(Background Image: Henrik Lehnerer/Shutterstock)

HUMANS IN SPACE

How the research of USRA scientists could help make possible the human exploration of Mars.

Essay by W. David Cummings. Design by Erin Senoz.

Less than six months after President Eisenhower created NASA in July 1959, the Soviet Union's Luna 1 spacecraft passed the Moon and entered orbit around the Sun, becoming the first space vehicle to leave Earth orbit. Three months later, Luna 2 became the first spacecraft to impact the Moon, and a few weeks after that, Luna 3 obtained the first photographs of the far side of the Moon. This series of firsts was preceded by Sputnik and crested on 12 April 1961, with Yuri Gagarin's orbiting the Earth inside a Vostok spacecraft. For those keeping score, the Soviet Union was winning the space race. Five days later, a paramilitary group sponsored by the U.S. Central Intelligence Agency launched a failed attempt to overthrow Cuba's Fidel Castro. As historian and space policy expert John Logsdon describes the time:

> *The fiasco of the Bay of Pigs reinforced Kennedy's determination, already strong, to approve a program aimed at placing the United States ahead of the Soviet Union in the competition for firsts in space. It was one of the many pressures that converged on the president at the time, and thus its exact influence cannot be isolated. As president, Kennedy could treat few issues in isolation anyway, and there seems little doubt that the Bay of Pigs was in the front of his mind as he called Lyndon Johnson to his office on April 19 [1961] and asked him to find a "space program which promises dramatic results in which we could win.*[1]

A month later, on 25 May 1961, President John F. Kennedy addressed a joint session of congress. In his speech, the President made a bold announcement:

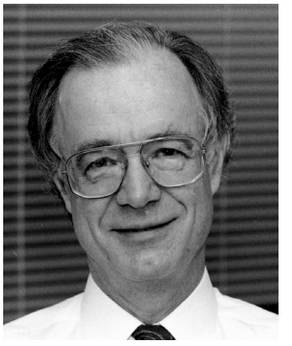
> *(T)his nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to the earth. No single space project in this period will be more impressive to mankind, or more important for the long-range exploration of space; and none will be so difficult or expensive to accomplish.*[2]

Kennedy's goal was accomplished on 24 July 1969, when the crew of Apollo 11 returned safely to Earth after a brief stay on the Moon. There were five subsequent Apollo explorations of the Moon, and the last, Apollo 17 in December of 1972, involved the only scientist-astronaut, the geologist Harrison Schmitt. Schmitt and fellow astronaut Eugene Cernan were the last humans to leave their footprints on the Moon.

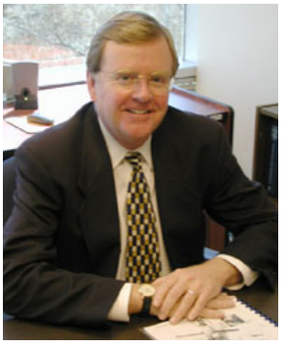
The U.S involvement of humans in space continued after the Apollo program with the

Jack Schmitt
Interim USRA Director of DSB,
1984-1987

Makoto Igarashi
USRA Director of DSB,
1987-1991



Alfred Coats
USRA Director of DSLS,
1991-2001



Adrian LeBlanc
USRA Director of DSLS,
2002-2010

hope of further human exploration of the solar system, especially the planet Mars. The Skylab space station was intermittently occupied from 1973 to 1979, and the Space Shuttle made its first flight on 12 April 1981.

NASA's study of the effects of the space environment on humans continued after the Apollo and Skylab programs, and in 1983 USRA created its Division of Space Biomedicine (DSB) to focus on the issues of human physiology in space. The DSB was later renamed the Division of Space Life Sciences (DSLS). It is co-located with USRA's Lunar and Planetary Institute near NASA's Johnson Space Center, south of Houston.

The founding Director of the DSLS was the former astronaut Dr. Harrison "Jack" Schmitt, who was officially an "Interim" director, but he led the Division for its first three years. Schmitt received a BS degree from Caltech in 1957 and a Ph.D. in geology from Harvard in 1964. He was a United States Senator from New Mexico from 1977 to 1983, and he had recently served as Chair of the NASA Advisory Council when he became the first director of USRA's space biomedical research program. Though not a biomedical researcher, Schmitt had first-hand knowledge about the various physiological effects and hazards associated with being in space, which included:

- Exposure to high-energy radiation, particularly solar and galactic cosmic rays
- Fluid shifts toward the head, chest, and upper body
- A loss of mass and strength in the muscles supporting the body against Earth gravity
- A loss of mass and strength in the weight-bearing bones of the body
- A decrease in the number of red blood cells in the body
- A disorientation and disequilibrium known as "space motion sickness" associated with entering a weightless environment[3]

The first topic of interest to NASA was space motion sickness, which affects 60% to 80% of astronauts during their first few days in the weightlessness of space. Some astronauts are unable to do much work during this period of adaptation to the space environment.

