SEMINARS IN
NEPHROLOGY

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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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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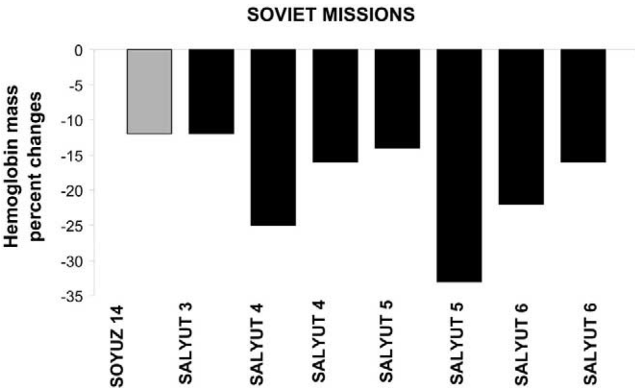

Figure 1 Changes of RBC mass in Soviet Missions. Data from Johnson et al,[9] Kimzey and Johnson,[10] Balkhovsky et al,[11] Legen'kov et al,[12] Rudniy et al,[13] Gazenko et al,[14] Yegorov,[15] and Johnson et al.[16]

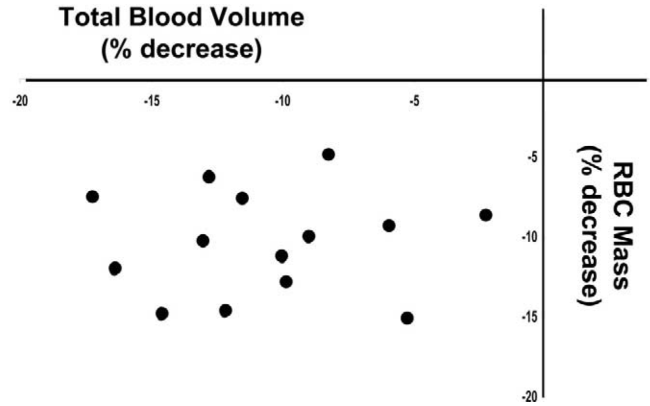

Figure 3 Relation between RBCM and plasma volume changes in 14 US missions.

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, 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.

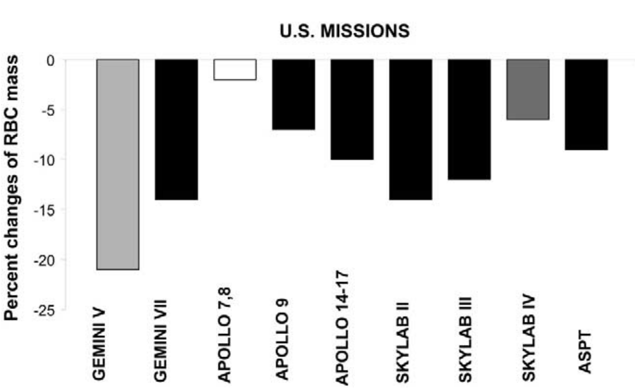

Figure 2 Changes of RBC mass in US missions. Data from Johnson et al,[9] Kimzey and Johnson,[10] Balkhovsky et al,[11] Legen'kov et al,[12] Rudniy et al,[13] Gazenko et al,[14] Yegorov,[15] and Johnson et al.[16]

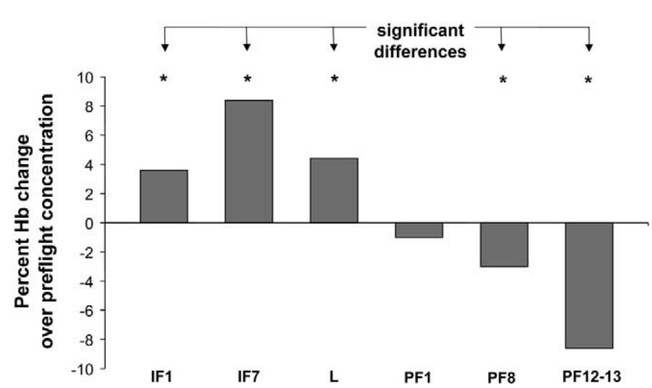

Figure 4 Hb level changes during Spacelab 1 mission. IF, inflight day; L, landing; PF, postflight day. Data from Leach and Johnson.[17]

