“Knowing is not enough; we must apply. Willing is not enough; we must do.”

—Goethe
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The Institute of Medicine was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

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COMMITTEE TO REVIEW NASA’S EVIDENCE REPORTS ON HUMAN HEALTH RISKS

CAROL E. H. SCOTT-CONNER (Chair), University of Iowa Carver College of Medicine, Iowa City
DANIEL R. MASYS (Vice Chair), University of Washington, Seattle
SUSAN A. BLOOMFIELD, Texas A&M University, College Station
KAREN S. COOK, Stanford University, CA
ELEANOR A. O’RANGERS, Space Medicine Associates, LLC, Belcamp, MD
SCOTT E. PARAZYNSKI, UTMB Center for Polar Medical Operations, Galveston (Resigned)
JAMES A. PAWELCZYK, Pennsylvania State University, University Park
ROBERT L. SATCHER, JR., University of Texas MD Anderson Cancer Center, Houston
JACK STUSTER, Anacapa Sciences, Inc., Santa Barbara, CA
PREM S. SUBRAMANIAN, Johns Hopkins University School of Medicine, Baltimore, MD
GAYLE E. WOLOSCHAK, Northwestern University Feinberg School of Medicine, Chicago, IL
LAURENCE R. YOUNG, Massachusetts Institute of Technology, Cambridge

IOM Staff

CATHARYN T. LIVERMAN, Study Director
MARGARET A. MCCOY, Study Director
CLAIRE F. GIAMMARIA, Research Associate
JUDITH L. ESTEP, Program Associate
ANDREW M. POPE, Director, Board on Health Sciences Policy
Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council’s Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

PETER CAVANAGH, University of Washington Medical Center, Seattle
HARTMUT DERENDORF, University of Florida, Gainesville
NAOMI L. GERBER, George Mason University, VA
WARREN N. HARDY, Virginia Tech–Wake Forest Center for Injury, Biomechanics, Blacksburg
DAVID KLAUS, University of Colorado, Boulder
ANDREW G. LEE, Houston Methodist Hospital, TX
KRIS LEHNHARDT, George Washington University School of Medicine and Health Sciences, Washington, DC
MICHAEL A. WILLIAMS, Sinai Hospital, Baltimore, MD

Although reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by JOHN R. BALL, American College of Physicians, and ROBERT A. FROSCH, Harvard University. Appointed by the Institute of Medicine, they were responsi-

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ble for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.
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December 19, 2013

Mark Shelhamer, Ph.D.
Lyndon B. Johnson Space Center
2101 NASA Parkway
Houston, TX 77058

Dear Dr. Shelhamer:

The Institute of Medicine (IOM), at the request of the National Aeronautics and Space Administration (NASA), and with guidance from the IOM’s Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments (CAMMEE), has established the Committee to Review NASA’s Evidence Reports on Human Health Risks. This letter report is the first in a series of five reports. The committee will provide an independent review of the more than 30 evidence reports that NASA has compiled on human health risks for long-duration and exploration spaceflights.

In 2008, NASA asked the IOM to assess the process for developing the evidence reports.¹ The resulting report, Review of NASA’s Human Research Program Evidence Books: A Letter Report, provided an initial and brief review of the evidence reports. This letter report builds on the work of the 2008 IOM report and examines three evidence reports:

1. **Risk of Injury from Dynamic Loads** (Caldwell et al., 2012)
2. **Risk of Clinically Relevant Unpredicted Effects of Medication** (Wotring, 2011)

¹The original evidence book was “a collection of evidence reports created from the information presented verbally and discussed within the NASA HRP [Human Research Program] in 2006” (NASA, 2013a).
3. Risk of Spaceflight-Induced Intracranial Hypertension and Visual Alterations (Alexander et al., 2012)

COMMITTEE’S TASK AND STUDY PROCESS

To review the three NASA evidence reports listed on page 1, the IOM assembled a 12-member committee with expertise in aerospace medicine, occupational health, radiation medicine, human performance, ophthalmology, internal medicine, physiology and cardiovascular health, pharmacokinetics, behavioral health and sociology, and biomedical informatics. Committee biosketches are included in Appendix B. The committee’s task, detailed in Box 1, was to review each evidence report in response to nine specific questions. In summary, this report examines the quality of the evidence, analysis, and overall construction of each report; identifies existing gaps in report content; and provides suggestions for additional sources of expert input.

 BOX 1
 Review of NASA’s Evidence Reports on Human Health Risks
 Statement of Task

NASA has requested a study from the Institute of Medicine (IOM) to provide an independent review of more than 30 evidence reports on human health risks for long-duration and exploration spaceflight. The evidence reports, which are publicly available, are categorized into five broad categories: (1) behavioral health and performance; (2) human health countermeasures (with a focus on bone metabolism and orthopedics, nutrition, immunology, and cardiac and pulmonary physiology); (3) radiation; (4) human factors issues; and (5) exploration medical capabilities. The reports are revised on an ongoing basis to incorporate new scientific information. In conducting this study, an IOM ad hoc committee will build on the 2008 IOM report Review of NASA's Human Research Program Evidence Books. That report provided an assessment of the process used for developing the evidence reports and provided an initial review of the evidence reports that had been completed at that time.

Each year, NASA staff will identify a set of evidence reports for committee review. Over the course of the study, all evidence reports will be reviewed. The committee will hold an annual scientific workshop to receive input on the evidence reports it is reviewing that year and an update on the recent literature. The committee will issue an annual letter report that addresses the following questions relevant to each evidence report:
1. Does the evidence report provide sufficient evidence, as well as sufficient risk context, that the risk is of concern for long-term space missions?
2. Does the evidence report make the case for the research gaps presented?
3. Are there any additional gaps in knowledge or areas of fundamental research that should be considered to enhance the basic understanding of this specific risk?
4. Does the evidence report address relevant interactions among risks?
5. Is input from additional disciplines needed?
6. Is the breadth of the cited literature sufficient?
7. What is the overall readability and quality?
8. Is the expertise of the authors sufficient to fully cover the scope of the given risk?
9. Has the evidence report addressed previous recommendations made by the IOM in the 2008 letter report?

The committee approached its task by analyzing each evidence report’s overall quality, which included readability; internal consistency; the source and breadth of cited evidence; identification of existing knowledge and research gaps; authorship expertise; and, if applicable, response to recommendations from the 2008 IOM letter report, described above. In the 2008 letter report, the IOM urged NASA to “require authors to use categories of evidence in future versions of the evidence books, while recognizing that experience with the explicit categorization of evidence may be refined over time, particularly regarding the categories used” (IOM, 2008, p. 12). Nevertheless, NASA still only encourages authors “to label evidence according to the ‘NASA Categories of Evidence’” (NASA, 2013a). Thus, efforts to characterize and compare the quality of evidence cited in individual evidence reports are difficult.

During the course of the study, the committee also gathered evidence from existing literature and relevant experts in the field. The committee held three conference call meetings and one in-person meeting in conjunction with a public workshop (see Appendix A). At the workshop, the committee invited individuals with expertise related to one of the three evidence reports to analyze NASA’s evidence reports and answer committee questions, focusing on the following:

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2NASA has identified three categories of evidence that could be included in each evidence report, including data from controlled experiments, observational studies, and expert opinion (NASA, 2013a).
REVIEW OF NASA’S EVIDENCE REPORTS ON HUMAN HEALTH RISKS

- How well is the risk understood?
- What, if any, are the major sources of disagreement in the literature pertaining to this risk?
- What are the main gaps in knowledge or fundamental research about the risk?
- What is known about interactions between the risk and other risks identified in NASA’s evidence reports?

In addition to identifying whether individual evidence reports noted specific interactions between risks, the committee also conducted a co-citation analysis to attempt to quantify how many times the same reference (e.g., article, book, technical reference, policy, or website) was cited by multiple evidence reports. Such an analysis could be used by NASA to bolster discussions of risk interactions in updated evidence reports or to trigger further literature searches.

During the course of this effort, however, substantial variability in the formatting, internal consistency, and completeness of the references contained in many of the individual evidence reports became apparent, making the exercise arduous and results difficult to confirm. For improved quality and consistency and to aid in systematic assessments of this type for new and updated evidence reports, the committee strongly encourages NASA to choose a preferred citation format for all evidence reports and to require all writing teams to use that format. For example, the Citation-Name (C-N) standard of the Council of Science Editors’ style manual (CSE, 2006) would have many benefits for purposes of citation analysis, such as listing the first author name in the body text. As an alternate, the Citation-Sequence (C-S) standard also lends itself to automated methods of extracting titles, authors, dates of publication, and other relevant parts of the literature being cited by the evidence reports. Authors of NASA evidence reports should be encouraged to adhere to standard guidelines for systematic reviews (Huguet et al., 2013; Lefebvre et al., 2013; Wallace et al., 2013). This was noted in the recommendations of the 2008 IOM letter report.