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With the help of USRA's John R. Sevier, Deputy Director of the DSB, Schmitt began to bring visiting scientists to NASA's Johnson Space Center, and the DSB started to conduct workshops on topics such as *Pharmacological Approaches to Space Motion Sickness*, and *Emergency Medicine in Space*. USRA formed a Space Adaptation Working Panel to make recommendations to NASA regarding flight and ground investigations that would, among other things, help understand the causes of space motion sickness and lead to the development of effective countermeasures.

To help guide its efforts, USRA appointed a Science Council of eminent research physicians. The initial chair of the Science Council for the Division of Space Biomedicine was Dr. Bobby R. Alford, who was the Vice President and Dean of Academic Affairs at the Baylor College of Medicine in Houston.

In 1986, the USRA Board of Trustees appointed Makoto Igarashi, MD, of the Baylor College of Medicine as the next Director of the Division. Dr. Igarashi was a distinguished vestibular researcher and had served as Director of the Otopathology Section of the U.S. Naval Aerospace Medical Research Institute before joining the Baylor College of Medicine.

Igarashi's appointment was significant. The human vestibular system had been implicated in the problem of space motion sickness, because part of the system is critically influenced by gravity. Two sacs of the vestibular organ, the utricle and the saccule, contain calcium carbonate crystals, called otoliths, which are embedded in a gel-like substance that also contains the cilia of hair cells. When a person bends her head on Earth, the otoliths respond to gravity and tend to slide "downhill." This causes the cilia of the hair cells in the gelatinous material to bend, which in turn causes a signal to be sent to the brain.

In the weightless environment of space, the otoliths do not move under the influence of gravity, and the cilia of the hair cells do not bend. However, the vestibular apparatus in the semicircular canals of the inner ear and other inputs to the brain (e.g., from the visual system) indicate motion in the same way that they would on Earth. In weightlessness, therefore, the brain receives conflicting signals when the head moves, and this is thought to be the cause of space motion sickness.

In a matter of a few days or less, the brain adjusts to a new "space normal," and the symptoms of space motion sickness go away. But for the short-duration Shuttle flights, space motion sickness was a serious impediment, and the next Director of the Division of Space Life Sciences, Dr. Alford C. Coats, was also an expert in vestibular investigations. Dr. Coats was a professor at the Baylor College of Medicine, and, in addition, he was the director of the Cochlear Function and Vestibular Laboratories at the Methodist Hospital in Houston.[4]

As longer stays of U.S. astronauts became possible on Skylab and the International Space Station (ISS), other effects of the space environment on humans came under closer scrutiny.

The loss of calcium from the bones is problematic for long duration exposure to the space environment, e.g., on a trip to Mars, as well as for astronauts after they return from such missions. In some parts of the skeleton, the rate of destruction of bone cells substantially outpaces the rate of creation of bone cells. The loss of bone cells is particularly acute in the load-bearing parts of the skeleton. The overall average rate of bone loss is approximately 1% to 1.5% per month, and it is not clear whether the bone mineral density stabilizes at a lower level in space or continues to diminish. It is also unclear whether all the bone mineral loss is recovered for individuals who return to Earth.[5] In any case, ultimate recovery might take several years, and there is evidence of changes in bone architecture.

A study in 1979 of the average calcium balance as measured by body inflow and outflow of calcium for astronauts on all three Skylab missions demonstrated the effect of the space environment on total-body calcium levels.[6] In 2007, Dr. Adrian LeBlanc, who was the Director of the DSLS at the time, showed that the total-body calcium levels did not tell the whole story. LeBlanc was the lead author of a review paper that noted, for the Skylab missions:

> (B)one loss was inhomogenous; i.e., no loss occurred in the upper extremities, while there were significant losses in the calcaneus [heel bone]; and the regional losses on a percentage basis could be much greater than percentage changes in total body bone mineral.[7]

In collaboration with researchers from NASA and other organizations, USRA researchers have investigated bone loss and helped to develop countermeasures through ground-based spaceflight analogs, including bed rest studies, the development of exercise and dietary prescriptions, pharmacological approaches, and the use of the Digital Astronaut model. For example, LeBlanc of USRA and Dr. Toshio Matsumoto of the University of Tokushima in Kuramoto, Japan, were the principal investigators on an important study to evaluate the effects of bisphosphonates used by astronauts as a countermeasure to space-flight-induced bone loss. Bisphosphonates are medications that block the breakdown of bone and are used to treat osteoporosis. The study found that