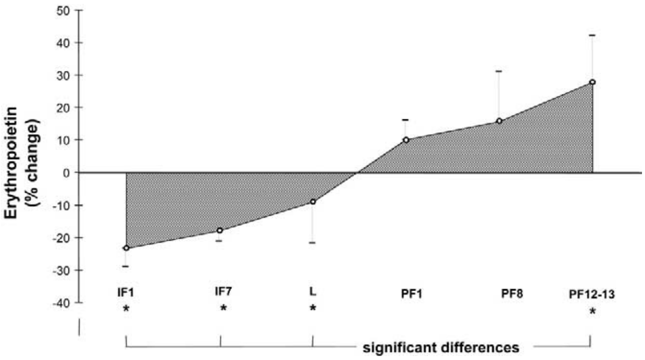

Figure 5 Erythropoietin changes during Spacelab 1 mission. IF, inflight day; L, landing; PF, postflight day. Reprinted from Leach et al[18] with permission from Elsevier.

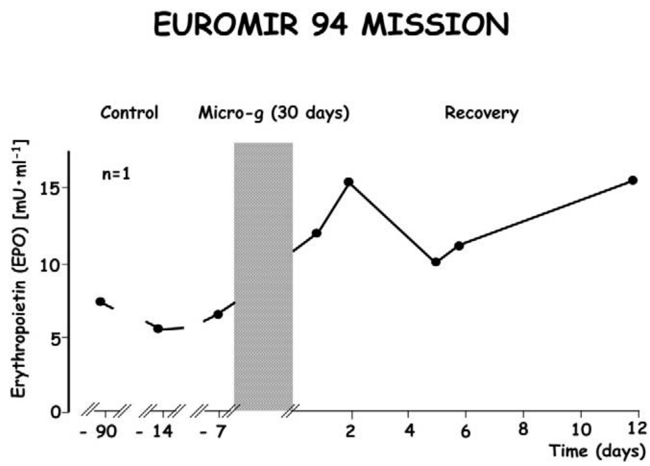

Figure 7 Erythropoietin time course during Euromir 94 mission lasting 30 days. Modified from Gunga et al.[5]

European Studies

Erythropoietin concentration was measured in 1 cosmonaut and 6 controls. In the cosmonaut, before flight, the erythropoietin concentration was 15.1 mU/mL, immediately after landing the erythropoietin concentration was 12.1 mU/mL, and on postflight day 7 the erythropoietin concentration was 25.0 mU/mL (in excess to the ± 3 standard deviations (SD) range). The control group showed small variations within the ± 3 SD range.[19]

In a short-term space flight (<10 days) in the course of the German D-2 mission,[5,20,21] considerable interindividual variations in the erythropoietin adaptation to microgravity was disclosed in the 4 participating astronauts (Fig 6). The erythropoietin concentration averaged 9.3 ± 2.2 mU/mL (mean ± SD) 2 days before flight, 6.0 ± 5.15 mU/mL on inflight day 4, 5.6 ± 3.3 mU/mL immediately after landing, 7.4 ± 3.4 mU/mL on day 7 after landing, and 11.0 ± 2.1 mU/mL on day 15 after landing. These data were in good keeping with those of Leach et al[17,18] described previously. The study also disclosed the absence of a circadian rhythm, a finding not confirmed by Branch et al.[22]

