ering of felsic continental crust (which is relatively rich in quartz and feldspar) rather than an increased mafic rock contribution (*8*). Reconciling the interpretations of these isotope records with Macdonald *et al.*'s record of tropical ophiolite exposure will help to elucidate the connection between climate, erosion, and weathering.

Future studies should test whether the findings are typical only for the Phanerozoic or also for the preceding eons. For example, if the convecting mantle is the main reservoir for CO_2 that newly enters Earth's surface-lithosphere-system, because most subducted carbon is not recycled back (*9*) and is incorporated into the lithosphere in the long term (*9*, *10*), then the mantle degassing rate might also decrease in the long term as the reservoir becomes depleted. This effect may be balanced by the long-term increase in solar radiation.

Advances in reconstructing paleogeographic settings, particularly subduction zones (*11*), may help to determine whether Macdonald *et al.*'s hypothesis is also relevant for previous glaciation periods, like those during the Neoproterozoic (1000 to 541 million years ago). In this case, further processes may also be considered, such as extensive ridge volcanism (*12*) or decreasing solid Earth degassing before the Neoproterozoic glaciations (715 to 595 million years ago) (*13*).

Researchers should also aim to reconstruct metamorphic and recycled CO_2 and its dynamics (*1*), because this source of CO_2 is a counterpart to the enhanced weathering of mafic rocks. Reconstructions of paleogeographic features such as those conducted by Macdonald *et al.* and others allow direct comparisons between observations related to CO_2 sinks and sources with long-term climate variability, and future improvements will trigger new modeling efforts to understand these observations. ■

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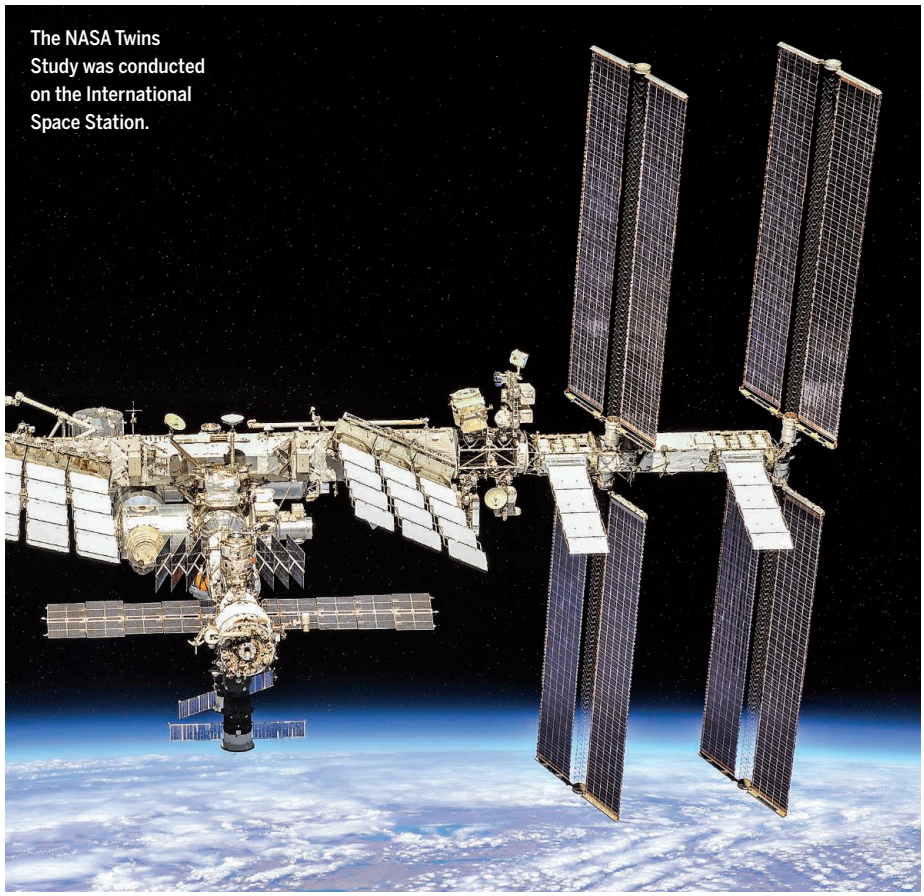

The NASA Twins Study was conducted on the International Space Station.

PHOTO: NASA/ROSCOSMOS/FLICKR/CC BY-NC-ND

PHYSIOLOGY

Hazards of human spaceflight

A 1-year mission in space has many biological consequences

By **Markus Löbrich**[1] *and* **Penny A. Jeggo**[2]

In Einstein's famous twin paradox, the effect of special relativity causes aging to slow in one twin during travel in a high-speed rocket through space while the body of the Earth-bound twin undergoes the same wear and tear that all humans experience on Earth (*1*). However, real space travels present far more realistic challenges that can potentially compromise the health of the more adventurous twin. On page 144 of this issue, Garrett-Bakelman *et al.* (*2*) investigate the manifold biological consequences of a journey in space endured by an astronaut during a 1-year mission onboard the International Space Station (ISS) compared with his identical twin on Earth. The challenges encountered in space include noise, isolation, hypoxia, and disrupted circadian rhythm (body clock). Furthermore, exposure to ionizing radiation (IR) and weightlessness, also called microgravity, could cause important health risks.

IR is an omnipresent threat to human life because it can damage the integrity of important biomolecules, first and foremost the genetic information stored within our DNA. IR derives from radioactive material inside Earth, solar flares, and cosmic rays from outside the Solar System. Cosmic ionizing radiation comprises high-energy charged particles that are deflected and stopped by Earth's magnetic field and its atmosphere, effectively protecting us from excessive IR exposure. However, the IR load increases when we leave the shielded Earth, more so the further away we travel. Furthermore, surface gravity has shaped life on Earth, and most, if not all, physi-

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ological processes have adapted to it. It is, therefore, easy to envisage that weightlessness can have consequences for space travelers.

