

## Out of Thin Air: The Evolving Enigma of Erythropoietin and Neocytolysis

In this issue, Rice and colleagues (1) explore the mechanisms underlying a rapid decrease in red cell mass that occurs during descent from high altitude to sea level, a process known as *neocytolysis*. The sequence of events that they describe is instructive not only for its physiologic implications but also for its demonstration of how keen observation in one setting can be translated into useful knowledge in another. While it seems logical at first to think of altitude on mountains as analogous to altitude in a spacecraft, in reality the environments could not be more dissimilar. Mountainous altitude is characterized by greatly diminished oxygen availability but gravity conditions that are essentially the same as those at sea level, whereas space travel is characterized by the same oxygen availability as at sea level but in a setting of greatly diminished gravity. How, then, can one condition shed light on the other?

The key issues in this paradox appear to be not only what the red cells see but also where the body sees the red cells. On the one hand, mountain dwellers develop increased red cell mass because oxygen delivery is decreased to oxygen sensors in the renal peritubular cells, stimulating the production of an “enhancer-binding factor” for the erythropoietin (*EPO*) gene. Activation of the *EPO* gene increases the level of erythropoietin itself, which in turn increases erythrocyte production. On descent to sea level, the increased erythrocyte mass, with its increased oxygen content, signals the kidney to shut down erythropoietin production.

Astronauts, in contrast, encounter the mirror image of this sequence. On entering microgravity, capacitance vessels collapse because the weight of the blood no longer forces the vascular walls apart. Blood is then redistributed centrally, where vascular filling is less dependent on gravity. The heart and kidneys then sense increased blood volume and set into motion a series of events that leads to diuresis, producing a 20% decrease in plasma volume over about the next 24 hours (2–4). In the spacecraft setting, oxygen concentration is normal since sea level pressure conditions are maintained at 1 atm. Under these normoxic conditions, hemoconcentration with its attendant increase in hematocrit suppresses

erythropoietin production as effectively as the mountain dweller’s descent from altitude.

Earthbound athletes have taken advantage of the physiologic altitude-associated increases in red cell mass to enhance physical endurance. The unproven hypothesis underlying this idea is that increased blood oxygen-carrying capacity in polycythemic states might improve athletic performance. Since exogenous “doping” with erythropoietin is considered unsportsmanlike at best and illegal at worst (5), the concept of letting the body produce its own erythropoietin seemed both scientifically attractive and morally more acceptable. In the purest moral form of this process, some athletes preparing for the 1968 Olympic Games in Mexico City (2380 meters or 7800 feet above sea level) arrived early and did some of their training at high altitude, presumably increasing both their physical conditioning and their red cell volume simultaneously. Stepping to the edge of the moral slippery slope, studies were then performed on endurance athletes who agreed to sleep at a simulated altitude of 3000 meters in a “nitrogen house” while training at sea level (6). This latter experimental approach, at least in short-term studies, did not increase reticulocyte production or hemoglobin levels. The reasons for this lack of effectiveness are not known with certainty but may be related to the relatively short exposure to hypoxic conditions; the fact that erythropoietin production depends not only on hypoxia but also on additional factors (such as ferritin availability and presence of reactive oxygen species) (7); or, conceivably, the see-saw effect of erythropoietin stimulation followed by neocytolysis.

Rice and colleagues studied the flip side of this question to determine how a sudden decrease in erythropoietin level may have produced a decrease in red cell mass at a rate faster than would be expected from normal erythrocyte aging. They identified an apparent lytic effect on newly minted erythrocytes while leaving the older erythrocytes intact. Although their data provide compelling evidence that flux in erythropoietin levels is associated with such an effect, answers to the complicated question of how blood cell populations are expanded or contracted in response to changing environmental conditions are still incomplete.

Erythropoietin is the chief hemopoietic growth factor that supports viability, proliferation, and differentiation of progenitor cells in the erythroid lineage. The erythropoietin molecule interacts with a specific erythropoietin receptor on these cells. The erythropoietin receptor molecule itself has three different domains: extracellular, transmembrane, and cytoplasmic (8). When stimulated by erythropoietin, the cytoplasmic portion of the receptor that is proximal to the membrane interacts with Janus 2 tyrosine kinase (JAK-2), resulting in phosphorylation of several proteins and a cascade of erythroid-specific signals (9). Some of these signals lead to growth stimulation and differentiation in the erythroid cell line, a process known as *erythroid mitogenesis*. In addition to its mitogenic effect, erythropoietin also inhibits programmed cell death (also known as apoptosis) in erythroid precursors, an effect that also encourages expansion of the erythrocyte population (10). Recent evidence suggests that the mitogenic effects and the apoptosis-inhibiting effects of erythropoietin can be separated from one another both biochemically and functionally (11). As expected, withdrawal of erythropoietin, such as that which occurs after descent from altitude, may selectively shift the balance toward cell death. The piece of this puzzle that is still missing is an understanding of the mechanism of enhanced destruction of human erythrocytes, cells that have already lost their nucleus and therefore should not be susceptible to apoptosis.