This report follows the format of the 2008 IOM letter report and, with the exception of the foregoing remarks, is divided into three sections, which include the committee’s responses to each of the questions listed in its statement of task for the three evidence reports examined. Although no formal recommendations are included in this report, the committee’s observations are intended to inform and improve NASA’s ongoing efforts to update individual evidence reports.
RISK OF INJURY FROM DYNAMIC LOADS

Astronauts face the risk of injury from the transfer of large amounts of kinetic energy associated with many aspects of spaceflight, including launch and landing. As with terrestrial transportation, considerable research has gone into restraint systems and preventive measures that will enable the astronauts to withstand these extreme forces. The evidence report Risk of Injury from Dynamic Loads ("Injury Report"; Caldwell et al., 2012) currently focuses primarily on spinal injury. In addition, the Injury Report specifically states that it addresses the risk of injury due to dynamic load, defined as transient loads (less than or equal to 500 milliseconds) that "are most likely to occur during launch, pad or launch abort, and landing" (Caldwell et al., 2012, p. 6). The report further specifies a standard trapezoidal load profile, acknowledging that measured acceleration on the subject may have a different load profile.

Does the Evidence Report Provide Sufficient Evidence, as Well as Sufficient Risk Context, That the Risk Is of Concern for Long-Term Space Missions?

The Injury Report provides the context for many of the risks associated with dynamic loading during launch, abort, landing, and anomalous events. Development of new vehicles and propulsion systems may pose additional and unpredictable risks. Furthermore, information on other contexts in which dynamic loads may cause injury to astronauts should be considered in the Injury Report. For example, injuries may be incurred during extravehicular activity (EVA). In addition, injuries incurred from dynamic loads such as those that may be encountered during exploration of the lunar or Martian surface under conditions of reduced but significant gravity are not sufficiently considered (e.g., injuries from rover accidents or walking on extraterrestrial surfaces). For example, based on analog experience, it is likely that injuries on the Martian surface will include trauma to the hands, arms, legs, and feet, with estimates of 4.2 injuries among a crew of 6 on Conjunction Class expeditions (long stay) and 1.3 injuries during Opposition Class expeditions (short stay), based on Antarctic incidence rates (adjusted down) (Stuster, 2010). Rates actually experienced by astronauts may be higher because of deconditioning.

The supporting evidence for the Health Research Ratings for this risk ("Controlled" for an International Space Station [ISS] mission of 12
months; “Acceptable” for lunar and near-Earth asteroid missions; and “Insufficient” for a Mars mission) (NASA, 2013c) needs further context and explanation in the report. Every mission begins with takeoff and ends with a landing, with potential for significant injury at both ends. The retirement of the shuttle has led to the current reliance on Soyuz and future reliance on commercial vehicles, which may pose new and unforeseen risks to occupants (Brinkley, 2013). Relevant issues being considered in the design of vehicles for lunar, near-Earth asteroid, and Mars missions will be important to add as more information develops.

**Does the Evidence Report Make the Case for the Research Gaps Presented?**

The Injury Report clearly states the case for each of the research gaps presented in the report.

**Are There Any Additional Gaps in Knowledge or Areas of Fundamental Research That Should Be Considered to Enhance the Basic Understanding of This Specific Risk?**

The committee identified several additional gaps that could be explored in the Injury Report. Consideration should be given to expanding this report to encompass a broader range of mechanical stress profiles and injurious situations that might be amenable to mitigation strategies. This would appear relevant to the kind of analyses and research contained in this evidence report, although they could be considered in a separate report.

*Vibration and Other High-Frequency Stress*

The Injury Report is limited by constraining the definition of “dynamic loading” to a single impulse (trapezoid comprised of onset, load, and offset). Some dynamic loads such as vibration may also be oscillatory in nature, however, and the frequency, amplitude, and duration of such oscillations are important variables to consider. The concern with oscillatory loading in the Ares I launch system is a relatively recent example of a knowledge and research gap that is not addressed by the evidence report. Furthermore, the effect of sustained thrust (such as might be en-
countered with innovative propulsion systems) or the superimposition of loading from sustained thrust and vibration should be explored.

*Standardization of Instrumentation and Methodology to Measure Dynamic Load*

Standards need to be developed to ensure consistency of data across multiple launch and vehicle configurations. Without such standardization, accurate comparison becomes difficult, if not impossible, and the effects of mitigation strategies are difficult to ascertain.

*Varying Vehicle Designs*

Current access to the ISS is provided by the Soyuz. Several aerospace companies are involved in designing potential crew vehicles and launch systems for future U.S. spaceflight. Each vehicle will likely have a different dynamic load profile; thus, the risk from dynamic loads will be specific to each crew vehicle and launch system. The definition of design reference missions is neither sufficient to characterize the complexity of these vehicles and launch systems nor appropriate to define the potential differences in risk among them.

A standardized method of measuring dynamic load should be employed as part of a comprehensive evaluation of new (and old—e.g., Soyuz) vehicles in order to improve the understanding of how dynamic loads are transferred to occupants and to maximize occupant protection for each vehicle (Pintar et al., 2012).

*Extraterrestrial and Extravehicular Activity*

The Injury Report provides appropriate consideration to dynamic loading during launch and landing and the extent to which launch/entry suits may affect the load experienced by crew members. However, little attention is paid to the dynamic load issues that could occur during an inflight EVA or during falls in an extraterrestrial environment, such as lunar, asteroid, or Martian surfaces. In the latter case, issues such as total mass and center of mass of suit components, deconditioning of crews, irregular terrain, lower but significant gravity than that experienced on Earth (after a period of time in zero-G), and design of rover vehicles could change the risk to crew.
Additional Research Gaps

Basic and applied research gaps and mitigation strategies that deserve additional consideration include the following:

- Anthropometric, age, and sex differences
- The potential for various other types of injuries, including soft tissue damage, traumatic brain injury, and internal organ injury
- Development of data at the lower end of the injury spectrum. Current models cannot be accurately extrapolated to the low injury severity/probability extreme. In addition, injuries that are not life-threatening on Earth (e.g., extremity fractures, soft-tissue injuries) could be more severe or difficult to manage in space (Pintar et al., 2012)
- Influence of deconditioning on the design of adequate protection and restraint systems (e.g., cervical-spine data) and on the design of rover/EVA suits for use during surface exploration
- The role that physical fitness (preflight and during flight) plays in preventing injury or mitigating the effects of injury on operational requirements
- Effect of individual crew variation on protection and restraint systems (e.g., NASCAR) and on rover/EVA suit design for use during surface exploration
- Application of known principles of injury prevention into an integrated system of occupant protection (e.g., NASCAR)
- Development of effective head and neck protection and restraint systems that provide protection to the cervical spine and brain even under conditions of deconditioning. For example, can effective helmets be made that weigh less or that are braced against the shoulders so that the deconditioned neck muscles are not forced to potential failure
- Potential applications of air bag-type technology to vehicle occupant protection
- Concepts of “energy attenuation” so that dynamic impact energy is absorbed rather than stored (elastic) and returned to vehicle occupant
Does the Evidence Report Address Relevant Interactions Among Risks?

The executive summary of the evidence report clearly states the potential effects of crew-related factors such as age, anthropometrics, and sex on the risk of injury and goes on to specify that “spaceflight deconditioning has been shown to degenerate the structural and tissue response in the musculoskeletal system which imply the crewmember may have a lower tolerance to dynamic loads” (Caldwell et al., 2012, p. 6). The interactions between health risks associated with dynamic loads and health risks associated with microgravity environments are not adequately explored in the Injury Report.

Cross-referencing is needed to a number of relevant evidence reports, which will be reviewed by the committee in subsequent letter reports, including the following: Risk of Impaired Performance Due to Reduced Muscle Mass, Strength, and Endurance (Baldwin et al., 2008); Risk of Reduced Physical Performance Capabilities Due to Reduced Aerobic Capacity (Moore et al., 2010); Risk of Orthostatic Intolerance during Re-exposure to Gravity (Platts et al., 2008); Risk of Intervertebral Disc Damage (Sibonga et al., 2008a); Risk of Bone Fracture (Sibonga et al., 2008b); and Risk of Accelerated Osteoporosis (Sibonga et al., 2008c).

The interactions with human factors issues should be considered. In particular, the report should address the design of restraints to minimize inadvertent or volitional behavior that degrades safety. In addition, the Injury Report should acknowledge that potentially survivable injuries (such as extremity fractures or soft-tissue injuries) may be harder to treat or more susceptible to infection during spaceflight. The Injury Report should include cross-referencing and information on interactions between the risk of injury due to dynamic loads and the evidence reports on inflight medical capabilities (Archibald and Kelleher, 2013), unpredicted effects of medication (Wotring, 2011), and altered immune responses (Crucian et al., 2009).

What Is the Overall Readability and Quality?

The committee believes that the focus and readability of the Injury Report could be improved by professional editing. The report’s text should be tightened to focus on materials that are directly relevant and not extraneous to the problem; much of the text provides an uncritical
assemblage of various models, some of which are not directly applicable to the current situation. Material of largely historic interest could be summarized with hyperlink references to further descriptions for the interested reader; alternatively, it could be moved to an appendix. More current data are needed from other disciplines, such as incorporating cross-references to deconditioning (musculoskeletal and cardiovascular). Moreover, the committee identified examples of imprecise, inconsistent, and incorrect word usage throughout the report.

The Injury Report would also benefit from a thorough and critical discussion of such models as the Hybrid III FE, which may be of direct applicability. Other models of potential applicability, including the Mathematical Dynamic Modeling (MADYMO), Total Human Model for Safety–Finite Element (THUMS FE), and Test Device for Human Occupant Restraint (THOR) (as well as those from the Global Human Body Models Consortium), are only briefly discussed in the Injury Report and would benefit from greater explication (Nightingale, 2013). The committee notes that these models have been best validated at the extremes of energy transfer, yet even lower-impact injuries may be significant in the space environment.