The largely unknown risks imposed by microgravity and IR exposure during spaceflight are currently limiting endeavors to visit Mars, warranting intensive research dedicated to their effects on astronauts. The ISS represents an ideal test bed to study long-term effects of weightlessness and increased IR exposure. Although the ISS orbits Earth relatively closely (~400 km from Earth's surface), its high speed and the concomitant centrifugal force counteract Earth's gravity, creating a weightless environment. The study by Garrett-Bakelman *et al.* followed an astronaut before, during, and after a 1-year stay at the ISS, the time approximately required for a return journey to Mars. The beauty of this study is the availability of an identical twin, serving as the perfect genetic control on Earth. Although the findings reflect the biological response of human beings with a particular genetic composition—that of the identical twins—and might differ for other astronauts, the availability of a genetic control minimizes false-positive results. Another strength of the study is the comprehensive biological analysis coupled with physiological and cognitive tests over the expected time frame needed to reach Mars, providing an unprecedented source of information. Biological samples were extensively monitored by state-of-the art techniques, including "-omics" approaches that identify global changes in gene or protein expression and connect them to the activation of particular stress response pathways.

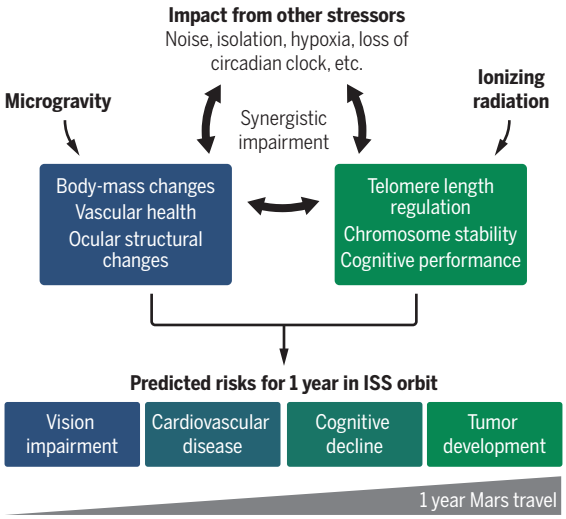
The findings reveal many molecular, physiological, and behavioral changes induced by the space environment (see the figure), which Garrett-Bakelman *et al.* classified into low-risk, mid-level risk, and high-risk groups. The low-risk category included changes in the gastrointestinal microbiome and in body mass, whereas the mid-level risk category included alterations in collagen regulation and intravascular fluid management. Genomic instability, assessed by chromosomal aberrations, was placed into the potentially higher-risk group because it confers a risk of developing cancer. The structural abnormalities observed in the chromosomes of the traveling twin are typical of IR exposure (*3*). In particular, inversions of chromosomal fragments likely result from the space-specific charged particles and arose at a frequency consistent with the encountered radiation dose of 146 millisieverts (mSv) (a measure for the biological effectiveness of radiation), which is equivalent to 50 years of natural background radiation on Earth (*4*). Chromosome translocations, although observed previously in astronauts (*5*), arose with unexpectedly high frequency before declining postflight. Furthermore, telomeres—repetitive sequences that protect chromosome ends—predominantly became lengthened during the flight, but a few were shortened. Although largely returning to normal length postflight, critically short or lost telomeres persisted, a known consequence of exposure to charged particles (*6*). The expression of DNA repair genes remained up-regulated in the traveling twin postflight, reflecting the presence of persistent chromosomal damage.

Other severe biological effects could relate to microgravity, causing a headward fluid shift and pronounced changes in the vascular physiology, with distended arteries and veins in the upper body (*7*). The traveling twin showed increased carotid artery distension and thickening of the two innermost layers of the carotid wall, potentially representing early changes associated with cardiovascular and cerebrovascular diseases. He also exhibited abnormalities in the retinal vasculature, with choroid thickening and increased choroidal folding, features potentially compromising vision (*8*). Evaluations of the cognitive capacity of the traveling twin did not show major deficits during space travel but revealed significant diminutions postflight. Although impacts of microgravity on brain physiology have been reported, space-relevant IR exposure can affect cognition and neuronal circuit excitability in mice (*9*, *10*).

The observed effects reported by Garrett-Bakelman *et al.* are arguably broader and more pronounced than might have been expected, particularly for the more IR-specific responses such as genomic instability, persistently up-regulated expression of DNA damage response genes, and cognitive function decline. But the more microgravity-specific alterations in the neuro-ocular system and severe vascular physiology changes could also potentially couple with the known impact of IR on cataract formation and cardiovascular diseases. Both pathologies are known to arise at significant rates in people who have been exposed to IR doses above ~500 mSv (*11*). Such exposure levels, although not encountered during the 1-year ISS flight, will be received during travel to Mars, where the dose rate exceeds that on the ISS by about fivefold, and total dose estimates range up to 1000 mSv (*12*). Consequently, during Mars travel, the spectrum of biological effects will shift, placing more weight on IR-induced effects and those reacting synergistically with the microgravity responses. To understand the details of such shifts and their long-term consequences will be important for future studies and the development of countermeasures. Undoubtedly, the study by Garrett-Bakelman *et al.* represents more than one small step for mankind in this endeavor. ■

A year in orbit

A 1-year mission aboard the International Space Station (ISS) caused multiple alterations that arose from microgravity, ionizing radiation, and other stressors. These changes likely impose health risks.



The impact of ionizing radiation will be five times greater for Mars travel.

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