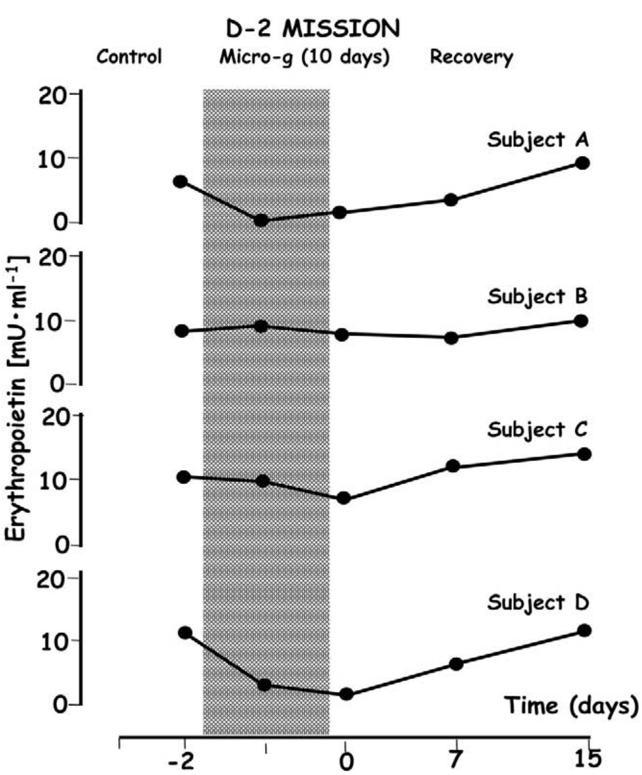

Figure 6 Percent erythropoietin changes during German 2 mission in 1993 lasting 10 days. Modified from Gunga et al.[5]

Data from a midterm mission lasting 30 days (Euromir 94) showed (Fig 7) an increased erythropoietin concentration on postflight days 1, 2, 5, 6, and 12. Postflight concentrations exceeded preflight value by 50% to 100%.[23]

Gunga et al[5,21] studied 1 cosmonaut during a long-term space mission lasting 135 days (Euromir 1994-E). The erythropoietin concentration was 14.4 mU/mL at 14 days before the launch, 19.4 mU/mL (+34.7%) on day 1 after landing, 46.3 mU/mL(+221.5%) on day 2 after landing, and 43.1 mU/mL (+199.3%) on day 5 after landing. The Hb concentration decreased from 15.3 g/dL before launch to 12.4 g/dL 2 days after landing (Fig 8). These data hold great potential because they refer to erythrocytes produced under microgravity conditions and should be matched with Russian data obtained in long missions lasting 96 to 185 days.[5,20,21]

During the German Mir 97 mission, Gunga et al[5,24] studied erythropoietin concentration (Fig 9), transferrin receptor, thrombopoietin, and vascular endothelial growth factor. The data pointed to a low inflight erythropoietin and transferrin receptor concentration. Thrombopoietin increased during microgravity days and decreased postflight. Vascular endothelial growth factor was doubled during early inflight days and decreased thereafter, thus suggesting an association with intravascular fluid shift.

The Advent of Neocytolysis

On Gemini V, red cell mass was studied by labeling red cells 7 days before launch. A shortened survival was observed. However, when experiments were planned for Gemini VII, RBCs were labeled 10 days before launch, and a normal sur-

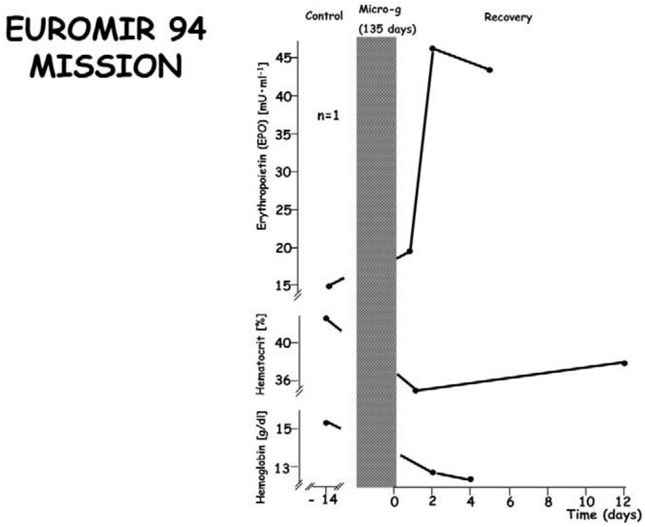

Figure 8 Erythropoietin, Ht, and Hb changes during the Euromir 1994-E mission lasting 135 days. Modified from Gunga et al.[5]

vival rate was seen. It is a pity that the value of the experiment on Gemini V indicating death of younger RBCs was not understood and was explained as a result of mild hemolysis from unknown causes. This was the silent birth of neocytolysis in space, a process of selective hemolysis.[7,25]

It also should be taken into consideration that studies on Apollo, Skylab, and Spacelab 1 missions disclosed a decrease of reticulocytes, pointing either to reduced eryhropoiesis, a hemolytic process, and/or a sequestration mechanism.