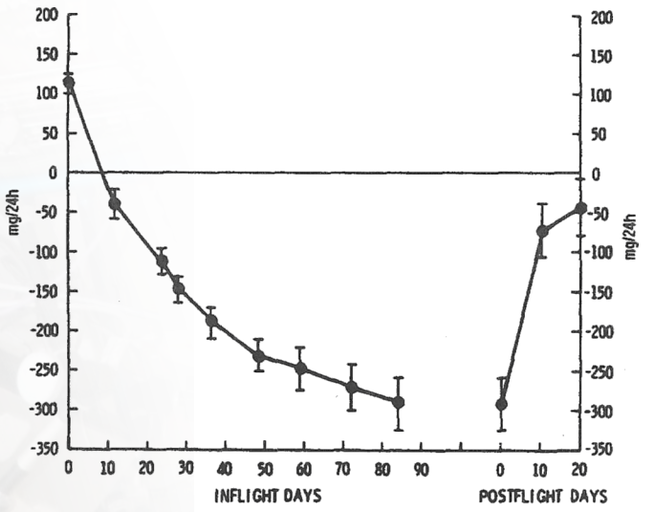


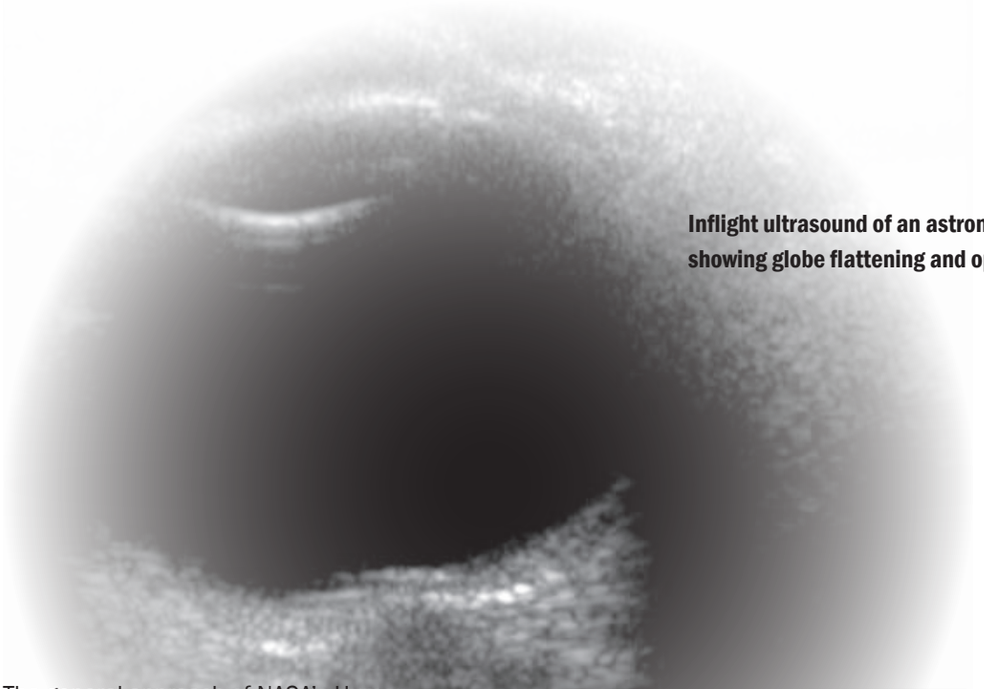
Fig. 2. Calcium balance as a function of Skylab flight duration (mean ±SE).

the use of bisphosphonates in conjunction with routine, in-flight exercise significantly lessened the losses in bone mineral density of the spine, hip, and pelvis in the astronauts.[8]

Partly as the result of the research of USRA staff at the DSLS, exercise devices on the ISS have been improved. However, musculoskeletal and cardiovascular-related risks to astronaut health and performance have not been eliminated. USRA researchers are working on approaches to exercise that will provide higher intensity workouts of shorter duration and still accomplish the protection from bone loss during long-duration human space missions. USRA-led research was the first to show that exercise alone, using equipment similar to what is available to astronauts on the ISS, is able to fully protect cardiovascular and muscular health during 14 days of bed rest.[9] This higher intensity exercise program was also evaluated during 70 days of bed rest and 6 months of spaceflight.

Lori Ploutz-Snyder
USRA Lead Scientist, Exercise Physiology & Countermeasure Development

Background image of Astronaut Sunita Williams measuring maximum oxygen intake during a high-intensity workout on the International Space Station. Courtesy of NASA.
Portraits at left: Igarashi courtesy of Baylor College of Medicine; Schmitt courtesy of Heartland Institute.



Inflight ultrasound of an astronaut's right eye, showing globe flattening and optic disc edema.[14]

The general approach of NASA's Human Research Program is to first identify and understand health and performance risks for human space flight and then to develop countermeasures to remove or reduce the risk to acceptable levels. A risk that was not fully understood at the time of the formation of the DSB/DSLS, but which later became the subject of intense research, is the effect of weightlessness on vision.