Additional information is needed at levels where energy transfer minimally exceeds the threshold for producing injuries. The models are best suited to provide information on catastrophic events, but smaller impacts may also be important in deconditioned astronauts because they would be difficult to treat in space. In this respect, injuries easily treated on Earth may be problematic in space (IOM, 2001). The currently available physical and numerical surrogates are not designed or validated for the impact directions important to spaceflight. Models are needed that can assess vertical loading. Critical analyses of the strengths and weaknesses of the various models, the available dummies, injury predictors, and injury scales are needed in the Injury Report.

Presentations received by the IOM committee emphasized that risk mitigation for dynamic loads is best addressed using a systems engineering approach. For example, NASCAR utilizes a combination of seat shell design, conformal seating, neck restraint, helmet design, crush zones in the vehicle, and crushable walls to reduce motion and lower peak acceleration forces during crashes.

Expanding the discussion to include external factors associated with each crew vehicle and launch system, utilizing a systems engineering approach, would be a significant addition to the Injury Report. One approach suggested in NASA’s Risk Master Logic Diagram for the Injury
Report would be to consider the astronaut suit-vehicle as a “system of systems” (NASA, 2013d), as shown in Figure 1.

Furthermore, additional sources of relevant data that could be cited and further explored include data on pressure suits and existing human spaceflight data on the incidence and severity of vertebral disc herniation after spaceflight related to flight duration and landing impact severity. Inflight data are critical to the next steps in addressing injury from dynamic loads, and improved access to this data is needed.

A critical revision of Section 3.2.2 on sex differences is needed, with the inclusion of all relevant data. Statements about sex differences may not be supported by recent research, including data on risk of injury in the thoracic spine (Buhrman, 2013).

Another area needing significant development is Section 3.2.4 on spaceflight deconditioning. The effect of compliance with restraint systems and the ability to brace for impacts (relevant to deconditioned muscles) in particular need to be considered (Brinkley, 2013). Relevant research areas (such as bed-rest studies) need to be more fully explored.

**Is the Breadth of the Cited Literature Sufficient?**

As noted above, the Injury Report needs to discuss a wider breadth of research and should highlight relevant literature from those areas. This report does an excellent job of providing the full references in a consistent format.

**Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?**

The Injury Report was developed after the 2008 IOM letter report. Thus, there were no specific IOM recommendations on this topic. The 2008 report emphasized the need for external and periodic review, and it is commendable that the Injury Report and its associated research plan have been reviewed by NASA’s Occupant Protection Risk Standing Review Panel (Pintar et al., 2012). Still, the committee notes that the Injury Report did not use quality-of-evidence criteria as recommended in the 2008 IOM report, and, as discussed, the consistency and organization of the discussion could be improved.
FIGURE 1 Risk master logic diagram.
SOURCE: NASA, 2013d.
Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk? Is Input from Additional Disciplines Needed?

The authors have clearly assembled a credible but somewhat uncritical presentation of available models, some of which are no longer in active use. Additional expertise in relevant disciplines should be sought. For example, experience and expertise from the automotive industry and from NASCAR and other extreme sports could be incorporated into this document. NASA’s overview of the evidence report states that the Occupant Protection Team at NASA has developed a forward plan to develop new standards for protecting the crew during dynamic phases of flight. In collaboration with external peers in industry, academia, and other government agencies, the Team will develop and validate the standards using a combination of data mining, testing, analysis, simulation, and expert opinion (NASA, 2013c).

Data obtained from this collaboration should be incorporated into the Injury Report. NASA should continue to seek input from other disciplines in which occupants are exposed to dynamic loads.

RISK OF CLINICALLY RELEVANT UNPREDICTED EFFECTS OF MEDICATION

The evidence report titled Risk of Clinically Relevant Unpredicted Effects of Medication (“Medication Report”) characterizes the risks of clinically relevant, unpredicted effects of medication during spaceflight of short to medium duration in low Earth orbit. Risks associated with medication use by astronauts include those due to altered pharmacokinetics (PK)/pharmacodynamics (PD), likely alterations in medication stability, and such other factors as an increased potential for microorganism antibiotic resistance. The Medication Report also identifies specific factors that contribute to risk uncertainty, including a lack of systematically and consistently collected data during spaceflight, potential for astronaut self-diagnosis and risk for polypharmacy, and insufficient ground-based models on which reasonable hypotheses regarding medication PK/PD may be generated.

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3The title listed on NASA’s Human Research Roadmap summary website (NASA, 2013b), Risk of Clinically Relevant Unpredicted Effects of Medication, is not the same as the title on the report itself, Risk of Therapeutic Failure Due to Ineffectiveness of Medication. The implied scope of each title is significantly different.
The understanding of these risks is limited. Most available evidence is based on case studies, anecdotal reports, and extrapolation from ground-based models of microgravity physiology and well-accepted principles of pharmacology and physiology. NASA’s decision to include the risk of clinically relevant unpredicted effects of medication as an evidence report is valid, however, if the a priori assumption is made that exposure to microgravity alters total body/organism physiology, this will impact medication PK/PD.

Does the Evidence Report Provide Sufficient Evidence, as Well as Sufficient Risk Context, That the Risk Is of Concern for Long-Term Space Missions?

Drawing on well-accepted physiological and pharmacological principles, as well as the limited anecdotal data and case studies available from short- or medium-duration low Earth orbit flights, the Medication Report provides sufficient risk context and makes a compelling case to further monitor and evaluate the risks associated with medication use during spaceflight. Given the paucity of data on medication use in any spaceflight, the need for monitoring and evaluation of this risk should be extended to all potential flight scenarios, including suborbital and orbital flights, and expedition class missions (which would include both microgravity exposure during flight and partial gravity exposure after landing).

The Medication Report contains straightforward and concise descriptions of many factors that may affect medication effectiveness (e.g., PK/PD) during spaceflight. Building on this foundation, the Medication Report cites studies that establish a sensible concern about inflight medication use and properly notes that a lack of data and systematic evaluation, with the exception of some preliminary drug stability work, hinders formal evaluation of the level and severity of risks associated with medication use in space.

As noted above, the lack of data on medication risk during spaceflight leads to insufficient characterization of risks associated with all design reference missions, such as ISS-12, lunar, and near-Earth asteroid missions. Differences in duration, destination, and equipment between individual missions raise questions of pharmacologic significance, including medication packaging and shelf life, radiation effects on drugs, and the physiologic and pathophysiologic states of crew members (Bayuse, 2013). Moreover, all of the risks discussed are relative to a mi-
crogravity environment. The Medication Report could address the research needs for partial gravity environments (such as lunar, asteroid, or Martian gravity), which should be part of scenario planning for those missions.

**Does the Evidence Report Make the Case for the Research Gaps Presented?**

In general, the Medication Report provides good context and support for the research gaps identified. Research gaps are spread across the report by section and are collapsed into five broad categories on NASA’s Human Research Roadmap summary website (NASA, 2013b). It would be helpful to include these categories in the Medication Report’s executive summary as well. Individual research gaps are presented below with committee assessment and commentary.

**Pharm01: We Do Not Know How Medications Are Used During Spaceflight**

The committee agrees that a lack of knowledge about how medications are used during spaceflight remains a high-priority research gap, with implications for the operational safety of all spaceflight missions. As described in the Medication Report, there is no mandatory systematic collection of data on medication usage during spaceflight. The current approaches to acquiring inflight data on medication use and associated clinical indications and outcomes (including adverse events) are post hoc, uneven, and dependent on the memory and voluntary participation of astronauts in completing surveys about events that may have happened months earlier (IOM, 2008). Similar observations were made by NASA’s Pharmacology Risk Standing Review Panel (Venitz et al., 2011) and in testimony before the committee (Marshburn, 2013).

The Medication Report does not adequately emphasize the need for procedural infrastructure and research on the systems to recognize and to preempt unsafe practices. As described in the Medication Report, astronauts are allowed to self-administer medications included in prepacked medication kits (Wotring, 2011). Astronauts are also permitted to carry personal items, including medications and supplements (Venitz et al., 2011). An astronaut may choose to consult or inform a flight surgeon about medication use during the mission, but it is not required (Wotring, 2011). Even when information about medication use is available, it may
not be complete or accurate. During postflight debriefs, individual crew members may not recall each medication use, result, or adverse effect (Wotring, 2011). Medications taken in error during spaceflight, such as an astronaut inadvertently taking a stimulant instead of a sleeping aid, have also occurred (Marshburn, 2013). A growing knowledge base on patient safety in terrestrial health care settings suggests that such small medication errors may be harbingers of major errors with potential clinical impact (McDowell et al., 2009). Of crucial importance, the apparent imbalance between privacy issues and required documentation of medication use creates a situation in which it is nearly impossible to learn from current experience.

In addition, the Medication Report should emphasize the need for more information on what drug residues (e.g., parent drug and metabolites) appear in astronauts' urine after medication use and in what concentrations. Lack of information about astronaut medication use during spaceflights and the use of closed-loop urine processing systems on the ISS and possibly other expedition class flight platforms (Marshburn, 2013) has important implications for the health of other crew members. Without more data about current filtration system efficacy in removing drug residues and the toxicological implications of unintended astronaut exposures to these residues, mitigation of the risks associated with clinically unpredicted effects of medication during spaceflight should remain a high priority.