In 1995, Udden et al[25,26] reported data obtained from 3 crew members of the NASA shuttle mission STS-40 lasting 9 days who were injected with 51Cr-RBCs 21 days before launch. They showed (Table 1) that blood volume was reduced by 12% from the second inflight day to landing. The study also evaluated (1) RBCM, which was reduced by 12% during inflight days; (2) plasma volume, which was reduced by 23% during inflight day 2 and by 12% at the end of the space mission; (3) serum erythropoietin, which was suppressed immediately after launch and remained low during the mission and increased after landing as a response to postflight anemia; and (4) iron erythron turnover, which was normal. The study disclosed a very rapid change in plasma volume (although a long-lasting suspicion had been made, no data existed in the literature) and, more importantly, showed an increased ratio of total body to venous hematocrit under microgravity (0.88 at 1 gravity and 1.01 during inflight day 2), thus showing that astronauts were in a status of plethora.

Finally, serial measurements of 51Cr counts/min × mL RBC were performed and the slope of the time-dependent changes was calculated. The slope depended on the dilution of RBC by new unlabeled cells, and from the rate of 51Cr elution from labeled cells. The slope of the function during flight was significantly less ($P < .01$) than the preflight value. Thus, the study disclosed a lack of replacement with younger RBCs.

In another study performed on 6 crewmembers from the

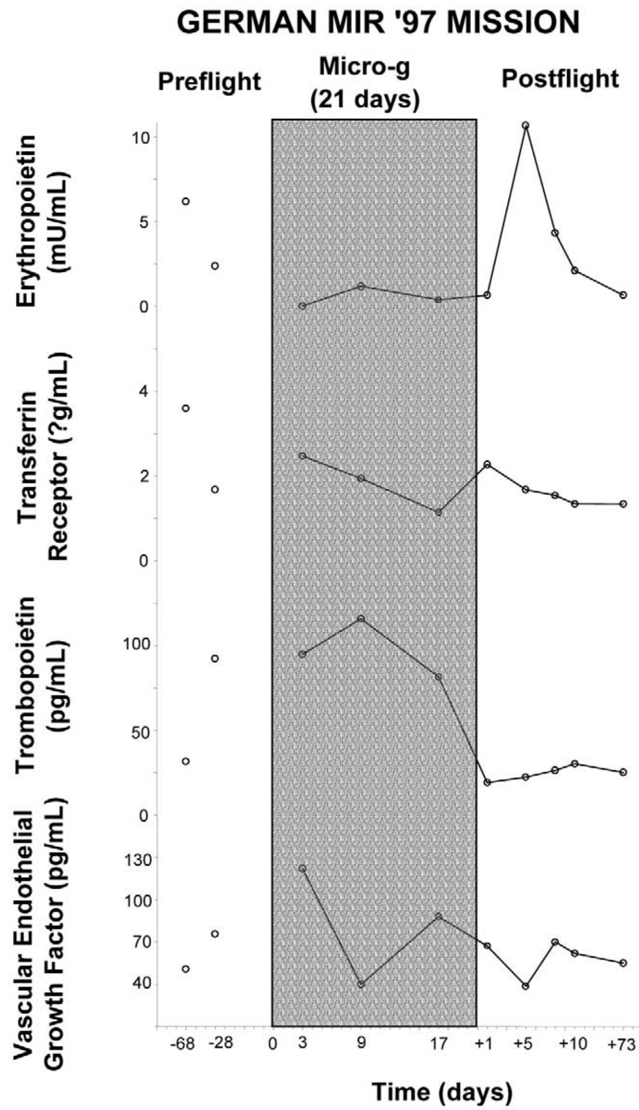

Figure 9 Erythropoietin levels during German Mir 97 mission lasting 21 days. Modified from Gunga et al.[5]

US SLS1 and SLS2 missions, the same group[25] indicated that specific 51Cr activity exceeded predicted values of 6%. The relative inflight increase in 51Cr-specific activity indicated that fewer new RBCs were produced. They associated this

Table 1 RBCM and Total Blood Volume in 3 Crew Members of STS-40 at 1*g* and During Inflight Days 2 and 8

Crew Member	1 *g*	IF2	IF8
RBMC (mL)			
1	1,676	1,654	1,518
2	2,216	2,191	2,043
3	1,829	1,806	1,668
TBV (mL)			
1	4,953	3,800 (−1153)	4,467 (−486)
2	5,777	5,046 (−731)	5,154 (−623)
3	5,777	4,794 (−456)	4,808 (−532)