The first case of optic disc swelling, known as papilledema, in an astronaut was reported during a six-month mission on the ISS in 2005. The astronaut lost visual acuity during the flight. A post-flight examination of the astronaut was conducted, and an increase in intracranial pressure was suspected as the cause of the papilledema and other abnormalities in the eyes, such as folds in choroidal layers of the surface of the eyes. For patients on the ground, papilledema and choroidal folds are serious signs of some underlying condition that if left untreated can cause loss of vision.

In the summer of 2009, NASA held a Papilledema Summit, which was attended by 41 experts in ophthalmology and related fields. Several cases of papilledema in astronauts were discussed. The panel of experts expressed doubt that increased intracranial pressure is the underlying cause of disc edema and choroidal folds. They noted that patients on the ground with increased intracranial pressure do not experience a loss in visual acuity, but they generally suffer from headaches and visual obscurations. These are opposite to the symptoms that had been reported for astronauts.[10] It was clear that a new phenomenon had been encountered and, as a result of the Summit, NASA formally established papilledema and related abnormalities that could lead to vision loss as a new risk for long-duration spaceflight.[11]

Neal Pellis became the fifth director of the USRA DSLS in October of 2010.

As the focus of research in space-related human physiology continued to shift, in 2010, USRA appointed its fifth director of the DSLS, Dr. Neal Pellis, a microbiologist who had worked for NASA for sixteen years.[12] In that year, the DSLS hosted a meeting to further examine vision issues related to spaceflight, and a large panel of experts identified elevated intracranial pressure as the probable cause of disc edema and other eye-related abnormalities that were being experienced by astronauts. This assessment was reinforced in 2011 by a case study led by Dr. Thomas H. Mader of the Alaska Native Medical Center in Anchorage. The Mader team studied data from seven astronauts after long-duration exposure to weightlessness, and they documented vision changes in approximately 300 additional astronauts. Based on their findings, the Mader team reported:

> *After 6 months of space flight, 7 astronauts had ophthalmic findings, consisting of disc edema in five, globe flattening in 5, chorodial folds in 5, cotton wool spots … in 3, nerve fiber layer thickening … in 6, and decreased near vision in 6 astronauts. … The 300 postflight questionnaires documented that approximately 29% and 60% of astronauts on short and long-duration missions, respectively, experienced a degradation in distant and near visual acuity. Some of these vision changes remain unresolved years after flight.*[13]

Also in 2011, NASA held a Visual Impairment Intracranial Pressure (VIIP) Summit, and the panel of experts at this meeting advised that the rise in intracranial pressure might not be the sole cause of the various, observed changes in the eyes of the astronauts. The panel members were perplexed that none of the astronauts with disc edema and other symptoms complained of headaches or visual obscurations. They noted that in a terrestrial setting, more than 90% of patients with elevated intracranial pressure experienced headaches.[15]

As a result of the research conducted, NASA's Human Research Program (HRP) Evidence Report, *Risk of Spaceflight-Induced Intracranial Hypertension and Vision Alterations* summarizes the threat as follows:

> *Over the last 40 years there have been reports of visual acuity impairments associated with spaceflight through testing and anecdotal reports. Until recently, these changes were thought to be transient, but a comparison of pre and postflight ocular measures have identified a potential risk of permanent visual changes as a result of microgravity exposure. There are limited pre and postflight measures to define the risk and even less in-flight data is available. These data show that there is a subset of crewmembers that experience visual performance decrements, cotton-wool spot formation, choroidal fold development, optic-disc edema, optic nerve sheath distention, and/or posterior globe flattening with varying degrees of severity and permanence. These changes define the visual impairment/intracranial pressure (VIIP) syndrome.*[16]

The report also cited four cases of disc edema for astronauts studied by the Mader team, where the pressure of the cerebral spinal fluid measured after the flights was borderline high or above normal, indicating increased intracranial pressure.[17]