During this century, the medical aspects of human space travel will probably become progressively more important in our quest to understand the universe. Rice and colleagues discuss the implications of these findings for physiologic conditions on Earth, but the space program must concentrate on potentially adverse effects on human performance produced by neocytolysis in the course of interplanetary travel. The development of anemia during exposure to microgravity is well documented. During the Skylab mission in the mid-1970s, reticulocyte counts in astronauts were found to be diminished to about 44% of the mean preflight values (12). A decade later, on SpaceLab 1, serum erythropoietin levels were found to decrease by 23% within 24 hours after launch (13). In space, the red cell mass decreases by 10% to 15% over a few days.

These effects, while predictable, can be quite complicated. For instance, on a mission to Mars, the process

of hematologic adaptation would begin immediately on exposure to microgravity, leading to a decreased red cell mass caused by centripetal blood redistribution. Microgravity-induced anemia would persist throughout a year-long mission to Mars and should present no serious health problems during space travel. As long as the cabin pressure remains at 1 atm and microgravity persists, hematologic stability seems likely.

As the spacecraft descends to the surface of Mars, however, two changes will take place. First, gravity will be reasserted, albeit at a Martian level of only 0.38 times the force of gravity found on Earth. Blood will therefore be redistributed toward the periphery, and volume sensors will demand plasma volume expansion, worsening (at least acutely) the anemia experienced during the journey. Second, atmospheric conditions will change dramatically. Once an astronaut steps out of the spacecraft capsule onto the Martian surface (where atmospheric pressure is 0.14 PSI as opposed to 14.7 PSI on Earth), a pressure suit will be required to provide approximately 4.3 PSI (based on the suits currently used by the National Aeronautics and Space Administration) in order to maintain life. Without this pressure suit, nitrogen would bubble out of solution from the blood and clog blood vessels in a lethal version of the deep-sea diver's "bends." Finally, the relatively low atmospheric pressure inside the pressure suit will require a higher fraction of inspired oxygen to provide sufficient blood oxygen content for normal activity. An astronaut's daily life would be a cycle of atmospheric pressure changes punctuated by transition from the habitat module with near-normal pressure to outside, where he or she would explore the surface in a pressure suit. How much time is spent outside the spacecraft capsule and how much time is spent on the Martian surface will largely determine the hematologic state of the astronaut on the home-bound journey.

Meanwhile, back on Earth, consideration of the practical effects of fluctuating erythropoietin levels has a broad, immediate, and intensely clinical importance among the millions of patients with severe chronic obstructive pulmonary disease. One of the recognized advantages of supplemental oxygen therapy in a chronically hypoxic patient is the resultant decrease in red cell mass, which consequently limits susceptibility to hyperviscosity syndromes and thromboembolic disease. Pre-

sumably, the process of neocytolysis in persons descending from altitude described by Rice and colleagues also occurs in these patients with chronic lung disease.

Although our understanding of the processes involved in readjustment of red cell mass is improving, many important questions remain to be answered, even as we recognize the increasing number and complexity of molecules that orchestrate these homeostatic mechanisms. Does neocytolysis produce preventable side effects in patients with chronic obstructive pulmonary disease or other conditions? Can modification of the speed of neocytolysis be of benefit to patients with chronic obstructive pulmonary disease? Is it appropriate to limit the decrease in red cell mass in patients with chronic obstructive pulmonary disease by administration of erythropoietin while improving oxygen content of the blood by providing supplemental oxygen therapy? Should we search for other methods of rapidly shutting down erythropoietin production in patients with other causes of hyperviscosity in order to decrease risk rapidly? None of these questions can yet be answered, but the lessons learned from space medicine have already produced some important information in this area. A deeper understanding of neocytolysis may be particularly helpful in exploring the expanding universe of possibilities.

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