Data from Udden et al.[25]

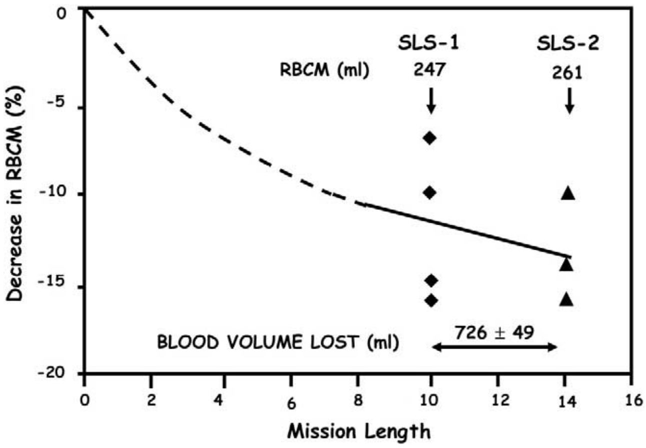

Figure 10 Red blood cell mass and mission length. Reprinted from Udden et al[25] with permission from the American Physiological Society.

finding with data that were published early in the 1950s that was related to resident highlanders descending rapidly to sea level.[27-29] Alfrey et al[30,31] and Rice et al[32,33] therefore were ready to propose the mechanism of neocytolysis, a physiologic down-regulator of red cell mass in space and on descent from altitude. The mechanism allows quick adaptation to an RBCM exceeding needs. This is not caused by erythropoietin changes, which need at least 6 days to achieve its effects. Practically, a space mission lasting 10 days corresponds to an approximately 700-mL blood phlebotomy (Fig 10), aggravated by the inability to reinstate plasma volume loss. The process is self-limited and can reduce red cell mass by 10% to 15% and is driven by the level of plethora and by the level of erythropoietin. It has been suggested that erythropoietin acting on endothelial cells induces cytokine production, which in turn affects phagocytes by influencing the expression of adhesion molecule receptors on neocytes.

What Will Occur on Mars?

Harris and Epstein[34] have made the case of astronauts going to Mars where gravity is 38% of that on Earth, thus allowing the voyagers to have some blood redistribution. However, out of cabin on Mars they will have the problem of atmospheric pressure, which is 0.14 PSI compared with 14.7 PSI on Earth, associated with a gravity that is 38/100 of that on Earth.

Neocytolysis in Patients on Maintenance Hemodialysis

Studies on astronaut anemia offer a sound theoretical and practical demonstration that a lot may be learned in space to promote life on Earth. Studies at the Methodist Hospital in Houston[35] have shown that neocytolysis occurs even in patients on maintenance hemodialysis with a baseline erythropoietin level of less than 25 U/mL 3 days after the last weekly injection (usual dose 50 μg/kg 3 times/wk). By analyzing the 51Cr-RBC survival curve it was possible to observe that the slope during the first 9 days when erythropoietin was withheld was steeper than the slope from day 10 onward ($-3.15\% \pm 0.30\%$ versus $-1.32\% \pm 0.25\%$) ($P < .02$). The study also provided evidence for a normal isotopic enrichment of stool porphyrins during erythropoietin therapy, which increased after erythropoietin withdrawal for 10 days. Therefore, it was possible to conclude that to prevent the risk for neocytolysis, patients on maintenance hemodialysis should avoid erythropoietin administration schedules associated with hormonal levels going from peaks to nadirs and vice versa.[35,36]

Effects of Head-Down Tilt on Erythropoietin Levels

The model of head-down tilt (−6°) has been used as a model of spaceflight for more than 30 years and is associated with cephalic fluid shift. Data obtained in the course of a well performed study in human beings are available on the effects on erythropoietin, Hb, and hematocrit levels.

Leach and Johnson[17] compare data on Spacelab 1 with data obtained during a head-down (−6°) bed rest study of identical length (10 days) in young people matched for age, sex, and weight. At the end of the head-down study the data showed a statistically significant reduction of plasma volume (which had not been found in space), and a reduction of RBCM that was disclosed on postflight day 8, whereas in real microgravity on Spacelab 1 it had appeared on landing. So, the effects on erythrokinetic were less pronounced during and after the head-down tilt. However, the observation period might have been too short for this purpose.