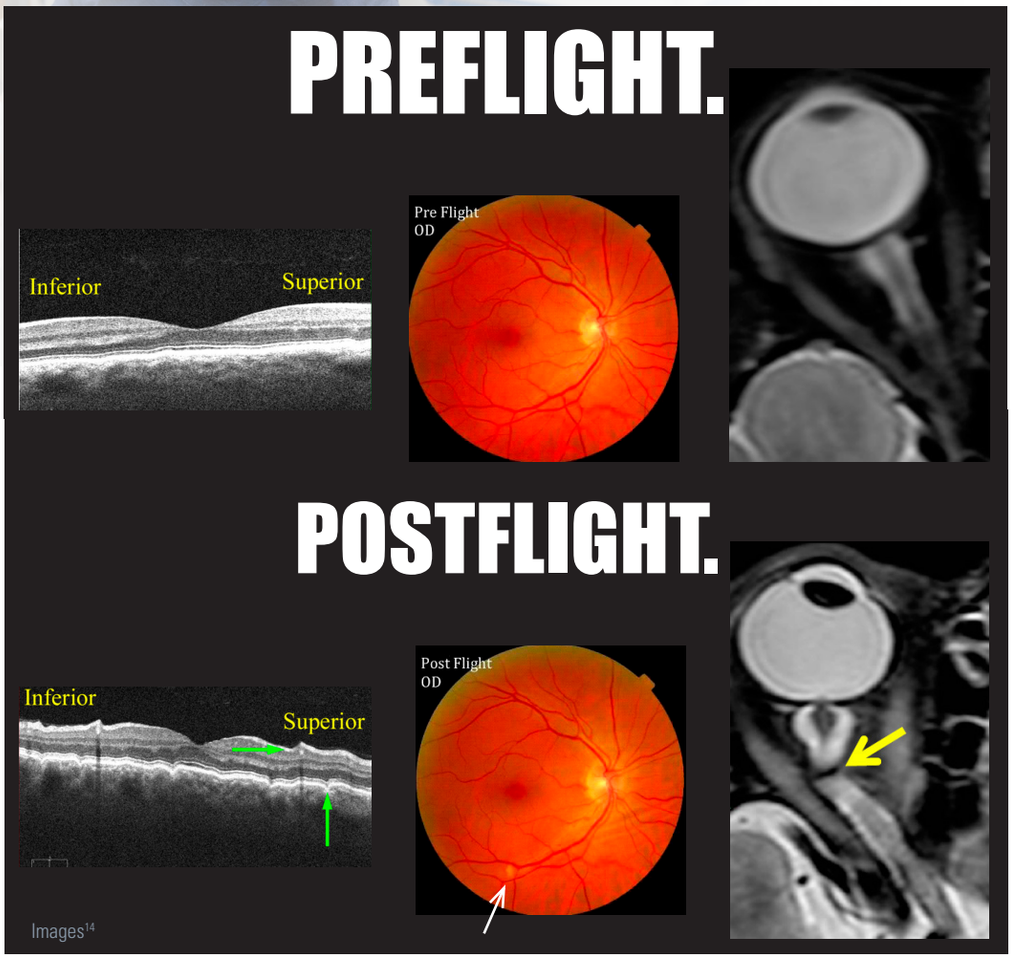
Beyond the health risk to the astronauts, instances of visual impairment in orbit can risk operations. There has been one case of a visual field defect on orbit such that the astronaut had to tilt his head 15 degrees to view instruments and procedures.[18]

As with other human and performance risks of spaceflight, USRA scientists and engineers are working with NASA and other colleagues to find solutions to the VIIP syndrome. Dr. Christian Otto of USRA is the lead scientist for the NASA VIIP Risk program. Dr. Otto is experienced in remote medicine, high altitude medicine, and polar medicine, having worked in the Canadian High Arctic, and as a medical researcher on Mounts Everest, McKinley, and Logan.

Christian Otto
USRA Lead Scientist,
NASA VIIP Risk program

The working hypothesis for the cause of VIIP is that the headward fluid shift that occurs when astronauts begin weightlessness results in increased intracranial pressure that is transmitted to the optic nerve. Among other things, this increased pressure causes globe flattening and optic disc edema. In addition, the elevated intracranial pressure constricts the central vein that allows blood to drain from the back of the eye, and since arterial blood continues to flow into the eye, the result is an increase in intraocular pressure.[19]

A study of 14 astronauts in 2015 by Otto and his colleagues demonstrated that 5 of the 6 astronauts who showed flattening of their eye globes prior to flight had a significant increase in the production of cerebral spinal fluid (CSF) as measured post flight. The authors of the report of the study concluded:



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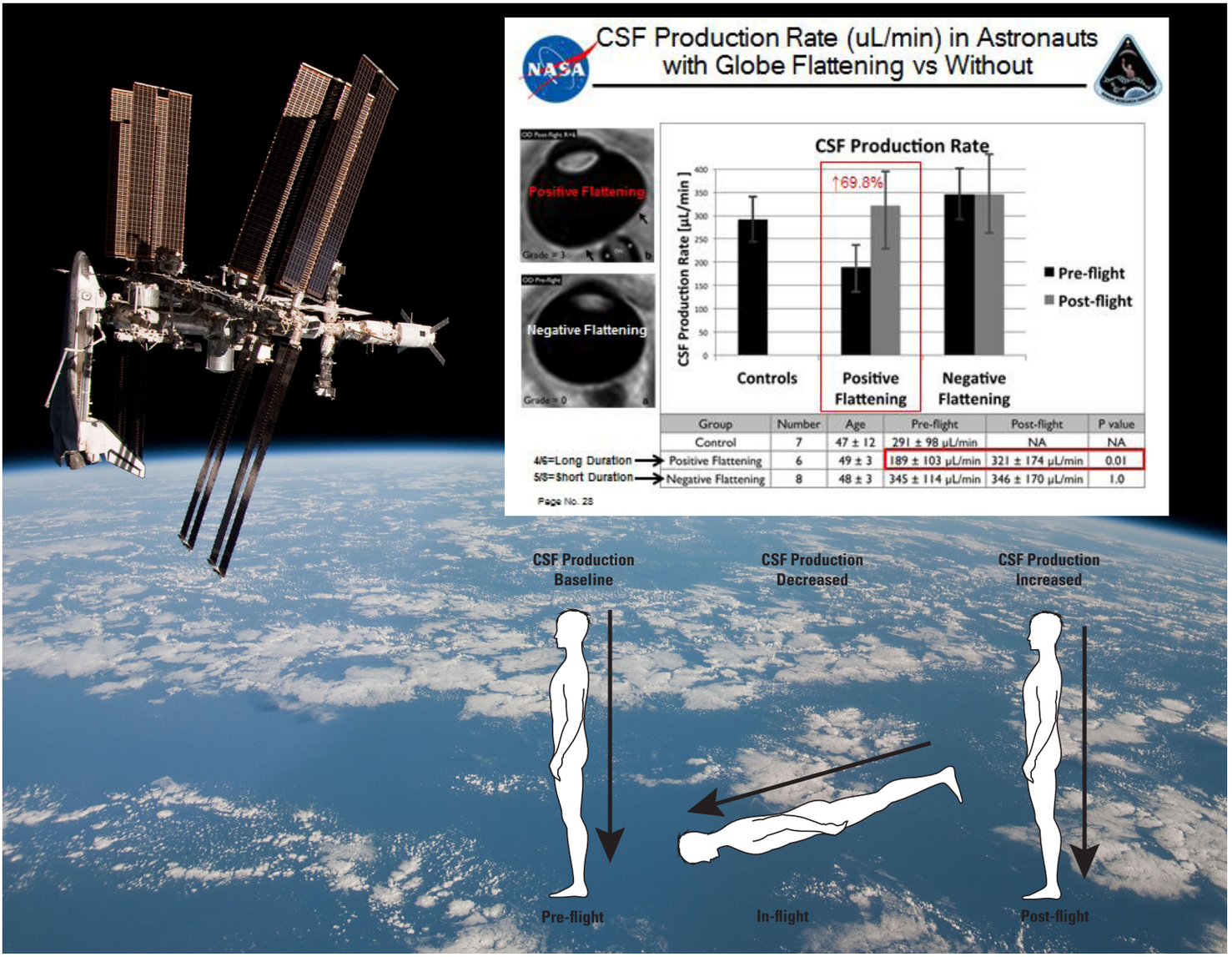


Top: Analysis of cerebral spinal fluid (CSF) production for 14 astronauts.[20] **Bottom:** Conceptual model of CSF production rate at different phases of space flight. The arrows indicate the direction of fluid shifts.[20] **Background:** The International Space Station and the Docked Space Shuttle Endeavor, 2011. (NASA/ESA)

Increased CSF production rate in postflight astronauts with positive posterior globe flattening is compatible with the hypothesis of microgravity-induced intracranial hypertension. We propose that CSF production rate is significantly downregulated during space flight in this subgroup due to greater susceptibility to microgravity-induced cephalad fluid shifts. A new steady state of intracranial pressure and CSF production rate is then established, but remains above the preflight baseline, resulting in pathologic modification of the orbital structures. Upon return to normal gravity the cephalad fluid shift reverses, causing an abrupt decrease in ICP [Intracranial Pressure] stimulus with respect to the in-flight level. This sudden drop in ICP triggers a compensatory CSF upregulation to reestablish homeostasis.[20]

The VIIP problem is complex, and there are a number of unanswered questions. Why, for example, are some astronauts affected and others are not? Dr. Sara Zwart, a Senior Scientist in USRA's DSLS, has examined the possibility that the ophthalmic changes observed in some of the astronauts could be related to individual differences in a particular metabolic pathway. This possibility was described in a paper published in 2012, for which Zwart was the lead author:

> *Factors that could contribute to the ophthalmic changes observed in some crewmembers after*

VIIP is now one of the risks listed in NASA's Human Research Roadmap that must be resolved before long-duration human missions can be undertaken.

