decreases after a few days and is in inverse correlation with central venous pressure. Studies under simulated microgravity conditions in human beings (bed rest, head-down tilt at −6°, water immersion) and in rats provide further insight in unraveling the mechanism of astronauts' anemia, a problem difficult to study in space because of the limited availability of spaceflights.**
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**KEYWORDS** space, anemia, blood volume, plasma volume, astronauts, bed rest, head-down bed rest, water immersion, suspended rats, Gauer-Henry reflex

The history of space conquest started on October 4, 1957, when Russians launched Sputnik 1, which was followed by the manned mission of Yuri Gagarin on April 12, 1961, with Vostok 1.[1,2] The development of programs both by the Soviet Union and by the United States started the era of human adaptation to microgravity conditions, which is associated with significant organ alterations. In fact, our ancestral predecessors (Australopithecines) evolved in the Rift Valley of East Africa (under mild altitude hypoxia that was aggravated by colder and drier climates[3-6]). Therefore, an increase in blood volume and an increase in red blood cell mass (RBCM) occurred. That also means that an increased whole-body oxygen transport capacity was acquired. In the same location they also acquired the bipedal position. Because of the height of the site (1,000-2,000 meters above sea level) their hemoglobin concentration increased and therefore human beings now live with a surplus of 2 g/dL of hemoglobin (Hb). To survive, we need 77.5 mL of blood per kg of body weight, 70% of which is contained below heart level.[3-6] This is a unique condition.

Human biology and human health in space became a hot topic by necessity and now we can exploit the knowledge obtained in space to handle diseases here on Earth. Therefore, it is not surprising if a very popular logo of the European Space Agency is for Research in Space for Health on Earth. The topic of anemia gives emphasis to this concept because it deals with a cause of anemia originating from RBCM exceeding bodily needs.

Astronaut anemia immediately became a stimulating topic both for Soviet and United States missions. Interesting data were collected during Gemini IV and Gemini V missions, the former lasting 4 days and 56 minutes, the latter lasting 7 days, 18 hours, and 56 minutes. Plasma volume, red cell mass, and the total body-to-peripheral-hematocrit ratio were reduced. Data indicated a decrease of RBCM of 12.2% in Gemini IV and of 20% in Gemini V. Plasma volume underwent a reduction of 8.3% in Gemini IV and of 6.75% in Gemini V. The decrease in RBCM was seen as a result of a mild hemolysis of unknown cause.[7]

In 1982, Cogoli[8] reviewed reports appearing from 1975 to 1979.[9-16] Figures 1 and 2 are based on those data[9-16] and

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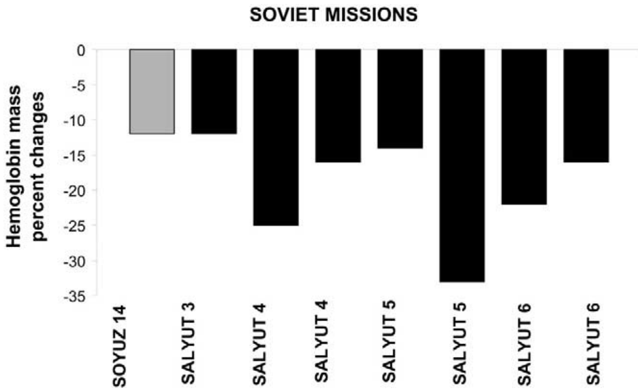


**Figure 1** Changes of RBC mass in Soviet Missions. Data from Johnson et al,[9] Kimzey and Johnson,[10] Balkhovsky et al,[11] Legen'kov et al,[12] Rudniy et al,[13] Gazenko et al,[14] Yegorov,[15] and Johnson et al.[16]

show the percent changes in Hb mass in Soviet missions and the percent changes of RBCM in US missions. In the course of 8 Soviet missions, the reduction was in the range of 12% to 33%. In 9 US missions the decrease in RBCM was in the range of 2% to 21%. The relationship between changes of RBCM and changes of plasma volume in various US missions is shown in Figure 3. In 1982 another review put a major emphasis on erythroid hypoplasia of the marrow and on suppressed erythropoiesis as a cause of astronaut anemia.[5]

## Experimentum Crucis

To understand the pathophysiology of astronaut anemia, Leach et al[17,18] addressed the problem of increased destruction/reduced production of RBCs during space missions with an interesting protocol. They performed the *experimentum crucis*, after Francis Bacon and Isaac Newton; meaning to find the proper way at cross roads: the experiment which helps to find the proper direction at the cross roads. They studied the influence of microgravity conditions on factors involved in erythrokinetics in the course of a 10-day Spacelab 1 mission in November of 1983. Results were published in 1984 and 1988. A report that appeared in *Science*[17] provided data on erythrocyte levels, Hb levels, plasma levels, blood volume,