A group of 8 young men were enrolled for a head-down tilt study of 6 weeks duration followed by an additional recovery week.[5,21] During the study erythropoietin levels were measured, and subsequently the patients were followed-up for an additional week. Blood was drawn 2 days before patients were placed in tilt position (pre-2), on head-down tilt days 2, 14, 28, 35, 42, and on recovery days 1 and 7. In total, there were 8 blood samples, for a total volume of less than 500 mL in 51 days.[21]

In general (Fig 11), a statistically significant suppression of

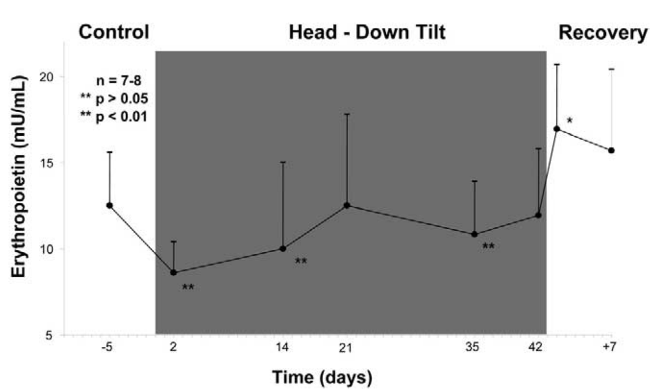

Figure 11 Erythropoietin levels during 6 weeks of head-down tilt. Modified from Gunga et al.[21]

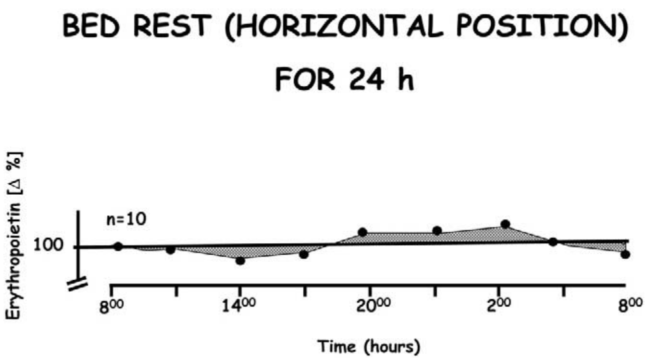

Figure 12 Erythropoietin during bed rest. Absence of a circadian rhythm. Reprinted from Gunga et al[21] with permission from the American Physiological Society.

erythropoietin levels occurred while on head-down tilt. A nadir concentration was disclosed on head-down day 2 and a peak on recovery day 1 (+41%). Significant changes of Hb concentrations occurred during the head-down tilt as shown in Table 1.

However, data were not confirmed during a 16-day head-down tilt at −6° in 7 adult men. Possible reasons for this include the following: (1) experiment was not long enough, (2) RBC volume was not bound tightly to erythropoietin, (3) dissociation between RBC volume and erythropoietin, (4) decreased responsiveness of colony-forming units-erythroid (CFU-e) to erythropoietin, and (5) downregulation of CFU-e.[22]

Bed rest is the most commonly used model to investigate the effects of microgravity on Earth. Gunga et al[21] studied the effects of 24-hour bed rest (8 AM to 8 AM on erythropoietin concentration in 10 young healthy men in the horizontal position who were allowed water and food ad libitum. Blood was drawn every 3 hours. The study showed the stability of erythropoietin concentration over time (Fig 12), which pointed to the absence of a circadian rhythm.[21] These results are at variance with data on hospitalized patients[37] and with data from Branch et al.[22]

Effects of Head-Out Water Immersion on Erythropoietin

Head-out water immersion, which has been used as a microgravity model during the past 40 years, was applied to 8 young healthy men at the University of Berlin[21] to investigate its effects on erythropoietin levels. The immersion time in warm water lasted 60 minutes. Erythropoietin levels were studied 60 minutes before immersion, after 30 minutes of immersion, and 15 minutes and 24 hours after immersion. The data in Table 2 show increased erythropoietin levels 24 hours after immersion. The procedure decreased the central venous pressure of 4 cm H_2O, corresponding to a phlebotomy of 600 mL of blood. The data point to an activation of receptors of the intrathoracic low-pressure system. These findings are in good keeping with the findings of Miller et al[38] in human beings, showing that a phlebotomy of 450 mL induces a 50% increase of erythropoietin levels and an increase of reticulocyte counts. Furthermore, they are in agreement with the findings of Ehmke et al[39] in conscious dogs showing that a 20% reduction of blood volume by hemorrhage increases erythropoietin levels 1.5-fold within 5 hours. In that study, a 3-fold increase of erythropoietin levels was achieved through a 0.12-hematocrit level reduction in the course of an isovolemic exchange transfusion replacing blood with dextran.