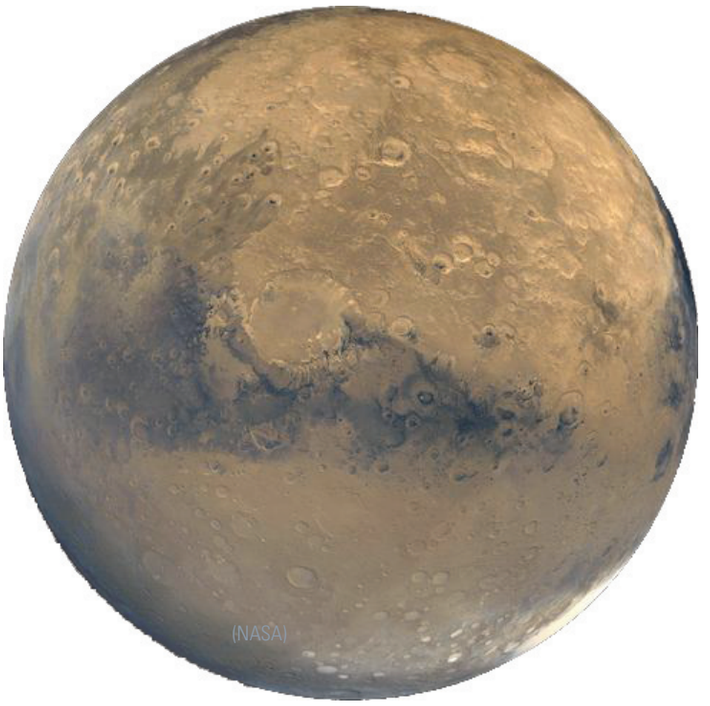
Sara Zwart
USRA Senior Scientist,
DSLS

long-duration spaceflight include microgravity-induced fluid shifts..., increased intracranial pressure, optic nerve sheath changes, and/or changes in intraocular pressure.... At this point, the unifying pathologic mechanism is hypothesized to be prolonged exposure to the effects of cephalad fluid shifts that occur during microgravity exposure. The question remains, however: why are only ~ 20% of crewmembers affected when all crewmembers presumably experience fluid shifts on exposure to microgravity? Furthermore, why would one crewmember be affected during a particular mission when a fellow crewmember on the same mission (and exposed to the same environment) did not have ophthalmic changes? The evidence provided here suggests that this phenomenon could be explained by crewmembers who have ophthalmic changes have an altered metabolic pathway involving Hcy, cystathionine, 2MCA, and MMA. Our data show that an association exists between ophthalmic changes and higher concentrations of intermediates of the [metabolic] pathway involving these enzymes.[21]

Hcy (homocysteine), cystathionine, 2MCA (2-methylcitric acid), and MMA (methylmalonic acid) are metabolites that are involved in folate- and vitamin B-12-dependent 1-carbon transfer metabolism. Zwart and her colleagues found that concentrations of these metabolites were 25% - 45% higher in astronauts with ophthalmic changes than in those without them.[22] Further, this correlation was found to exist in data taken preflight as well as during flight and post flight, suggesting the possibility that genetic differences among the astronauts might be responsible for who is, and who is not, predisposed to develop changes in vision during exposure to microgravity.

Zwart and her colleagues suggested possible ways that an altered 1-carbon transfer metabolic pathway could be linked to ophthalmic changes, based on clinical data. They then summarized their findings, as follows.

In summary, preexisting chemical differences, which have little or no demonstrable effect under Earth-gravity conditions, may set the stage for pathologic changes in affected astronauts during prolonged microgravity exposure. The existing data suggest that vision issues during spaceflight are associated with a difference in the folate- and vitamin B-12-dependent 1-carbon transfer pathway. Given the magnitude of the issue, follow-up with genetic analyses to examine the potential for polymorphisms in the



(NASA)

pathway is required to provide a definitive answer. This association has important implications for future space travelers. Beyond that, these findings, taken together with the documented relationship between polymorphisms in the folate- and vitamin B-12-dependent 1-carbon pathway and predisposition to risk of clinical outcomes related to vascular events found in clinical practice, could have profound implications for a sizeable population of individuals on Earth.[23]

As of this writing, the cause of visual impairment and elevated intracranial pressure among some astronauts during exposure to microgravity is not fully understood. It is now one of the risks listed in NASA's Human Research Roadmap that must be resolved before long-duration human missions can be undertaken.

In his 1961 speech, President Kennedy said that a human mission to the Moon would be "important for the long-range exploration of space." It certainly was important for the human spirit of exploration, and it was important for lunar and planetary science, as well. It eventually led to a USRA research program that well demonstrated the vision of James Webb, the NASA Administrator who pushed to create an association of universities that could assist NASA in solving critical problems, such as finding a path that will one day make it possible for humans to explore Mars.

[1] Logsdon, John M. The decision to go to the moon: Project Apollo and the national interest. Cambridge, MA: MIT Press, 1970; p. 112.

[2] Kennedy, J. F. (1961). Special message to the congress on urgent national needs. The American Presidency Project, as retrieved from http://www.presidency.ucsb.edu/ws/?pid=8151.

[3] In 1994, Barbara J. Lujan of USRA and Ronald J. White of NASA produced a curriculum supplement for secondary schools titled *Human Physiology in Space*. Most of these physiological effects and hazards are well-covered in their manual, the development of which was co-sponsored by NASA, the National Institutes of Health, USRA, and the University of Texas Southwestern Medical Center [Lujan, B. J. and White, R. J. (1994). Human physiology in space: A curriculum supplement for secondary schools. Washington, DC: National Aeronautics and Space Administration]. Since 1994, other, subtler effects of the low-gravity environment on humans have been discovered through research carried out by USRA staff and researchers at other organizations.