Concerns about patient privacy further complicate efforts to assess risks associated with medication use during spaceflights. NASA must comply with the Privacy Act of 1974 (NASA, 2009), but experts disagree about the scope of permissible disclosure within NASA under the Act (IOM, 2001). NASA has stated that “medical issues that arise immediately pre-flight or in-flight are discussed among operational, medical, and astronaut management on a need-to-know basis, giving due consideration to privacy, crew member health and safety, and mission impact” (U.S. Congress, 2007). Viewing self-administration of medications as a crew occupational health and safety issue, rather than primarily as data collection for a research protocol, comports with an earlier IOM recommendation that NASA adopt “an occupational health model for the collection and analysis of astronaut health data, giving priority to the creation and maintenance of a safe work environment” (IOM, 2001, p.

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4Data mining of current medical data, in light of these numerous uncertainties, should be regarded as strictly hypothesis-generating.

5Public Law 93-579 (December 31, 1974).
and would do much to help improve the policies, procedures, and associated technical infrastructure (e.g., barcoding of medications) in this context.

NASA’s Medication Report should place greater emphasis on knowledge gaps that result from the lack of real-time data collection on medication use and related health outcomes. Currently, it may not be possible to determine the exact cause of, and circumstances leading to, a medically and operationally significant event. Moreover, the current lack of reports on medication-related adverse events does not indicate the absence of adverse events or, conversely, medication safety and efficacy. A more systematic approach to medication risk assessment would, in the spirit of a learning health care system (IOM, 2007), utilize each experience of an astronaut taking a medication for a health condition to improve care for all future crew members who encounter the same health condition. The evidence report on vision impairment and intracranial pressure (discussed later in this report) provides an example of how critical medical information can be collected and disseminated from case studies while maintaining patient confidentiality. The Medication Report should underscore the benefit of increased data collection and transparency on both NASA’s research and operations.

**Pharm02: We Do Not Know How Long Medications May Be Safe and Effective Beyond Their Expiration Dates**

The committee agrees that this is an important research gap that has clear operational relevance, as outlined in the risk report.

**Pharm03: We Do Not Know the Extent to Which Spaceflight Alters Pharmacokinetics**

The committee agrees that the evaluation of pharmacokinetics during spaceflight is a fundamentally important area of investigation. As noted in the Medication Report, PK evaluations have been limited to a few subjects and medications (acetaminophen, scopolamine/dextroamphetamine) and were conducted during short-duration shuttle missions (Wotring, 2011). This gap is accentuated by a lack of appropriate ground-based models to accurately characterize spaceflight-induced changes in PK/PD. If the entirety of human physiology is altered during spaceflight, then it is reasonable to assume that PK/PD will be altered in some manner (Nicolau, 2013). Whether PK/PD alterations will manifest or have clini-
cal relevance remains to be determined, and future research should examine PK and PD simultaneously (Bayuse, 2013).

From the limited inflight data on acetaminophen and scopolamine/dextroamphetamine, it appears that altered gastrointestinal function (e.g., altered splanchnic blood flow, gastrointestinal pH, motility, transit time, or a combination of all these factors) during spaceflight may play a role in oral drug absorption. Thus, this research gap should include evaluation of alternative routes of drug administration and associated dosage forms, as well as oral formulations that would have a higher probability of absorption and subsequent therapeutic efficacy. Relevant to this is research performed during parabolic flight in 1990 that examined the impact of microgravity on aerosol dispersion of several medications (Lloyd et al., 1991). This evaluation was not cited in the Medication Report.

**Pharm04: We Do Not Know the Extent to Which Spaceflight Alters Pharmacodynamics**

The committee agrees that this is an important research gap and opportunity because the expected influences on PK, including microgravity, radiation, and physiologic changes associated with long-duration flights, would also reasonably be expected to influence PD. As with PK, there are no well-characterized and reliable ground-based models available presently.

**Pharm05: We Do Not Know the Extent to Which Current Antimicrobial Therapies Are Effective Against Microbes That Have Been Altered by Spaceflight**

The committee agrees that this is a research gap with high relevance to clinical management of infections, in an environment where infections have been demonstrated to occur. Altered growth or virulence and a shift in minimum inhibitory concentrations for antibiotic susceptibility have been documented in experiments for both *Staphylococcus aureus* and *Escherichia coli* cultures grown on the space shuttle and in the Russian Salyut programs (Gasset et al., 1994; Tixador et al., 1981, 1985, 1994). A number of research teams, in publications spanning 2000 to 2007, demonstrated that *Salmonella typhimurium* grown on the space

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6The committee will review NASA’s evidence reports Risk of Adverse Health Effects Due to Alterations in Host Microorganism Interactions and Risk of Crew Adverse Health Event Due to Altered Immune Response in subsequent letter reports.
shuttle exhibited altered gene expression and enhanced virulence compared with ground-based control cultures (Nickerson et al., 2000; Wilson et al., 2002a,b, 2007). It should be noted, however, that a recent publication by Hammond and colleagues (2013), suggested that salmonella virulence may not be affected by spaceflight. However, significant differences in study design, including the strain of *Salmonella typhimurium* studied, may account for the discordant findings between research terms.

The balance of preliminary evidence suggests that differences in microbial growth patterns, gene expression, and the potential for increased antibiotic resistance may occur during spaceflight. Therefore, systematic evaluation of all flown antimicrobials, under conditions mimicking long-duration spaceflight missions, are needed to evaluate the PD interactions of these antimicrobials with space-grown pathogens that astronaut crews are likely to encounter. Moreover, the PK of antimicrobials during spaceflight have not been characterized at all and should be included as part of the study design for these investigations. The interactions of host (human) immunity deficits, microbial changes induced by spaceflight (for both those microbes passed between crew members as well as those comprising individuals’ microbiomes), PK/PD, and drug stability changes due to spaceflight represent complex processes that need to be characterized in order to determine whether infection can be effectively treated during long-duration missions. These research questions are also closely linked to research gaps related to preflight immunizations and other infectious disease–related prophylaxis that could be undertaken prior to spaceflight.

**Are There Any Additional Gaps in Knowledge or Areas of Fundamental Research That Should Be Considered to Enhance the Basic Understanding of This Specific Risk?**

The committee believes that the following topics, some of which are noted in the narrative of the Medication Report, could be elevated to the status of “research gap”:
Research Areas Pertaining to Drug Pharmacokinetics/Dynamics

- Drug–drug interactions and how these may be modulated by the spaceflight environment
- Pulmonary physiology during spaceflight and potential impact of EVA on PK/PD
  - A corollary to this issue may include the behavior of and effectiveness of aerosol dosage forms in microgravity
- Effect of exercise on drug disposition during spaceflight
- Effect of spaceflight-induced changes in fluid/electrolyte distribution on drug PD (which is of particular concern with the arrhythmogenic potential of certain medications on top of electrolyte abnormalities, such as hypomagnesemia)
- Impact of spaceflight on chronic, age-related comorbidities (e.g., hypertension, dyslipidemia). Certain comorbid conditions in terrestrial medicine can impact PK/PD, so it is reasonable to question whether these conditions will influence physiology in space.
- Medications aimed at ameliorating symptoms associated with adjustment to microgravity (e.g., motion sickness, sleep disturbances, nasal congestion)
- Effect of circadian shifting on PK/PD
- Interaction of spaceflight with potential sex and age differences in PK and PD
- Impact of nutrition on PD
- Influence of pharmacogenomics on drug disposition
- The potential impact of microbiome changes in microgravity, which raises several research considerations, including the following:
  - Evaluation of the potential for pathogenic changes to an individual’s microbiome and the clinical significance of these changes on disease manifestation and propagation of disease among flight crew
  - Determination of how gastrointestinal microfloral changes in microgravity may moderate various metabolic processes (such as immunity and energy metabolism) and alter drug PK/PD

7The committee will review NASA’s evidence report Risk Factor of Inadequate Nutrition in a subsequent letter report.
Medication Countermeasures (Drug Pharmacology in Space)

- Identification and validation of effective medication countermeasures against a variety of adverse physiologic consequence of flight (such as bone loss, increased intracranial pressure [ICP], and intraocular pressure [IOP]), which may be mission-limiting events.

Other Related Research Gaps

- Crew medical training. Crew medical officers have been traditionally assigned as part of flight crews during the shuttle program. Most crew medical officers are nonphysicians and have additional responsibilities apart from their medical duties (Marshburn, 2013). Questions pertaining to the quality of training, knowledge retention by the crew medical officers, and the potential for overconfidence in treating medical conditions without flight surgeon consultation may affect the risks associated with medication use in space, especially for exploration class missions if crews assume greater autonomy.

- Enhancement of the pharmacology database. Efforts to explore information needs of the crew regarding pharmacology are needed, including the need for a comprehensive list or database of medications available in medical kits (with information on the drug name, terrestrial doses, and terrestrial adverse events), notes on adverse events recorded during spaceflight, contraindications, drug–drug/drug–nutrient interactions, and spaceflight expiration date. A similar recommendation was made by NASA’s Pharmacology Standing Review Panel (Venitz et al., 2011).

Does the Evidence Report Address Relevant Interactions Among Risks?

The Medication Report enumerates general PK/PD issues that have relevance to other risks and body system-specific PD that are relevant to central nervous system, cardiovascular, gastrointestinal, skeletal, muscular, and immunologic systems, as well as multisystem radiation effects. The previously mentioned co-citation analysis revealed that many cited articles discuss medication use in the context of other human health risks.
Because medication efficacy is essential to the successful management of many health conditions, it is important to better understand the interconnectivity between medication efficacy and other risks of spaceflight, and this issue should be highlighted throughout the evidence reports.