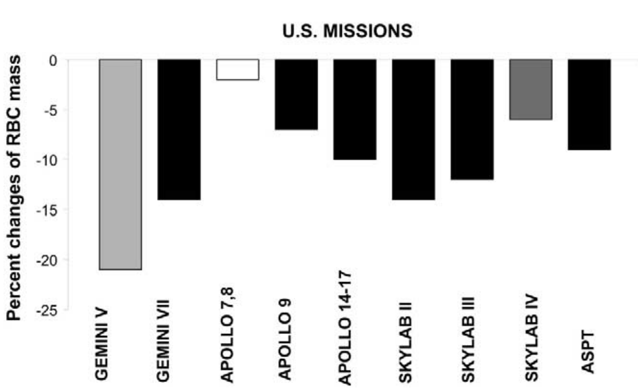


**Figure 2** Changes of RBC mass in US missions. Data from Johnson et al,[9] Kimzey and Johnson,[10] Balkhovsky et al,[11] Legen'kov et al,[12] Rudniy et al,[13] Gazenko et al,[14] Yegorov,[15] and Johnson et al.[16]

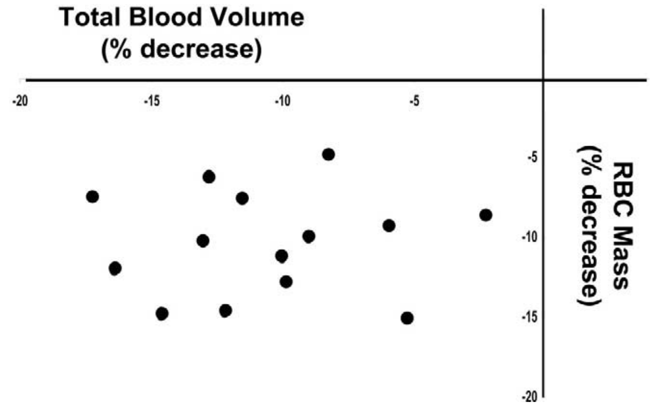


**Figure 3** Relation between RBCM and plasma volume changes in 14 US missions.

reticulocytes, and RBCM. Figure 4 is compiled from that report and is centered on Hb changes in space in relation to preflight concentrations. Blood was drawn before flight, during inflight days 1 and 7, on landing, and on postflight days 1, 8, and 12/13. On postflight day 8, the Hb concentration was reduced by 10.3% ± 0.7% ($P < .05$ versus preflight), and on postflight day 12/13 the reduction averaged 8.8% ± 1.3% ($P < .05$). RBCM before flight averaged 27.54 ± 0.57 mg/kg body weight and was reduced significantly on landing by −9.3% ± 1.67.8% and on postflight day 8 by −6.04% ± 0.72%. On postflight days 12/13, RBCM was not different from preflight concentrations, thus indicating that the loss of RBCM was around 1% per day. This finding lead the investigators to exclude any space-related inhibition on erythropoiesis.

When Leach et al[18] finally were able to measure erythropoietin concentration correctly, they found that a significant reduction in its level occurs from preflight day 1 and still was evident on landing. During postflight days a trend of erythropoietin concentration to increase greater than the preflight value was uncovered. The increase was significant on postflight days 12/13 (Fig 5). Erythropoietin positively correlated with reticulocyte count, thus suggesting a correlation with RBC production.

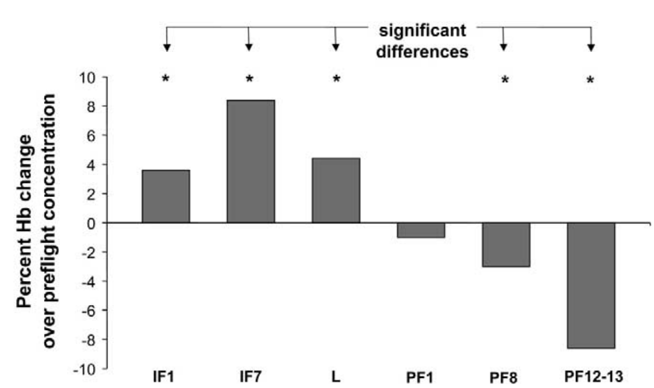


**Figure 4** Hb level changes during Spacelab 1 mission. IF, inflight day; L, landing; PF, postflight day. Data from Leach and Johnson.[17]