Anemia in Rats Under Real and Simulated Microgravity

Iliyn et al[40] studied the various effects of space flight in rats aboard the Cosmos-605 Biosatellite for 22 days (36 of 40 animals survived under microgravity conditions). The study included peripheral blood counts during the first postflight day and they compared them with rats living at 1g. The data showed the stability of RBC counts, hemoglobin level, and hematocrit level, and a decrease in reticulocyte and in erythroblastic cells, as well as a reduction of the erythroid and lymphocitary elements in the spleen. Thus, a suggestion that accelerated hemolysis takes place in space could be made.

Leon et al[41] in 1978 reported on RBC survival in rats after 19.5 days aboard Cosmos 782 and showed a shortened lifespan (−5.4%) and an increased hemolysis. In rats aboard Cosmos 936 (18 days in space) and Cosmos 1129 (19 days under microgravity), humoral and femoral bone marrow was studied, and showed (compared with a control group on Earth) a reduced number of CFU-s, which went back to normal on the 25th day postflight. Increased hemolysis caused by weightlessness also has been shown,[42] which could be counteracted by simultaneous centrifugation by normalizing the hemolytic rate during the postflight early stages.

Hemathopoiesis also was studied by Dunn et al[43,44] in a terrestrial model of antiorthostatic hypokinetic/hypodynamic rats (suspended rats) suitable to mimic some cardiovascular,[40] bone,[41] and muscle changes,[45] associated with the cephalic fluid shift occurring in space, by adopting a head-down angle of 20°. Animals were studied before, during, and after a 7-day suspension. Results showed a reduced plasma and blood volume, reduced RBCM, transient increase of hematocrit level, erythropoietin suppression, and reduced mean corpuscolar volume (MCV). The reticulocyte count was suppressed during suspension and normalized after 7 days, radioiron was suppressed during suspension and normalized thereafter. In general, the effects in rats were of greater magnitude than in human beings. Although it is dif-

Table 2 Effects of Water Immersion on Erythropoietin

Experimental Setting	Erythropoietin (mU/mL)
1 hour before immersion	15.5 ± 3.4
30-minute immersion	16.7 ± 2.7
15 minutes after immersion	16.1 ± 3.2
24 hours after immersion	19.8 ± 4.6*

*Statistically significant changes. Data from Gunga et al.[21]

ficult to speculate by using rats because of their high metabolic activity,[5] the role of the different head-down angle between men and rats (−6° versus −20°) might prove relevant. However, Lange et al,[46] in rats studied during the 8-day Spacelab-3 mission, showed increased RBC, hematocrit, and hemoglobin levels in the presence of a normal bone marrow, normal spleen cell differentials, and normal erythropoietin concentration.

Is a Reduced Plasma Volume a Prerequisite to Reduced Blood Cell Mass?

Changes in plasma volume and the reduction of erythropoiesis in spaceflight always have been described as associated. The studies on neocytolysis showed the existence of this link. The study on the descent from altitude to sea level also implied this link, thus showing that the signal to reduce RBCM originates in central circulation. However, we are far from knowing the mechanism. Regarding data in space, we know that in moderate altitude, people showed increased erythropoietin concentrations in plasma after ascent,[6] but a few days later the concentration was reduced, in association with a reduction in central venous pressure.

According to Kirsch,[6] we have to explore further the relationship between reduced plasma volume and reduced RBCM, which might be essential for the fine regulation of oxygen transport. Therefore, Kirsch[6] integrated the reduction in RBCM in the Gauer-Henry reflex loop.