What Is the Overall Readability and Quality?

Overall, the Medication Report is of high quality and readability, achieving the goal of being readable by a science-literate, nonspecialist audience and including useful introductory tutorials for most of the topics described. Because spaceflight data are lacking, the Medication Report emphasizes analog data such as for bed rest, which is not necessarily a good model for spaceflight changes in PK/PD. In this regard, the quality of the evidence leaves substantial room for improvement.

Because of the lack of spaceflight data and challenges with current models discussed in the Medication Report and above, the committee believes that the HRP Research Rating, which rates the risk of clinically relevant unpredicted effects of medication as “controlled” for three design reference missions, needs to be reexamined. No data on medication risk are sufficient to ascertain whether such risk has been satisfactorily mitigated for any design reference mission scenario.

Is the Breadth of the Cited Literature Sufficient?

The Medication Report appears to be relatively comprehensive in its scope, with the exception of the aerosol dispersion data (mentioned on page 17).

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?


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8This rating is included on NASA’s website, which provides the report overview and direct link to the evidence report (NASA, 2013b).
Due to Ineffectiveness of Medication, Medication Interaction, or Unan-
ticipated Idiosyncratic Reaction (IOM, 2008). The original title remains
and is different from the title NASA uses to list the Medication Report.
The 2008 letter report also included five additional gaps in knowledge
for NASA to consider in evidence report updates:

1. **Gap 1.** How does genetic variation contribute to differences in
drug effectiveness and side effects in the space environment?
The issue of genetic variation in drug metabolism is discussed
beginning on page 29 of the Medication Report, but it is not
identified as a specific knowledge gap.

2. **Gap 2.** What potential interactions with alcoholic beverages
might be anticipated (if the crew is international and if alcohol is
allowed in-mission)? This issue is not addressed in the Medication
Report.

3. **Gap 3.** How will the natural degradation associated with long
storage periods be mitigated for long-duration space travel?
This subject was incorporated in the current evidence report in
Research Gap PH 9 regarding the stability of drugs during long-
duration spaceflight. The intervening operational change to use
original packaging wherever feasible is an implicit response to
this challenge (Bayuse, 2013), but the results of this change in
terms of lengthening the shelf life of drugs have yet to be sys-
tematically assessed.

4. **Gap 4.** What classes of drugs should be taken on a mission, what
quantities should be taken, and how can the risk of the inability to
treat be minimized, especially during long-duration exploration-
class missions?

5. **Gap 5.** The decision on which classes of therapeutic agents and
which drugs to take will impact which conditions can be treated.
A methodology for decision making should be included.

Gaps 4 and 5 point to the intersection of two reports, Risk of Clinically
Relevant Unpredicted Effects of Medication and Risk of Unacceptable
Health and Mission Outcomes Due to Limitations of Inflight Medical
Capabilities. They remain research and operational challenges.
Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk? Is Input from Additional Disciplines Needed?

This is a single-authored evidence report that could be strengthened by inclusion of authors with diverse expertise. For example, a clinical co-author, preferably a clinical pharmacist with knowledge of drug interactions, would strengthen the author team. Specific benefit may be gained by adding a gastroenterology specialist with expertise in oral drug absorption and gastrointestinal factors that may result in altered drug absorption. Inclusion of an infectious disease specialist, with specific expertise in antimicrobial resistance and antibiotic PD/PK, may also be appropriate.

The report could benefit from the involvement of independent, multidisciplinary researchers and clinicians, including clinical pharmacists, military clinicians, and experts in extreme environment medicine (including those with Antarctic medical experience).

RISK OF SPACEFLIGHT-INDUCED INTRACRANIAL HYPERTENSION AND VISION ALTERATIONS

Visual blur has been reported by astronauts for many years, but only recently, with longer-duration spaceflights, have additional optic changes been noted, including optic disc swelling and choroidal folds. As described in NASA’s evidence report Risk of Spaceflight-Induced Intracranial Hypertension and Vision Alterations (“Vision Report”), 15 crew members on long-duration spaceflights have experienced optic and visual changes (some of which have been short-lived and others that have persisted after the flight), and some have also had borderline elevated ICP as measured as varying single points of time after flight (Alexander et al., 2012). Additional reports have been received of changes in visual acuity. The causes of the anatomical and visual changes have not yet been determined.

Does the Evidence Report Provide Sufficient Evidence, as Well as Sufficient Risk Context, That the Risk Is of Concern for Long-Term Space Missions?

The Vision Report is clear in describing the importance of the ocular and vision changes and providing the context for the potential acute and
long-term impacts on spaceflight and astronaut health. Because this is such a newly identified risk, there is value in the case reports that are discussed and the level of detail provided on research on the numerous potential etiologies for the changes noted in the ocular fundus. Reports of optic disc edema and chorioretinal changes are well substantiated in the report, and the data are thoroughly presented and well supported. Regardless of cause, these changes are concerning and have been associated with vision loss in terrestrial analogs (Mader et al., 2013).

It is not stated directly, but it seems evident that the increased ICP hypothesis arose secondarily after the optic disc edema was observed. Similarly, there are very limited data on the actual changes in vascular dynamics in microgravity (Miller, 2013). Therefore, we have limited evidence to support the hypothesis that increased ICP is responsible for the observed optic disc swelling and choroidal folds.

**Does the Evidence Report Make the Case for the Research Gaps Presented?**

As visual impairment and intracranial pressure (VIIP)9 issues are recent developments and have been studied in case report form only, the need for further research and existence of knowledge gaps is indisputable. There is still debate about the mechanism and causality of the observed effects. The committee urges the authors of the evidence report to delete references to the term “VIIP syndrome” in the Vision Report to eliminate the suggestion of any causal link, unless and until such a causal link has been proven (see further discussion below).

The Vision Report identifies a number of gaps in knowledge that are centered on the proposed mechanism of visual impairment. The committee discussed each of the gaps identified in the Vision Report and provides suggestions of areas to be considered as additional research gaps.

**VIIP1: What Is the Etiology of Visual Acuity and Ocular Structural and Functional Changes Seen in Flight and Postflight?**

The Vision Report does a thorough job of citing data from a number of sources regarding the need to understand the changes occurring in the

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9The Vision Report defines VIIP as “visual impairment/intracranial pressure,” (Alexander et al., 2012, p. 1), which the committee interpreted as “visual impairment and intracranial pressure.”
eye during spaceflight. More emphasis could be placed on the need to obtain additional standardized baseline information regarding the optic nerve and retinal structure from new astronauts before they begin their training. The methods being proposed to study the eye findings include spectral domain optical coherence tomography, which has the potential to identify important changes in the retinal, optic nerve, and choroidal anatomy. The committee is concerned that the Vision Report makes a strong assumption that high ICP is the cause of ocular disc swelling and urges that alternate mechanisms be explored thoroughly. Optic disc swelling may also result from local ischemia of the nerve, venous engorgement, inflammation, or accumulation of locally toxic substances, for example (Miller, 2013). The choroidal folds and striae documented are not characteristic of the Paton lines seen with papilledema (Mader, 2013; Miller, 2013). The choroidal folds are more likely to result from increased choroidal thickness (Mader, 2013), which would also explain the observed hyperopic shifts that occur even with short-term spaceflight. The opening pressures on lumbar puncture reported by Mader and colleagues (2013) were no higher than 28.5 cm H2O. Recent work by Avery and colleagues (2010) demonstrated that normal individuals under age 19 may have opening pressures as high as 28 cm H2O, and revised criteria for the diagnosis of idiopathic intracranial hypertension have established 25 cm H2O as the cutoff for adults (with debate that it might be even higher) (Friedman et al., 2013). The Vision Report should include additional information to explain that lumbar puncture provides only a “snapshot” of ICP at a moment in time and may under- or overestimate the real ICP. Furthermore, ICP varies with time of day and activity, and sustained periods of ICP elevation may be missed by lumbar puncture alone (Williams, 2013).

The committee urges the Vision Report authors to more closely examine the alternative etiologies for the optic disc swelling, as well as the potential long-term consequences of this seemingly reversible problem. It is possible that it is papilledema (swelling from elevated ICP), but other causes, such as fluid shifts, alteration of ocular blood flow, and multifactorial effects (radiation, nutritional status, acceleration/deceleration), need to be considered. Other physical changes that occur in flight, such as extended strenuous exercise (with the Advanced Resistance Exercise Device) or chronic constipation and associated Valsalva maneuvers, have been suggested as possible explanations for increased ICP or central venous pressure in the head. Although these elevations would be expected to be transient, research on terrestrial-based correlates (e.g., weightlifters
Contributing factors existing prior to flight should be considered in the Vision Report, including the effect of extensive prior exposure to strenuous high G-force training (Williams, 2013).

The Vision Report acknowledges that research is still in its initial phases; therefore, it is important for the Vision Report to examine and question the scientific rationale. For example, comparing inflight noninvasive ICP monitoring with pre- and postflight lumbar puncture is unlikely to provide useful data. Lumbar puncture generates data for a single moment and is subject to numerous variables; in terrestrial medicine, lumbar puncture is not considered equivalent to ICP monitoring data, which provides a more realistic and relevant view of ICP for making clinical decisions. Assessing genetic or anatomic susceptibility may be useful, but only after a better understanding of the underlying process is reached. Finally, impaired lymphatic drainage, which may also affect ICP, should be considered.