[4] Coats continued USRA's practice of bringing visiting scientist to the Division from U.S and non-U.S. research institutions. For example, Dr. Gilles Clément from the French National Center for Scientific Research (CNRS) was a frequent visitor.

[5] NASA's Evidence Book, Risk of bone fracture (2008). Human Research Program, Human Health Countermeasures Element. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center.

[6] Rambaut, P. C., and Johnston, R. S. (1979). Prolonged weightlessness and calcium loss in man. Acta Astronautica, 6, 1113-1122.

[7] LeBlanc, A. D., Spector, E. R., Evans, H. J., and Sibonga, J. D. (2007). Skeletal responses to space flight and the bed rest analog: A review. J. Musculoskelet Neuronal Interact, 7(1), 33-47; p. 45.

[8] LeBlanc, A., Matsumoto, T., Jones, J., Shapiro, J., Lang, T., Shackelford, L., Smith, S. M., Evans, H., Spector, E., Ploutz-Snyder, R., Sibonga, J., Keyak, J., Nakamura, T., Kohri, K., and Ohshima, H. (2013). Bisphosphonates as a supplement to exercise to protect bone during long-duration spaceflight. Osteoporosis International, 24(7), 2105-2114.

[9] Ploutz-Snyder LL, Downs M, Ryder J, Hackney K, Scott J, Buxton R, Goetchius E, Crowell B. Integrated Resistance and Aerobic Exercise Protects Fitness During Bed Rest. Medicine and Science in Sports and Exercise. Feb;46(2):358-68, 2014.

[10] Watkins, S. D. and Barr, Y. R. (2010) Papilledema summit: Summary Report. NASA/TM-2010-216114. Washington, DC: National Aeronautics and Space Administration; p. 7.

[11] Personal communication with Dr. Christian Otto, a leading operational space medicine researcher, in 2015.

[12] Dr. Pellis received his Ph.D. in Microbiology from Miami University, Oxford, Ohio in 1972 and was awarded a postdoctoral fellowship in Microbiology at Stanford University in Palo Alto, California. He joined the NASA Johnson Space Center in October 1994, after serving on the faculties of the Northwestern University Medical School and the University of Texas Medical School, and after directing the Department of Surgical Oncology Research Laboratory at the University of Texas M. D. Anderson Cancer Center. From 1994 to 2003, Dr. Pellis led NASA's biotechnology cell science program. He was assigned to NASA Headquarters as ISS Program Scientist from May 2002 through August 2003. Following that assignment, he served as Associate Director of the Biological Sciences and Applications Office working on exploration cell science.

[13] Mader, T. H., Gibson, C. R., Pass, A. F., Kramer, L. J., Lee, A. G., Fogarty, J., Tarver, W. J., Dervay, J. P., Hamilton, D. R., Sargsyan, A., Phillips, J. L., Tran, D., Lipsky, W., Choi, J., Stern, C., Kuyumjian, R., and Polk, J. D. (2011) Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. *Ophthalmology*, 118(10), 2058-2069; p. 1.

[14] Nelson, E. S., Mulugeta, L., and Myers, J. G. (2014). Microgravity-induced fluid shift and ophthalmic changes. Life, 4, 621-665; p. 627.

[15] Fogarty, J. A., Otto, C., Kerstman, E., Oubre, C., and Wu, J. (2011). The visual impairment intracranial pressure summit report. NASA/TP-2011-216160. Washington, DC: National Aeronautics and Space Administration; p. 1.

[16] NASA's Evidence Report, Risk of spaceflight-induced intracranial hypertension and vision alterations (2012). Human Research Program, Human Health Countermeasures Element, Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; p. 2.

[17] Ibid. p. 19.

[18] Ibid. p. 2.

[19] Otto, C. (2011) Risk of microgravity-induced visual impairment and elevated intracranial pressure (VIIP). NASA Information Briefing.

[20] Kramer, L. A., Hasan, K. M., Sargsyan, A. E., Wolinsky, J. S., Hamilton, D. R., Riascos, R. F., Carson, W. K., Heimbigner, J., Patel, V. S., Romo, S., and Otto, C. (2015). MR-derived cerebral spinal fluid hydrodynamics as a marker and a risk factor for intracranial hypertension in astronauts exposed to microgravity. J. Magn. Reson. Imaging. doi: 10.1002/jmri.24923; p. 9.

[21] Zwart, S. R., Gibson, C. R., Mader, T. H., Ericson, K., Ploutz-Snyder, R., Heer, M., and Smith, S. M. (2012) Vision changes after spaceflight are related to alterations in folate- and vitamin B-12-dependent one-carbon metabolism. *The Journal of Nutrition*, 142(3), 427-431; pp. 428-429.

[22] Ibid. p. 428.

[23] Ibid. pp. 430-431.