Effects of Spaceflight on Stem Cell Erythropoiesis

Studies aboard shuttle missions Discovery (STS-63) and Endeavor (STS-69) have disclosed significant effects on CD34+ bone marrow progenitor cells cultured in vitro.[47] During the 11 to 13 days under microgravity conditions, a reduction of total cell numbers occurred, along with an increased acceleration of maturation and differentiation of primitive stem cells toward the macrophage lineage. A reduction in erythroid progenitors and glycophorin a–positive cells occurred, which was independent of erythropoietin, thus pointing to a direct effect.

Are There Any Additional Factors in the Genesis of Spaceflight Anemia?

There are other factors in the genesis of astronaut anemia, and we are far from exhausting our knowledge. The role of reticuloendothelial cells and their relation to signals received from endothelial cells and the erythropoietin receptors on the latter cells, are of paramount importance.[32] In addition, epinephrine/norepinephrine depletion, which occurs in space, might have a role. This suspicion is corroborated by findings in the Bradbury-Eggleston syndrome, which is characterized by norepinephrine/epinephrine depletion. In such patients, those who have the lowest cell mass also show the most depleted sympathetic nerve activity and a reduced erythropoietin response.[48]

Effects of Space Flight on Iron Metabolism

In space, ferritin levels increase by 50% to 60%,[49] which indicates that there is increased iron storage originating from hemolysis of newly formed RBCs.[50,51] However, the increase of ferritin levels might be caused by inflammation. Therefore, iron content in ferritin has to be measured to overcome this bias.[52] With this approach a decrease in the iron content of ferritin has been shown. On the other hand,[53] the concentration of transferrin receptors (which is reduced by iron load) was found to be reduced after flight.[49] Finally, one has to take into consideration that dietary iron intake is high in space,[54] also because of increased reabsorption owing to the limitation of fibers in foods.[49]

Conclusions

We have reviewed data originating from space related to research in real and simulated gravity conditions in human beings and animals. Space-related research has shown that astronaut anemia is not different from that seen in people rapidly descending to sea levels from a high altitude. Adaptation to microgravity halts the release of new RBCs, selectively hemolyzes newly formed RBCs, and normally destroys old RBCs. This is made possible through an adaptation process that starts by sensing a reduced request for blood, probably driven by easier oxygen delivery. Anemia is associated with reduced erythrocyte volume and with intracellular volume, which tends to increase.[55]

At the very beginning of the space era, because of the preoccupation with the future of the space enterprise, the point was made that anemia developing in space was not a life-threatening event and there was no risk for the average human being going into space. However, the *experimentum crucis* excluding the occurrence of anoxia during extravehicular activities in space has not been performed. Therefore, experiments should be designed to exclude the anoxic complication. Such a study will provide an insight into the adjustment needed to adapt the oxygen supply to needs under microgravity. It is obvious that the use of erythropoietin to prevent anemia may be part of future space-related research.[49]

A final comment—the advent of neocytolysis has been an occasion to create a neologism. It tells us the point from which we left. We started from erythrolysis, a neologism introduced by Pace et al[29] in 1956 to describe RBC destruction occurring in altitude-acclimatized individuals to sea level.

Neocytolysis may have been understood since the Gemini mission.[5] For that mission, 2 astronauts were injected with labeled chromium 7 days before flight. Returning to Earth

Table 3 Studies on Anemia During Spaceflights Gemini V and Gemini VII

Gemini Mission	% Changes PV	% Changes RBCM	^{51}Cr RBC survival (%) Corrected Value	^{51}Cr RBC survival (%) Normal Value
V	−8.9	−21.7	58*	65-78
	−4.6	−21.9	56*	65-78
VII	+17.9	−19.0	48†	51-65
	+10.4	−7.3	54†	51-65

*7 days before launch.
†10 days before launch. Data from Gunga.[5]

they showed reduced plasma volume (−6.75%), reduced RBCM (−21.5%), and decreased ratio between total body hematocrit and peripheral venous hematocrit levels (−8.3%). For the first time it was possible to calculate the survival percentages, corrected for RBCM survival, of 57%, which was below a normal value of 65% to 78%. Data were processed along with data from the Gemini VII mission, whose astronauts had been injected with labeled RBC 10 days before the experiment, and therefore gave different results. As sometimes happens in science, scientists were unable to find the novelty because it was unexpected. Unexpected findings on many occasions introduce the novelty (Table 3).

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