Although the refractive changes that occur can be compensated by the use of spectacles and do not seem to have long-term consequences, the report does not address other long-term risks to visual function, such as cataract formation. The lens is extremely radiosensitive, and premature cataract formation is a known risk with occupational exposure, with extensive evidence available from commercial and military aviation. Cataract development after even extended orbital missions may not pose a problem on return to Earth because treatment is widely available, but prolonged radiation exposure during a mission to Mars, for example, could have significant visual consequences that might not be treated effectively in the absence of advanced microsurgical capability. In addition, exposure to space radiation may be even more cataractogenic than exposure to radiation on Earth. The visual impairments that could result will require countermeasures designed to prevent and/or compensate for their occurrence. Impacts on subsequent flights for crew members with significant vision changes are a concern and an impetus for identifying effective preventive and countermeasures. The committee applauds NASA’s effort to document and analyze each clinical event related to the risk of spaceflight-induced intracranial hypertension and vision alterations. These efforts should serve as a model for ongoing assessment of other spaceflight-related risks.
To address the existing gaps in knowledge about VIIP concerns, researchers must determine the rate at which the abnormalities develop and if they eventually stabilize or even regress. As in VIIP1, the most promising studies currently planned seem to involve the optical coherence tomography (OCT) investigations of changes in retinal and optic nerve function. A limitation of OCT of the optic nerve is that it can only detect swelling and not axonal disruption or internal structural changes, which can be measured by scanning laser polarimetry (Mader, 2013). Scanning laser polarimetry is not yet available in a portable device, but development of an instrument could be encouraged. High-quality on-orbit fundus photos remain useful for monitoring disc status. Color Doppler ultrasound to evaluate ocular blood flow could be a useful method to determine if ischemia may be involved in the ocular pathology. Comparison to pre- and postflight measurements is advised. Screening of visual function is necessary to find refractive changes and to institute compensatory methods, but is unlikely to be sensitive enough to detect meaningful structural changes before OCT or ultrasound. Thus, measuring visual function may have operational relevance but lacks sensitivity for VIIP specifically. As noted in the Vision Report, IOP is currently measured on NASA crew members on the ISS. The correlation between ICP and IOP is not established, however, it is important for the report to emphasize that using IOP as a surrogate for ICP is not reliable, and the correlation should not be made. The Vision Report notes that empiric treatment with acetazolamide could be studied as a means of ameliorating VIIP. However, it is important to further explain that acetazolamide use increases the risk for renal calculi and would lower IOP. Thus, it could worsen choroidal swelling and potentially the optic disc swelling.

The Vision Report could include more information on the challenges of ICP measurement. If the ICP elevation is not the cause of the optic disc swelling, then the risk that increased ICP poses may be less than originally postulated (Williams, 2013). Direct ICP measurement initiated on orbit, such as by lumbar puncture, is unlikely to be acceptable to astronauts. Invasive devices placed terrestrially and used on orbit carry several potential risks (e.g., infection, cerebrospinal fluid leak and intracranial hypotension, failure of hardware). Real-time, noninvasive ICP monitoring would allow for data collection, although the inherent need
for averaging the readings over several seconds might mask dynamic variation and spikes. In addition, indirect ICP measurement methods (noninvasive) are still being validated in research settings. Because the ICP may rise during sleep when astronauts are stationary, monitoring may be most practical during rest. Monitoring over 48 hours could be effective in identifying variations in the ICP that could have clinical and operational relevance. It is also important to note that the validation of either phased or continuous noninvasive ICP monitoring, which would be done against the gold standard of invasive ICP monitoring, will take several years, and ultimately it may not provide a meaningful answer because of the sampling issue. Validation studies of noninvasive ICP monitoring could explore whether sampling issues associated with these noninvasive methods can overcome the current inability to demonstrate ICP transients, such as B-waves or plateau waves that are demonstrated with continuous ICP monitoring. However, the committee is cognizant that many researchers have been unsuccessful in past attempts to do so. The Vision Report could explore the benefits and risks of other preventive and treatment scenarios, such as consideration to forego additional testing and start empirical treatment with an ICP-lowering agent such as acetazolamide and assessment of ocular and ICP changes. However, the committee cautions that empiric treatment with typical terrestrial agents such as acetazolamide or topiramate does carry significant risks, such as renal calculi, dehydration, and impaired cognition.

VIIP12: What Are the Suitable Ground-Based Analogs to Study the VIIP Spaceflight-Associated Phenomenon?

The topic of suitable ground-based analogs is a valid research gap, but the focus needs to be expanded beyond models of increased ICP or fluid shifts to explore other possible etiologies, such as ischemia or local toxicity. Literature on various models is cited extensively in the report. These models include human bed rest and various animal systems. The ideal animal model would be one that spends much of its time upright but sleeps supine (nonhuman primate). The cost is likely prohibitive, however. Hindlimb suspension in rodents and similar unloading systems appear unlikely to mimic the fluid shifts and vascular changes that could contribute to high ICP and/or optic disc swelling (Williams, 2013). The Vision Report could note that it may be too early to choose a specific model without a better understanding of the pathogenesis of VIIP, and premature selection of a model system may lead to inappropriate conclu-
sions. It is important for the Vision Report to explain why rodents and rabbits are a poor model for VIIP and how their optic disc structure differs markedly from the human one. The rodent lacks a lamina cribrosa, making its eyes unsuitable as a model because having scleral and disc compliance comparable to that in humans would be necessary (Williams, 2013). The relevance of bed rest for modeling spaceflight-induced changes in the eye and specifically to intracranial pressure is not clear and has numerous potential confounders, including the difference in distribution of extracellular fluids and redistribution of vascular volumes that are quite different in microgravity than in the bed-rest models (with or without head-down tilt) (Williams, 2013). A recent review article that can be cited in the next iteration of the Vision Report summarizes data about ICP and IOP changes that have been observed in bed rest and parabolic flight models, with changes reported in the seconds or minutes after positional changes (Qvarlander et al., 2013). Because VIIP was not observed until the advent of long-term flight lasting several months, the relevance of short-term changes is significantly lessened (Taibbi et al., 2013).

**VIIP13: What Are the Safe and Effective Countermeasures to Mitigate Changes in Ocular Structure and Function and Intracranial Hypertension for Spaceflight? (Countermeasures)**

The Vision Report correctly notes that it is difficult to judge the safety and efficacy of countermeasures because the actual causes of the optic disc swelling, vision impairment (when present), and potentially elevated ICP are not known, nor have elevations in ICP been verified in flight yet. The report addresses the concern that use of the Advanced Resistance Exercise Device may contribute to the ocular changes because of increased intra-abdominal pressure and secondary ICP elevation. However, even if changes occur during exercise, it would not explain the other eye findings of choroidal folds, and the risk/benefit of changing the exercise program is not clear. Another potential problem with medical countermeasures to lower ICP is that they will lower IOP as well, which may be undesirable. Examples that could be added to the report include acetazolamide, which not only lowers IOP but increases the risk of renal calculi. Topiramate, which may lower ICP in patients with idiopathic intracranial hypertension via its weak carbonic anhydrase activity, often causes cognitive slowing (Miller, 2013). Hydrochlorothiazide is a strong diuretic and would produce undesirable effects. Further research is needed on whether the renal buffering system compensates for the acid/base disor-
der caused by chronically cabin-elevated FiCO₂ or whether other mitigation efforts to reduce elevated CO₂ are necessary. This effect has been observed in ICU patients in whom hyperventilation is performed to reduce ICP acutely by reducing pCO₂; the efficacy of the procedure ceases within hours.

How Are Fluids Redistributed in Flight?

The issue of fluid redistribution deserves continued investigation in the context of other studies aimed at understanding cardiovascular and cerebrovascular changes in spaceflights. The Vision Report notes the lack of conclusive data on the relationship between the observed eye changes and potentially elevated ICP; further details on research into other potential explanations could be added. Reduction of lymphatic drainage from the intracranial compartment also needs further evaluation. The fluid dynamics in the region may be much more complex at a local tissue compartment level and may not be related directly to the gross cephalad movement of fluid that is described in the cardiovascular models. Changes in lymphatic drainage will also influence fluid distribution and should be considered. Finally, complex regional and local vascular dynamics may need to be evaluated, such as orbital and facial blood flow and venous drainage (Mader, 2013).

Are There Any Additional Gaps in Knowledge or Areas of Fundamental Research That Should Be Considered to Enhance the Basic Understanding of This Specific Risk?

The committee identified several additional research gaps that could be explored in the evidence report:

- sex and age differences;
- potential for a biologic toxin to accumulate at the optic nerve head or within the nerve sheath;
- systematic approach to assessment of long-term impacts of VIIP on terrestrial visual function;
- time course of VIIP development and potential stabilization; and
- need for collection of baseline data from all incoming astronauts to determine if there are anatomic or genetic factors that may predispose to VIIP and to detect any preexisting changes to the
optic fundus that are already there from a stressful training environment or other causes. Specific areas of investigation would include assessment of scleral compliance and rigidity, deformability of the orbital and optic nerve head vasculature, and perhaps enhanced depth OCT imaging of lamina cribrosa structure.

