# Space Travel: An Integrative View from the Scientists of the Topical Team "Stress and Immunity"

2

Sarah Baatout, Alexander Choukèr, Ines Kaufmann, Nicola Montano, Siegfried Praun, Dominique de Quervain, Benno Roozendaal, Gustav Schelling, and Manfred Thiel

For centuries, mankind has struggled to understand the profound complexity governing the principles of life and the universe. This quest has taken him on scientific journeys far and wide: from the exquisitely simple atomic structure of our DNA to the hellish and chaotic depths of our sun, the energy source for all life on Earth, and

The European Space Agency has supported the teaming up of international experts in "Topical Teams". Topical Teams are open structures lead by European researchers which should address a scientific field in which gravity and access to space or planetary bodies constitute important cornerstones. The founding members of the Topical Team "Stress and Immunity", as listed in alphabetical order as authors of this perlude, were significantly involved in the realization of this book, contributed to it and authored this chapter as a group.
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S. Baatout
Belgian Nuclear Research Center, Foundation of Public Utility, SCK-CEN, Mol, Belgium

A. Choukèr (✉)
Coordinator of the Topical Team "Stress and Immunity",
Department of Anaesthesiology, University of Munich, Germany
e-mail: alexander.chouker@med.uni-muenchen.de

I. Kaufmann • G. Schelling
Department of Anaesthesiology, University of Munich, Germany

N. Montano
L. Sacco Hospital, University of Milan, Milan, Italy

S. Praun
V&F Analyse- und Messtechnik GmbH Absam, Austria

D. de Quervain
University of Basel, Basel, Switzerland

B. Roozendaal
Department of Neuroscience, University Medical Center, University of Groningen, Groningen, The Netherlands

M. Thiel
Department of Anesthesiology, Medical Faculty of Mannheim, University of Heidelberg, Germany

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beyond. Scientific, artistic, and social discoveries are what drive us as humans, and what distinguish us from all other species with which we share this planet. One of the fundamental questions that still troubles us is how life began on this planet and whether it exists elsewhere in the universe. This deep desire to understand and search for life has taken humans on exploratory journeys to the extremes of our planet: from the depths of our oceans to the heights of our mountains, and from the cold of Antarctica to the darkness of space. Fifty years ago, Yuri Gagarin marked a defining moment in the history of human exploration when he became the first human to escape the clutches of Earth's gravitational pull. Yet in 1960, before he launched into space, it was not even clear if humans could survive in a zero-gravity environment. At no stage in our evolution had we been prepared for such an environmental stress. From the moment life began in the "pre-biotic soup," some 3 billion years ago, all life on earth, Eukaryotes, Prokaryotes, and Archaea alike, have been shaped by the universal force of gravity. Within the space of a few minutes however, the most complex of these organisms, a human, Yuri Gagarin, seemingly "skipped" this evolutionary force and successfully coped with the absence of gravity. Since his historic 108-min voyage, others have survived for months not only in weightlessness, but also in extreme isolation and confinement, darkness, and danger. However, adapting to such hostile and unnatural conditions is not without any repercussions and is accompanied by adverse physiological and psychological effects, which, over the last decades, have been shown to disrupt almost all organ systems. Whilst our presence has extended beyond low Earth orbit to the moon, manned exploration beyond Earth's vicinity into the depths of our solar system requires a much more detailed understanding of the adaptation of human beings to extreme environments. Major questions remain: What are the principal and most important environmental and social threats to physical and mental health of crews during long-duration space flight missions, and how can we prevent and mitigate the adverse effects from adaptation to these threats?

It was Hans Selye who first used the term "stress" in the 1930s to describe how a biological system might adjust to the challenges and demands associated with major environmental changes (Selye 1936). He realized that when a complex organism is challenged by noxious conditions, the resulting symptoms are independent of the quality of the conditions, i.e., the qualitative end-result of different stressor types is the same. Rather, it is the quantitative effects that vary however. He also recognized that stressful conditions directly affect neural pathways, such as the autonomic nervous system, but also indirectly affect other organ systems, e.g., the immune system. The steps involved in the adaptation process to chronic stress are gradual and the biological system either builds up resistance to the stress and maintains a healthy physiological and psychological equilibrium, or succumbs to the stress, resulting in disequilibrium.