This list is not comprehensive and would need to be modified as the study of this risk continues. Variations in these anatomic features may correlate with the risk of vision impairment and intracranial pressure, and identifying and recognizing these risk factors may allow for appropriate countermeasures to be developed.

**Does the Evidence Report Address Relevant Interactions Among Risks?**

The Vision Report identifies the possible contributions of radiation exposure, environmental hazards (increased CO₂ levels), nutritional effects (although elevated sodium levels may be beneficial rather than harmful in this context), and cardiovascular changes. Because the cause of the VIIP changes are still not certain, broad consideration of other factors should be maintained, although directed research into one particular area cannot be recommended yet. There is a much broader risk posed by visual impairment regarding any sort of perceptual interface, and the complexity of visual tasks is likely only to increase. Consideration should be given to the risk of inadequate medical treatment capability once the problem occurs.

**What Is the Overall Readability and Quality?**

The Vision Report is well written and reads well, although highlighting the main points of each data review could help to focus the analyses and to improve understanding by non-experts. The committee did identify some errors in the interpretation of the cited literature. For example, the section on optic disc edema, increased ICP, and mechanical deformation of the globe makes numerous statements about the pathogenesis of papilledema that are either purely hypothetical (globe deformation starts the process) or possibly incorrect (vascular compromise is part of the process). There is also confusion of terminology, wherein ICP elevation and venous pressure elevation are sometimes used interchangeably.
Finally, the discussion of correlation between IOP and ICP fails to differentiate high ICP from trauma and cerebral edema from other causes. Because many of the studies cited were performed in acutely ill patients, extreme caution must be exercised in applying the findings to healthy crew members.

Is the Breadth of the Cited Literature Sufficient?

The literature search appears extensive and covers many decades of work in the United States and other countries. Understandably, the literature on VIIP itself is sparse, but what exists has been included. There do not appear to be any glaring omissions.

The committee is pleased to see that this topic is the source of an exploratory effort by NASA to use an online Wikipedia process to gain additional information (Wikipedia entry: Visual impairment due to intracranial pressure, 2013). Topics such as this have the potential to greatly benefit from this type of continuous input, because rapid literature growth is anticipated. As with any feedback of this nature, however, the input will have to be carefully verified.

Has the Evidence Report Addressed Previous Recommendations Made by the IOM in the 2008 Letter Report?

VIIP was not described in 2008, and only refractive changes were noted. No specific recommendations were made in the prior report.

Is the Expertise of the Authors Sufficient to Fully Cover the Scope of the Given Risk? Is Input from Additional Disciplines Needed?

The authors have extensive space research experience. It may be beneficial to include a neurologist, neurosurgeon, or physiologist with expertise in ICP and cerebrospinal fluid circulation as authors in subsequent versions of the Vision Report to assist in the interpretation of ICP-related issues. A vascular expert, with specific research interests in the lymphatic system, could also provide valuable input.
SUMMARY

This is the first of five letter reports, which will review the entire series of NASA’s evidence reports on human health risks. This letter report reviewed the following three evidence reports: Risk of Injury from Dynamic Loads, Risk of Clinically Relevant Unpredicted Effects of Medication, and Risk of Spaceflight-Induced Intracranial Hypertension and Vision Alterations. The evidence reports differ in readability and quality, including variable degrees of supporting evidence and context for each risk. In addition to gaps noted in each evidence report, the committee identified other factors that may influence the level and severity of specific risks during spaceflight that should, therefore, be included in subsequent versions of individual evidence reports. Although the evidence reports would benefit generally from more diverse authorship across various disciplines, the committee is encouraged by NASA’s commitment to improving the quality of its evidence reports, seeking input from numerous internal and external reviewers, such as this committee and NASA’s Standing Review Panels. NASA’s dedication to more in-depth understanding of health risks associated with spaceflight will contribute to improved risk mitigation strategies and enhanced performance capabilities for future human spaceflight endeavors.

Sincerely,

Carol E. H. Scott-Conner, Chair
Daniel R. Masys, Vice Chair
Committee to Review NASA’s Evidence Reports on Human Health Risks
References


First Meeting of the Committee to Review NASA’s Evidence Reports on Human Health Risks

Telephone Conference

Wednesday, August 7, 2013

OPEN SESSION

11:30 a.m.  Official Charge to the Committee
            Mark Shelhamer, Chief Scientist, Human Research Program, NASA

11:50 a.m.  Discussion of Statement of Task with the Committee
            Facilitator: Carol Scott-Conner, Committee Chair

12:45 p.m.  Public Session Adjourn
Second Meeting of the
Committee to Review NASA’s Evidence Reports
on Human Health Risks

National Academy of Sciences Building
2101 Constitution Avenue, NW
Lecture Room
Washington, DC

Monday, September 30, 2013

OPEN SESSION

9:00 a.m. Welcome
Carol Scott-Conner, Committee Chair

9:15 a.m. Panel 1: Risk of Injury from Dynamic Loads
Facilitator: Larry Young, Committee Member

  • Jim Brinkley, Air Force Research Laboratory, Retired
  • John R. Buhrman, Air Force Research Laboratory
  • Roger Nightingale, Duke University

10:45 a.m. Break

11:00 a.m. Panel 2: Risk of Spaceflight-Induced Intracranial Hypertension/Vision Alterations
Facilitator: Prem Subramanian, Committee Member

  • Tom Mader, Alaska Native Medical Center
  • Michael Williams, Sinai Hospital of Baltimore
  • Neil Miller, Johns Hopkins University

12:30 p.m. Lunch
1:15 p.m.  Panel 3:  Risk of Clinically Relevant Unpredicted Effects of Medication  
Facilitator: Eleanor O’Rangers, Committee Member  
- Tina Bayuse, Wyle Science, Technology and Engineering Group  
- Tom Marshburn, NASA  
- Peter Bauer, NASA  
- David Nicolau, Hartford Hospital  

2:45 p.m.  Public Testimony—Registered Speakers  
Moderator: Carol Scott-Conner, Committee Chair  

3:15 p.m.  Public Session Adjourn
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Committee Biosketches

Carol E. H. Scott-Conner, M.D., Ph.D., M.B.A. (Chair), is a professor in the Department of Surgery, University of Iowa, Iowa City. Dr. Scott-Conner received her undergraduate training in electrical engineering from the Massachusetts Institute of Technology and worked as an engineer before attending medical school at New York University (NYU). She received her M.D. from NYU in 1976 and completed a residency in surgery there at 1981. After leaving NYU, she joined the faculty at Marshall University and then moved to the University of Mississippi. During her tenure there, she earned a Ph.D. in anatomy from the University of Kentucky and an M.B.A. In 1995, she became professor and head of surgery at the University of Iowa. Dr. Scott-Conner has been active on 22 editorial boards and has written more than 200 original papers, abstracts, reviews, and book chapters. She is certified by the National Board of Medical Examiners and the American Board of Surgery and has a certification of added qualifications in surgical critical care. Dr. Scott-Conner has served on a number of Institute of Medicine (IOM) committees, and she chairs the IOM Standing Committee on Aerospace Medicine and the Medicine of Extreme Environments.

Daniel R. Masys, M.D. (Vice-Chair), is an affiliate professor of biomedical and health informatics at the University of Washington School of Medicine, joining the Department of Biomedical Informatics and Medical Education in 2011. Previously, he served as professor and chair of the Department of Biomedical Informatics and professor of medicine at the Vanderbilt University School of Medicine. An honors graduate of Princeton University and the Ohio State University College of Medicine, he completed postgraduate training in internal medicine, hematology, and medi-
cal oncology at the University of California, San Diego (UCSD), and the Naval Regional Medical Center, San Diego. He served as chief of the International Cancer Research Data Bank of the National Cancer Institute, National Institutes of Health, and was director of the Lister Hill National Center for Biomedical Communications, which is a computer research and development division of the National Library of Medicine. He also served as director of Biomedical Informatics at the UCSD School of Medicine, director of the UCSD Human Research Protections Program, and professor of medicine. Dr. Masys is an elected member of the Institute of Medicine (IOM). He is a diplomate of the American Board of Internal Medicine in medicine, hematology, and medical oncology. He is a fellow of the American College of Physicians and fellow and past president of the American College of Medical Informatics. Dr. Masys served as a member of the IOM Committee on Aerospace Medicine and Medicine of Extreme Environments and chaired the 2008 IOM review of NASA’s Human Research Program evidence books.

Susan A. Bloomfield, Ph.D., earned her B.S. in biology at Oberlin College (Ohio) and her M.A. in physical education (exercise physiology) at the University of Iowa. After completing a Ph.D. (exercise physiology) at Ohio State University, Dr. Bloomfield joined the faculty in the Department of Health & Kinesiology at Texas A&M University in 1993, where she currently holds the rank of professor and is director of the Bone Biology Laboratory. In addition, she serves as assistant provost in the Texas A&M Office of Graduate and Professional Studies. Her research interests focus on the integrative physiology of bone, with specific reference to adaptations to disuse, microgravity, and caloric deficiency and how the sympathetic nervous system, altered blood flow, and endocrine factors modify those adaptations. More recent work has focused on the independent and combined effects of partial weight bearing and simulated space radiation on the integrity of bone and muscle, involving several experiments at Brookhaven National Laboratory. Collaborations with muscle biologists have enabled definition of concurrent changes in muscle-bone pairs with disuse and/or radiation exposure. Her work has been funded by the National Space Biomedical Research Institute (NSBRI), the Department of Defense, and, currently, NASA’s Space Biology Program. From 2000 to 2012, Dr. Bloomfield served as the associate lead for the Bone Loss (later, Musculoskeletal Alterations) Team within the NSBRI, and she has served on numerous NASA and European Space Agency review panels during the past 14 years. She is a member
of the Texas A&M Department of Nutrition & Food Sciences graduate faculty and is an associate member of the Texas A&M University Health Sciences Center School of Graduate Studies.

**Karen S. Cook, Ph.D.**, is the Ray Lyman Wilbur Professor of Sociology, director of the Institute for Research in the Social Sciences, and vice provost of the Faculty Development and Diversity Office at Stanford University. She conducts research on social interaction, social networks, and trust. She has edited and coedited a number of books in the Russell Sage Foundation Trust Series, including *Trust in Society* (2001); *Trust and Distrust in Organizations: Emerging Perspectives*; *eTrust: Forming Relationships in the Online World*; and *Whom Can We Trust?* She is co-author of *Cooperation Without Trust?*, and she co-edited *Sociological Perspectives on Social Psychology*. In 1996 she was elected to the American Academy of Arts and Sciences and in 2007 to the National Academy of Sciences. In 2004 she received the Cooley-Mead Award from the American Sociological Association’s Social Psychology Section for career contributions to social psychology.

**Eleanor A. O’Rangers, Pharm.D.**, is president, chief executive officer, and co-founder of Space Medicine Associates, LLC, which provides multidisciplinary space medicine and bioastronautics consultation, training, and oversight for both the commercial launch industry and the personal space traveler. Dr. O’Rangers has worked in the pharmaceutical industry as a medical director for a major pharmaceutical brand and also served as a field-based scientist. Currently, she consults for the pharmaceutical industry primarily on cardiometabolic drug development. A clinical pharmacist by training, with a subspecialization in cardiovascular pharmacology, Dr. O’Rangers maintains an active interest in microgravity pharmacokinetics/dynamics and has lectured and published on the subject. She has served as a pharmacology member of the Nutrition and Clinical Care Integrated Projects Team at the NASA–Johnson Space Center, whose mission is to provide a nonagency perspective on pharmacology and nutrition research needs for the U.S. manned spaceflight program. She was involved in the development of monographs for space shuttle and ISS medications. In addition, Dr. O’Rangers serves as the sole civilian pharmacist specialist for the Curriculum and Examination Board, U.S. Special Operations Command, Department of Defense. She has also organized a number of space medicine program tracks and space
medical emergency simulations for the National Space Society’s International Space Development Conference.

James A. Pawelczyk, Ph.D., is associate professor of physiology, kinesiology, and medicine at The Pennsylvania State University. Dr. Pawelczyk served as a payload specialist on STS-90 Neurolab (April 17 to May 3, 1998); the experiments on-board the space shuttle Columbia flight focused on the effects of microgravity on the brain and nervous system. Dr. Pawelczyk is a former member of the NASA Life Sciences Advisory Subcommittee, Office of Biological and Physical Research, and he served as a member of NASA’s ReMaP Task Force in 2002, which was charged with reprioritizing research on the space station. Dr. Pawelczyk’s research areas include central neural control of the cardiovascular system and compensatory mechanisms to conditioning and de-conditioning. He received his M.S. physiology from The Pennsylvania State University and his Ph.D. in biology (physiology) from the University of North Texas. He chaired the National Research Council (NRC) Decadal Survey on Biological and Physical Sciences in Space: Integrative and Translational Research for the Human System Panel and chaired an Institute of Medicine (IOM) report on NASA’s directed research programs in 2012. He has served on several NRC and IOM committees and recently completed rotations on the IOM’s Committee on Aerospace Medicine and the Medicine of Extreme Environments and the NRC’s Space Studies Board.

Robert L. Satcher, Jr., M.D., Ph.D., earned a Ph.D. in chemical engineering from the Massachusetts Institute of Technology in 1993 and an M.D. from Harvard Medical School in 1994. His medical specialties are orthopedics and oncology, and he has done much work in treating bone cancer in adults and children. Selected as an astronaut candidate by NASA in 2004, he completed his training 2 years later. He was aboard the space shuttle Atlantis that journeyed to the International Space Station for almost 11 days in November 2009. Classified as a mission specialist, he studied the influence of zero gravity on muscles and bone density as well as the effects of space on the immune system. He also used his surgical training to install an antenna and help repair two robotic arms on the space station. Dr. Satcher is an orthopedic surgeon at the MD Anderson Cancer Center in Houston, Texas.
**Jack Stuster, Ph.D.,** is vice president and principal scientist of Anacapa Sciences, Inc., a human factors and applied behavioral sciences research firm. He received a bachelor’s degree in experimental psychology from the University of California, Santa Barbara, and master’s and Ph.D. degrees in anthropology from the same institution. Dr. Stuster is a certified professional ergonomist, specializing in the measurement and enhancement of human performance in extreme environments. He has analyzed the tasks performed by U.S. Navy SEALs, SEAL delivery-vehicle pilots and navigators, explosive ordnance disposal technicians, crews of high-speed hovercraft, maintenance personnel, and military leaders. Dr. Stuster’s work for NASA began in 1982 with a systems analysis of space shuttle refurbishing procedures and has been followed by studies of conditions on Earth that are analogous to space missions. Dr. Stuster has been awarded Fellow status by the Human Factors and Ergonomics Society and the Borneo Research Society. He was a member of the Science Council of NASA’s Institute for Advanced Concepts and is now a member of the External Advisory Council of the National Space Biomedical Research Institute. He has also served on several government advisory groups, including the standing committee of the National Academies Board on Army Science and Technology to support the efforts of the Joint Improvised Explosive Device Defeat Organization, for which he received a patriotic Civilian Service Commendation in 2011. He currently serves as principal investigator of the Journals Flight Experiment and of the development of the Cultural Depot, an information-sharing system for use by special operations personnel.

**Prem S. Subramanian, M.D., Ph.D.,** is an associate professor of ophthalmology, neurology, and neurosurgery at the Wilmer Eye Institute, chief of the Neuro-Ophthalmology Division, and director of the Thyroid Eye Disease Center at Wilmer’s Bethesda office. He specializes in neuro-ophthalmology, with special interest in the treatment of thyroid eye disease, disorders that cause double vision in adults, and orbital and skull base tumors. His clinical practice includes patients with all types of disorders of the optic nerve and orbit, including disorders of intracranial pressure and cerebral venous sinus disease. Dr. Subramanian is the principal investigator in clinical trials on treatments for thyroid eye disease and idiopathic intracranial hypertension. Dr. Subramanian received his bachelor’s degree in chemistry from Princeton University and his M.D. and Ph.D. (in molecular and human genetics) from the Baylor College of Medicine. He completed an internship and ophthalmology residency at
Walter Reed Army Medical Center and then completed a fellowship in neuro-ophthalmology at the Wilmer Eye Institute. Dr. Subramanian served as director of neuro-ophthalmology at Walter Reed for 4 years before joining the Wilmer faculty and maintains a faculty appointment at the Uniformed Services University of the Health Sciences.

Gayle E. Woloschak, Ph.D., is a professor in the Department of Radiology, Feinberg School of Medicine, Northwestern University. Her research interests include studies of the molecular biology of lymphocyte and motor neuron abnormalities in DNA repair–deficient mice, studies of radiation-inducible nanoparticles, and analysis of molecular mechanisms of oncogenesis in radiation-induced tumors. She received her Ph.D. in medical sciences (microbiology) from the Medical College of Ohio and did postdoctoral training in the Departments of Immunology and Molecular Biology at the Mayo Clinic. Dr. Woloschak was a senior molecular biologist and group leader of the Biosciences Division, Argonne National Laboratory, and a senior fellow at Nanosciences Consortium, Argonne National Laboratory–University of Chicago. She has served as a member on the National Institutes of Health’s radiation study section and on the National Research Council’s Committee on the Evaluation of Radiation Shielding for Space Exploration and has chaired NASA’s peer-review radiation biology committee.

Laurence R. Young, Sc.D., is the Apollo Program Professor of Astonautics and professor of health sciences and technology at the Massachusetts Institute of Technology (MIT). He was the founding director (1997–2001) of the National Space Biomedical Research Institute. Dr. Young is a full member of the International Academy of Astronautics. He received an A.B. from Amherst College; a certificate in applied mathematics from the Sorbonne, Paris, as a French government fellow; and S.B. and S.M. degrees in electrical engineering and an Sc.D. degree in instrumentation from MIT. He joined the MIT faculty in 1962 and co-founded the Man-Vehicle Laboratory, which does research on the visual and vestibular systems, visual-vestibular interaction, flight simulation, space motion sickness, and manual control and displays. In 1991 Professor Young was selected as a payload specialist for Spacelab Life Sciences 2. He spent 2 years in training at the Johnson Space Center and served as alternate payload specialist during the October 1993 mission. He was chairman of the Harvard–MIT Committee on Biomedical Engineering and Physics and the interdepartmental Ph.D. Program in Biomedical Engineering, and he
directs the Harvard–MIT Program in Bioastronautics. Dr. Young is a member of the Institute of Medicine (IOM) and the National Academy of Engineering and has served on many IOM and National Research Council committees, including current service on the IOM Committee on Aerospace Medicine and the Medicine of Extreme Environments.