Stress research has expanded tremendously since then and Selye probably never imagined that it would transcend Earth's boundaries. Space flight is associated with a very distinct and unique combination of stressors: zero-gravity, radiation, altered microbial flora, isolation, confinement, altered day/night cycles and closed loop environments. Such stressors will be experienced in the extreme during inter-planetary travel. These combined and multi-factorial challenges affect many organ functions, including immunity, and overall health. Moreover, in the case of the immune system for example, changes can influence other physiological systems, and even feedback with neural pathways in a bidirectional manner (Tracey 2009).

Although astronauts are exceptionally well selected, trained, and healthy individuals, some are now known to be particularly prone to health alterations during the course of space flight. When challenged by complex stressful conditions, e.g., space flight, individuals react differently and adjustment to the conditions can fail. The "milieu intérieur" (*Claude Bernard, 1813–1878*) is no longer able to maintain "coordinated physiological processes which maintain most of the steady states in the organism," as they "are so complex and so peculiar to living beings – involving, as they may, the brain and nerves, the heart, lungs, kidneys and spleen, all working cooperatively" (Cannon 1932). This concept of "homeostasis" is extended further by the notion of homeodynamics, i.e., "the stability of the internal milieu toward perturbation" (Lloyd et al. 2001).

Although studying specific cellular models and simple biological organisms under conditions of simulated weightlessness, increased radiation, or isolation and confinement can help unravel the neurophysiological consequences of standardized emotional and physiological strains, no organ, especially in the case of humans, can be considered as a stand-alone entity. For this reason, new integrative and holistic approaches to the understanding of stress responses and individual predispositions and reactions to stress have started to evolve. With the help of research on the International Space Station and in analogous conditions and environments – e.g., group isolation and confinement in chamber studies (e.g., MARS500) or field operational conditions (e.g., Antarctica or sub-aquatic habitats) – the impact of distinct emotional and physical stressors, or a combination thereof, can be investigated. This will eventually help with the understanding of the incremental effects of stress on organ allostasis, from an allostatic load to overload with subsequent exhaustion and failure to re-establish an appropriate equilibrium.

Because allostasis is a continuous and evolving process, efficient and simple tools to monitor physiological and behavioral adaptation processes and consequences during long-duration deep space missions are needed to enable early detection of disease and early implementation of appropriate countermeasures. Given that the reaction to stress can vary between individuals, how can we design strategies to meet the astronauts' individual needs under evolving and unpredictable conditions? This may prove very difficult and will require new technologies and devices. Should we select astronauts based on the presence of genetic characteristics that confer resistance to stress? The new technological tools of molecular biology, such as micro-arrays, will help to understand the genetic and epigenetic (e.g., DNA-methylation, post-transcriptional regulation) reasons for (mal) adaption, and therapeutic consequences. If genetic testing were to provide the potential to select and de-select candidates, this would have important ethical, social, and psychological implications. However, because "reading genes" is not equivalent to "understanding genes" and because human complexity goes beyond genetic heritage, identification of genetic polymorphisms that appear to correlate with a higher predisposition to physiological and behavioral stresses should not disqualify a potential space flight candidate. Although polymorphisms in genes, for example, genes regulating sleep (Goel et al. 2009), or traumatic memory encoding, or DNA repair, may possibly lead to increased risk, individuals may have unidentified genetic resistance to other space-related stress factors, as well as behavioral resistance that may mitigate genetic risk. "The right stuff" seems very likely to be a very complex mix of gene–environment interactions. Given the ethical implications, the use of genetic analysis is *not* to define candidates who are suitable or not suitable for space flight, *but* rather to identify possible risks in order to personalize the frequency and mode of physiological and psychological assessments and countermeasures in space, and during rehabilitation upon return to Earth.

There is much left to qualify and quantify but with time we will refine the physiological, psychological, and pharmaceutical factors and interventions that will allow humans to travel inter-planetary distances. Along the way, these developments will not only benefit our space agencies but also wider society. Stress has the ability to alter the function of virtually every single organ system and cell type in the human body. The study of healthy humans experiencing high levels of stress in confinement and isolation, and in other space analogous environments, allows us to draw clear causal links between stress and physiological disequilibrium and disease. Understanding the interaction between stress and the human body and mind will lead to better healthcare not only for astronauts, but also for the vast majority of us who will never escape gravity's pull. Every single person on this planet experiences stress and no one is completely immune to its effects.

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The topics addressed in this prelude will be presented also in the parts II to VI of this volume. In addition, the following sources have been used to compile this prelude:

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